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TABLE OF CONTENTS

Journal of the
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Journal of the
Philippine Medical Association
2016 - 2017 VOLUME 95, NUMBER 1

Editorial Office:
2nd 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;
E-mail: info@philippinemedicalassociation
philmedas@yahoo.com

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Journal of the
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2016 - 2017 VOLUME 95, NUMBER 1

MESSAGE

The issue of the Philippine Medical Association Journal this year, contains case reports, research papers of Filipino physicians carefully selected for publication by the Committee on Publications from more than three dozens of original research papers and materials submitted from the different health care institutions, specialty organizations, medical schools and universities.

Great transformations have been observed in recent years with the emergence of a dynamically changing healthcare landscape with the dawning of the ASEAN Integration. For one, the Continuing Professional Development Law or Republic Act 10912 had redefined professional competency to include other aspects of professionalism. Research materials in this issue of the PMA Journal , however, should maintain the professional and academic boundaries that serve as our guidepost in the practice of the medical profession. It delights me to know that the Committee on Publications and the specialty societies based in accredited training institutions throughout the country are working hand in hand in contributing their share in this issue of the Journal of the Philippine Medical Association.

IRINEO C. BERNARDO III, M.D.
President

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Philippine Medical Association
2016 - 2017 VOLUME 95, NUMBER 1

EDITOR'S *notes*

Extending Frontiers

It has been said time and again that the surest way to advance in academic endeavours is to do research. Adding to the knowledge base and contributing new data to the existing body of work will undoubtedly add a modicum of respect to anyone's professional standing. The corresponding curriculum vitae becomes all the more impressive if it is punctuated with these so-called scientific papers and articles. But we do not stop there. One achieves greater relevance if the research finds print, that is, gets published in a recognized journal, one which is worthy of note and with substantial readership. This is exactly why the Journal of the Philippine Medical Association is in place.

Therein lies its reason for being. We offer another venue where expert and systematic inquiry can be disseminated to a discerning audience. Again, this is easier said than done. Year in and year out, there is a call for papers. Year in and year out, this is met by various challenges. Year in and year out, we end up not being too ideal in our quest for distinction and excellence, tools that are necessary to compete at a high level.

Yet, this does not mean that we give up, it does not mean that we adopt a cavalier attitude, nor maintain a stand that is nothing short of optimistic. That is why we persist, that is why we go against all odds. And we are proud to mention that we are seeing evident positive changes amidst all these limitations. For one, there are more submissions. Secondly, the quality seems to be improving. Call it an increased awareness, or a maturing mindset, or a growing acceptance of the natural order of things. Globalization and international recognition admittedly have something to do with this perceived transformation.

Hence, your medical journal will continue to work towards its mandate. We will proceed to do our share and be your partner in generating information and enhancing progress in health and medicine. For now, we select articles that are heterogeneous, not being restricted to one discipline; and expansive, not representative of just one institution. With this issue, we have chosen both original researches and stimulating case reports. It is our hope that with such a direction in mind, we are able to reach a wider circulation. For the coming issues, we would be open to other genres, especially those that emphasize the art of medicine. Experiences in clinical practice, reflections on healing, and physician-patient-caregiver partnerships are more than welcome.

Ours is a time to move forward.

AJBAJ, Jan 2017

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.

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Ethical Cosiderations

In the conduct and reporting of research, the JPMA adheres to the ethical considerations set forth by the ICMJE with respect to authorship and 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.

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(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 authorsí 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 type 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 abstractr, identify three to ten keywords or short phrases that will assist in indexers 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

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

A Cross-Sectional Study on the Impact of Acne Vulgaris on the Quality of Life among High School Students in Pasig City, Philippines

Vanessa Anne C. Bernal, MD, DPDS and Elizabeth V. Sanchez, MD, FPDS

Abstract

Background: Acne vulgaris affects approximately 85% of people between 12 to 24 years of age. Although neither debilitating nor life threatening, it has a significant impact on the social, psychological, and emotional functioning of affected individuals.

Objective: To determine the association of age, gender and acne severity to health-related quality of life (QOL) among Filipino high school students

Methods: A cross sectional study was conducted among students in two high schools, one public and one private. Six regions in the face and trunk were assessed with Global Acne Grading Scale (GAGS) for acne severity. A validated Filipino version of Cardiff Acne Disability Index (CADI) questionnaire was self-administered by students to measure QOL. Logistic regression analysis was performed to determine predictors for QOL impairment. All data were processed using STATA 12.0.

Results: The 216 participants were 14 years old on average, with the two sexes being almost equal in proportions. Median GAGS score was 8 (range, 0-36), while median CADI score was 3 (range, 0-13). Increased age (OR, 1.438; *P* = .033) and grade level (OR, 1.652; *P* = .017) were associated with a more severe acne and greater impairment of QOL.

Conclusions: Among the factors investigated, only age was found to correlate significantly with QOL impairment. GAGS score and gender were not significant predictors. QOL evaluations in the clinics are necessary to better manage acne vulgaris in adolescents.

Keywords: *acne vulgaris, quality of life, adolescence, Global Acne Grading Scale, Cardiff Acne Disability*

Dermatology, Skin and Cancer Foundation, Inc., Pasig City, Philippines
3rd Place, Philippine Dermatological Society, Annual Research Forum (2015)
2nd Place, Quirino Memorial Medical Center, Annual Residents' Research Contest (2015)

INTRODUCTION

Acne vulgaris is a common disorder of the pilosebaceous unit that affects approximately 85% of people between 12 and 24 years of age.[1] Lesions range from mild comedones to severe nodules or cysts, with possible associated scarring, and are found mainly on the face and upper trunk. Although not a life-threatening disease, it can impart significant impact upon an individual's social, psychological, and emotional functioning.[2]

Acne prevalence peaks during adolescence, a crucial stage in growth marked by accelerated, sometimes turbulent, physical, psychological, and social development. Add this to the "disfigurement" caused when located in exposed areas of the body, acne vulgaris has been related to feelings of embarrassment, reduced self-esteem, low self-assertiveness, poor self-image, and self-consciousness. The negative feelings are only exacerbated by taunting and perceptions of judgment or scrutiny.[3,4] Some young patients may even be so adversely affected as to develop social inhibition and phobia. Moreover, depression and suicidal ideation were found to be significantly higher among individuals with acne than among those with other dermatological problems, such as alopecia areata and atopic dermatitis, something surpassed only in cases of severe psoriasis.[5]

With its considerable psychosocial impact, recent studies have focused on the assessment of quality of life (QOL) in patients with acne. Some used validated instruments, like general health-related QOL indexes and specific acne-related measures, and were able to demonstrate a significant negative effect of acne on QOL. This was noted to be comparable to when having asthma, epilepsy, or diabetes.[6] Results, however, regarding the correlation of QOL to age, gender, race, and acne severity have been inconsistent.

In the Philippines, dermatologists, and even lay people, are aware of the psychosocial and emotional effects of acne vulgaris in the teenage population. Yet, this aspect of the disease is seldom noted or managed. There also exists a lack of quantitative studies among Filipinos that measure the impact of the condition in this age group. As such, we aimed to assess the impact of acne vulgaris on QOL measures among Filipino high school students, with the goal of highlighting its psychosocial effects and, hopefully, improve its current state of management. At the same time, we provide a baseline study for future investigations focusing on acne-related QOL in adolescent students.

REVIEW OF RELATED LITERATURE

Acne tends to exert negative effect on the psychological well-being of individuals, as evidenced by several studies. Uhlenhake *et al*. noted that the prevalence of depression among these persons was three to four times that in the general population.[7] Depressive symptoms was also shown to have a positive correlation with acne severity of secondary school students, with a higher frequency of suicidal thoughts and attempts when there was perception of a "problem acne."[8] A study by Uslu and colleagues among high school students showed that there was a direct correlation between the subjective, and not the objective, severity of acne and symptoms of depression and anxiety.[9] Symptoms of body dysmorphic disorder have been associated with acne patients, with the risk doubled with the requirement of isotretinoin therapy.[10] The level of loneliness and anxiety among those affected was comparable to that seen in serious illnesses such as diabetes, cancer, epilepsy, and cystic fibrosis.[11] Effects were also noted to equal that of patients with asthma.[6]

Most of these non-dermatologic effects of acne have been attributed to its prevalence in adolescence, anatomical distribution of lesions, misconception regarding etiology, and peer pressure.[5] Adolescence being a time of major changes in the physical, emotional, and social dimensions of a person, this stage is susceptible to issues concerning appearance, self-image, and self-esteem. Acne lesions are easily visible if they appear in areas not usually covered by clothing, such as the face, upper trunk, and upper arms. In a survey conducted by Tan *et al*., people thought that acne develops from poor skin hygiene, which may cause feelings of shame and guilt among patients.[12]

Because of the increasing body of evidence relating acne vulgaris to psychosocial impairment, recent studies have focused on quantifying the impact of acne on quality of life of patients. According to the World Health Organization, QOL is an "individual's perception of their position in the context of culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns."[13] Measuring the QOL allows the clinician to see the disease in the point of view of the patient. General health measures can be used to compare skin diseases like acne with other disease entities that are not necessarily dermatologic. Dermatology-specific measures, on the other hand, can be used to compare the QOL of patients with different skin diseases. Examples are the Dermatology Life Quality Index (DLQI) and Skindex. Acne-specific measures, to which the Cardiff Acne Disability Index (CADI) belongs, are designed specifically for acne.[6]

Knowledge of the QOL of patients suffering from acne allows a clinician to tailor his management for enhanced patient compliance.[6] A greater effect on QOL has implications on self-esteem, body image, and relationships with others.[14] The psychological, social, and emotional impact of acne on patients have been demonstrated with the use of different validated QOL instruments. The degree of impact of acne vulgaris varies among different countries, with India having a lower magnitude of impact as compared to others.

The correlation between acne severity and QOL has been studied, yielding varying results. Tasoula *et al*. noted that the impact of acne on the QOL of adolescents in Greece was proportional to its severity.[14] Similarly, Pawin *et al*. observed a significant correlation of perceived severity of acne and relationships with friends, as well as with feelings of anger, sadness, anxiousness, and shame.[11] However, in an investigation of university students in Turkey, no correlation was found between acne severity and QOL.[15] It was noted that acne, even of mild severity, can significantly affect psychological status.[16] The disproportionality between QOL and acne severity may also be reflective of some disparity between the viewpoints of patients and clinicians.[17]

Variations have been reported on the impact of acne vulgaris on QOL in opposite sexes. In a study on adolescents, acne was seen to have more impact on the QOL of females.[14] In contrast, Walker *et al*. showed no significant difference between QOL mean scores of the two sexes.[18]

As to age, studies have shown that older patients tend to be more affected by acne vulgaris than younger patients. In a study by Lasek *et al*., it was noted that older patients with acne had a lower QOL compared to younger counterparts.[19] The greater effect may be due to the prolonged duration of having acne, poor response to tried treatments, and social implications in the adult population, such as difficulty in getting a job.[5]

OBJECTIVES

General objective

To determine the impact of acne vulgaris to health-related quality of life among Filipino high school students

Specific objectives

1. To measure the acne severity of high school students by Global Acne Grading Scale (GAGS)
2. To assess quality of life of these students using Cardiff Acne Disability Index (CADI)
3. To describe how age and grade level, gender, and acne severity correlate with CADI scores

METHODS

This cross-sectional investigation took place in two co-educational schools situated in Pasig City, Philippines. One was public and another was private, and each had four year levels of high school. Permission to conduct the study was initially sought from the principal of each school, as well as the Schools Division Superintendent of Pasig City.

A standard data collection tool divided into three sections was utilized in data collection. The first part asked about the participant's gender, age, and year level. The second portion consisted of the Global Acne Grading Scale (GAGS). The third part was a validated Filipino version of the Cardiff Acne Disability Index (CADI). The first two portions were filled up by the primary investigator as the examination and interview proper progressed.

Acne severity

For GAGS assessment, six facial and truncal regions were examined and scored, namely: forehead, right cheek, left cheek, nose, chin, and chest and upper back. A subscore was computed for each region by multiplying the region-specific factor (2 for each of forehead, right cheek, and left cheek; 1 for each of nose and chin; and 3 for the chest and upper back) with the area's most severe lesion (1 for comedone, 2 for papule, 3 for pustule, and 4 for nodule). Local scores were added to obtain the global score. A total GAGS score of 1–18 is considered mild, 19–30 is moderate, 31–38 is severe, and > 38 is very severe.

Quality of life

The CADI is a validated five-item questionnaire designed for use in teenagers and young adults.[21] The answer to every question corresponds to a score (3, 2, 1, 0 for answers a, b, c, and d, respectively). Individual item scores were summated to obtain the CADI score. Any item left unanswered was given a score of zero. If more than one item was left unanswered, the respondent of the questionnaire was dropped from the study. Indices may range from 0 to 15, with a higher score denoting greater QOL impairment. For this study, a score of 1–4 was considered mild impairment, 5–10 was moderate, and 11–15 was severe.

Statistical analysis

Continuous and categorical variables were presented using descriptive statistics: median (range), mean ± SD, and count (%). All valid data was included in the analysis and no imputation was required. Ordinal regression analysis was utilized to analyze the association of age and year level, gender, and GAGS score to the quality of life, as assessed by the CADI score, among these students afflicted with acne vulgaris. Data encoding and analysis were performed using STATA 12.0.

