



# JOURNAL OF THE PHILIPPINE MEDICAL ASSOCIATION

Volume 104, Number 2

January - May 2026

**Clinico-Pathologic Factors of Endometrial Cancer in Young Filipino Women and Its Effect on Overall Survival Rate in a Tertiary Government Hospital**

*Amor Mae M. Pasigon, MD; Jimmy A. Billod, MD, MhCA, FPOGS, FSGOP, FICS*

**When Severe Cutaneous Adverse Reactions Evolve: Drug Reaction with Eosinophilia and Systemic Symptoms Progressing to Toxic Epidermal Necrolysis in a Filipino Patient**

*Angela Gayle Velayo, MD; Joanne Charisse Sy, MD; Camille Noelle Camara, MD; Benedicto dL. Carpio, MD, FPDS; Eileen Regalado-Morales, MD, FPDS; Amelita Tanglao-de Guzman, MD, FPDS, FDSP-PDS; Armelia Andrea Lapitan-Torres, MD, FPDS; Faye Elinore Kison, MD, DPDS; Matthew David Parco, MD, MBA, DPDS*

**A Study of Excimer Laser with Itraconazole versus Itraconazole Monotherapy in the Management of Onychomycosis: A Single-Center, Assessor-Blinded Randomized Control Trial**

*Michaela Gabrielle G. Guieb, MD; Andrea Marie Bernales-Mendoza, MD, FPDS; Ma. Cricelda Rescober-Valencia, MD, FPDS*

**Paraneoplastic Erythema Annulare Centrifugum Associated with T-Cell Non-Hodgkin Lymphoma in a 45-Year-Old Filipino Male**

*Yzabel N. Vergel de Dios, MD, DPDS; Maria Rosa Noliza F. Encarnacion, MD, FPDS; Andrea Marie Bernales-Mendoza, MD, FPPS; Vilma C. Ramilo, MD, FPDS*

**Pyuria in Cervical Cancer Patients Undergoing Concurrent Chemotherapy and Radiotherapy**

*Richard G. Malicdan, MD; Jimmy A. Billod, MD, MHCA, FPOGS, FSGOP*

**Lupus Panniculitis Masquerading as Mastitis: A Diagnostic Challenge in a 17-Year-Old Female Patient**

*Janine Michele T. Lovino-Ty, MD, DPDS; Reuben Mitchell M. Manuel, MD, DPDS; Jolene Kristine G. Dumlao, MD, FPDS*

**Knowledge, Attitudes and Practices of Personal Mosquito-Repellent Methods Among Adult Filipinos**

*Jenika Gracia P. Simbillo-Rivera, MD, DPDS; Lucille Sabrina F. Ferrer, MD, FPDS, FPSVI, Mari Carlota B. Najera, MD, FPDS*

**Knowledge, Attitudes and Practices of Outpatients on Topical Corticosteroid Use in a Tertiary Hospital: A Pilot Study**

*Janice G. Rigos, MD, DPDS; Maria Aurora H. Rosario, MD, FPDS*

**Clinical Profile and Selected Viral Genome Sequence Analysis of SARS-CoV-2 Infected Pediatric Patients in a Tertiary Military Hospital in Quezon City from January 2021 - July 2023: A Cross-Sectional Study**

*Deen Mark G. Toroy, MD, DPPS*

**Giant Lupus Vulgaris Presenting as Two Ulcerative Plaques in a Filipino Female: A Case Report**

*Gabrielle Nicole R. Mendoza, MD; Elisa Rae L. Co, MD, FPDS; Katherine Joy B. Sayo-Aguiling, MD, FPDS*

**Sibling Pair with Incomplete Feature of Netherton Syndrome: A Case Report**

*Leonard Jansen M. Cua, MD; Matthew David S. Parco, MD, DPDS; Faye Elinore V. Kison, MD, DPDS; Camelia Faye R. Tuazon, MD, FPDS; Benedicto dL. Carpio, MD, FPDS; Eileen R. Morales, MD, FPDS; Armelia L. Torres, MD, FPDS; Amelita Tanglao-De Guzman, MD, FPDS-FDSP-PDS*

**The Use of Double M-Plasty Technique for Excisional Biopsy on a Rare Case of Poroid Hidradenoma in 68-Year Old Filipino Male: A Case Report**

*Celina Faye C. Manalastas, MD; Ma. Christina Gulfan, MD, FPDS; Mary Grace Anne Calvarido, MD, FPDS, FDSP-PDS*



# TABLE OF CONTENTS

## Journal of the PHILIPPINE MEDICAL ASSOCIATION VOLUME 104, NUMBER 2     January - May 2026

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>Clinico-Pathologic Factors of Endometrial Cancer in Young Filipino Women and Its Effect on Overall Survival Rate in a Tertiary Government Hospital</b><br><i>Amor Mae M. Pasigon, MD; Jimmy A. Billod, MD, Mhca, FPOGS, FSGOP, FICS</i>                                                                                                                                                                                                                                                     | <b>1</b>  |
| <b>When Severe Cutaneous Adverse Reactions Evolve: Drug Reaction with Eosinophilia and Systemic Symptoms Progressing to Toxic Epidermal Necrolysis in a Filipino Patient</b><br><i>Angela Gayle Velayo, MD; Joanne Charisse Sy, MD; Camille Noelle Camara, MD; Benedicto dL. Carpio, MD, FPDS; Eileen Regalado-Morales, MD, FPDS; Amelita Tanglao-de Guzman, MD, FPDS, FDSP-PDS; Armelia Andrea Lapitan-Torres, MD, FPDS; Faye Elinore Kison, MD, DPDS; Matthew David Parco, MD, MBA, DPDS</i> | <b>7</b>  |
| <b>A Study of Excimer Laser with Itraconazole versus Itraconazole Monotherapy in the Management of Onychomycosis: A Single-Center, Assessor-Blinded Randomized Control Trial</b><br><i>Michaela Gabrielle G. Guieb, MD; Andrea Marie Bernales-Mendoza, MD, FPDS; Ma. Cricelda Rescober-Valencia, MD, FPDS</i>                                                                                                                                                                                  | <b>15</b> |
| <b>Paraneoplastic Erythema Annulare Centrifugum Associated with T-Cell Non-Hodgkin Lymphoma in a 45-Year-Old Filipino Male</b><br><i>Yzabel N. Vergel de Dios, MD, DPDS; Maria Rosa Noliza F. Encarnacion, MD, FPDS; Andrea Marie Bernales-Mendoza, MD, FPPS; Vilma C. Ramilo, MD, FPDS</i>                                                                                                                                                                                                    | <b>32</b> |
| <b>Pyuria in Cervical Cancer Patients Undergoing Concurrent Chemotherapy and Radiotherapy</b><br><i>Richard G. Malicdan, MD; Jimmy A. Billod, MD, MHCA, FPOGS, FSGOP</i>                                                                                                                                                                                                                                                                                                                       | <b>35</b> |
| <b>Lupus Panniculitis Masquerading as Mastitis: A Diagnostic Challenge in a 17-Year-Old Female Patient</b><br><i>Janine Michele T. Lovino-Ty, MD, DPDS; Reuben Mitchell M. Manuel, MD, DPDS; Jolene Kristine G. Dumlao, MD, FPDS</i>                                                                                                                                                                                                                                                           | <b>43</b> |

|                                                                                                                                                                                                                                                                                                                                                                   |    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| <b>Knowledge, Attitudes and Practices of Personal Mosquito-Repellent Methods Among Adult Filipinos</b><br><i>Jenika Gracia P. Simbillo-Rivera, MD, DPDS; Lucille Sabrina F. Ferrer, MD, FPDS, FPSVI, Mari Carlota B. Najera, MD, FPDS</i>                                                                                                                         | 47 |
| <b>Knowledge, Attitudes and Practices of Outpatients on Topical Corticosteroid Use in a Tertiary Hospital: A Pilot Study</b><br><i>Janice G. Rigos, MD, DPDS; Maria Aurora H. Rosario, MD, FPDS</i>                                                                                                                                                               | 54 |
| <b>Clinical Profile and Selected Viral Genome Sequence Analysis of SARS-CoV-2 Infected Pediatric Patients in a Tertiary Military Hospital in Quezon City from January 2021 - July 2023: A Cross-Sectional Study</b><br><i>Deen Mark G. Toroy, MD, DPPS</i>                                                                                                        | 63 |
| <b>Giant Lupus Vulgaris Presenting as Two Ulcerative Plaques in a Filipino Female: A Case Report</b><br><i>Gabrielle Nicole R. Mendoza, MD; Elisa Rae L. Co, MD, FPDS; Katherine Joy B. Sayo-Aguiling, MD, FPDS</i>                                                                                                                                               | 76 |
| <b>Sibling Pair with Incomplete Feature of Netherton Syndrome: A Case Report</b><br><i>Leonard Jansen M. Cua, MD; Matthew David S. Parco, MD, DPDS; Faye Elinore V. Kison, MD, DPDS; Camelia Faye R. Tuazon, MD, FPDS; Benedicto dL. Carpio, MD, FPDS; Eileen R. Morales, MD, FPDS; Armelia L. Torres, MD, FPDS; Amelita Tanglao-De Guzman, MD, FPDS-FDSP-PDS</i> | 82 |
| <b>The Use of Double M-Plasty Technique for Excisional Biopsy on a Rare Case of Poroid Hidradenoma in 68-Year Old Filipino Male: A Case Report</b><br><i>Celina Faye C. Manalastas, MD; Ma. Christina Gulfan, MD, FPDS; Mary Grace Anne Calvarido, MD, FPDS, FDSP-PDS</i>                                                                                         | 91 |



Journal of the  
**PHILIPPINE MEDICAL ASSOCIATION**  
VOLUME 104, NUMBER 2 ▪ January – May 2026

**Editorial Office:**

2<sup>nd</sup> Floor PMA Building, North Avenue, Quezon City 1105 Philippines  
Contact Numbers: +(632) 929-7361; +(632)929-6366; Fax: +(632) 929-6951  
Website: [www.philippinemedicalassociation.org](http://www.philippinemedicalassociation.org);  
E-mails: [info@philippinemedicalassociation](mailto:info@philippinemedicalassociation)

**MARIA CHRISTINA H. VENTURA, MD**

Chair, Committee on Publication  
Editor-in-Chief, Journal of the Philippine Medical Association

**ARNEL M. ASIÑO, MD**

**REBECCA Y. SISON, MD**

Editors

**PMA NATIONAL OFFICERS AND GOVERNORS 2025–2026**

**HECTOR M. SANTOS JR., MD**

President

**LUZ P. ACOSTA-BARRIENTOS, MD**

Vice President

**WILFREDO S. TAGLE, MD**

National Treasurer

**MILDRED M. MAÑALAC-MARIANO, MD**

Secretary General

**MA. REALIZA G. HENSON, MD**

Asst. Secretary General

**CAROLYN D. ALMORA, MD**

Northeastern Luzon

**MARIA RONELLA T. FRANCISCO-MALLARI, MD**

Central Tagalog

**REYNALDO Q. PESCADERA III, MD**

Western Mindanao

**FREDERICK MARS B. UNTALAN, MD**

Northwestern Luzon

**FERDINAND M. MACABABBAD, MD**

Southern Tagalog

**DINAH B. GONZALES-ABELLA, MD**

Northern Mindanao

**MICHAEL J. DIZON, MD**

Central Luzon

**OFELIA SAMAR-SY, MD**

Bicol

**RASHID DY CHIN, MD**

Southeastern Mindanao

**ALEJANDRO Y. TAN, MD**

Manila

**DOUGLAS P. PANERIO, MD**

Western Visayas

**NARIMAN LAO TAHA, MD**

Northcentral Mindanao

**JOSEPH RYLAN G. FLORES, MD**

Quezon City

**PETER Y. MANCAO, MD**

Central Visayas

**ERIC T. MONTESCLAROS, MD**

Caraga

**GLADNESS HENNA A. MARTINEZ, MD**

Rizal

**AVITO H. SALINAS, MD**

Eastern Visayas

# Journal of the PHILIPPINE MEDICAL ASSOCIATION

## Instruction for Authors

### General Information

The Journal of the Philippine Medical Association (JPMA) is the official publication of the Philippine Medical Association (PMA).

The JPMA is published twice in a year at the PMA Office, 2nd Floor, PMA Building, North Avenue, Quezon City 1105, Philippines. It publishes original scientific papers pertinent to medicine and allied fields. It also considers for republications of previously published articles, either in their original or modified forms, provided they are accompanied by written permission from the publisher and principal author.

Statements and opinions expressed in the articles and communications herein are those of the author(s) and not necessarily those of the Editor(s) or the publisher. The editor(s) and publisher disclaim any responsibility or liability for such materials and do not guarantee, warrant or endorse any product or services advertised in this publication.

No part of the articles and communications published in the JPMA may be reproduced without the written permission of the publisher.

### Editorial Policies

The JPMA is a peer-review journal designed to meet the continuing education requirements of PMA members and the medical community. It adheres to the guidelines established by the International Community of Medical Journal Editors (ICMJE); however, for purposes of this issue, the previously circulated JPMA Instructions for Authors, although with some modifications, are still being followed.

### Ethical Considerations

In the conduct and reporting of research, the JPMA adheres to the ethical considerations set forth by the ICMJE with respect to authorship and contributorship, editorship, peer review, conflicts of interest, right to privacy and confidentiality of patients, study participants as well as authors and reviewers; and, the protection of human subjects and animals in research.

All financial or personal relationships that could be viewed as presenting a potential conflict of interest must be disclosed by the author(s) and all participants in the review and publication process.

In experiments involving human subjects, authors must indicate in their reports whatever procedures are compliant with the standards of the responsible institutional and national committee on human experimentation as well as with the Helsinki Declaration of 1975, as revised in 2000. In case of doubts as to the procedures, authors must show proof of approval of their institutional review body or its equivalent.

In experiments involving animals, authors must indicate in their reports compliance with the institutional and national guide for laboratory animal experimentation.

### Manuscript Preparation

This section is primarily based on the previous and existing JPMA Instructions to Contributors but with some modifications based on the ICMJE recommendations. A completely revised version based on the guidelines of the ICMJE will be published in the next issue.

Accompanied by a cover letter from the principal author, the manuscripts, figures, tables, photographs, and references should be submitted in duplicate (an original and a copy) and typed double-space (including legends and footnotes) on one side of a white bond paper, 8.5 and 11 inches properly numbered consecutively on the upper right-hand corner of each page beginning with the title page. Illustrations must also be in duplicates. An electronic copy of the articles in a CD must be submitted.

The first page should contain the title, subtitle (if any), all authors' full names and highest earned academic degrees, and hospital or institutional affiliations. It must also include disclaimer, if any.

For the original article, an abstract must be typed at the beginning of each paper after the title. It must contain, in structured format, the following: background or context of the study, objectives, methods, results and conclusions of the study, as appropriate. It must not be more than 300 words. No footnotes/ references must be in the abstract. For other articles, an unstructured abstract may be preferred. Below the abstract, identify three to ten keywords or short phrases that will assist in indexing in cross-indexing the article.

Abbreviations and nomenclatures: the use of abbreviations should be minimized and preferably confined to tables only; non-standard abbreviations must be accompanied by legends.

Generic names of drugs are preferred. Trade names may be given only once at the end of the paper or in the acknowledgement and should follow the generic name in parenthesis.

References are to be cited consecutively in the text as superscripts numbers. At the end of each article, references should be listed consecutively in the numerical order as they appeared in the text.

### Advertisement

Interested advertisers shall be sent advertising rates and requirements upon request.

The editors and publishers do not guarantee, warrant or endorse any product or service advertised in this publication. Neither do they guarantee any claims made by the manufacturer of such product or service.

### Submission

Manuscripts, correspondence, and all materials for review and publication should be sent to the Editor-in-Chief of the Journal of Philippine Medical Association at the Editorial Office.

Subscription and advertisements, including change of address should be sent to the PMA Secretariat at 2<sup>nd</sup> floor PMA Building, North Avenue, Quezon City, 1105 Philippines.

Journal of the  
**PHILIPPINE MEDICAL ASSOCIATION**  
VOLUME 104, NUMBER 2 ▪ January–May 2026

**Editorial**

Artificial intelligence, as we know it today, has become an integral part of our daily lives. Technology has been advancing and information has become accessible using our fingertips. In fact, for those in the know, even using eye movement has been another access point. Knowledge and research is evidently much faster. Where then does this place the young researcher. Case reports are highly encouraged so that new knowledge is shared as part of the journey of a residency training program.

It is the aim of this publication to create a supplement for case reports coming into the new fiscal year. This will also give way to more space for original research articles to be featured. As we move towards publishing more, it is believed that AI will also be used more. As such, acknowledgment to the extent with corresponding authorship responsibilities is expected.

For further learning, the Asia Pacific Association of Medical Editors (APAME) 2026 Conference is scheduled for August 20-21, 2026 with the theme, Publication Quality and Ethics in the AI-Age: Empowering Editorial Excellence in the Asia Pacific. The Philippine Association of Medical Journal Editors (PAMJE), an affiliate society of the Philippine Medical Association, is the lead society for this. The Journal of the Philippine Medical Association is a member of PAMJE. This is an open invitation for editors and reviewers to attend this conference at the Henry Sy Building, University of the Philippines Manila.

**Maria Christina H. Ventura, MD, FPPS**  
Editor-in-Chief

# Clinico-Pathologic Factors of Endometrial Cancer in Young Filipino Women and Its Effect on Overall Survival Rate in a Tertiary Government Hospital\*

Amor Mae M. Pasigon, MD<sup>1</sup>; Jimmy A. Billod, MD, MhCA, FPOGS, FSGOP, FICS<sup>2</sup>

## ABSTRACT

**Introduction:** Endometrial cancer is one of the leading cancers affecting Filipino women, mostly affecting the older women; however, 5% of those with endometrial cancer are diagnosed before the age of 40. Only a few studies in the Philippines have been published regarding the clinico-pathologic factors and its association with overall survival rate of young women.

**Objective:** This study identified the prevalence and the different clinico-pathologic factors present in young patients diagnosed with endometrial cancer and its association with overall survival rate of these patients seen at a tertiary hospital in Baguio City, from January 2016 to December 2020.

**Methodology:** A retrospective cross-sectional study was done, with use patients' medical records. Frequencies and percentages of the different clinico-pathologic factors identified were done. Kaplan-Meier method was used for the overall survival rate, and association of the different clinico-pathologic factors with overall survival rates was identified using Multivariate Cox proportional hazard regression calculated at 95% confidence interval and significance level of 5%.

**Results:** The prevalence of young patients with endometrial cancer is 6.52%, with majority of patients being obese (56%), nulligravid (68%) and regularly menstruating (68%). Hypertension (28%) diabetes (16%) and PCOS (8%) were also noted as comorbidities but most of them had none. Mostly had endometrioid type (96%), <50% myometrial invasion (92%), Stage I (76%), with no involvement of LVSI, Lymph nodes and ovaries. There was a 100% survival rate on the 1st year, 90% on the 3rd year and 60% on the 5<sup>th</sup> year, with a mean survival time of 68 months. All of the patients underwent primary surgical treatment.

**Conclusion:** The overall survival rate of patients in this institution on the 1<sup>st</sup> year is good at 100%. In the study, there is no one significant clinic-pathologic factor that is associated with increased overall survival rate in young patients with endometrial cancer.

Keywords: Young patients, Endometrial Cancer, Clinico-pathologic Factors, Overall Survival Rate

## INTRODUCTION

Endometrial cancer is the 3<sup>rd</sup> most common genital tract malignancy and ranks 8<sup>th</sup> among all cancers affecting Filipino women<sup>1</sup> which affects mainly those at the age of 60, 90% of cases are found in women over 50 years of age and 20% will be diagnosed before menopause. Interestingly, even with these statistics, there is still 5% of the population who will develop **endometrial cancer before the age of 40.**<sup>2</sup> Even with the said percentage of young patients with endometrial cancer, a number is also being seen and treated in Baguio City. For the treatment of these young patients, there is a dilemma especially for those who are desirous of pregnancy, and the risk of having early menopause since current local guidelines recommend surgical management in the initial management of patients with endometrial carcinoma.<sup>3</sup> This radical surgery is a concern for young patients with

the disease who still are desirous of pregnancy and ovarian preservation is now an interest as part of the conservative management for younger patients. A lot of factors should be considered when counselling patients regarding treatment options, which would include the type, grade, and extent of their disease<sup>3</sup>.

Since these patients are young, the survival of this patients is of interest since they are still at their prime, yet acquiring cancer is a concern and knowing such might decrease their quality of life. Many studies have been published regarding factors that contribute to the overall survival rate of young patients with endometrial cancer but only a few studies were done in the Philippines. Some of the factors identified that were associated with improved overall survival rate include younger age, a

---

*Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.*

**\*Department of Obstetrics and Gynecology, Baguio General Hospital and Medical Center**

**<sup>1</sup>Primary Author; <sup>2</sup>Supervising Consultant**

\*Podium Category, Annual Research and Interesting Case Presentation, BGHMC 2023

\*Oral Presentation, Asia & Oceania Federation of Obstetrics & Gynaecology (AFOG) Congress, Busan South Korea, May 2024

well-differentiated endometrioid type, lower stage and no involvement of the lymph nodes.<sup>2,4,5,6,7</sup>

This study aimed to determine the clinical and pathologic factors associated with endometrial cancer among patients  $\leq 40$  years old from January 2016-December 2020 seen at a tertiary hospital in Baguio City and their impact on the overall survival rate.

## METHODOLOGY

This is a retrospective cross-sectional study conducted at the Department of Obstetrics and Gynecology, Baguio General Hospital and Medical Center which identified the clinico-pathologic factors present in patients  $\leq 40$  years of age diagnosed through histopathologic means with endometrial cancer from January 2016-December 2020 who was managed and followed up in the said institution.

This study underwent technical review by the Department of Obstetrics and Gynecology, and the Technical Review Board of the Baguio General Hospital and Medical Center, and was approved by the Ethics Review Committee of the same institution.

Records of patients  $\leq 40$  years of age at the time of diagnosis of Endometrial Cancer from January 2016- December 2020 were obtained from the medical records and the histopathologic results were obtained from the Department of Pathology of Baguio General Hospital and Medical Center. The tool used in data collection is a Data Abstraction Form and a code number was assigned per patient.

Age, BMI, Gravidity/ Parity, Age of Menarche, Interval of Menstruation, Use of OCP, Conorbidities, Family history of cancer, Primary management (medical vs surgical) and initiation of chemotherapy were the factors determined in this study. Histopathologic data for those who underwent surgical intervention included the Histologic Type, Myometrial invasion, Stage, Lymphovascular space invasion, presence of Lymph node metastasis and Ovarian metastasis. Data were presented as frequencies and percentages.

Records of their follow ups in this institution were done to identify the overall survival rate of these patients. Those that were lost to follow-up were noted and included in the statistical analysis as dropouts. The number of months each patient has lived from the time of diagnosis were determined and collated. The 1-year, 3-year and 5-year survival rates were determined using Kaplan-Meier method. The association of the different clinico-pathologic factors with overall survival rates were determined using Multivariate Cox proportional hazard regression was used, and was calculated at 95%

confidence interval<sup>12</sup>. A  $P < 0.05$  was considered statistically significant.

## RESULTS

Based on the review of records, a total of 25 patients were included in the study who were  $\leq 40$  years old diagnosed with endometrial cancer from January 2016 December 2020, with a prevalence rate of 6.52%. There is increase in the number of patients with increase in age, with almost half of the subjects (48%) are aged 36-40 years old, with the youngest being 25 years old. More than half of them was classified as Obese (56%) based on the Asia Pacific classification of BMI, 68% were nulligravid and have regular interval of menses, and only one had a history of OCP use. Hypertension was prevalent at 28%, followed by diabetes at 16%, and PCOS (8%) as concomitant comorbidity among patients. Three patients had family history of cancer in the family, which were ovarian and breast cancers. All of the patients underwent surgery, and no patient underwent primary medical treatment. 84% of the patients did not undergo adjuvant chemotherapy (Table 1). The 4 patients that underwent chemotherapy were at an advanced stages or had recurrence.

With regards to histologic types, majority are of Endometrioid type at 96%, with only 1 patient having a mucinous type. 84% of patients had  $< 50\%$  myometrial invasion. 76% were at Stage I, 16% were at Stage III, and 4% were at Stage II and IV. 24%, 20% and 8% of patients have lymphovascular invasion, lymph node metastasis and ovarian metastasis, respectively. Most of them had absence of the said parameters. (Table 1).

Table 1. Clinico-pathologic profile of patients  $\leq 40$  years of age with endometrial cancer

| CLINICO-PATHOLOGIC FACTORS  |               | FREQUENCY<br>n=25 | PERCENTAGE<br>% |
|-----------------------------|---------------|-------------------|-----------------|
| Age                         | $\leq 25$ y/o | 1                 | 4               |
|                             | 26-30 y/o     | 3                 | 12              |
|                             | 31-35 y/o     | 9                 | 36              |
|                             | 36-40 y/o     | 12                | 48              |
| BMI<br>(kg/m <sup>2</sup> ) | $< 18$        | 0                 | 0               |
|                             | 18-22         | 3                 | 12              |
|                             | 23-25         | 0                 | 0               |
|                             | 25-30         | 8                 | 32              |
|                             | $> 30$        | 14                | 56              |
| Gravidity                   | 0             | 17                | 68              |
|                             | 1             | 4                 | 16              |
|                             | 2             | 2                 | 8               |
|                             | 3             | 0                 | 0               |
|                             | $> 3$         | 2                 | 8               |

|                                     |                    |    |     |
|-------------------------------------|--------------------|----|-----|
| <b>Parity</b>                       | 0                  | 17 | 68  |
|                                     | 1                  | 5  | 20  |
|                                     | 2                  | 1  | 4   |
|                                     | 3                  | 0  | 0   |
|                                     | >3                 | 2  | 8   |
| <b>Interval of Menses</b>           | Regular            | 17 | 68  |
|                                     | Irregular          | 8  | 32  |
| <b>Use of OCP</b>                   | yes                | 1  | 4   |
|                                     | no                 | 24 | 96  |
| <b>Comorbidities</b>                | DM                 | 4  | 16  |
|                                     | PCOS               | 2  | 8   |
|                                     | Metabolic Syndrome | 0  | 0   |
|                                     | hypertension       | 7  | 28  |
|                                     | others             | 0  | 0   |
| <b>Family history</b>               | Endometrial        | 0  | 0   |
|                                     | Ovarian            | 2  | 8   |
|                                     | Colon              | 0  | 0   |
|                                     | Breast             | 1  | 4   |
|                                     | Others             | 0  | 0   |
| <b>Primary management</b>           | Surgical           | 25 | 100 |
|                                     | Medical            | 0  | 0   |
| <b>Use of Systemic Chemotherapy</b> | Yes                | 6  | 24  |
|                                     | No                 | 19 | 76  |

|                              |                                                  |    |    |
|------------------------------|--------------------------------------------------|----|----|
| <b>Histologic Type</b>       | Endometrioid                                     | 24 | 96 |
|                              | Mucinous Carcinoma                               | 1  | 4  |
|                              | Serous Carcinoma                                 | 0  | 0  |
|                              | Clear Cell Carcinoma                             | 0  | 0  |
|                              | Neuroendocrine Carcinoma                         | 0  | 0  |
|                              | Mixed Cell Adenocarcinoma                        | 0  | 0  |
|                              | Carcinosarcoma / Malignant Mixed Mullerian Tumor | 0  | 0  |
|                              | Others                                           | 0  | 0  |
| <b>Myometrial invasion</b>   | < 50%                                            | 23 | 92 |
|                              | > 50%                                            | 2  | 8  |
| <b>Intraoperative Stage</b>  | I                                                | 19 | 76 |
|                              | II                                               | 1  | 4  |
|                              | III                                              | 4  | 16 |
|                              | IV                                               | 1  | 4  |
| <b>LVI</b>                   | PRESENT                                          | 6  | 24 |
|                              | ABSENT                                           | 19 | 76 |
| <b>Lymph Node Metastasis</b> | PRESENT                                          | 5  | 20 |
|                              | ABSENT                                           | 20 | 80 |
| <b>Ovarian Metastasis</b>    | PRESENT                                          | 3  | 12 |
|                              | ABSENT                                           | 22 | 88 |

The overall survival rate of the sample patients in this institution, based on the Kaplan-Meier method (Figure 1) showed 100% survival on the 1st year, 90% on the 3rd year and 60% on the 5<sup>th</sup> year, with a mean survival

time of 68 months. Comparison of survival rates of those who underwent primary medical versus surgical treatment was not possible because all of the samples underwent primary surgical treatment.

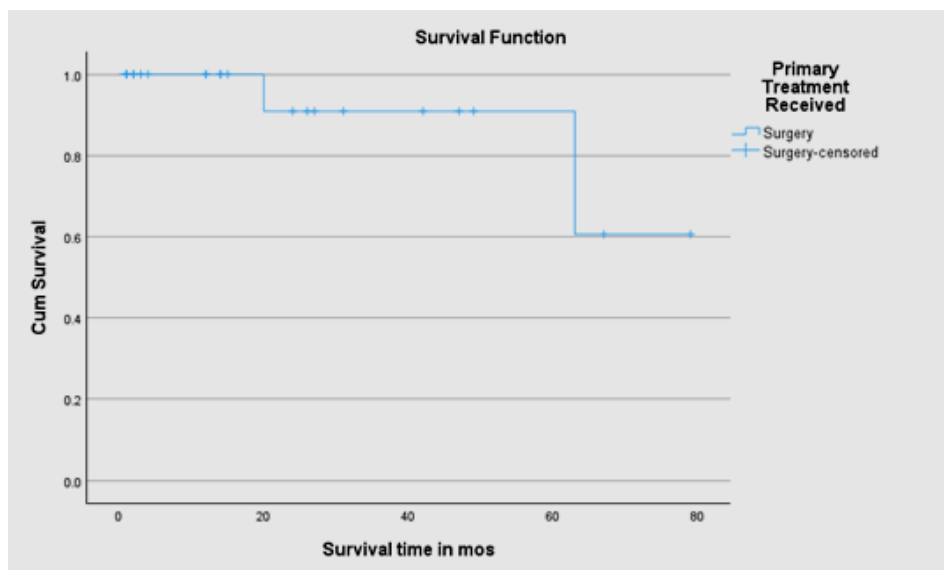


FIGURE 1. Survival rates of individual patients <=40 years of age with endometrial cancer



Table 2. Multivariate Cox proportional hazard regression table

| Variables in the Equation   |      |       |      |                |       |        | 95.0% CI for Exp(B) |             |
|-----------------------------|------|-------|------|----------------|-------|--------|---------------------|-------------|
|                             | B    | SE    | Wald | df             | Sig.  | Exp(B) | Lower               | Upper       |
| Age                         | .000 | 1.343 | .000 | 1              | 1.000 | 1.000  | .072                | 13.911      |
| BMI                         | .000 | 4.690 | .000 | 1              | 1.000 | 1.000  | .000                | 9828.543    |
| OBscore                     | .000 | 3.071 | .000 | 1              | 1.000 | 1.000  | .002                | 410.864     |
| IntOfMenses                 | .000 | 3.071 | .000 | 1              | 1.000 | 1.000  | .002                | 410.864     |
| OCPuse                      |      |       | .    | 0 <sup>a</sup> | .     |        |                     |             |
| Comorb                      | .000 | 2.803 | .000 | 1              | 1.000 | 1.000  | .004                | 243.203     |
| FamHxofCancer               | .000 | 6.226 | .000 | 1              | 1.000 | 1.000  | .000                | 199296.992  |
| Surgery                     |      |       | .    | 0 <sup>a</sup> | .     |        |                     |             |
| ChemoUse                    | .000 | 5.606 | .000 | 1              | 1.000 | 1.000  | .000                | 59147.615   |
| HistologicType              |      |       | .    | 0 <sup>a</sup> | .     |        |                     |             |
| MyometrialInvasion          | .000 | 7.100 | .000 | 1              | 1.000 | 1.000  | .000                | 1106446.881 |
| IntraoperativeStage         | .000 | 2.732 | .000 | 1              | 1.000 | 1.000  | .005                | 211.619     |
| Lymphovascularspaceinvasion | .000 | 4.690 | .000 | 1              | 1.000 | 1.000  | .000                | 9828.543    |
| Lymphnodemetastasis         |      |       | .    | 0 <sup>a</sup> | .     |        |                     |             |
| Ovarianmetastasis           |      |       | .    | 0 <sup>a</sup> | .     |        |                     |             |

a. Degree of freedom reduced because of constant or linearly dependent covariates

Due to constant or linearly dependent covariates, some of the covariates were dropped from the computation. Accounting all the different risk factors, it is shown in Table 2 that there is no one significant factor that is associated with increased overall survival rate since the value of Sig is  $>0.05$ .

## DISCUSSION

Risk factors in acquiring endometrial carcinoma are the states where unopposed estrogen is noted, which would include nulliparity, obesity<sup>2,8,9</sup>, presence of polycystic ovarian syndrome (PCOS)<sup>4</sup> and family history of cancer in the family<sup>8,9</sup>. In the study, most of them were nulligravid and obese. Only 2 had a history of PCOS, and 3 having family history of cancer. Given any age, one of the strong risk factors for developing endometrial carcinoma is obesity, noted to increase the probability by two to five-fold, which is explained by the increased estrogen levels because of the peripheral conversion of androstenedione to estrone in adipose tissues.<sup>4</sup> Comorbidities identified to be associated with endometrial cancer were Diabetes and Metabolic syndrome, however in our study, hypertension was prevalent, followed by Diabetes and PCOS. Diabetes was already established to exhibit hyperinsulinemia and insulin resistance, which would decrease the production of sex hormone binding globulin (SHBG), leading to increased estrogen levels, increasing exposure to this hormone, thus promoting proliferation of the endometrium which could lead to cancer<sup>11</sup>. Having PCOS also increases the exposure to estrogen with prolonged anovulation<sup>12</sup>. Hypertension

was noted to be a strong risk factor at 61% based on a meta-analysis, but was also noted that the result could not exclude the possibility of confounding variables such as obesity and diabetes, which is related to hypertension<sup>13</sup>.

Majority of patients in the study had a stage 1 disease at the time of diagnosis,  $<50\%$  myometrial invasion, endometrioid type of endometrial cancer, and without involvement of LVSI, lymph nodes and ovaries. It was noted that patients who are older have tendencies to have a higher stage and grade as compared to the younger patients<sup>4</sup> and that there is generally better prognosis for those diagnosed with stage I disease and endometrioid histologic type of endometrial carcinoma.<sup>5</sup> Statistically, there was no identified independent risk factors associated with increased survival rates in our study. This could probably be explained by the small number of patients included in the study, with most of the data also being censored due to the most of the samples being lost to follow up. A study by Biler et al, also investigated clinicopathological characteristics, treatment, survival and prognosis of endometrial cancer in women  $\leq 40$  years of age who underwent surgical treatment, and only noted CA125 as a prognostic factor for increased survival.<sup>14</sup> The use of CA 125 in our setting, however, is still not recommended for routine clinical use, but may be requested for the management planning of certain patients who are unable to undergo comprehensive surgical staging and those with high-risk endometrial cancer histology.<sup>3</sup> Another study noted that there was no

significant correlation was found when age, reproductive history, smoking history, race, past medical history, or family history, was compared with histologic grade or surgical stage of the tumor.<sup>2</sup> Association between cancer cell type and stage of the disease was noted to be statistically significant.<sup>2</sup> Both factors were also noted to have a positive association with recurrence and survival.<sup>2</sup>

The recommended management for endometrial cancer is generally complete surgical staging, that is, extrafascial hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy<sup>3</sup>; however, options for a more conservative approach in their treatment have become an interest, since hysterectomy would result to infertility, and oophorectomy would lead to these patients experiencing the effects of early menopause in young patients.<sup>15</sup> Medical management with progesterone is the main treatment used. Shah and Wright have compiled several studies which reported use of progesterone therapy in management of endometrial carcinoma. Two of these studies had 60% and 67% complete response rate with progesterone therapy for 24 and 26 weeks, respectively. Recurrence was also noted in those who initially responded to the therapy for both studies, 19% and 47%, respectively.<sup>15</sup> These could all explain why patients underwent and consented to undergo primary surgical management for endometrial cancer.

Another point of interest which is being studied recently is ovarian preservation as conservative management for young patients with endometrial cancer, since premature menopause is prevented, decreasing the risk for osteoporosis and cardiovascular disorders, and it was noted that women less than 50 years of age who undergo menopause have 12a higher overall mortality rate.<sup>15</sup> In the study, all underwent bilateral salpingo-oophorectomy, and most of the patients had no metastasis to the ovaries, making it a good opportunity for discussion regarding ovarian preservation for young patients; however, some studies have shown that young women are at risk of developing synchronous ovarian malignancies in up to 29%.<sup>14</sup> It is also important to note that there is approximately 5% incidence of ovarian metastasis in women with clinical stage I endometrial cancer.<sup>16</sup> Counselling patients regarding their treatment options, weighing the risks and benefits is very important in these subset of patients

## CONCLUSION

The prevalence of young patients with endometrial cancer in among  $\leq 40$  y/o women in a Tertiary Hospital in Baguio City from January 2016-

December 2020 is 6.52%, majority are obese, nulligravid, regularly menstruating and no history of OCP use. Mostly had no known comorbidities, but those that do had Hypertension, Diabetes and history of PCOS. On histopathologic results, most of the patients had Endometrioid type of Endometrial cancer, with  $<50\%$  myometrial invasion, Intraoperatively Staged as I, without involvement lymphovascular space, lymph nodes and ovaries. The survival rate of young Filipino women in our institution showed 100% survival on the 1st year, 90% on the 3rd year and 60% on the 5th year, with a mean progression free survival time of 68 months. Since there were no patients who underwent primary medical management, the comparison of survivals with those who underwent primary surgical management was not possible. For this study, there is no one significant factor among those identified that is associated with increase survival.

## RECOMMENDATIONS

Data registry for patients with endometrial cancer should be established to be able to easily retrieve records of patients. A multicenter, prospective cross-sectional study is also an option to better follow up patients and to increase the sample population. A longer duration for collection of data is recommended to be able to include as much patient as possible for the data to be more robust and for statistical analysis to be more valid.

## REFERENCES

1. Laudico AV, Mirasol-Lumague MR, Medina V, Mapua CA, Valenzuela FG, Pukkala E. Philippine Cancer Facts and Estimates. Philippine Cancer Society 2015.
2. Pellerin GP, Finan MA. Endometrial cancer in women 45 years of age or younger: A clinicopathological analysis. *Am J Obstet Gynecol* 2005; 193:1640–4.
3. Society of Gynecologic Oncologist of the Philippines, Inc. Treatment guidelines. Manila: Society of Gynecologic Oncologist of the Philippines, Inc. 2019.
4. Lobo RA, Gershenson DM, Lentz GM, Valea FA. Neoplastic Diseases of the Uterus. In: *Comprehensive Gynecology*, 7th ed. Philadelphia: Elsevier, 2017; 714–732.
5. Garg K, Soslow RA. Endometrial Carcinoma in Women Aged 40 Years and Younger. *Arch Pathol Lab Med*, 2014; 138: 335–342.
6. Lee NK, Cheung MK, Shin JY, Husain A, Teng NN, Berek JS. Prognostic Factors for Uterine Cancer in Reproductive-Aged Women. *ACOG*, 2007; 109(3): 655–662.



7. Muallem MZ, Sehouli J, Almuheimid J, Richter R, Joukhadar R, Plett H. Risk Factors of Lymph Nodes Metastases by Endometrial Cancer: A Retrospective One-center Study. *Anticancer Res*, Aug 2016; 36 (8) 4219-4225.
8. Haidopoulos D, Simou M, Akrivos N, Rodolakis A, Vlachos G, Fotiou S. Risk factors in women 40 years of age and younger with endometrial carcinoma. *Acta Obstet Gynecol*, 2010; 89: 1326–1330.
9. Macaurog BA, Toral JAB. Clinical characteristics and prognosis of young Filipino women ages 30 and below with endometrial cancer: A ten-year retrospective cohort study. *PJGO*, 2019; 16(1): 19-24.
10. Gilani Modaress M, Cheraghi F, Zamani N. Ovarian metastasis in endometroid type endometrial cancer. *Int J Fertil Steril*. 2011 Oct;5(3):148-51. Epub 2011 Dec 22. PMID: 25101158; PMCID: PMC4122829.
11. Yang X, Wang J. The Role of Metabolic Syndrome in Endometrial Cancer: A Review. *Front Oncol*, 2019; 9:744.
12. Disaia P, Creasman W, Mannell R, McMeekin S, Mutch D. *Clinical Gynecologic Oncology*, 9th ed. Philadelphia: Elsevier, 2018; 121-154.
13. Aune D, Sen A, Vatten LJ. Hypertension and the risk of endometrial cancer: a systematic review and meta-analysis of case-control and cohort studies. *Sci Rep*. 2017 Apr 7;7:44808. doi: 10.1038/srep44808. Erratum in: *Sci Rep*. 2018 Apr 06;8:46961. PMID: 28387226; PMCID: PMC5384280.
14. Biler A, Solmaz U, Erkilinc S, Gokcu M, Bagci M, Temel O. Analysis of endometrial carcinoma in young women at a high-volume cancer center. *Int J Surg*, 2017; 44: 185-190.
15. Shah MM, Wright JD. Management of Endometrial Cancer in Young Women. *Clin Obstet Gynecol*, 2011; 54(2): 219-225.
16. Gilani Modaress M, Cheraghi F, Zamani N. Ovarian metastasis in endometroid type endometrial cancer. *Int J Fertil Steril*. 2011 Oct;5(3):148-51. Epub 2011 Dec 22. PMID: 25101158; PMCID: PMC4122829.

## When Severe Cutaneous Adverse Reactions Evolve: Drug Reaction with Eosinophilia and Systemic Symptoms Progressing to Toxic Epidermal Necrolysis in a Filipino Patient

Angela Gayle Velayo, MD<sup>1</sup>; Joanne Charisse Sy, MD<sup>1</sup>, Camille Noelle Camara, MD<sup>1</sup>; Benedicto dL Carpio, MD, FPDS<sup>2</sup>; Eileen Regalado-Morales, MD, FPDS<sup>3</sup>; Amelita Tanglao-De Guzman, MD, FPDS, FDSP-PDS<sup>4</sup>; Armelia Andrea Lapitan-Torres, MD, FPDS<sup>5,6</sup>; Faye Elinore Kison, MD, DPDS<sup>6</sup>; Matthew David Parco, MD, MBA, DPDS<sup>5,6</sup>

### INTRODUCTION

Severe cutaneous adverse reactions (SCARs) are rare but life-threatening drug-induced hypersensitivity syndromes that include drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). These conditions carry high morbidity and mortality, with DRESS reported to have a mortality rate of up to 10% and TEN reaching 25–35%.<sup>5,8</sup> Although traditionally regarded as distinct entities, emerging evidence suggests that DRESS and TEN may represent different clinical expressions within a shared immunopathogenic spectrum, driven primarily by T-cell-mediated responses.<sup>9</sup>

A wide range of medications has been implicated in SCARs, most notably anticonvulsants, sulfonamides, antibiotics, and allopurinol.<sup>10,13</sup> More recently, non-classical culprit drugs such as fenofibrate and leflunomide have been identified as rare but important triggers.<sup>4,14</sup> Fenofibrate, in particular, has been linked to DRESS through case reports describing systemic involvement and histopathologic confirmation.<sup>14</sup> Early recognition and discontinuation of these atypical culprit agents are crucial to preventing progression and improving patient outcomes.

We report the case of a Filipino woman who developed DRESS, which progressed to TEN, most likely secondary to fenofibrate. This case contributes to the evolving understanding of SCAR overlap, highlights the diagnostic and therapeutic challenges, and underscores the importance of early recognition and prompt withdrawal of the offending drugs.

### CASE PRESENTATION

A 50-year-old Filipino woman with a longstanding history of ankylosing spondylitis and type 2 diabetes mellitus, well-controlled with oral hypoglycemic agents, was admitted to our institution for evaluation of fever and morbilliform cutaneous lesions. Her medication history was notable for the initiation of leflunomide, fenofibrate, and semaglutide approximately two months prior to presentation. She denied any personal or family history of drug hypersensitivity or other known autoimmune disease, as well as any recent infectious illnesses.

Two weeks prior to admission, the patient developed undocumented fever, aphthous ulcers, chills, and sore throat. She self-medicated with paracetamol 500 mg/tablet, 1 tablet every 4 hours as needed for the fever, which resulted in temporary defervescence. No cutaneous lesions were observed during this period.

One week prior to admission, she noted the onset of multiple erythematous macules, papules, and patches on the lower back, which subsequently spread centrifugally to involve the face, chest, abdomen, and bilateral upper and lower extremities, with associated moderate pruritus graded 5/10 in severity. Fever, chills, and sore throat persisted, prompting consultation at the emergency department and subsequent admission under the Internal Medicine service.

On the fifth day of admission, the patient was referred to the Dermatology service for further evaluation, co-management of cutaneous findings, and consideration of a skin punch biopsy. At that time, she exhibited a resolving morbilliform erythematous eruption involving more than 50% of the body surface area. Oral aphthous ulcers were persistent, and no lymphadenopathy was appreciated. Laboratory evaluation revealed leukopenia and elevated liver enzymes, including transaminitis and

---

*Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.*

<sup>1</sup>Resident, Department of Dermatology, Ospital ng Maynila Medical Center, Manila, Philippines

<sup>2</sup>Chairman Emeritus, Department of Dermatology, Ospital ng Maynila Medical Center, Manila, Philippines

<sup>3</sup>Chairman, Department of Dermatology, Ospital ng Maynila Medical Center, Manila, Philippines

<sup>4</sup>Dermatopathology Consultant, Department of Dermatology, Ospital ng Maynila Medical Center, Manila, Philippines

<sup>5</sup>Training Officer, Department of Dermatology, Ospital ng Maynila Medical Center, Manila, Philippines

<sup>6</sup>Research Coordinator, Department of Dermatology, Ospital ng Maynila Medical Center, Manila, Philippines

hyperbilirubinemia, while renal function remained within normal limits. Based on the clinical features and medication history, the initial impression was Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with leflunomide identified as the most likely culprit medication and fenofibrate and semaglutide as less probable alternative causes. All outpatient medications were withheld by the main service as a precautionary measure.

At the time of dermatologic examination, the patient had a total RegiSCAR score of 2 (fever 0, lymphadenopathy 1, eosinophilia 1, skin involvement >50% body surface area 1, skin lesion suggesting DRESS -1, organ involvement 1, resolution  $\geq$  15 days -1), which indicated probable DRESS. Given that the cutaneous eruption was already resolving and systemic symptoms could not be reliably evaluated due to ongoing corticosteroid therapy (hydrocortisone 100 mg IV, Day 4), biopsy was deferred. Adjunctive therapy was initiated with clobetasol propionate 0.05% lotion, triamcinolone acetonide 0.1% lotion, and emollients. Supportive measures included normal saline irrigation and wound care. The patient's symptoms gradually improved, with resolution of fever and cutaneous lesions. She was subsequently discharged by the main service with the following medications paracetamol 500 mg/tablet, sitagliptin 100 mg/tablet, pregabalin + mecobalamin 75/75 mg/tab, nebivolol 5mg/tablet, fenofibrate 100 mg/tab, carbenoxolone 2% oral gel, chlorhexidine gargle, and clobetasol propionate 0.05% lotion. Close outpatient follow-up was advised.

Two days after discharge, the patient was re-admitted under the main service due to recurrence and progression of the previous cutaneous eruption. The lesions demonstrated increased erythema, size, and thickness, with widespread distribution over the face, trunk, back, and extremities. Crusting and fissuring of the lips were also noted, accompanied by recurrent undocumented fever, severe arthralgia (pain severity 10/10), and facial swelling. She was subsequently referred back to the dermatology service for further evaluation.

On physical examination, multiple, well-defined, non-blanching erythematous to violaceous, macules and papules were observed, some coalescing into patches and plaques with overlying scales, involving the face, neck, trunk, bilateral upper and lower extremities, including palms and soles. In addition, pustules on an erythematous base were present in the bilateral axilla (Figure 1). Facial edema (Figure 2) and cheilitis with crusting and scaling of the lips were documented, although no oral mucosal lesions were observed. Tender lymphadenopathy was

appreciated in the bilateral posterior cervical, bilateral inguinal, and posterior popliteal areas. On re-admission, a second RegiSCAR assessment yielded a score of 4 (fever 0, lymphadenopathy 1, eosinophilia 1, skin involvement >50% body surface area 1, skin lesion suggesting DRESS 1, organ involvement 1, resolution  $\geq$  15 days -1), this corresponded to a probable case of DRESS, probably secondary to 1) fenofibrate 2) leflunomide and 3) semaglutide.

A 4mm punch biopsy was performed on an indurated papule on the left thigh (Figure 3). Histopathologic examination revealed an epidermis of normal thickness with overlying basketweave orthokeratosis. Focal vacuolar alteration with associated exocytosis of lymphocytes was observed at the dermoepidermal junction. In the dermis, a superficial perivascular and interstitial lymphocytic infiltrate was identified, accompanied by scattered interstitial eosinophils (Figure 3). These findings were signed out as Superficial Perivascular Dermatitis with Eosinophils, compatible with a diagnosis of DRESS.

The patient was managed with intravenous hydrocortisone (200 mg every 12 hours), clobetasol propionate 0.05% lotion, triamcinolone acetonide 0.1% lotion, and mupirocin 2% ointment. This regimen led to a marked decrease in erythema and scaling of previous lesions, with partial resolution into hyperpigmented patches, reduction in number of previous non-blanching lesions on the palms and dorsum of the feet, and decrease in facial swelling. However, residual scaling with minimal crusting of lip lesions persisted.

By the ninth day of admission, the patient was transitioned to oral prednisone (20 mg twice daily), with continued improvement of cutaneous lesions into hyperpigmented patches during subsequent days.

On the fourteenth day of admission, however, the patient developed recurrence of erythema and increase in scaling of prior lesions on the trunk, as well as yellowish crusting of lesions on the chest and back (Figure 4), associated with severe stinging pain (10/10) and skin fragility, characterized by detachment of the skin upon removal of clothing. Recurrent febrile episodes (maximum temperature: 39.1°C) accompanied by chills, odynophagia, dysphagia and dysgeusia were noted. In addition, new erythematous patches with erosions and overlying yellowish crusts developed on the medial upper eyelids, accompanied by mucoid discharge, along with increased crusting of previous lip lesions.

Additional findings included minimal facial swelling and whitish patches on the hard palate, without evidence of lymphadenopathy. Given the apparent clinical deterioration, there was a high index of suspicion for

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

The SCORTEN prognostic score was 3 (age >40 years, heart rate >120 bpm, and body surface area involvement >10%), corresponding to a predicted mortality rate of 35.8%. The working assessment was DRESS progressing to SJS/TEN overlap, most probably secondary to 1) leflunomide, 2) fenofibrate, and 3) semaglutide.

Drug causality was subsequently assessed using the Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN), which identified Fenofibrate (score 7, very probable) as the most probable culprit. Leflunomide (score 4, probable) and Semaglutide (score 2, possible) were also considered, as all three agents had been initiated concurrently.

A 5-mm punch biopsy obtained from an eroded patch on the right forearm demonstrated full-thickness epidermal necrosis with confluent necrotic keratinocytes accompanied by neutrophils. Much of the upper epidermis was lost. Numerous neutrophils were arranged in a linear distribution at the base of the necrotic epidermis, with formation of an intraepidermal pustule. Prominent vacuolar interface changes were noted, while the dermis revealed only a sparse superficial perivascular lymphocytic infiltrate without eosinophils or additional neutrophils (Figure 5). The specimen was signed out as consistent with Stevens – Johnson Syndrome/ Toxic Epidermal Necrolysis Overlap.