Ethical considerations

The study was designed to be consistent with the ethical principles contained within the Declaration of Helsinki and the National Guidelines for Biomedical/Behavioral Research of the National Ethics Committee (NEC) of the Philippines. The Institutional Review Board (IRB) approved the protocol before commencement. No deviation from approved procedure was committed during the study. All participants were given clear and complete instructions about the study's design and goal before eliciting assent. Withdrawal from the study for any reason was allowed at any time. The investigators were available for any questions or clarifications raised. Study participants were not financially remunerated but rewarded with medical attention.

Confidentiality of subjects was maintained. Only the investigators or authorized representatives of regulatory agencies were allowed to have direct access to any of the information in the source documents.

Results

There were 216 high school participants recruited, composed of 53% female and with a group mean (±SD) age of 14.5 ± 1.4 years (Table 1). Grades 8 and 10 were slightly less represented than grades 7 and 9. Of the participants, 98.5% had acne. GAGS median score was 8 (range: 0–36), while median CADI score was 3 (range: 0–13).

Table 1 **Profile of 216 High School Students with Acne Vulgaris**

Age (years)	14.5 ± 1.4
Female	114 (53)
Grade level	
7	56 (26)
8	47 (22)
9	64 (30)
10	49 (23)
Global Acne Grading Severity†	8 (0–36)
Cardiff Acne Disability Index‡	3 (0–13)

Values are given as follows: age as mean ± SD; gender and year levels as count (%); acne scoring instruments as median (range).
†Acne severity based on GAGS: 0, no acne; 1–18, mild; 19–30, moderate; 31–38, severe; > 38, very severe.
‡Quality of life impairment based on CADI: 1–4, mild; 5–10, moderate; 11–15, severe.
Percentages may not add up to 100 due to rounding.

GAGS subscores showed that, of the six facial and truncal regions, the forehead and both cheeks were the most commonly acne affected areas (Table 2).

Table 2 **Global Acne Grading Severity Subscores of 216 High School Students with Acne Vulgaris**

	Median (Range)
Forehead	2 (0–8)
Right cheek	2 (0–8)
Left cheek	2 (0–8)
Nose	1 (0–4)
Chin	0 (0–4)
Chest and upper back	0 (0–12)

Values are given as median (range).

QOL measurement by CADI revealed 50% of students to have experienced a little aggressiveness, frustration, or embarrassment due to acne (Table 3). Social life and relationships were personally assessed as not affected for 53% and occasionally for 43%. Almost three-fourths (71%) were not into avoiding public changing all the time. Neither depression nor miserable feelings were present in 30%, while more than half (52%) was usually occasionally concerned over their acne. By personal perception, acne was thought to be a minor problem in almost half (47%) and not a problem for about a third (32%) of the patient.

Table 3 **Itemized Cardiff Acne Disability Index of High School Students with Acne Vulgaris (*N* = 216)**

	Frequency (%)
Item 1. Nitong nakaraang buwan, ikaw ba ay naging agresibo, inis o napahiya dahil sa pagkakaroon ng pimples/tagyawat? (As a result of having acne, during the last month have you been aggressive, frustrated or embarrassed?)	
(a) Labis-labis (Very much indeed)	3 (1)
(b) Labis (A lot)	11 (5)
(c) Bahagya (A little)	109 (50)
(d) Hindi (Not at all)	93 (43)
Item 2. Sa iyong palagay, nakapigil ba ang pagkakaroon mo ng pimples/tagyawat sa pakikisalamuha mo sa iba, sa pag-attend mo sa mga okasyon/party, o sa pakikitungo mo sa ibang kasarian (opposite sex) sa nakaraang buwan? (Do you think that having acne during the last month interfered with your daily social life, social events or relationships of the opposite sex?)	
(a) Sobra-sobra, lahat ng ginagawa ko ay apektado (Severely, affecting all activities)	6 (3)
(b) Sobra, halos lahat ng ginagawa ko ay apektado (Moderately, in most activities	3 (1)
(c) Minsan, sa ilang mga gawain lang (Occasionally, or in some activities)	93 (43)
(d) Hindi (Not at all)	114 (53)
Item 3. Sa nakaraang buwan, umiwas ka ba sa pagbibihis sa harap ng ibang kaibigan/kaklase o sa pagsuot ng swimsuit/backless dahil sa iyong pimples/tagyawat? (During the last month have you avoided public changing facilities or wearing swimsuit costumes because of your acne?)	
(a) Palagi (All of the time)	5 (2)
(b) Madalas (Most of the time)	12 (6)
(c) Paminsan-minsan (Occasionally)	45 (21)
(d) Hindi (Not at all)	154 (71)
Item 4. Paano mo mailalarawan ang iyong damdamin/feelings tungkol sa itsura ng balat mo nitong nakaraang buwan? (How would you describe your feelings about the appearance of your skin over the last month?)	
(a) Sobrang malungkot at miserable (Very depressed and miserable)	6 (3)
(b) Madalas na nababahala/nalulungkot (Usually concerned)	32 (15)
(c) Paminsan-minsan nababahala/nalulungkot (Occasionally concerned)	113 (52)
(d) Hindi nababahala/nalulungkot (Not bothered)	65 (30)
Item 5. Sa iyong palagay, gaano kalala ang iyong pimples/tagyawat sa ngayon? (Please indicate how bad you think your acne is now:)	
(a) Pinakamalalang problema (The worst it could possibly be)	11 (5)
(b) Isang malalang problema (A major problem)	35 (16)
(c) Isang magaang na problema (A minor problem)	101 (47)
(d) Hindi problema (Not a problem)	69 (32)

Values are given as count (%).

Medians of the total GAGS scores were all within the category of mild acne (Table 4). They were lowest in grade 7 and highest in grade 10. The ranges also increased when comparing a grade level against the one immediately below it (e.g., grade 8 vs. grade 7). The worst condition recorded in grade 7 was moderate acne (GAGS score of 25), while it was severe acne in grade 10 (GAGS score of 36). For the forehead, cheeks, and nose, median GAGS subscores across all grade levels were 2, 2, 2, and 1, respectively. Noticeable differences, however, were evident in the maximum values registered, which generally tended to increase with greater seniority. The chin displayed more apparent differences in subscores, with recorded medians of 0 (range, 0–2) and 1 (range, 0–4) for grades 7 and 10, respectively. Overall GAGS subscore for the chest and upper back became nonzero only in the females of grade 10 (median, 3; range, 0–9).

Median CADI scores increased almost consistently with higher year levels. It was interpreted mild (median, 1; range, 0-7) for grade 7 and moderate (median, 5; range, 0-11) for grade 10.

Table 4 **Acne Severity and Quality of Life Summarized by Year Level and Gender (*N* = 216)**

	Grade 7		Grade 8		Grade 9		Grade 10	
	Male	Female	Male	Female	Male	Female	Male	Female
GAGS†	7 (0–25)	5 (0–21)	7.5 (0–22)	7 (0–19)	11 (0–30)	7 (0–22)	11 (2–30)	12 (2–36)
Forehead	2 (0–6)	2 (0–6)	2 (0–4)	2 (0–6)	2 (0–6)	2 (0–8)	2 (0–8)	2 (0–8)
Right cheek	2 (0–6)	2 (0–4)	2 (0–4)	2 (0–4)	2 (0–8)	2 (0–4)	2 (0–8)	2 (0–8)
Left cheek	2 (0–6)	0 (0–4)	2 (0–6)	2 (0–6)	2 (0–6)	2 (0–8)	2 (0–6)	2 (0–8)
Nose	1 (0–1)	1 (0–2)	1 (0–4)	1 (0–1)	1 (0–4)	1 (0–4)	1 (0–4)	1 (0–4)
Chin	0 (0–1)	0 (0–2)	0.5 (0–2)	0 (0–2)	1 (0–2)	0 (0–3)	1 (0–4)	1 (0–3)
Chest and upper back	0 (0–9)	0 (0–6)	0 (0–6)	0 (0–6)	0 (0–6)	0 (0–6)	0 (0–12)	3 (0–9)
CADI‡	1 (0–4)	1 (0–7)	2 (0–6)	4 (0–10)	4 (0–10)	3.5 (0–13)	5 (0–13)	5 (2–11)

Values are given as median (range).

†GAGS, Global Acne Grading Scale. Interpreted as: 0, no acne; 1–18, mild; 19–30, moderate; 31–38, severe; > 38, very severe.

‡CADI, Cardiff Acne Disability Index. Interpreted as: 1–4, mild; 5–10, moderate; 11–15, severe.

Multiple regression modeling was able to confirm the trends observed. The relative odds of having a worse CADI score was 1.438 if with greater age (95% CI, 1.030–2.007; *P* = .022) and 1.652 if with higher grade level (95% CI, 1.093–2.497; *P* = .017). The odds of greater QOL impairment was increased by 1.687 times in the female gender, but this did not achieve statistical significance (Table 5).

Table 5 **Regression Model for Cardiff Acne Disability Index**

	Odds Ratio	95% CI	*P*-value
Age	1.438	1.030–2.007	**.033**
Female	1.687	0.992–2.868	.053
Year level	1.652	1.093–2.497	**.017**
GAGS score interpretation			
Mild vs. No acne	1.056	0.274–4.077	.936
Moderate vs. No acne	0.920	0.196–4.302	.915
Severe vs. No acne	3.171	0.048–207.623	.589

Goodness of fit of the ordinal logistic regression model (r^2) was 11.07%, with P < .0001.
CI, confidence interval. GAGS, Global Acne Grading Scale.

DISCUSSION

The CADI is composed of a set of questions pertaining to different QOL facets. This study showed that about 8 to 9 out of 10 students answered choice (c) or (d) for almost all items in CADI, so that, overall, the median CADI score obtained was 3. This corresponds to mild QOL impairment, comparable to findings obtained in similar studies from India and Malaysia.[22,23]

CADI scores have been found to be significantly associated with age, with the older age group having a higher degree of QOL impairment as compared to the younger age group. This was found to be similar to the results obtained by Jones-Caballero *et al.* where Skindex-29, a QOL questionnaire, was used in 1,878 patients under the care of 252 clinicians in Spain.[17] Such findings may be due to the noted increased severity of acne vulgaris in the older age group (Table 4), similar to findings in Malaysia.[23] In a study conducted by Ismail and Mohammed-Ali (2012) in Erbil City, they found that older patients, age group 21-25 years, had QOL impairments ranging from moderate to severe.[26] This age-related difference may be due to acne vulgaris being more prevalent during adolescence, leading to better social acceptance of their condition. It was also reported that negative feelings towards acne vulgaris accumulate from the self and the community as a person ages.[26]

Reports have been made of increased psychological impairment with greater acne severity,[6,14] but other studies found no correlation.[14,15,24,25] Our results also indicated no association, although median GAGS and CADI scores increased with higher grade levels. It should be noted, however, that in this study, students across grade levels generally had only mild acne severity that may have positively affected their CADI scores (Table 1). The lack of correlation, however, shows that mild acne could have just as much an effect on adolescents' psychology as severe acne.[16] Also, the goodness of the fit of the model only came up to 11.07%, indicating that there other factors, internal or external, likely at play in the QOL of acne patients.

In this study, QOL impairment was more associated with the female population, though the difference between genders was not statistically significant. This may be from women generally having more concern over their appearances than men.[26] However, the lack of significant difference might also be reflecting how males are now becoming more aware of their skin condition.[23] The inverse phenomenon was highlighted in a study conducted in Egypt, wherein males were found to have more impairment in QOL than females.[27]

One of the limitations of this study was that it examined the impact of acne vulgaris on the QOL of Filipino high school students at a single point in time. This limitation may be overcome in future studies by using a prospective study design. Also, increasing the scope of the study will be able to uncover more fully the dynamics involved between acne and QOL of teenagers.

CONCLUSION

Acne vulgaris was shown to impart a mild QOL impairment among Filipino high school students, with older students being significantly more affected than their younger counterparts. Gender marginally exceeded significant correlation with QOL, perhaps pointing to an increased awareness in males of their skin condition. GAGS score was likewise not a significant predictor for QOL impairment, indicating that mildly afflicted individuals may be affected as much as those with more severe conditions.

Our results demonstrate the importance of QOL evaluation in managing adolescent patients with acne; severity alone may not be enough to adequately assess the impact of acne on an adolescent. In addition, it is recommended that future studies on acne vulgaris, especially interventional ones, should include quality of life measures as part of the parameters.

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The Appropriate Grading Tool to Assess Acne Severity in Face-to-face Consultation and Digital Skin Images*

Karen B. Mabilin-Prieto, MD[1]
Elizabeth P. Prieto, MD, FPDS[2]
Jerlyn Maureen P. Servas, MD[3]

Abstract

Background: Acne vulgaris is a multifactorial disease of the pilosebaceous unit affecting adolescents and young adults. This study examined whether acne assessment measures, validated for face-to-face use, can be used to assess acne lesions captured from digital images. The use of digital images is a useful and innovative way to continue delivery of follow-up care to patients despite barriers such as distance and time.

Objective: To determine the most appropriate acne-grading tool to assess the acne severity during face-to-face consultations and in digital skin images.

Method: A total of eighteen patients with facial acne vulgaris were included. Two dermatologists-in-training evaluated the acne-severity during face-to-face visit using validated acne assessment measures: Total Inflammatory Lesion Count (TILC), LEEDS Technique and Investigator's Global Assessment (IGA). Digital images obtained during initial consult were presented to the same raters during weeks 6 and 12 and graded accordingly. Cohen's kappa was used to measure agreement between evaluations of two raters and acne grading tools.

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[1]Corresponding Author, Resident in training (during the study), Department of Dermatology, East Avenue Medical Center, Quezon City, Philippines
[2]Co-Author, Training Officer, Department of Dermatology, East Avenue Medical Center, Quezon City, Philippines
[3]Co-Author, Resident in training (during the study), Department of Dermatology, East Avenue Medical Center, Quezon City, Philippines

Results: Raters had significant moderate agreement in ratings using the three grading tools during face-to-face visit but Investigator's Global Assessment had the highest measure of concordance. Ratings on the digital images by each rater during week 6 and 12 had significant substantial agreements based on Total Inflammatory Lesion Count. The inter rater reliability had significant moderate agreement in ratings of digital images during week 12 using Total Inflammatory Lesion Count and Investigator's Global Assessment. Total Inflammatory Lesion Count had the highest intra rater agreement during ratings of face-to-face and digital skin images, while LEEDS had the lowest measure of concordance.

Conclusion: All the three acne severity tools may be used for evaluating acne severity during face-to-face consultation. The Investigator's global assessment may best be used for face-to-face assessments while the total inflammatory lesion count may best be used in digital skin images.

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Key words: *acne assessment, acne grading tool, digital skin images*

INTRODUCTION

Acne vulgaris is a common dermatological condition primarily affecting the vast majority of adolescents and young adults. It is one of the most common dermatological problems encountered in Out Patient Clinics of Dermatology. [1]

Although easy to diagnose, the polymorphic nature of acne vulgaris and its varied extent of involvement do not permit simple evaluation of its severity. Because the acne lesions may vary in number during the natural course of the disease, various measurements have been developed, based on clinical examination and photographic documentation, to assess the clinical severity of acne vulgaris. [2]

The Leeds Revised Acne Grading System, published in 1998, provides a photographic standard for acne grading of the face, back and chest. This system is comprised of 12 facial grades.

In 1996, Lucky et al.[6] assessed the reliability of acne lesion counting. Acne counts were recorded on a template divided into five facial segments: Right and left sides of the forehead, right and left cheeks and chin. The nose and the area around it were excluded. Counts of each lesion type were recorded within each segment of the template. Total lesion count, along with total inflammatory lesions and comedonal counts, were then calculated. They concluded that reliability of acne lesion counting was excellent when performed by the same trained rater over time.

The grading scale for overall severity by Allen and Smith Jr. has been the template for global assessments in many acne trials as an Investigator's Global Assessment (IGA) scale. It was based solely on descriptive text, not on photographs, and also added the dimension of increasing extent of facial involvement. It further demonstrated the severity scale correlated with inflammatory and non-inflammatory lesion counts. [7]

Technology offers new ways to deliver care to dermatology patients. Dermatology is a specialty long accustomed to using images in many aspects of its practice, including education, surveillance, and patient follow-up. High quality digital cameras are now widely available. Although initially adopted by patients as consumer devices, physicians and patients have been looking to explore the healthcare applications for such devices. [3]

Digital imaging in dermatology care has been highlighted as a priority area for research for both the American Telemedicine Association, and internationally by the UK's National institute for Health and Clinical Excellence. The application of this methodology could provide dermatologists a tool for ongoing care, allowing them to remotely monitor patient progress.[3] Digital images and clinical information can be transferred from patient to clinician over the internet allowing asynchronous, remote assessment.[3] Acne patients are well suited to this approach given that they are generally technologically able, require ongoing follow-up but have a non-malignant condition.

Although many acne-grading tools have been validated, in our institution, the most appropriate acne -grading tool has not been established when used in face-to-face setting and in evaluating acne in digital images.

This study was therefore designed to explore on the acne assessment measure which, can be used in the evaluation of acne observed from in person visit (face-to-face consult) and in digital images.

The importance of this study is to have standardized system in the grading of acne vulgaris not only during face-to-face consultation but also in digital images that we can be used consistently in clinical practice and research. This is also important to achieve uniformity in grading because this will further help in better disease management and more efficacious treatment. Lastly, the use of digital images is a useful and innovative way to continue delivery of follow-up care to patients despite barriers such as distance and time by determining whether the existing acne assessment measure can also be used in the evaluation of acne observed from digital images.

OBJECTIVES

General Objective

1. To determine the most appropriate acne grading tool to evaluate the acne severity of patients during face-to-face consultations and in digital skin images at the Dermatology Out Patient Department of a Tertiary Government Hospital?

Specific Objectives

1. To determine the demographic profile of the patients diagnosed with acne vulgaris.
2. To determine the most appropriate acne grading tool during face-to-face consultation of acne vulgaris patients.
3. To determine the most appropriate acne grading tool for digital skin images of acne vulgaris patient.
4. To compare the grading based on most appropriate grading tool that is applicable for both face-to-face consultation and digital skin images.

METHODS

This is a cross-sectional prospective study on the appropriate acne-grading tool to assess acne severity in face-to-face consultation and in digital skin images.

A total of eighteen subjects clinically diagnosed with facial acne vulgaris were enrolled in the study. Those who had drug-induced acneiform eruptions and with acne lesions on other body regions (i.e. trunk, back) were not included in the study.

This study was conducted at the East Avenue Medical Center Department of Dermatology – Out Patient Department. Prior to conducting the study, the research was submitted and approved by the Institutional Ethics Review Board.

The primary investigator (PI), enrolled the patient in the study, accomplished the data collection form and have the informed consent forms signed. The digital images of every enrolled subject were captured by the primary investigator using a Canon Ixus 16.1 megapixel digital camera in digital macro mode without flash. This camera was chosen for its ease of use and high quality image reproduction. The light source was an overhead fluorescent with some natural light through examining room windows.

In the first part of the study, the primary investigator presented the patient diagnosed with acne vulgaris to two senior dermatology residents (Raters A and B) and were graded using Total inflammatory lesion count, LEEDS acne assessment technique, and Investigator's Global Assessment. The grading of two raters were compared to determine the **inter-rater agreement** in grading of acne severity during **in-person visits (face-to-face consultation)**.

In the second part of the study, digital skin images captured during the initial consult of the patient were presented to Raters A and B at a later date (during the 6th and 12th week from the time of recruitment). Photos were evaluated using Total inflammatory lesion count, LEEDS acne assessment technique, and Investigator's Global Assessment. To evaluate the **inter rater agreement for the digital skin images**, the acne grading of Rater A and Rater B, 12 weeks after recruitment, were compared. To evaluate the **intra rater agreement for the digital images**, grading of the digital skin images by Rater A alone and Rater B alone during the 6^{th} and 12^{th} week after recruitment were compared. To evaluate the **intra rater agreement between face-to-face and digital images**, the grading of Rater A alone and Rater B alone at the time of recruitment (face-to-face consult) and the grading of the digital images 12 weeks after were compared *(Figure 1)*.

For Total inflammatory lesion count (TILC), raters were asked to count all non-inflammatory and inflammatory lesions from the set of three facial digital images and acne grading was based on a tabulated severity score composed of Mild, Moderate and Severe. The Leeds Technique was done by comparing the patient's acne severity to a standard photographic template and assigning a score from *0 to 12*. The Investigator's Global Assessment (IGA) used a validated 6-point rating scale ranging from clear to very severe. Both raters were trained with sets of practice images prior to carrying out their formal assessments. *(Appendix A)*

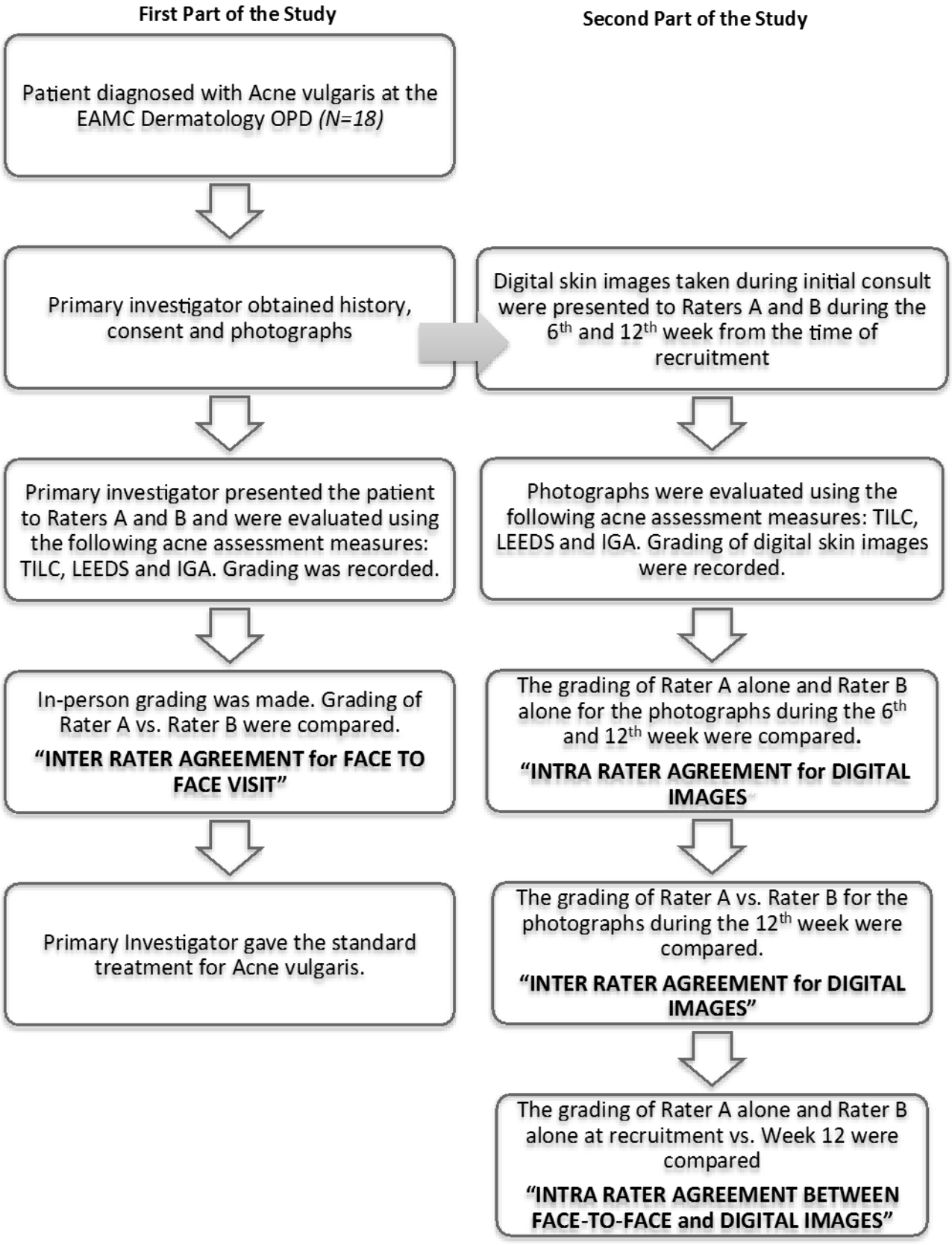

Figure 1. *Study Flow Diagram*

Statistical Methods

All valid data from 18 evaluable subjects were included in the analysis. Missing values were not replaced or estimated during analysis. Summary statistics were presented in tables or graphs and reported as median (range) for quantitative demographic and clinical characteristics (e.g. age) or n (%) for qualitative measures (e.g. sex, age group). Cohen's kappa was used to measure agreement between evaluations of two raters and between acne grading tools: *Total inflammatory Lesion Count (TILC), Leeds Assessment Score (LEEDS), and Investigator's Global Assessment (IGA)*. Interpretation of kappa was based on the following:

Kappa	Agreement
<0	Less than chance agreement
0.01 – 0.20	Slight agreement
0.21 – 0.40	Fair agreement
0.41 – 0.60	Moderate agreement
0.61 – 0.80	Substantial agreement
0.81 – 0.99	Almost perfect agreement

Source: Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.

Chi-square test was used to compare proportions. Conclusions are based on a 5% level of significance. SPSS v20 was used in data processing and analysis.

RESULTS

A total of 18 subjects aged 14 to 37 years participated in the study. Majority were females belonging to the 10 to 30 years age group (p = 0.777; Table 1).

Table 1. Distribution of the study subjects according to age and sex

Age (Years)	Male	Female	All
	n (%)	n (%)	n (%)
10-20	2 (11.1)	6 (33.3)	8 (44.4)
20-30	1 (5.6)	6 (33.3)	7 (38.9)
30-40	1 (5.6)	2 (11.1)	3 (16.7)
All	4 (22.2)	14 (77.8)	18

All subjects had unremarkable findings in the review of systems. Majority had unremarkable past medical history (13, 72.2%) while 3 subjects had allergy (16.7%) on either seafood (2) or chicken (1) and 2 had bronchial asthma (11.1%). Most subjects had family history of acne vulgaris (14, 77.8%) or diabetes (1, 5.6%) while the rest had unremarkable family medical history. Subjects varied from students (10, 55.6%): elementary (3, Grade 9), high school (1), college student (6); employed (6, 33.3%): nurse (1), technical assistant (1), caregiver (1), teacher (1), dental technician (1) and program manager (1) to unemployed (2, 11.1%). Diet was either mixed (16, 88.9%), mostly beef and pork (1, 5.6%) or fatty food (1, 5.6%). Clinical assessments of acne vulgaris were mild (8, 44.4%), moderate (8, 44.4%)

Table 2. Inter rater agreement for face-to-face visit (Rater A vs. Rater B)

Acne Grading Tool	Kappa	Level of Agreement
Investigators Global Assessment	0.559*	Moderate Agreement
Total Inflammatory Lesion Count	0.492*	Moderate Agreement
LEEDS Technique	0.430*	Moderate Agreement

Raters had significant moderate agreement in ratings using the three grading tools during the face-to-face visit *(Table 2)*. Investigator's Global Assessment (IGA) had the highest measure of concordance (k = 0.559, p = 0.000).