The two biopsies highlight the histopathologic progression of the patient's condition. Initial biopsy revealed superficial perivascular dermatitis with eosinophils, consistent with DRESS. In contrast, the subsequent biopsy revealed full-thickness epidermal necrosis with intraepidermal pustule formation and sparse dermal inflammation without eosinophils - findings characteristic of SJS/TEN. Taken together, these sequential findings provide pathologic confirmation of clinical progression from DRESS to SJS/TEN overlap.

The patient was initiated on intravenous immunoglobulin at 30 g/day (0.4 g/kg/day) and empiric intravenous vancomycin 1 g every 12 hours. Despite these interventions, her condition deteriorated, and she developed septic shock leading to multiorgan failure, to which she ultimately succumbed.

## **CASE DISCUSSION**

### **Etiology**

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a life-threatening multiorgan

adverse reaction that can be secondary to a myriad of drugs or by its metabolites. It is a hypersensitivity reaction often caused by anticonvulsants such as phenytoin, carbamazepine and phenobarbital, sulfa drugs and antibiotics such as penicillins.<sup>1</sup> Etiologic factors are unclear, however in a review of literature by De et. al, it stated its link with lymphocytic activation, drug metabolic enzyme defects, eosinophilia and human herpesvirus- 6 reactivation and Epstein-Barr virus.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but severe mucocutaneous disorders that represent a spectrum of the same disease process, primarily distinguished by the extent of epidermal detachment. These are strongly linked to drug exposure, with medications being recognized as the most critical precipitating factors. High-risk drugs commonly implicated include antibacterial sulfonamides, aromatic anticonvulsants (such as carbamazepine, phenytoin, and phenobarbital), allopurinol, oxycam nonsteroidal anti-inflammatory drugs, lamotrigine, and nevirapine.<sup>11</sup>

There is limited literature on SCAR overlap syndromes. Overlapping SCARs are defined as cases fulfilling the criteria for definite or probable diagnosis of at least 2 ADRs according to scoring systems. One study suggests that even if ambiguities among SCARs are not rare, confirmation of overlap cases are rare.<sup>1</sup>

### **Epidemiology**

SCARs are rare and globally, there is an estimated 0.4-1.2 cases per million per year. Mortality rates range from 14%-70% SJS/TEN occurs in 1-2 cases per 1 million persons per year while DRESS occurs in 1 case per 10,000 medication exposures.<sup>12</sup>

In the Philippines, prevalence rates were estimated at 2.66–9.32/10,000 patients. However, this estimate is based on the Philippine Dermatological Society-Health Information System (PDS-HIS), with data coming from accredited dermatology training institutions which is not representative of the population.<sup>12</sup>

### **Pathophysiology**

It is still not understood why certain individuals develop such severe immune response to medications and why effector cells are especially directed to the skin and other epithelia. Most literature indicates that drug specific T cell activation and genetic susceptibility are possible causes of this syndrome.<sup>11</sup>

DRESS and SJS-TEN are type IV hypersensitivity reactions which are T cell mediated, causing delayed hypersensitivity. Recent immunohistochemical and functional studies have demonstrated that distinct T-cell subsets and their effector functions contribute to the clinical variability observed among these SCARs. Specifically, drug-reactive T cells can recruit and activate various inflammatory cells such as monocytes, eosinophils, and neutrophils, and orchestrate cutaneous inflammation through the secretion of cytokines and chemokines. Granulysin has been identified as the principal cytokine inducing epidermal destruction in SJS-TEN. In contrast, eotaxin and interleukin-5 (IL-5) are associated with the eosinophilic inflammation observed in DRESS. To further explain the heterogeneity of these reactions, there was a proposed subclassification of Type IV hypersensitivity reactions based on cytokine profiles and effector cell recruitment. These include Type IVa (monocyte-dominant), Type IVb (eosinophil-dominant), and Type IVD (neutrophil-dominant) reactions.<sup>1</sup>

### Histopathology

Histologic findings in DRESS remain variable, with changes involving both the epidermis and dermis. No pathognomonic feature has been identified; however, according to Sasidharanpillai et al., the presence of varying combinations of epidermal hyperplasia, spongiosis, and parakeratosis, in the background of a lymphocyte-predominant dermal infiltrate with occasional atypia, may favor a diagnosis of DRESS in the appropriate clinical setting.<sup>15</sup> In relation to our case, the findings paralleled those described by Sasidharanpillai et al., particularly the presence of interface change, lymphocyte exocytosis, and a lymphocyte-predominant infiltrate.<sup>15</sup> Although epidermal hyperplasia and parakeratosis were absent, the combined histologic and clinical features were consistent with the diagnosis observed in our patient.

Meanwhile, in the early stages of SJS/TEN, the epidermis shows sparse apoptotic keratinocytes within the suprabasal layers. With disease progression, epidermal detachment and epidermolysis develop, accompanied by subepidermal vesiculation from extensive vacuolar alteration and confluent keratinocyte necrosis. Apoptosis may also involve adnexal structures. The papillary dermis typically demonstrates a moderately dense mononuclear infiltrate, mainly lymphocytes and macrophages, with occasional eosinophils and extravasated erythrocytes.<sup>11</sup> In our patient, the biopsy revealed full-thickness epidermal necrosis with confluent necrotic keratinocytes and prominent vacuolar interface changes, findings that parallel those described in SJS/TEN.

### History and Physical Examination

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) typically develops 2–8 weeks after drug exposure and may present with or without cutaneous involvement. Prodromal features include fever, malaise, and pruritus, followed by widespread eruptions that may affect more than 50% BSA, often progressing to erythroderma in a subset of cases. Characteristic findings include symmetrical facial edema, mucosal involvement, and generalized lymphadenopathy.<sup>12</sup>

Systemic manifestations are frequent, occurring in up to 90% of patients, with the liver most commonly affected. Hepatitis with persistent elevation of liver enzymes is the hallmark feature, however, involvement of the kidneys, lungs, heart, and endocrine system are also often present. Renal impairment is usually mild but may progress to interstitial nephritis, while pulmonary manifestations range from cough to pleural effusion. Cardiac complications, including eosinophilic myocarditis, though rare, may be life-threatening. Endocrine sequelae such as thyroiditis can develop months after resolution and warrant long-term monitoring.<sup>12</sup>

Hematologic findings are notable for eosinophilia in the majority of cases, accompanied by leukocytosis or transient cytopenias. Symptoms may persist even after discontinuation of the offending drug, highlighting the protracted and relapsing nature of DRESS and the importance of prolonged surveillance for late-onset organ involvement.<sup>12</sup>

In our patient, lymphadenopathy, eosinophilia, skin involvement >50% body surface area, skin lesions suggesting DRESS, and organ involvement were present yielding a RegiSCAR of 4 corresponding to a possible case of DRESS.

Epidermal necrolysis, encompassing Stevens–Johnson syndrome (SJS), SJS–TEN overlap, and toxic epidermal necrolysis (TEN), is a severe cutaneous adverse reaction (SCAR) classified by the extent of skin detachment: <10% BSA in SJS, 10–30% in overlap, and >30% in TEN. Onset usually occurs within four weeks of drug exposure, often preceded by nonspecific prodromal symptoms. The disease typically begins with erythematous macules that evolve into bullae, epidermal detachment, and mucosal erosions, with a positive Nikolsky sign. Mucous membrane involvement is seen in most patients, commonly affecting ocular and oral sites, sometimes leading to long-term sequelae.<sup>12</sup>

Systemic complications are common and may involve the respiratory tract, gastrointestinal system, and kidneys. Symptoms include fever, malaise, ocular stinging, photophobia, and painful erosions. Laboratory findings



are nonspecific, though hematologic, hepatic, and renal abnormalities may indicate organ involvement. Prognostication relies on validated severity scoring systems, with SCORTEN being the most widely used and consistent predictor of mortality.<sup>12</sup>

In relation to our patient, she noted severe stinging pain and skin fragility, characterized by detachment of the skin upon removal of clothing, febrile episodes, chills, odynophagia, dysphagia and dysgeusia. Upon physical examination erythematous patches with erosions and overlying yellowish crusts developed on the medial upper eyelids, accompanied by mucoid discharge, along with increased crusting of previous lip lesions. These findings are consistent with SJS-TEN.

### **Treatment and Management**

Management of DRESS and SJS/TEN shares key principles, including early withdrawal of the culprit drug, close monitoring for systemic complications which often requires intensive care unit (ICU) management and supportive care such as wound care, fluid and electrolyte management, and nutritional support. Immunomodulatory therapy may be considered in severe cases, though regimens differ between conditions. In DRESS, systemic corticosteroids are most commonly used to control acute symptoms and prevent long-term autoimmune complications, with alternatives such as cyclosporine or N-acetylcysteine in selected cases. For SJS/TEN, corticosteroids may offer benefit if started early, but infection risk remains a concern; cyclosporine and TNF- $\alpha$  inhibitors (etanercept, infliximab) have shown promising outcomes in reducing disease progression and hospitalization, while IVIg has not demonstrated consistent survival benefit.<sup>12</sup>

### **Clinical Course and Prognosis**

While there are no available markers to predict disease outcomes,<sup>7</sup> the clinical course and prognosis of DRESS vary across drugs. Prognosis tends to be better when the offending drug is immediately identified and withdrawn at the acute phase, and adequate treatment has been initiated. However, despite discontinuation of the offending drug, relapses may still occur, as there is a latency period between drug administration and onset of the disease.<sup>6</sup> Laboratory investigations are often performed at a later time when DRESS is already suspected, as the onset of cutaneous lesions has happened much earlier, contributing to longer latency

time.<sup>1</sup> While mortality is reported at only 3.8%, it remains to be the most unfavorable complication of DRESS which is secondary to fulminant hepatitis or heart failure, other indicators for poor prognosis include eosinophil count greater than  $6000 \times 10^3/\mu\text{L}$ , thrombocytopenia, leukocytosis and coagulopathy.<sup>2</sup> In this context, the present case underscores the likelihood of DRESS secondary to fenofibrate. Previous reports have documented cases of hepatitis and eosinophilia occurring without skin manifestations, and Safrano et al. (2014) noted that fenofibrate may induce DRESS.<sup>14</sup> They emphasized the importance of clinician awareness of this potential adverse effect to allow prompt drug withdrawal at the onset of suggestive symptoms and thereby prevent serious outcomes.

### **Case Relevance**

This case emphasizes that DRESS and TEN are not always distinct conditions but may lie on a clinical continuum. Sequential clinical reassessment, structured use of diagnostic tools (RegiSCAR, SCORTEN), and early recognition of drugs with higher risk profiles, such as Fenofibrate, are critical for timely management. This case illustrates the rare progression of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) to Toxic Epidermal Necrolysis (TEN). Such sequential evolution is uncommon but clinically important, as it highlights the dynamic spectrum of severe cutaneous adverse reactions. The diagnosis was supported by histopathologic findings that documented features of both DRESS and TEN at different stages, making this report particularly significant. Using the Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN),<sup>16</sup> Fenofibrate scored 7 (very probable), Leflunomide scored 4 (probable), and Semaglutide scored 2 (possible). Hence, Fenofibrate was identified as the most likely culprit drug. However, the probability of causality from Leflunomide (probable) and Semaglutide (possible) cannot be entirely ruled out, particularly as all three drugs were initiated simultaneously. Notably, the presence of ankylosing spondylitis, an autoimmune disease, may have predisposed the patient to an increased risk of drug eruptions. By capturing this progression, the case highlights the importance of early recognition, vigilant monitoring, and timely intervention in patients with severe drug reactions, ultimately contributing to better understanding and management of these life-threatening conditions.

## SUMMARY AND CONCLUSION

This case highlights a rare but fatal instance of probable Fenofibrate-induced DRESS progressing to TEN. Recognition of culprit drugs, such as Fenofibrate, is critical. Early withdrawal, prompt treatment, and structured application of RegiSCAR and SCORTEN can guide prognosis and management. Despite multidisciplinary interventions, mortality remains high once progression to TEN occurs.

## REFERENCES

1. Bouvresse S, Valeyrie-Allanore L, Ortonne N, Konstantinou MP, Kardaun SH, Bagot M, et al. Toxic epidermal necrolysis, dress, AGEP: Do overlap cases exist? *Orphanet Journal of Rare Diseases*. 2012 Sept 25;7(1). doi:10.1186/1750-1172-7-72
2. Calle AM, Aguirre N, Ardila JC, Cardona Villa R. Dress syndrome: A literature review and treatment algorithm. *World Allergy Organization Journal*. 2023 Mar;16(3):100673. doi:10.1016/j.waojou.2022.100673
3. De, A., Rajagopalan, M., Sarda, A., Das, S., & Biswas, P. (2018). Drug reaction with eosinophilia and systemic symptoms: An update and review of recent literature. *Indian Journal of Dermatology*, 63(1), 30. [https://doi.org/10.4103/ijd.ijd\\_582\\_17](https://doi.org/10.4103/ijd.ijd_582_17)
4. Fatima M, Azimi SS, Ashwini S, Radhakrishna MH. Leflunomide induced atypical dress: A case report and literature review. *Mediterranean Journal of Rheumatology*. 2023;34(1):91. doi:10.31138/mjr.34.1.91
5. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson Syndrome. *Orphanet Journal of Rare Diseases*. 2010 Dec;5(1). doi:10.1186/1750-1172-5-39
6. Husain Z, Reddy BY, Schwartz RA. Dress syndrome. *Journal of the American Academy of Dermatology*. 2013 May;68(5). doi:10.1016/j.jaad.2013.01.033
7. Lee H. Drug reaction with eosinophilia and systemic symptoms (DRESS) [Internet]. 2025 [cited 2025 Sept 9]. Available from: <https://www.uptodate.com/contents/drug-reaction-with-eosinophilia-and-systemic-symptoms-dress#H1488969955>
8. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current perspectives on Stevens-Johnson Syndrome and toxic epidermal necrolysis. *Clinical Reviews in Allergy & Immunology*. 2017 Nov 29;54(1):147–76. doi:10.1007/s12016-017-8654-z
9. Miyagawa F, Asada H. Current perspective regarding the immunopathogenesis of drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/dress). *International Journal of Molecular Sciences*. 2021 Feb 21;22(4):2147. doi:10.3390/ijms22042147
10. Mockenhaupt M. The current understanding of Stevens–Johnson syndrome and toxic epidermal necrolysis. *Expert Review of Clinical Immunology*. 2011 Nov;7(6):803–15. doi:10.1586/eci.11.66
11. Orringer JS, McMichael AJ, Margolis DJ, Enk AH, Bruckner AL, Amagai M, et al. *Fitzpatrick's dermatology*, 9E. The McGraw-Hill Companies, Inc; 2019.
12. Preclaro IA, Liwag KI, Tabalon-Morales M, Iniego-Rodas MaC. Severe cutaneous adverse reactions: A narrative literature review. *Journal of the Philippine Dermatological Society*. 2024 Nov;33(2):67–79. doi:10.4103/jpds.jpds\_38\_24
13. Roujeau J-C, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *New England Journal of Medicine*. 1995 Dec 14;333(24):1600–8. doi:10.1056/nejm199512143332404
14. Safrano L, Bourneau-Martin D, Le Clech C, Chennebault J-M, Jamet A, Drablier G, et al. Suspicion of fenofibrate-related drug reaction with eosinophilia and systemic symptoms (dress) syndrome: A case report. *Therapies*. 2014 Sept;69(5):461–4. doi:10.2515/therapie/2014054
15. Sasidharanpillai S, Govindan A, Riyaz N, Binitha M, Muhammed K, Khader A, et al. Drug reaction with eosinophilia and systemic symptoms (dress): A histopathology based analysis. *Indian Journal of Dermatology, Venereology, and Leprology*. 2016;82(1):28. doi:10.4103/0378-6323.168934
16. Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, et al. Alden, an algorithm for assessment of drug causality in Stevens–Johnson Syndrome and toxic epidermal necrolysis: Comparison with case–control analysis. *Clinical Pharmacology & Therapeutics*. 2010 Apr 7;88(1):60–8. doi:10.1038/clpt.2009.252



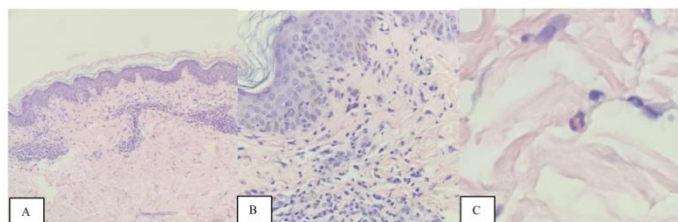
## FIGURES



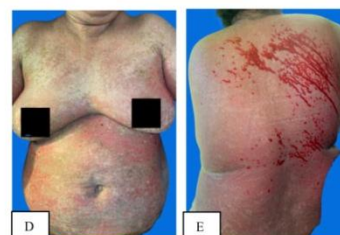
[Figure 1]. Images upon referral. Multiple, well-defined, erythematous, some dusky macules & papules coalescing into patches and plaques. Multiple, well-defined, erythematous, non-blanching macules.



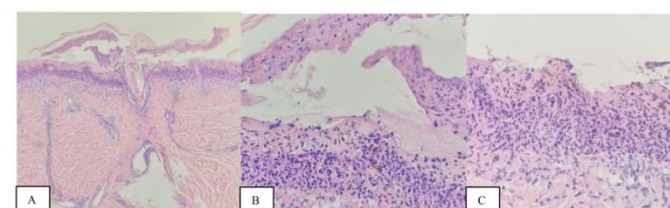
[Figure 2]. Image shows facial edema and cheilitis with crusting and fissuring of the lips.



[Figure 3]. Initial skin biopsy (H&E staining). (A) Normal epidermal thickness with basketweave orthokeratosis, (B) focal vacuolar alteration with lymphocytic exocytosis at the dermoepidermal junction, and superficial perivascular lymphocytic infiltrates with scattered (C) eosinophils.



[Figure 4]. Images on fourteenth day of admission. (A-H) Increase in erythema and scaling of the previous lesions on the trunk with noted bleeding points, (I) yellowish crusting of the eyelid, (J) hemorrhagic crust and suppuration of the lips, (K) whitish patch on the palate, and (L) positive Nikolsky sign



[Figure 5]. Repeat skin biopsy (H&E staining). (A) Full-thickness epidermal necrosis with confluent necrotic keratinocytes, (B) linear neutrophilic infiltrates at the basal epidermis, (C) prominent vacuolar interface change, dermal edema, sparse superficial perivascular lymphocytes,

## APPENDIX A

## Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN)

| Criterion                                                                        | Values                                    | Rules to apply                                                                                                         | Range     | Patient Score                                                                                                                  |
|----------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------|-----------|--------------------------------------------------------------------------------------------------------------------------------|
| <b>Delay from initial drug component intake to onset of reaction (index day)</b> | Suggestive +3                             | From 5 to 28 days                                                                                                      | -3 to 3   | +2                                                                                                                             |
|                                                                                  | Compatible +2                             | From 29 to 56 days                                                                                                     |           |                                                                                                                                |
|                                                                                  | Likely +1                                 | From 1 to 4 days                                                                                                       |           |                                                                                                                                |
|                                                                                  | Unlikely -1                               | >56 Days                                                                                                               |           |                                                                                                                                |
|                                                                                  | Excluded -3                               | Drug started on or after the index day                                                                                 |           |                                                                                                                                |
|                                                                                  |                                           | In case of previous reaction to the same drug, only changes for: Suggestive: +3 (1-4 days), Likely: +1 (5-56 days)     |           |                                                                                                                                |
| <b>Drug present in the body on index day</b>                                     | Definite 0                                | Drug continued up to index day or stopped <5× elimination half-life <sup>a</sup> before index day                      | -3 to 0   | 0<br>(Fenofibrate, Leflunomide, Semglutide)                                                                                    |
|                                                                                  | Doubtful -1                               | Drug stopped >5× elimination half-life <sup>a</sup> but with organ dysfunction or drug interactions <sup>b</sup>       |           |                                                                                                                                |
|                                                                                  | Excluded -3                               | Drug stopped >5× elimination half-life <sup>a</sup> without dysfunction or interactions <sup>b</sup>                   |           |                                                                                                                                |
| <b>Prechallenge/rechallenge</b>                                                  | Positive specific for disease and drug: 4 | SJS/TEN after use of same drug                                                                                         | -2 to 4   | +4 (Fenofibrate)<br><br>Not done/<br>unknown<br>(Leflunomide, Semglutide)                                                      |
|                                                                                  | Positive specific for disease or drug: 2  | SJS/TEN after similar <sup>c</sup> drug or other reaction with same drug                                               |           |                                                                                                                                |
|                                                                                  | Positive unspecific: 1                    | Other reaction after similar <sup>c</sup> drug                                                                         |           |                                                                                                                                |
|                                                                                  | Not done/unknown: 0                       | No known previous exposure                                                                                             |           |                                                                                                                                |
|                                                                                  | Negative -2                               | Exposure without reaction                                                                                              |           |                                                                                                                                |
| <b>Dechallenge</b>                                                               | Neutral 0                                 | Drug stopped (or unknown)                                                                                              | -2 or 0   | 0                                                                                                                              |
|                                                                                  | Negative -2                               | Drug continued without harm                                                                                            |           |                                                                                                                                |
| <b>Type of drug (notoriety)</b>                                                  | Strongly associated 3                     | "High-risk" drug per case-control studies <sup>d</sup>                                                                 | -1 to 3   | +1 (Fenofibrate)<br><br>+2 (Leflunomide)<br><br>0 (Semglutide)                                                                 |
|                                                                                  | Associated 2                              | Definite but lower risk drug per case-control studies <sup>d</sup>                                                     |           |                                                                                                                                |
|                                                                                  | Suspected 1                               | Several reports, ambiguous epidemiology (drug "under surveillance")                                                    |           |                                                                                                                                |
|                                                                                  | Unknown 0                                 | All other drugs including newly released ones                                                                          |           |                                                                                                                                |
|                                                                                  | Not suspected -1                          | No evidence of association from previous epidemiology study <sup>a</sup> with sufficient exposed controls <sup>c</sup> |           |                                                                                                                                |
| <b>Other cause</b>                                                               | Possible -1                               | Rank all drugs from highest to lowest intermediate score. If ≥1 drug score >3, subtract 1 from others.                 | -1        | 0                                                                                                                              |
| <b>Final score</b>                                                               | —                                         | Total of all criteria                                                                                                  | -12 to 10 | <b>7 (Fenofibrate)<br/>Very Probable</b><br><br><b>4 (Leflunomide)<br/>Probable</b><br><br><b>2 (Semaglutide)<br/>Possible</b> |

Final score -12 to 10

<0, very unlikely; 0-1, unlikely; 2-3, possible; 4-5, probable; ≥6, very probable.<sup>16</sup>

## A Study of Excimer Laser with Itraconazole versus Itraconazole Monotherapy in the Management of Onychomycosis: A Single-Center, Assessor-Blinded Randomized Control Trial

Michaela Gabrielle G. Guieb, MD<sup>1</sup>; Andrea Marie Bernales-Mendoza, MD, FPDS<sup>2</sup>; Ma. Cricelda Rescober-Valencia, MD, FPDS<sup>3</sup>

### ABSTRACT

**Background:** Onychomycosis, a prevalent and persistent fungal infection affecting nails, can be caused by dermatophytes, yeasts, and non-dermatophyte molds, impacting 5-10% of the global population. Oral medications like itraconazole are commonly used but have drawbacks such as extended treatment duration and side effects. Laser therapy is emerging as a promising alternative to mitigate systemic side effects and address nail abnormalities, and studies have shown its effectiveness in eradicating fungi.

**Objectives:** The study aimed to evaluate the effectiveness and safety of excimer laser treatment for onychomycosis and compare it with itraconazole alone by evaluating clinical improvement using the onychomycosis severity index (OSI).

**Methods:** Baseline onychomycosis severity was assessed using the OSI conducted by a third-party assessor. Nail scrapings were examined with potassium hydroxide and fungal culture. Oral antifungals were administered for 2-3 months. Group A received oral antifungals monotherapy, while Group B received oral antifungals and underwent excimer laser treatment weekly for 2-3 months with assessments conducted at seven timepoints: baseline, 2nd, 4th, 8th, and 12th weeks before each treatment, and at 16th, 20th, and 24th weeks from baseline.

**Results:** Fifteen patients (mean age  $51.9 \pm 15.6$  years; 53.3% female) were enrolled, with a mean disease duration of 93 months and an average of five nails affected. Distolateral subungual onychomycosis was the predominant clinical type, most frequently caused by *Candida* and *Aspergillus species*. Both the excimer laser plus itraconazole group and itraconazole monotherapy group showed progressive clinical and mycological improvement during follow-up. By week 16, complete clinical clearance was achieved in 26.7% of patients in the combination group and 40.0% in the monotherapy group with similar results at weeks 20 and 24, while by week 12, 93.3% in both groups were KOH-negative and 100% had negative fungal cultures. No adverse effects were reported. Recurrence occurred in 6.7% in the combination group and two patients 13.3% in the monotherapy group. Dermoscopic features improved in both groups, with no statistically significant differences observed between treatment arms at any time point (all  $p > 0.05$ ).

**Conclusion:** Excimer laser therapy is a safe and effective adjunct for onychomycosis, achieving outcomes comparable to oral antifungal monotherapy, with high clearance rates, low recurrence, and no adverse effects. The 308-nm excimer laser may be considered a valuable adjunct for patients unresponsive to or unsuitable for systemic therapy and immunocompromised patients.

**Keywords:** excimer laser, itraconazole, onychomycosis, fungal infection

### INTRODUCTION

Onychomycosis, which constitutes roughly half of all nail disorders, is a prevalent, persistent fungal infection affecting either the nail plate or nail bed. It is brought about by dermatophytes, yeasts, and nondermatophyte molds<sup>1</sup> Onychomycosis is a widespread infection with a high global prevalence, impacting 5-10% of the global population. Dermatophytes are responsible for over 60% of

onychomycosis cases, and mixed infections involving both dermatophytes and non-dermatophytes may occur in up to 40% of onychomycosis cases.<sup>2</sup>

The simplest method for detecting fungi is a 20% potassium hydroxide (KOH) preparation, though its sensitivity is limited to 40-60% while another option is culture on Sabouraud 2% dextrose agar with up to 70% false negatives, partly due to prior antifungal use.<sup>1</sup>

---

*Disclosures:* The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

\* Department of Dermatology, Jose R. Reyes Memorial Medical Center, Manila, Philippines

<sup>1</sup>Dermatology Resident, Jose R. Reyes Memorial Medical Center, Sta. Cruz Manila, Philippines.

<sup>2,3</sup>Dermatology Consultant, Jose R. Reyes Memorial Medical Center, Sta. Cruz Manila, Philippines.



Modern diagnostic methods such as conventional polymerase chain reaction (PCR), real-time PCR techniques, and matrix-assisted laser desorption ionization-time of flight mass spectrometry have become reliable for on-site identification of dermatophytes, yeasts, and non-dermatophyte molds in onychomycosis, assuming sufficient nail material is collected.<sup>3</sup>

Treatment options for fungal nail infections encompass both topical and oral agents. Nevertheless, creams and other topical treatments often prove ineffective in addressing nail fungus due to the formidable barrier posed by the hardness of the nail plate, making it challenging for topical medications to penetrate. The primary oral medications commonly employed for treating onychomycosis include griseofulvin, terbinafine, itraconazole, and ketoconazole. However, oral antifungal agents often require longer treatment durations and an increased likelihood of side effects. This necessitates daily intake for 8 weeks when addressing fungal infections of the fingernails and 12 weeks for toenails. Common adverse effects include headaches, gastrointestinal disturbances, skin rash, and elevated liver enzyme levels.<sup>4</sup> Itraconazole is frequently prescribed for one week per month over a span of 2 to 3 months. However, it can potentially interact with commonly used medications like the antibiotic erythromycin or asthma drug fluticasone.<sup>49</sup>

The utilization of lasers in addressing nail abnormalities presents itself as a promising choice to mitigate the systemic adverse effects associated with oral treatments. Additionally, it offers an alternative for patients who cannot undergo oral treatments due to preexisting organ dysfunction or potential drug interactions.<sup>5</sup> Laser systems are frequently employed to treat onychomycosis. They work by selectively photothermolysis, which inhibits fungal growth. However, the effectiveness of this treatment varies depending on the specific equipment utilized.<sup>17</sup>

This study aimed to assess the efficacy of the excimer laser in treating onychomycosis and intends to provide an adjunctive procedure to patients who have persistent lesions of onychomycosis and for individuals in which oral antifungals are contraindicated.

## OBJECTIVES

### General Objective

Evaluated the efficacy and safety of excimer laser in the treatment of onychomycosis

### Specific Objectives:

1. Determined the baseline characteristics of patients undergoing excimer laser with itraconazole vs itraconazole monotherapy such as age, sex, duration of disease, severity, clinical type, location, number of diseased nail, type of fungi
2. Determined the significant difference in the percentage reduction of severity of onychomycosis using OSI at weeks 2, 4, 8, 12, 16, 20 and 24.
3. Assessed clinical improvement in terms of severity using OSI for onychomycosis at weeks 2, 4, 8, 12, 16, 20 and 24
4. Determined the mycologic cure of both groups on KOH or culture examination at baseline and week 12
5. Evaluated the tolerability, safety and adverse effects of excimer laser in treating onychomycosis
6. Monitored recurrence of lesions at weeks 16, 20 and 24 after the last treatment session
7. Compared the baseline and week 12 photographs and dermoscopy findings

### Statement of the Hypothesis:

Null Hypothesis (H<sub>0</sub>):

There was no significant difference in the efficacy and safety between excimer laser with itraconazole and itraconazole monotherapy in the treatment of onychomycosis among Filipinos.

Alternative Hypothesis (H<sub>a</sub>):

There was a significant difference in the efficacy and safety between excimer laser with itraconazole and itraconazole monotherapy in the treatment of onychomycosis among Filipinos.

## REVIEW OF RELATED LITERATURE

### Epidemiology

Onychomycosis has a worldwide prevalence estimated at approximately 10%, affecting up to 20% of individuals aged over 60, up to 50% of those over 70, and about one-third of people with diabetes.<sup>41</sup> In the United States, around 80% of cases of toenail onychomycosis are attributed to *Trichophyton rubrum*, while other infections are typically caused by *Trichophyton mentagrophytes* or *Epidermophyton floccosum*. Less frequently, toenail fungal infections may also involve *Candida parapsilosis* or *Fusarium species*.<sup>29</sup>

According to recent epidemiological studies that have been published, the worldwide prevalence of onychomycosis is approximately 5.5%.<sup>9,10</sup> Even when individuals receive appropriate oral antifungal therapy,

10% to 53% of patients still experience recurrence, which can manifest as either relapse or reinfection.<sup>11</sup>

In South America, the average prevalence was at its highest, reaching 18.8%. Meanwhile, in Europe, the mean prevalence stood at 8.9%, which was similar to North America at 9.0%. In Asia, the mean prevalence was 12.1%.<sup>3</sup>

In healthy adults in the United States, the typical nail growth rate is approximately 1.5 mm per month for toenails and 3-3.5 mm per month for fingernails.<sup>28</sup> Given this average growth rate, an effective treatment would ideally result in a completely replaced, clear fingernail in a healthy adult around 6 months after starting treatment. Similarly, it would lead to a fully replaced, clear great toenail approximately 12 months into the treatment.<sup>27</sup>

In the Philippines, findings revealed that fungal infections are the second most common reason for medical consultations, affecting approximately 12.98% of cases. Among these consultations, the most prevalent fungal conditions were pityriasis versicolor (25.34%), followed by tinea corporis (22.63%), tinea cruris (16.7%), and tinea pedis (16.38%).<sup>43</sup> Currently based from our research and knowledge, there is no data on the prevalence of onychomycosis in the Philippines.

### **Risk factors**

Onychomycosis is a persistent fungal infection that affects the nail structure, encompassing the nail bed, nail plate, or matrix. Risk factors for onychomycosis include a weakened immune system, aging, diabetes, psoriasis, and nail issues. Other factors include past dermatological problems like excessive sweating and athlete's foot, and external factors such as tight-fitting shoes, injuries, and poor nail care. Additionally, the presence of certain medical conditions like cancer, vein problems, reduced blood circulation, obesity, and inflammatory bowel disease can also elevate the risk.<sup>2,31</sup>

The primary risk factor for onychomycosis is advancing age, likely attributed to factors such as diminished peripheral circulation, extended exposure to pathogenic fungi, recurrent nail injuries, less effective immune function, and a slower rate of nail growth.<sup>34</sup> Diabetes, which is another significant comorbidity in onychomycosis patients, affects around one-third of them. Additionally, individuals living with human immunodeficiency virus (HIV) are at an elevated infection risk, affecting one in four HIV-positive individuals. There is a suggestion that diabetes combined with onychomycosis may lead to reduced treatment effectiveness, possibly due to high blood sugar

levels or inadequate foot hygiene. Cure rates for diabetic patients with onychomycosis reached 13.0%, compared to 18.8% in non-diabetic individuals, although these differences did not reach statistical significance.<sup>33</sup> While onychomycosis can manifest at any age, its occurrence becomes more prevalent as individuals age. It notably affects approximately 50% of individuals over the age of 70 and is relatively uncommon among pediatric populations.<sup>32</sup>

### **Recurrence rate and complications**

Onychomycosis poses a challenge to effective treatment, and recurrences are frequent, often stemming from the challenges associated with maintaining long-term adherence to therapy.<sup>8</sup> It is a major health concern due to its potential to cause pain, discomfort, physical limitations, and negative psychological and social impacts on individuals' personal and professional lives. Research has shown that this condition significantly impairs the quality of life and overall well-being of those affected, leading to distress and reduced functionality and mental health.<sup>39,40</sup>

The use of ciclopirox 8% nail lacquer results in mycologic cure rates ranging between 29% and 36%. Studies have demonstrated that when itraconazole was administered, the combined clinical and mycologic cure rates reached 60.9%, while for the terbinafine group, it was 64.7%.<sup>36</sup> A new topical agent under imidazole, luliconazole, has received approval for treating tinea infections. Research findings indicate that the daily application of luliconazole 5% nail solution exhibited clinical effectiveness in treating onychomycosis, and it was found to be well-tolerated with no reports of severe adverse drug reactions.<sup>44</sup> In addition, a daily application of efinaconazole topical solution at a concentration of 10% could serve as a valuable topical choice for addressing mild to moderate onychomycosis.<sup>46</sup> Over 25% of patients achieved complete cures, while nearly two-thirds of those with mild onychomycosis were deemed successful in their treatment by the 52<sup>nd</sup> week.<sup>45</sup>

Typically, topical medications are often ineffective due to their inability to penetrate the nail plate effectively. Meanwhile, oral antifungal drugs carry a significant risk of causing liver and kidney toxicity, along with potential drug interactions. These limitations linked to oral antifungal treatment for onychomycosis underscore the demand for a safer yet equally efficient alternative.<sup>4</sup> The highest incidence of drug-induced liver injury caused by antifungal medications is associated with voriconazole (32.45%), followed by fluconazole (19.37%), and itraconazole (14.51%).<sup>38</sup>

Recurrence is a frequent occurrence in onychomycosis, affecting between 10% and 53% of patients.<sup>37</sup> It may manifest one year or longer after the initial infection has been successfully treated. Patients with a genetic inclination or those belonging to susceptible groups, such as the elderly or individuals with diabetes, have a higher likelihood of experiencing a recurrence. In the elderly, physical injury may trigger a relapse.<sup>37</sup>

Nails that have 100% dystrophy or affect the lunula can prove challenging to treat because they may have sustained permanent damage to the nail matrix. This permanent damage can potentially reduce the overall effectiveness of treatment when assessed across a group of individuals. Conversely, nails with minimal distal changes may not accurately represent the target population for this procedure. Therefore, it is advisable that the study population should encompass nails with a minimum of 25% involvement of the nail area and no more than 75% involvement of the nail area.<sup>27</sup>

### Laser therapy

In contrast to topical and oral treatments, laser therapy presents a more hopeful approach for managing the condition in individuals with diabetes, elderly patients who cannot tolerate medications, and those dealing with liver or kidney issues.<sup>35</sup>

Subsequently, laser therapies like long-pulsed 1064-nm neodymium-doped yttrium aluminium garnet (Nd:YAG) lasers, short-pulsed 1064-nm Nd:YAG lasers, CO<sub>2</sub> lasers, pulsed dye laser and lasers operating at wavelengths of 870-nm, 930-nm, and 1320-nm have started to surface as novel treatments for addressing onychomycosis.<sup>24,5</sup>

The precise mechanism of action underlying laser treatment for fungal nail infections remains somewhat unclear, although various hypotheses have been proposed. It is suggested that antifungal effects may be triggered through local hyperthermia, as well as the photothermal impact of the laser beam's penetration through the nail plate and its interaction with the nail bed.<sup>30</sup> Specifically, the laser beam is believed to be absorbed by the melanin found on the cell walls of the fungi. This absorption potentially inhibits fungal growth through pigment photothermolysis, affecting the nail matrix and nail plate.<sup>18,6</sup> Another study reported that these methods were aimed at creating micro-channels in the nails to facilitate the enhanced absorption of topical antifungal agents.<sup>5</sup> In the previous year, an article discussing laser systems for the emerging field of onychomycosis treatment was published in

the Journal of the American Podiatric Medical Association. By January 2012, the United States FDA had granted approval to four laser systems for the "temporary improvement of clear nail appearance in onychomycosis." These approvals were granted based on the concept of "substantial equivalence" to previously established devices with comparable technical features and uses. Laser therapy seems to hold promise as an alternative to conventional pharmacotherapy; however, it is essential that these systems have undergone limited clinical trials.<sup>6</sup>

A study showed that the effectiveness of laser therapy for onychomycosis was approximately 63%. In comparison, the mycological effectiveness of itraconazole pulse therapy and continuous terbinafine therapy for onychomycosis were 79.6% and 84.8%, respectively. Therefore, the overall efficacy of laser treatment was moderately lower than that of traditional oral antifungal treatments. However, laser therapy had the advantage of fewer reported side effects, such as liver and kidney damage or gastrointestinal reactions.<sup>17</sup>

In practice, 1064-nm Nd:YAG lasers and CO<sub>2</sub> lasers are more commonly utilized than 1320-nm Nd:YAG lasers. Numerous studies found that the combination of laser treatment with topical drugs yielded significantly higher mycological and clinical efficacy compared to laser treatment monotherapy.<sup>17</sup> Another study illustrated that fungal nail infections can be efficiently and securely managed using the Q-Switched Nd:YAG 1064-nm/532-nm laser. Moreover, it can be employed in conjunction with systemic oral antifungal medications, resulting in a more concise treatment duration.<sup>18</sup>

In the case of fungal cells, particularly the mycelium enclosed by the chitin wall, heat dissipates slowly between laser pulses, leading to a gradual temperature increase within the mycelium, unlike the surrounding tissue, which efficiently disperses heat through tissue and water. Furthermore, lasers can disrupt the proteins essential for fungi to break down keratin. Additionally, changes in keratin, such as reduced disulfide bond intensity (at 490-590 cm) and modifications in  $\beta$ -sheet-dominant structures, have been observed following laser treatments.<sup>26</sup>

Notably, recent research has revealed a light absorption peak at 415 nm for *Trichophyton rubrum*, a pathogen responsible for onychomycosis. A similar absorption peak is observed in onychomycotic nails but is absent in healthy nails. This absorption peak is likely associated with mitochondrial cytochrome c found in fungi. Utilizing a wavelength in this range enables the laser to selectively target the fungi.<sup>26</sup>



## Excimer laser

The 308-nm xenon-chloride excimer laser, a novel form of phototherapy, utilizes ultraviolet B (UVB) radiation and consists of a combination of a noble gas and a halide. Currently, the 308-nm excimer laser has been proven effective in the treatment of various skin conditions, including vitiligo, psoriasis, atopic dermatitis, alopecia areata, allergic rhinitis, folliculitis, granuloma annulare, lichen planus, mycosis fungoides, palmoplantar pustulosis, pityriasis alba, CD30+ lymphoproliferative disorder, leukoderma, prurigo nodularis, localized scleroderma and genital lichen sclerosus.<sup>14</sup> The 308-nm wavelength, which closely resembles the 311-nm used in nb-UVB phototherapy, is believed to operate through a similar mechanism. Ultraviolet B spectrum radiations are known to have immunosuppressive effects, including the induction of apoptosis in T-lymphocytes and immunomodulatory effects.<sup>20</sup>

Radiation with a wavelength less than 300-nm is highly efficient at eradicating microorganisms. Ultraviolet C radiation at a wavelength of 253.7-nm is especially potent in this regard. This particular range is referred to as the germicidal zone. Ultraviolet C radiation has limited penetration capabilities and does not reach beyond the layer of dead skin cells. It does not directly kill the cells but rather inflicts damage to their DNA, rendering the cells non-functional.<sup>19</sup> A study confirmed through testing that fungi can be effectively eradicated using minimal parameters, specifically with an energy pulse of 144 mJ and an energy density of 0.74 J/cm<sup>2</sup>, without any subsequent regrowth. With these parameters, it becomes feasible to administer 200 pulses at a repetition frequency of 10 Hz.<sup>19</sup> Ultraviolet C radiation eliminates fungi by damaging their DNA. The research findings indicate that ultraviolet C radiation does not penetrate the fingernail deeply enough to harm the underlying soft tissue significantly. Fungi can be effectively eradicated by exposing them to low doses of radiation generated by an excimer laser.<sup>19</sup>

The benefits of monochromatic excimer laser therapy, when compared to other types of phototherapies, are highlighted as follows: reduced exposure to ultraviolet doses, shorter treatment duration, and, most importantly, the ability to precisely target specific areas of the skin without affecting the surrounding normal skin. Excimer lasers have limited tissue absorption depth, enabling the removal of microscopic tissue layers with minimal damage to the neighboring areas.<sup>19</sup>

Among patients undergoing this treatment, there have been reports of mild pain during irradiation.

Fortunately, this discomfort is generally well-tolerated and typically resolves within a day.<sup>7</sup>

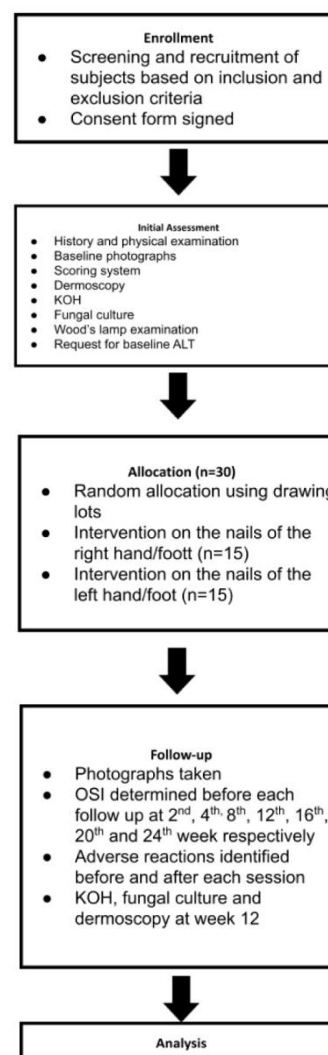
Regarding potential complications arising from laser therapy for onychomycosis, it documented the incidence of such complications is relatively low, which reaffirms its effectiveness as a treatment option for this condition. Nevertheless, it is essential to acknowledge potential side effects, which can include sensations of pain, heat, or tingling, as well as temporary darkening of the nail.<sup>7</sup>

## RESEARCH DESIGN

The study was a single-center, assessor-blinded, randomized control trial study among eligible participants at the Jose R. Reyes Memorial Medical Center, Department of Dermatology from January 2024 to June 2025.

## METHODOLOGY

### Conceptual Framework



The approval of the Institutional Review Board (IRB) and the Chair of the Department of Dermatology was obtained before conducting this experimental study.

### Recruitment and initial evaluation

Recruitment and screening was done via face-to-face consultation at the outpatient complex of the Department of Dermatology, Jose R. Reyes Memorial Medical Center after gaining approval from the IRB.

An in-vitro pilot study with 5 onychomycotic nail specimens was done. The agar plates were inoculated with the 5 specimens circularly at 1, 3, 5, 7, 9, and 11 o'clock. The culture media was marked to distinguish the right and left sides for a comparison of sides. Afterward, the cultures were incubated for a maximum of 30 days at 30° C.<sup>47</sup>

Each fungal culture was treated with a different setting. The fungal culture was divided into equal quadrangles. The upper left part was treated with a 150 mj/cm<sup>2</sup> single dose. The lower left part was treated with a 300 mj/cm<sup>2</sup> single dose. The upper right part was treated with a 150 mj/cm<sup>2</sup> thrice a week for one week. The lower right part was treated with a 300 mj/cm<sup>2</sup> thrice a week for one week. Laser treatment was done without covering the fungal cultures and without cooling. The distance between the hand piece and culture was equal. For protection, the investigator wore latex gloves and goggles to cover the eyes. After treatment, the cultures were incubated at 30° C and the temperature remained constant throughout the study. The specimens were checked right after if the fungal species survived or not via KOH examination.

The initial phase involved screening to determine eligibility. The study was introduced with outlining the procedure, potential outcomes, and any adverse reactions. The primary investigator provided information on conventional treatment alternatives. Patients signed an informed consent form to enroll in the study, followed by a comprehensive history and physical examination.

Onychomycosis severity index is a scoring system used to categorize the severity of onychomycosis into mild, moderate, or severe cases. This classification was determined by multiplying the score for the extent of nail involvement (ranging from 0 to 5) by the score for the proximity of the infection to the nail matrix (ranging from 1 to 5). Baseline scoring was done by a third-party assessor (board certified dermatologist) on the nails of both hands. Baseline photographs were taken using a 12-megapixel camera (*iPhone 11, Apple*) in a single, well-lit room.

A Wood's lamp was placed above the nails under

a dark room. It was used to observe any specific fluorescent pattern on the nails.<sup>15</sup>

Dermoscopy photos were evaluated by another third-party assessor (board certified dermatologist) on the nails of both hands or feet.

Nail scrapings were gathered from the proximal border of the onycholytic area using a surgical blade 15 (scalpel number 3, Secheron Germany). Before collecting the samples, the affected area was cleaned with 70% ethyl alcohol to eliminate bacteria and debris. For the purpose of isolating yeasts and non-dermatophyte molds, sabouraud dextrose agar was utilized. The cultures were incubated at a temperature of 25°C for a maximum period of 30 days, with daily monitoring to assess fungal growth.<sup>16</sup> The identification of fungal species involved the examination of both the macroscopic (macromorphology) and micromorphological characteristics of isolated colonies. Two licensed medical technologists independently assessed both the KOH preparations and fungal culture results. One assessor is a licensed medical technologist and certified medical laboratory scientist with over six years of experience in clinical laboratory science, nuclear medicine, and dermatopathology. This assessor holds certifications from the Professional Regulation Commission (PRC), the American Society for Clinical Pathology, and the American Society for Clinical Pathology and Commission on Graduates of Foreign Nursing Schools International. The second assessor is a graduate of the Medical Colleges of Northern Philippines and a licensed medical technologist certified by the PRC, with two years of experience as a generalist in a secondary laboratory and four years of experience in a primary laboratory. He was mentored by a highly experienced medical technologist with over 20 years of expertise in the field.

### Randomization, treatment allocation and blinding

All participants received the interventional treatment on the nails of one side of the hand or feet. Randomization whether the treatment was done on the right or left determined using simple allocation by drawing lots. Paper slips numbered from one to thirty were placed into a box. A patient randomly selected one slip, and if the number was even, the treatment was administered on the right side; otherwise, it was on the left. This way, the number of patients who were treated on the right side was equal to patients treated on their left. The primary investigator and all participants were aware of the treated side. A blinded third-party assessor not involved in the study did the assessment for the nails of both hands.

### Technical Information

An excimer laser device (*Exciplex® Excimer Light Machine*) was used in this study. It is a portable, handheld monochromatic excimer light device with a wavelength of 308 nm.



Figure 1. Excimer laser device

### Study Intervention

All patients received the intervention on the same side on each subsequent visit. Before each session, patients were asked to thoroughly wash and dry their hands, and to remove nail polish, if present.

All patients were given oral antifungals (itraconazole 100mg capsule 2 capsules twice daily 7 days) for 2-3 months after having their alanine aminotransferase (ALT) levels were determined. Group A hand received oral antifungal for 2-3 months. Group B hand received oral antifungal for 2-3 months and excimer laser weekly for 2-3 months.

Treatment with excimer laser repeated every week, starting after initial assessment at baseline for a total of 12 sessions. Assessment of each participant was done at 7 timepoints: at baseline, 2<sup>nd</sup>, 4<sup>th</sup>, 8<sup>th</sup>, and 12<sup>th</sup> week before each treatment session as well as after the last treatment at 16<sup>th</sup>, 20<sup>th</sup> and 24<sup>th</sup> from the baseline. The total study duration was 6 months.

### Clinical Assessment

During the follow-up appointments, photographs were taken both before and right after each treatment session using a 12-megapixel camera (*iPhone 11, Apple*). These photographs served for documentation and evaluation purposes and maintained the consistent settings, patient positioning, and lighting conditions for all images. Evaluation of clinical outcomes will be conducted separately for the nails of both hands.

A third-party assessor (board certified dermatologist) who was not part of the study performed a manual evaluation of the nails. He used the OSI scoring

system for this assessment. Any adverse effects noted during previous sessions, including but not limited to pigmentation issues, erythema, edema and pruritus, were documented before each subsequent treatment. Furthermore, immediate assessment of any adverse reactions was conducted after each treatment session.

### Primary and Secondary Endpoints

The primary endpoint of this study was reduction of mean percentage difference in the OSI on the treated and untreated side between the baseline and each follow-up.

The secondary endpoints of this study was the change in OSI on the treated and untreated side between the baseline and each follow-up.

### Stopping guidelines

The intervention was discontinued for any participant who experiences moderate to severe adverse reactions, such as burns or increase in liver enzymes 3x, even if it occurs just once. Additionally, any participant who chooses to no longer take part in the study was free to withdraw at any time.

### STUDY SUBJECTS

Patients assessed with onychomycosis via KOH examination and fungal culture at the outpatient department of Dermatology, Jose R. Reyes Memorial Medical Center were enrolled in this study.

### Inclusion Criteria

- Filipino
- Male or female
- At least 18 years old
- Signed informed consent
- Have a clinical diagnosis of distal subungual onychomycosis in the nail of at least two digits, with 20% to 50% clinical involvement of the target nail, without dermatophytomas or lunula (matrix) involvement, without lunular or proximal involvement
- Exhibit positive mycology results (KOH or fungal culture)
- Willing to refrain from using polish or other medication
- Have undergone a washout period of topical steroids, topical antifungals and systemic antifungals for nails of 6 months before study enrollment
- Able to complete the study and comply with follow up period

### Exclusion Criteria

- Less than 18 years old
- Females who are pregnant, plan to become pregnant during the study, or are nursing a child
- Persons who are hypersensitive to antifungal medications
- Persons who have received systemic antifungal therapy for any reason within 3 months, or topical antifungal therapy on the toenails or skin immediately adjacent to the toenails within 3 weeks prior to the start of the study
- Persons who have received an investigational drug within 4 weeks of the first dose of study product, or who are scheduled to receive an investigational drug other than the study product during the study
- Persons who have participated in a clinical trial for the systemic treatment of onychomycosis of the toenails within 6 months prior to the first dose of study product
- Persons who are not prepared to give up use of any nail cosmetic products for the duration of the study
- Persons who have any known immunodeficiency or history of malignancy in the last 4 years, excluding nonmelanoma skin cancer
- Persons currently suffering from any disease or condition, that could include abnormal laboratory tests, and/or who are currently using medication which in the opinion of the investigator may affect the evaluation of the study product or place the subject at undue risk
- Persons with psoriasis, lichen planus, or other medical conditions known to induce nail changes, other abnormalities or can cause nail breakdown that can predispose to secondary fungal infection
- Persons with a history of any condition that could possibly affect absorption of drug (e.g., gastrectomy), uncontrolled diabetes, clinically significant peripheral vascular disease or peripheral circulatory impairment, or has had any major illness within 30 days prior to the screening examination
- Persons with a history of drug or alcohol abuse within the past 2 years

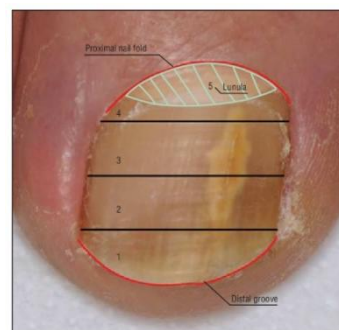
### ASSESSMENT INSTRUMENTS

Photographs at baseline and on subsequent follow-up were taken using a 12-megapixel camera (iPhone 11, Apple).

Onychomycosis severity index was employed to assess the severity of onychomycosis, with the following grading system: 0 indicating the absence of onychomycosis, 1-5 representing mild onychomycosis, 6-15 denoting moderate onychomycosis, and 16-35 signifying severe onychomycosis (See Table 1).<sup>21</sup>

**Table 1. Onychomycosis severity index (OSI) of onychomycosis**

| Area of involvement |        | Proximity of disease to matrix         |        | Presence of dermatophytoma or subungual hyperkeratosis >2mm |        |
|---------------------|--------|----------------------------------------|--------|-------------------------------------------------------------|--------|
| Affected nail %     | Points | Amount of involvement from distal edge | Points | Present                                                     | Points |
| 0                   |        | <1/4                                   | 1      | No                                                          | 0      |
| 1-10                |        | 1/4-1/2                                | 2      | Yes                                                         | 10     |
| 11-25               | 2      | >1/2-3/4                               | 3      |                                                             |        |
| 26-50               | 3      | >3/4                                   | 4      |                                                             |        |
| 51-75               | 4      | Matrix involvement                     | 5      |                                                             |        |
| 76-100              | 5      |                                        |        |                                                             |        |



**Figure 2. Onychomycosis severity index (OSI)<sup>21</sup>**

Fungal culture was conducted both at the beginning of the treatment (baseline) to confirm the presence of the fungi.

Potassium hydroxide examination was conducted both at the beginning of the treatment (baseline) and 12 weeks after the treatment to determine mycological cure, defined as negative results in microscopy and culture. Potassium hydroxide test was graded using the semi-quantification of fungal hyphae in the KOH mount using hyphal index for this assessment.

**Table 2. Semi-quantification of fungal hyphae in the potassium hydroxide (KOH) mount using hyphal index<sup>48</sup>**

| KOH mount finding (per 100 fields)                      | Grading according to the Hyphal Index |
|---------------------------------------------------------|---------------------------------------|
| Absence of fungal hyphae                                | 0                                     |
| Presence of up to 4 hyphae                              | 1+                                    |
| Number of hyphae present between Hyphal Index 1+ and 3+ | 2+                                    |
| Presence of multiple hyphae                             | 3+                                    |

The occurrence of any adverse reactions was recorded and documented during each of the follow-up assessments. This comprehensive approach ensured that any potential adverse effects were carefully monitored and recorded for a more in-depth understanding of the treatment's safety profile.

The recurrence of lesions was documented and carefully recorded. If any signs or symptoms resurface, they underwent evaluation using the KOH examination. A positive result from the KOH examination served as confirmation of the recurrence.

## STATISTICAL/ DATA ANALYSIS PLAN

### Sample Size Calculation

This paper used the following formula to calculate the required sample size for the study.

$$n = 2 \frac{\{Z_{\alpha/2}\sqrt{2(P)(1-P)} + Z_{1-\beta}\sqrt{(P_1)(1-P_1) + (P_2)(1-P_2)}\}^2}{(P_1 - P_2)^2}$$

Where:

P<sub>1</sub> is the prevalence of outcome in unexposed group

P<sub>2</sub> is the prevalence of outcome in the exposed group

P is ((P<sub>1</sub>+P<sub>2</sub>)/2

α is level of significance

β is 1 – Power of test

Following the paper of Weber et al. (2018), this paper used a 95% significance level, 80% power, 40.00% for P<sub>1</sub> (expected clinical improvement for itraconazole alone) and 90.00% for P<sub>2</sub> (expected clinical improvement for excimer laser with itraconazole). The parameters yielded a required sample size of 30.

$$n = 2 \frac{\{1.96\sqrt{2(0.65)(1-0.65)} + 0.84\sqrt{(0.4)(1-0.4) + (0.9)(1-0.9)}\}^2}{(0.4 - 0.9)^2} \approx 30$$

Given that the trials were conducted intrabody, 15 individuals were recruited for the study.

### Data Analysis Plan

Categorical variables were summarized as frequencies and percentages, and continuous variables were presented as means with standard deviations. Comparisons of categorical outcomes, including OSI, mycologic results, adverse effects, and dermoscopic findings, were performed using Pearson's chi-squared test or Fisher's exact test, as appropriate. A significance level of 5% was applied for all statistical analyses. Analyses were conducted using STATA version 16.1 and Microsoft Excel.

**Table 3. Baseline Demographic and Clinical Characteristics of the Patients**

| Variables                                                   | Values      |
|-------------------------------------------------------------|-------------|
| <b>Age, mean ± SD (years)</b>                               | 51.9 ± 15.6 |
| <b>Sex, n (%)</b>                                           |             |
| Female                                                      | 8 (53.3%)   |
| Male                                                        | 7 (46.7%)   |
| <b>Body part treated, n (%)</b>                             |             |
| Foot                                                        | 8 (53.3%)   |
| Hand                                                        | 7 (46.7%)   |
| <b>Laterality of Excimer Laser with Itraconazole, n (%)</b> |             |
| Left                                                        | 7 (46.7%)   |
| Right                                                       | 8 (53.3%)   |
| <b>Duration of disease, mean ± SD (months)</b>              | 93.1 ± 94.1 |
| <b>Number of nails affected, mean ± SD</b>                  | 5.1 ± 3.5   |
| <b>Severity, n (%)</b>                                      |             |
| Mild                                                        | 5 (33.3%)   |
| Moderate                                                    | 3 (20.0%)   |
| Severe                                                      | 7 (46.7%)   |
| <b>Clinical type, n (%)</b>                                 |             |
| Distolateral subungual onychomycosis                        | 12 (80.0%)  |
| Total dystrophic onychomycosis                              | 2 (13.3%)   |
| Mixed onychomycosis                                         | 1 (6.7%)    |
| <b>Fungi, n (%)</b>                                         |             |
| Candida                                                     | 6 (40.0%)   |
| Aspergillus                                                 | 5 (33.3%)   |
| Trichophyton                                                | 2 (13.3%)   |
| None                                                        | 2 (13.3%)   |
| <b>Wood's lamp, n (%)</b>                                   |             |
| Negative                                                    | 15 (100.0%) |

Table 3 presents the baseline demographic and clinical characteristics of the 15 patients included in the study. The mean age of the participants was 51.9 ± 15.6 years, comprising 8 females (53.3%) and 7 males (46.7%). Lesions were located on the foot in 8 patients (53.3%) and on the hand in 7 patients (46.7%). The excimer laser combined with itraconazole was applied to the left side in 7 patients (46.7%) and the right side in 8 patients



(53.3%). The mean duration of disease was  $93.1 \pm 94.1$  months, and the mean number of nails affected was  $5.1 \pm 3.5$ .

Regarding clinical severity, 5 patients (33.3%) had mild, 3 (20.0%) had moderate, and 7 (46.7%) had severe onychomycosis. The most common clinical type was distolateral subungual onychomycosis (12 patients; 80.0%), followed by total dystrophic onychomycosis (2 patients; 13.3%) and mixed onychomycosis (1 patient; 6.7%). Culture results identified *Candida species* in 6 patients (40.0%), *Aspergillus species* in 5 (33.3%), and *Trichophyton species* in 2 (13.3%), while 2 patients (13.3%) had no fungal growth. All patients tested negative under Wood's lamp examination.

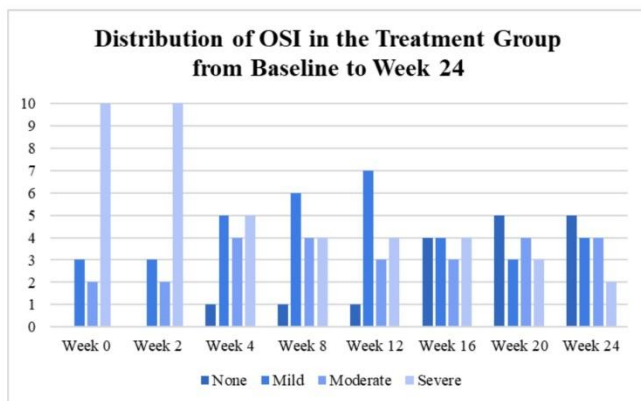


Figure 3. Distribution of OSI in the treatment group from baseline to week 24

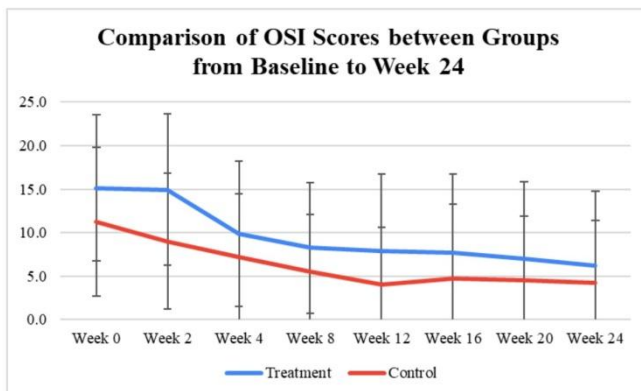


Figure 4. Comparison of OSI scores between groups from baseline to week 24

Table 4. Comparison of OSI between treatment groups at baseline and follow-up visits

| Variables       | Excimer Laser<br>with<br>Itraconazole<br>(n 15) | Itraconazole<br>Monotherapy<br>(n 15) | p-values <sup>1</sup> |
|-----------------|-------------------------------------------------|---------------------------------------|-----------------------|
| Baseline, n (%) |                                                 |                                       |                       |
| Absent          | -                                               | -                                     | .868                  |
| Mild            | 3 (20.0%)                                       | 5 (33.3%)                             |                       |
| Moderate        | 2 (13.3%)                                       | 2 (13.3%)                             |                       |
| Severe          | 10 (66.7%)                                      | 8 (53.3%)                             |                       |
| Week 2, n (%)   |                                                 |                                       |                       |
| Absent          | -                                               | 1 (6.7%)                              | .401                  |
| Mild            | 3 (20.0%)                                       | 6 (40.0%)                             |                       |
| Moderate        | 2 (13.3%)                                       | 2 (13.3%)                             |                       |
| Severe          | 10 (66.7%)                                      | 6 (40.0%)                             |                       |
| Week 4, n (%)   |                                                 |                                       |                       |
| Absent          | 1 (6.7%)                                        | 1 (6.7%)                              | .895                  |
| Mild            | 5 (33.3%)                                       | 6 (40.0%)                             |                       |
| Moderate        | 4 (26.7%)                                       | 5 (33.3%)                             |                       |
| Severe          | 5 (33.3%)                                       | 3 (20.0%)                             |                       |
| Week 8, n (%)   |                                                 |                                       |                       |
| Absent          | 1 (6.7%)                                        | 2 (13.3%)                             | .631                  |
| Mild            | 6 (40.0%)                                       | 7 (46.7%)                             |                       |
| Moderate        | 4 (26.7%)                                       | 5 (33.3%)                             |                       |
| Severe          | 4 (26.7%)                                       | 1 (6.7%)                              |                       |
| Week 12, n (%)  |                                                 |                                       |                       |
| Absent          | 1 (6.7%)                                        | 3 (20.0%)                             | .369                  |
| Mild            | 7 (46.7%)                                       | 9 (60.0%)                             |                       |
| Moderate        | 3 (20.0%)                                       | 2 (13.3%)                             |                       |
| Severe          | 4 (26.7%)                                       | 1 (6.7%)                              |                       |
| Week 16, n (%)  |                                                 |                                       |                       |
| Absent          | 4 (26.7%)                                       | 6 (40.0%)                             | .602                  |
| Mild            | 4 (26.7%)                                       | 6 (40.0%)                             |                       |
| Moderate        | 3 (20.0%)                                       | 1 (6.7%)                              |                       |
| Severe          | 4 (26.7%)                                       | 2 (13.3%)                             |                       |
| Week 20, n (%)  |                                                 |                                       |                       |
| Absent          | 5 (33.3%)                                       | 5 (33.3%)                             | .641                  |
| Mild            | 3 (20.0%)                                       | 6 (40.0%)                             |                       |
| Moderate        | 4 (26.7%)                                       | 2 (13.3%)                             |                       |
| Severe          | 3 (20.0%)                                       | 2 (13.3%)                             |                       |
| Week 24, n (%)  |                                                 |                                       |                       |
| Absent          | 5 (33.3%)                                       | 5 (33.3%)                             | .505                  |
| Mild            | 4 (26.7%)                                       | 7 (46.7%)                             |                       |
| Moderate        | 4 (26.7%)                                       | 1 (6.7%)                              |                       |
| Severe          | 2 (13.3%)                                       | 2 (13.3%)                             |                       |

<sup>1</sup>\*\* - significant at the 1% level; \* - significant at the 5% level.

Table 4 summarizes the OSI classifications for patients in the excimer laser with itraconazole combination group and the itraconazole monotherapy group at baseline and during follow-up visits through week 24.

At baseline, most patients in both groups presented with severe onychomycosis (66.7% in the combination group and 53.3% in the monotherapy group), with no significant difference in OSI classifications between groups (p 0.868).

Over time, both groups demonstrated a progressive improvement toward milder disease categories. By week 16, 26.7% of patients in the

combination group and 40.0% in the monotherapy group showed no signs of onychomycosis. Similar patterns were observed at weeks 20 and 24, where the proportion of patients with absent or mild disease continued to increase in both groups.

Despite these favorable trends, no statistically significant differences were observed between the two treatment groups at any time point (all p > 0.05), indicating comparable efficacy of excimer laser plus itraconazole combination therapy and itraconazole monotherapy in reducing disease severity over the 24-week follow-up period.

**Table 5. Comparison of Mycological Outcomes Between Treatment Groups at Baseline and Follow-Up Visits**

| Measure               | Time Point | Variables   | Excimer Laser with Itraconazole (n 15) | Itraconazole Monotherapy (n 15) | p-values <sup>1</sup> |
|-----------------------|------------|-------------|----------------------------------------|---------------------------------|-----------------------|
| KOH, n (%)            | Baseline   | 3+          | 5 (33.3%)                              | 5 (33.3%)                       | 1.000                 |
|                       |            | Spores      | 3 (20.0%)                              | 3 (20.0%)                       |                       |
|                       |            | Yeast Cells | 1 (6.7%)                               | 1 (6.7%)                        |                       |
|                       |            | None        | 6 (40.0%)                              | 6 (40.0%)                       |                       |
|                       | Week 12    | Spores      | 1 (6.7%)                               | 1 (6.7%)                        | 1.000                 |
|                       |            | None        | 14 (93.3%)                             | 14 (93.3%)                      |                       |
| Fungal Culture, n (%) | Baseline   | Positive    | 13 (86.7%)                             | 13 (86.7%)                      | 1.000                 |
|                       |            | Negative    | 2 (13.3%)                              | 2 (13.3%)                       |                       |
|                       | Week 12    | Negative    | 15 (100.0%)                            | 15 (100.0%)                     | 1.000                 |

Table 5 compares the mycological outcomes between the combination therapy group (excimer laser with itraconazole) and the itraconazole monotherapy group at baseline and week 12 follow-up. At baseline, both groups demonstrated comparable distributions of KOH findings (p 1.000). By week 12, the majority of patients in both groups were KOH-negative (93.3%), with only one patient in each group remaining positive for spores, and no significant difference was observed between groups (p 1.000).

For fungal culture, baseline positivity was equally high in both groups (86.7%), while all patients achieved negative cultures by week 12 (100%). Again, no statistically significant differences were observed between the two treatment arms (p1.000).

**Table 6. Comparison of adverse effects and recurrence between treatment groups at follow-up visits**

| Variables                     | Excimer Laser with Itraconazole (n 15) | Itraconazole Monotherapy (n 15) | p-values <sup>1</sup> |
|-------------------------------|----------------------------------------|---------------------------------|-----------------------|
| <b>Adverse Effects, n (%)</b> |                                        |                                 |                       |
| Absent                        | 15 (100.0%)                            | 15 (100.0%)                     | 1.000                 |
| <b>Recurrence, n (%)</b>      |                                        |                                 |                       |
| Present                       | 1 (6.7%)                               | 2 (13.3%)                       | .500                  |
| Absent                        | 14 (93.3%)                             | 13 (86.7%)                      |                       |

<sup>1</sup>\*\* - significant at the 1% level; \* - significant at the 5% level.

Table 6 summarizes the adverse effects and recurrence rates in both groups. No adverse effects were reported in either the combination therapy or monotherapy group. Recurrence was observed in one patient (6.7%) in the combination therapy group with *Trichophyton species* and in two patients (13.3%) in the monotherapy group with *Trichophyton species* and *Aspergillus species*, with no statistically significant difference between groups (p 0.543).

**Table 7. Comparison of dermoscopy findings between treatment groups at baseline and follow-up visits**

| Measure                             | Time Point | Variables | Excimer Laser with Itraconazole (n 15) | Itraconazole Monotherapy (n 15) | p-values <sup>1</sup> |
|-------------------------------------|------------|-----------|----------------------------------------|---------------------------------|-----------------------|
| Longitudinal White Striae, n (%)    | Baseline   | Positive  | 10 (66.7%)                             | 11 (73.3%)                      | .500                  |
|                                     |            | Negative  | 5 (33.3%)                              | 4 (26.7%)                       |                       |
|                                     | Week 12    | Positive  | 6 (40.0%)                              | 6 (40.0%)                       | 1.000                 |
|                                     |            | Negative  | 9 (60.0%)                              | 9 (60.0%)                       |                       |
| Jagged Proximal Edge, n (%)         | Baseline   | Positive  | 8 (53.3%)                              | 8 (53.3%)                       | 1.000                 |
|                                     |            | Negative  | 7 (46.7%)                              | 7 (46.7%)                       |                       |
|                                     | Week 12    | Positive  | 7 (46.7%)                              | 7 (46.7%)                       | 1.000                 |
|                                     |            | Negative  | 8 (53.3%)                              | 8 (53.3%)                       |                       |
| Intermittent Spiked Pattern, n (%)  | Baseline   | Positive  | 13 (86.7%)                             | 14 (93.3%)                      | .500                  |
|                                     |            | Negative  | 2 (13.3%)                              | 1 (6.7%)                        |                       |
|                                     | Week 12    | Positive  | 11 (73.3%)                             | 12 (80.0%)                      | .500                  |
|                                     |            | Negative  | 4 (26.7%)                              | 3 (20.0%)                       |                       |
| Chromonychia                        | Baseline   | Positive  | 15 (100.0%)                            | 14 (93.3%)                      | .500                  |
|                                     |            | Negative  | -                                      | 1 (6.7%)                        |                       |
|                                     | Week 12    | Positive  | 12 (80.0%)                             | 11 (73.3%)                      | .500                  |
|                                     |            | Negative  | 3 (20.0%)                              | 4 (26.7%)                       |                       |
| Distal Irregular Termination, n (%) | Baseline   | Positive  | 13 (86.7%)                             | 12 (80.0%)                      | .500                  |
|                                     |            | Negative  | 2 (13.3%)                              | 3 (20.0%)                       |                       |
|                                     | Week 12    | Positive  | 10 (66.7%)                             | 10 (66.7%)                      | .650                  |
|                                     |            | Negative  | 5 (33.3%)                              | 5 (33.3%)                       |                       |
| Trachyonychia, n (%)                | Baseline   | Positive  | 7 (46.7%)                              | 6 (40.0%)                       | .500                  |
|                                     |            | Negative  | 8 (53.3%)                              | 9 (60.0%)                       |                       |
|                                     | Week 12    | Positive  | 4 (26.7%)                              | 5 (33.3%)                       | .500                  |
|                                     |            | Negative  | 11 (73.3%)                             | 10 (66.7%)                      |                       |
| Linear Edge, n (%)                  | Baseline   | Positive  | 10 (66.7%)                             | 9 (60.0%)                       | .500                  |
|                                     |            | Negative  | 5 (33.3%)                              | 6 (40.0%)                       |                       |
|                                     | Week 12    | Positive  | 6 (40.0%)                              | 7 (46.7%)                       | .500                  |
|                                     |            | Negative  | 9 (60.0%)                              | 8 (53.3%)                       |                       |

<sup>1</sup> \*\* - significant at the 1% level; \* - significant at the 5% level.

Table 7 presents the dermoscopic findings at baseline and Week 12. At baseline, both treatment groups demonstrated comparable proportions of longitudinal white striae, jagged proximal edge, intermittent spiked pattern, chromonychia, distal irregular termination, trachyonychia, and linear edge, with no significant differences across any parameter (all  $p > 0.05$ ). At week 12, reductions were observed in positive dermoscopic signs in both groups, although the differences between combination therapy and monotherapy remained statistically non-significant for all features

## DISCUSSION



Figure 5. Representative clinical photographs at baseline, week 4, week 8, week, 12 and week 24 for both excimer laser with itraconazole and itraconazole monotherapy groups



Figure 6. Representative clinical photographs at baseline, week 4, week 8, week 12 and week 24 for both excimer laser with itraconazole and itraconazole monotherapy groups

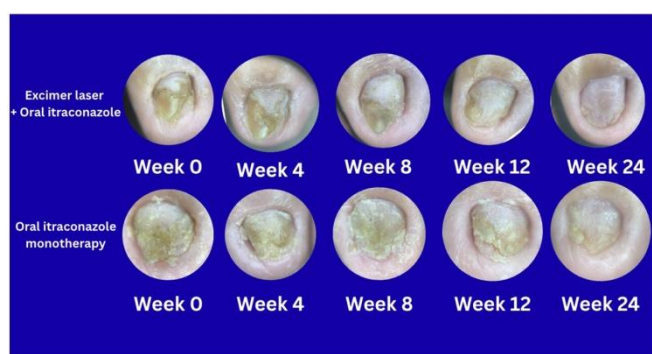


Figure 7. Representative clinical photographs at baseline, week 4, week 8, week 12 and week 24 for both excimer laser with itraconazole and itraconazole monotherapy groups

This study evaluated the efficacy and safety of excimer laser in the treatment of onychomycosis. There was no significant difference observed between both treatment groups for OSI, KOH, fungal culture, dermoscope, adverse effects and recurrence in 24 weeks. Both groups demonstrated progressive improvement toward milder classifications, with no statistically significant differences between them. By week 12, the majority of patients in both groups were KOH-negative, with only one patient per group remaining positive for spores, and all fungal cultures had converted to negative. No adverse effects were reported in either the combination therapy or the monotherapy group.

Given that ultraviolet c radiation has fungicidal properties, both the oral antifungal medication and the excimer laser were effective in eradicating the fungus.<sup>6</sup> Itraconazole inhibits the fungal cytochrome P450-dependent enzyme lanosterol 14- $\alpha$ -demethylase, thereby blocking the conversion of lanosterol to ergosterol and disrupting fungal cell membrane synthesis. It demonstrates fungistatic activity against yeast-like fungi and fungicidal activity against *Aspergillus*

*species*.<sup>51</sup> As demonstrated in previous studies, fungi are highly sensitive to ultraviolet radiation, with even relatively low-power wavelengths in the ultraviolet spectrum capable of consistently destroying them.<sup>6</sup>

Excimer lasers exhibit minimal tissue absorption depth, enabling the precise removal of microscopic tissue layers while minimizing collateral damage to surrounding areas. Studies have shown that only a small radiation dose is required to eradicate fungi, an advantage in preventing injury to the soft tissue beneath the nail.<sup>19</sup>

The results indicate that nails do not transmit radiation at wavelengths below 400-nm. Importantly, when irradiating the nail with a laser in the ultraviolet c spectrum, there is no concern of ultraviolet penetration into the underlying skin, thereby avoiding potential adverse thermal, biochemical, or photophysical effects.<sup>19</sup>

Recurrence occurred in one patient from the combination therapy group and in two patients from the monotherapy group. Notably, even with appropriate oral antifungal treatment, recurrence remains common, affecting 10% to 53% of patients, and may present either as relapse or reinfection.<sup>11</sup>

Reductions in dermoscopic features such as longitudinal white striae, jagged proximal edge, intermittent spiked pattern, chromonychia, distal irregular termination, trachyonychia, and linear edge were observed in both groups by week 12, with no statistically significant differences between combination therapy and monotherapy. A previous study similarly reported clearance of white opalescent areas and the appearance of whitish-yellowish zones progressing toward the distal nail unit following three sessions of laser therapy. Simple dermoscopy thus serves as a practical tool for evaluating treatment outcomes.<sup>52</sup>

Excimer laser is also cost-effective, with an estimated cost ranging from (350)-(800 per session for a total of 8-12 sessions amounting (2,800)-(9,600, making it a practical alternative to prolonged systemic or topical therapy. Compared to itraconazole 100mg capsule 2 capsules twice daily 7 days for 2-3 months from (5,000-(10,000 with (90-120 per capsule.

## CONCLUSION

In conclusion, excimer laser therapy proved to be a safe and effective adjunct in the management of onychomycosis, demonstrating comparable outcomes to oral antifungal monotherapy in terms of clinical, mycological, and dermoscopic parameters, with no reported adverse effects. Both treatment approaches achieved high rates of fungal clearance and progressive



improvement, with low recurrence observed over 24 weeks. The 308-nm excimer laser can be considered a new and effective tool in the treatment of onychomycosis, particularly for patients who do not respond to standard medications or are unsuitable for systemic antifungal therapy. This method may serve as an efficient alternative for managing chronic nail fungal infections, particularly in patients with diabetes, those for whom traditional treatments are inappropriate, immunocompromised individuals, and those who are refractory to therapy. Furthermore, both modalities may be used in combination to optimize therapeutic outcomes.

### LIMITATIONS OF THE STUDY

The study was an operator-dependent procedure. As of this writing, there is still no standardized treatment protocol for the treatment of onychomycosis using this device and further standardization and certification is needed for its application on onychomycosis. The duration of relapse from the last session of treatment was unknown beyond three months after the last session and further studies are needed to support its efficacy on long term control of onychomycosis.

The primary investigator and study subjects cannot be blinded because all participants will receive the treatment on the nails of each hand and foot.

The treatment groups included both hands and feet, which may have influenced the study results due to several factors.

### RECOMMENDATION

Long-term follow-up studies spanning 3 to 5 years are recommended to evaluate the sustained efficacy, recurrence rates, and overall clinical outcomes of excimer laser therapy for onychomycosis. Continuous monitoring will help determine its lasting impact, safety profile, and potential role as a standard alternative treatment in chronic or refractory cases.

### DISCLOSURES

The primary investigator personally funded this study and neither the primary nor co-investigators received any sponsorship from any manufacturer, distributor or company.

### ETHICAL CONSIDERATIONS

This study was conducted in accordance with the ethical principles based on the Declaration of

Helsinki and the National Guidelines for Biomedical Research of the National Ethics Committee (NEC) of the Philippines. The research protocol was submitted for approval to the IRB of Jose R. Reyes Memorial Medical Center, and to the Chair of the Department of Dermatology before commencing the study.

Only the primary investigator, co-authors and residents-in-charge of the patient have access to subjects' medical charts. Subjects who met the inclusion criteria was required to sign an informed consent form, stating their permission to have their clinical data and photographs be taken. The procedure was properly explained and possible side effects were discussed with the patient. The investigator only included the patient's age, sex and necessary information such as diagnosis and treatment outcomes. The patient's name, contact number and address were taken during enrollment for follow-up purposes. Code names were assigned to each participant and their names as well as their other personal information did not appear on any of the data collection tools.

After the study period, the participant had the option to receive the same treatment on the untreated side of the face free of charge care of the primary investigator or to receive conventional treatment options for onychomycosis.

### DATA PROTECTION PLAN

All data obtained from this study were stored in the primary investigator's database with projected storage duration of 10 years in case the investigators need to review the source data should there be questions about the results. These data were used solely for the study and the principal investigator and co-authors can access these data. We will destroy the data after the said duration. Data collection commenced after approval of the IRB and lasted for twelve months duration of the study.

### BIBLIOGRAPHY

1. Dembskey, N., & Abrahamse, H. (2021, August). The efficacy of phototherapy for the treatment of Onychomycosis: an observational study. In *Photonics* (Vol. 8, No. 9, p. 350). MDPI.
2. Tosti A, Hay R, Arenas-Guzmán R. Patients at risk of onychomycosis - risk factor identification and active prevention. *J Eur Acad Dermatol Venereol*. 2005;19:13-16.
3. Sigurgeirsson B, Baran R. The prevalence of onychomycosis in the global population - A literature



- study. *J Eur Acad Dermatol Venereol*.2013;28(11): 1480-1491. doi:10.1111/jdv.12323.
4. Iorizzo, M., Piraccini, B. M., Rech, G., & Tosti, A. (2005). Treatment of onychomycosis with oral antifungal agents. *Expert opinion on drug delivery*, 2(3),435-440.
5. Dhawan, S., & Sharma, K. (2022). Evolving role of lasers in nail therapeutics.*Cosmoderma*, 2.
6. Kyplov~, J., Jelinek, M., Urzov~, J., Miksovský, J., Dusek, K., & Bauerov~, L. (2014, April). Assessment of the suitability of excimer lasers in treating onychomycosis. In *Journal of Physics: Conference Series* (Vol. 497, No. 1, p.012022). IOP Publishing.
7. Watanabe, D., Kawamura, C., Masuda, Y., Akita, Y., Tamada, Y., & Matsumoto, Y. (2008). Successful treatment of toenail onychomycosis with photodynamic therapy. *Archives of dermatology*, 144(1), 19-21.
8. Sigurgeirsson, B., & Baran, R. (2014). The prevalence of onychomycosis in the global population-a literature study. *Journal of the European Academy of Dermatology and Venereology*, 28(11), 1480-1491.
9. Rafat, Z., Hashemi, S. J., Saboor-Yaraghi, A. A., Pouragha, B., Taheriniya, A., Moosavi, A., ... & Basiri, S. (2019). A systematic review and meta-analysis on the epidemiology, casual agents and demographic characteristics of onychomycosis in Iran. *Journal de Mycologie Medicale*, 29(3), 265-272.
10. Halvae, S., Daie-Ghazvini, R., Hashemi, S. J., Khodavaissy, S., Rahimi-Foroushani, A., Bakhshi, H., & Kamali Sarvestani, H. (2021). A mycological and molecular epidemiologic study on onychomycosis and determination in vitro susceptibilities of isolated fungal strains to conventional and new antifungals. *Frontiers in Cellular and Infection Microbiology*, 11, 693522.
11. Shemer, A. (2012). Update: medical treatment of onychomycosis. *Dermatologic therapy*, 25(6), 582-593.
12. Tchernev, G., Penev, P. K., Nenoff, P., Zisova, L. G., Cardoso, J. C., Taneva, T., & Kanazawa, N. (2012). Onychomycosis: modern diagnostic and treatment approaches. *Wiener Medizinische Wochenschrift* (1946), 163(1-2), 1-12.
13. Zang, K., Sullivan, R., & Shanks, S. (2017). A retrospective study of non-thermal laser therapy for the treatment of toenail onychomycosis. *The Journal of Clinical and Aesthetic Dermatology*, 10(5), 24.
14. Mehraban, S., & Feily, A. (2014). 308nm excimer laser in dermatology. *Journal of lasers in medical sciences*, 5(1), 8-12.
15. Sato, T., Asahina, Y., Toshima, S., Yaguchi, T., & Yamazaki, K. (2020). Usefulness of Wood's Lamp for the Diagnosis and Treatment Follow-up of Onychomycosis. *Medical Mycology Journal*, 61(2), 17-21.
16. Weber, G. C., Firouzi, P., Baran, A. M., Bolke, E., Schrupf, H., Buhren, B. A., & Gerber, P. A. (2018). Treatment of onychomycosis using a 1064-nm diode laser with or without topical antifungal therapy: a single-center, retrospective analysis in 56 patients. *European Journal of Medical Research*, 23(1), 1-8.
17. Ma W, Si C, Kasyanju Carrero LM, Liu HF, Yin XF, Liu J, Xu Y, Zhou B. Laser treatment for onychomycosis: A systematic review and meta-analysis. *Medicine (Baltimore)*.2019Nov;98(48):e17948.doi:10.1097/MD.00000000000017948.PMID:31770202;PMCID: PMC6890331.
18. Kalokasidis K, Onder M, Trakatelli MG, Richert B, Fritz K. The Effect of Q-Switched Nd:YAG 1064(nm)/532(nm) Laser in the Treatment of Onychomycosis In Vivo. *Dermatol Res Pract*. 2013;2013:379725. doi: 10.1155/2013/379725. Epub 2013 Dec 14. PMID: 24396343; PMCID: PMC3875102.
19. Urzov~ J, Jelinek M, Miksovsky J, Kyplov~ J. Treatment of Onychomycosis Using Radiation of Excimer Laser. *Adv Mater Res*. 2013;647:636-641. doi:10.4028/www.scientific.net/amr.647.636.
20. Salavastru CM. Excimer Laser Therapy. In: Katsambas AD, Lotti TM, Dessinioti C, D'Erme AM, editors. *European Handbook of Dermatological Treatments*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2015. p. 1183-1189.
21. Carney C, Tosti A, Daniel R, et al. A new classification system for grading the severity of onychomycosis: onychomycosis severity index. *Arch Dermatol*. 2011;147(11):1277-1282.
22. Nasif GA, Amin AA, Ragaie MH. Q-switched Nd: YAG laser versus itraconazole pulse therapy in treatment of onychomycosis: A clinical dermoscopic and mycologic study. *J Cosmet Dermatol*. 2023;22(6): 1757-1763.
23. Kandpal R, Arora S, Arora D. A Study of Q-switched Nd:YAG Laser versus Itraconazole in Management of Onychomycosis. *J Cutan Aesthet Surg*. 2021Jan-Mar;14(1):93-100. doi: 10.4103/JCAS.JCAS\_29\_20. PMID:34084015; PMCID: PMC8149989.

24. Ledon JA, Savas J, Franca K, Chacon A, Nouri K. Laser and light therapy for onychomycosis: a systematic review. *Lasers Med Sci.* 2014 Mar;29(2):823-9. doi:10.1007/s10103-012-1232-y. Epub 2012 Nov 20. PMID: 23179307.
25. Shi, J., Li, J., Huang, H., Permatasari, F., Liu, J., Xu, Y., Luo, D. (2017). The efficacy of fractional carbon dioxide (CO2) laser combined with terbinafine hydrochloride 1% cream for the treatment of onychomycosis. *Journal of Cosmetic and Laser Therapy*,19(6),353-359.doi:10.1080/14764172.2017.1334
26. Gupta AK, Foley KA, Versteeg SG. Lasers for Onychomycosis. *J Cutan Med Surg.* 2016;21(2):114-116. doi:10.1177/1203475416677722.
27. US Food and Drug Administration. Medical Devices and Clinical Trial Design for the Treatment or Improvement in the Appearance of Fungally-Infected Nails: Draft Guidance for Industry and FDA Staff. 2015. [URL:http://www.fda.gov/downloads/Medical Devices/DeviceRegulationandGuidance/GuidanceDocuments/UCM431312.pdf]. Accessed August 19, 2016.
28. Yaemsiri S, Hou N, Slining MM, He K. Growth rate of human fingernails and toenails in healthy American young adults. *J Eur Acad Dermatol Venereol.* 2010;24(4):420-423.
29. Gupta A, Daniel III C. Factors that may affect the response of onychomycosis to oral antifungal therapy. *Australas J Dermatol.* 1998 Nov;39(4):222-224.
30. Li Y, Xu J, Zhao JY, et al. Self-controlled study of onychomycosis treated with long-pulsed Nd:YAG 1064-nm laser combined with itraconazole. *Chin Med J.*2016;129:1929-1934.
31. Lipner SR, Scher RK. Onychomycosis: Clinical overview and diagnosis. *J Am Acad Dermatol.* 2019 Apr;80(4):835-851. doi: 10.1016/j.jaad.2018.03.062. Epub2018 Jun 28. PMID: 29959961.
32. Falotico JM, Lipner SR. Updated Perspectives on the Diagnosis and Management of Onychomycosis. *Clin Cosmet Investig Dermatol.* 2022 Sep 15;15:1933-1957. doi: 10.2147/CCID.S362635. PMID: 36133401; PMCID: PMC9484770.
33. Elewski BE, Tosti A. Risk Factors and Comorbidities for Onychomycosis: Implications for Treatment with Topical Therapy. *J Clin Aesthet Dermatol.* 2015 Nov;8(11):38-42. PMID: 26705439; PMCID: PMC4689496.
34. Elewski BE, Charif MA. Prevalence of onychomycosis in patients attending a dermatology clinic in northeastern Ohio for other conditions. *Arch Dermatol.* 1997 Sep;133(9):1172-3. PMID: 9301602.
35. Ortiz AE, Avram MM, Wanner MA. A review of lasers and light for the treatment of onychomycosis. *Lasers SurgMed.*2014Feb;46(2):117-24.doi:10.1002/lsm.22211.Epub 2013 Dec 24. PMID: 24375507.
36. Pajaziti L, Vasili E. Treatment of Onychomycosis - a Clinical Study. *Med Arch.*2015 Jun;69(3):173-6. doi: 10.5455/medarh.2015.69.173-176. Epub 2015 Jun10. PMID: 26261386; PMCID: PMC4500298.
37. Gupta AK, Elewski BE, Rosen T, Caldwell B, Pariser DM, Kircik LH, Bhatia N, Tosti A. Onychomycosis: Strategies to Minimize Recurrence. *J Drugs Dermatol.*2016 Mar;15(3):279-82. PMID: 26954312.
38. Zhou ZX, Yin XD, Zhang Y, Shao QH, Mao XY, Hu WJ, Shen YL, Zhao B, Li ZL. Antifungal Drugs and Drug-Induced Liver Injury: A Real-World Study Leveraging the FDA Adverse Event Reporting System Database. *Front Pharmacol.* 2022Apr28;13:891336.doi:10.3389/fphar.2022.891336. PMID:35571077;PMCID: PMC9098189.
39. Scher RK. Onychomycosis: a significant medical disorder. *J Am Acad Dermatol.*1996 Sep;35(3 Pt 2):S2-5. doi:10.1016/s0190-9622(96)90061-4.PMID:8784302.
40. Gupta AK, Mays RR. The Impact of Onychomycosis on Quality of Life: A Systematic Review of the Available Literature. *Skin Appendage Disord.* 2018Oct;4(4):208-216. doi: 10.1159/000485632. Epub 2018 Feb 13. PMID: 30410887; PMCID: PMC6219228.
41. Thomas J, Jacobson GA, Narkowicz CK, Peterson GM, Burnet H, Sharpe C.Toenail onychomycosis: an important global disease burden. *J Clin Pharm Ther.*2010 Oct;35(5):497-519.doi:10.1111/j.1365-2710.2009.01107.x.PMID:20831675.
42. Ghannoum M, Isham N. Fungal nail infections (onychomycosis): a never-ending story?. 2014. *PLoS pathogens*, 10(6), e1004105.
43. Handog EB, Dayrit JF. Mycology in the Philippines, revisited. *Nihon Ishinkin Gakkai Zasshi.* 2005;46(2):71-6. doi: 10.3314/jjmm.46.71. PMID: 15864250.
44. Watanabe S, Kishida H, Okubo A. Efficacy and safety of luliconazole 5% nail solution for the treatment of onychomycosis: A multicenter, double-blind, randomized phase III study. *J Dermatol.*2017Jul;44(7): 753-759.doi:10.1111/1346-8138.13816.Epub2017 Mar 23. PMID: 28332720.

45. Rodriguez DA. Efinaconazole Topical Solution, 10%, for the Treatment of Mild and Moderate Toenail Onychomycosis. *J Clin Aesthet Dermatol*. 2015 Jun;8(6):24-9. PMID: 26155324; PMCID: PMC4479366.
46. Lipner SR, Scher RK. Efinaconazole in the treatment of onychomycosis. *Infect Drug Resist*. 2015 Jun 1;8:163-72. doi:10.2147/IDR.S69596. PMID: 26082652; PMCID: PMC4459619.
47. Hees H, Raulin C, Baumler W. Laser treatment of onychomycosis: an in vitro pilot study. *J Dtsch Dermatol Ges*. 2012 Dec;10(12):913-8. English, German. doi:10.1111/j.1610-0387.2012.07997.x. Epub 2012 Aug 17. PMID: 22897199.
48. Chandramohan A, Srinivas CR. Hyphal Index Following a Potassium Hydroxide Mount in Dermatophytosis. *Cureus*. 2021 Dec 21;13(12):e20576. doi:10.7759/cureus.20576. PMID: 35103155; PMCID: PMC8776321.
49. Shirwaikar AA, Thomas T, Shirwaikar A, Lobo R, Prabhu KS. Treatment of onychomycosis: an update. *Indian J Pharm Sci*. 2008 Nov; 70(6): 710-4. doi:10.4103/0250-474X.49088. PMID: 21369429; PMCID: PMC3040862.
50. Tsuboi R, Mochizuki T, Ito H, Kawano S, Suzuki Y, Naka W, Hata Y, Hamaguchi T, Maruyama R. Validation of a lateral flow immunochromatographic assay for tinea unguium diagnosis. *J Dermatol*. 2021 May;48(5):633-637. doi:10.1111/1346-8138.15838. Epub 2021 Mar 8. PMID: 33686693.
51. Kurn H, Wadhwa R. Itraconazole. [Updated 2023 Apr 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK557874/>
52. Arsiwala SZ, Arsiwala N. Role of Dermoscopy in Laser Therapy. *Indian Dermatol Online J*. 2023 Aug 29;14(5):585-593. doi: 10.4103/idoj.idoj\_325\_22. PMID: 37727557; PMCID: PMC10506824.

## Paraneoplastic Erythema Annulare Centrifugum Associated with T-Cell Non-Hodgkin Lymphoma in a 45-Year-Old Filipino Male

Yzabel N. Vergel de Dios, MD, DPDS<sup>1\*</sup>; Maria Rosa Noliza F. Encarnacion, MD, FPDS<sup>1</sup>; Andrea Marie Bernales-Mendoza, MD, FPDS<sup>1</sup>; Vilma C. Ramilo, MD, FPDS<sup>1</sup>

### ABSTRACT

Erythema annulare centrifugum (EAC) is a figurate erythema with an unknown pathogenesis, considered a hypersensitivity reaction to various antigens including malignancies. Rarely, EAC in the setting of an underlying paraneoplastic syndrome is termed paraneoplastic erythema annulare centrifugum (PEACE). We report a case of generalized PEACE in a 45-year-old Filipino male with T-cell non-Hodgkin's lymphoma who presented with a widespread intensely pruritic annular erythematous papules and plaques associated with multiple tender lymphadenopathies. Lymph node biopsy was done which revealed T-cell non-Hodgkin lymphoma. Diagnosis was made histopathologically, with typical features of superficial perivascular lymphocytic infiltrates in a coat sleeve pattern. Treatment with systemic corticosteroids and oral antihistamines resulted to significant reduction in pruritus and eventual resolution of lesions.

Keywords: *annular, erythema annulare centrifugum, antifungal, corticosteroid*

### INTRODUCTION

Erythema annulare centrifugum (EAC) is an uncommon inflammatory skin disorder typically characterized by expanding annular and arcuate erythematous plaques that clear centrally and sometimes present with a fine scale inside the advancing edges (trailing scale) <sup>[1]</sup>. Considered as a reactive condition, the pathogenesis for this disease remains unclear however a wide variety of inciting causes have been identified, including exposure to drugs, infections, autoimmune diseases and cancer <sup>[2]</sup>. In the setting of an underlying malignancy, it is termed as paraneoplastic erythema annulare centrifugum eruption (PEACE) <sup>[3]</sup>. We report a case of generalized EAC associated with T-cell non-Hodgkin's lymphoma in a Filipino male, investigation of the lesions and cancer work-up eventually led to the diagnosis of PEACE.

### CASE REPORT

A 45-year-old Filipino man was referred to the dermatology service who presented with multiple ill to well-defined irregularly shaped annular to polycyclic erythematous papules and plaques topped with thin whitish scales of 1 month duration that started on his chest, abdomen and shoulders (Fig.1). Lesions were associated with extreme pruritus, and in the interim slowly progressed and became more erythematous and generalized affecting his entire body with sparing of the intertriginous areas, the scalp, nails and oral mucosae. Concomitantly the patient experienced significant weight

loss of 25kg in a span of one month with sudden onset of cough, colds, sore throat, hoarseness, easy fatigability, orthopnea and night sweats. Physical examination revealed enlarged bilateral tonsils and firm, non-tender lymphadenopathies over the submental, submandibular, suboccipital, axillary and inguinal areas. Four-millimeter punch biopsies taken from erythematous plaques over the abdomen and upper back showed superficial perivascular lymphocytic infiltrates in a coat sleeve pattern (Fig. 2). The patient was treated with clobetasol propionate 0.05% ointment and intravenous diphenhydramine, which provided relief of pruritus and significant improvement of the lesions. Biopsy of a cervical lymph node revealed diffuse distribution of small round cells with scanty cytoplasm & monotonous round dark nuclei. Immunohistochemical stains were also done which showed all cells are immunoreactive to LCA and some cells are reactive for both CD5 and CD20, supporting a diagnosis of Low-grade B-cell lymphoproliferative disorder, such as lymphoma.

### DISCUSSION

Erythema annulare centrifugum (EAC) is considered as an uncommon inflammatory hypersensitivity reaction whose pathogenesis is not completely understood <sup>[1]</sup>. A wide variety of inciting causes have been reported, such as infections, drugs, pregnancy; with the most ominous associations being from malignancies <sup>[5]</sup>. Paraneoplastic erythema annulare centrifugum eruptions

*Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.*

<sup>1</sup>Department of Dermatology, Dr. Jose N. Rodriguez Memorial Hospital and Sanitarium, Manila, Philippines

\*Corresponding Author

are most commonly associated with lymphoproliferative malignancies, specifically lymphoma and leukemia, often preceding the cancer diagnosis<sup>[6]</sup>. In a retrospective study of 66 patients with EAC, lesions in 48 patients preceded the diagnosis of the associated malignancy<sup>[6]</sup>. Although the specific pathogenesis for PEACE is unclear, it is postulated that an adequate volume of tumor load is required to produce associated antigens or cytokines that promote the development of the apparent clinical skin lesions<sup>[7]</sup>. The presentations of EAC may be localized or generalized<sup>[4]</sup>; however, only a few cases of generalized EAC has been documented.

Clinicopathologic correlation is essential for the diagnosis of EAC since annular eruptions are also seen in several disorders such as mycosis fungoides, subacute cutaneous lupus erythematosus, tinea corporis, Hansen's disease, secondary syphilis, and other figurate erythemas (erythema migrans, erythema marginatum and erythema gyratum repens). The histopathology of EAC is classically defined by dense, tightly cuffed perivascular infiltrates described as a "coat-sleeve", a pattern also encountered in secondary syphilis and tumid lupus erythematosus. However, key findings for these differentials, such as numerous plasma cells and histiocytes typical of syphilis, and increased mucin deposits of mucin seen in tumid lupus were not found in this case<sup>[9]</sup>.

An important differential diagnosis, erythema gyratum repens (EGR), an established paraneoplastic disorder, parallels the clinical and histologic features of PEACE, presenting as a figurate erythema with perivascular infiltrates on biopsy.

Currently, there are no standard guidelines in the treatment of EAC. Common treatments include topical corticosteroids, vitamin D analogs, antifungals and antibiotics. Symptomatic EAC can be treated with antihistamines if there is associated pruritus. Having an established underlying trigger, the management of PEACE is also centered the proper work-up, staging, and subsequent treatment of the underlying malignancy.<sup>[11]</sup> Nearly all reported cases of PEACE had eventual resolution of the lesions following successful cancer treatment<sup>[7]</sup>. Understanding that an sudden eruption of EAC can be a paraneoplastic phenomenon is critical as it could lead to earlier cancer diagnosis and treatment<sup>[8]</sup>.

## CONCLUSION

EAC is a reactive condition to a variety of underlying diseases. Clinically, the lesion resembles other annular erythemas, and clinicopathological correlation is important in making the diagnosis.<sup>[8]</sup> Paraneoplastic EAC although rare must be considered when encountering

annular erythematous plaques especially in the background of possible malignancies. Searching for the underlying condition should be the first step in the management of EAC<sup>[7,10]</sup>. An important differential is EGR which shows clinicopathologic resemblance to EAC, it is important to clinically distinguish the two as we did in our case.

## STATEMENT OF AUTHORSHIP

All authors participated in the data collection and analysis and approved the final version submitted.

## AUTHOR DISCLOSURES

All authors declared no conflicts of interest.

## FUNDING SOURCE

This study has no funding support

## REFERENCES

1. McDaniel, Brianna, and Christopher Cook. "Erythema Annulare Centrifugum." *Nih.gov*, StatPearls Publishing, 27 Aug. 2021, [www.ncbi.nlm.nih.gov/books/NBK482494/](http://www.ncbi.nlm.nih.gov/books/NBK482494/).
2. Mir, Adnan, et al. "Erythema Annulare Centrifugum." *Dermatology Online Journal*, vol. 18, no. 12, 1 Dec. 2012, [escholarship.org/uc/item/1hs6v82m](http://escholarship.org/uc/item/1hs6v82m), 10.5070/D31hs6v82m.
3. Mu EW, Sanchez M, Mir A, Meehan SA, Pomeranz MK: Paraneoplastic erythema annulare centrifugum eruption (PEACE). *Dermatol Online J*. 2015, 21:13030.
4. Kim KJ, Chang SE, Choi JH, et al. Clinicopathologic analysis of 66 cases of erythema annulare centrifugum. *J Dermatol*. 2002;29(2):61-67
5. Yaniv R, et al. Erythema annulare centrifugum as the presenting sign of Hodgkin's disease. *Int J Dermatol* 1993; 32: 59
6. Thompson, Hannah J., et al. "Paraneoplastic Erythema Annulare Centrifugum Associated with Mycosis Fungoides." *JAAD Case Reports*, vol. 17, 5 Oct. 2021, pp. 65–68, [www.ncbi.nlm.nih.gov/pmc/articles/PMC8640728/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC8640728/), 10.1016/j.jidcr.2021.09.027.
7. Chodkiewicz, Hubert M., and Philip R. Cohen. "Paraneoplastic Erythema Annulare Centrifugum Eruption: PEACE." *American Journal of Clinical Dermatology*, vol. 13, no. 4, Aug. 2012, pp. 239–246, 10.2165/11596580-000000000-00000.
8. Pitchford, Chase A, et al. "Paraneoplastic Erythema Annulare Centrifugum Eruption (PEACE) Associated with Metastatic Colorectal Adenocarcinoma." *Cureus*, 2 Oct. 2021, 10.7759/cureus.18443.