Table 3. Intra rater agreement for digital images (Week 6 vs. Week 12)

Acne Grading Tool	Kappa	*p*-value	Level of Agreement
Total Inflammatory Lesion Count			
Rater A	0.620*	0.004	Substantial Agreement
Rater B	0.776*	0.000	Substantial Agreement
LEEDS Technique			
Rater A	0.250	0.081	Fair Agreement
Rater B	0.221	0.071	Fair Agreement
Investigator's Global Assessment			
Rater A	0.330	0.069	Fair Agreement
Rater B	0.100	0.502	Slight Agreement

** Significant at 5% level*

Ratings on the digital images by each rater during Week 6 and Week 12 assessments had significant substantial agreements based on Total Inflammatory Lesion Count *(Table 3)*. Individual ratings based on LEEDS and Investigator's Global Assessment had fair or slight agreements.

Table 4. Inter rater agreement for digital images at week 12 (Rater A versus Rater B)

Acne Grading Tool	Kappa	*p*-value	Level of Agreement
Total Inflammatory Lesion Count	0.519*	0.000	Moderate Agreement
LEEDS Technique	0.354*	0.000	Fair Agreement
Investigator's Global Assessment	0.536*	0.000	Moderate Agreement

** Significant at 5% level*

Raters had significant moderate agreement in ratings of digital images using Total Inflammatory Lesion Count (TILC) and Investigator's Global Assessment (IGA). Both raters had fair agreement in ratings using LEEDS Technique *(Table 4)*.

Table 5. Intra rater agreement on face-to-face and digital images

Acne Grading Tool	Kappa	*p*-value	Level of Agreement
RATER A			
Total Inflammatory Lesion Count	0.349	0.060	Fair Agreement
LEEDS Technique	0.000	1.000	Less than Chance Agreement
Investigator's Global Assessment	0.330	0.069	Fair Agreement
RATER B			
Total Inflammatory Lesion Count	0.786*	0.000	Substantial agreement
LEEDS Technique	0.406*	0.003	Moderate agreement
Investigator's Global Assessment	0.411*	0.007	Moderate agreement

** Significant at 5% level*

Day 1 and Week 12 ratings of Rater A using either Total Inflammatory Lesion Count (TILC) or Investigator's Global Assessment (IGA) had fair agreement while LEEDS, on the other hand, had the lowest measure of concordance (k = 0.000, p = 1.000; *Table 5*). Ratings of Rater B using either Investigator's Global Assessment or LEEDS, however, had significantly moderate agreements while Total Inflammatory Lesion Count had a significantly substantial agreement. Day 1 and Week 12 ratings using LEEDS had the lowest measure of concordance (k = 0.406, p = 0.003).

DISCUSSION

Acne vulgaris is a common dermatological condition primarily affecting the vast majority of adolescents and young adults. Although many acne-grading tools have been validated in face-to-face setting, the reliability when used to assess digital images has not been well studied in our setting. This study brings out the most applicable acne-grading tool to assess the acne severity of patients during face-to-face consultations and digital skin images in the Dermatology Out Patient Department of a Tertiary Government Hospital.

Demographics

In this study, majority of patients were females comprising of 77.8% of the study population as also observed in the studies of both Al-Ameer et al[11] and Ikaraoha et al.[12] Several studies stated that acne develops earlier in females than in males due to their earlier onset of puberty. The most common involved age group was 10 to 20 years old comprising of 44.4% of the subjects. The prevalence of acne at a given age has been shown to be highly dependent on the degree of sexual maturity. [13] Acne is a disease primarily of adolescence. It is triggered by the initiation of androgen production by the adrenal glands and gonads, and it usually subsides after the end of growth. However to some degree, acne may persist beyond adolescence in a significant proportion of individuals particularly women. [14]

Majority of the subjects had unremarkable past medical history (13, 72.2%). Other past medical conditions reported were allergies to food and bronchial asthma. Most subjects had family history of acne vulgaris (14, 77.8%). A study by Rajar et al[19] found that 50% of adults with acne had a first-degree relative parent, sibling and child who had acne. This suggests, that some people may have a genetic predisposition. In another study, there is some evidence, primarily from twin studies, to suggest that acne may be an

inherited disease.[20] There is also a tendency towards severe acne in patients with a positive family history for acne. [21]

In this study most of the subjects were students (55.6%). Other occupations reported were nurse, caregiver, teacher, dental technician and program manager. In a study of Goulden et al[22] occupation have been shown not to be significant etiologic factor in the development of acne vulgaris.

Diagnostic Agreement

This study examined whether acne assessment measures validated for face-to-face use, can be used to assess acne lesions captured from digital skin images. Results showed that the inter-rater and intra rater reliability of the dermatologists' evaluations differed based on the acne assessment measures used: Total inflammatory lesion count (TILC), LEEDs acne assessment technique, and Investigator's Global Assessment (IGA).

Inter rater agreement for face-to-face setting

The inter rater agreement for face-to-face setting was used to determine the most consistent acne assessment measure between different raters in evaluating acne vulgaris during in person visits.

Raters had significant moderate agreement in ratings using the three acne grading tools during the face-to-face visit but the Investigator's Global Assessment (IGA) had the highest measure of concordance (ƙ = 0.559) followed by Total inflammatory lesion count (TILC), (ƙ = 0.492) and lastly, the LEEDS technique (ƙ = 0.430). This finding shows that all these acne-grading tools may be applicable during in -person visits but the Investigator's Global Assessment (IGA) may be best used since it had the highest measure of concordance among the three. The Investigator's Global Assessment (IGA) is the physician's over-all or global assessment of the condition proposed by the US FDA in 2005. This grading system recognizes the complexities in severity determination of acne. It involves determining the severity of acne, based on observing the dominant lesions, evaluating the presence or absence of inflammation and estimating the extent of involvement.[15] This is composed of ordinal scale with six severity grades, each defined by distinct and clinically relevant morphological descriptions that would minimize inter-observer variability. The more detailed descriptive text has resulted in this system being considered to provide even greater reliability than other global assessments. [16]

In contrast with the study by Tan et al[17], inter-rater reliability of the acne measures in a face-to-face setting was found to be highest for Total inflammatory lesion count.

Intra rater agreement for digital images (Week 6 vs. Week 12)

The purpose of the intra rater agreement for digital images at week 6 versus week 12 was to determine the most consistent acne-grading tool used by the same rater in evaluating photographs at different times.

Ratings on the digital images by each rater during Week 6 and Week 12 assessments had significant substantial agreements based on Total inflammatory lesion count (TILC) with ƙ = 0.620 and ƙ = 0.776 measure of concordance for Raters A and B respectively. Meanwhile, individual ratings of the digital skin images based on LEEDS technique and Investigator's Global Assessment (IGA) had fair or slight agreements only (Table 3). Both raters A and B had the highest intra rater reliability in Total Inflammatory Lesion Count (TILC) because in the counting procedure, primary acne lesions are evaluated and accounted for independently thus providing a more objective data in digital images.

In the study of Lucky et al[18] in 1996, the reliability of acne lesion counting was assessed. Total lesion counts along with non-inflammatory and inflammatory lesions were calculated. The study concluded that the reliability of acne lesion counting (TILC) was excellent when performed by the same trained rater over time, which was likewise observed in this study. Another study by Bergman et al[3] found out the Total inflammatory lesion count (TILC) to be the most reliable acne assessment measure that can be used to evaluate digital images obtained from subjects with inflammatory acne lesions.

Inter rater agreement for digital images at week 12 (Rater A vs. Rater B)

The inter rater agreement for digital images between two different raters was used to assess which acne-grading tool will have the highest measure of concordance in evaluating digital skin images.

Concordance between two dermatologists receiving photographs alone at Week 12 had significant moderate agreement in ratings of digital images using both Total inflammatory lesion count (k = 0.519) and Investigator's Global Assessment (k = 0.536) but with only fair agreement in ratings of digital images using LEEDS (k = 0.354) (Table 4). This results showed that Total inflammatory lesion count and Investigator's Global Assessment are applicable for grading digital skin images but Total Inflammatory Lesion Count may be best used for evaluating photographs since it had the highest measure of intra -rater agreement (Rater A : k = 0.620, Rater B: k = 0.776) compared to Investigator's Global Assessment and LEEDS *(Table 3)*.

It was observed in this study that the inter-rater reliability *(Table 3)* was less than the intra-rater reliability *(Table 4)* for each assessment tool in evaluating digital skin images, reflecting a disparity in scoring between raters. This underscores the importance of having the same rater evaluate a subject throughout the course of a treatment period or study. [3]

Intra rater agreement on face-to-face and digital images (Day 1 vs. Week 12)

The intra rater agreement for face-to-face consult and digital images was used to evaluate which acne grading tool will have a higher measure of concordance when used by each individual rater during face-to-face consult and digital skin images.

The ratings of Rater A at Day 1 (face-to-face setting) and Week 12 (digital images) had the highest measure of concordance for Total inflammatory lesion count (TILC) (k = 0.349) while LEEDS had the lowest measure of concordance (k = 0.000, *p* = 1.000). Ratings of Rater B using Total inflammatory lesion count (TILC) had a significantly substantial agreement (k = 0.786) however had moderate agreements using either Investigator's Global Assessment (IGA) or LEEDS. The ratings using LEEDS technique also had the lowest measure of concordance (k = 0.406, *p* = 0.003). Individual raters had higher intra rater reliability using TILC in face-to-face setting and digital skin images.

Several studies have evaluated the use of digital images to make diagnoses and triage patient referrals.[8,9] A study by *Bergman et al* [3] in 2008, determined whether a specific assessment tool designed to grade acne during face-to-face visits could be applied to the evaluation of digital images. It demonstrated that digital images of inflammatory acne lesions could reliably be evaluated using certain clinical assessment tools. In this study the Total Inflammatory Lesion Count was found to be the most reliable acne assessment measure for evaluating digital skin images, which was consistent in the result of this study.

The LEEDS technique consistently had the lowest measure of concordance among the other acne -grading tools. In LEEDS technique each raters were asked to compare the patient's acne severity to a standard photographic manual with an assigned acne severity score. The study of Tan et al[23] in 2013 stated that the standard LEEDS image could be inadequate in portraying facial acne grades and cannot accurately represent the spectrum of the acne severity. There is a current need for images that will correspond accurately to a categorical acne scale.[23] Thus, Total inflammatory lesion count (TILC) and Investigator's Global Assessment (IGA) are more objective acne-grading tools in evaluating acne severity.

CONCLUSION

Acne is a very common dermatologic condition that affects individuals around the world. The grading system is one of the main issues because there is no global standardized grading. Additionally, grading is a subjective measure that varies from one dermatologist to another (inter-rater reliability) and it may also vary for the same dermatologist at different times for the same patient (intra rater reliability). This can be attributed to the tedious process of counting lesions in various types of acne.

All the three acne severity tools may be used for evaluating acne severity during face-to-face consultation. The Investigator's global assessment may best be used for face-to-face assessments while the total inflammatory lesion count may best be used for evaluating acne severity in digital skin images.

RECOMMENDATION

This study recommends the use of a combined acne assessment measure, the Investigator's Global Assessment and Total Inflammatory Lesion Count *(Appendix B)* that can allow for a more comprehensive approach to evaluate acne severity from a clinical and investigational application. A uniform and standard acne-grading tool is important to accurately assess acne severity as this influences treatment selection and assessment of response to therapy.

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APPENDIX A ACNE GRADING TOOLS

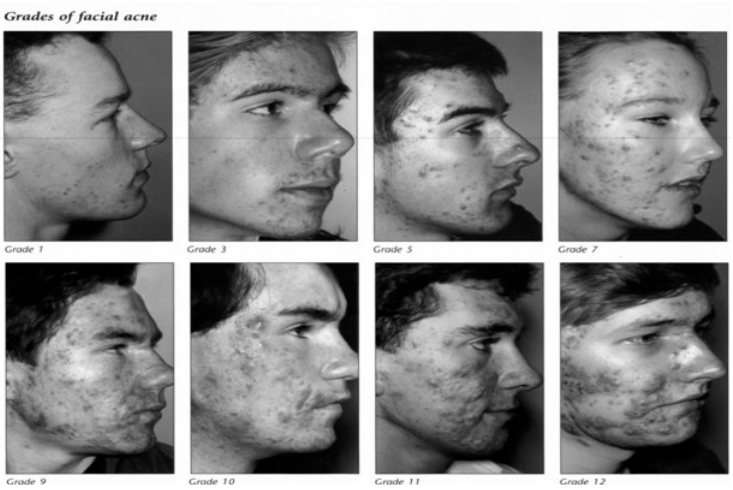
I. **Total Inflammatory Lesion Count (TILC)**

Count all non-inflammatory and inflammatory lesions and grade based on the severity score below:

Severity	**Definition**
Mild	<20 comedones or <15 inflammatory lesions or <30 total lesions
Moderate	20 to 100 comedones, or 15-50 inflammatory lesions, or 30 to 125 total lesions
Severe	>5 cysts, or total comedone count >100, or total inflammatory lesion count >50 or >125 total lesions

II. **LEEDS Technique**

Compare the patient's acne severity from the digital images to the standard photographic manual by assigning a score.



III. Investigator's Global Assessment Scale (IGA)

Using a validated 6-point grading scale, rate the patient's acne from clear to very severe.