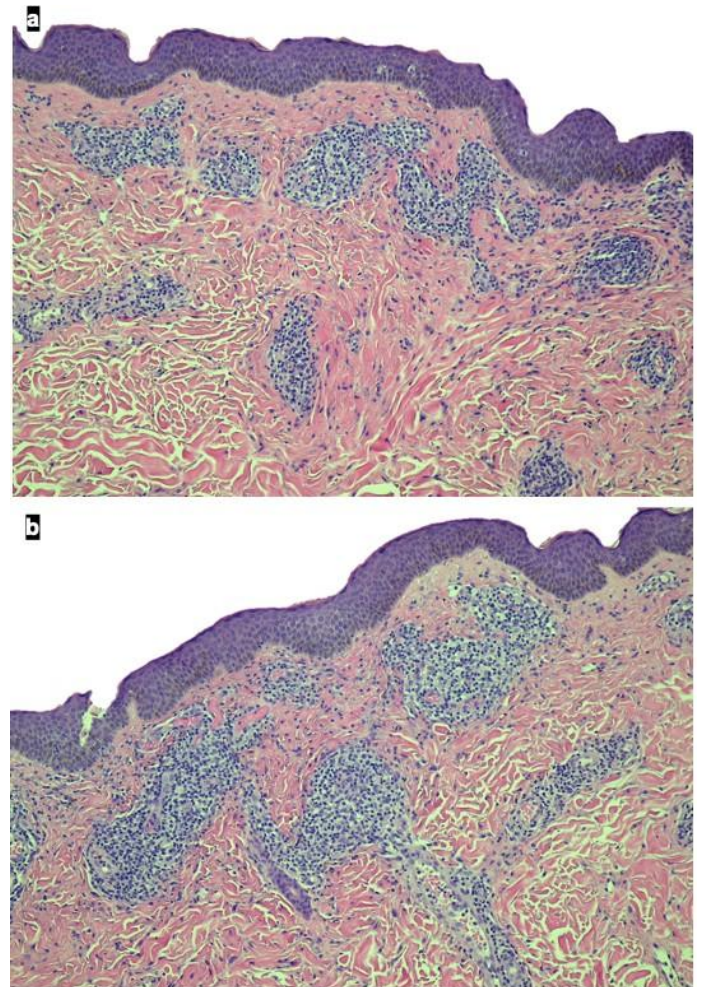


9. Weyers W, Diaz-Cascajo C, Weyers I: Erythema annulare centrifugum: results of a clinicopathologic study of 73 patients. *Am J Dermatopathol*. 2003, 25:451-62. 10.1097/00000372-200312000-00001
10. Honma M, Fujii M, Iinuma S, Komatsu S, Ishida-Yamamoto A, Iizuka H. Erythema annulare centrifugum simulating erythema gyratum repens. *The Journal of Dermatology*. 2010 Sep 29;38(2):192-3.
11. Batycka-Baran, A, et al. "Erythema Annulare Centrifugum Associated with Ovarian Cancer." *Acta Dermato Venereologica*, vol. 95, no. 8, 2015, pp. 1032-1033, 10.2340/00015555-2138.

## Figures



**Figure 1.** Widespread annular and irregularly-shaped erythematous plaques over the face, trunk, back, bilateral upper and lower extremities (A, B); with fine, thin, whitish scales (C)



**Figure 2.** High power (A) and (B) views showing superficial perivascular lymphocytic infiltrates in a coat-sleeve pattern (Hematoxylin & eosin, 40x)



## Pyuria in Cervical Cancer Patients Undergoing Concurrent Chemotherapy and Radiotherapy\*

Richard G. Malicdan, MD<sup>1</sup>; Jimmy A. Billod, MD, MHCA, FPOGS, FSGOP<sup>1</sup>

### ABSTRACT

**Background.** Cervical cancer is the second most common malignancy in women, with gold standard treatment of external beam radiation concurrent with chemoradiotherapy (CCRT) which has acute toxic effects on the genitourinary tract. Such changes are challenging, clinical interpretation of urinalysis and one of which is pyuria. Recent evidence is scarce when it comes to differentiating between radiation and infection induced cystitis. **Objectives.** This study aims to determine the prevalence of pyuria in cervical cancer patients receiving chemotherapy radiation treatment in a tertiary training government hospital from 2018- 2020. Furthermore, it sought to determine the incidence of pyuria with positive urine culture among patients receiving CCRT. **Materials and Method.** The study utilized quantitative descriptive retrospective review of 102 cervical cancer patients in terms of their urinalysis and culture results during CCRT treatment.

**Results and Discussion.** The prevalence of pyuria is at 56.86% (58/102) with positive urine culture at 18.97 %. 58 patients had pyuria, where 44 of them had no growth, 3 had growth with no important pathogen, and 11 were culture positive. Antibiotics therapy was prescribed in 50 of 58 patients who had pyuria. Moreover, pyuria and urine culture have a significant relationship at 0.01 level of significance. **Conclusion.** Patients aged 41-50 years old, with stage 3B cervical cancer, in their initial treatment would most likely have sterile pyuria without culture growth and still be prescribed with antibiotic therapy.

**Keywords:** Pyuria, Cervical Cancer, CCRT, Culture Growth and Antibiotics Therapy

### INTRODUCTION

Cervical cancer ranks second as the most prevalent type among women ages 15 to 44 in other developing nations and in the local setting<sup>1</sup>, with 85% of recorded mortality<sup>2</sup>. Presently, the standard treatment of locally advanced cervical cancer (LACC) include external beam radiotherapy with concurrent cisplatin-based chemotherapy (CCRT) with brachytherapy<sup>3,4</sup>. CCRT indisputably improves LACC outcomes rather than radiotherapy alone<sup>5</sup> but it also causes urinary toxicity<sup>6</sup> like genitourinary tract inflammation, most common is urinary tract infection<sup>7</sup>. UTI (Urinary Tract Infection) has an estimated incidence of 25%- 83%<sup>8,9</sup>, and although common, there are challenges in terms of clinical interpretation on pyuria. Sterile pyuria is broadly defined as the presence of leucocytes (generally >10 WBC/hpf) in the urine in the absence of demonstrable urinary tract infection. There are various reasons why pyuria has become challenging. There is an overlap between pyuria and other condition like urinary tract infection, radiation cystitis and asymptomatic non-visible hematuria, plus the absence of symptoms makes it difficult to justify

treatment<sup>10</sup>. In the institution where the study took place, patients undergo weekly urinalysis before CCRT. Any patient suspected of having urinary tract infection is subjected to antibiotic treatment and CCRT is interrupted. Antibiotic therapy is initiated in both cases where urinalysis shows pyuria, elevated leukocyte esterase, and nitrite levels. Same is true in asymptomatic pyuria, as empirical antibiotic therapy can be initiated while waiting for confirmation by urinary culture<sup>11</sup>. The decision for management rest on the clinician's judgement. In the institution, majority of cases go for the later rather than the former as sterile pyuria, in many cases, is caused by an infection<sup>10</sup>. But most often than not, urine cultures of urinalysis showing UTI have no culture growth, which may mean that the delay in treatment and antibiotic therapy may be deemed unnecessary and harmful. It can lead to antibiotic resistance, adverse drug effects, *C. difficile* infection, and contribute unnecessarily to medical care<sup>12</sup>. Aside from possible over treatment, delays in CCRT happen and when treatment duration exceeds >56 days, research shows that treatment time impacts pelvic failure

*Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.*

<sup>1</sup>Department of Obstetrics and Gynecology, Baguio General Hospital and Medical Center

\*3<sup>rd</sup> Place Philippine Obstetrical and Gynecological Society midyear convention research contest 2023

\*1<sup>st</sup> Place Philippine Obstetrical and Gynecological Society Region 1 research contest 2023

\*Poster Presentation XXVIII Asia Oceania Federation of Obstetrics and Gynecology, Busan South Korea 2024



(PF) and is associated with brachytherapy delay and a higher incidence of acute toxicities<sup>13</sup>.

There are numerous gaps identified when dealing with pyuria among cervical cancer patients. First is the scarcity of evidences to clinically differentiate infectious and radiation cystitis, as the diagnosis of UTI in the general population is not applicable to the population subjected to pelvic radiation therapy<sup>14</sup>. Second, research and guidelines on the management of pyuria are inadequate due to diagnostic challenges, absence of management guidelines, and specimen collection issues. Differentiating pyuria from UTI can be quite problematic which results to inconsistent management like ignoring finding, over investigation and possibly unnecessary secondary care referral<sup>10</sup>. The lack of guidelines and the presentation of symptoms results in excessive use of resources that increase treatment cost, loss of resources, and compromises patient safety by excessive, unjustified use of antibiotics<sup>14</sup>. These beg the question on the incidence of misdiagnosis, over treatment, and unnecessary delay of treatment. Third is the diagnostic capacity of urinalysis in diagnosing pyuria. Studies show that it has not been formally studied in women receiving pelvic radiotherapy for gynecologic malignancies<sup>15</sup>. Urinalysis specimen are most of the time contaminated even if using ideal collection technique<sup>16</sup> due to vaginal leukocytes and inappropriate sample collection<sup>17</sup>. Aside from that, a recent study concluded that urinalysis, both dipstick, and microscopic evaluation, has slightly less diagnostic accuracy for predicting UTI in women undergoing pelvic radiotherapy<sup>15</sup>. Combined with the status quo regarding pyuria, these reality cast doubt and difficulty for physicians on the appropriate management i.e. antibiotic treatment, and delay of therapy.

Hence, this study's main objective is to determine the percentage of pyuria with positive urine cultures in cervical cancer patients undergoing CCRT. Specifically to determine the clinical profile of patients undergoing CCRT, urine culture growth, prevalent microorganisms present on urine culture, percentage of antimicrobial treatment on those with sterile pyuria and correlation between pyuria and positive urine culture.

## MATERIALS AND METHODS

This is a quantitative study that utilized chart review. Previous records of cervical cancer patients who had undergone concurrent chemo and radiotherapy was retrieved from the medical records, electronic medical records of the tertiary training government hospital. The data gathered comprised of the identified independent

variables and demographics. The data was collected by the primary investigator.

The charts and medical records were selected randomly by Microsoft excel. Patients with urinalysis and urine culture results were sorted. Urinalysis with results of pyuria were compared with urine culture if there will be bacterial growth. Bacterial growth on culture were noted. Urinalysis results of patients were compared based on their cycle of treatment to know if treatment it had contributed to the urinalysis results. All data were recorded in the data abstraction form (appendix C).

Exclusion criteria include sufficient lack of variables recorded in the chart, presence of excessive or confounding co-morbidities, and/or the presence of confounding factors that sufficiently degrade the validity of data from the chart.

Charts with incomplete or missing data were managed appropriately. This research followed 2 out of 3 recommendations of Altman and Bland (2007) where the main ways of handling missing data in a retrospective analysis includes: (a) omitting variables which have many missing values; (b) omitting individuals who do not have complete data.

## RESULTS

### Pyuria

Out of the 102 sample population, during their 25 days of treatment with external pelvic radiotherapy simultaneous with weekly Cisplatin regimen. 44 did not have pyuria hence prevalence is at 56.86% (n=58). (Figure 1)

Urine culture was done on those who had pyuria, where three specific outcomes were identified, more than 75% of them had no growth (n= 44), while positive culture yield is at 18.96% (n=11) and only 3 had no important pathogens. More importantly, it should be noted that 50 of the 58 pyuria positives received antibiotic therapy amidst having only 11 positive culture result.

### Age

The mean age of the study population is 48.94. Majority of Cervical Cancer patients belong to age group of 41-50 years old at more than 33% of the study population, which also shows that they have the most incidence of sterile pyuria at 32.76%. Meanwhile, the youngest age group (<30 years old) has the least number of cervical cancer patients at 1.96%.

### Stage of Cancer

Stage 3B has the highest number of patients at 68 (66.67%) followed by stage 3A at 24 (23.53%). The least



number is stage 4B with just 1 patient. Same trend is also seen when it comes to the presence of pyuria in terms of cancer staging where 43 (74.14%) stage 3B has pyuria with 7 of them as culture positive and 33 without growth. Although, it should also be considered that there is no equal distribution of sample population among the stages.

### **Type of Patient**

All the 102 patients included in this study are newly diagnosed cervical cancer.

### **Stage of Treatment**

The peak incidence of pyuria is at the start of treatment at 24.14% which is followed by a decline, only to increase again on the 5<sup>th</sup> week of treatment at 22.41%. The week with the least incidence of pyuria is the last week of treatment which is close to the end of receiving pelvic radiotherapy and chemotherapy. Only those who had an incidence of pyuria were included in this demographic hence the total of 58. (Table 1)

Table 1 shows the demographic characteristics of cervical cancer patients undergoing CCRT. 58 patients out of the total 102 had pyuria while 11 out of the 58 had culture growth. The mean age of the study population was 48.94. Most of them at stage 3B, least at 4B. Peak incidence of pyuria was noted at the initiation of treatment and at the 5<sup>th</sup> week.

### **Prevalent organisms and Antibiotic therapy**

The total number of patients with pyuria and positive urine culture was 18.97%. The highest isolates were gram negative bacteria, with *K. pneumoniae* (27.27%) followed by ESBL organisms (18.18%) as shown in table 2. Out of the 50 patients who received antibiotics, the most prescribed is Ciprofloxacin at 38% of the cases (n=19) followed by Fosfomycin at 14% (n=7) and then Ceftriaxone and Cefuroxime with each at 12% (n=6). The least prescribed is Meropenem and Ampicillin Sulbactam at 6% each (n=3).

### **Pyuria and urine culture**

Chi square test was done to determine the relationship between pyuria and positive urine culture. Since 102 is more than the critical value 11.34, we reject the null hypothesis hence, there is a statistically significant relationship between pyuria and urine culture. However, it should be noted that chi-square test cannot establish a causal relationship or the odds of having a positive culture with pyuria symptoms. The study cannot also do odds

ratio as this is a retrospective study and urine culture is not usually done on patients with no pyuria (Table 4).

### **Discussion**

18.97% of patients with pyuria are culture positive that is similar to another study at 18.8% on the management of pyuria among hospital admitted patients with non-urinary infections<sup>18</sup>. Meanwhile, other studies analyzed the effectiveness of urinalysis parameters in predicting positive urine culture in gynecologic cancer patients receiving pelvic radiotherapy<sup>15</sup>, where 34.9% (n=84) urine cultures were positive for growth. Another study evaluated the appropriateness of empiric treatment based on microbial urine culture data and susceptibility testing of 6950 urine where 34.5% (n = 2400) revealed positive results where 26.8% (n=214) were prescribed empiric antibiotics that failed to have appropriate coverage of the identified pathogens<sup>19</sup>. Worst, 14.6% of the cases (n = 117) identified microorganisms to be resistant to the antibiotics prescribed. This can be a possible scenario as antibiotic prescription precedes awaiting culture results. Currently, prescribing antibiotics is seen as outweighing the benefits over the risk for cervical cancer patients who might develop further morbidity due to pyuria.

In terms of age, the findings are similar to an Indian study on cervical cancer patients<sup>20</sup> where majority were in the age group of 45–54 (31.76%), followed by 55–64 (29.15%) and only one-fifth (19.87%) were below the age of 45. The idea that older women are the most affected group with cervical cancer can be due to poor awareness on cervical cancer among the older population and/or differences in healthcare-seeking behavior<sup>21</sup>. Health education across age groups focused on screening, signs and symptoms and when to seek consult should be highlighted to ensure that these age groups receive timely and life saving intervention. Moreover, younger women should be receiving mandatory shots for cervical cancer in order to prevent it on a later age.

For the stage of cancer, a similar study of 216 patients with gynecologic malignancies undergoing external pelvic radiotherapy (EBRT) were studied periodically every week for any evidence of urinary tract infection (UTI) and they found out that patients with stage III cervical cancer (33.3%) has the most infections with 50% having repeated UTI episodes amidst antibiotic treatment<sup>22</sup>. With a high prevalence, the Philippine setting has a high burden of cervical cancer and this can be due to low screening further compounded by the lack of basic knowledge on prevention. Prophylactic HPV vaccination has already been approved yet national or government



vaccination policy has ever been implemented as of yet<sup>23</sup>.

All the patients included in the study were 102 newly diagnosed cervical cancer patients. It can be due to the high mortality rate associated with advance cancer. In fact, the Philippines has a mortality-to-incidence ratio of 0.51<sup>2</sup> and 75% of Filipino cervical cancer patients are diagnosed at advanced stages<sup>23</sup>. However, some studies have reported that the recurrence rate for those with stage III to IVB Cervical cancer is as high as 70%<sup>24,25</sup>. With all the new cases being diagnosed everyday, it is not surprising that a huge percentage of women at 81.9% have poor knowledge about cervical cancer and it's screening (85.5%) hence a meager 7.22 % had undergone screening<sup>26</sup>. This means that poor knowledge leads to late diagnosis hence advance stages in new cases are being detected. Hence, it is the duty of physicians to help mass education, offer screening suggestions especially to high risk women and conduct community based education.

As for the stage of treatment, the result of the study implies that pyuria should be expected on the first week of treatment hence patients should be monitored closely at the initial phase of treatment and on week 5 of their treatment in order to enhance timely interventions and prevent morbidity associated with pyuria. Moreover, the result of the study also begs to question whether the administration of antibiotics is judicious enough especially at the initial phase of treatment. The study on pyuria among cervical cancer patients are scarce to rare, hence, related published literature specifically studying the weekly treatment and its correlates have no yield in any online search engine.

In terms of bacterial growth among the 11 culture positives, it should be noted that in the institution where this study took place, it is common practice to prescribe antibiotics to cervical cancer patients with sterile pyuria once they undergo CCRT. This means that while waiting for urine culture results, antibiotic management has been initiated regardless of the results. This is to prevent possible morbidities associated with the infection especially if urinalysis shows any of the following: positive leucocyte esterase, positive nitrite, and elevated bacterial counts. Moreover, patient may not return for follow up at the oncology clinic and since physicians deal with a huge number of patients, individually checking culture results is challenging. Pyuria was most strongly associated with infection caused by gram-negative bacilli<sup>27</sup>. In a similar Ethiopian study<sup>28</sup> on cancer patients with urinary tract infections during treatment, where majority are cervical cancer patients (36.6%), (6.3%) were culture positive cases with *Escherichia coli* (44.4%) as the most isolated followed

by *Klebsiella pneumoniae* (22.2%) and some ESBL organisms were also identified and tagged as main sources of drug resistance. This is similar to the other findings<sup>15</sup> when *Escherichia coli* was also the most common isolate in the culture of 19/134 (22.6%) women undergoing pelvic radiotherapy.

For the antibiotics prescribed to the 50 patients, Ciprofloxacin was the most prescribed antibiotics amidst current guideline on sterile pyuria by the Philippine Society for Microbiology and Infectious Diseases (2013) says that quinolones like Ciprofloxacin should never be used as first line of treatment due to Quinolones having high efficacy and high propensity for collateral damage. In terms of antibiotic management<sup>28</sup>, there is a high resistance rates to Ampicillin 12 (66.7%), Augmentin 11(61.1%), and Ceftriaxone 10 (55.6%) while a low resistance rate was detected for Meropenem 2(11.1%), and Ciprofloxacin 3 (16.7%). Such result is opposite to the findings of another study<sup>15</sup> where 23.8% of pathogens were resistant to trimethoprim/sulfamethoxazole, 16.7% were resistant to ciprofloxacin, and 11.1% were resistant to nitrofurantoin. In the current study, only ciprofloxacin, ceftriaxone an meropenem were prescribed. Recently, resistance to fluoroquinolones and trimethoprim-sulfamethoxazole (TMP-SMX) has been on the increasing among common UTI pathogens<sup>29</sup> with an increasing prevalence of extended-spectrum  $\beta$ -lactamase and other multi-drug resistant organisms<sup>30,31,32</sup>. Several strategies have been suggested on how to minimize the misuse and overuse of antibiotics in order to avoid increasing antibiotic resistance<sup>33,34,35</sup>; like identifying factors beyond the infection itself that may affect antibiotic treatment. Hence, it is still important to consider that not all pyuria in cervical cancer patients undergoing CCRT should be treated with antibiotics. Culture results and timing of pyuria should be considered. This results show that physicians must always rely on guidelines by waiting on culture studies to check which antibiotic is the identified bacteria susceptible.

Lastly, there is a statistically significant relationship between pyuria and urine culture, however a causal relationship cannot be established. Meanwhile, a recent study<sup>36</sup> defined the relationship of pyuria and positive bacterial growth in urine culture in 46,127 patients in acute care. Their study concluded that pyuria alone did not provide adequate diagnostic accuracy to predict bacteriuria hence antibiotic treatment based on urine analysis alone is insufficient. Moreover, a study<sup>27</sup> stated that pyuria is less strongly correlated with CAUTI and it should not be used as the sole criterion to initiate antibiotics.



## CONCLUSION

This study concludes that more than half of the patients undergoing CCRT will have pyuria is seen mostly in patients aged 41-50 years old, with stage 3B cervical cancer and who are starting their treatment. Most patients will have no growth in their urine culture however. Direct correlation of pyuria and urine culture is not established hence urine culture result is needed prior to initiation of antibiotics.

## RECOMMENDATIONS

The researchers recommend future studies on the following: a) Correlating antibiotic sensitivity analysis to the prescribed antibiotics, b) explore outcomes of those treated with antibiotics and those who were not prescribed antibiotics regardless of culture status c) correlate specific urinalysis parameters to culture outcomes, d) Prospective studies could be done to establish a causal relationship by odds ratio between pyuria and positive urine culture through adding urine culture on patients without pyuria and e) Recurrent pyuria on patients with recurrent cervical cancer. This study also recommends each hospitals treating cervical cancer patients to have a registry which is a specialized online hospital data base that contains all labs, diagnostics, biopsy, treatment and outcomes for easy access of accurate and available data for the continuous treatment of patients.

The results of this present study can be used by clinicians to decide on their judicious use of antibiotics on cervical cancer patients undergoing CCRT. Comparing to other studies, the present study considered the week of treatment and focused on the higher stages of the disease, which is not found in other studies.

## References

1. Department of Health Philippines(2020) Uterine Cervix Cancer. Retrieved from <https://www.doh.gov.ph/press-release/9TH-HPV-SUMMIT-HIGHLIGHTS-ASIA-OCEANIAS-COMMITMENT-FOR-CERVICAL-CANCER-ELIMINATION>. Accessed on October 02, 2020
2. World Health Organization (2020). Cervical Cancer. Retrieved from [https://www.who.int/en/news-room/fact-sheets/detail/human-papillomavirus-\(hpv\)-and-cervical-cancer](https://www.who.int/en/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer). Accessed on October 02, 2020.
3. Cho, O., & Chun, M. (2018). Management for locally advanced cervical cancer: new trends and controversial issues. *Radiation oncology journal*, 36(4), 254–264. Retrieved from <https://doi.org/10.3857/roj.2018.00500>
4. Todo, Y., & Watari, H. (2016). Concurrent chemoradiotherapy for cervical cancer: background including evidence-based data, pitfalls of the data, limitation of treatment in certain groups. *Chinese journal of cancer research = Chung-kuo yen cheng yen chiu*, 28(2), 221–227. <https://doi.org/10.21147/j.issn.1000-9604.2016.02.10>
5. Datta, N. R., Stutz, E., Liu, M., Rogers, S., Klingbiel, D., Siebenhüner, A., Singh, S., & Bodis, S. (2017). Concurrent chemoradiotherapy vs. radiotherapy alone in locally advanced cervix cancer: A systematic review and meta-analysis. *Gynecologic oncology*, 145(2), 374–385. Retrieved from <https://doi.org/10.1016/j.ygyno.2017.01.033>
6. Viswanathan, A. N., & Gaffney, D. K. (2017). Cervical cancer: A global health crisis. *Cancer*, 123(13), 2404–2412. <https://doi.org/10.1002/cncr.30667>
7. Jakubowicz, J., Blecharz, P., Skotnicki, P., Reinfuss, M., Walasek, T., & Luczynska, E. (2014). Toxicity of concurrent chemoradiotherapy for locally advanced cervical cancer. *European journal of gynaecological oncology*, 35(4), 393–399.
8. Gordon L.(2014). Cranberry in radiotherapy: dispelling the myths. A review of the literature. *J Radiother Pract*. 2014;13(1):98–105. doi: 10.1017/S1460396913000320
9. Bonetta, A., & Di Pierro, F. (2012). Enteric-coated, highly standardized cranberry extract reduces risk of UTIs and urinary symptoms during radiotherapy for prostate carcinoma. *Cancer management and research*, 4, 281–286. Retrieved from <https://doi.org/10.2147/CMAR.S35342>
10. Rees, J.& Manley, J. (2015). Assessment of sterile pyuria in primary care. *British Journal of Family Medicine* , 3 (3), 2015. Retrieved from <https://www.bjfm.co.uk/assessment-of-sterile-pyuria-in-primary-care#:~:text=Non%2Dinfectious%20causes,likely%20to%20be%20extremely%20low>. Accessed October 02, 2020.
11. Gupta, K., Hooton, T. M., Naber, K. G., Wulft, B., Colgan, R., Miller, L. G., Moran, G. J., Nicolle, L. E., Raz, R., Schaeffer, A. J., Soper, D. E., Infectious Diseases Society of America, & European Society for Microbiology and Infectious Diseases (2011). International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clinical infectious diseases : an official*



- publication of the Infectious Diseases Society of America, 52(5), e103–e120. <https://doi.org/10.1093/cid/ciq257>
12. Hines, A., Rupp, M. & Schooneveld, T. (2014). Urinary Tract Infection and Asymptomatic Bacteriuria Guidance. Reviewed and Approved by Antimicrobial Stewardship Subcommittee of Pharmacy and Therapeutics Committee of the Nebraska Medical Center. Retrieved from <https://www.unmc.edu/intmed/divisions/id/asp/clinical-pathways/docs/uti-asbu-guidance-final.pdf>. Accessed on October 02, 2020.
  13. Song, S., Rudra, S., Hasselle, M., Dorn, P., Mell, L., Mundt, A., Yamada, S., Lee, N., & Hasan, Y. (2013). The effect of treatment time in locally advanced cervical cancer in the era of concurrent chemoradiotherapy. *Cancer*. 119. 10.1002/cncr.27652.
  14. Xavier, V. F., Gabrielli, F., Ibrahim, K. Y., Gomes, M., Guimarães, R., Abdala, E., & Carvalho, H. A. (2019). Urinary infection or radiation cystitis? A prospective evaluation of urinary symptoms in patients submitted to pelvic radiotherapy. *Clinics (Sao Paulo, Brazil)*, 74, e1388. <https://doi.org/10.6061/clinics/2019/1388>
  15. Shuford, R. A., Dulaney, C. R., Burnett, O. L., 3rd, Byram, K. W., & McDonald, A. M. (2016). Evaluating the Role of Urinalysis for Suspected Cystitis in Women Undergoing Pelvic Radiotherapy. *International journal of gynecological cancer: official journal of the International Gynecological Cancer Society*, 10.1097/IGC.0000000000000714. Advance online publication. <https://doi.org/10.1097/IGC.0000000000000714>
  16. Frazee, B. W., Enriquez, K., Ng, V., & Alter, H. (2015). Abnormal urinalysis results are common, regardless of specimen collection technique, in women without urinary tract infections. *The Journal of emergency medicine*, 48(6), 706–711. <https://doi.org/10.1016/j.jemermed.2015.02.020>
  17. Glen, P., Prashar, A., & Hawary, A. (2016). Sterile pyuria: a practical management guide. *The British journal of general practice : the journal of the Royal College of General Practitioners*, 66(644), e225–e227. <https://doi.org/10.3399/bjgp16X684217>
  18. Hooker, J. B., Mold, J. W., & Kumar, S. (2014). Sterile pyuria in patients admitted to the hospital with infections outside of the urinary tract. *Journal of the American Board of Family Medicine : JABFM*, 27(1), 97–103. Retrieved from <https://doi.org/10.3122/jabfm.2014.01.130084> <http://www.cdc.gov/cancer/international/statistics.htm>. Accessed October 02, 2020
  19. Alkhalwaldeh R, Abu Farha R, Abu Hammour K, Alefishat E. The Appropriateness of Empiric Treatment of Urinary Tract Infections in a Tertiary Teaching Hospital in Jordan: A Cross-Sectional Study. *Antibiotics*. 2022; 11(5):629. <https://doi.org/10.3390/antibiotics11050629>
  20. Jain, A., Ganesh, B., Bobdey, S. C., Sathwara, J. A., & Saoba, S. (2017). Sociodemographic and Clinical Profile of Cervical Cancer Patients Visiting in a Tertiary Care Hospital in India. *Indian journal of medical and paediatric oncology : official journal of Indian Society of Medical & Paediatric Oncology*, 38(3), 291–295. [https://doi.org/10.4103/ijmpo.ijmpo\\_20\\_16](https://doi.org/10.4103/ijmpo.ijmpo_20_16)
  21. Ertem G. (2009). Awareness of cervical cancer risk factors and screening behaviour among nurses in a rural region of turkey. *Asian Pac J Cancer Prev*. 2009;10:735–8.
  22. Prasad, K. N., Pradhan, S., & Datta, N. R. (1995). Urinary tract infection in patients of gynecological malignancies undergoing external pelvic radiotherapy. *Gynecologic oncology*, 57(3), 380–382. <https://doi.org/10.1006/gyno.1995.1158>
  23. Domingo, E. J., & Dy Echo, A. V. (2009). Epidemiology, prevention and treatment of cervical cancer in the Philippines. *Journal of gynecologic oncology*, 20(1), 11–16. <https://doi.org/10.3802/jgo.2009.20.1.11>
  24. Friedlander M, Grogan M. Guidelines for the treatment of recurrent and metastatic cervical cancer. *Oncologist* (2002) 7:342–7. doi: 10.1634/theoncologist.2002-0342
  25. Sankaranarayanan R, Swaminathan R, Brenner H, Chen K, Chia KS, Chen JG, et al. Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol* (2010) 11:165–73. doi: 10.1016/S1470-2045(09)70335-3
  26. Harsha Kumar, H., & Tanya, S. (2014). A Study on Knowledge and Screening for Cervical Cancer among Women in Mangalore City. *Annals of medical and health sciences research*, 4(5), 751–756. <https://doi.org/10.4103/2141-9248.141547>
  27. Tambyah PA, Maki DG. The Relationship Between Pyuria and Infection in Patients With Indwelling Urinary Catheters: A Prospective Study of 761 Patients. *Arch Intern Med*. 2000;160(5):673–677. doi:10.1001/archinte.160.5.673
  28. Sime, W. T., Biazin, H., Zeleke, T. A., & Desalegn, Z. (2020). Urinary tract infection in cancer patients and antimicrobial susceptibility of isolates in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. *PloS one*, 15(12), e0243474. <https://doi.org/10.1371/journal.pone.0243474>



29. Chardavoyne, P. C., & Kasmire, K. E. (2020). Appropriateness of Antibiotic Prescriptions for Urinary Tract Infections. *The western journal of emergency medicine*, 21(3),633–639. <https://doi.org/10.5811/westjem.2020.1.45944>
30. Bidell MR, Palchak M, Mohr J, et al. Fluoroquinolone and third-generation-cephalosporin resistance among hospitalized patients with urinary tract infections due to *Escherichia coli*: Do rates vary by hospital characteristics and geographic region? *Antimicrob Agents Chemother*. 2016;60(5):3170–3.
31. Dancer SJ, Kirkpatrick P, Corcoran DS, et al. Approaching zero: temporal effects of a restrictive antibiotic policy on hospital-acquired *Clostridium difficile*, extended-spectrum beta-lactamase-producing coliforms and methicillin-resistant *Staphylococcus aureus*. *Int J Antimicrob Agents*. 2013;41(2):137–42.
32. Sanchez GV, Babiker A, Master RN, et al. Antibiotic resistance among urinary isolates from female outpatients in the United States in 2003 and 2012. *Antimicrob Agents Chemother*.2016;60(5):2680–3.
33. Laxminarayan R., Van Boeckel T., Frost I., Kariuki S., Khan E.A., Limmathurotsakul D., Larsson D.G.J., Levy-Hara G., Mendelson M., Outtersson K., et al. The Lancet Infectious Diseases Commission on antimicrobial resistance: 6 years later. *Lancet Infect. Dis*. 2020;20:e51–e60.doi: 10.1016/S1473-3099(20)30003-7. [PubMed] [CrossRef] [Google Scholar]
34. Molstad S., Lofmark S., Carlin K., Erntell M., Aspevall O., Blad L., Hanberger H., Hedin K., Hellman J., Norman C., et al. Lessons learnt during 20 years of the Swedish strategic programme against antibiotic resistance. *Bull. World Health Organ*. 2017;95:764–773. doi: 10.2471/BLT.16.184374.
35. Holmes A.H., Moore L.S., Sundsfjord A., Steinbakk M., Regmi S., Karkey A., Guerin P.J., Piddock L.J. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet*. 2016;387:176–187. doi: 10.1016/S0140-6736(15)00473-0. [PubMed] [CrossRef] [Google Scholar]
36. Cheng, B., Zaman, M., & Cox, W. (2022). Correlation of Pyuria and Bacteriuria in Acute Care. *The American journal of medicine*, 135(9), e353–e358. <https://doi.org/10.1016/j.amjmed.2022.04.022>

## FIGURES

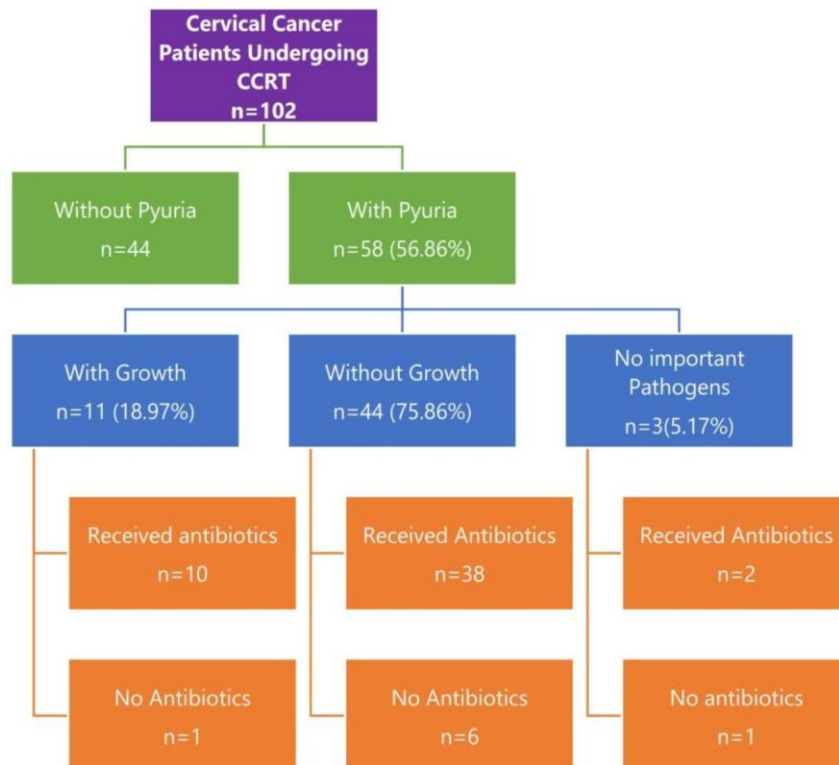


Figure 1. Pyuria among Cervical Cancer Patients undergoing Concurrent Chemoradiotherapy at a tertiary government hospital from 2018 to 2020.

**Table 1. Demographic characteristics of Cervical Cancer patients while undergoing Concurrent Chemotherapy and Radiotherapy from 2018-2022 at a government tertiary hospital.**

| Demographic Characteristics | Total, n (%) | Sterile Pyuria | Culture Status |           |                        | Antibiotics                 |
|-----------------------------|--------------|----------------|----------------|-----------|------------------------|-----------------------------|
|                             | f(%)         | f(%)           | With Growth    | No Growth | No Important Pathogens | Prescribed with antibiotics |
| Age                         | Mean ± SD    | 48.94 ± 11.84  |                |           |                        |                             |
| <30 years old               | 2 (1.96)     | 1 (1.72)       | 0              | 1         | 0                      | 1                           |
| 31-40 years old             | 22           | 16 (27.59)     | 2              | 13        | 1                      | 12                          |
| 41-50 years old             | 34           | 19 (32.76)     | 5              | 14        | 0                      | 17                          |
| 51-60 years old             | 25           | 11(18.97)      | 3              | 6         | 1                      | 10                          |
| >60 years old               | 19           | 11(18.97)      | 1              | 10        | 1                      | 10                          |
| Total                       | 102          | 58             | 11             | 44        | 3                      | 50                          |
| Stage of Cancer             |              |                |                |           |                        |                             |
| Stage 3A                    | 24(23.53)    | 10 (17.24)     | 3              | 7         | 0                      | 9                           |
| Stage 3B                    | 68(66.67)    | 43 (74.14)     | 7              | 33        | 3                      | 37                          |
| Stage 4A                    | 9(8.82)      | 4 (6.90)       | 1              | 3         | 0                      | 3                           |
| Stage 4B                    | 1 (0.98)     | 1(1.72)        | 0              | 1         | 0                      | 1                           |
| Total                       | 102          | 58             | 11             | 44        | 3                      | 50                          |
| 3. Type of Patient          |              |                |                |           |                        |                             |
| New                         | 102          | 58(100)        | 11             | 44        | 3                      | 50                          |
| Recurrent                   | 0            | 0              | 0              | 0         | 0                      | 0                           |
| Total                       | 102          | 58             | 11             | 44        | 3                      | 50                          |
| 4. Stage of Treatment       |              |                |                |           |                        |                             |
| Week 1                      | 14 (24.1)    | 14 (24.1)      | 3              | 10        | 1                      | 11                          |
| Week 2                      | 10 (17.2)    | 10 (17.2)      | 2              | 8         | 0                      | 8                           |
| Week 3                      | 6(10.3)      | 6(10.3)        | 1              | 4         | 1                      | 5                           |
| Week 4                      | 7(12.1)      | 7(12.1)        | 1              | 6         | 0                      | 6                           |
| Week 5                      | 13(22.4)     | 13(22.4)       | 3              | 9         | 1                      | 13                          |
| Week 6                      | 6(10.3)      | 6(10.3)        | 1              | 5         | 0                      | 5                           |
| Week 7                      | 2(3.4)       | 2(3.4)         | 0              | 2         | 0                      | 2                           |
| Total                       | 58           | 58             | 11             | 44        | 3                      | 50                          |

**Table 2. The prevalent microorganisms found in the urine culture of cervical cancer patients with pyuria.**

| Microorganisms                       | Type          | f         | %          |
|--------------------------------------|---------------|-----------|------------|
| Pseudomonas paucimobilis (-)         | Gram Negative | 1         | 9.09       |
| Klebsiella pneumoniae (-)            | Gram Negative | 3         | 27.27      |
| Proteus mirabilis(-)                 | Gram Negative | 1         | 9.09       |
| Enterobacter cloacae (-)             | Gram Negative | 1         | 9.09       |
| Streptococcus agalacticus(+)         | Gram Positive | 1         | 9.09       |
| Serratia marcescens(-)               | Gram Negative | 1         | 9.09       |
| Escherichia coli (-)                 | Gram Negative | 1         | 9.09       |
| ESBL (E.COLI and Klebsiella Oxytoca) | Gram Negative | 2         | 18.18      |
|                                      |               | <b>11</b> | <b>100</b> |

**Table 3. Antibiotics Prescribed to Cervical Cancer Patients with Pyuria**

| Antibiotics   | Frequency | Percentage |
|---------------|-----------|------------|
| Ciprofloxacin | 19        | 38         |
| Fosfomycin    | 7         | 14         |
| Ceftriaxone   | 6         | 12         |
| Cefuroxime    | 6         | 12         |
| Ofloxacin     | 6         | 12         |
| Ampicillin    | 3         | 6          |
| Sulbactam     | 3         | 6          |
| Meropenem     | 3         | 6          |
| Total         | 50        | 100        |

**Table 4. Chi Square test of Independence between pyuria and urine culture among cervical cancer patients undergoing CCRT.**

| Chi-Sq | p-value  | x-crit   | significance | Decision    |
|--------|----------|----------|--------------|-------------|
| 102    | 5.77E-22 | 11.34487 | yes          | REJECT NULL |

\*Significant at 0.01 level of significance



## Lupus Panniculitis Masquerading as Mastitis: A Diagnostic Challenge in a 17-Year-Old Female Patient\*

Janine Michele T. Lovino-Ty, MD, DPDS<sup>1</sup>; Reuben Mitchell M. Manuel, MD, DPDS<sup>1</sup>;  
Jolene Kristine G. Dumlao, MD, FPDS<sup>1</sup>

### ABSTRACT

**Introduction:** Lupus mastitis is a rare manifestation of lupus panniculitis characterized by inflammation of the subcutaneous fat tissue and occurs in approximately 2-3% of systemic lupus erythematosus (SLE) patients. It may present as breast mass, axillary lymphadenopathy, fibrosis, or calcifications, which must be differentiated from infection and malignancy.

**Case Report:** A 17-year-old female presented with a 4-month history of multiple tender pruritic erythematous nodules with erosions and ulcerations on the right breast, which subsequently increased in size and number, extending to the right lateral neck associated with periorbital swelling. She was initially managed under pediatric service as a case of facial cellulitis and breast abscess. Extensive laboratory and imaging studies—including blood chemistries, cultures, radiographs, ultrasonography, and computerized tomography (CT) scans—were performed. She received several courses of oral antibiotics, antifungal agents, analgesics, and intravenous corticosteroids, with no clinical improvement, prompting referral to our service. A 4-mm punch biopsy revealed superficial and deep perivascular dermatitis with panniculitis. Additional findings of leukopenia, anemia, proteinuria with granular casts, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and positive for antinuclear antibody (ANA) supported a diagnosis of lupus panniculitis. She was given hydroxychloroquine 200 mg/day and prednisone 20 mg/day, resulting in marked improvement of lesions after one month.

**Discussion:** This case highlights the diagnostic challenges posed by lupus panniculitis masquerading as mastitis and emphasizes the need for a comprehensive evaluation in complex dermatologic cases. Early recognition and appropriate treatment of this condition can improve patient outcomes and prevent unnecessary interventions.

**Keywords:** Chronic cutaneous lupus erythematosus, lupus panniculitis, lupus mastitis

### INTRODUCTION

Lupus mastitis is a rare manifestation of lupus panniculitis marked by inflammation of the subcutaneous fat tissue. It occurs more commonly in women, with a mean age of onset of 36 years.<sup>1</sup> It affects about 2-3% of patients with SLE and may be the initial manifestation of the disease. It may present as breast mass, axillary lymphadenopathy, fibrosis, and calcifications.<sup>2</sup> It can mimic malignancy or infection and therefore should be differentiated from them.<sup>3</sup> We describe a case of lupus panniculitis presenting as lupus mastitis highlighting the importance of a thorough diagnostic approach in such challenging cases<sup>4</sup>.

### CASE REPORT

A 17-year-old female presented with a 4-month history of multiple tender pruritic erythematous nodules with erosions and ulcerations on the right breast, which subsequently increased in size and number affecting the right lateral neck, associated with periorbital swelling.

Review of systems, past medical history, family history, and sexual history were unremarkable. She was admitted under pediatric service and was initially diagnosed with facial cellulitis and breast abscess. Comprehensive diagnostic investigations were performed, including blood chemistries; gram stain and cultures of blood, wound, and tissue samples; chest radiography; ultrasonography of both breasts and the whole abdomen; computed tomography (CT) scans of the cranium, orbits, and chest; and biopsies of breast and submandibular tissue. Chest radiography revealed minimal right pleural effusion. Breast ultrasound revealed a large mass with a small pocket of fluid on the right breast, while chest CT scan showed swelling of the right breast parenchyma and areas of subcutaneous edema, both of which were consistent with a right breast abscess. Gram stain and cultures of blood, wound, and tissue samples yielded no growth. She received several courses of oral antibiotics, antifungal agents, analgesics, and intravenous corticosteroids, with

---

*Disclosures:* The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

<sup>1</sup>Consultant, Southern Isabela Medical Center Department of Dermatology and Venereology

no clinical improvement, prompting referral to our service.

Upon dermatologic examination, multiple well-demarcated erythematous to hyperpigmented indurated plaques were noted on the left periorbital area, submandibular region, neck, trunk, bilateral arms, and right breast, with multiple firm, tender nodules on the right breast (Figure 1).



FIGURE 1. DERMATOLOGIC EXAMINATION (A., B., C. and D. Multiple well-demarcated erythematous to hyperpigmented indurated plaques on the left eye, submandibular area, neck, trunk, and bilateral arms. B. Multiple firm tender nodules on the right breast.

A 4-mm punch biopsy was performed on lesions located on the left arm and trunk. Hematoxylin and eosin (H&E) staining of the left arm revealed basket-weave orthokeratosis, vacuolar interface changes, and mild lymphocytic infiltrate involving the superficial and deep perivascular areas, adnexal structures, and fat lobules consistent with superficial and deep perivascular dermatitis with panniculitis (Figures 2A and 2B). While the lesion on the trunk revealed mildly atrophic epidermis, focal vacuolar interface changes consistent with superficial perivascular dermatitis and post-inflammatory pigmentary changes (Figure 3). Additionally, Alcian blue staining revealed increased dermal mucin deposition (Figure 2C). These histopathologic findings supported the diagnosis of lupus panniculitis.

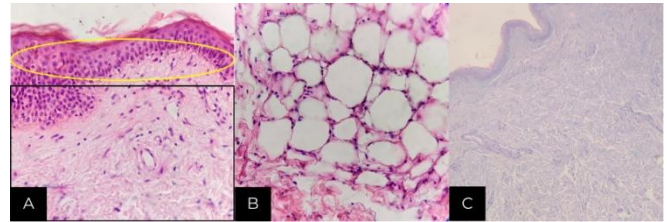


FIGURE 2. SKIN PUNCH BIOPSY ON THE LEFT ARM (A. H&E stain, LPO: Section shows vacuolar interface changes marked by yellow circle and mild inflammatory infiltrate composed of lymphocytes marked by black box; B. H&E stain, HPO: Section shows lobular panniculitis; C. Alcian blue stain: Section shows increased dermal mucin deposition)

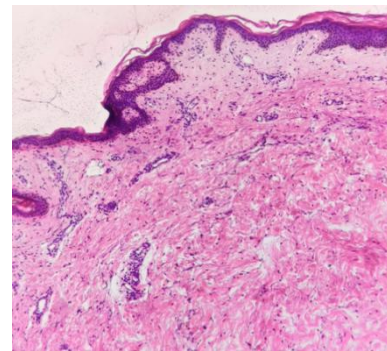


FIGURE 3. SKIN PUNCH BIOPSY ON THE TRUNK (H&E stain, LPO: Section shows mildly atrophic epidermis, focal vacuolar interface changes, mild dermal edema, and a sparse inflammatory infiltrate.

Comprehensive laboratory investigations revealed leukopenia, anemia, proteinuria and hematuria with granular casts on urinalysis, elevated ESR and CRP, with normal levels of complement component 3 (C3). Furthermore, the patient tested positive ANA with a value of 447, with negative anti-double-stranded-DNA (dsDNA) antibody.

The clinical presentation, laboratory results, and histopathologic findings supported the diagnosis of lupus panniculitis. The patient also met the American College of Rheumatology (ACR) criteria for systemic lupus erythematosus (SLE), based on the presence of discoid rash, proteinuria, hematuria, and granular casts on urinalysis, anemia and leukopenia on complete blood count, and positive ANA.

She was started on hydroxychloroquine 200 mg/day, with ophthalmologic clearance prior to initiation. Prednisone 20 mg/day (0.5 mg/kg/day) was also given, along with omeprazole 20 mg/day and vitamin D with calcium supplementation. Supportive measures included the use of mild soap, emollients, and strict photoprotection. After one month of treatment,

significant reduction in erythema and swelling of lesions with residual hyperpigmentation was observed (Figure 4). She was then discharged improved, and regular outpatient visits were scheduled. However, she was subsequently lost to follow-up.



**FIGURE 4.** 1 MONTH OF AFTER TREATMENT (Lesions showed decrease in swelling and erythema with residual hyperpigmentation.)

## DISCUSSION

Lupus mastitis is a rare, benign inflammation of the deep subcutaneous fat tissues of the breast, seen in around 2–3% of systemic lupus erythematosus patients. It is part of the presentation of lupus panniculitis. It could be the first symptom of the disease and can appear concurrently with, before, or after other DLE or SLE symptoms. It is more prevalent in females, with a female-to-male ratio of 4.5:1. The age of onset ranges from 20 to 60 years, with the average age of 36 years old.<sup>2,5</sup> It was encountered in a majority of black women.<sup>6</sup>

Lupus mastitis may present as breast mass, axillary lymphadenopathy, fat necrosis, fibrosis, and calcifications.<sup>2</sup> Lupus mastitis and periorbital edema are rare initial manifestations of Lupus Panniculitis.<sup>7</sup> Often, the clinical presentation of lupus mastitis may mimic breast infection and malignancy.<sup>2,6</sup> Although uncommon, lupus mastitis should be considered in the differential diagnosis of a suspicious breast mass and distinguished from the latter diagnosis. It is the extension of lupus panniculitis on the mammary gland and presents clinically as a painful subcutaneous mass or with cutaneous involvement such as thickening and discoloration.<sup>5,6</sup> In an article published by Pessôa et al, imaging findings can be inconclusive. Magnetic resonance imaging (MRI) may reveal skin thickening, fat stranding, and heterogeneous contrast enhancement with variable enhancement curves. Mammography frequently demonstrates large dystrophic calcifications with fat necrosis in advanced cases, along with focal or diffuse, asymmetric, ill-defined masses. Ultrasonography often shows ill-defined hypoechoic

areas, architectural distortion, and echotextural changes, commonly hyperechoic due to infiltration. The differential diagnosis must be ruled out with histopathological study, as there is no absolute imaging finding that differentiates it from LM.<sup>8</sup> Skin biopsy is the diagnostic procedure of choice for and the key histopathologic features include a lymphocytic infiltrate involving the fat lobules and hyaline necrosis of the fat lobules.<sup>5</sup> Special stains and direct immunofluorescence may aid in diagnosis but are not required. Laboratory investigations should always be performed to rule out or confirm other organ involvement. They are not only useful in initial diagnostics but also for evaluation of prognosis and activity.<sup>7</sup>

The first line of treatment for lupus panniculitis is antimalarial therapy, most commonly hydroxychloroquine at a dosage of 200 mg to 400 mg/day, which typically produces a clinical response in 6–8 weeks. Systemic corticosteroids are often used in combination with antimalarial drugs during the initial phase of treatment to achieve disease control. Other systemic treatments include dapsone, mycophenolate mofetil, cyclophosphamide, thalidomide, IVIG, and rituximab. Overlying cutaneous lesions can be treated with topical or intralesional steroids. Lupus panniculitis follows a chronic, relapsing–remitting course. Lesions can be debilitating, but they rarely have a long-term impact on patients' survival. Most patients have a favorable prognosis, and lupus panniculitis is generally considered a marker of a less severe form of systemic lupus erythematosus.<sup>9</sup>

We presented a rare case of lupus mastitis. This case highlights the diagnostic challenges posed by lupus panniculitis masquerading as mastitis and emphasizes the need for a comprehensive evaluation in complex dermatologic cases. The presence of a breast mass initially led to diagnostic uncertainty, as imaging and laboratory findings were inconclusive, necessitating histopathologic confirmation through biopsy. Despite reports of exacerbation during the biopsy, when confronted with this diagnostic challenge, it may be beneficial to confirm the diagnosis. Given the rarity of this condition, misdiagnosis is possible, often resulting in delayed or inappropriate management. Hence, a multi-specialty approach and proper clinicopathologic correlation are needed to arrive at an appropriate diagnosis and management plan. Early recognition and appropriate treatment of lupus panniculitis can improve patient outcomes and prevent unnecessary interventions.



## REFERENCES:

1. Mullaaziz, D., Maden, S., Deren, O., & Özkayalar, H. (2020). Periorbital lupus erythematosus profundus: A case report and review of the literature. *TURKDERM*, 54(3), 114–116. <https://doi.org/10.4274/turkderm.galenos.2020.32068>
2. Oktay, A., Habib Ahmad Esmat, Aslan, Ö., & Ismayil Mirzafarli. (2022). Lupus Mastitis in a Young Female Mimicking a Breast Carcinoma; a Rare Entity Through a Case Report and Review of the Literature. *Meme Sağlığı Dergisi/Meme Sağlığı Dergisi*, 18(1), 13–15. <https://doi.org/10.4274/ejbh.galenos.2021.6361>
3. Mazed, C., Aguiar, R., & Barcelos, A. (2022). Lupus mastitis – the copycat. *Scandinavian Journal of Rheumatology*, 1–3. <https://doi.org/10.1080/03009742.2022.2076348>
4. Roongta, R., Joshi, S., Chattopadhyay, A., & Ghosh, A. (2022). Lupus Mastitis. *Reumatología Clínica (English Edition)*, 18(5), 312–313. <https://doi.org/10.1016/j.reumae.2021.05.006>
5. Lupus panniculitis in an ANA-negative systemic lupus... : Journal of the Philippine Dermatological Society. (2024). LWW. <https://journals.lww.com/jpds/abstract/2021/30010/lupus-panniculitis-in-an-ana-negative-systemic.8.aspx>
6. Béatrice Voizard, Lalonde, L., Lilia Maria Sanchez, Richard-Chesnay, J., David, J., Labelle, M., Mona El Khoury, & Trop, I. (2017). Lupus mastitis as a first manifestation of systemic disease: About two cases with a review of the literature. *European Journal of Radiology*, 92, 124–131. <https://doi.org/10.1016/j.ejrad.2017.04.023>
7. Worm, M., Zidane, M., Eisert, L., Fischer-Betz, R., Foeldvari, I., Günther, C., Iking-Konert, C., Kreuter, A., Müller-Ladner, U., Nast, A., Ochsendorf, F., Schneider, M., Sticherling, M., Tenbrock, K., Wenzel, J., & Kuhn, A. (2021). S2k guideline: Diagnosis and management of cutaneous lupus erythematosus – Part 1: Classification, diagnosis, prevention, activity scores. *JDDG: Journal Der Deutschen Dermatologischen Gesellschaft*, 19(8), 1236–1247. <https://doi.org/10.1111/ddg.14492>
8. Pessôa, A., & Célia, M. (2020). Lupus Mastitis as Differential Diagnosis of Breast Mass. *Journal of Case Reports*, 162–165. <https://doi.org/10.17659/01.2020.0043>
9. Cooper, E. E., Pisano, C. E., & Shapiro, S. C. (2021). Cutaneous Manifestations of “Lupus”: Systemic Lupus Erythematosus and Beyond. *International Journal of Rheumatology*, 2021,1–19. <https://doi.org/10.1155/2021/6610509>

## Knowledge, Attitudes and Practices of Personal Mosquito-Repellent Methods Among Adult Filipinos

Jenika Gracia P. Simbillo-Rivera, MD, DPDS<sup>1\*</sup>; Lucille Sabrina F. Ferrer, MD, FPDS, FPSVI<sup>1</sup>;  
Mari Carlota B. Najera, MD, FPDS<sup>1</sup>

### ABSTRACT

**Background:** Vector-borne infections account for over 17% of all infectious diseases, which are prevalent in tropical and subtropical regions. Low-income communities have limited access to physical and chemical vectors, which reduce the chance of cutaneous symptoms, allergic reactions, secondary bacterial infections, and eventually, systemic disease.

**Objectives:** This study aims to identify the knowledge, attitudes, and practices on personal mosquito-repellent methods among adult Filipinos.

**Methods:** A descriptive, observational study was conducted among adult Filipinos aged 18 to 59 years old in the outpatient department of a tertiary referral hospital and in the partner community or barangay health center.

**Results:** Among the 215 participants, most were female, single, between the ages of 18 and 37, lived in Barangay Tapuac, Dagupan City and reside in concrete houses. Low knowledge scores were found in 80.47%, and positive overall attitude scores in 92.09%. The majority of mosquito-repellent methods used were insecticide sprays (71.16%), but other unconventional methods like mosquito-repelling plants (14.42%), and vitamin B and garlic pills (3.26%) were also utilized. Over 90% of respondents said they would consult a healthcare provider for information regarding mosquito-repellent measures.

**Conclusion:** Understanding adult Filipinos' knowledge, attitudes, and practices regarding personal mosquito-repellent use enables dermatologists in both community and institutional settings to provide evidence-based patient education on effective, cost-efficient vector control and to contribute meaningfully to collaborative public health initiatives.

**Keywords:** Mosquito repellents, community dermatology, prospective descriptive

**Commercial funding:** The study did not receive any commercial or external funding support.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

### INTRODUCTION

Vector-borne illnesses consist of approximately 17% of all infectious diseases, with dengue considered as the most rapidly spreading mosquito-borne viral disease worldwide. Pathogens such as parasites, virus, and bacteria are transmitted by these vectors, which include mosquitoes, fleas, lice, ticks, and bugs.<sup>1</sup> Developing countries in the tropical and subtropical areas are at risk, including the Philippines, where more than 13,000 cases were reported in March 2021.<sup>1,2,3</sup> In 2019, Region 1 of the Philippines reported 9% increase in the number of cases, involving 25 mortalities. Majority of confirmed dengue cases in the Philippines were males, while most deaths were female patients. Children aged 5-9 years old were the most severely affected population.<sup>4</sup> Aside from dengue, mosquitoes transmit many other diseases including malaria, Chikungunya virus, Zika virus, and West Nile virus. Thus, emphasis on the prevention of these disease is essential. These include, but are not limited to,

environmental cleaning, protective clothing, limited time outdoors, and safe use of mosquito repellents.<sup>5,6</sup> A significant milestone is that a dengue vaccine was first licensed in 2015.<sup>7</sup>

Various mosquito repellents are available in the market. Physical and chemical vector control augment mosquito bite prevention, leading to decrease in incidence of cutaneous manifestations, allergic reaction, and systemic disease.<sup>8,9</sup> Most individuals complain of intense pruritus, and skin manifestations may be aggravated by scratching or manipulation and may lead to secondary bacterial infection.<sup>10</sup> Physical vector control include wearing of light-colored clothing with good coverage, staying indoors, sanitation of possible mosquito habitats, and use of mosquito nets and lanterns.<sup>3,9,11</sup> Chemical vector control are composed of synthetic compounds such as DEET, picaridin, and IR3535, and as DEET, picaridin, and IR3535, and natural compounds

---

*Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.*

<sup>1</sup>Region 1 Medical Center, Dagupan City, Pangasinan

\*Principal Author

such as oil of lemon eucalyptus, citronella oil, and catnip oil.<sup>9</sup> Broad-spectrum DEET is the most widely used active ingredient in mosquito repellents, which generally has an effective safety profile, and are safer in 10% to 35% concentrations.<sup>3,6,9,12</sup> Examples of non-topical mosquito repellents are bracelets, wristbands, patches, candles, coils, and stickers, which usually contain citronella.<sup>3,11</sup> Access to effective product is often limited in developing countries. In one online survey, unconventional strategies arose such as use of a telephone application, burning animal dung, and avoidance of sugar, meat, and bananas.<sup>3</sup> Indigenous people in the Philippines use numerous plant species to drive off mosquitoes.<sup>13</sup>

In developing countries where there is a high incidence of mosquito-borne illnesses, there is often limited access to effective repellent products. Because of this, various traditional and home remedies are used across a variety of groups and cultures.<sup>3</sup> Among the Ayta people in Pampanga, Philippines, different parts of native plants such as stems of *ipil-ipil*, leaves of *kakawati*, fruit of *kupang*, and root of *pandakake*, are used for their repellent activity. In addition, there is cultural heritage perseveration through these methods.<sup>13</sup> Grown in tropical and subtropical regions are *Azadirachta indica* or commonly known as neem, in which seed kernels exhibited repellent efficacy against female *Anopheles* mosquitoes which induce malaria.<sup>14</sup> In Southeast Asia, dried peel of lanzones are also burned exuding aromatic smoke to deter mosquitoes.<sup>15</sup>

Many patients not only present with cutaneous manifestations, but also allergic reaction and systemic infections, due to mosquito bites. The clinicians' working knowledge on the primary and secondary strategies and the patients' understanding of the disease transmission and knowledge, attitudes, and practices on mosquito-repellent methods will help the reduction of individuals having mosquito-related illness. Information on registered, readily available, and effective prophylactic mosquito repellents would not only prevent disease, but also mitigate allergic reaction severity.<sup>8,9,16</sup> This study aims to identify the knowledge, attitudes, and practices on personal mosquito-repellent methods among adult Filipinos.

## METHODS AND MATERIALS

A descriptive, observational study design was employed. Participants, selected through convenience sampling, completed a validated questionnaire available

in both English and Filipino languages. The survey gathered information on demographic data, environmental history, past medical history of mosquito-borne diseases, knowledge of various mosquito-borne diseases and mosquito-repellent types, attitudes toward environmental modification and health-seeking behavior, and practices and traditions involving mosquito repellents. The study was conducted over a six-month period at the outpatient department of a tertiary government hospital and a partner municipal health center. Respondents were adult Filipinos aged 18 to 59 years old without serious psychological illnesses requiring emergent intervention. A sample size of 215 was calculated using Slovin's formula.

## RESULTS

Among the participants, 161 (74.88%) were in the range of 18 to 37 years old (Table 1). More than half were female (68.37%), single (64.19%), and Roman Catholic (78.14%). Most were college graduates (43.26%), followed by those who finished post-graduate (25.12%) and high school levels (25.12%). Eighty-three (38.6%) were unemployed, and 56 (26.05%) were students. Almost 30% (64 participants) have an estimated family income of less than 11,000 pesos. A great majority of respondents are from Dagupan City (53.49%), followed by Calasiao (13.02%) and Binmaley (6.05%) [Table 2]. Three respondents were not from Pangasinan. Of those from Dagupan, most are from Barangay Tapuac (32.17%), followed by Bonuan (21.74%). Of those from Calasiao, most reside in Nagsaing (17.86%). At 70.23% (151 participants), a vast majority reside in a stand-alone houses, with buildings made of concrete material (83.26%), living with 2-5 household members (60.47%) [Table 3]. More than half have flush type with tanks (60.93%), with water supplied through pipes (79.53%). Less than half have no presence of body of water nearby their house (49.77%), very closely. Majority also have presence foliage nearby at 80.47% (42 participants) [Table 3]. Respondents get most of their information on mosquito-repellent methods on television (54.42%) followed by internet search engines (41.86%) and from healthcare workers (40%) [Table 4].



**Table 1.** Demographic profile (n = 215)

| Demographic Profile                                                                                                                                                                                                                                                                                                                    | Frequency | %     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-------|
| <b>Age group (in years)</b>                                                                                                                                                                                                                                                                                                            |           |       |
| 18-37                                                                                                                                                                                                                                                                                                                                  | 161       | 74.88 |
| 38-59                                                                                                                                                                                                                                                                                                                                  | 54        | 25.12 |
| <b>Sex</b>                                                                                                                                                                                                                                                                                                                             |           |       |
| Female                                                                                                                                                                                                                                                                                                                                 | 147       | 68.37 |
| Male                                                                                                                                                                                                                                                                                                                                   | 68        | 31.63 |
| <b>Civil status</b>                                                                                                                                                                                                                                                                                                                    |           |       |
| Single                                                                                                                                                                                                                                                                                                                                 | 138       | 64.19 |
| Married                                                                                                                                                                                                                                                                                                                                | 74        | 34.42 |
| Widowed                                                                                                                                                                                                                                                                                                                                | 2         | 0.93  |
| Annulled                                                                                                                                                                                                                                                                                                                               | 1         | 0.47  |
| <b>Religion</b>                                                                                                                                                                                                                                                                                                                        |           |       |
| Roman Catholic                                                                                                                                                                                                                                                                                                                         | 168       | 78.14 |
| Born Again Christian                                                                                                                                                                                                                                                                                                                   | 25        | 11.63 |
| Iglesia ni Cristo                                                                                                                                                                                                                                                                                                                      | 8         | 3.72  |
| Baptist                                                                                                                                                                                                                                                                                                                                | 5         | 2.33  |
| Atheist                                                                                                                                                                                                                                                                                                                                | 2         | 0.93  |
| Latter-day Saints                                                                                                                                                                                                                                                                                                                      | 2         | 0.93  |
| Unanswered                                                                                                                                                                                                                                                                                                                             | 2         | 0.93  |
| Jehovah's Witness                                                                                                                                                                                                                                                                                                                      | 1         | 0.47  |
| Orthodox Catholic                                                                                                                                                                                                                                                                                                                      | 1         | 0.47  |
| Seventh-day Adventist                                                                                                                                                                                                                                                                                                                  | 1         | 0.47  |
| <b>Education</b>                                                                                                                                                                                                                                                                                                                       |           |       |
| College graduate                                                                                                                                                                                                                                                                                                                       | 93        | 43.26 |
| Post-graduate                                                                                                                                                                                                                                                                                                                          | 55        | 25.58 |
| High school graduate                                                                                                                                                                                                                                                                                                                   | 54        | 25.12 |
| Less than high school                                                                                                                                                                                                                                                                                                                  | 13        | 6.05  |
| Jehovah's Witness                                                                                                                                                                                                                                                                                                                      | 1         | 0.47  |
| <b>Occupation</b>                                                                                                                                                                                                                                                                                                                      |           |       |
| Unemployed                                                                                                                                                                                                                                                                                                                             | 83        | 38.6  |
| Student                                                                                                                                                                                                                                                                                                                                | 56        | 26.05 |
| House wife                                                                                                                                                                                                                                                                                                                             | 13        | 6.05  |
| Business owner                                                                                                                                                                                                                                                                                                                         | 7         | 3.26  |
| Post-Graduate Intern                                                                                                                                                                                                                                                                                                                   | 7         | 3.26  |
| Physician                                                                                                                                                                                                                                                                                                                              | 6         | 2.79  |
| Sales                                                                                                                                                                                                                                                                                                                                  | 5         | 2.33  |
| Government Employee                                                                                                                                                                                                                                                                                                                    | 3         | 1.4   |
| Pharmacist                                                                                                                                                                                                                                                                                                                             | 3         | 1.4   |
| Driver                                                                                                                                                                                                                                                                                                                                 | 2         | 0.93  |
| Jeepney Driver                                                                                                                                                                                                                                                                                                                         | 2         | 0.93  |
| Accountant, Architect, Cashier, Casual Employee, Construction Worker, Driver, Farmer, Fisherman, Healthcare Worker, Housekeeper, Housewife, Medical Representative, Medical Technician, Online Seller, Pharmacy Assistant, Policeman, Sail Officer, Seller (Unspecified), Teacher, Tricycle Driver, Turbine Specialist, Vendor, Welder | 1         | 0.47  |

| <b>Estimated family income (in Philippine peso)</b> |    |       |
|-----------------------------------------------------|----|-------|
| Less than 11,000                                    | 64 | 29.77 |
| 11,001-23,000                                       | 48 | 22.33 |
| 23,001-47,000                                       | 42 | 19.53 |
| 47,001-82,000                                       | 21 | 9.77  |
| 234,001 and above                                   | 19 | 8.84  |
| 140,001-234,000                                     | 12 | 5.58  |
| 82,001-140,000                                      | 7  | 3.26  |
| Not specified                                       | 2  | 0.93  |

**Table 2.** Demographic profile of participants (n = 215)

| City/Town       | Barangay         | Frequency | %     |
|-----------------|------------------|-----------|-------|
| Alaminos (n=3)  | Not specified    | 3         | 100   |
| Balungao (n=1)  | Poblacion        | 1         | 100   |
| Bayambang (n=2) | Telbang          | 1         | 50    |
|                 | Not specified    | 1         | 50    |
| Binalonan (n=1) | Not specified    | 1         | 100   |
| Binmaley (n=13) | Naguilayan       | 3         | 23.08 |
|                 | Dulag            | 2         | 15.38 |
|                 | Baybay Lopez     | 1         | 7.69  |
|                 | Buenlag          | 1         | 7.69  |
|                 | Canaoalan        | 1         | 7.69  |
|                 | Poblacion        | 1         | 7.69  |
|                 | San Isidro Norte | 1         | 7.69  |
|                 | Not specified    | 3         | 23.08 |
| Bolinao (n=1)   | Luna             | 1         | 100   |
| Bugallon (n=3)  | Banaga           | 2         | 66.67 |
|                 | Bolaoen          | 1         | 33.33 |
| Calasiao (n=28) | Nagsaing         | 5         | 17.86 |
|                 | Bued             | 3         | 10.71 |
|                 | San Miguel       | 3         | 10.71 |
|                 | Dinalaoan        | 2         | 7.14  |
|                 | Longos           | 2         | 7.14  |
|                 | Macabito         | 2         | 7.14  |
|                 | Ambunao          | 1         | 3.57  |
|                 | Gaban            | 1         | 3.57  |
|                 | Lucao            | 1         | 3.57  |
|                 | Malabago         | 1         | 3.57  |
|                 | Mancup           | 1         | 3.57  |
|                 | Poblacion West   | 1         | 3.57  |
|                 | Not specified    | 5         | 17.86 |
| Dagupan (n=115) | Tapuac           | 37        | 32.17 |
|                 | Bonuan           | 25        | 21.74 |
|                 | Lucao            | 10        | 8.7   |
|                 | Pantal           | 10        | 8.7   |
|                 | Malued           | 6         | 5.22  |
|                 | Mangin           | 3         | 2.61  |
|                 | Mayombo          | 3         | 2.61  |
|                 | Salapingao       | 3         | 2.61  |
|                 | Calmay           | 2         | 1.74  |
|                 | Amado            | 1         | 0.87  |
|                 | Arellano         | 1         | 0.87  |
|                 | Bateng           | 1         | 0.87  |

|                         |                   |   |       |
|-------------------------|-------------------|---|-------|
|                         | Maligaya          | 1 | 0.87  |
|                         | Poblacion         | 1 | 0.87  |
|                         | Poblacion Oeste   | 1 | 0.87  |
|                         | Pogo Grande       | 1 | 0.87  |
|                         | Pugaro            | 1 | 0.87  |
|                         | Not specified     | 8 | 6.96  |
| La Union (n=2)          | Rabon             | 1 | 50    |
|                         | Not specified     | 1 | 50    |
| Lingayen (n=6)          | Domalandan        | 1 | 16.67 |
|                         | Libsong           | 1 | 16.67 |
|                         | Libsong West      | 1 | 16.67 |
|                         | Poblacion         | 1 | 16.67 |
|                         | Tonton            | 1 | 16.67 |
|                         | Wawa              | 1 | 16.67 |
| Manaoag (n=4)           | Bucao             | 1 | 25    |
|                         | Calaocan          | 1 | 25    |
|                         | Inamotan          | 1 | 25    |
|                         | Pantal            | 1 | 25    |
| Mangaldan (n=8)         | Bari              | 2 | 25    |
|                         | Banaoang          | 1 | 12.5  |
|                         | Davin             | 1 | 12.5  |
|                         | Malabago          | 1 | 12.5  |
|                         | Nibaliw           | 1 | 12.5  |
|                         | Salay             | 1 | 12.5  |
|                         | Not specified     | 1 | 12.5  |
| Mangatarem (n=1)        | Paul              | 1 | 100   |
| San Carlos (n=6)        | Colingling        | 1 | 16.67 |
|                         | Malacanang        | 1 | 16.67 |
|                         | Parayao           | 1 | 16.67 |
|                         | PNR Station Site  | 1 | 16.67 |
|                         | San Pedro         | 1 | 16.67 |
|                         | Not specified     | 1 | 16.67 |
| San Fabian (n=5)        | Bolasi            | 1 | 20    |
|                         | Cayanga           | 1 | 20    |
|                         | Poblacion         | 1 | 20    |
|                         | Poblacion         | 1 | 20    |
|                         | Sagud-Bahley      | 1 | 20    |
| San Fernando City (n=1) | Parian            | 1 | 100   |
| San Jacinto (n=4)       | Guibel            | 1 | 25    |
|                         | San Guillermo     | 1 | 25    |
|                         | Not specified     | 2 | 50    |
| San Manuel (n=1)        | Cabacaraan        | 1 | 100   |
| San Quintin (n=1)       | Alac              | 1 | 100   |
| Sta. Barbara (n=4)      | Maningding        | 1 | 25    |
|                         | Not specified     | 3 | 75    |
| Sual (n=2)              | Tondol            | 1 | 50    |
|                         | Not specified     | 1 | 50    |
| Urdaneta (n=2)          | Nancamaliran East | 1 | 50    |
|                         | San Vicente       | 1 | 50    |
| Not specified (n=1)     | Not specified     | 1 | 100   |

**Table 3.** Environmental history (n = 215)

| Demographic Profile                           | Frequency | %     |
|-----------------------------------------------|-----------|-------|
| <b>Type of house</b>                          |           |       |
| Stand-alone house                             | 151       | 70.23 |
| Apartment                                     | 56        | 26.05 |
| Informal settlement                           | 5         | 2.33  |
| Condominium                                   | 3         | 1.40  |
| <b>Material of house</b>                      |           |       |
| Mostly concrete                               | 179       | 83.26 |
| Mostly wood                                   | 28        | 13.02 |
| Nipa hut                                      | 6         | 2.79  |
| Mostly corrugated metal                       | 2         | 0.93  |
| <b>Number of household members</b>            |           |       |
| 2-5                                           | 130       | 60.47 |
| 6 and above                                   | 43        | 20    |
| Lives alone                                   | 42        | 19.53 |
| <b>Type of toilet facility</b>                |           |       |
| Flush type with tank                          | 131       | 60.93 |
| Pour flush toilet                             | 77        | 35.81 |
| Pit latrine                                   | 7         | 3.26  |
| <b>Main water source</b>                      |           |       |
| Piped water supply                            | 171       | 79.53 |
| Handpumps                                     | 42        | 19.53 |
| Shallow wells                                 | 1         | 0.47  |
| Streams and/or ponds                          | 1         | 0.47  |
| <b>Presence of body of water nearby house</b> |           |       |
| None                                          | 107       | 49.77 |
| Natural                                       | 98        | 45.58 |
| Artificial                                    | 10        | 4.65  |
| <b>Presence of foliage nearby house</b>       |           |       |
| Yes                                           | 173       | 80.47 |
| No                                            | 42        | 19.53 |

**Table 4.** Sources of basic knowledge of mosquito-repellent methods (n = 215)

| Source                  | Frequency | %     |
|-------------------------|-----------|-------|
| Television              | 117       | 54.42 |
| Internet search engines | 90        | 41.86 |
| Healthcare workers      | 86        | 40    |
| Social media            | 83        | 38.6  |
| Family or peers         | 49        | 22.79 |
| Print advertisements    | 29        | 13.49 |

Questions on knowledge were on the kinds of mosquito-borne disease, possible modes of transmission, symptoms, mosquito habitat and types of repellents (Table 5). A significant majority had poor knowledge scores at 80.47% (173 participants).

**Table 5.** Knowledge scores on personal mosquito-repellent methods among adult Filipinos (n = 215)

|      | Frequency | %     |
|------|-----------|-------|
| Good | 12        | 5.58  |
| Fair | 30        | 13.95 |
| Poor | 173       | 80.47 |

Interestingly, 85.12% (184 participants) and 89.3% (192 participants) have positive attitude scores with the intention to modify the environment, and health-seeking attitudes, respectively (Table 6). Overall, 92.09 (198 participants) have positive attitude scores.

**Table 6.** Attitude scores on personal mosquito-repellent methods among adult Filipinos (n = 215)

|                                        | Frequency | %     |
|----------------------------------------|-----------|-------|
| <b>Intention to modify environment</b> |           |       |
| Negative                               | 32        | 14.88 |
| Positive                               | 183       | 85.12 |
| <b>Health-seeking behaviors</b>        |           |       |
| Negative                               | 23        | 10.7  |
| Positive                               | 192       | 89.3  |
| <b>Overall Attitude scores</b>         |           |       |
| Negative                               | 17        | 7.91  |
| Positive                               | 198       | 92.09 |

Not surprisingly, among the 215 respondents, there was a vast majority of mosquito-repellent methods used (Table 7). Insecticide sprays (153 respondents, 71.16%) were the most used, followed by mosquito coils (119 respondents, 55.35%), spray-in mosquito repellents with DEET (113 respondents, 55.35%), bed nets (108 respondents, 50.23%), long sleeves and/or pants (62 respondents, 28.84%), electric insect zapper, swatter or racket (62 respondents, 28.84%), essential oils or humidifiers (56 respondents, 26.05%), wearing of light-colored clothing, citronella candles, and mosquito repelling plants (31 respondents each, 14.42% each), patch or stickers (26 respondents, 12.09%), sonic repellents (9 respondents, 4.19%), wristbands or bracelets (8 respondents, 3.72%), and medications such as vitamin B or garlic pills (7 respondents, 3.26%). Although multiple mosquito-repellent methods are employed, only 45.58% (98 respondents), and 50.23% (108 respondents) use of

adult Filipino respondents only use these always and occasionally, respectively (Table 7). More than 90% (202 participants) responded that they will consult health workers for mosquito bites or symptoms of mosquito-borne diseases, while 3% will not consult, and almost 2% will go to a faith healer (Table 7).

**Table 7.** Practices on personal mosquito-repellent methods among adult Filipinos (n = 215)

|                                                                                    | Number of responses (Yes) | %     |
|------------------------------------------------------------------------------------|---------------------------|-------|
| <b>Mosquito-repellent methods used</b>                                             |                           |       |
| Insecticide spray                                                                  | 153                       | 71.16 |
| Mosquito coils                                                                     | 119                       | 55.35 |
| Spray-in mosquito repellent with DEET                                              | 113                       | 52.56 |
| Bed nets                                                                           | 108                       | 50.23 |
| Long sleeves and/or long pants                                                     | 62                        | 28.84 |
| Electric insect zapper, swatter or racket                                          | 62                        | 28.84 |
| Essential oils or humidifiers                                                      | 56                        | 26.05 |
| Light-colored clothing                                                             | 31                        | 14.42 |
| Citronella candles                                                                 | 31                        | 14.42 |
| Mosquito repelling plants                                                          | 31                        | 14.42 |
| Patches or stickers                                                                | 26                        | 12.09 |
| Sonic repellents                                                                   | 9                         | 4.19  |
| Wristbands or bracelets                                                            | 8                         | 3.72  |
| Medications such as vitamin B or garlic pills                                      | 7                         | 3.26  |
| <b>Frequency of practicing mosquito-repellent methods</b>                          |                           |       |
| Frequent                                                                           | 98                        | 45.58 |
| Occasional to rare                                                                 | 108                       | 50.23 |
| Never                                                                              | 9                         | 4.19  |
| <b>Person to consult for mosquito bites or symptoms of mosquito-borne diseases</b> |                           |       |
| Count of Healthcare worker (doctor, nurse, and/or barangay health worker)          | 202                       | 93.95 |
| Faith healer                                                                       | 4                         | 1.86  |
| I will not consult                                                                 | 7                         | 3.26  |

## DISCUSSION

Vector-borne diseases comprise of more than 700,000 deaths per year worldwide, which mostly affect the tropical and subtropical countries, and inexplicably burden the poverty-stricken population remarkably during outbreaks. Substantial health, economic, and social burden are inflicted in the gravely affected geographic areas.<sup>2</sup> In this study, the low knowledge scores highlight the need for health education about the various mosquito-borne diseases, including their transmission,



environmental factors, cutaneous symptoms, and potentially serious side effects. Since college graduates and current students made up the majority of the respondents, fundamental health education may be targeted at these groups.

The World Health Organization (WHO) looks into preventing disease and responding to outbreaks by promoting behavioral change, improving access to water and sanitation, and vector control.<sup>1</sup> Most participants in this study live in areas with ponds, swamps, and other wetland habitats that may be infested by mosquitoes. Furthermore, pit latrines, which can harbor mosquito eggs, are still being used as toilet facilities. Fortunately, given that the majority of participants scored highly on attitude items overall, they are likely to be more inclined to make environmental adjustments and to follow medical recommendations. Given that most respondents reside in concrete houses, it is beneficial to note that one study found that the risk of mosquito bites was reduced in structures with cement walls.<sup>17</sup>

Access to efficacious repellent products can be challenging in developing nations with high rates of mosquito-borne illnesses. As a result, many different traditional and home treatments are utilized by a variety of communities and cultures.<sup>3</sup> Based on their estimated monthly family income, most participants either live on or below the poverty threshold.<sup>18</sup> Inevitably, a minority of the participants used some unconventional mosquito control methods such as mosquito-repelling plants and vitamin B or garlic pills. In more areas, many consumers may still have trouble in choosing the most cost-effective options due to the vast number of products. These may contain diverse active ingredients in different concentrations are available in the market, especially in the modern age where some non-registered ones are sold online.<sup>10</sup> This is supported by the fact that a significant portion of our respondents use internet search engines to find information about mosquito-repellent methods. Some repellents used come in contact with the skin such as patches or stickers, wristbands, bracelets or oils, which may predispose patients to cutaneous diseases such as contact dermatitis.<sup>9</sup>

## CONCLUSION

Data gathered on the knowledge, attitudes, and practices regarding personal mosquito-repellent methods among adult Filipinos, will guide patient education and serve as a reference for future studies on insect- or arthropod bite-related issues in the field of dermatology, particularly at the community level. Beyond treatment, emphasis should be prioritized on prevention and the

promotion of collaborative public efforts, with dermatologists playing a key role in both community and institutional settings.

## RECOMMENDATIONS

Repellent methods for other insects not covered in this research, such as, but not limited to, ants, cockroaches, and ticks, may be further investigated at the community level, and extended to include pediatric and geriatric population.

## REFERENCES

1. World Health Organization. *Vector-borne diseases*. Published 2021. Accessed May 2021. <https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases#:~:text=Key facts,infection transmitted by Anopheline mosquitoes.>
2. Scott TW. Dengue. In: Resh VH, Cardé RT, eds. *Encyclopedia of Insects*. 2<sup>nd</sup> ed. Elsevier; 2009:257-259. doi:10.1016/B978-0-12-374144-8.00078-3
3. Moore EL, Scott MA, Rodriguez SD, et al. An online survey of personal mosquito-repellent strategies. *PeerJ*. 2018;2018(7):1-25. doi:10.7717/peerj.5151
4. Department of Health. *2019 Dengue Monthly Report No. 8*. Published online 2019.
5. Lucas JB. The National Institute for Occupational Safety and Health. *Contact Dermatitis*. 1977;3(2):96-101. doi:10.1111/j.1600-0536.1977.tb03696.x
6. Katz TM, Miller JH, Hebert AA. Insect repellents: Historical perspectives and new developments. *J Am Acad Dermatol*. 2008;58(5):865-871. doi:10.1016/j.jaad.2007.10.005
7. Nolan T, O'Brien K, Farrar J, et al. *SAGE Working Group On Dengue Vaccines And Vaccination*. Published 2018.
8. Elston DM. Prevention of arthropod-related disease. *J Am Acad Dermatol*. 2004;51(6):947-954. doi:10.1016/j.jaad.2004.06.011
9. Nguyen Q-BD, Vu M-AN, Hebert AA. Insect repellents: An updated review for the Clinician. *J Am Acad Dermatol*. Published online 2018. doi:10.1016/j.jaad.2018.10.053
10. Lo WL, Mok KL, Dorothy S, Pui Y. Which insect repellents should we choose? Implications from results of local market survey and review of current guidelines. *Pac J Public Health*. Published online 2018. doi:10.1177/1024907918773630

11. Rodriguez SD, Chung HN, Gonzales KK, et al. Efficacy of some wearable devices compared with spray-on insect repellents for the yellow fever mosquito, *Aedes aegypti* (L.) (Diptera: Culicidae). *J Insect Sci.* 2017;17(1). doi:10.1093/jisesa/iew117
12. Yoon JK, Kim KC, Cho Y, et al. Comparison of repellency effect of mosquito repellents for DEET, citronella, and fennel oil. *J Parasitol Res.* 2015;2015:361021. doi:10.1155/2015/361021
13. Obico J, Ragragio E. A survey of plants used as repellents against hematophagous insects by the Ayta people of Porac, Pampanga Province, Philippines. *Philipp Sci Lett.* 2014;7(2):179-186.
14. Dapar M., Okwori V. E al. Mosquito repellent property of *Azadirachta Indica* extract (fruit bark and seed kernel). *Sci Res J.* 2015;3(6):1-4. [www.scirj.org](http://www.scirj.org)
15. Techavuthiporn C. *Langsat—Lansium Domesticum*. In: Preedy VR, ed. *Handbook of Food Chemistry*. Elsevier Inc.; 2018. doi:10.1016/b978-0-12-803138-4.00036-8
16. Steen CJ, Carbonaro PA, Schwartz RA. Arthropods in dermatology. *J Am Acad Dermatol.* 2004;50(6):819-842l. doi:10.1016/j.jaad.2003.12.019
17. Ngadjeu CS, Doumbe-Belisse P, Talipouo A, et al. Influence of house characteristics on mosquito distribution and malaria transmission in the city of Yaoundé, Cameroon. *Malar J.* 2020;19(1):1-14. doi:10.1186/s12936-020-3133-z
18. Philippine Statistics Authority. *Poverty Statistics Update First Semester 2021*. Published online 2021.

# Knowledge, Attitudes and Practices of Outpatients on Topical Corticosteroid Use in A Tertiary Hospital: A Pilot Study\*

Janice G. Rigos, MD, DPDS<sup>1</sup>; Maria Aurora H. Rosario, MD, FPDS<sup>1</sup>

## ABSTRACT

**Background.** Topical corticosteroids (TCs) form the mainstay of treatment for many skin conditions hence they are the most commonly prescribed drugs by dermatologists and primary care physicians especially in an outpatient setting.<sup>1,2</sup>

**Objectives.** While long term side effects of topical corticosteroids have been studied, this study aims to assess the current knowledge, attitudes, and practices of Dermatology patients on TC use.

**Methods.** This is a descriptive, prospective study that made use of researcher-made questionnaires with 17 questions composed of 3 parts to assess the knowledge, attitudes and practices of the participants. Conducted in Dermatology clinic at a tertiary hospital over a period of 2 months. It utilized purposive sampling technique consisting of newly registered patients with a history of topical corticosteroid application.

**Results.** Out of 52 patients, 50 completed the questionnaires with a 96% response rate. All 50 participants applied topical corticosteroid prior to consultation with ketoconazole + clobetasol propionate cream (n=36) being the most common and 84% are not aware of its corticosteroid content. Our data showed that 30% of the participants believe that TCs have no side effects.

**Conclusions.** This is the first study that has used a validated researcher-made questionnaires to explore the knowledge, attitudes and practices of patients on topical corticosteroids use at the dermatology clinic in a tertiary hospital. The results of this study correlates with the previous studies in terms of poor knowledge, attitude and practices of patients regarding topical corticosteroids. Trained and Board-certified Dermatologists would help to control misuse of topical medications among patients.

**Keywords:** corticosteroids, dermatologists, nonprescription drugs, topical administration, self medication

## INTRODUCTION

Topical corticosteroids (TCs) form the mainstay of treatment for many skin conditions hence they are the most commonly prescribed drugs by dermatologists and primary care physicians especially in an outpatient setting.<sup>1,2</sup> These drugs are generally safe and effective and side effects are rare when used appropriately. Currently available TCs differ widely, and knowledge of such differences is fundamental for proper prescribing practices. It is important to consider the indication, patient's age, potency, frequency, duration, vehicle, site of lesion, severity of disease, and associated adverse effects whenever prescribing topical corticosteroid.<sup>3</sup>

In the Philippines, TCs are easily available as over-the-counter drugs. Unfortunately, these topical drugs are increasingly being abused and misused by patients due to its availability, affordability and immediate effects.<sup>4,5</sup> Unreasonable prescription of TCs can result in unwanted effects.<sup>6</sup> Topical corticosteroids can cause cutaneous side effects such as atrophy, striae, telangiectasia, hypopigmentation, acne, rosacea, perioral dermatitis, and

hypertrichosis, as well as systemic side effects like cataracts, hyperglycemia, and hypothalamic-pituitary-adrenal suppression.<sup>7</sup>

While long term side effects of topical corticosteroids have been studied, the knowledge, attitudes and practices of dermatology outpatients particularly in a tertiary hospital in Pangasinan has not been identified. This study aims to assess the current knowledge, attitudes, and practices of dermatology outpatients of a tertiary hospital. Such data would encourage the improvement of continuing medical education (CME) programs on dermatological therapies and health teaching to patients to ensure their safety.

## Significance

The responsibility to educate patients the proper knowledge, attitudes and practices regarding the use of topical steroids lies primarily with healthcare professionals.<sup>3,7,8</sup> Previous studies have highlighted the severity of topical steroid abuse and its side effects such as atrophy, striae, telangiectasia, hypo and

*Disclosures:* The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.

\*1st Runner-up, RIMC Research Competition 2021; Finalist, PMA Annual Resident Research Contest 2022; RImc Gawad Saliksik Awardee 2023; PDS Research Publications Awardee 2023

<sup>1</sup>Consultant, Department of Dermatology, Region 1 Medical Center, Dagupan City



hyperpigmentation, acne, rosacea, perioral dermatitis, and hypertrichosis.<sup>5,7</sup> Although these side effects were already proven, still, many patients self-medicate with over-the-counter topicals.

Since only few tertiary government hospital caters to patients in Pangasinan and nearby provinces where patients frequently self-medicate, it is essential for primary care physicians and dermatologists to be information-wise in educating them regarding proper application of topical corticosteroids and their side effects thus preventing self-medication.

The results of this study will benefit not just the patients and clinicians but also the institution because the data gathered will improve the quality of care rendered not just by Dermatologists but Non Dermatologists as well.

### Definition of Terms

**Knowledge** – defined as the patient's perception on topical corticosteroids through experience with application

**Attitudes** – defined as the patient's awareness and understanding on how topical medications work

**Practices** – defined as the patient's preferences on the site of application and how to apply topical medications

**Corticosteroids** – defined in this study as a topical medication containing steroids to reduce inflammation and irritation in cream, ointment or lotion form applied directly to the skin

### Objectives

This study aims to assess the knowledge, attitudes and practices among dermatology outpatients on topical corticosteroids use.

### Assessment of Knowledge

1. To identify some of the most commonly used topical steroids based on age, gender, educational status and occupation
2. To identify their main source of the topical steroids used (healthcare professionals including physicians, nurses and pharmacists; social media; websites; family; friends)
3. To identify their knowledge on what topical corticosteroids are used for
4. To evaluate their knowledge on the health hazards of topical corticosteroids
5. To assess their knowledge on how long topical steroids should be applied
6. To know how often should they apply these topicals

### Assessment of Attitude

1. To identify their reasons for using topical steroids
2. To know their perception on topical steroid safety
3. To find out their discernment on the efficacy of topical steroid application
4. To know the effects of topical steroid observed on the applied site

### Assessment of Practice

1. To evaluate their persistence to seek professional consults
2. To know the subjects' areas of topical steroid application
3. To identify their dosing schedule compliance
4. To know if the subjects are applying any emollients during application of topical steroids
5. To know the amount of topicals the subject applied

### REVIEW OF RELATED LITERATURE

Application of self-medicated topical corticosteroids (TC) is an increasing problem encountered by dermatologists and primary care physicians.<sup>3,7</sup> The exact magnitude of the problem is not clear, but there have been recent efforts to quantify the practices among patients.

A multi-center trial from India by Saraswat et al., which screened 2926 patients with facial dermatosis, showed that 433 (14.8%) patients were using TCs over a long period in an unsupervised manner.<sup>4</sup> In this study, TC was being used for various purposes, including fairness/general purpose cream, after shave, and acne.<sup>4</sup> Of note, was the fact that non-physician recommendations for TC were obtained in 257 (59.3%) of the patients, of which more than 90% were for potent/super-potent steroids.<sup>4</sup>

A study conducted by Dr. TS Nagesh in India showed that TCs were prescribed by general practitioners in 302 (49.5%) patients. Friends had suggested these medicines in 191 (31.2%) patients, followed by pharmacists in 71 (11.6%) patients. Others like family members had given the creams in 39 (6.3%) patients. General practitioners are often the first point of contact for most of the patients. Educating the patients regarding steroid abuse would help in reducing the incidence of topical steroid-related side effects.<sup>8</sup>

One study done by Soniya et al (2017) pointed out that majority of their subjects used single agent and Clobetasol propionate 0.05% was the most commonly (164/370; 44.32) abused TC in contrast to some other studies such as Rathod PR, Shankar R, and Sawant's study entitled Clinical study of topical corticosteroids misuse in

which betamethasone valerate 0.1% was the main TC abused.<sup>1</sup>

TCs are frequently misused as fairness creams due to their potent bleaching action and as an anti-inflammatory agent in different dermatoses according to the study done by Soniya Meena et al (2015).<sup>1</sup> Fungal infection in 194 (52.43%) patients was the main reason for using TCs. Other reasons include acne 95 (25.68%), melasma 43 (11.62%), achieving fairness in 31 (8.38%) patients. Furthermore, majority of patients used TC as per advice of pharmacist (129; 34.83%) and only a few patients were TC advised by dermatologists (18/370; 4.87%).<sup>1</sup>

The common side effects found in the study done by Nagesh et al (2016) were acne, pigmentation, redness, itching, burning sensation, striae, and aggravation of existing skin problem. It has also been noted that many of their subjects were not aware of the fact that the problems they were facing were due to the long-term use of steroids.<sup>8</sup>

Locally, there is one case report regarding application of topical corticosteroid entitled "A fatal case of staphylococcal scalded skin syndrome associated with iatrogenic Cushing syndrome due to potent topical steroid application in a 3-month-old female: A case report" by Milana-Martinez JK et al (2018). The case have emphasized the risks related to abuse of steroid-containing preparations and the importance of education to prevent catastrophic outcomes of inappropriate steroid use.<sup>9</sup>

Lastly, the Food and Drug Administration Philippines have recently published an advisory to the public on November, 2019 due to the use of products widely available and sold in the internet and unlicensed establishments.<sup>10</sup> The general public was advised to avoid topical medications without proper consultation from dermatologists.<sup>10</sup>

## METHODS AND MATERIALS

### Study Design

This is a descriptive, prospective study that made use of researcher-made questionnaires reviewed and validated by the Institutional Review Board of Region 1 Medical Center to ensure content relevance, clarity and ethical compliance prior to administration. It is composed of three parts to assess the following: 1) Knowledge on topical corticosteroids, 2) Attitudes on topical corticosteroid application, and 3) Practices on topical corticosteroid.

### Study Setting

This study was conducted in Dermatology Outpatient Clinic at a tertiary institution over a period of two months after approval from the institution's Research Committee.

### Study Population

The study will utilize purposive sampling technique consisting of all newly registered outpatients seen in the Dermatology Clinic of a tertiary hospital with history of topical corticosteroid (whether plain and/or combination) application who meet the inclusion criteria.

### Inclusion Criteria

The study included newly registered dermatology outpatients of ages 18 and above, either male or female, with history of topical corticosteroid (pure and in combination) application in any form and potency continuously for at least 7 days long or intermittently in the past 15 days and beyond with or without previous consultation from another institution were included in this study.

### Exclusion Criteria

Patients ages 17 and below and those with no history of topical corticosteroid (pure and in combination) application in any form and potency, or those with history of previous topical corticosteroid application continuously for 6 days or less in duration or intermittent application in the past 14 days or less are excluded from the study.

Former dermatology outpatients for follow up and those not consenting to answering the questionnaire were also excluded from this study

### Study Procedure

All eligible dermatology patients were asked for history of previous topical corticosteroid use prior to consult.

A survey about the subject's knowledge on the commonly used topical corticosteroids was performed at least two weeks before the start of the actual study. A list of commonly used topical corticosteroid were identified before letting the actual subjects answer the questionnaire.

All qualified subjects for a period of two months were given a validated questionnaire with 17 questions regarding knowledge, attitude and practices on topical corticosteroid use.

In cases where the participant would not want to continue, he or she may withdraw from the study anytime.

All data collected were organized, coded and analyzed using appropriate descriptive and inferential statistical methods to address the study objectives. Frequencies were presented in tables as fractions and percentages.

In line with observing strict ethical standards during the data collection process, the following were considered:

1. All patients were provided the detailed consent form. Only those with signed forms either by patient themselves or immediate guardians were considered as participants of the study
2. Patients and their guardians were informed that they can back out anytime from the study, those who did backout or those who did not participate still received similar standards of care
3. Gifts and financial assistance were not provided to those who did not participate in this investigation
4. All participating patients were assured that their personal information will not be disclosed nor divulged to anyone, including the management of the institution
5. All data collected were stored securely and will be retained for 5 years and subsequently be deleted in compliance with institutional policy.
6. There are no conflicting interests, nor sources of funds. Financial requirements of this research were solely shouldered by the main proponent.

### **Ethical/ Biosafety Clearance**

The study does not involve handling of hazardous specimen or materials which may pose threat to the community, thus this section will not apply.

### **RESULTS**

Out of 52 patients, 50 completed the questionnaires with a 96% response rate (Table 1). The age of the participants ranged from 18-77 years wherein majority of the respondents are 18-27 years of age (n=27, 54%). There were 33 females and 17 male participants. Most respondents are high school graduates (n=33, 66%) who work mostly as housewives (n=25, 24%) followed by students (n=16, 32%). Respondents are all residents of Pangasinan with majority coming from Dagupan City (n=16, 32%).

All 50 participants applied topical corticosteroid prior to consultation with Ketoconazole+Clobetasol Propionate cream (n=36) being the most common and 84% are not aware of its corticosteroid content (Table 2). Among those who applied this cream, most are aged 18-

27 years (n=17), and 23 out of 36 users are females and high school graduates, among them 8 are housewives.

### **KNOWLEDGE**

The participants' knowledge on topical corticosteroid use is presented in Table 3. Most common source of information about topical corticosteroids among patients is from social media (34%, n=17) followed by family members (18%, n = 9) and TV/radio advertisements (16%, n=8). 34 of the participants got their topical corticosteroids from their family and friends (68%, n=34), while 12 (24%) got it from the pharmacy. Only 2 patients got their topical corticosteroids from a dermatologist and 6 patients got it from a general physician.

With regards to the purpose of applying topical corticosteroid, most of the participants think it is for itchiness (n=40) followed by redness (n=11), infection (n=4), pimple/acne (n=4), swelling (n=3) and whitening (n=1). Our data also showed that majority of the participants (30%, n=15) believe that there is no side effects of applying topical corticosteroids and 9 (18%) participants have no idea at all. Participants' knowledge on duration of topical corticosteroids application revealed 50% for 1 week followed by 26% for 1 month application. While for the frequency, most patients got the recommended twice daily application of topical corticosteroids with 38%.

### **ATTITUDES**

Participants' attitudes towards the application of topical corticosteroid is illustrated in Table 4. The main reason for application of corticosteroid among majority of the respondents is for itchiness (n=46) followed by redness (n=10). Some answered infection (n=6), whitening (n=2) and hypopigmentation (n=1). On topical corticosteroid safety, 74% of the participants believe it is safe to apply topical corticosteroids (n=37) while 26% (n=13) think it is not safe.

30 (60%) out of 50 respondents are not satisfied with the outcome of topical corticosteroid application. The most common effect observed on the affected areas is both drying of the skin (n=15) and worsening of the skin condition (n=15) followed by peeling (n=13) and darkening of the skin (n=11). Some also experienced lightening of the affected area (n=6), thinning of the skin (n=5) and stretchmarks (n=1) while 2 answered no side effects observed.

## PRACTICES

The practices of the participants on topical corticosteroid use is showed on table 5. 36 (72%) out of 50 participants do not seek consult before applying topical corticosteroid and the most common reason behind is because of scarcity of time (36%, n=18) followed by no budget for consult (30%, n=15). The 14 participants who seek consult prior application of topical corticosteroids do it every 2 weeks (n=6) or at least monthly (n=6).

Most respondents applied topical corticosteroids on their feet (n=20), back (n=17), face (n=16), hands (n=15), and chest (n=14). The rest of the respondents answered arms, abdomen, legs, axilla, elbow, knees, genital areas and scalp. Most patients applied the topicals for 4 weeks (28%, n=14) followed by 2 weeks (26%, n=13) as frequent as needed (42%, n=21) and majority of them applied the topical corticosteroids without emollients (63%, n=32) while some have used lotion (n=7), oil (n=5), and petroleum jelly (n=30).

## DISCUSSION

Indeed a problem encountered by dermatologists and primary care physicians is the application of self-medicated topical corticosteroids especially in rural areas like in Pangasinan as majority of the participants of this study had been given creams by family members.<sup>3,7</sup> In the study by Soniya et al (2017), they pointed out that majority of their subjects use Clobetasol propionate 0.05% similar with pour result which is Ketoconazole + Clobetasol Propionate cream.

### Knowledge

Participants had a poor general understanding of topical corticosteroids. They mostly got information from social media and are either given by family members or bought without prescription thinking that these topicals have no adverse effects when applied to the skin. Unlike the study by Dr. TS Nagesh in India showed that TCs were prescribed by general practitioners in 302 (49.5%) patients, some by friends (n=191, 31.2%). This could be modified by providing health education from healthcare workers in social media preferably by dermatologists even if the respondents have good understanding on the duration and frequency of topical corticosteroids application.

### Attitudes

Topical corticosteroid use leading to various skin damage is one of the dilemma dermatologists are facing in their practice. Our data showed that majority thinks

these topicals are safe to use with itchiness being the major concern. However most of them are not satisfied with the outcome because their skin condition did not improve. Patients should be warned with the use of these topicals since some thinks it could be used for aesthetic purposes. In the study done by Nagesh et al (2016) it has been noted that their subjects were not aware that their problems were due to the long term effects of topical steroids. In some countries like India<sup>(8)</sup>, there were reported cases of steroid induced dermatitis due to topical corticosteroid misuse for cosmetic purposes.

### Practices

In a study conducted in Jordan involving pharmacy students, it was observed that self medication with topical corticosteroid was very prevalent<sup>(7)</sup> which is similar with the result of this study. This is concerning since most of the respondents applied these topical on different areas of the body that could be very sensitive to corticosteroids without the knowledge on the possible local and systemic effects of topical corticosteroids.

The limitation of this study is the inability to establish a direct association between the health education provided by prescribing physicians and the patients' responses, as the questionnaire was administered only to patients.

## CONCLUSION

This is the first study that has used a validated researcher-made questionnaires to explore the knowledge, attitudes and practices of patients on topical corticosteroids use at the dermatology clinic in a tertiary hospital. The results of this study correlates with the previous studies in terms of poor knowledge, attitude and practice of patients regarding topical corticosteroids. The outcome showed that topical corticosteroids were most often used in conditions where it should be avoided leading to various untoward effects.