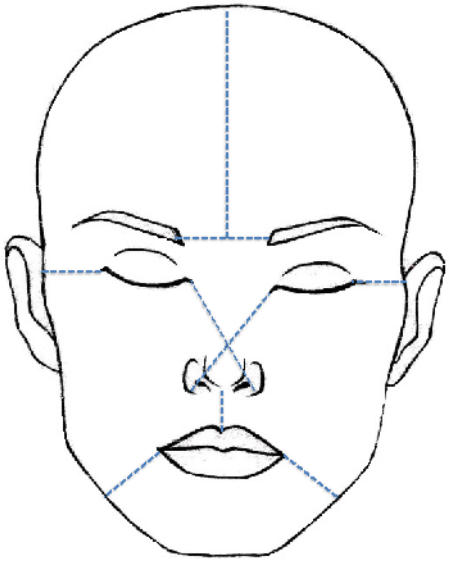
SCORE	GRADE	DESCRIPTION
0	**Clear**	Normal appearing, clear skin with no evidence of acne vulgaris
1	**Almost Clear**	Rare non-inflammatory lesions present with rare non-inflamed papules
2	**Mild**	Some comedones are present with few papules and pustules (no nodules)
3	**Moderate**	Several to many comedones, papules, pustules: One small nodule may be present
4	**Severe**	Many comedones, numerous papules and pustules; Few nodules and cysts
5	**Very Severe**	Highly inflammatory lesions predominate, variable number of comedones, many papules, pustules and many nodulocystic lesions

APPENDIX B **RECOMMENDED ACNE GRADING TEMPLATE**

Name: _____ Age/Sex:_____ Date:_____

I. TOTAL INFLAMMATORY LESION COUNT

Count all non-inflammatory and inflammatory lesions and give the acne grading based on the severity score below:



Facial Template

	RIGHT FOREHEAD	LEFT FOREHEAD	RIGHT CHEEK	LEFT CHEEK	CHIN	TOTAL NO. OF LESIONS
NON-INFLAMMATORY LESIONS						
Open comedones						
Closed comedones						
INFLAMMATORY LESIONS						
Papules						
Pustules						
Nodules						
Cysts						

SEVERITY	DEFINITION
MILD	<20 comedones or <15 inflammatory lesions or <30 total lesions
MODERATE	20 to 100 comedones or 15-50 inflammatory lesions, or 30 to 125 total lesions
SEVERE	>5 cysts, or Total comedone count >100, or Total inflammatory lesion count >50, or 125 total lesions

ACNE SEVERITY GRADE: _____

II. INVESTIGATOR'S GLOBAL ASSESSMENT (IGA)

Using the 6-point grading scale below, rate the patient's acne from Clear to Very Severe (Score 0 to 5)

SCORE	GRADE	DESCRIPTION
0	**Clear**	Normal appearing, clear skin with no evidence of acne vulgaris
1	**Almost Clear**	Rare non-inflammatory lesions present with rare non-inflamed papules
2	**Mild**	Some comedones are present with few papules and pustules (no nodules)
3	**Moderate**	Several to many comedones, papules, pustules: One small nodule may be present
4	**Severe**	Many comedones, numerous papules and pustules; Few nodules and cysts
5	**Very Severe**	Highly inflammatory lesions predominate, variable number of comedones, many papules, pustules and many nodulocystic lesions

ACNE SEVERITY GRADE: _____

A Clinical Trial on the Safety and Efficacy of Oil of Bergamot 30% and Sun Exposure combination versus Sun Exposure alone in the Management of Residual Hypomelanosis of Pityriasis Versicolor

Ma. Eleanor Cathryn DR. Salonga, M.D, DPDS[a]
Ma. Luisa Abad-Venida, M.D, FPDS[b]
Lillian Lopez-Villafuerte, M.D, FPDS[b]

Abstract

This study compared the safety and efficacy of Oil of Bergamot with sun exposure, and that of sun exposure alone in the management of the resulting hypomelanosis of Pityriasis versicolor. There was indeed a difference in the melanin and erythema indices between the two treatments with results favoring the former in terms of improvement of the condition of interest.

Introduction: Pityriasis versicolor is a skin problem in a tropical country like the Philippines. It is characterized by pinkish to hypopigmented patches usually affecting trunk and extremities. The residual hypomelanosis of this condition is a common concern for most patients. There is no known treatment for it except to wait for its spontaneous resolution for a period of six months or more, a solution which is unacceptable for many. Oil of Bergamot is an extract from the plant Citrus bergamia containing the active ingredients of 5-methoxypsoralen and 8-genoxypsoralen, members of psoralen compound which is currently being used along with UVA (PUVA) for several dermatologic conditions such as Vitiligo and Progressive Macular Hypomelanosis. It is a photosensitizing and phototoxic agent which aids in the turning back of melanocytes in conditions characterized by reduced pigment cells.

Methods: This was a single-blind study among patients aged 11 to 65 years old diagnosed with Pityriasis versicolor clinically and through a confirmatory KOH examination. There were 28 patients that were included in the study with no dropouts. Patients were instructed to split their backs into halves, right and left, one side subjected to application of oil followed by 30-minute sun exposure while the other was solely subjected to sun exposure, with the assignment of treatment sides decided by a third party. The duration of treatment was four weeks with weekly determination of melanin and erythema indices via a mexameter.

[a] *Primary author , Department of Dermatology, Jose R. Reyes Memorial Medical Center*
[b] *Consultants, Department of Dermatology, Jose R. Reyes Memorial Medical Center*

Results: ANOVA of repeated measures was used to determine if there was a difference between the two treatment groups for both the dependent variables melanin and erythema. With a p value of <0.0001, the melanin and erythema significantly improved after the treatment of oil of bergamot and sun exposure.

Conclusion: The combination of Oil of bergamot and 30-minute sun exposure significantly increased the melanin and erythema levels of the hypomelanotic lesions brought about by Pityriasis versicolor as compared to sun exposure alone**.** Adverse reactions were limited and were of mild intensity demonstrating that a short contact with the oil is sufficient enough to produce the needed erythema but inadequate in yielding strong hypersensitivity reactions.

Keywords: Hypomelanosis; Pityriasis versicolor; Oil of bergamot; Mexameter; melanin index; erythema index

INTRODUCTION

Skin color has always been an important issue since time immemorial. Many individuals, particularly during olden times, would look primarily on one's complexion, unfortunately deducing judgments solely from it. Though the latter seems no longer taking place these days, the habit of giving so much value on a person's skin appearance still holds true up to this modern time. This is where the role of us, dermatologists, comes in. We are entrusted to take well care of the largest organ system in a human's body.

Pigmentation whether in the form of hyper- or hypomelanosis is a taxing dermatologic problem to both the clinician and patient. It is a condition which on the part of the former, is extremely difficult to manage while for the latter, there is exhaustion on the waiting process for its resolution. While there are several products and procedures available in the market to address skin darkening, there is barely anything known to public for its opposite. Several dermatoses bring about alteration in skin color. For hyperpigmentation, causes vary from sun damage to hypersensitivity reactions to contact dermatitis. As for hypopigmentation, sources include inflammatory dermatoses such as psoriasis and seborrheic dermatitis, dermatophytoses, mycosis fungoides, vitiligo and many others.

In the Philippines, being a tropical country, Saprophyte infections are not infrequent, with Pityriasis versicolor being one of the most commonly seen cases. It is characterized by slightly scaling macules that can be hypopigmented, pink or salmon-colored or hyperpigmented. This superficial mycosis which is common among young adults is said to be caused by the yeast Malasezzia sp., of which M. globosa and M. sympodialis most frequently have been identified in scales of lesions.[1] Current management for this infection includes several topical antifungal preparations such as Selenium sulfide, 2.5%, Ketoconazole, Ciclopirox etc. However, these treatments while they can manage to relieve the redness and pruritus, the residual hypopigmentation remains to be unsolved.

Oil of Bergamot, an essential oil from Citrus bergamia (Bergamot orange) which is being used in various expensive fragrances, is proven to be an effective treatment for Vitiligo. Bergaptene, also known as 5-methoxypsoralen and Bergamotin, also called as 5-Geranoxypsoralen, are the major furocoumarin contents of this oil, and regarded as highly photoreactive psoralens.[2] Therefore, products containing Bergamot oil are said to be photosensitizing and highly phototoxic causing erythema and eventual repigmentation to occur in vitiligo patients.

On the other hand, Narrowband UVB light therapy (NB-UVB) is a treatment which uses the optimal part of the UVB light spectrum to cause repigmentation of one's natural skin coloring.[3] This mechanism of action is currently taken into advantage as treatment for hypopigmented dermatoses such as vitiligo and progressive macular hypomelanosis.

Therefore, it is the aim of this study to work around the strong points of these two treatments as a means of finding an effective and safe treatment to the challenging repercussions of Pityriasis versicolor which is decreased skin pigmentation. However, with the highly demanding requirement in the frequency of hospital visits as well as the cost of Narrowband UVB treatment, in this experimental research, sun exposure will serve as its alternative.

REVIEW OF RELATED LITERATURE

Pityriasis versicolor (also known as Tinea versicolor) is a common skin complaint characterized by various pigmentary changes of the skin, usually affecting the chest, back, neck and arms. The patches may be pink, coppery brown or paler than surrounding skin, which can often be associated with pruritus. The hyperpigmentation or hypopigmentation of skin depends on the outcome of interactions between Malassezia yeasts and the skin, such as lipoperoxidation process, stimulus of inflammatory cell to melanocytes, and increased thickness of keratin layer.[4]

Confirmation of diagnosis is made in two ways: The first one is via 10 % to 20% Potassium Hydroxide (KOH) microscopy wherein hyphae and yeast cells are seen resembling the so-called 'spaghetti and meat-balls'. The second one is by means of Wood's light (long wave Ultraviolet A) which shows a yellow-green fluorescence over the affected areas among one out of three patients.[5]

Pityriasis versicolor is more common in hot, humid climates or in those who sweat heavily, so it may recur each summer. It does not appear to predispose affected areas to sunburn even when it causes pale white marks.[6] It is here where the cosmetic concern comes in, the consequent hypopigmented patches over the affected areas.

The oil of Bergamot, an essential oil extracted from Citrus bergamia or Bergamot orange which is a fragrant fruit the size of an orange, with a yellow color similar to a lemon, is widely being used in the perfume industry. The oil has the ability to combine with an array of scents to form a bouquet of aromas which complement each other. Approximately one third of all men's and about half of women's perfumes contain bergamot essential oil.[7]

Having 5-methoxypsoralen and 5-geranoxypsoralen as its components, Bergamot oil is both photosensitizing and phototoxic. Its photosensitizing properties aid in turning back on melanocytes in conditions with reduced amount of the said pigment cells given the proper stimulation via ultraviolet light.[8] Taking lead of this property the oil is being used as one of the treatment for vitiligo, a skin condition characterized by depigmented patches due to destruction of melanocytes as well as of other dermatologic conditions characterized by hypopigmentation. In a study done by Kinley et.al they made use of hairless mice to assess the epidermal melanogenesis induction of topical furocoumarins (active ingredient of Bergamot oil) along with UVA radiation. Each subject was subjected into a 12-day application of topical furocoumarin followed by exposure to subphototoxic doses of UVA.

The results of which have shown evidences of melanogenesis such as increased density and size of melanocytes.[9] In another experimental study of Romano et.al the in vitro activity of Bergamot oil against clinical isolates of dermatophytes was determined. The outcome of which suggested its potential use against common species of dermatophytes.[10] In a similar study done by the same group of researchers, they measured the Minimum Inhibitory Concentration (MIC) of bergamot oil against clinical isolates of Candida species from which the group have found a probable usage of Citrus bergamia as a topical treatment against Candidal infections.[11] These studies therefore make the Oil of Bergamot more appealing in the management of Pityriasis versicolor not only in terms of its value in the restoration of skin color but as well as the possibility of decreasing the growth and thus recurrence, of Malasezzia infection.

Interestingly, similar hypomelanotic conditions such as vitiligo and progressive macular hypomelanosis can both be managed with either Narrowband UVB or topical/oral Psoralen and UVA (PUVA). In a study done by Wu CS et. al., they have proposed that PUVA is best used in the active stages of vitiligo as it slows down the destruction of melanocytes (MC) thereby creating a favourable environment for MCs to survive. On the other hand, NBUVB irradiation will best suit stable vitiligo with its ability to stimulate both proliferation and migration of MCs.[12] Conversely, Progressive Macular Hypomelanosis (PMH), a condition characterized by ill-defined, nummular, hypopigmented spots on the skin due to decreased pigmentation of epidermis has been shown to be effectively and safely treated using NBUVB. In a small uncontrolled and non-blinded clinical trial done by Kim MB et.al, 9 out of 16 patients (56.2%) experienced more than 90% repigmentation while 13 of 16 patients (81.3%) had at least 50% repigmentation after several weekly sessions of NBUVB.[13] While in 2010, Duarte et al. reviewed patients seen in a phototherapy clinic between 1997 and 2008 to evaluate the therapeutic response to PUVA photochemotherapy or Narrowbandband UVB. No significant difference between these two treatments after 16 sessions or three months of treatment has been found with majority of the patients showing more than 50% of skin repigmentation, with 65% classified as cured or much improved.[14]

Whereas, the exact mechanism of hypopigmentation in pityriasis versicolor is not known with recent discoveries pointing towards a role of tryptophan-derived metabolites of Malassezia furfur, similarly it can take advantage of phototherapy relying on its ability to induce maturation of existent melanocytes thus accelerating the repigmentation process.[15]

Both UVA and UVB comprised a certain portion of sun's rays thereby making direct exposure to sunlight, a good source of UV radiation. In particular, UVB are the main rays which are said to cause sunburn. However, excessive exposure to sunlight can increase an individual's predisposition to skin cancers such as melanoma and squamous cell carcinoma. In as much as UV radiation is warranted amongst patients with dermatologic conditions which can benefit from exposure to phototherapy but with limited ability to obtain such in a hospital facility due to lack of time and/or for financial reasons making direct sunlight exposure a good alternative, it is of importance still to advise avoidance of sun from 10 am to 4 pm when UVR intensity is at its peak in so doing, eluding the harmful consequences of too much sun exposure.[16]

Accordingly, proving the efficacy of these different modes of treatment for pigmentary disorders will be difficult if done in a subjective way. Therefore, to minimize this point of error, the researcher will be using a device used to measure skin color that would provide a reproducible means and sensitive means of quantifying small skin color differences. Park es et al. in 2006 have concluded that the Mexameter is an objective pigment-measuring device which can be used to achieve a more accurate diagnosis of hypopigmentary disorders, and that the relative melanin index which represents the relative pigment levels, might be a more effective parameter than the melanin index (MI) itself for comparing pigmentation differences.[17]

In conclusion, the researcher took advantage of the strong points of these literatures with some modifications in order to allow its feasibility in the current setting of the trial with much consideration to the study patients.