With topical corticosteroids being used widely as over-the-counter drugs, especially for wrong indications such as fairness, the role of dermatologists and other healthcare providers becomes important. Although some of the respondents are aware of the adverse effects of TCs, there is still a need to strengthen the clinical awareness on the possible local and systemic effects. Dermatologists and other healthcare providers are still the first point of contact for most of the patients hence training them would definitely help to control misuse of topical medications among patients.



## References

1. Soniya Meena, [Lalit Kumar Gupta](#), [Ashok Kumar Khare](#), [Manisha Balai](#), [Asit Mittal](#), [Sharad Mehta](#), and [Garima Bhatni](#). Topical Corticosteroids Abuse: A Clinical Study of Cutaneous Adverse Effects. *Indian Journal of Dermatology*. 2017; 62(6): 675
2. Amina Mahdy, Nadia Hussain, Doaa Al Khalidi, Amira S A Said . Knowledge, Attitude, and Practice Analysis of Corticosteroid Use Among Patients: A Study Based in The United Arab Emirates. *National Journal of Physiology, Pharmacy, and Pharmacology*. 2017; 7.1234409022017
3. Sarah F. Alsukait, MBBS, Najd M. Alshamlam, MBBS, Zeina Z. Alhalees, MBBS, Sami N. Alsuwaidan, MD, Abdulmajeed M. Alajlan, MD. Topical corticosteroids knowledge, attitudes, and practices of primary care physicians. *Saudi Medical Journal*. 2017.6.17586
4. Saraswat A, Lahiri K, Chatterjee M, Barua S, Coondoo A, Mittal A, et al. Topical corticosteroid abuse on the face: A prospective, multicenter study of dermatology outpatients. *Indian Journal of Dermatology, Venereology and Leprology*. 2011;77:160-6.
5. Sinha, Amit & Kar, Sumit & Yadav, Nidhi & Madke, Bhushan. (2016). Prevalence of Topical Steroid Misuse Among Rural Masses. *Indian Journal of Dermatology*. 61. 119. 10.4103/0019-5154.174081
6. Dr Mohammed Abdullah A Al-Zahrani<sup>1</sup> , Professor Shamsun Nahar<sup>2</sup> , Dr Sami Abdullah Al-Zahrani<sup>3</sup> , Dr Ramzy Ahmed Al-Zahrni<sup>3</sup>. Knowledge, Attitude, and Practice of Primary Care Physicians Regarding Common Dermatological Disorders in Abha City, Kingdom of Saudi Arabia. *International Organization of Scientific Research Journals*. 2017; ISSN: 2319-4219
7. [Karalikkattil T.](#) [Ashique, Feroze](#) [Kaliyadan, Shilpa Mohan, Shreya Vijayan](#), and [Dilip Chandrasekhar](#). Knowledge, Attitudes and Behavior Regarding Topical Corticosteroids in a Sample of Pharmacy Students: A Cross Sectional Survey. *Journal of Indian Association of Dermatologists, Venereologists and Leprologists*. 2018; 9(6): 432–434
8. Nagesh, T & Akhilesh, A. (2016). Topical Steroid Awareness and Abuse: A Prospective Study among Dermatology Outpatients. *Indian Journal of Dermatology*. 2016; 61. 618. 10.4103/0019-5154.193666.
9. Milana-Martinez JK, Coe ER, Zabala DA, Tangtatco JA, Lacuesta-Gutierrez MP. A fatal case of staphylococcal scalded skin syndrome associated with iatrogenic Cushing syndrome due to potent topical steroid application in a 3-month-old female: A case report. *Journal of Philippine Dermatological Society*. 2018; 27(2): 70-73.
10. Food and Drug Administration Philippines. (2019). Incorrect Use of Anti-Fungal Corticosteroid Combination Therapy. FDA Advisory No. 2019-388. Retrieved from <https://www.fda.gov.ph/fda-advisory-no-2019-388-incorrect-use-of-anti-fungal-corticosteroid-combination-therapy>

**Table 1. Demographic characteristics of the participants in a Dermatology Outpatient (N=50)**

| Age (years)          | Frequency (n) | Percent (%) |
|----------------------|---------------|-------------|
| 18-27                | 27            | 54          |
| 28-37                | 10            | 20          |
| 38-47                | 5             | 10          |
| 48-57                | 6             | 12          |
| 58-67                | 1             | 2           |
| 68-77                | 1             | 2           |
| <b>Sex</b>           |               |             |
| Female               | 33            | 66          |
| Male                 | 17            | 34          |
| <b>Education</b>     |               |             |
| College Graduate     | 11            | 22.0        |
| Elementary Graduate  | 5             | 10.0        |
| High School Graduate | 33            | 66.0        |
| Post Graduate        | 1             | 2.0         |
| <b>Occupation</b>    |               |             |
| barber               | 1             | 2.0         |
| driver               | 1             | 2.0         |
| farmer               | 2             | 4.0         |
| fish deboner         | 1             | 2.0         |
| gov't employee       | 2             | 4.0         |
| health care worker   | 3             | 6.0         |
| houseboy             | 1             | 2.0         |
| housewife            | 12            | 24.0        |
| law enforcer         | 1             | 2.0         |
| sales                | 1             | 2.0         |
| sampler              | 1             | 2.0         |
| seaman               | 1             | 2.0         |
| self employed        | 2             | 4.0         |
| student              | 16            | 32.0        |
| unemployed           | 4             | 8.0         |
| waitress             | 1             | 2.0         |
| <b>Address</b>       |               |             |
| Agno                 | 1             | 2.0         |
| Aguilar              | 2             | 4.0         |
| Alaminos             | 1             | 2.0         |
| Bayambang            | 1             | 2.0         |
| Binmaley             | 3             | 6.0         |
| Burgos               | 1             | 2.0         |
| Calasiao             | 6             | 12.0        |
| Dagupan City         | 16            | 32.0        |
| Lingayen             | 4             | 8.0         |
| Mangaldan            | 5             | 10.0        |
| San Fabian           | 1             | 2.0         |
| San Jacinto          | 1             | 2.0         |
| Sta. Barbara         | 4             | 8.0         |
| Urdaneta City        | 4             | 8.0         |

**Table 2. Topical corticosteroid applied prior to consultation**

| Topical Corticosteroid                                               | Frequency (n) | Percent (%) |
|----------------------------------------------------------------------|---------------|-------------|
| BL cream (Ketoconazole+Clobetasol Propionate)                        | 36            | 72          |
| Triderm (Betamethasone Dipropionate+Gentamicin Sulfate+Clotrimazole) | 4             | 8           |
| Halovate (Halobetasol Propionate)                                    | 0             | 0           |
| Dermovate (Clobetasole Propionate)                                   | 9             | 18          |
| Elica lotion/cream/ointment (Momeatasone Furoate)                    | 6             | 12          |
| Tricort (Triamcinolone Acetonide)                                    | 0             | 0           |
| Betnovate (Betamethasone Valerate)                                   | 4             | 8           |
| Desowen (Desonide)                                                   | 0             | 0           |
| Cortizan (Hydrocortisone)                                            | 1             | 2           |
| Others                                                               | 2             | 4           |
| <b>Awareness of Content</b>                                          |               |             |
| Yes                                                                  | 8             | 16          |
| No                                                                   | 42            | 84          |

**Table 3. knowledge on topical corticosteroids use**  
**Q1. Source of topical corticosteroids information**

|                            | Frequency (n) | Percent (%) |
|----------------------------|---------------|-------------|
| Social media               | 17            | 34.0        |
| TV/Radio advertisements    | 8             | 16.0        |
| Posters                    | 2             | 4.0         |
| Others: Family             | 9             | 18.0        |
| Others: Friends            | 5             | 10.0        |
| Others: Healthcare workers | 7             | 14.0        |
| Others: Neighbor           | 2             | 4.0         |
| Total                      | 50            | 100.0       |

**Q2. Source of topical corticosteroids**

|                                                                                     | No | Yes |
|-------------------------------------------------------------------------------------|----|-----|
| Dermatologist/ <i>Espesyalista ng sakit sa balat</i>                                | 48 | 2   |
| Doctor but not Dermatologist/ <i>Doktor na hindi espesyalista ng sakit sa balat</i> | 44 | 6   |
| Nurse/ <i>Nars</i>                                                                  | 50 | 0   |
| Pharmacist/ <i>Parmasyutiko</i>                                                     | 38 | 12  |
| Family or friends/ <i>Kamag-anak o kaibigan</i>                                     | 16 | 34  |
| Beautician or Salon/ <i>Mga nagtatrabaho sa salon</i>                               | 49 | 1   |

**Q3. Purpose of applying topical corticosteroids**

|                                    | No | Yes |
|------------------------------------|----|-----|
| Whitening/ <i>Pampaputi</i>        | 49 | 1   |
| Itchiness/ <i>Pangangati</i>       | 10 | 40  |
| Redness / <i>Pamumula</i>          | 39 | 11  |
| Infection/ <i>Inpeksyon</i>        | 44 | 6   |
| Pimples or Acnes/ <i>Tagihawat</i> | 46 | 4   |
| Swelling/ <i>Pamamaga</i>          | 47 | 3   |

**Q4. Awareness of side effects**

|                                                | No | Yes |
|------------------------------------------------|----|-----|
| Itchiness/ <i>Pangangati</i>                   | 38 | 12  |
| Burning sensation/ <i>Paghapdi ng balat</i>    | 39 | 11  |
| Thinning of the skin/ <i>Pagnipis ng balat</i> | 46 | 4   |
| Darkening/ <i>Pangingitim</i>                  | 46 | 4   |
| Lightening/ <i>Pamumuti</i>                    | 45 | 5   |
| Infection/ <i>Inpeksyon</i>                    | 48 | 2   |
| None/ <i>Wala</i>                              | 35 | 15  |
| I don't know/ <i>Hindi ko alam</i>             | 41 | 9   |

**Q5. Duration of application**

|                                | Frequency | Percent |
|--------------------------------|-----------|---------|
| 1 week/ <i>Isang lingo</i>     | 25        | 50.0    |
| 2 weeks/ <i>Dalawang lingo</i> | 8         | 16.0    |
| 1 month/ <i>Isang buwan</i>    | 13        | 26.0    |
| Others                         | 4         | 8.0     |
| Total                          | 50        | 100.0   |

**Q6. Frequency of application**

|                                                  | Frequency | Percent |
|--------------------------------------------------|-----------|---------|
| Once daily/ <i>Isang beses sa isang araw</i>     | 14        | 28.0    |
| Twice daily/ <i>Dalawang beses sa isang araw</i> | 19        | 38.0    |
| As needed/ <i>Kung kinakailangan</i>             | 16        | 32.0    |
| Others                                           | 1         | 2.0     |
| Total                                            | 50        | 100.0   |

**Table 4. Attitudes on topical corticosteroids use****Q7. Reason for topical corticosteroid application**

|                              | No | Yes |
|------------------------------|----|-----|
| Whitening/ <i>Pampaputi</i>  | 48 | 2   |
| Itchiness/ <i>Pangangati</i> | 4  | 46  |
| Redness/ <i>Pamumula</i>     | 40 | 10  |
| Infection/ <i>Inpeksyon</i>  | 44 | 6   |
| Others                       | 49 | 1   |

**Q8 Safety of topical corticosteroid application**

|       | Frequency (n) | Percent (%) |
|-------|---------------|-------------|
| Yes   | 37            | 74.0        |
| No    | 13            | 26.0        |
| Total | 50            | 100.0       |

**Q9. Satisfaction with the outcome**

|       | Frequency (n) | Percent (%) |
|-------|---------------|-------------|
| Yes   | 20            | 40.0        |
| No    | 30            | 60.0        |
| Total | 50            | 100.0       |

**Q10. Effects observed on the applied site**

|                                                     | No | Yes |
|-----------------------------------------------------|----|-----|
| Lightening of the skin/ <i>Pamumuti ng balat</i>    | 44 | 6   |
| Darkening of the skin/ <i>Pangingitim ng balat</i>  | 39 | 11  |
| Dryness/ <i>Panunuyo ng balat</i>                   | 35 | 15  |
| Peeling/ <i>Pagbabalat</i>                          | 37 | 13  |
| Worsening of condition/ <i>Paglala ng kondisyon</i> | 35 | 15  |
| Thinning of the skin/ <i>Pagnipis ng balat</i>      | 45 | 5   |
| Stretchmarks                                        | 49 | 1   |
| No effect                                           | 48 | 2   |

**Table 5. Practices on topical corticosteroid application****Q11. Consult before application of topical corticosteroid**

|       | Frequency (n) | Percent (%) |
|-------|---------------|-------------|
| Yes   | 14            | 28.0        |
| No    | 36            | 72.0        |
| Total | 50            | 100.0       |

**Q12. Frequency of consult**

|                                            | Frequency (n) | Percent (%) |
|--------------------------------------------|---------------|-------------|
| No answer                                  | 36            | 72.0        |
| Weekly/ <i>Linggo-linggo</i>               | 2             | 4.0         |
| Every 2 weeks/ <i>Kada dalawang linggo</i> | 6             | 12.0        |
| Monthly/ <i>Buwan-buwan</i>                | 6             | 12.0        |
| Total                                      | 50            | 100.0       |

**Q13. Reason for self medication**

|                                                                                      | Frequency (n) | Percent (%) |
|--------------------------------------------------------------------------------------|---------------|-------------|
| No answer                                                                            | 13            | 26.0        |
| I do not have time/ <i>Wala akong panahon</i>                                        | 18            | 36.0        |
| I have no payment/ <i>Wala akong pambayad</i>                                        | 15            | 30.0        |
| There is no reason to consult a doctor/ <i>Walang dahilan para pumunta sa doctor</i> | 2             | 4.0         |
| Others: Due to pandemic                                                              | 2             | 4.0         |
| Total                                                                                | 50            | 100.0       |

**Q14: Areas of application**

|                                                  | No | Yes |
|--------------------------------------------------|----|-----|
| Face/ <i>Mukha</i>                               | 34 | 16  |
| Chest/ <i>Dibdib</i>                             | 36 | 14  |
| Abdomen/ <i>Tiyan</i>                            | 38 | 12  |
| Back/ <i>Likod</i>                               | 33 | 17  |
| Arms/ <i>Braso</i>                               | 37 | 13  |
| Axilla/ <i>Kili-kili</i>                         | 44 | 6   |
| Elbows/ <i>Siko</i>                              | 44 | 6   |
| Hands/ <i>Kamay</i>                              | 35 | 15  |
| Legs/ <i>Hita</i>                                | 38 | 12  |
| Knees/ <i>Tuhod</i>                              | 46 | 4   |
| Feet/ <i>Paa</i>                                 | 30 | 20  |
| Genital areas/ <i>Maselang bahagi ng katawan</i> | 48 | 2   |
| Others: scalp                                    | 48 | 2   |

**Q15. Duration of application**

|          | Frequency (n) | Percent (%) |
|----------|---------------|-------------|
| 1 week   | 10            | 20.0        |
| 2 weeks  | 13            | 26.0        |
| 3 weeks  | 1             | 2.0         |
| 4 weeks  | 14            | 28.0        |
| 8 weeks  | 5             | 10.0        |
| 12 weeks | 4             | 8.0         |
| 16 weeks | 1             | 2.0         |
| 24 weeks | 2             | 4.0         |
| Total    | 50            | 100.0       |

**Q16. Frequency of application**

|                                                  | Frequency (n) | Percent (%) |
|--------------------------------------------------|---------------|-------------|
| Once daily/ <i>Isang beses sa isang araw</i>     | 8             | 16.0        |
| Twice daily/ <i>Dalawang beses sa isang araw</i> | 20            | 40.0        |
| As needed/ <i>Kung kinakailangan</i>             | 21            | 42.0        |
| Others                                           | 1             | 2.0         |
| Total                                            | 50            | 100.0       |

**Q17. Other products applied with topical corticosteroid**

|                         | Frequency (n) | Percent (%) |
|-------------------------|---------------|-------------|
| None/ <i>Wala</i>       | 32            | 64.0        |
| Lotion/ <i>Losyon</i>   | 7             | 14.0        |
| Petroleum jelly         | 3             | 6.0         |
| Oil/ <i>Langis</i>      | 5             | 10.0        |
| Others: <i>Katialis</i> | 1             | 2.0         |
| Powder                  | 2             | 4.0         |
| Total                   | 50            | 100.0       |



## Clinical Profile and Selected Viral Genome Sequence Analysis of SARS-CoV-2 Infected Pediatric Patients in a Tertiary Military Hospital in Quezon City from January 2021-July 2023: A Cross-Sectional Study\*

Deen Mark G. Toroy, MD, DPPS

### ABSTRACT

**Background:** SARS-CoV-2 displays distinct characteristics in terms of virulence and disease severity in pediatric population. Hence, patient's clinical profile and viral genome may contribute to patient's symptoms and disease severity.

**Objectives:** To determine the clinical profile and to analyze selected viral genome sequence of pediatric patients infected with SARS-CoV-2 in a Tertiary Military Hospital in Quezon City from January 2021 – July 2023.

**Methods:** This is a single center cross sectional study determining the SARS-CoV-2 infected pediatric patients' clinical profile consisting of age, sex, residence, comorbidities, presenting symptoms, hospitalization and disease severity. Selected samples were subjected to next generation sequencing to analyze the SARS-CoV-2 genome sequence. All data were recorded with utmost confidentiality.

**Results & Conclusion:** From January 2021 to July 2023, a total of 630 pediatric patients who got tested for SARS-CoV-2 RT-PCR were confirmed to have SARS-CoV-2. Two hundred thirty nine (239) were included in this study. Among the study population, 61.51% were male, more than 60% were less than 4 years old and residing in Quezon City. In terms of clinical presentation, 78% had mild symptoms, 20% had radiologic findings of pneumonia, 40% presented with fever, 12% with diarrhea, and 8% with dyspnea. Ten percent (10%) of patients had concomitant seizure disorder. More than 70% were admitted to the hospital and all of the study subjects recovered from the illness. Only ten samples were subjected to next generation sequencing and all were Omicron variants. Majority of the SARS-CoV-2 virus belong to Clade 22B and 23E; and identified pangolin lineages were BA.5.2, BA.2.3.20, XBB.1.5, GJ.1.2 and FL.23.2.

Keywords: SARS-CoV-2, next generation sequencing, viral variants, clinical outcomes

### INTRODUCTION

The novel coronavirus, SARS-CoV-2, has led to a highly contagious disease that cause a pandemic worldwide. The virus rapidly spreads and evolves as it course from one continent to the other. It was also observed that several strains of this virus cause different clinical symptoms in different patients. Most notable are the *alpha*, *beta*, *gamma*, *delta* and *omicron* variants. Interestingly, infected pediatric population presented different clinical outcomes compared to adults with different strains of virus.<sup>1</sup> During the pandemic, researches on SARS-CoV-2 and their clinical impact then became an interesting field in epidemiology and infectious disease. There are several published researches on SARS-CoV-2 and their outcomes, likewise there are several published researches on the limited genome sequence analysis of SARS-CoV-2 in the Philippines. However, these researches are gathered in the adult population. There is no published research paper yet dedicated to SARS-CoV-2 and their clinical symptoms on pediatric population in the Philippines. Hence, this research was created to investigate the clinical profile of SARS-CoV-2 infected

pediatric population and even further look into their viral genome sequences.

Due to the rapid development of technology, specifically in the field of molecular biology, next generation sequencing (NGS) was developed in studying viral evolution. The use of NGS technology has become a widely accepted method for outbreak tracking and genomic epidemiology.<sup>1</sup> Detecting new mutations in SARS-CoV-2 allows the researchers to reconstruct unknown routes of infection and provide a molecular basis for SARS-CoV-2 diagnostic development, vaccine design and drug discovery.<sup>2,3</sup> Hence, viral genomic diversity become an important field in determining viral virulence, transmissibility and disease severity.

There were several researchers worldwide reporting the NGS of SARS-CoV-2 and correlating their clinical symptoms. In the Philippines, coding of SARS-CoV-2 genome was first initiated in August 30, 2020.<sup>4</sup> But due to its high cost and rarity, limited specimen were subjected to NGS.<sup>4</sup> In recent times, there were little researches on SARS-CoV-2 genomic sequence in the Philippine settings,<sup>4</sup> more so in the pediatric population.

---

*Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.*

\* **Armed Forces of the Philippines Medical Center – Victoriano Luna General Hospital, Victoriano Luna Avenue, Quezon City, Philippines**

Thus, this research aims to determine the clinical profile of SARS-CoV-2 infected pediatric patients and analyze selected viral genome sequence in a tertiary military hospital in Quezon City. Determining this genome profile will be a vital data that will contribute in the study of SARS-CoV-2 viral evolution in pediatric population in the Philippines. Data in this research could be of a great value in future reference, especially in the field of epidemiology and vaccine development.

## OBJECTIVES

### General Objectives

To determine the clinical profile and to analyze the selected viral genome sequence of pediatric patients infected with SARS-CoV-2 in a Tertiary Military Hospital in Quezon City from January 2021 – July 2023.

### Specific Objectives:

1. To determine the clinical profile of patients infected with SARS-CoV-2 in a military hospital in Quezon City from January 2021 – July 2023:
  - a. Age
  - b. Sex
  - c. Place of Residence
  - d. Comorbidities
  - e. Presenting Symptoms
  - f. Hospitalization
  - g. Disease severity
2. To analyze the SARS-CoV-2 genome sequence of selected pediatric population using next generation sequencing in a Tertiary Military Hospital in Quezon City from January 2021 – July 2023.

## ETHICAL CONSIDERATION

Whole-genome sequencing was performed by collecting the oropharyngeal / nasopharyngeal samples that were collected in the context of routine diagnosis. No additional samples were collected for this study. Clinical profiles were retrieved from the medical files and anonymized before analysis. Ethical approval was obtained from the AFP Medical Center Research Ethics Committee.

## REVIEW OF RELATED LITERATURE

During the late December 2019, a novel coronavirus was detected in Wuhan, China. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has become a global concern taking millions of life throughout the globe.<sup>5</sup> The novel virus is capable of rapid transmission through the respiratory epithelium that

infects every population that varies from age, race and gender.

This virus is detected through Reverse Transcription Polymerase Chain Reaction (RT PCR) collected from samples of the oral and nasal area of patients.<sup>5</sup> But during the pandemic, the virus evolved, from subvariants that causes minimal symptoms to severe and critical outcomes. Disease morbidity and mortality differs from different variants, e.g. the delta variants was more virulent and capable of infecting the pediatric population.<sup>6</sup> Hence, the use of next generation sequencing (NGS), a technology used to investigate the genetic makeup of all living forms capable of sequencing billions of nucleic acid fragments simultaneously has been widely use in studying viral variants.<sup>7</sup>

According to the Philippine Pediatric Society (PPS) most children and adolescents infected with SARS-CoV-2 present with mild to moderate symptoms and only a small percentage (0.9%) of patients develop severe and critical disease.<sup>8</sup> There are several theories formulated attempting to explain the difference in severity and susceptibility of children compared to adults that includes reduced number of ACE 2 receptors and immature immune systems.<sup>8</sup>

However it was observed that weekly COVID-19 hospitalization rates in children and adolescents have varied throughout the pandemic.<sup>9</sup> Peaking initially in January 2021 (1.5 per 100,000 population), again in September 2021 with predominance of the Delta (B.1.617.2) variant (1.8 per 100,000 population), and then again in January 2022 with predominance of the Omicron variant (7.1 per 100,000 population). These differences in viral peak opened up a new door of possible different outcomes with different strains of viruses.<sup>9</sup> The viral genomic sequencing may posed a great potential in the field of epidemiology and medicine.

Infected pediatrics patient's clinical profile may greatly contribute to their outcome, this include age, sex, comorbidities and their initial presentation.<sup>8</sup> On the contrary, viral strains may not affect the outcome of most patients, but the COVID-19 variants lead to different outcomes manifesting a unique behavior.<sup>9</sup> This may indicate that SARS-CoV-2 viral genomic diversity could be a key in their viral virulence.

Like other viruses, SARS-CoV-2 evolves over time. Most mutations in the SARS-CoV-2 genome have no impact on viral function. However the following notable SARS-CoV-2 variants has different clinical outcomes.<sup>10</sup> The Alpha (B.1.1.7 lineage) was first identified in the United Kingdom in late 2020 and subsequently became the first globally dominant variant. Alpha was

approximately 50 to 75 percent more transmissible than previously circulating strains and it was associated with greater disease severity.<sup>10</sup>

Another is the Beta (B.1.351 lineage), also known as 20H/501Y.V2, was identified and predominated in South Africa in late 2020.<sup>10</sup> The main concern with Beta variant was immune evasion: convalescent and post-vaccination plasma did not neutralize viral constructs with Beta spike protein as well as those with wild-type spike protein.

The Gamma (P.1 lineage), known as 20J/501Y.V3, was first identified in Japan in December 2020. Main concern with this variant is several mutations increasing concern about increased transmissibility and an impact on immunity.<sup>10</sup>

The Delta (B.1.617.2 lineage) lineage was first identified in India in December 2020 and been the most prevalent variant worldwide until emergence of the Omicron variant. Delta variant was more transmissible and was associated with a higher risk of severe disease, hospitalization and death.<sup>10</sup>

Lastly, the Omicron (B.1.1.529) was first reported from Botswana and very soon thereafter in South Africa in November 2021. Sublineages of this variant have increasingly greater replication advantages and faster spread, however the risk of severe disease or death with Omicron infection is lower than with prior variants of concern.<sup>10</sup>

### **COVID 19 in Pediatric Population**

During the Omicron dominant periods, weekly hospitalization rates were particularly high in infants younger than six months and in children age six months through four years, who were not eligible for vaccination until June 2022.<sup>11</sup>

Among children age 5 to 11 years (who became eligible for vaccination in early November 2021), hospitalization rates were approximately twice as high in unvaccinated than in vaccinated children (19 versus 9 per 100,000) during the period of early Omicron predominance (December 19, 2021 to February 28, 2022). Higher proportions of unvaccinated than fully vaccinated adolescents had COVID-19 as the primary reason for hospitalization (70 versus 41 percent) and required intensive care (30 versus 16 percent).<sup>11</sup>

Several studies support that, COVID-19 disease severity may be related to the strain of SARS-CoV-2. In observational studies in children and adolescents, the rates of admission to the ICU and mechanical ventilation were lower with the Omicron than the Delta variant.<sup>11</sup>

In recent times, the cases of COVID 19 in our country are closely monitored including the variants that is currently dominant. The use of NGS technology has become a widely accepted method for outbreak tracking and genomic epidemiology.

### **SIGNIFICANCE OF THE STUDY**

This is one of the novel studies in the Philippines using next generation sequencing (NGS) to determine the SARS-CoV-2 genome sequence infecting pediatric patient in a tertiary military hospital. This paper may strengthen the importance of determining viral genome as a guide in the management and predicting outcomes of COVID-19 infected pediatric patients. This will greatly contribute to the contemporary studies worldwide on SARS-CoV-2 variants, the demographics they infect and their clinical symptoms. This can also serve as a literature in other future studies on SARS-CoV-2 genome sequencing and their clinical symptoms. Furthermore, this paper emphasized the importance of NGS and molecular biology in studying viral evolution as a part of diagnostic, therapeutic and vaccine development.

In the field of pediatrics, specifically during the COVID-19 pandemic, the viral NGS result was one of the vital data that contribute to the study of the virus. The different viral genome was correlated to the variant, and each variants display distinct characteristics and outcomes. With the aid of NGS, medical personnel become aware of the circulating virus variant and their behavior. This data helps in planning and formulation of strategies by our medical front-liners, especially during the virulent waves of delta and gamma, wherein healthcare providers become wary and vigilant as cases are expected to be moderate to severe. On the other hand, during the omicron wave, medical personnel expect a spike in number of infected patients but generally milder cases. With the advent of molecular technology, our understanding of infectious disease become wider and critical. We can identify the genetic make-up of pathogens and correlate it to their virulence. We can develop vaccines congruent to their specific molecular structures. The future of medical research maybe gearing towards understanding the genomic characteristics of the pathogen and its host, and this research is one of those paper pioneering this molecular approach.

### **SCOPE AND LIMITATION**

This is a single center cross sectional study assessing the clinical symptoms of SARS-CoV-2 infected pediatric patients in a tertiary military hospital. This involves all pediatric patients seen in V Luna Medical

Center from January 2021 – July 2023 that underwent SARS-CoV-2 RT PCR which revealed positive. In addition, selected samples were subjected to next generation sequencing for analysis. The major limitation of this study is the small number of sample, 10 sequences, hence testing association with other variables were not possible.

## METHODOLOGY

### *Study Design*

This is a single center cross sectional study determining SARS-CoV-2 genome sequence and patients' clinical profile in V Luna Medical Center from January 2021 to July 2023. Samples of throat and nasal swabs underwent SARS-CoV-2 RT-PCR and selected samples were subjected to next generation sequencing processed by Armed Forces Research Institute of Medical Sciences (AFRIMS).

### *Study Population and Setting*

Sample population composed of pediatric patients positive for SARS-CoV-2 RT PCR tested in V Luna Medical Center from January 2021 to July 2023. Their demographic and clinical data were retrieved from medical files, including the general data, symptoms, and course of the disease. In addition, selected SARS-CoV-2 RT PCR positive samples with Cycle Threshold of <30 underwent next generation sequencing.

### *Sample Collection*

Nasopharyngeal and oropharyngeal swabs were collected using Dacron-tipped swabs by clinical personnel.<sup>12</sup> Samples were collected from pediatric patients under investigation for COVID-19, patients seeking clinical care and showing signs of COVID-19-like illness.<sup>12</sup> Swabs were stabilized in various Universal Transport Media (Copan, CA, USA; Sansure Biotech, Hunan, China; and Sanli, Liuyang, China), temporarily stored at 4°C, transferred to freezers ( $-80 \pm 20^\circ\text{C}$ ), and tested within 24 to 72 hours.<sup>12</sup>

### *SARS-CoV-2 Real-Time RT-PCR Testing*

Nasopharyngeal and oropharyngeal swabs were collected by clinical staff and rRT-PCR testing was performed. The swabs were heat inactivated at 65°C for 10 minutes and viral RNA was extracted using the NATCH CS automated nucleic acid extraction machine (Sansure Biotech, Hunan, China) or manual RNA extraction kits: QIAmp viral RNA mini kit (Qiagen, Germantown, MD, USA), Sansure RNA one-step nucleic acid release reagent (Sansure, Biotech, Hunan, China), and GenAmplify RNA

extraction kit (Manila HealthTek, Manila, Philippines) following manufacturers' instructions.<sup>12</sup> Briefly, specimens were thawed and an aliquot of 200  $\mu\text{L}$  (Sansure) or 140  $\mu\text{L}$  (QIAmp and GenAmplify) of each specimen was used for RNA extraction and eluted in 50  $\mu\text{L}$  following manufacturer's instructions of each kit.<sup>12</sup> The following SARS-CoV-2 rRT-PCR kits were used following testing conditions and CT cutoff values indicated by each manufacturer: Sansure (Sansure Biotech, Hunan, China), 40 CT; BGI Genomics (Shenzhen, China), 37 CT; modified Berlin assay, 38 CT; and modified U.S. Centers for Disease Control and Prevention (CDC, USA) assay, 38 CT. The extracted nucleic acid was amplified using the following PCR machines: ABI 7500 (Applied Biosystems, CA, USA), QuantStudio 7 (Applied Biosystems, CA, USA), SLAN96P (Sansure Biotech, Hunan, China), and MA6000 (Sansure Biotech, Hunan, China).<sup>12</sup> Selected specimens also underwent GeneXpert PCR SARS-CoV-2 testing.

### *SARS-CoV-2 Genome Sequencing and Phylogenetic Analysis*

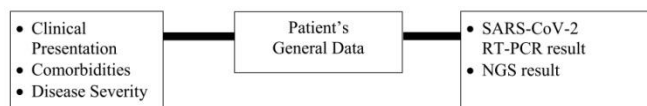
SARS-CoV-2 genome from 10 selected positive specimens (CT < 30) were sequenced in the in-house molecular laboratory, using a iSeq (Illumina, USA), the results of which were reported and described<sup>12</sup> (Table 1).

### *Phylogenetic Analysis*

Phylogenetic analysis was performed using sequences from this study and sequences retrieved from GenBank and GISAID databases on August 24, 2020.<sup>12</sup> The tree was generated using IQ-tree v.1.6.12 using the generalized time-reversible (GTR + F + I) model and 1,000 bootstrap replicates. Multiple sequence alignments were performed using "Multiple Alignment using Fast Fourier Transform" v7.407 with the default setting.<sup>12</sup> The phylogenetic tree was drawn with FigTree v1.4.4 and lineage was determined using Pangolin v.2.0.4 (github.com/cov-lineages/pangolin), including the lineage and the clade of the 23 coding-complete genome sequences from this study.<sup>12</sup> The genome comparisons to the Wuhan-Hu-1 reference genome (GenBank accession number NC\_045512.2) were visualized using BRIG v0.95.<sup>12</sup>

## Conceptual Framework

**Figure 1:** Shows the correlation of SARS-CoV-2, patient's clinical profile and NGS data





#### Inclusion Criteria:

1. All pediatric patient 18 years old and below who consulted in VLMC from January 2021 – July 2023.
2. All pediatric patient who were positive with SARS-CoV-2 RT-PCR with and without symptoms.
3. All pediatric patient who were positive for SARS-CoV-2 RT-PCR and underwent next generation sequencing of SARS-CoV-2.

#### Exclusion Criteria:

1. Non pediatric age group
2. Positive for SAR-CoV-2 RT-PCR done outside VLMC

#### Operational Definition of Terms

**SARS-CoV-2.** The novel coronavirus is the main variable of concern in this paper and includes, determination of its variants and their clinical outcomes in pediatric population.

**Reverse Transcription Polymerase Chain Reaction (RT-PCR).** RT-PCR is the diagnostic test for SARS-CoV-2, all subjects in this paper were positive for SARS-CoV2 RT-PCR before proceeding to NGS.

**Next Generation Sequencing (NGS).** Selected subjects in this paper underwent NGS in order to identify the SARS-CoV-2 genomic make-up and viral variants. Qualified samples are those with cycle threshold (CT) value of <30.

#### Data Collection

Epidemiological, clinical, and disease severity data were extracted from electronic medical records provided by V Luna Medical Center Record Section and Department of Pediatrics Database. All data of patient's NGS was provided by the AFRIMS. All data records were matched with previously assigned sample IDs and used as anonymized dataset for downstream analyses. All data collected will be treated with utmost confidentiality.

#### Statistical Interpretation

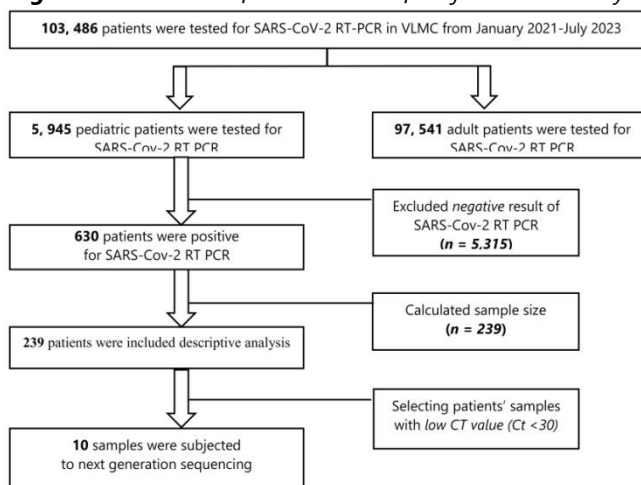
Measures of central tendency/dispersion and proportion were used to describe quantitative and categorical variables.

## RESULTS

From January 2021 to July 2023, the Department of Pathology and Laboratory of V Luna Medical Center tested 103, 486 patients for SARS-CoV-2 RT-PCR, among which 5,945 (5.7%) were pediatric patients. Six hundred thirty (10%) pediatric patients were positive for SARS-

CoV-2. And only 10 (1.5%) pediatric patients were subjected to next generation sequencing.

**Figure 2: Flow chart of the selection of subjects in the study.**



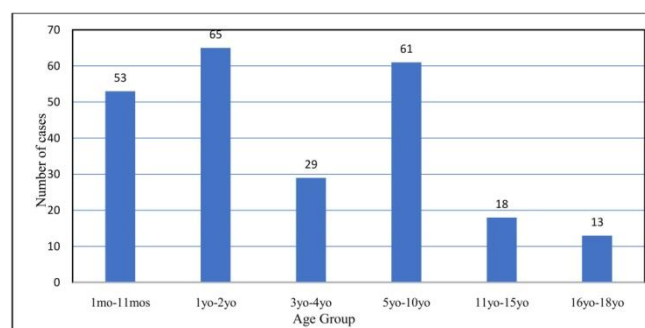
A total of 239 patients were included in the study, and majority were male 61.51% (n = 147) vs female 38.49% (n = 92) as shown below (Table 1).

**Table 1:** Shown is the sex distribution of subjects included in the study

| Gender | f   | %     |
|--------|-----|-------|
| Male   | 147 | 61.51 |
| Female | 92  | 38.49 |

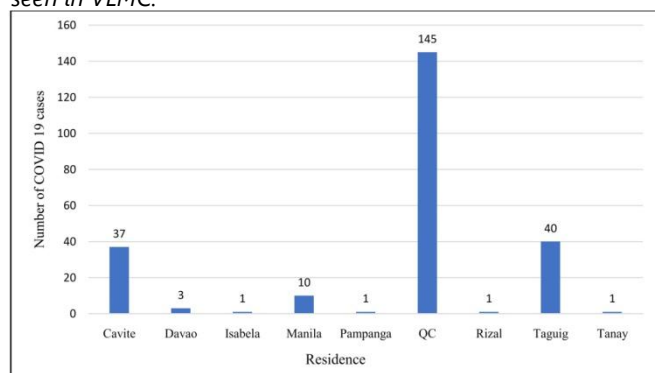
Majority of the subjects were less than 4 years old. One to two years old comprised 27% (n=65), 1mo-11mos 22% (n=53) and 3-4 years old (n=29) as shown in Figure 3 below.

**Figure 3: Age distribution of pediatric COVID 19 cases seen in VLMC.**



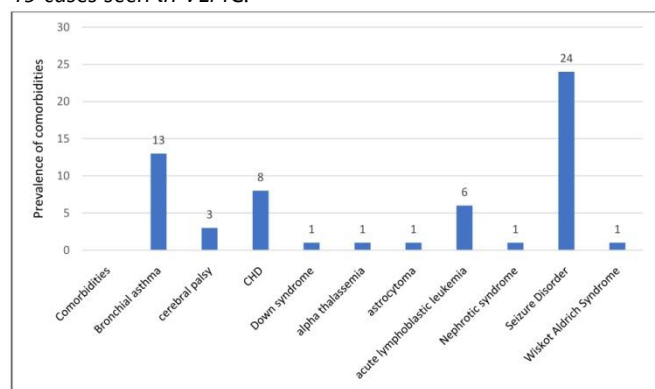
Most of the patients were from Quezon City 60.67% (n = 145), followed by Taguig 16.74% (n = 40) and Cavite 15.48% (n = 37) as shown below (Figure 4).

**Figure 4:** Residence distribution of pediatric COVID 19 cases seen in VLMC.



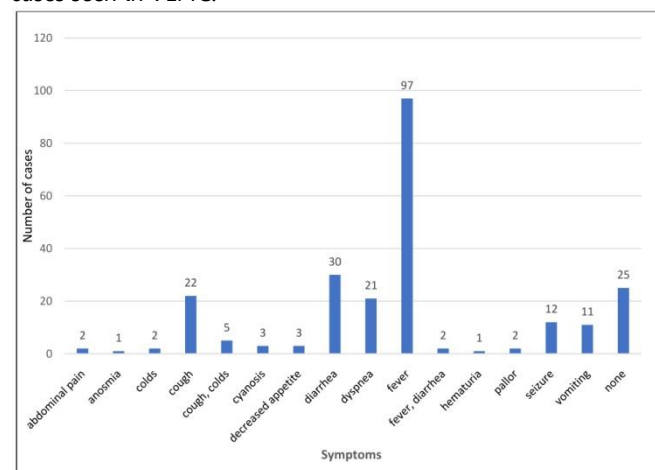
A quarter of the patients has comorbidities 38% (n = 59) while those with no comorbidities comprised 61% (n = 180) as shown below (Figure 5).

**Figure 5:** Prevalence of comorbidities among pediatric COVID 19 cases seen in VLMC.



Most of the patients presented with fever 40% (n = 97) followed by diarrhea 12% (n = 30), cough 9% (n = 22) and dyspnea 8% (n = 21) as shown below (Figure 6).

**Figure 6:** Distribution of symptoms of pediatric COVID 19 cases seen in VLMC.



Majority of the patients were admitted comprising 76% (n = 183) while 23% (n = 56) were advised for home isolation as shown below (Table 2).

**Table 2:** Shown is the number of subjects who were admitted in the hospital

| Hospitalization | f   | %     |
|-----------------|-----|-------|
| Yes             | 183 | 76.57 |
| No              | 56  | 23.43 |

Most of the patients present with mild symptoms, 78% (n = 187), followed by moderate symptoms 20% (n = 49) and 1% (n = 3) had severe symptoms as shown below (Table 3).

**Table 3:** Shown is the disease severity distribution of subjects included in the study.

| Disease Severity | f   | %     |
|------------------|-----|-------|
| Mild             | 187 | 78.24 |
| Moderate         | 49  | 20.50 |
| Severe           | 3   | 1.26  |

More than half of the patients 61% (n = 148) had normal chest X-ray results, while 20% (n = 50) have pneumonia as shown below (Table 4).

**Table 4:** Shown is the chest x-ray results of subjects included in the study.

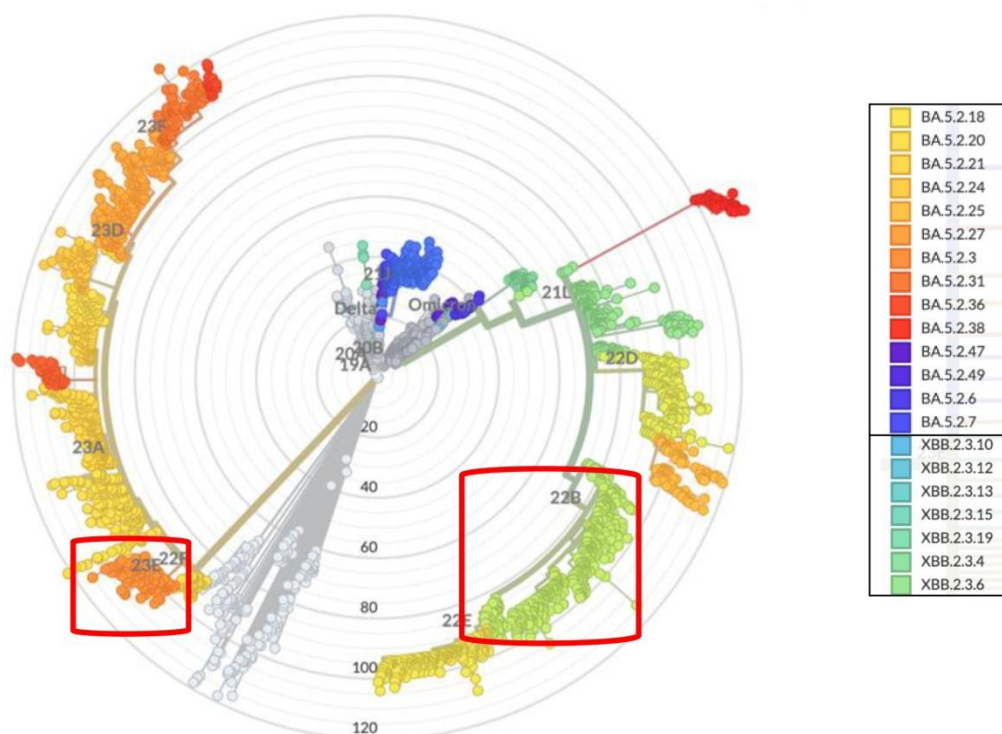
| Chest X-ray  | f   | %     |
|--------------|-----|-------|
| Pneumonia    | 50  | 20.92 |
| Cardiomegaly | 3   | 1.26  |
| Normal       | 148 | 61.92 |
| Not done     | 38  | 15.90 |

Out of 239 SARS-CoV-2 positive patients, only ten (10) samples were subjected to NGS Illumina iSeq100™. NGS was only done for specimen with low cycle threshold value (CT value < 30) that correlates to high viral load (equivalent to ~10,000–100,000 viral genome copies/mL) (Table 7).<sup>7</sup> Genome-wide characterization of SARS-CoV-2 isolates from 10 samples collected, generated 10 high-quality sequences using iSeq (Illumina, USA) as shown in Table 6. These ten samples revealed Ct value of less than 30: specimen (1) 27.11 – 28.27; specimen (2) 20.78 – 20.68; specimen (3) 15.50; specimen (4) 22.22 – 22.35; specimen (5) 21.68 – 22.10; specimen (6) 16.42 – 16.79; specimen (7) 17.90 – 19.70; specimen (8) 15.79 – 17.90; specimen (9) 27.75 – 34.42 and specimen (10) 19.93 – 20.75.

**Table 5:** Ten SARS COV-2 genome sequence showing the sequences length, ambiguous base, median depth of cover, clades and lineage.

| Sample Number | Obtained consensus sequences length (bp) <sup>a</sup> | Number of "N" (ambiguous base) | Percent reference coverage <sup>b</sup> | Median depth of coverage (x) | Nextclade Clade | Lineage (pangolin) | Cycle Threshold |       |       |
|---------------|-------------------------------------------------------|--------------------------------|-----------------------------------------|------------------------------|-----------------|--------------------|-----------------|-------|-------|
|               |                                                       |                                |                                         |                              |                 |                    | N1              | N2    | RP    |
| 1             | 28829                                                 | 984                            | 96.73                                   | 3557                         | 22B (Omicron)   | BA.5.2             | 27.11           | 28.27 | 28.98 |
| 2             | 27814                                                 | 2024                           | 94.11                                   | 1351                         | 22B (Omicron)   | BA.5.2             | 20.86           | 20.78 | 31.76 |
| 3             | 28738                                                 | 1102                           | 96.98                                   | 2708                         | 22B (Omicron)   | BA.5.2             | 15.50           | 14.99 | 26.29 |
| 4             | 29287                                                 | 555                            | 98.47                                   | 6576                         | 21L (Omicron)   | BA.2.3.20          | 22.35           | 22.22 | 26.17 |
| 5             | 28247                                                 | 1596                           | 95.59                                   | 1509                         | 23A (Omicron)   | XBB.1.5, VOI*      | 21.68           | 22.10 | 28.29 |
| 6             | 29354                                                 | 489                            | 98.23                                   | 5806                         | 23D (Omicron)   | FL.23.1            | 16.42           | 16.79 | 29.66 |
| 7             | 29360                                                 | 484                            | 98.22                                   | 4458                         | 23E (Omicron)   | GJ.1.2             | 19.70           | 17.90 | 27.3  |
| 8             | 23573                                                 | 6263                           | 80.90                                   | 979                          | 23A (Omicron)   | XBB.1.5, VOI*      | 15.78           | 17.94 | 30.78 |
| 9             | 29352                                                 | 492                            | 98.21                                   | 5818                         | 23E (Omicron)   | GJ.1.2             | 27.75           | 34.42 | 32.00 |
| 10            | 23759                                                 | 6084                           | 85.81                                   | 978                          | 23E (Omicron)   | GJ.1.2, VUM*       | 19.93           | 20.75 | 29.83 |
| Ave.          | 27831.3                                               | 2,007.3                        | 94.3                                    |                              |                 |                    |                 |       |       |

**Figure 7:** Shown is the complete phylogenetic tree of the novel SARS-CoV-2.<sup>13</sup> Highlighted is the major lineages 22B, 23E and their sub-lineages that were detected in this study. (Image lifted from Nextstarin.org)



Furthermore, pangolin lineages identified the following lineages: BA.5.2, BA.2.3.20, XBB.1.5, GJ.1.2 and FL.23.2 as shown in Table 5.

Specimens 1, 2 and 3 revealed Omicron BA.5.2 lineages, the Illumina run on these 3 clinical specimens obtained consensus sequences length of 28, 829 bp; 27, 814 bp and 28, 738 bp respectively. Mapping against Wuhan SARS-CoV-2 reference (NC\_045512) revealed percent reference coverages of 96.73%, 94.11% and 96.98% respectively. These 3 specimens were collected from July to August 2022. Subjects were two males and one female, two were 2-year-old and one is 1-year-old, all were from Quezon City and they all came in due to fever. Two of the subjects were managed as COVID 19 Mild while the other one is managed as COVID 19 Moderate due to the findings of pneumonia on chest x-ray. None of the subjects has comorbidities and all have good clinical outcomes.

Specimens 5 and 8 revealed Omicron XBB.1.5 lineage, the Illumina run obtained consensus sequences length of 28, 247 bp and 23, 573 bp respectively. And mapping against Wuhan SARS-CoV-2 reference (NC\_045512), the percent reference coverages revealed 95.59% and 80.90% respectively. These specimens were collected last April and May 2023. Subjects were two males, one is 1-year-old and one is 4-year-old, all were from Quezon City and they came in due to cough, colds and fever. One subject was managed as COVID 19 Mild while the other one is managed as COVID 19 Moderate due to the findings of pneumonia on chest x-ray. One subject has PTB and bronchial asthma, and all subjects have good clinical outcomes.

Specimen 7, 9 and 10 revealed Omicron GJ.1.2 lineage, the Illumina run obtained consensus sequences length of 29, 360 bp; 29, 352 bp and 23, 759 bp respectively. Further, mapping against Wuhan SARS-CoV-2 reference (NC\_045512) showed percent reference coverages of 98.22%, 98.21% and 85.81% respectively. These 3 specimens were collected from March, May and June 2023. All subjects were female, one is 3-year-old, one is 2-year-old and one is 9-month-old; two is from Quezon City and one is from Tanay, and they all came in due to fever. One of the subject was managed as COVID 19 Mild while the other two were managed as COVID 19 Moderate due to the findings of pneumonia on chest x-ray. One of the subject has global developmental delay, hypothyroidism and nephrolithiasis but all have good clinical outcomes.

The other 2 specimens revealed unique lineages. Specimen 4 revealed Omicron lineage BA.2.3.20 with percent reference coverage of 98.47%. The specimen was extracted from a 3-year-old, male, from Quezon City with bronchial asthma. He was managed as COVID 19 Moderate due to pneumonia on chest x-ray and was discharged with no complications. On the other hand, the specimen 6 revealed Omicron lineage FL.23.1 with percent reference coverage of 98.23%. The specimen was taken from a 4-year-old, male from Quezon City. He was managed as COVID 19 Mild and was discharged with no complications.

In terms of demographics and clinical profile, the sex distribution of these 10 patients with NGS was 60% (n = 6) males, and 40% (n = 4) females as shown below (Table 6).

**Table 6:** Shown is the sex distribution of subjects included in the study.

| Gender | f | %  |
|--------|---|----|
| Male   | 6 | 60 |
| Female | 4 | 40 |

Most of the subject in this study are ages 3 years old to 4 years old 40% (n = 4) with mean age distribution of 2.45 years old as shown in Table 7.

**Table 7:** Shown is the age distribution of subjects included in the study

| Age           | f |
|---------------|---|
| 1mo – 11 mos  | 1 |
| 1yo -2yo      | 2 |
| 2yo 1mo -3yo  | 3 |
| 3yo 1mo – 4yo | 4 |

Majority of the patients are living in Quezon City 90% (n = 9) and 1 subject is outside Metro Manila as shown below (Table 8).

**Table 8:** Shown are the residence of subjects included in the study.

| Residence                 | f | %  |
|---------------------------|---|----|
| Quezon City, Metro Manila | 9 | 90 |
| Tanay Rizal               | 1 | 10 |



In terms of comorbidities, 60% (n = 6) have comorbidities in which 2 have bronchial asthma-controlled, pulmonary tuberculosis, umbilical hernia and hydrocele (Table 5). One patient is a 9 month old with multiple comorbidities: global developmental delay, congenital hypothyroidism and nephrolithiasis as shown below (Table 9).

**Table 9:** Shown are the number of subjects with comorbidities.

| Comorbidities | f | %  |
|---------------|---|----|
| Yes           | 4 | 40 |
| No            | 6 | 60 |

The most prevalent symptoms presented by the subjects were cough 100% (n = 10), followed by fever 70% (n = 7), and colds 20% (n = 2) as shown below (Table 10).

**Table 10:** Shown is the common symptoms of subjects included in the study.

| Symptoms | f  | %   |
|----------|----|-----|
| Cough    | 10 | 100 |
| Fever    | 7  | 70  |
| Colds    | 2  | 20  |

The severity of COVID 19 was based on the PIDS-P guidelines,<sup>14</sup> wherein 60% (n = 6) were moderate risk due to pneumonia in Chest X-ray (n = 5) and/or concomitant comorbidities (n = 1) as shown below (Table 11 & 12).

**Table 11:** Shown is the disease severity of subjects included in the study.

| Severity | f | %  |
|----------|---|----|
| Mild     | 4 | 40 |
| Moderate | 6 | 60 |

**Table 12:** Shown is chest X-ray results of subjects included in the study.

| Chest X-ray | f | %  |
|-------------|---|----|
| Pneumonia   | 5 | 50 |
| Normal      | 3 | 30 |

**Table 13:** Shown is number of hospitalized subjects included in the study.

| Hospitalization | f | %  |
|-----------------|---|----|
| Yes             | 6 | 60 |
| No              | 4 | 40 |

Patients who were tagged COVID-19 moderate were hospitalized for treatment and close monitoring. None of the patients presented with severe disease and no accounted mortality during the course of the disease as shown below (Table 11).

## DISCUSSION

In this study, we successfully sequenced and characterized ten (10) SARS-CoV-2 samples from COVID-19 pediatric patients, collected between January 2021 and July 2023, using iSeq (Illumina, USA) in AFRIMS in Quezon City. All samples collected were Omicron variant.

This is congruent to the report of the Philippine Surveillance and Analysis of COVID-19 in Children Nationwide (SALVACION) database wherein COVID-19 cases in the Filipino pediatric population were Omicron variant and presented with mild-to-moderate symptoms (89.5%).<sup>15</sup> In correlation, all patients in this study presented with mild to moderate symptoms and generally had good prognosis and clinical outcomes.

### SARS-CoV-2 and Pediatric Age Group

Generally, children have milder disease severity than adults.<sup>3</sup> Age becomes significant in terms of vaccine eligibility.<sup>3,6</sup> Several study supports that those with no vaccines are more susceptible to the disease compared to those with vaccines.<sup>3,6,16</sup> In a study by Yigit *et al*, unvaccinated and incompletely vaccinated children had a higher risk of COVID-19 infection compared to those who were fully vaccinated with an odd ratio of 4.8 and 1.83 respectively.<sup>16</sup> Since SARS-CoV-2 vaccines were only given to 5 years old and older, those 4 years old and below are susceptible to contact infection.<sup>3,6</sup> This was as also reflected in this study wherein majority are below 4 years old, 61% (n=147) and were not eligible to receive the vaccine.

### SARS-CoV-2, Residence, Sex and Comorbidities

The current circulating variant becomes the widely detected variant in a given period of time and place. In terms of the study setting, the Omicron variant invaded Philippines in the late December 2021, and it was also the most dominant variant in children.<sup>15</sup> In correlation, all 10 subjects with NGS in this study were infected by Omicron variant. Also, these samples were collected from July 2022 and onwards, hence detecting this variant was generally expected.<sup>15</sup>

In terms of sex, majority of the subjects in this study were male, 61% (n=147). The difference in sex distribution of the infectious disease is hypothesized to be due to the effect of hormones.<sup>16</sup> In a study by Zaher *et al*,

the *estrogen* in female enhances T cell activity, stimulates interferon production, increase growth of B cells and antibody production.<sup>16</sup> All of these boost female's immune system and became a protective mechanism against infection. In contrast, the presence of androgen makes males more susceptible to viral infection.<sup>16</sup> An interesting finding that was recently discovered proposed that expression of TMPRSS2 receptors in *pneumocytes* is androgen-dependent.<sup>17</sup> TMPRSS2 expression is an important enzyme in SARS-CoV-2 cell entry.<sup>17</sup> Thus, abundant testosterone level in male directly elevates TMPRSS2 expression therefore increasing the probability of viral entry.<sup>17</sup>

Lastly, the presence of comorbidities greatly affect the COVID-19 severity.<sup>18,19</sup> This was supported by a meta-analysis by *Tsankov et al* and *Widjanarko et al*, wherein those patient with comorbidities have higher risk of developing severe disease with an odd ratio of 1.79 and 4.07 respectively.<sup>18,19</sup> Moreover, studies showed that COVID-19 patient with comorbidities has a higher risk of mortality with relative risk ratio of 2.81.<sup>18</sup> In correlation, in this study 24% (n=12) of patient classified as moderate COVID-19 have preexisting comorbidities, supporting finding that comorbidities affects patient outcomes and prognosis.

### **SARS-CoV-2 Variants and Disease Severity**

Reports on SARS-CoV-2 revealed that the Gamma and Delta waves lead to severe diseases in children.<sup>21</sup> This was seen in the massive increase in number of admitted children due to COVID-19 during these 2 waves. On the other hand, Omicron was observed to be more contagious but has lesser disease severity.<sup>21,22</sup> This was also observed in this study wherein all subjects (n=10) were infected by Omicron variant and generally have lesser disease severity and good clinical outcomes.

### **Omicron, the most dominant in children**

The dominance of Omicron variant in pediatric population was theorized to be due to its mode of cellular entry. According to the PIDS-P COVID-19 guidelines, in contrast to adults, pediatric population are more resistant to former SARS-CoV-2 variants due to children's innate low amount of TMPRSS2 in type I alveolar epithelial cells, and ACE2 receptors in type II alveolar epithelial cells<sup>14</sup>; and both are vital for viral entry.<sup>14</sup> However, the Omicron variant is unique, that it has higher affinity to ACE2 receptor and solely needs this receptor to invade a host, thus making unvaccinated pediatric patient more vulnerable.<sup>22</sup>

Aside from efficient viral entry, the Omicron adapt a more advantageous behavior to spread. A study of *Montarrayos et al* revealed that Omicron has 6 times higher incidence rate than other variants due to higher effective reproduction number (Rt).<sup>23</sup> Interestingly, a study by *Chatterjee et. al* also shows that Omicron viral load is unique, in that they are concentrated in the upper airway, mostly in the nose, windpipe, and throat, but less in the lower respiratory system.<sup>24</sup> This location makes it easier for the virus to be incorporated to respiratory droplets and spread more efficiently. Coupling a faster viral reproduction and concentrated location in the upper respiratory tract, makes omicron more contagious than the previous variants.<sup>24</sup>

Lastly, the most important factor in Omicron's virulence is the viral structure itself. It was proposed by the study of *Maldonado-Cabrera et. al.* that Omicron's higher mutation rate compared to other variants makes them variant of concern.<sup>25</sup> This was supported by a study of *Chavda et. al.*, wherein Omicron variant has the highest number of alteration sites, with a staggering 60 substitutions, insertions, and deletions, whereas the second most diverse variant, Delta, has only 22 mutations.<sup>26</sup> This diversity in its protein enables them to take an alternative cell entry pathway (endosomal fusion pathway) and subsequently escaping the host immune system more efficiently. The combined aforementioned characteristics of Omicron could explain why all the subjects in this study are infected by the said variant, as it has more mutations, advantageous behavior to spread and with the most viral load.<sup>26</sup>

### **Omicron is Less Virulent**

But despite its higher infection rate, Omicron infected patients had mild to moderate symptoms. As supported by several published studies done in Miami, Ohio and Mexico,<sup>21,22,23</sup> in comparison to Gamma and Delta variants, Omicron variant caused less severe disease in pediatric population despite its higher incidence rate. Like in this study, all patients presented with cough, colds, fever and loose stool but majority did not require hospital admission.

However, there are other contrasting studies on Omicron's lesser disease severity. A study by *Lam et. al.*, revealed that Omicron caused croup-like symptoms in pediatric patient in Hongkong comparing to pre-omicron era leading to more admission cases.<sup>20</sup> It was proposed that the possible explanations for greater morbidity is due to its higher transmissibility in younger populations compared with other variants<sup>21</sup>, along with children's lack of eligibility for SARS-CoV-2 vaccines, this makes this

population more susceptible to omicron.<sup>21</sup> Likewise, a study by *Han et. al.*, also observed that omicron cases had higher peak fever and higher rate of croup and febrile seizures compared with the previous waves.<sup>17</sup>

Despite this contrasting studies, strong evidences from a systematic review composed of researches from 52 countries worldwide concluded that comparing to Delta variant, Omicron still pales in disease severity.<sup>27</sup> There are no established evidence explaining its lesser disease morbidity, but a study of *Mukherjee et. al* hypothesized that this is due to omicron's low effectivity in counteracting the host cell *interferon* response.<sup>28</sup> Interferon, a cytokine that plays an important role in the activation of body's immune defenses.<sup>28</sup> Thus, Omicron's failure in suppressing interferon, enables the innate immune system to easily recognize and destroy the virus.<sup>28</sup>

### **Omicron and the Increasing Seizure Incidence**

In comparison to other variants, several studies show that Omicron wave leads to more seizure incident.<sup>29,30</sup> This was also congruent in this study wherein 10% of the patient had seizures. Studies of *Kim et. al.* and *Tokuyama et. al.*, hypothesized that interferon is mainly involved in the increasing incidence of febrile seizure in Omicron wave.<sup>29,30</sup> Because omicron had higher viral replication, this induces higher concentrations of host interferons, a principal components of an innate immune response.<sup>30</sup> This higher amount of interferon then develops to a more intense innate immune reactions, thus leading to higher grade fever and subsequently higher risk of febrile convulsions.<sup>29,30</sup>

### **SARS-CoV-2 in Children, the Role of Energy Allocation**

There are different researches proposing hypothesis on pediatric resistance to severe COVID-19. Although there are no concrete and established evidences yet, there are theories that became popular in the field of immunology. Since pediatric population manifests different physiology compared to adults, they respond differently in encountering diseases.<sup>31</sup> Human are born defenseless with immature systems, hence, there is a strong evolutionary pressure to mature over time.<sup>31</sup> And one important aspect that is unique in pediatric population, is the rapid growth early in life.<sup>31</sup> This then leads to dilemma of *energy allocation trade off*, is it whether to invest this energy to produce immune defenses or to prioritize growth?<sup>32</sup> Children's body will likely favor growth unless the pathogen will lead to life-threatening outcomes.<sup>32</sup> In the study of *Brodin*, he called this phenomenon, *disease tolerance* in children, an

immune defense strategy activated when the immune response to a pathogen is more damaging than the pathogen itself.<sup>33</sup> The body prevents production and activation of immune response, and tolerates the pathogen rather than resisting it, thereby allocating most of the energy to growth and development.<sup>33</sup> *Brodin* then concluded that there are higher energy allocation to growth in younger population compared to adult.<sup>33</sup> This is one of the hypothesis explaining why children have lesser COVID-19 disease severity compared to adults, children produce less cytokines and inflammatory agents.<sup>33</sup> Interestingly, male also has higher energy allocation to growth compared to female.<sup>34</sup> This is congruent to our study, wherein 61% (n=147) were less than 4 years old and 61% (n=147) were male, and majority presented with mild symptoms.

### **Limitation of Next Generation Sequencing**

Overall, this study was relatively limited by a small number of population, with just merely ten (10) sequences, this make correlation and drawing conclusions difficult. This limitation is due to the rarity of NGS and its cost effectiveness, it is not routinely done, moreso in the developing countries like the Philippines. Despite the small sample, this study supported the findings of other researches that preceded it, a valuable information in understanding the spread and evolution of SARS-CoV-2 in pediatric population in the Philippines. This novel coronavirus was widely studied during the pandemic, but despite the rampant chaos it brought in the community, there were few published literatures of variant outcomes in pediatric population, as well as the aftermath of its rapid evolution.

### **CONCLUSION**

From January 2021 to July 2023, a total of 630 pediatric patients who got tested for SARS-CoV-2 RT-PCR were confirmed to have SARS-CoV-2. Two hundred thirty nine (239) were included in this study. Among the study population, 61.51% were male, more than 60% were less than 4 years old and residing in Quezon City. In terms of clinical presentation, 78% had mild symptoms, 20% had radiologic findings of pneumonia, 40% presented with fever, 12% with diarrhea, and 8% with dyspnea. Ten percent (10%) of patient had concomitant seizure disorder. More than 70% were admitted to the hospital and all of the study subjects recovered from the illness.

Only ten (10) samples were subjected to next generation sequencing and all were Omicron variant. Despite the homogenous variant, the isolated viruses have different lineages with some tagged as variant of interest

and variant under monitoring. Omicron's dominance may be attributed to its abundant mutation, high effective reproduction number and higher affinity to ACE2 receptors compared to other variants. Also, majority of the patients presented with mild symptoms such as fever and cough, and generally had good clinical outcomes. This could be associated to Omicron's inefficient suppression of the host cell interferon response as opposed to other variants, making it more susceptible to the innate immunity defenses.

## RECOMMENDATION

Based on the study conclusion, the following recommendation were deduced;

1. To continue using next generation sequencing as part of work-up especially in complicated, unknown and severe cases of SARS-CoV-2 and other viral infections.
2. To correlate viral sequence of the SARS-CoV-2 to previous endemic coronavirus in the Philippines and identify mutated sequences that may correlate to its novelty and virulence.

## REFERENCES

1. Koboldt, D. C., Steinberg, K. M., Larson, D. E., Wilson, R. K., & Mardis, E. R. (2013). The next-generation sequencing revolution and its impact on genomics. *Cell*, 155(1), 27-38.
2. Saravanan, K. A., Panigrahi, M., Kumar, H., Rajawat, D., Nayak, S. S., Bhushan, B., & Dutt, T. (2022). Role of genomics in combating COVID-19 pandemic. *Gene*, 823, 146387.
3. Sironi, M., Hasnain, S. E., Rosenthal, B., Phan, T., Luciani, F., Shaw, M. A., ... & González-Candelas, F. (2020). SARS-CoV-2 and COVID-19: A genetic, epidemiological, and evolutionary perspective. *Infection, Genetics and Evolution*, 84, 104384.
4. Velasco, J. M., Chinnawirotpisan, P., Joonlasak, K., Manasatienkij, W., Huang, A., Valderama, M. T., & Klungthong, C. (2020). Coding-complete genome sequences of 23 SARS-CoV-2 samples from the Philippines. *Microbiology resource announcements*, 9(43), e01031-20.
5. Lai, C. C., Shih, T. P., Ko, W. C., Tang, H. J., & Hsueh, P. R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *International journal of antimicrobial agents*, 55(3), 105924.
6. Rashedi, R., Samieefar, N., Akhlaghdoust, M., Mashhadi, M., Darzi, P., & Rezaei, N. (2022). Delta variant: The new challenge of COVID-19 pandemic, an overview of epidemiological, clinical, and immune characteristics. *Acta Bio Medica: Atenei Parmensis*, 93(1).
7. Slatko, B. E., Gardner, A. F., & Ausubel, F. M. (2018). Overview of next-generation sequencing technologies. *Current protocols in molecular biology*, 122(1), e59.
8. Dans, L. F., Ong-Lim, A. L. T., Arciaga, R. S., Capili, D. I. S., Garcia, D. E. C., & Jiao, A. G. Q. Philippine Pediatric Covid-19 Living Clinical Practice Guidelines as of March 2022.
9. Deville, J. G., Song, E., & Ouellette, C. P. (2021). COVID-19: Clinical manifestations and diagnosis in children. *Up to Date*.
10. Alpert, T., Brito, A. F., Lasek-Nesselquist, E., Rothman, J., Valesano, A. L., MacKay, M. J., & Grubaugh, N. D. (2021). Early introductions and transmission of SARS-CoV-2 variant B. 1.1. 7 in the United States. *Cell*, 184(10), 2595-2604.
11. Deville, J. G., Song, E., & Ouellette, C. P. (2021). COVID-19: Clinical manifestations and diagnosis in children. *Up to Date*.
12. Velasco, J. M., Navarro, F. C., Diones, P. C., Villa, V., Valderama, M. T., Tabinas, H., ... & Fernandez, S. (2021). SARS-CoV-2 among military and civilian patients, Metro Manila, Philippines. *Military Medicine*, 186(7-8), e760-e766.
13. Roemer, C., Neher, R. Nextstrain / Nextclade / SARS-CoV2. <https://nextstrain.org/nextclade/sars-cov-2>. Data updated 2024-01-15.
14. Philippine Pediatric Society Pediatric Infectious Disease Society Of The Philippines. Interim Guidelines On The Screening, Assessment And Clinical Management Of Pediatric Patients With Suspected Or Confirmed Coronavirus Disease 2019 (Covid-19). *Version 4, 06 February 2021. Page 13*.
15. Quebral, E. P. B., Badua, C. L. D., Maramba-Lazarte, C. N. C., & Tantengco, O. A. G. (2022). The Current State of COVID-19 Infection in Filipino Children. *Journal of Paediatrics and Child Health*, 58(5), 936-937.
16. Yonker, L. M., Gilboa, T., Ogata, A. F., Senussi, Y., Lazarovits, R., Boribong, B. P., ... & Fasano, A. (2021). Multisystem inflammatory syndrome in children is driven by zonulin-dependent loss of gut mucosal barrier. *The Journal of Clinical Investigation*, 131(14).



17. Han, M. S., Kim, K. M., Oh, K. J., Chang, J. Y., Lee, S. Y., Choi, J. E., ... & Sun, J. (2023). Distinct clinical and laboratory features of COVID-19 in children during the pre-delta, delta and omicron wave. *The Pediatric Infectious Disease Journal*, 42(5), 423-428.
18. Tsankov, B. K., Allaire, J. M., Irvine, M. A., Lopez, A. A., Sauvé, L. J., Vallance, B. A., & Jacobson, K. (2021). Severe COVID-19 infection and pediatric comorbidities: a systematic review and meta-analysis. *International Journal of Infectious Diseases*, 103, 246-256.
19. Widjanarko, M. W., Nindya, M., Fernandez, G., & Jovito, A. (2022). Comorbidities and COVID-19 severity in pediatric patients: systematic review and meta-analysis. *Paediatrica Indonesiana*, 62(1), 51-60.
20. Lam, M. C., & Lam, D. S. (2024). The Omicron variant of COVID-19 and its association with croup in children: a single-centre study in Hong Kong. *Hong Kong Med J*, 30(1), 44-55.
21. Wang L, Berger NA, Kaelber DC, Davis PB, Volkow ND, Xu R. Incidence rates and clinical outcomes of SARS-CoV-2 infection with the Omicron and Delta variants in children younger than 5 years in the US. *JAMA Pediatr* 2022;176:811-3
22. Scudellari, M. (2022). Omicron's surprising anatomy explains why it is wildly contagious. *Scientific American*.
23. Montarroyos, S. S., Ladd, B. F., Mestre, M., & Cardenas, G. (2023). Classification of SARS-CoV-2 Pediatric Hospitalizations: Delta vs Omicron Variant. *Hospital Pediatrics*, 13(10), 940-944.
24. Chatterjee, S., Bhattacharya, M., Nag, S., Dhama, K., & Chakraborty, C. (2023). A detailed overview of SARS-CoV-2 omicron: its sub-variants, mutations and pathophysiology, clinical characteristics, immunological landscape, immune escape, and therapies. *Viruses*, 15(1), 167.
25. Maldonado-Cabrera, A., Colin-Vilchis, J. A., Haque, U., Velazquez, C., Alvarez Villaseñor, A. S., Magdaleno-Márquez, L. E., ... & Gallego-Hernández, A. L. (2023). SARS-CoV-2 variants of concern and clinical severity in the mexican pediatric population. *Infectious Disease Reports*, 15(5), 535-548.
26. Chavda, V. P., Bezbaruah, R., Deka, K., Nongrang, L., & Kalita, T. (2022). The Delta and Omicron variants of SARS-CoV-2: what we know so far. *Vaccines*, 10 (11), 1926.
27. Wiedenmann, M., Ipekci, A. M., Araujo-Chaveron, L., Prajapati, N., Lam, Y. T., Alam, M. I., ... & Goutaki, M. (2023). SARS-CoV-2 variants of concern in children and adolescents with COVID-19: a systematic review. *BMJ open*, 13(10), e072280.
28. Mukherjee, A. G., Wanjari, U. R., Murali, R., Chaudhary, U., Renu, K., Madhyastha, H., ... & Gopalakrishnan, A. V. (2022). Omicron variant infection and the associated immunological scenario. *Immunobiology*, 227(3), 152222.
29. Kim, J. M., Park, E. G., Lee, J. Y., Kim, Y. H., Kim, Y., Kim, H. S., ... & Han, S. B. (2023). Characteristics of febrile seizures with SARS-CoV-2 infection.
30. Tokuyama, K., Kitamura, T., Maruyama, K., Toriumi, S., Murano, Y., Yoneoka, D., ... & Shimizu, T. (2023). High number of seizures and unconsciousness in patients with SARS-CoV-2 omicron variants: a retrospective study. *Frontiers in Pediatrics*, 11, 1273464.
31. Hochberg, Z. E. (2011). Evolutionary perspective in child growth. *Rambam Maimonides medical journal*, 2(3).
32. Medzhitov, R., Schneider, D. S., & Soares, M. P. (2012). Disease tolerance as a defense strategy. *Science*, 335(6071), 936-941.
33. Brodin, P. (2022). SARS-CoV-2 infections in children: Understanding diverse outcomes. *Immunity*, 55(2), 201-209.
34. Yigit, M., Ince, Y. E., Kalayci, F., Santafloriglu, B., Kurt, F., Ozkaya-Parlakay, A., ... & Senel, E. (2022). The impact of childhood and parental vaccination on SARS-CoV-2 infection rates in children. *The Pediatric Infectious Disease Journal*, 41(10), 841-845.

# Giant Lupus Vulgaris Presenting as Two Ulcerative Plaques in a Filipino Female: A Case Report\*

Gabrielle Nicole R. Mendoza, MD<sup>1</sup>; Elisa Rae L. Coo, MD, FPDS<sup>2</sup>;  
Katherine Joy B. Sayo-Aguiling, MD, FPDS<sup>2</sup>

## ABSTRACT

Lupus vulgaris is a form of cutaneous tuberculosis (CTB) caused by the bacterium *Mycobacterium tuberculosis* (MTB). It is characterized by a usually solitary, long-lasting skin lesion that most commonly develops on the head or neck, especially the nose, cheek, earlobe, or scalp. A 69-year-old Filipino female presented with a 20-year history of progressively growing erythematous ulcerative plaques on the right arm and ear, with associated mild pruritus and pain. She appeared to be immunocompetent with no clinically apparent underlying focus of TB infection. Tuberculin skin test (TST) was done, which showed a positive reaction (an induration of 11mm), and histopathologic examination revealed a chronic granulomatous dermatitis that is focally positive for acid-fast bacilli. She was given anti-tuberculosis therapy (ATT) with subsequent resolution of the lesions.

**Keywords:** Lupus vulgaris, Cutaneous tuberculosis, Giant lupus vulgaris

## INTRODUCTION

Lupus vulgaris (LV) is a chronic and progressive form of cutaneous tuberculosis (CTB) caused by *Mycobacterium tuberculosis* (MTB). It is usually characterized by the development of skin lesions on the head and neck region and typically begins on the nose, cheek, earlobe, or scalp, with gradual spread to the adjacent areas.<sup>1</sup> In most cases, lesions are solitary, but multiple areas can be affected. Although this is considered a rare form of tuberculosis, its prevalence has been increasing in recent years, particularly in immunocompromised individuals.<sup>2</sup>

Typically, the characteristic lesions manifest as a discrete red-brown, friable macule or papule with a smooth or hyperkeratotic surface. As the condition advances, these papules may transform into atrophic, ulcerated plaques and develop crusted nodules that are usually less than 10cm in size.<sup>3</sup> If left untreated, LV progresses over several years and can lead to noticeable disfigurement.<sup>4</sup> Diagnosis requires a high index of suspicion, as it can mimic various dermatological conditions such as Spitz nevus and lupus erythematosus in early stages, rosacea, port-wine stains, sarcoidosis, deep fungal infections, and leprosy.<sup>5</sup> Thorough clinical examination, histopathological analysis, and microbiological investigations are essential for accurate

diagnosis. Skin biopsy specimens typically demonstrate granulomatous inflammation with caseating necrosis, which is characteristic of tuberculosis (TB) infection.<sup>6</sup> The management includes a standard multidrug anti-tuberculosis therapy (ATT). The duration of treatment varies based on the severity of the disease and the individual's response to therapy. Surgical measures such as excision of affected tissue or laser therapy may be necessary for extensive or aesthetically concerning lesions.<sup>5,7,8</sup>

In this case report, we present a detailed clinical and histopathological description of a patient with giant LV, highlighting the challenges encountered in diagnosis. Through this report, we also aim to contribute to the limited pool of existing literature on multiple LV and emphasize the importance of early recognition and appropriate treatment to prevent complications and improve patient outcomes.

## CASE REPORT

A 69-year-old Filipino female presented with a few erythematous plaques with well-defined borders on her right proximal arm and right ear. Twenty years prior to consult, she noted two discrete asymptomatic erythematous papules on her right arm with no recalled

*Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.*

\*This paper was recognized as a Finalist in the 31st Annual Residents' Research Competition of the Philippine Medical Association (May 17, 2025). It was also presented at the Department of Dermatology Research Forum, JRRMMC (September 13, 2024) and the Interesting Case Category of the JRRMMC Interdepartmental Research Forum (November 2022), and was featured as an e-poster in the Philippine Dermatological Society Annual Convention (November 2024).

\*Department of Dermatology, Jose R. Reyes Memorial Medical Center, Manila Philippines

<sup>1</sup>Dermatology Resident at Jose R. Reyes Memorial Medical Center, Manila Philippines

<sup>2</sup>Consultant Dermatologist at Jose R. Reyes Memorial Medical Center, Manila Philippines

history of trauma. No fever, cough, nor joint pains were noted at that time. No consults and no interventions were done. There was no known history of contact with an active case of TB. General and systemic examinations were normal. Interval history showed a gradual increase in the size of the lesions with peripheral expansion, which coalesced to form an erythematous plaque.

One year prior to consult, the plaque progressed and developed white to greenish foul-smelling discharge and was associated with mild pruritus graded 3/10. She sought consult with multiple private physicians and was given unrecalled topical and oral antibiotics with no subsequent improvement.

One week prior to consult, the patient noted a new onset solitary erythematous patch on the right ear that progressed to a moist plaque now also associated with purulent foul-smelling discharge with pruritus (3/10) and persistent dull pain (3/10). Persistence of symptoms prompted consult at our institution.

On physical examination, there were two well-defined, irregularly-shaped erythematous, moist, ulcerative plaques with hemorrhagic crusting on the right ear and infra-auricular area measuring 11 x 7 cm, and right deltoid measuring 25 x 17 cm (FIGURE 1). Diascopy was positive for the 'apple-jelly' sign. No mucosal lesions or regional lymphadenopathies were noted. Dermoscopic evaluation of the lesions revealed yellow-orange clods and fine telangiectasias with pinkish red background and yellow-white scales (FIGURE 2).

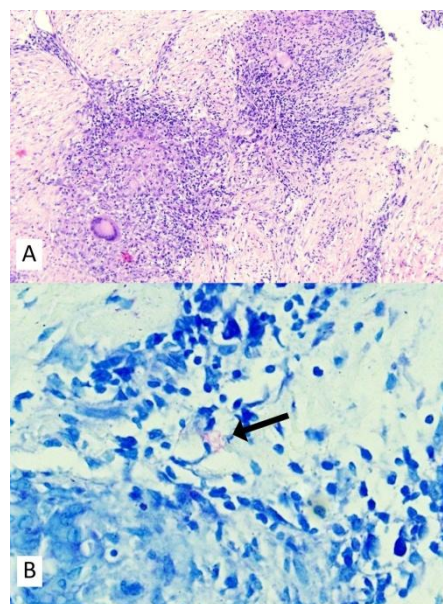


**FIGURE 1.** Few well-defined irregularly-shaped erythematous, moist ulcerative plaques with hemorrhagic crusting on the A) right proximal arm measuring 25 x 17 cm, and B) on the right ear measuring 11 x 7 cm.



**FIGURE 2.** Dermoscopy of: A) and B) the right proximal arm with yellow-orange clods and fine telangiectasias with pinkish red background and yellow-white scales, C) the right ear with yellow-orange clods.

A 4mm skin punch biopsy performed on her ear and her right arm revealed orthokeratosis, pseudoepitheliomatous hyperplasia, and nodular granulomatous infiltrates consisting of lymphocytes, histiocytes, plasma cells and Langhans giant cells in the superficial and mid-dermis (FIGURE 3A). Fite Faraco staining of the right arm showed acid-fast bacilli (FIGURE 3B). Periodic Acid Schiff stain was negative for fungal spores and hyphae. The tuberculin skin test (TST) was positive with an induration of 11mm. Wound acid-fast bacilli smear and sputum Gene Xpert were both negative. QuantiFERON-TB Gold (QFT-G) was positive. Polymerase Chain Reaction (PCR) for MTB DNA and tuberculosis culture were not done.



**FIGURE 3.** Hematoxylin and eosin stain from the right arm showing A) nodular granulomatous infiltrates with Langhans giant cells in the superficial and mid-dermis, B) Positive for acid-fast bacilli (Fite Faraco stain).



Screening for extracutaneous focus of TB infection was negative. Clinical, dermoscopic, and microscopic features were consistent with the diagnosis of LV. She was started on ATT to complete six months of treatment. She was also instructed on daily wound care and to apply mupirocin 2% ointment using sandwich dressing twice daily for one month. On one month of follow-up, there was a noted decrease in size and discharge of the lesions, with resolution of pruritus and pain (FIGURE 4A, 4B, & 4C). Her response to treatment further strengthened the diagnosis. After completion of treatment, there was resolution of lesions with only hyperpigmentation and atrophic scarring present on both her right arm and ear (FIGURE 4D, 4E, & 4F).



**FIGURE 4.** Comparative photos of the patient on A), B), and C) one month after initiation of therapy, and D), E), and F) after completion of therapy.

## DISCUSSION

LV is a form of CTB that has a chronic and progressive course. It usually occurs in individuals with moderate to high immunity against the bacillus. A prior study reported an incidence of 8.6 cases per 100,000 in a Philippine tertiary care center, with the highest rates in men aged 11-20.<sup>9</sup> LV has been observed to occur in individuals who were previously diagnosed with TB verrucosa cutis, scrofuloderma, and, less commonly, following BCG vaccination or primary inoculation.<sup>8,10</sup> This

patient was a 69 year-old female with an unrecalled history of BCG vaccination.

The usual belief is that LV emerges from a primary focus in either lymph nodes, bones, or joints, commonly associated with lymph node, joint, or bone TB.<sup>5,11</sup> Alternatively, it can result from the reactivation of a latent cutaneous focus due to previous silent bacteremia, direct inoculation, or from lympho-hematogenous extension.<sup>11,12</sup> However, in this case, no focus of underlying TB infection was detected since the patient denied joint pains, cough, dyspnea, or mucosal lesions, and had negative screening tests for extracutaneous TB infection. Similar to this patient, most case reports found no internal focus of infection upon screening.

In the early stages, the skin lesions may be seen as discrete, reddish-brown papules that coalesce to form an asymptomatic plaque. As the disease progresses, the lesions may become larger with a slightly raised border, central atrophy, and a soft, gelatinous surface. Dermoscopy can be used to identify well-focused, linear-branching telangiectasias on a diffuse or localized, structureless, yellow to orange background, and whitish, reticular streaks. However, these features are not specific to LV and can also be seen in cutaneous sarcoidosis.<sup>14</sup> Upon blanching using diascopic pressure, the lesions usually reveal a characteristic brownish-yellow color or "apple-jelly" color.<sup>14</sup> Similar to this, our patient initially presented with an erythematous papule on the right deltoid and eventually the right ear that gradually progressed to an ulcerative plaque with dermoscopic features of yellow-orange clods on an erythematous background with apple-jelly color upon application of diascopic pressure.

LV lesions are most commonly found on the head and neck, particularly on the nose and cheek. However, recent studies have shown that the predilection sites can vary by locality. In Europe, over 80% of the lesions are found in the head and the neck.<sup>15</sup> They are rarely found on the extremities, buttocks, or trunk.<sup>16,17</sup> However, according to another study done by Bilen et al (2000), lesions on the legs and buttocks were found to be a common occurrence in Asia.<sup>17</sup> More specifically, lesions are more often seen on the trunk, elbows, and knees in India and the Philippines.<sup>9,18</sup> LV commonly presents as a single lesion, with few case reports with findings of multiple lesions.<sup>19,20,21,22,23,24</sup> To the best of our knowledge, there have been limited case reports of solitary plaques affecting only the ear,<sup>27</sup> and no case reports have been identified that involve both the ear and the unilateral proximal arm.



Regarding the size of the lesion, it is usually small in size, and gradually grows peripherally to reach 0.5cm–10cm.<sup>3,19</sup> The classification of giant LV based on size lacks consensus or standardization but is usually greater than 10cm.<sup>8,20,27</sup> Considering the measurements reported in previous studies for giant LV lesions, and with this patient's lesion measuring 25 x 17cm, we believe that this case qualifies as giant LV as well.

Diagnosis usually relies on clinical suspicion and histopathological features.<sup>8,28,29</sup> The definitive diagnosis of LV is the isolation of MTB from a culture of the skin lesion. However, this is often difficult to achieve, as the lesions are usually paucibacillary.<sup>18</sup> Positive PCR results for *M. tuberculosis* can strengthen the diagnosis of tuberculosis even in paucibacillary forms.<sup>8,30</sup> Interferon-gamma release assays (IGRAs) measure the immune response to MTB antigens and are more accurate than other tests in areas where TB is common and in people who have been vaccinated with BCG.<sup>31</sup> QFT-G is increasingly being used in the Philippines to diagnose LV because it is more sensitive than the PPD test, and it can also detect tuberculosis in patients who have been vaccinated against BCG.<sup>32</sup> Previous studies found that QFT-G had a sensitivity of 89% and a specificity of 99% in the diagnosis of CTB.<sup>33</sup> These findings suggest that QFT-G is a valuable tool for the diagnosis of CTB. In this case, the patient was positive for both the PPD and QFT-G tests.

Histopathologically, the epidermis may be atrophic or hypertrophic, with acanthosis, papillomatosis, and even pseudoepitheliomatous hyperplasia. The reticular dermis may contain well-formed tuberculous granulomas, often with Langhans giant cells, or foreign body-like granulomas. There may also be sarcoidosis-like granulomas. The lymphocytic infiltrate is dense, and caseous necrosis is rare, but it may be present in small foci in the center of the granuloma. Acid-fast bacilli are not readily found even with culture due to its paucibacillary nature.<sup>12,19,20</sup> In line with this, our patient presented with nodular granulomatous infiltrates with Langhans giant cells in the superficial and mid-dermis. Interestingly, she was focally positive for acid-fast bacilli with Fite-Faraco stain which is rarely seen in this condition. Current literature found that CTB typically responds well to standard ATT, with clinical improvement expected after 4 to 6 weeks.<sup>8,34</sup> However, it is essential to tailor the treatment to the patient's individual requirements, taking into account their overall health, immune status, type of CTB, severity of cutaneous involvement, disease stage, medication compliance, and side effects. If left untreated, LV lesions can remain for years, gradually increasing in size. This can lead to scarring, deformation, and

disfigurement that can be severe.<sup>5,26</sup> The risk of malignant transformation of lesions into squamous cell carcinoma (SCC) is estimated to be between 0.5% and 10.5%, typically occurring after 25–30 years of untreated LV.<sup>22,35</sup> In line with this, our patient had a 20-year history of two gradually enlarging and ulcerating plaques that did not show signs of malignant transformation to SCC.

#### **DATA PLAN**

All data obtained from this study will be stored for 10 years in the private clinic of the patients' dermatologists in case the investigators need to review the source data should there be questions about the results. These data will be used solely for the study and the principal investigator and co-authors will have access to this data. We will destroy the data after the said duration. Data collection will commence after approval of the IRB and will last for the 4 month duration of the study.

#### **ETHICAL CONSIDERATION**

This case report involves no more than minimal risk and will use only the medical data of patients. Secured data acquisition will be implemented involving only the authors and the private dermatologists in charge of the patient's records. Only necessary information such as diagnosis, ICD-10 codes used, family history and treatment outcome will be collected and no other revealing personal information will be recorded throughout the study. Only redacted data were recorded under a non-disclosure agreement. The protocol was submitted to and approved by the Institutional Review Board. No code names were used for the patient as the authors only included the patient's race, age and sex.

#### **CONCLUSION**

We report a case of LV in a 69-year-old immunocompetent Filipino female, which presented with an uncommon size and an unusually large size. The patient had two well-defined, irregularly-shaped ulcerative plaques located on the right deltoid and right ear, extending to the right infra-auricular area, measuring 25 x 17 cm and 11 x 7 cm respectively. Interestingly, these lesions had progressed over a period of twenty years without a clinically apparent underlying focus of infection. By contributing our case to the limited pool of information on giant LV, we can potentially enhance the understanding of this disease and aid in establishing more standardized criteria for its classification, especially in terms of lesion size. Additionally, this case underscores the importance of maintaining a high index of clinical suspicion, particularly when lesions occur in atypical

locations. Clinical and histopathological correlation remains essential for early diagnosis of this disease. In this regard, the QFT-G can serve as a helpful adjunctive test to strengthen the diagnosis in challenging cases. Early detection and treatment are crucial to prevent complications such as permanent disfigurement and the risk of malignant transformation.

## BIBLIOGRAPHY

- Sethi A (2019). Chapter 157. Tuberculosis and infections with atypical mycobacteria. Goldsmith L.A., & Katz S.I., & Gilchrist B.A., & Paller A.S., & Leffell D.J., & Wolff K(Eds.), Fitzpatrick's Dermatology in General Medicine, 9e. McGraw Hill.
- Sehgal VN, Srivastava G, Sharma S, et al. (2007). Lupus vulgaris: a neglected entity. *Indian J Dermatol Venereol Leprol*. 73(3):198-200.
- Bleeker-Rovers, C. P., & De Vries, H. J. C. (2017). Dermatologic Manifestations of Systemic Infections. In *Infectious Diseases (Fourth Edition)* (4th ed., Vol. 1, pp. 113–121). Elsevier. <https://doi.org/10.1016/b978-0-7020-6285-8.00013-7>
- Singh P, Myneedu VP, Arora J, et al. (2017). Lupus vulgaris: a clinico-histopathological study of a 35-year series from a tertiary care center in South India. *Int J Mycobacteriol*. 6(1):54-58.
- Scollard, D. M., Dacso, M. M., & Abad-Venida, M. L. (2015). Tuberculosis and Leprosy: Classical Granulomatous Diseases in the Twenty-First Century. *Dermatologic clinics*, 33(3), 541–562. <https://doi.org/10.1016/j.det.2015.03.016>
- Khopkar US, Khopkar SU, Mahajan SA, et al. (2011). Lupus vulgaris: unusual presentation as mutilating ulcer of hand. *Indian J Dermatol Venereol Leprol*. 77(6):759-762.
- Sharma VK, Puri KJ. (1995). Lupus vulgaris: unusual presentations over the face. *Int J Dermatol*. 34(3):207-209.
- Wang, Z. Z., & Wang, H. (2022). Giant Lupus Vulgaris with Negative T-SPOT.TB, a Case Report and Literature Review. *Clinical, cosmetic and investigational dermatology*, 15, 1119–1123. <https://doi.org/10.2147/CCID.S366136>
- Villaroman, C. J. J., & Abad-Venida, M. L. (2015). A ten-year retrospective study on cutaneous tuberculosis at the Jose R. Reyes Memorial Medical Center. *Journal of the Philippine Dermatological Society*, 24(1), 15–21. Retrieved from [https://journals.lww.com/jpds/abstract/2015/24010/a\\_ten\\_year\\_retrospective\\_study\\_on\\_cutaneous.3.aspx](https://journals.lww.com/jpds/abstract/2015/24010/a_ten_year_retrospective_study_on_cutaneous.3.aspx)
- Parmar, N. V., Al Falasi, A., & Almualla, A. (2021). Bacillus Calmette-Guérin vaccine-induced lupus vulgaris in a 3-year-old child. *Anais brasileiros de dermatologia*, 96(5), 636–638. <https://doi.org/10.1016/j.abd.2020.07.022>
- Pai, V., Naveen, K., Athanikar, S., Dinesh, U., Divyashree, A., & Gupta, G. (2014). A clinico-histopathological study of lupus vulgaris: A 3 year experience at a tertiary care centre. *Indian Dermatology Online Journal*, 5(4), 461. doi:10.4103/2229-5178.142497
- Santos, J. B. dos, Figueiredo, A. R., Ferraz, C. E., Oliveira, M. H. de, Silva, P. G. da, & Medeiros, V. L. S. de. (2014). Cutaneous tuberculosis: epidemiologic, etiopathogenic and clinical aspects - Part I. *Anais Brasileiros de Dermatologia*, 89(2), 219–228. doi:10.1590/abd1806-4841.20142334
- Gunawan H, Achdiat PA, Hindritiani R, Essary ED, Ningtias LD, Siregar EP, et al. (2018). Various cutaneous tuberculosis with rare clinical manifestations: a case series. *Int J Mycobacteriol*, 7(3): 288–91.
- Theodosiou, G, Papageorgiou, M, & Mandekou-Lefaki, I. (2018). An unusual presentation of lupus vulgaris and the practical usefulness of dermatoscopy. *Case Reports in Dermatological Medicine*, 2018. <https://doi.org/10.1155/2018/1036162>
- Thomas S, Suhas S, Pai KM, Raghu AR. (2005). Lupus vulgaris-report of a case with facial involvement. *Br Dent J*. 198: 135-37
- Senol, M., Ozcan, A., Mizrak, B., Turgut, A. C., Karaca, S., & Kocer, H. (2003). A case of lupus vulgaris with unusual location. *The Journal of dermatology*, 30(7), 566–569. <https://doi.org/10.1111/j.1346-8138.2003.tb00435.x>
- Bilen, N., Apaydin, R., Harova, G., Bayramgürler, D., & Paksoy, N. (2000). Lupus vulgaris on the buttock: report of two cases. *Journal of the European Academy of Dermatology and Venereology : JEADV*, 14(1), 66–67. <https://doi.org/10.1046/j.1468-3083.2000.00007-2.x>
- Kakakhel, K. U., & Fritsch, P. (1989). Cutaneous tuberculosis. *International journal of dermatology*, 28(6), 355–362. <https://doi.org/10.1111/j.1365-4362.1989.tb02478.x>
- Frankel, A., Penrose, C., & Emer, J. (2009). Cutaneous tuberculosis: a practical case report and review for the dermatologist. *The Journal of clinical and aesthetic dermatology*, 2(10), 19–27.
- Sacchidanand, S, Sharavana, S, Mallikarjun, M, & Nataraja, HV (2012). Giant lupus vulgaris: A rare presentation. *Indian Dermatology Online Journal*, 3(1), 34–36. <https://doi.org/10.4103/2229-5178.93498>

21. Jimenez, KS & Medina, DM (2022). Non-healing ulcers as an atypical presentation of lupus vulgaris in an adult filipino: a case report. *The Filipino Family Physician*. 60(1), 187-194.
22. Zawirska A, Adamski Z, Stawicka E, & Schwartz, RA. (2009). Cutaneous squamous cell carcinoma developing in lupus vulgaris exfoliatus persistent for 40 years. *Int J Dermatol*, 48:125-7.
23. Adil M, Amin SS, Saeed N, Mohtashim M, Priya A, Alam M. (2018). A case of giant lupus vulgaris. *Tropical Doctor*. 48(3):254-256. doi:10.1177/0049475518760949
24. Ngbea JA, Ochoga MO, Malu KN et. al. (2015). Lupus vulgaris of the eye and nose in a 10 year old child: a clinicopathological diagnosis. *Int J Health Sci Res*. 5(3):425-429.
25. Kumar, B., & Muralidhar, S. (1999). Cutaneous tuberculosis: a twenty-year prospective study. *The International Journal Of Tuberculosis And Lung Disease : The Official Journal Of The International Union Against Tuberculosis And Lung Disease*, 3(6), 494-500.
26. Gogia, S. & Agarwal, A. (2013). Solitary lupus vulgaris of the pinna: A rare presentation. *Indian Journal of Otolaryngology*, 19(1), 30-32. <http://doi.org/10.4103/0971-7749.108164>
27. Zhao, J., Jia, Y., Keyal, U., Bhatta, A., & Ng How Tseung, K. Y. (2015). Giant facial cutaneous tuberculosis. *Indian Journal of Dermatology, Venereology, and Leprology*, 81(1), 95. doi:10.4103/0378-6323.148610
28. Rahman, M. A., Asaduzzaman, A., Mahmud, M. M., Chowdhury, A. M., Rahman, M. M., Haque, M. A., & Haque, S. (2018). Role of polymerase chain reaction in the diagnosis of cutaneous tuberculosis. *Journal of Pakistan Association of Dermatologists*, 28(3), 277-283. Retrieved from <https://www.jpap.com.pk/index.php/jpap/article/view/1262>
29. Afsar, F. S., Afsar, I., Diniz, G., Asilsoy, S., & Sorguç, Y. (2008). Lupus vulgaris in a pediatric patient: a clinicopathological diagnosis. *Brazilian Journal of Infectious Diseases*, 12(2). <https://doi.org/10.1590/s1413-86702008000200011>
30. Akoglu, G., Karaduman, A., Boztepe, G., Ozkaya, O., Sahin, S., Erkin, G., & Kolemen, F. (2005). A case of lupus vulgaris successfully treated with antituberculous therapy despite negative PCR and culture. *Dermatology (Basel, Switzerland)*, 211(3), 290-292. <https://doi.org/10.1159/000087027>
31. Pahal P, Pollard EJ, Sharma S. PPD Skin Test. [Updated 2023 Apr 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK556037/>
32. Chua, NSD & Rovira, MVRM. (2016). An unusual case of lupus vulgaris and the use of interferon-gamma release assay (Quantiferon-TB Gold Test) as an aid in supporting the diagnosis. *St. Luke's Healthcare Journal*, 11(02), 94-98.
33. Almaguer-Chávez J., Ocampo-Candiani J., Rendón A. (2009). Current panorama in the diagnosis of cutaneous tuberculosis. *Actas Dermo-Sifiliográficas*. 100(7):562-570. doi: 10.1016/S0001-7310(09)71904-0.
34. Ramam M, Mittal R, Ramesh V. (2005). How soon does cutaneous tuberculosis respond to treatment? Implications for a therapeutic test of diagnosis. *Int J Dermatol*. 44:121-4.
35. Gooptu C, Marks N, Thomas J, & James MP. (1998). Squamous cell carcinoma associated with lupus vulgaris. *Clin Exp Dermatol*, 23:99-102.
36. Lai, C. C., Tan, C. K., Lin, S. H., Liu, W. L., Liao, C. H., Huang, Y. T., & Hsueh, P. R. (2011). Diagnostic value of an enzyme-linked immunospot assay for interferon-γ in cutaneous tuberculosis. *Diagnostic microbiology and infectious disease*, 70(1), 60-64. <https://doi.org/10.1016/j.diagmicrobio.2010.11.012>
37. Santos, J. B., Figueiredo, A. R., Ferraz, C. E., Oliveira, M. H., Silva, P. G., & Medeiros, V. L. (2014). Cutaneous tuberculosis: diagnosis, histopathology, and treatment - part II. *Anais brasileiros de dermatologia*, 89(4), 545-555. <https://doi.org/10.1590/abd1806-4841.20142747>
38. Nowowiejska, J., Krahel, J., Baran, A., & Flisiak, I. (2020). Lupus vulgaris of the auricle. *Dermatology Review/Przegląd Dermatologiczny*, 107(1), 78-83. <https://doi.org/10.5114/dr.2020.93976>
39. Parajuli, Niraj & Jha, Harendra & Jonkman, Marcel. (2019). Giant Arcuate Lupus Vulgaris with Rapid Progression: A Case Report. *Journal of Nepal Medical Association*. 57. 10.31729/jnma.4453.
40. Afsar, FS, Afsar, I, Diniz, G, Asilsoy, S, & Sorgue, Y (2008). Lupus Vulgaris in a Pediatric Patient: A Clinicopathological Diagnosis. *The Brazilian Journal of Infectious Diseases*. 12(2):152-154.
41. Pugalia N, Madke B, Jawade S (June 16, 2023) Multifocal Lupus Vulgaris: A Rare Presentation. *Cureus* 15(6): e40495. doi:10.7759/cureus.40495
42. Murugan S, Vetrichevel T P, Subramanyam S, Subramanian A. (2011). Childhood multicentric lupus vulgaris. *Indian J Dermatol*. 56:343-4
43. Prabha, N., Daman-Arora, R., Khare, S., & Sharma, A. (2019). Lupus Vulgaris of the Pinna-A Case Report. *Iranian journal of otorhinolaryngology*, 31(105), 247-249.

## Sibling Pair with Incomplete Feature of Netherton Syndrome: A Case Report\*

Leonard Jansen M. Cua, MD<sup>1</sup>; Matthew David S. Parco, MD, DPDS<sup>2</sup>; Faye Elinore V. Kison, MD, DPDS<sup>3</sup>; Camelia Faye R. Tuazon, MD, FPDS<sup>4</sup>; Benedicto dL. Carpio, MD, FPDS<sup>5</sup>; Eileen R. Morales, MD, FPDS<sup>6</sup>; Armelia L. Torres, MD, FPDS<sup>7</sup>; Amelita Tanglao-De Guzman, MD, FPDS-FDSP-PDS<sup>8</sup>

### ABSTRACT

**Introduction:** Netherton Syndrome (NS) is characterized by a triad of congenital ichthyosiform erythroderma, trichorrhexis invaginata, and atopic diathesis. Diagnosis of NS poses a challenge due to its variable presentation and overlap with other dermatological conditions. Herein, we report a case of NS in a sibling pair, underscoring the challenges in diagnosis and genetic implications of this condition.

**Case Summary:** We present a case of an 8-year-old female and a 7-year-old male sibling pair, with Netherton Syndrome, who initially presented with atopic dermatitis and erythroderma without hair shaft abnormalities. Further investigation and genetic testing revealed homogeneous SPINK5 gene mutations in both patients, leading to the diagnosis of NS.

**Conclusion:** Early recognition and diagnosis of Netherton Syndrome are essential for proper management. In patients with early-onset atopic dermatitis resistant to treatment and recurrent erythroderma, further investigation is needed to exclude other diagnoses like Netherton Syndrome.