GENERAL OBJECTIVE

To compare the safety and efficacy of Oil of Bergamot 30% and sun exposure combination versus sun exposure alone in the restoration of the normal skin color in post-hypopigmented lesions of Pityriasis-versicolor.

SPECIFIC OBJECTIVES:

1. To measure the pigmentation level of the skin by means of Mexameter at weeks 0,1,2,3, and 4 of treatment.
2. To discern the relationship between Melanin Index and the erythema measurement.
3. To determine the adverse effects associated with the use of both treatments via patient's self--assessment forms.

METHODOLOGY

STUDY DESIGN

A single-blinded clinical trial on the safety and efficacy of oil of Bergamot 30% and sun exposure combination versus sun exposure in the management of the accompanying hypomelanosis of Pityriasis versicolor among normal healthy patients with Pityriasis versicolor, who were diagnosed at the Dermatology Out-Patient Department of Jose R. Reyes memorial Medical Center.

STUDY POPULATION

Normal healthy male and female patients aged 11 to 65 years old with Pityriasis versicolor over back area. Diagnosis was made by means of clinical history and examination and confirmed by means of Potassium hydroxide (KOH) examination. Duration and history of prior treatment was not considered. A total of 28 patients were enrolled in this study.

Exclusion criteria include known hypersensitivity reaction to any form of fragrances (known to contain Bergamot oil), and concomitant medical conditions known to be exacerbated by Ultraviolet exposure such as Lupus Erythematosus. Pregnant and breast-feeding mothers were also excluded from the study.

MATERIALS

The oil of Bergamot 30% was purchased by the researcher from a local supplier packaged in a plastic opaque jar ensuring its stability. Sunblock gel from another local company was also provided by the researcher to warrant the skin protection of non-involved skin areas of all study patients.

RANDOMIZATION, TREATMENT ALLOCATION, AND BLINDING

The randomization of back areas of the subjects was done by a third party via computer-generated method. The oil was handed to the subject by the said party who re-instructed the patient as to its application and as to which side should it be placed. In this experiment, the researcher as well as the physician performed the mexameter readings were blinded.

STUDY INTERVENTION AND ASSESSMENT

Diagnosed patients were treated primarily with topical and/or oral antifungal opted by the primary clinician. A repeat KOH was performed to check for clearance of dermatophyte infection.

On follow-up, the residual hypomelanosis was managed. Each patient had the affected body area divided into two areas. One area was subjected to the application of Bergamot oil 30% 30 minutes prior to sun exposure while the other side was directly exposed to the sun without any other intervention. Both sides had exposure between 6 am to 9 am to avoid the intense burning heat past the given time. In addition, patients were instructed to apply sunblock gel on normal skin, 30 minutes prior to going out while the involved areas with oil were washed off with water after heat exposure prior to the application of sunblock gel.

To address the possible result-altering external factors, every patient was instructed to have avoidance of sun exposure after the given time and to protect their skin upon stepping outside via use of umbrella and wearing of proper shirt at all times.

On doing the mexameter reading, two representative lesions were chosen from each side by the researcher and by the third party who handled the said device. The representative lesions that were chosen were based on which portion is the whitest or most hypopigmented of all. Photos were taken on every reading to mark the representative lesions.

CLINICAL ASSESSMENT

Baseline photos and mexameter readings were taken prior to the initiation of therapy. Patients were asked to follow-up on a weekly basis for a period of 4 weeks wherein a questionnaire regarding the adverse effects was requested to be answered. Repeat photography and Mexameter readings were done on every follow-up.

Primary endpoint was the restoration of normal skin color as per evidence of clinical photographs and the increase in the level of pigmentation via the mexameter. The grading were as follows: Grade 1 for < 50% of repigmentation or interpreted as slightly improved; Grade 2 for 50% to 79% of repigmentation or moderately improved; Grade 3 for 80% to 99% or much improved; Grade 4 for 100% or cured. Secondary endpoint was the number of weeks needed to achieve at least 50% of re-pigmentation.

STOPPING GUIDELINES

A subject would have been withdrawn from the study upon any signs of severe irritation such as blistering, intense erythema and pruritus. Patients who used other topical preparations or those who would were unable to comply with the proper sun exposure as well as the wearing of protective gears would have been taken out of the study.

SAMPLE SIZE

Based on the 2013 census of the JRRMMC Department of Dermatology, Out Patient Department, 237 cases of Pityriasis versicolor were seen out of the total of 30,328 patients. The researcher set the maximum permissible error at 5%, α at 5% and confidence level at 95%. Open Epi results indicated that a minimum of 28 patients was needed to achieve a 95%

level of confidence, precision of 5% given an estimated with outcome to be at 80%. The researcher needed minimum of 28 patients to achieve a 95% level of confidence, precision of 5% considering a 20% drop outs.

RESULTS

DISCUSSION

There were 28 patients enrolled in the study. Majority of which were males comprising 78.57% of the study population. The mean age of patients was 23.3 years old. In the study, each subject's back area was divided into two. One half of the back was subjected to application of Oil of Bergamot followed by 30-minute sun exposure while the other half was solely exposed to sun for a similar duration as the former. The mean percentage of melanin was 14.46% and erythema was 11.98% on baseline (see table 1).

ANOVA of repeated measures was used to determine if there was a difference between the two treatment groups for both the dependent variables melanin and erythema. With a p value of <0.0001, it can be concluded that the melanin and erythema significantly improved after the treatment of oil of bergamot and sun exposure (see table 2). A post hoc comparison (tukey) test was used to determine at which week showed marked improvement. With p-values of < 0.0001 for all the treatment weeks, it showed that using the combination of oil of bergamot and sun exposure significantly increased the percentage of erythema and melanin.

Fundamentally, the increase in the melanin and erythema values is projected amongst the areas subjected into the combination of the oil and sun exposure. As mentioned in the previous section, the aim of this study is directed on taking advantage of the oil of bergamot's photosensitizing and phototoxic properties. With sufficient stimulation of ultraviolet radiation, the melanocytes are expected to be stimulated following the application of the oil on a hypopigmented spot and thus, break open into a phototoxic reaction priming the development of erythema over the area and eventually leading to its repigmentation. As for the areas which were merely exposed to the sun, the increase in their melanin and erythema indices can be accounted by the induction of maturation of the existing melanocytes by the adequate amount of ultraviolet radiation received.

Conversely, adverse reactions were noted in a number of subjects in areas applied with the Oil of Bergamot. As mentioned, it is both photosensitizing and phototoxic prompting the development of some unwarranted symptoms among patients, particularly those with strong personal and/or family history of atopy. Reportedly, 5 out of 28 patients or 17.8% developed mild pruritus upon contact with the oil which eventually resolved with rinsing of the area. There were 3 out of 28 or 10.7% who experienced sting or a burning sensation upon application of the oil which once more disappeared after washing it off. There were however, only 2 out of 28 patients or 7.1% who had few papules over the area involved both of which having resolution following the application of an emollient cream for a few days. Fortunately, none of the 28 subjects had experienced blister formation. All of the symptoms mentioned were signs of a hypersensitivity reaction to the Oil of bergamot and sun exposure combination. On the other hand, sun exposure alone showed no capacity of inducing such reactions with none of the areas subjected to it had the development of the said symptoms.

With regards to the grading of improvement which has been set for this clinical trial, chi-square was used to determine the difference between the two groups and with a p value of 0.136, there was not much of a difference visually between the two. However, in terms of patient's satisfaction, majority of them verbally expressed their satisfaction with the usage of Bergamot oil along with the 30-min sun exposure pushing them to continue with the management even after the conclusion of their participation in this trial.

In conclusion, the combination of Oil of bergamot and 30-minute sun exposure significantly increased the melanin and erythema levels of the hypomelanotic lesions brought about by Pityriasis versicolor as compared to sun exposure alone. Adverse reactions were limited and were of mild intensity demonstrating that a short contact with the oil is sufficient enough to produce the needed erythema but inadequate in yielding strong hypersensitivity reactions.

As for the author's recommendation, it is recommended that subsequent trials will include a larger population with a longer duration of study. None of the patients have been noted to develop a 100% repigmentation of their lesions which is likely due to the very limited course of the clinical trial. It is also advisable that two arms will be assigned, one with the similar Oil of bergamot with sun exposure versus the other with no intervention at all. This is to see the difference in the repigmentation time between an interventional group and the one which will rely solely on spontaneous resolution.

TABLES AND FIGURES

Table 1. Demographic characteristics of patients on baseline

Subjects N=28	Mean
Age	23.3
Gender	22:6
Melanin	14.26%
Erythema	11.98%

Table 2. Melanin Index (Oil of Bergamot 30% + Sun Exposure)

	WEEK					
Patient	**0**	**1**	**2**	**3**	**4**	**Improvement**
1	200	234	296	297	312	2
2	360	427	457	494	506	1
3	80	87	96	99	99	1
4	374	417	450	499	520	1
5	101	143	183	187	198	3
6	325	390	471.2	481	507	2
7	170.33	209	255	258	281	2
8	215.3	280	308	318	340	2
9	213	240	289	315	343	2
10	257	290	328	332	360	1
11	300	330	401	425	465	2
12	197	224.2	294	313	325.33	2
13	220	256	357	372	401	3
14	336	361	408	420	474.67	1
15	223	234	314		355	2
16	198.2	217	284.33	301	330.33	2
17	115	137	165	201	214	3
18	320	347.67	398	427	484	2
19	234	269	322	334	360	2
20	280	317	356	371	426	2
21	219	245	290	315	336	2
22	303	338	389.3	429.3	478	2
23	180	200	264	286.67	329	3
24	236	292	329	336	384	2
25	254	299	326.33	353	396	2
26	165	194	256	270	304.67	3
27	301	386	469	475	494	2
28	312	357	423	434	499	2

Table 3. Melanin Index in Percentage Increase (Oil of Bergamot 30% + Sun Exposure)

	WEEK					
Patient	**0**	**1**	**2**	**3**	**4**	**Improvement**
1	200	17	48	48.5	56	2
2	360	18.6	26.9	37.2	40.5	1
3	80	8.8	20	23.8	23.8	1
4	374	11.5	20.3	33.4	39	1
5	101	41.5	81.18	85	96	3
6	325	20	45	48	56	2
7	170.33	23	50	51.3	65	2
8	215.3	30	43	48	58	2
9	213	12.7	35.6	47.8	61	2
10	257	12.8	27.6	29.2	40	1
11	300	10	33.7	41.7	55	2
12	197	13.8	49	58.9	65.1	2
13	220	16.3	62.2	69	82.3	3
14	336	7.4	21.4	25	41.2	1
15	223	4.9	40.8	45.7	59.1	2
16	198.2	9.5	43.5	51.8	66.6	2
17	115	19.1	43.5	74.8	86	3
18	320	8.6	24.3	33.4	51.2	2
19	234	15	37.6	42.7	53.8	2
20	280	13.2	27.1	32.5	52.1	2
21	219	11.9	32.4	43.8	53.4	2
22	303	11.6	28.5	41.7	57.8	2
23	180	11.1	46.7	59.3	82.8	3
24	236	23.7	39.4	42.4	62.7	2
25	254	17.7	28.5	39	55.9	2
26	165	17.6	55.1	63.6	84.6	3
27	301	28.2	55.8	57.8	64.1	2
28	312	14.4	35.6	39.1	60	2

Table 4. Melanin Index (Sun Exposure Alone)

	WEEK					
Patient	**0**	**1**	**2**	**3**	**4**	**Improvement**
1	169.67	200	227	242	274	2
2	295	381	399	435	483	2
3	146	166	169	172	178	1
4	382	417.33	496.33	521	545	1
5	194	212	248	257.67	280	1
6	293.33	324	371	396	410.67	1
7	150	170.33	184	198	205	1
8	264	304	363	385	401	2
9	260	295	338.33	347	360	1
10	227	259	298	316	347.33	2
11	313	369	398	439	457	1
12	164.67	174.	193	198	229	1
13	228	269	288	303	355.67	2
14	314.33	347	385	427	472.33	2
15	223	258	292	317	340.67	2
16	238	256	277	302.6	333	1
17	108	115	137	149	165	2
18	347	384	458	495	517	1
19	223	244.67	265	287	323.33	1
20	290	317	352	395	431	1
21	187	201.2	240	244	275	1
22	329	378	409	454	490	1
23	205	249	267	294	313	2
24	224.67	253	270.33	291	331	1
25	276	294	326	388	422	2
26	195	227.2	259	270	289	1
27	276	311	349	376	408	1
28	315	347	389	430.67	472	1

Table 5. Melanin Index in Percentage Increase (Sun Exposure Alone)

	WEEK					
Patient	**0**	**1**	**2**	**3**	**4**	**Improvement**
1	169.67	17.8	33.7	42.6	61.4	2
2	295	29.2	35.2	47.5	63.7	2
3	146	13.6	15.8	17.8	21.9	1
4	382	9.2	29.9	36.4	42.7	1
5	194	9.3	27.8	32.8	44.32	1
6	293.33	10.5	26.5	35	40	1
7	150	13.5	22.7	32	36.7	1
8	264	15.1	37.5	45.8	51.9	2
9	260	13.5	30.1	33.5	38.5	1
10	227	14	31.3	39.2	53	2
11	313	17.9	27.2	40.3	46	1
12	164.67	6	28.3	20.2	39	1
13	228	18	26.3	32.9	56	2
14	314.33	10.4	22.5	35.8	50.3	2
15	223	15.7	30.9	42.1	52.8	2
16	238	7.6	16.4	27.1	39.9	1
17	108	6.5	26.9	38	52.8	2
18	347	10.7	32	42.7	49	1
19	223	9.7	18.8	28.7	45	1
20	290	9.3	21.4	36.2	48.6	1
21	187	7.6	28.3	30.5	47	1
22	329	14.9	24.3	38	48.9	1
23	205	21.5	30.2	43.4	52.7	2
24	224.67	12.6	20.3	29.5	47.3	1
25	276	6.5	18.1	40.6	52.8	2
26	195	16.5	32.8	38.5	48.2	1
27	276	12.7	26.4	36.2	47.8	1
28	315	10.2	23.5	36.7	49.8	1

Table 6. Erythema Index (Oil of Bergamot 30% + Sun Exposure)

	WEEK				
Patient	**0**	**1**	**2**	**3**	**4**
1	265.33	286	331	348	395
2	399	433	427	455	479
3	362	384	408	447	470
4	385	429.67	467	488	475
5	245	288.33	288	292.33	315
6	354	400.67	447	460	484
7	227.33	274	290	311	347
8	247	267	296	327	365
9	226.67	288	344	361	387
10	292	314	374.67	412	438
11	321	379	401	458.33	489
12	200.67	215.33	236	250	294.67
13	241.2	268	285	323	361.67
14	367	402	424	496	562
15	269	296	337	354	395
16	238	256.33	289	307.67	345
17	139	155	179.67	197	219
18	358.2	395	458	501.33	540.67
19	283.33	297	321	375	424.67
20	303	328	371.33	414	455
21	256	277	293	336	384
22	311	338	343.33	366	429
23	215	264	301.67	316	355
24	267	294	345	380	407.33
25	298	347	356.33	382	422
26	202	236.67	251	274	314
27	319.67	344	379	428	479.67
28	344	381	417	475.33	524

Table 7. Erythema Index in Percentage Increase (Oil of Bergamot 30% + Sun Exposure)

	WEEK				
Patient	**0**	**1**	**2**	**3**	**4**
1	265.33	7.79	24.8	31.2	50.8
2	399	8.5	7.01	14	20
3	362	6.07	12.7	23.5	29.8
4	385	11.6	21.3	26.7	23.4
5	245	17.7	17.6	19.3	28.6
6	354	13.2	26.3	30	36.7
7	227.33	20.5	27.6	36.8	52.6
8	247	8.1	19.8	32.4	47.7
9	226.67	27	51.8	59.3	70.7
10	292	7.53	28.3	41.1	50
11	321	18.1	37.3	42.8	52.3
12	200.67	7.3	17.6	24.6	47.1
13	241.2	11.1	18.2	3.9	50
14	367	9.5	15.5	35.1	53.1
15	269	10	25.3	31.6	46.8
16	238	7.7	21.4	29.2	45
17	139	11.5	29.3	41.7	57.6
18	358.2	10.3	27.9	40	51
19	283.33	4.8	13.3	32.4	49.9
20	303	8.25	22.6	36.6	50.2
21	256	8.2	14.5	31.3	50
22	311	8.7	10.4	17.6	37.9
23	215	22.8	40.3	47	65
24	267	10.1	29.2	42.3	52.5
25	298	16.4	19.6	28.2	41.6
26	202	17.2	24.3	35.6	55.4
27	319.67	7.61	18.6	33.9	50
28	344	10.8	21.2	38.2	52.3

Table 8. Erythema Index (Sun Exposure Alone)

	WEEK				
Patient	**0**	**1**	**2**	**3**	**4**
1	269	322	327	323	371.6
2	363	418	410	457	482
3	248	266	256	260.33	316
4	405.67	425	447	471	508
5	232	265.67	297	274	306
6	312	348	395	370	399
7	184	211.67	235	248	276
8	298	339	378	363	389.33
9	283.67	341.67	357	368	374
10	254	297	315	328	352
11	346.33	388	397.67	411	453
12	213.2	246.33	255	278	299
13	265.33	294	310.67	328	352
14	346	371	399.33	416	440
15	272	301	315	347	368
16	266	285	298.33	312.67	330
17	159	189	219	237	231.67
18	380	412.33	437	459	464
19	245.67	268	295.67	302	339
20	319	348	369	381	410
21	208	246.67	263.67	272	319
22	355.33	386	401.33	417	454
23	237	252	274.33	290	307.67
24	242	268	294	318	339
25	290	319.67	337	342	384
26	234	250.67	282	305	317
27	305	347.33	384	372.67	385
28	338	360	395	415	425

Table 9. Erythema Management in Percentage Increase (Sun Exposure Alone)

	WEEK				
Patient	**0**	**1**	**2**	**3**	**4**
1	269	19.7	21.6	20	38.1
2	363	15.1	12.9	25.9	32.8
3	248	7.25	3.22	4.7	27.4
4	405.67	4.8	10.2	11.2	25.2
5	232	14.5	28	18.1	31.9
6	312	11.1	26.6	18.6	27.9
7	184	15	27.7	34.8	50
8	298	13.8	26.8	21.8	30.6
9	283.67	20.8	25.9	29.7	31.8
10	254	29	24	30.3	38.9
11	346.33	12	14.8	18.7	30.8
12	213.2	15.5	19.6	30.4	40.2
13	265.33	10.8	17.1	23.6	32.7
14	346	8.1	15.4	20.2	27.1
15	272	10.7	15.8	27.6	35.3
16	266	7.1	12.2	17.5	24
17	159	18.9	37.7	49.1	45.7
18	380	8.5	15	20.8	22.1
19	245.67	9.1	20.4	22.9	38
20	319	9.1	15.7	19.4	28.5
21	208	18.6	26.8	30.8	53.3
22	355.33	8.6	13	17.4	27.8
23	237	6.3	15.8	22.4	29.8
24	242	10.7	21.5	31.4	40.1
25	290	10.2	16.2	17.9	32.4
26	234	7.12	20.5	30.3	35.5
27	305	13.9	25.9	22.2	26.2
28	338	6.51	16.9	22.8	25.7

Table 10. ANOVA Table

Subjects N=28	Oil of bergamot and sun exposure				sun exposure alone				p value
weeks	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	
Melanin	16.07	39.38	46.94	59.61	12.85	26.61	35.71	47.43	<0.0001
Erythema	11.73	22.99	32.37	43.8	12.24	19.54	23.58	33.21	<0.0001

Figure 1. Graphic Comparison of Melanin Index

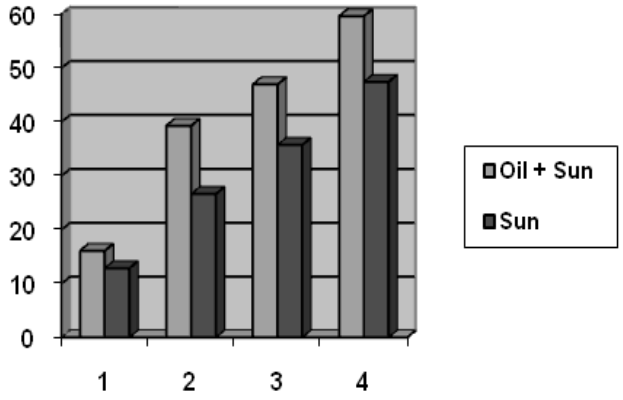
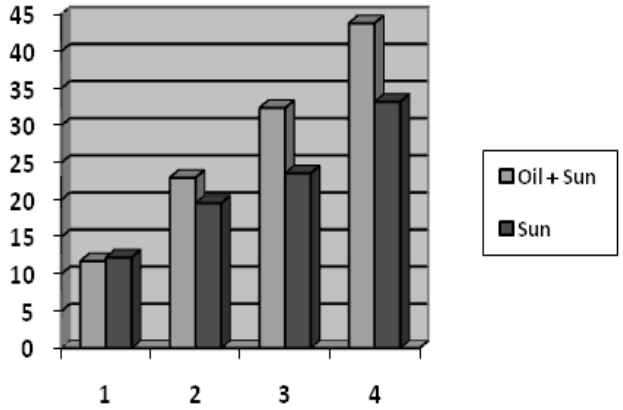


Figure 2. Graphic Comparison of Erythema Index



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A Randomized, Double-blind Placebo-controlled Clinical Trial on the Efficacy and Safety of Adapalene 0.1% Gel on the Closure of Neuropathic Ulcer among Leprosy Patients

Ma. Cricelda M. Rescober, M.D.[a]
Daisy Ismael-King, M.D., F.P.D.S[b]

INTRODUCTION

Leprosy is a chronic infectious disease principally affecting the skin, eyes, and the peripheral nerves. It is caused by the acid-fast, rod-shaped bacillus *Mycobacterium leprae*.[1] According to the World Health Organization, three million persons are suffering from the burden of the disease.[2] Damage to peripheral nerves is a key feature of leprosy and the motor and sensory loss that follow the disease is the basis of developing wounds, fissures, ulcerations, clawed hand, foot drop, and lagophthalmos. Neuropathic ulcers (NU) are one of the most common complications of leprosy seen in 10% of patients.[3] NU occur due to impairment of the sensory, motor, and autonomic nerve functions leading to lowered threshold for tissue damage.[4] They may arise in any part of the body and are divided into 2 groups: plantar and extra-plantar. Plantar ulcers, also called trophic ulcers or malum perforans pedis, are more common, comprising 70% of all NU. Ulcers occurring in other denervated sites, such as the dorsum and lateral malleolar region of the foot and hands are described under extra-plantar ulcers.[3] Aside from the loss of protective sensation on the foot, other factors such as repetitive moderate stress, callus formation, direct trauma, pressure, burns, and infection contribute to the development of NU.[5]

Despite recent and emerging advances in combating leprosy, management of NU in leprosy has taken a backseat. A recent systematic review of randomized controlled trials involving anyone with leprosy and damage to peripheral nerves treated with any measures designed to prevent damage with the aim of healing existing ulcers and preventing development of new ulcers identified eight trials with a total of 557 participants.[6] The quality of the trials was generally poor and interventions and outcome measures were diverse. Strategies in the approach to these frustrating ulcers have mainly been supportive including antibiotics, various wound dressings, and use of corrective shoes. Clinical trials exist in ulcer closure but these are few and deemed lacking.

The pathophysiology of chronic non-healing ulcers such as NU is marked by excessive infiltration of neutrophils that release significant amounts of enzymes such as collagenase or matrix metalloproteinase -8 (MMP-8) that is responsible for the breakdown of connective tissue matrix, and elastase that is capable of destroying essential healing factors such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-ß). Another marker of these chronic ulcers is an environment containing excessive reactive oxygen species that further damage the cells and healing tissues.[7]

The collagen molecule is characterized by repeating sequences of proline and hydroxyproline (HP). Collagen is important in all stages of wound healing and is critical in regaining tissue integrity and

[a] *Resident, Department of Dermatology, Jose R. Reyes Memorial Medical Center*
[b] *Consultant Staff, Department of Dermatology, Jose R. Reyes Memorial Medical Center*

strength. In particular, hydroxyproline is important because it gives the collagen molecule its stable helical configuration.[7] The initial cleavage of collagen by MMP-8 represents the rate-limiting step in the degradation of this extracellular matrix protein. In non-healing ulcers, there is increased collagenolytic activity, reflected by elevated levels of MMP-8, decreased HP, and lower levels of tissue inhibitor of matrix metalloproteinase-1 (TIMP-1). These findings suggest that overexpression and activation of MMP-8 may be involved in the pathogenesis of non-healing wounds.[8]

Retinoids have broad uses in dermatology and their role in wound healing has been widely studied. Preoperative use of retinoids is believed to enhance wound healing. However, there are mixed reviews regarding its efficacy in fresh and healing wounds. Vitamin A is an essential fat-soluble vitamin that plays an integral role in the maintenance of normal epidermis by promoting desquamation and maturation through a decrease in the production of keratin, keratohyalin granules, and desmosomes. Moreover, vitamin A also enhances would healing by stimulating angiogeneseis, collagen synthesis, and epithelialization.[9] Retinoids are synthetic and natural derivatives of vitamin A. They exert their activity on keratinocytes by binding to nuclear receptors, thereby regulating gene expression. .