**Keywords:** Netherton Syndrome, hair shaft abnormalities, atopic diathesis, case report, sibling pair

### INTRODUCTION

Netherton Syndrome (NS), first described by Comèl in 1949, is a rare genetic disorder with an estimated incidence of 1 in 200,000 live births.<sup>1</sup> It is caused by mutations in the serine protease inhibitor of the Kazal type 5 (SPINK5) gene on chromosome 5q32, encoding the lympho-epithelial Kazal-type-related inhibitor (LEKTI), a serine protease inhibitor of the epidermis, instrumental in maintaining skin barrier function.<sup>2</sup> As pathogenic autosomal recessive homozygous or compound heterozygous variants of the SPINK5 gene occur, a continual breakdown of the skin barrier with secondary inflammation occurs.<sup>2</sup> The deficiency of LEKTI in hair follicle inner root sheaths and the epidermal granular layer results in a loss of inhibition of serine proteinases and unopposed activity of kallikrein-related peptidase 5 (KLK5).<sup>2</sup> Unopposed KLK5 activates KLK7, KLK14 and elastase 2, leading to desmosomal cadherin component desmoglein 1 and other corneodesmosomal protein degradation, resulting in cell adhesion loss

desquamation, and early stratum corneum detachment, and ultimately severe skin barrier impairment.<sup>2</sup> KLK5 also triggers the secretion of proinflammatory proallergic cytokines through proteinase-activated receptor 2 (PAR2) signaling in keratinocytes.<sup>2</sup> Increased mediators, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), intracellular adhesion molecule 1 (ICAM-1), interleukin-8 (IL-8) and thymic stromal lymphopoietin (TSLP), heighten allergic predisposition and secondary inflammation.<sup>2</sup> Marked upregulation of T helper type 17 (TH17)/IL-23 pathway and IL-1 $\beta$  expression is also seen in NS patients.<sup>3</sup>

NS is clinically characterized by a triad of manifestations, including congenital ichthyosiform erythroderma, trichorrhexis invaginata (TI) (bamboo hair), and atopic diathesis.<sup>4</sup> Diagnosis of NS poses a challenge due to its variable presentation and overlap with other dermatological conditions. In this paper, we report a case of NS in a sibling pair, highlighting the challenges in diagnosing and managing this condition.

*Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.*

<sup>1</sup>Resident, Department of Dermatology, Ospital ng Maynila Medical Center

<sup>2</sup>Assistant Training Officer, Academic Head and Research Coordinator, Department of Dermatology, Ospital ng Maynila Medical Center

<sup>3</sup>Assistant Academic and Research Coordinator, Department of Dermatology, Ospital ng Maynila Medical Center

<sup>4</sup>Pediatric Dermatology Consultant, Department of Dermatology, Ospital ng Maynila Medical Center,

<sup>5</sup>Chairman Emeritus, Department of Dermatology, Ospital ng Maynila Medical Center

<sup>6</sup>Chairperson, Department of Dermatology, Ospital ng Maynila Medical Center

<sup>7</sup>Training Officer and Research Coordinator, Department of Dermatology, Ospital ng Maynila Medical Center

<sup>8</sup>Dermatopathologist, Department of Dermatology, Ospital ng Maynila Medical Center



## CASE REPORT

We present the case of an 8-year-old female and a 7-year-old male sibling, born to non-consanguineous parents, who both presented with atopic dermatitis and frequent erythroderma since infancy. The younger sibling was born to a then 24-year-old G2P2 mother. Both pregnancies and deliveries were unremarkable, and both had normal results for Newborn screening.

At birth, both siblings presented with erythematous papules, patches, and plaques on the bilateral cheeks without scaling. In the first few weeks of life, these initial lesions evolved to include the face, trunk, back, axilla, and bilateral extremities. The siblings were noted to be irritable, probably due to pruritus. They were initially diagnosed with Atopic Dermatitis and managed with topical steroids, moisturizing lotion, and petrolatum, which afforded temporary improvement of the lesions.

Both siblings developed recurrent exfoliative dermatitis during infancy up to early childhood, occurring at least twice a year. They had frequent admissions for "skin infection," where antibiotics and petrolatum would be prescribed.

Due to the chronicity and recurrence of the disease, the mother decided to seek a second opinion at our institution when the female sibling was 8 years old and the male sibling was 7 years old. The review of systems for both siblings was unremarkable. Past medical history revealed atopic diathesis in both siblings. Family history was positive for atopic dermatitis on the maternal side (see genogram).

On physical examination, both presented with generalized well-defined erythematous to hyperpigmented annular patches and plaques topped with polycyclic scales, more pronounced on the flexural areas. For the younger male sibling, there was yellow discoloration of the nails with onycholysis, while the elder female sibling had no nail changes. Neither presented with the characteristic bamboo hair, even under close examination through dermoscopy and light microscopy.

The siblings were clinically diagnosed as a case of Ichthyosis, probably epidermolytic ichthyosis versus Netherton Syndrome, due to the presence of atopic diathesis and Ichthyosis. However, hair shaft abnormalities were absent. Biopsies on both siblings revealed: 1) psoriasiform epidermal hyperplasia, 2) thin strands of parakeratosis (1-2 layers), 3) loss of most of the stratum corneum, some sections showing focal basketweave ortho-hyperkeratosis, 4) with normal granular layer, and no signs of epidermolytic hyperkeratosis, 5) widened intercellular spaces of keratinocytes in the epidermis without blistering, and 6) sparse to moderate superficial

perivascular infiltrate of lymphocytes and histiocytes. The assessment given was Psoriasiform Dermatitis with the differential diagnosis of Netherton Syndrome. Molecular genetic work-up was suggested.

Patients were referred to a tertiary pediatric institution for genetic counseling. A congenital ichthyosis panel was recommended and performed. Genetic testing confirmed homozygous mutations in the SPINK5 gene (Exon 10, c.880\_882del (p.Val294del)) and heterozygous mutations in the CYP4F22 gene (c.470G>A (p.Arg157His)) in both siblings, confirming the diagnosis of Netherton Syndrome [see **Figure 8**].

Both patients were treated with antihistamines, mineral oil for the scalp, tar shampoo, isotretinoin, emollients, and bleach baths, which afforded improvement of the symptoms. Prior to initiation of oral isotretinoin treatment, baseline laboratory tests (skeletal survey, complete blood count, urinalysis, kidney and liver function tests, lipid profile, fasting blood sugar, and serum cortisol) were performed, with regular follow-up tests. Due to chronic use of topical steroids, referral to Pediatric Endocrinology for evaluation for endocrine disorders and for co-management was done. The service recommended no further diagnostics and treatments, suggesting assessments to include growth velocity, weight, blood pressure, and general well-being, as the patients showed no signs of adrenal insufficiency. Regular teledermatology follow-up showed good compliance and tolerance to prescribed medications, with no significant adverse effects. Follow-up after 6 months of isotretinoin treatment [**Figure 9 and 10**] showed a decrease in the number and erythema of the previous erythematous patches and plaques topped with polycyclic scales. A trial of biologic, an IL-17A inhibitor, was recommended as a treatment option; however, due to financial constraints, it was not given.

## DISCUSSION

Netherton Syndrome presents with a spectrum of clinical manifestations ranging from mild to severe.<sup>4</sup> The congenital ichthyosiform erythroderma, characterized by generalized erythema and fine scales, typically manifests at birth and may resemble other forms of congenital ichthyosis, necessitating a thorough differential diagnosis.<sup>5</sup> Trichorrhexis invaginata (TI), resulting from abnormal formation of hair shafts, is pathognomonic for NS.<sup>6</sup> Atopic diathesis, including allergic rhinitis, asthma, and atopic dermatitis, is commonly observed in NS patients, reflecting immune response dysregulation.<sup>7</sup> Genetic testing plays a crucial role in confirming the diagnosis, with SPINK5 mutations identified in the

majority of cases.<sup>8</sup> NS is typically diagnosed upon the presence of allergic manifestations, with the presence of: history of NS in a sibling, identification of SPINK5 mutation by DNA sequencing, scaling erythroderma or hair shaft abnormalities.<sup>9</sup>

In diagnosing NS, a thorough history and physical exam is pertinent. Leung, et.al., presented a case report of an 8-year-old male with sparse hair and erythematous serpiginous patches topped with scales since childhood who was assessed with severe atopic dermatitis.<sup>10</sup> A careful physical exam in another institution revealed the triad of NS, clinching the diagnosis.<sup>10</sup> The presentation of NS in this sibling pair, however, highlights the importance of genetic testing in cases of incomplete features of a possible Netherton Syndrome. In cases presenting with chronic atopic diathesis and erythroderma not responsive to conventional treatment, further molecular testing should be considered for Netherton Syndrome. For dermatologists who encounter numerous pediatric patients, the differential of NS may be kept in mind when assessing patients with the diagnosis of chronic, recurrent, and severe atopic dermatitis<sup>9</sup> [see **Figure 11**]. In a case report by Saleem, et. al, the authors note that NS is usually misdiagnosed as atopic dermatitis due to the presence of allergic manifestations and eczematous skin lesions.<sup>9</sup> It is important to note that we should still include NS in our differentials even if the TI is not observed, as in our case. A similar case of a 2-year-old with NS did not have the pathognomonic symptom of TI.<sup>9</sup> In another case report by Guerra et al., two siblings who first presented with cheek erythema, and later with sparse Ichthyosis linearis circumflexa lesions on the face, trunk and proximal extremities, had the absence of both atopy and TI.<sup>11</sup> The diagnosis of NS was only determined upon genetic testing.<sup>11</sup> In our patients, the presence of skin lesions at birth, which is not a usual presentation of Atopic Dermatitis, should also prompt dermatologists to consider Netherton Syndrome and other genetic skin diseases. Misdiagnosis or delays in diagnosis can occur when the specific features of NS are not evident.

Genetic testing plays a crucial role in confirming the diagnosis, identifying causative mutations, facilitating genetic counseling and guiding family planning.<sup>12</sup> Management of NS involves a multidisciplinary approach focusing on symptomatic relief, prevention of complications, improving quality of life, and genetic counseling for affected families.<sup>4</sup> For this sibling pair, there was close collaboration with the patient's pediatrician who co-managed frequent systemic infections. Due to their rural location, access to pediatric subspecialties was unfortunately limited, but the family

was referred to geneticists who provided genetic counseling as part of their management. A recommendation for referral to Family Medicine for holistic care, addressing not only physical but also social, emotional, and overall well-being, was also made.

In the case of the sibling pair diagnosed genetically with NS, treatment strategies must be tailored to address the diverse manifestations and needs of each patient. Treatments include: emollients, topical therapies, topical corticosteroids, topical calcineurin inhibitors, UV phototherapy, systemic therapies such as oral retinoids and immunomodulators, supportive care, and multidisciplinary management.<sup>4</sup>

Natural and synthetic retinoids derived from vitamin A have been the primary treatment for ichthyosis in newborns to adults for decades.<sup>13</sup> They have shown efficacy in NS by modulating keratinocyte differentiation, proliferation, and reducing tissue inflammation, leading to less thickening, scaling, and erythema.<sup>14</sup> For NS, four retinoids (acitretin, alitretinoin, isotretinoin, and etretinate) have been utilized as therapy with varied outcomes.<sup>14</sup> A systematic review by Nouwen, et. al, noted six patients with NS improving with retinoids, with a reduction in the need for topical corticosteroids.<sup>14</sup> The authors noted retinoids were effective in NS patients in which scaling is more pronounced than erythema, suggesting that the benefits of such treatment may be suited for certain subtypes of NS, leaving retinoids as second-line treatment.<sup>14</sup>

Current investigation into the use of biologics for Netherton Syndrome is being done. Allergic and inflammatory pathways are upregulated in patients with NS as a result of SPINK5 gene mutation and LEKTI deficiency, particularly with both Th2 and Th17 pathways amplified and high levels of TNF- $\alpha$  and IgE present.<sup>15</sup> Seven biologics have been investigated, including those that target IgE (omalizumab), TNF- $\alpha$  (adalimumab, infliximab), IL 12 and IL-23 (ustekinumab), IL-4 and IL-13 (dupilumab), and IL-17 (secukinumab, ixekizumab).<sup>14</sup> In 18 previous cases, these treatments led to clinical improvement, reducing inflammatory lesions, desquamation, and pruritus. Quality of life, hair condition, and sleep improved, while the need for topical corticosteroids and infections decreased.<sup>14</sup> However, studies have shown that different cases of NS have responded to different biologic drugs available, with investigators suggesting that clinical phenotype, and presumably differences in pathway activity between patients, could lead to individual NS patients benefiting from different treatments.<sup>14</sup> For this sibling pair, secukinumab, an IL-17A inhibitor, was offered as a

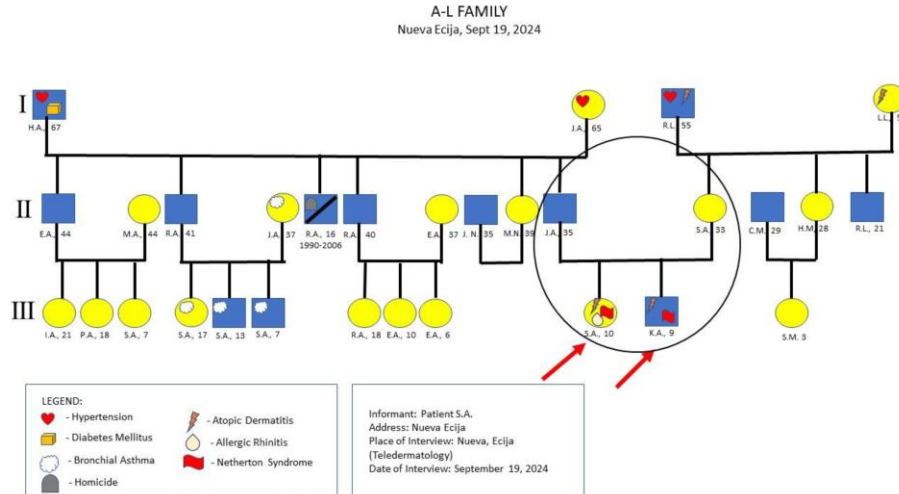
treatment option; however, consent to begin treatment was not obtained due to financial constraints. As such, oral isotretinoin, antihistamines, mineral oil, tar shampoo, topical corticosteroids, urea solution, emollients, and bleach baths were used, leading to symptom improvement, fewer admissions, and no significant side effects.

## CONCLUSION

Netherton Syndrome is a rare genetic disorder characterized by congenital ichthyosiform erythroderma, hair shaft abnormalities, and atopic diathesis. The management of Netherton Syndrome requires a multifaceted approach encompassing topical therapies, phototherapy, systemic agents, and supportive care. Early recognition and diagnosis are crucial for appropriate management. In patients who present with early-onset atopic dermatitis recalcitrant to treatment and frequent erythroderma, Netherton Syndrome should be considered, and further investigation is warranted. Individualized treatment plans should be tailored to address the specific needs and manifestations of each patient, with a focus on optimizing symptom control, preventing complications, and improving long-term outcomes. Close collaboration between healthcare providers and ongoing research efforts is essential to advance our understanding and management of this rare genetic disorder. Further research into the pathophysiology of NS and the development of targeted therapies is warranted to improve outcomes for affected individuals.

## REFERENCES

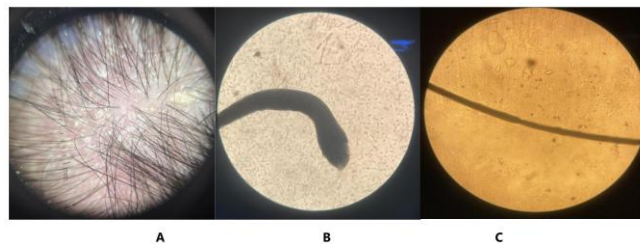
1. Emre S, Metin A, Demirseren D, et al. Two siblings with Netherton syndrome. *Turk J Med Sci*. 2010;40(5):819–823.
2. Hovnanian A. Netherton syndrome: skin inflammation and allergy by loss of protease inhibition. *Cell Tissue Res*. 2013;351(2):289–300. doi:10.1007/s00441-013-1558-1.
3. Paller AS, Renert-Yuval Y, Suprun M, Esaki H, Oliva M, Huynh TN, et al. An IL-17-dominant immune profile is shared across the major orphan forms of ichthyosis. *J Allergy Clin Immunol*. 2017;139(1):152–165. doi:10.1016/j.jaci.2016.07.019.
4. Barbati F, Giovannini M, Oranges T, et al. Netherton syndrome in children: management and future perspectives. *Front Pediatr*. 2021;9:645259. doi:10.3389/fped.2021.645259.
5. Boskabadi H, Maamouri G, Mafinezhad S. Netherton syndrome: a case report and review of literature. *Iran J Pediatr*. 2013;23(5):611–612.
6. Salodkar AD, Choudhary SV, Jadwani G, Singh A. Bamboo hair in Netherton's syndrome. *Int J Trichology*. 2009;1(2):143–144. doi:10.4103/0974-7753.58561.
7. Kumar R, Abhinandan HB, Mehta P, Jain S. Netherton's syndrome. *Indian J Paediatr Dermatol*. 2014;15(3):120–122. doi:10.4103/2319-7250.143665.
8. Raghunath M, Tontsidou L, Oji V, et al. SPINK5 and Netherton syndrome: novel mutations, demonstration of missing LEKTI, and differential expression of transglutaminases. *J Invest Dermatol*. 2004;123(3):474–483. doi:10.1111/j.0022-202X.2004.23220.x.
9. Saleem HMK, Shahid MF, Shahbaz A, Sohail A, Shahid MA, Sachmechi I. Netherton syndrome: a case report and review of literature. *Cureus*. 2018;10(7):e3070. doi:10.7759/cureus.3070.
10. Leung AKC, Barankin B, Leong KF. An 8-year-old child with delayed diagnosis of Netherton syndrome. *Case Rep Pediatr*. 2018;2018:9434916. doi:10.1155/2018/9434916.
11. Guerra L, Fortugno P, Pedicelli C, et al. Ichthyosis linearis circumflexa as the only clinical manifestation of Netherton syndrome. *Acta Derm Venereol*. 2015;95(6):720–724. doi:10.2340/00015555-2075.
12. Herz-Ruelas ME, Chavez-Alvarez S, Garza-Chapa JJ, Ocampo-Candiani J, Cab-Morales VA, Kubelis-López DE. Netherton syndrome: case report and review of the literature. *Skin Appendage Disord*. 2021;7(5):346–350. doi:10.1159/000514699.
13. Digiovanna JJ, Mauro T, Milstone LM, Schmuth M, Toro JR. Systemic retinoids in the management of ichthyoses and related skin types. *Dermatol Ther*. 2013;26(1):26–38. doi:10.1111/j.1529-8019.2012.01527.x.
14. Nouwen AEM, Schappin R, Nguyen NT, et al. Outcomes of systemic treatment in children and adults with Netherton syndrome: a systematic review. *Front Immunol*. 2022;13:864449. doi:10.3389/fimmu.2022.864449.
15. Malik K, He H, Huynh TN, Tran G, Mueller K, Doytcheva K, et al. Ichthyosis molecular fingerprinting shows profound TH17 skewing and a unique barrier genomic signature. *J Allergy Clin Immunol*. 2019;143(2):604–618. doi:10.1016/j.jaci.2018.03.021.



**Figure 1:** Genogram of the male and female sibling pair showing a family history of maternal Atopic Dermatitis, with Hypertension on both sides and Diabetes Mellitus on the paternal side. Consent on personal and family information was obtained.



**Figure 2:** Images of the 8 year old female sibling diagnosed with Netherton Syndrome. The patient presented with generalized, well-defined erythematous to hyperpigmented annular patches and plaques topped with polycyclic scales. There was involvement of the face and scalp (A), trunk and abdomen (E, F), and bilateral upper and lower extremities, with more pronounced polycyclic scales on the flexural areas (H, I). Nail findings were unremarkable (J).

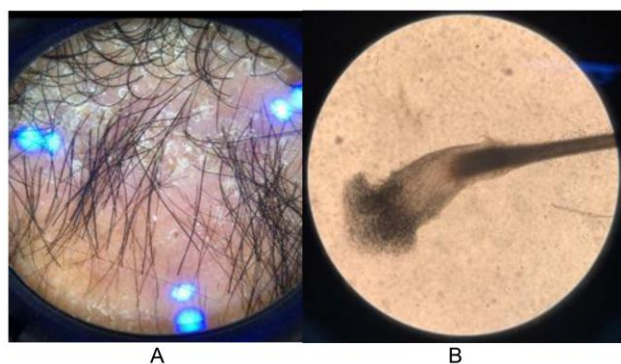


**Figure 3:** Hair examination of the 8 year old female sibling. While examination revealed erythematous patches topped with scales, sparse, brittle hair was not seen (A). Closer examination of the hair root (B) and hair shaft (C) did not reveal trichorrhexis invaginata.

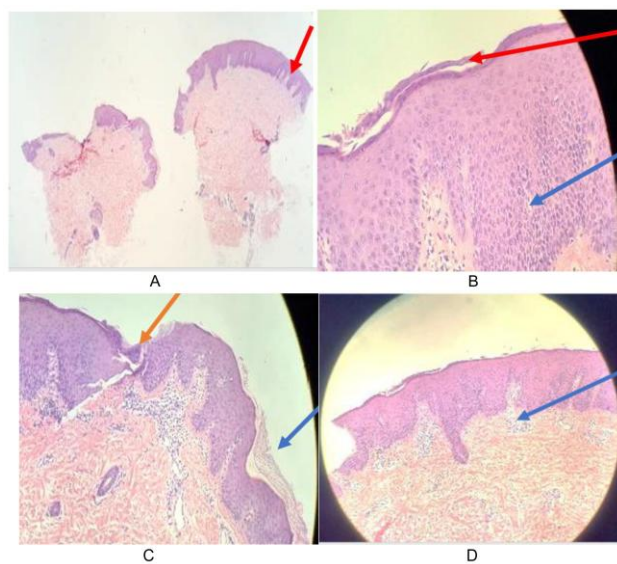




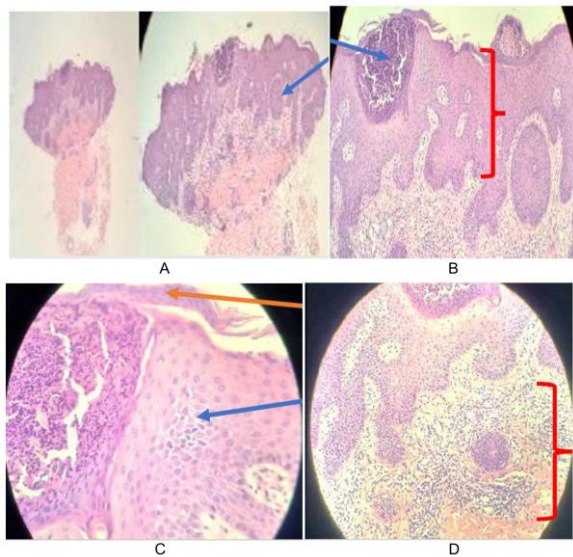
**Figure 4:** Images of the 7 year old male sibling diagnosed with Netherton Syndrome. The patient also presented with generalized, well-defined erythematous to hyperpigmented annular patches and plaques topped with polycyclic scales. There was involvement of the face and scalp (A), trunk and abdomen (E, F), and bilateral upper and lower extremities (G, H), with more pronounced polycyclic scales on the flexural areas (H, I). Nail findings revealed yellow discoloration with onycholysis (J).



**Figure 5:** Hair examination of the male sibling. Hair examination showed the absence of the classic trichorrhexis invaginata (A, B)



**Figure 6:** Biopsy report of the female sibling revealing 1) psoriasiform epidermal hyperplasia (A), 2) thin strands of parakeratosis (1-2 layers) (B, red arrow), 3) loss of most of the stratum corneum (C, red arrow), one section showing focal basketweave ortho-hyperkeratosis (C, blue arrow), 4) granular layer normal and showing no signs of degeneration or epidermolytic hyperkeratosis, 5) widened intercellular spaces of keratinocytes in the epidermis without blistering (B, blue arrow), and 6) sparse to moderate superficial perivascular infiltrate of lymphocytes and histiocytes (D).



**Figure 7:** Biopsy report of the male sibling, revealing 1) psoriasiform hyperplasia (A), subcorneal pustule (B, blue arrow) and ortho-hyperkeratosis (B, red bracket), 2) clusters of neutrophils, some forming small superficial pustules beneath thin parakeratotic strands (C, red arrow), 3) widened intracellular spaces without blister formation in the spinous layer (C, blue arrow) and 4) moderately dense superficial perivascular infiltrate of lymphocytes, histiocytes, eosinophils and melanophages; dilated small blood vessels (D, red bracket).

#### Variant details

CYP4F22, Exon 6, c.470G>A (p.Arg157His), heterozygous, Uncertain Significance

- This sequence change replaces arginine, which is basic and polar, with histidine, which is basic and polar, at codon 157 of the CYP4F22 protein (p.Arg157His).
- This variant is present in population databases (rs199641250, gnomAD 0.03%).
- This variant has not been reported in the literature in individuals affected with CYP4F22-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 1030320).
- Algorithms developed to predict the effect of missense changes on protein structure and function are either unavailable or do not agree on the potential impact of this missense change (SIFT: "Deleterious"; PolyPhen-2: "Probably Damaging"; Align-GVGD: "Class C0").
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

A

SPINK5, Exon 10, c.880\_882del (p.Val294del), homozygous, Uncertain Significance

- This variant, c.880\_882del, results in the deletion of 1 amino acid(s) of the SPINK5 protein (p.Val294del), but otherwise preserves the integrity of the reading frame. This variant also falls at the last nucleotide of exon 10, which is part of the consensus splice site for this exon.
- This variant is present in population databases (rs750225476, gnomAD 0.003%).
- This variant has been observed in individual(s) with Netherton syndrome (PMID: 16601670).
- This variant is also known as c.882+1\_882+3del.
- Variants that disrupt the consensus splice site are a relatively common cause of aberrant splicing (PMID: 17576681, 9536098). Algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant may disrupt the consensus splice site.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

#### Variant details

CYP4F22, Exon 6, c.470G>A (p.Arg157His), heterozygous, Uncertain Significance

- This sequence change replaces arginine, which is basic and polar, with histidine, which is basic and polar, at codon 157 of the CYP4F22 protein (p.Arg157His).
- This variant is present in population databases (rs199641250, gnomAD 0.03%).
- This variant has not been reported in the literature in individuals affected with CYP4F22-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 1030320).
- Algorithms developed to predict the effect of missense changes on protein structure and function are either unavailable or do not agree on the potential impact of this missense change (SIFT: "Deleterious"; PolyPhen-2: "Probably Damaging"; Align-GVGD: "Class C0").
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

B

SPINK5, Exon 10, c.880\_882del (p.Val294del), homozygous, Uncertain Significance

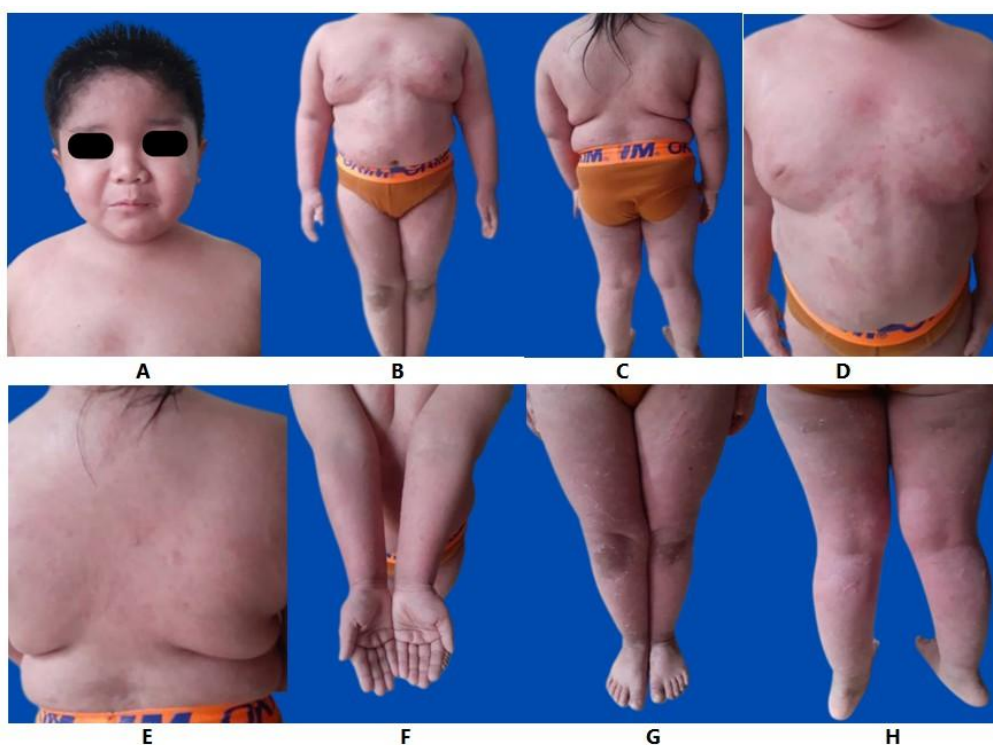
- This variant, c.880\_882del, results in the deletion of 1 amino acid(s) of the SPINK5 protein (p.Val294del), but otherwise preserves the integrity of the reading frame. This variant also falls at the last nucleotide of exon 10, which is part of the consensus splice site for this exon.
- This variant is present in population databases (rs750225476, gnomAD 0.003%).
- This variant has been observed in individual(s) with Netherton syndrome (PMID: 16601670).
- This variant is also known as c.882+1\_882+3del.
- Variants that disrupt the consensus splice site are a relatively common cause of aberrant splicing (PMID: 17576681, 9536098). Algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant may disrupt the consensus splice site.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

**Figure 8:** Genetic Testing Result for the female sibling (labeled A) and male sibling (labeled B). Results show homozygous variant c.880\_882del (p.Val294del) for the SPINK 5 gene and heterozygous variant c.470G>A (p.Arg157His) of the CYP4F22 gene for both siblings.

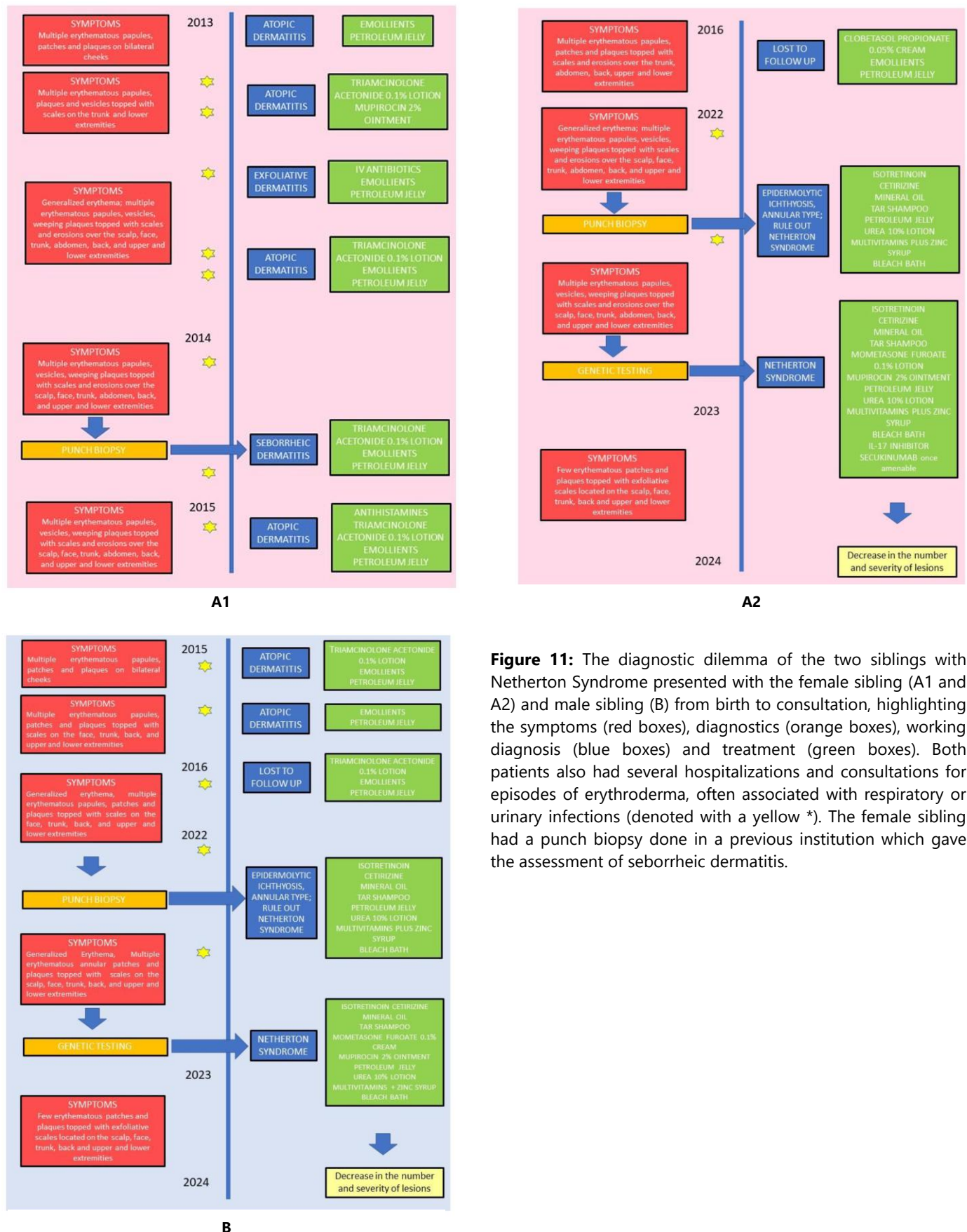




**Figure 9:** Follow up image through teler dermatology of the female Netherton Syndrome sibling after 6 months initiation of Isotretinoin. There was a noted decrease in the multiple erythematous patches and plaques, topped with scales over the face and scalp (A), trunk (D, E), upper extremities (F) and lower extremities (G, H).



**Figure 10:** Follow up image through teler dermatology of the male Netherton Syndrome sibling after 6 months initiation of Isotretinoin. There was a noted decrease in the multiple erythematous patches and plaques, topped with scales over the face and scalp (A), trunk (D, E), upper extremities (F) and lower extremities (G, H).



**Figure 11:** The diagnostic dilemma of the two siblings with Netherton Syndrome presented with the female sibling (A1 and A2) and male sibling (B) from birth to consultation, highlighting the symptoms (red boxes), diagnostics (orange boxes), working diagnosis (blue boxes) and treatment (green boxes). Both patients also had several hospitalizations and consultations for episodes of erythroderma, often associated with respiratory or urinary infections (denoted with a yellow \*). The female sibling had a punch biopsy done in a previous institution which gave the assessment of seborrheic dermatitis.



## The Use of Double M-Plasty Technique for Excisional Biopsy on a Rare Case of Poroid Hidradenoma in 68-Year Old Filipino Male: A Case Report\*

Celina Faye C. Manalastas, MD<sup>1</sup>; Ma. Christina Gulfan, MD, FPDS<sup>2</sup>; Mary Grace Anne Calvarido, MD, FPDS, FDSP-PDS<sup>2</sup>

### ABSTRACT

**Background:** Poroid hidradenoma is a benign neoplasm with eccrine differentiation. In literature, only few cases of poroid hidradenoma are reported. The description of this tumor, and its dermoscopic features are rarely reported. It commonly presents as a solitary, asymptomatic dermal nodule that can be solid and/or cystic, and ranges from flesh-colored to red to bluish in color, with a diameter between 1–2 cm. The most frequent site of involvement is the head and neck. The tumor has been documented in patients aged from 13 to 97 years, with peak incidence in the sixth decade of life. Poroid hidradenoma shows architectural features of hidradenoma and cytologic features of poroid neoplasms in histology. To prevent the recurrence of the lesion, a complete surgical excision of the lesion is required.

**Case Summary:** This is a case of a 68-year old Filipino male from a tertiary hospital in Pangasinan who presented with a 9-month history of solitary, skin colored papule on the right forearm, gradually increasing in size evolving into a solitary, erythematous, nodule with crusts, yellowish discharge, and bleeding. Based on clinicopathological correlation, a diagnosis of Poroid Hidradenoma was revealed. The lesion was surgically excised with a double M-plasty technique. The surgical wound healed well with normal scarring. No signs of recurrence were noted for the last 6 months after the surgical procedure. The patient was advised for a yearly follow-up for the first 2 years for monitoring.

**Conclusion:** Poroid hidradenoma may pose a diagnostic dilemma since only few cases of PH have been reported in literature. There is an inadequate discussion on the diagnosis, clinical features, and management of this neoplasm. It would be valuable to gain more information about the epidemiological features, rates of recurrence and malignant transformation of poroid hidradenoma if there are more case reported.

**Keywords:** *poroid hidradenoma, double M-plasty, eccrine neoplasm*

### INTRODUCTION

Poroid hidradenoma (PH) is a benign neoplasm with eccrine differentiation described by Abenzo and Ackerman in 1990. In literature, there is a dearth of cases of poroid hidradenoma are reported. The description of this tumor, and its dermoscopic features are rarely reported. Poroid hidradenoma usually presents as a solitary, asymptomatic dermal nodule that can be solid and/or cystic, and ranges from flesh-colored to red to bluish in color, with a diameter between 1–2 cm. The most frequent site of involvement is the head and neck. The tumor has been documented in patients aged from 13 to 97 years, with peak incidence in the sixth decade of life. (Somaiah et al., 2022). Poroid hidradenoma shows architectural features of hidradenoma and cytologic features of poroid neoplasms in histology. To prevent the recurrence of the lesion, a complete surgical excision of the lesion is required.

### Objective

To report a rare case of Poroid Hidradenoma and the surgical excisional technique done in a 68-year old Filipino Male.

### CASE REPORT

This is a case of a 68-year old Filipino male from a tertiary hospital in Pangasinan who presented with a 9-month history of a solitary, skin colored papule on the right forearm, gradually increasing in size, evolving to an erythematous nodule with crusts, yellowish discharge, and bleeding, accompanied by pruritus and tenderness with a pain scale 6/10. Patient admits to inflicting trauma on the lesion as a result of constant scratching. No other associated signs and symptoms such as fever was noted. No consult was done. No medications were taken nor applied. Concurrently, the patient had a longstanding 10-year history of multiple, skin colored papules in the upper extremities. Patient had it excised at another institution last 2012 with an unrecalled assessment. No biopsy was done. The lesions were gradually increasing in numbers and size, now noted to be multiple, well circumscribed, soft, movable skin colored nodules on the upper extremities. No other associated signs and symptoms such as pruritus, tenderness, fever, bleeding was noted. Persistence of the lesions prompted consult.

---

*Disclosures: The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.*

**\*Department of Dermatology, Region 1 Medical Center, Dagupan City**

**<sup>1</sup>Primary Author; <sup>2</sup>Co-Authors; <sup>2</sup>Consultants, Department of Dermatology**

**E-Poster was presented in the 5<sup>th</sup> Asian Society of Dermatopathology Annual Meeting last January 2024 at Osaka, Japan.**



The patient's past medical history was non-contributory. Family history was unremarkable, and no other family members had similar lesions. Physical examination revealed a solitary erythematous, 3 cm x 2.5 cm nodule on the antecubital fossa topped with crust and yellowish discharge (*Figure 1.*) and multiple well circumscribed, soft, movable skin colored nodules on the upper extremities. (*Figure 2.*)

Dermoscopy revealed the presence of crust, blue-grey pigmented areas, and a peripheric polymorphous vascular pattern with glomerular and hairpin vessels. (*Figure 3.*)

The lesions were surgically excised under local anesthesia in 2 sites: site A: solitary, erythematous, 3 cm x 2.5 cm nodule and site B: multiple, well circumscribed, soft, movable skin colored nodules on the right forearm. A double M-plasty excisional technique was done on site A and was carried out based on the following: A standard ellipse is marked surrounding the lesion to be excised. Points "A" on the main axis are placed 1 mm from the border of the lesion and points "B" are situated at the midpoint of the section between point "A" and the apex of the ellipse. The lines perpendicular to the long axis are then drawn through each point "B"; these lines will give 4 points "C" at the intersections of the perpendiculars with the outline of the ellipse, allowing 4 line segments "A to C" to be drawn. (*Figure 4.*) (Agorio et al., 2016) The lesion was excised in toto and the surgical defect closed primarily with the use of both dermal and epidermal sutures.

After the procedure, the patient was discharged with home medications on the same day with no complications reported. The patient was instructed to follow-up during the first and second post-operative week for staged removal of sutures. (*Figure 5.*) The surgical wound healed well with normal scarring. On follow-up, the patient received no further therapy, and no signs of recurrence were noted for the proceeding 6 months. The patient was advised yearly follow-up for the first 2 years for close monitoring.

Histopathologic findings on hematoxylin-and-eosin-stained paraffin sections of Specimen "A" revealed circumscribed dermal proliferation of cuboidal epithelial cells, some of which had an abundant pale cytoplasm. There was an area with inter-anastomosing array in continuity with the surface epidermis. Conspicuous foci of ductular differentiation with areas of necrosis were seen. The accompanying stroma was highly vascularized and sclerotic and holds a lymphohistiocytic infiltrate.

Occasional mitotic figures were also noted. There was a secondary bacterial infection present. Histological confirmation of the diagnosis was Poroid Hidradenoma. Based on clinicopathological correlation, a diagnosis of Poroid Hidradenoma was made. (*Figure 6.*)

Histopathologic findings on hematoxylin-and-eosin-stained paraffin sections of Specimen "B" revealed a well circumscribed, encapsulated, and lobulated lesion composed of proliferation of mature adipocytes with thin and hypocellular septa containing thin walled capillaries. No signs of malignancy were captured in the biopsy. Histological confirmation of the diagnosis was Lipoma. (*Figure 7.*)

## DISCUSSION

Poroid hidradenoma is an uncommon benign cutaneous variant of the eccrine poroma. It can occur in any age group but the highest incidence is seen in the sixth decade of life. Poroid Hidradenoma presents as a solitary, tender papule or nodule, well-circumscribed. The lesion usually measures from 1 to 2cm in diameter and is often asymptomatic. Poroid hidradenoma appears from flesh-colored to red to bluish in color but the presence of cystic parts may confer a blue color on the lesion caused by the Tyndall phenomenon. The most common sites of involvement are the head and neck regions, and less frequently involves the trunk and extremities, as seen in this patient. The clinical differential diagnoses of poroid hidradenoma may include hidroacanthoma simplex, dermal duct tumor, eccrine poroma, and apocrine hidradenomas, fibroma, fibrolipoma, dermatofibroma, hemangioma, pyogenic granuloma, epidermal inclusion cyst, basal cell epithelioma, and malignant eccrine poroma. As the possible differential diagnoses are varied, the clinical diagnosis of poroid hidradenoma may be challenging. Four histopathologic variants are identified in poromas according to the architectural features of the neoplasm: hidradenoma simplex or intraepidermal poroma, eccrine poroma, dermal duct tumor, and poroid hidradenoma. Poroid hidradenoma is a tumor with solid and cystic components, in which neoplastic poroid cells are all located within the dermis and without connection to the epidermis. This neoplasm presents the architectural features of hidradenoma, with solid and cystic areas and cytological features of poroid neoplasm such as poroid and cuticular cells. The diagnosis of poroid hidradenoma is based on clinico-pathologic examination. These cutaneous neoplasms are considered benign, but there is a risk of



malignant transformation which is less than 1%. Poroid hidradenoma is managed with total excision of the lesion which is curative, minimize the risk of malignant transformation and prevention of its recurrence. A double M-plasty technique is widely used for the resection of benign and malignant lesions. This technique is used to make direct closure of a wound possible with lower tension and a shorter scar length. It also has the advantage of leaving a scar that shows exactly where the lesion was located prior to removal of the lesion, which will enable us greater control over the width of the surgical margins and to minimize the need to excise excessive tissue. The prognosis of Poroid Hidradenoma is relatively good, complications and recurrence have rarely been reported. Up to this date, only few cases of PHs have been reported.

## CONCLUSION

Poroid hidradenoma is a form of hidradenoma with eccrine differentiation. It may pose a diagnostic dilemma since only few (17 cases) of PH have been reported in literature. There is an inadequate discussion on the background information of this neoplasm, the clinical diagnostics, its features, and treatment of poroid hidradenoma. In the previous case reports, poroid hidradenoma has a malignant transformation rate of 1%, but there was an insufficient evidence to support this. It would be valuable to gain more information about the epidemiological features, rates of recurrence, malignant transformation of poroid hidradenoma and its management if there are more case reported.

*There are no conflicts of interest with respect to the research, authorship, and/or publication of this case report.*

## REFERENCES

- (Agorio et al., 2016; Arwyn-Jones et al., 2016; Delfino et al., 2007; Liaqat et al., 2020; Lim et al., 2021; Lupu et al., 2022; Somaiah et al., 2022)
1. Agorio, C., Magliano, J., Brewer, J. D., & Bazzano, C. I. (2016). Double M-plasty for excisional biopsy of suspected melanoma. *Actas Dermo-Sifiliograficas*, 107(2), 164–165. <https://doi.org/10.1016/j.ad.2015.04.020>
  2. Arwyn-Jones, J., O'Hara, N., Leo, A. De, & Birch, J. (2016). Poroid Hidradenoma: Case Report and Excision Rationale. *Journal of Cancer Therapy*, 07(04), 270–274. <https://doi.org/10.4236/jct.2016.74028>
  3. Delfino, S., Toto, V., Brunetti, B., Marino, M. P., Baldi, A., & Persichetti, P. (2007). *Poroid Hidradenoma: A Case Report*. [https://doi.org/10.1007/978-1-4020-9008-7\\_10](https://doi.org/10.1007/978-1-4020-9008-7_10)
  4. Liaqat, H., Ammad Ud Din, M., & Malik, D. (2020). Poroid hidradenoma: A benign lesion masking as a malignant breast tumor. In *QJM* (Vol. 113, Issue 10, pp. 749–750). Oxford University Press. <https://doi.org/10.1093/QJMED/HCAA109>
  5. Lim, J. S., Kwon, E. S., Myung, K. B., & Cheong, S. H. (2021). Poroid hidradenoma: A two-case report and literature review. In *Annals of Dermatology* (Vol. 33, Issue 3, pp. 289–292). Korean Dermatological Association. <https://doi.org/10.5021/ad.2021.33.3.289>
  6. Lupu, M., Tebeica, T., Malciu, A. M., & Voiculescu, V. M. (2022). Poroid Hidradenoma: Dermoscopic and In Vivo Reflectance Confocal Microscopic Description. *Diagnostics*, 12(2). <https://doi.org/10.3390/diagnostics12020255>
  7. Somaiah, As., Reddy, R., Apoorva, H., & Eshwari, L. (2022). Poroid hidradenoma over dorsum of the hand. *Clinical Dermatology Review*, 6(2), 152. <https://doi.org/10.4103/cdr.cdr.521>
  8. Prohaska J, Sequeira Campos M, Crane JS. M-plasty. [Updated 2022 Sep 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482275/>

# FIGURES



Figure 1. Solitary erythematous, 3 cm x 2.5 cm nodule topped with crust and yellowish discharge on the antecubital fossa.



Figure 2. Multiple, well circumscribed, soft, movable skin colored nodules on the upper extremities. Ventral forearm, right (2a), medial forearm, right (2b), and medial forearm, left (2c).



Figure 3. Dermoscopy: crust, blue-grey pigmented areas, and a peripheric polymorphous vascular pattern with glomerular and hairpin vessels.

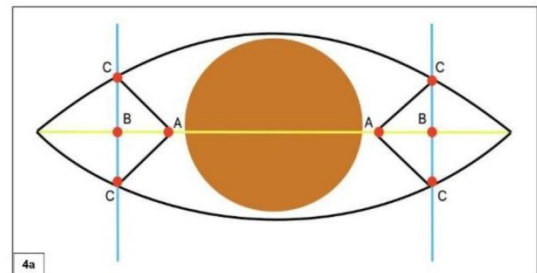


Figure 4. Skin markings for the Double M-plasty technique





Figure 5a. Surgical site A on 7<sup>th</sup> post-operative day



Figure 5b. Surgical site B on 7<sup>th</sup> post-operative day.

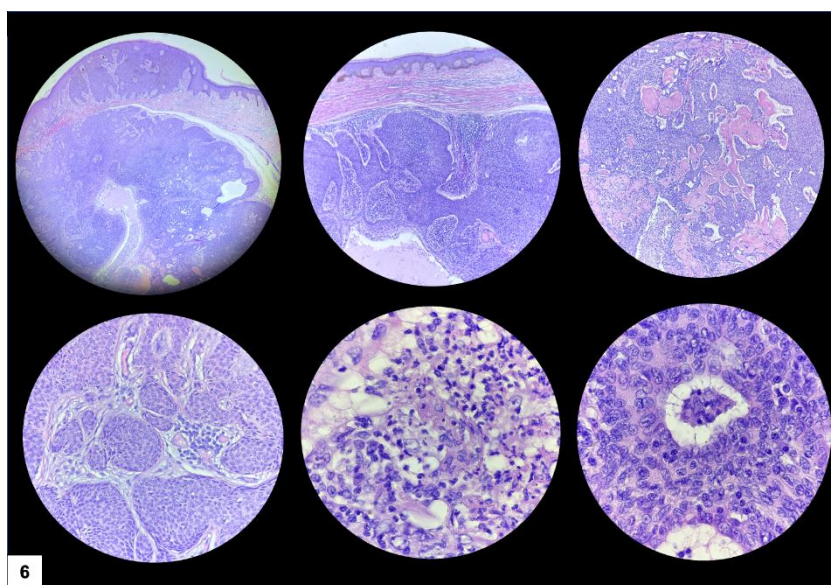


Figure 6. Circumscribed dermal proliferation of cuboidal epithelial cells, some of which had an abundant pale cytoplasm. There was an area with inter-anastomosing array in continuity with the surface epidermis. Conspicuous foci of ductular differentiation with areas of necrosis were seen. The accompanying stroma were highly vascularized and sclerotic and holds a lymphohistiocytic infiltrate.

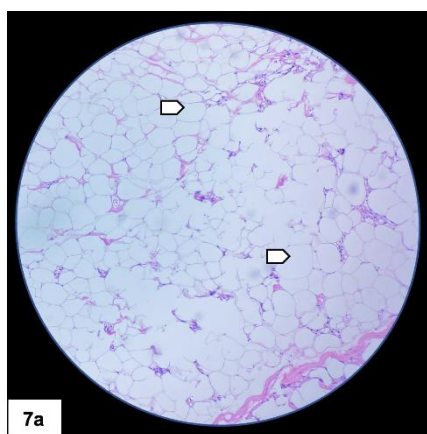


Figure 7a. Well circumscribed, encapsulated, and lobulated lesion composed of a proliferation of mature adipocytes (white arrow)

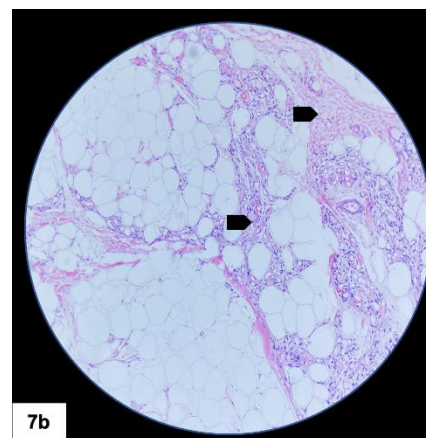


Figure 7b. Thin and hypocellular septa containing thin-walled capillaries (black arrow)