Topical tretinoin (all-*trans*-retinoic acid) has been found to have positive effects on wound healing.[10] The use of tretinoin on a poorly granulating wound bed increases epidermal thickness and cell turnover, leading to faster reepithelialization and granulation tissue formation.[11] It also stimulates angiogenesis in the superficial dermis which allows efficient delivery of oxygen and nutrients to the tissues. Endothelial cells secrete biologically active substances that include growth factors.[10] Moreover, tretinoin also increases granulation tissue formation by increasing collagen synthesis by way of downregulating MMP-8.[12]

A randomized, double-blind, clinical trial by Tom et al. assessed the efficacy of short-contact tretinoin versus placebo.[10] The study showed that applying tretinoin 0.0.5% solution for 10 minutes on diabetic foot ulcers once a day for 4 weeks was superior to placebo saline solution. A similar technique was used in a clinical trial by Chua et al. where short-contact (10 minutes) tretinoin 0.05% cream improved the healing of foot ulcers in leprosy patients versus the placebo cream.[13] However, irritation caused by topical tretinoin is often a concern. Short-contact application of tretinoin may cause mild to moderate pain on the surrounding skin and ulcer itself.[10] Also, tretinoin is relatively more expensive compared to other wound care medications limiting its use.

Adapalene is a new naphthoic acid derivative with strong retinoid agonistic properties and belongs to the third-generation retinoids. It is also known to behave similarly to tretinoin.[14] Animal studies suggest that adapalene contributes to the wound healing process resulting in enhancement of collagen production, angiogenesis, and granulation tissue formation.[14-15] It is also noted that adapalene is more stable and is less irritating than tretinoin because of its unique receptor specificity.[15]

Ulceration of the feet is the single most common cause of disability and dehabilitation of patients with leprosy. Because of its impact in the patient's physical, emotional, and social health, it is of utmost importance that there be continuing search for a solution. A simple and well-tolerated treatment that affords closure of ulcer will prevent further ulceration, susceptibilty to infection, risk of amputation, and ultimately, disability. Currently, there are no existing studies about the use of topical adapalene on neuropathic ulcers in leprosy patients. A randomized controlled trial is therefore needed to determine the efficacy and safety of a retinoid derivative such as adapalene that is similar to tretinoin in pharmacologic action but is cheaper, more stable, and with less adverse effects.

OBJECTIVES

The general objective of the study is to determine the efficacy and safety of adapalene 0.1% gel versus placebo in the closure of neuropathic ulcer among leprosy patients.

The specific objectives are to determine if patients treated with adapalene 0.1% gel compared to

those given placebo gel were significantly different in terms of 1.) Percent change of ulcer surface area from baseline to post-treatment, and 2.) Number of weeks for the ulcer to close, and 3.) Incidence of adverse events.

MATERIALS AND METHODS

Patients and Study Design

This is a prospective, randomized, double-blind, placebo-controlled clinical trial on leprosy patients who present with neuropathic ulcer, plantar or extra-plantar, at the Dermatology Outpatient Department of Jose R. Reyes Memorial Medical Center.

Patients recruited included male or female patients both newly or previously diagnosed with leprosy who presented with neuropathic ulcer, plantar or extra-plantar, treated or currently under multidrug therapy (paucibacillary or multibacillary) with at least two weeks washout period from any oral antibiotics or topical medications before the study enrollment period.

Excluded from the study were patients unable to give informed consent, with known bleeding disorders, pregnant or breastfeeding at the time of enrollment, who have infected ulcers or nearby tissues at time of enrollment, who have other systemic disorders that will impede wound healing such as diabetes mellitus, with clinical and radiological signs of osteomyelitis, and who have a known or documented allergy to adapalene and other retinoid derivatives.

A certificate of approval from the Institutional Review Board of Jose R. Reyes Memorial Medical Center was obtained prior to starting the clinical trial. Written informed consent was secured before initiating treatment.

Materials

Both adapalene 0.1% gel and placebo gel were obtained from local companies. Both were repackaged and put in a plastic opaque jar and labeled by numbers. Placebo gel was specially made so that it would be identical to the treatment in terms of color, texture, and odor.

Randomization, treatment allocation, and blinding

Randomization was performed by an uninvolved third party who did a computer-generated random sequence to balance the participants of the 2 treatment groups. The study was double-blind in such a way that all dispensed jars were similar in appearance and that neither the patient nor the investigator was aware to which the patient was assigned until after the completion of the study.

Study Intervention

The patients were instructed to clean the wound bed with cotton swab moistened with normal saline solution before applying adapalene 0.1% gel or placebo gel. They would then apply the assigned gel directly on the wound and leave it on for 10 minutes with special instructions to avoid surrounding normal skin. After 10 minutes, patients would rinse it off with normal saline solution. This procedure was done once a day for 4 weeks. The participants were allowed to receive routine wound care such as protection of the ulcerated area with appropriate dressings. Patients were also advised to wear open-toed soft sandals as standard protective footwear. Accepted footwear was defined as having a soft insole about 1 cm thick, a hard sole that cannot be pierced by sharp objects such as stones and thorns, and an upper that fits well and has straps or laces over the forefoot that can be loosened. These were provided by the investigator to preserve uniformity.

Clinical Assessment

Photographs of the ulcers were taken to evaluate and document initial size and appearance. The photographs were taken using Nikon Coolpix P310 under standardized lighting and positioning of the patient. Photographs and measurement of ulcer size and volume were taken every 2 weeks for a maximum of 16 weeks after the start of the study or until complete healing occurs, whichever occurred first. Manual planimetry, wherein the ulcer is traced on acetate with grids, was used to measure surface area. The number of grids that fit within the traced circumference was counted and multiplied by area in square centimeters to yield the surface area.[18] All partial grids divided by the tracing line by more than half were likewise included.

Primary endpoint is determined as 50% or greater reduction in the percent change in ulcer surface area and volume and from baseline until the end of the study. Secondary endpoint is defined as the number of weeks at which reduction in ulcer surface and volume was observed. Both endpoints will be assessed at every visit.

Any untoward effects encountered during the treatment such as erythema, edema, purulence, and burning sensation were noted.

Stopping guidelines

The study was to be stopped in patients who experienced excessive irritation defined as burning sensation, diffuse erythema, and pain on application. These patients were considered as withdrawals from the study. Those who did not comply with the treatment regimen, or those who used other topical medications were withdrawn from the study.

Drop-outs were defined as those who did not follow up within two weeks and whose outcome was unknown by the end of the study period.

Sample size

Since there is a small population of leprosy patients with neuropathic ulcer at Jose R. Reyes Memorial Medical Center, sample size was inferred from a similar clinical trial done at our institution which had 16 participants. For this study, sample size was doubled to 32 patients, with 16 participants in each study arm.

Data Processing and Analysis

Primary endpoint was computed as the percent change of the ulcer surface area from baseline to the end of the study. The differences between the size of the ulcer from the baseline to week 16 were assessed using analysis of variance (ANOVA) of repeated measures. A Post-Hoc Test, Tukey test, was used when ANOVA showed a significant result. Statistical analysis was performed with the use of STATA software (version 12.0). A p value < 0.05 was considered statistically significant.

RESULTS

Study Population

Thirty-eight patients were evaluated for eligibility between June 2013 and May 2014. Two did not qualify for the study because of the presence of infected ulcers; another 2 patients diagnosed with diabetes mellitus were excluded; and 2 patients who did not meet any exclusion criteria refused to participate in the study. A total of 32 patients were enrolled in the study, with 16 patients assigned to each arm **(Figure 1)**. There were no withdrawals nor drop-outs during the study.

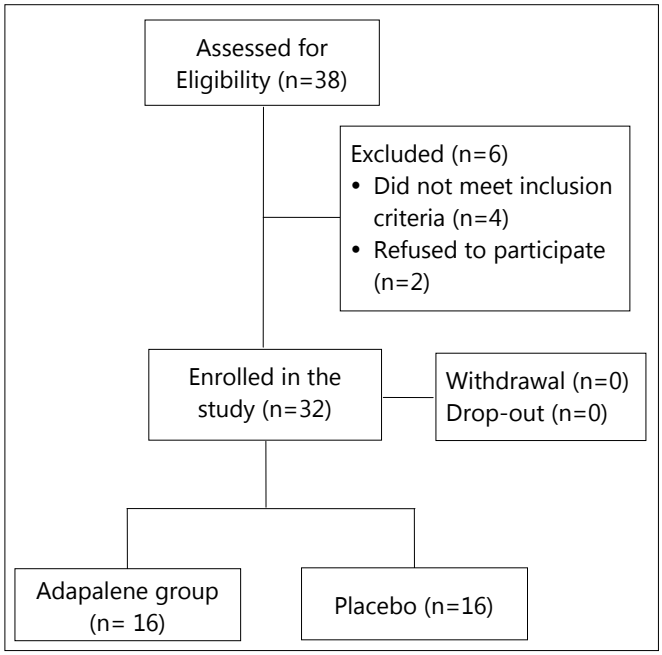

Figure 1. Patient Disposition

Majority of the subjects were comprised of males (75%) with 81.25% (13/16) from the treatment group and 68.75% (11/16) from the control group. Mean age for both groups was 55.18, 55.43 years for treatment group while 54.93 years for the control group. Mean size of the ulcer on baseline was 8.25 cms, measuring 9.875 cms for the treatment group and 6.625 cms for the control group. T-test and chi-square were done to determine if there was a significant difference in between groups prior to the initiation of the study. All the variables - age, gender and ulcer size on baseline were found to be not statistically different between the 2 groups **(Table 1)**.

Table 1. Patient Demographics

Subjects (n=32)	Adapalene gel (n=16)	Placebo (n=16)	P-value
Age (mean +/- SD)	55.4375 +/- 14.27096	54.9375 +/- 10.23037	0.7328
Gender (M:F)	13:3	11:5	0.4909
Ulcer size	9.875 +/- 7.99	6.625 +/- 3.324	0.500

Clinical Effects

In the treatment group, 15 (94%) of 16 ulcers demonstrated 50% or greater reduction in the surface area by the end of the study period. On the other hand, only 3 (19%) of 16 ulcers showed reduction of ulcer of 50% or greater. In terms of complete closure, there were 4 (25%) in the adapalene group and 2 (13%) in the placebo group by the end of the study. **Tables 2** and **3** show the summary of change in ulcer size throughout the 16-week treatment period of all patients.

Table 2. Change in ulcer size in the adapalene gel group

Patient	BL	2nd	4th	6th	8th	10th	12th	14th	16th	% Change
1	30	15	8	4	3	3	3	3	3	**90%**
2	19	17	16	10	8	6	3	3	2	**89%**
3	2	1	1	1	*0	0	0	0	0	**100%**
4	15	14	14	14	14	13	8	5	5	**67%**
5	2	3	3	3	4	4	4	4	5	-150%
6	21	20	18	16	16	15	15	6	5	**76%**
7	9	6	6	3	2	1	1	1	1	**89%**
8	2	2	1	1	*0	0	0	0	0	**100%**
9	9	4	4	4	3	3	3	2	2	**78%**
10	11	10	10	9	8	7	6	5	5	**55%**
11	7	6	4	4	4	3	3	3	3	**57%**
12	4	4	4	3	3	2	2	2	2	**50%**
13	4	7	5	1	*0	0	0	0	0	**100%**
14	3	2	1	1	*0	0	0	0	0	**100%**
15	12	12	10	9	5	4	4	3	3	**75%**
16	8	8	7	7	7	6	5	2	1	**88%**

Table 3. Change in ulcer size in the placebo group

Patient	BL	2nd	4th	6th	8th	10th	12th	14th	16th	% Change
1	7	7	7	7	8	8	8	8	8	-14%
2	5	5	5	5	4	4	4	4	4	20%
3	6	6	5	5	5	5	5	5	5	17%
4	4	4	4	4	4	4	4	4	4	0%
5	8	8	7	7	5	5	5	4	4	**50%**
6	7	7	6	6	6	6	6	6	6	14%
7	14	14	13	13	13	12	12	12	11	21%
8	5	5	4	3	2	*0	0	0	0	**100%**
9	2	2	2	2	1	1	*0	0	0	**100%**
10	12	11	12	12	13	13	15	15	15	-25%
11	3	3	3	3	3	3	3	3	3	0%
12	6	6	8	8	8	10	10	10	10	-67%
13	5	4	4	4	4	5	5	6	6	-20%
14	9	9	9	9	9	8	8	7	7	22%
15	10	10	10	10	8	8	8	8	8	20%
16	3	2	2	2	2	2	2	2	2	33%

**Closed completely*

The progress of ulcer healing in both groups with respect to mean surface area and time is shown below (**Figures 2 and 3**).

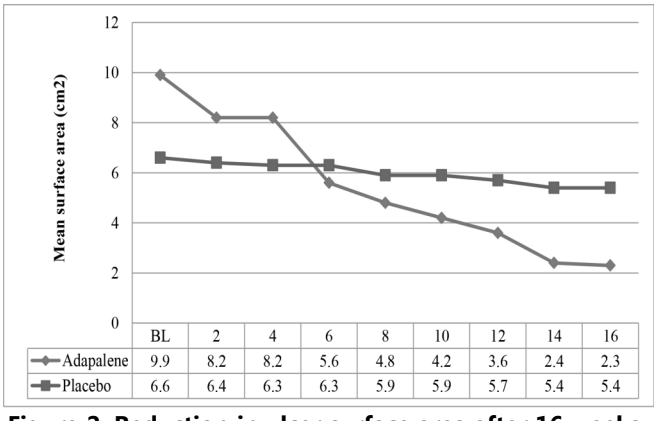

Figure 2. Reduction in ulcer surface area after 16 weeks of treatment

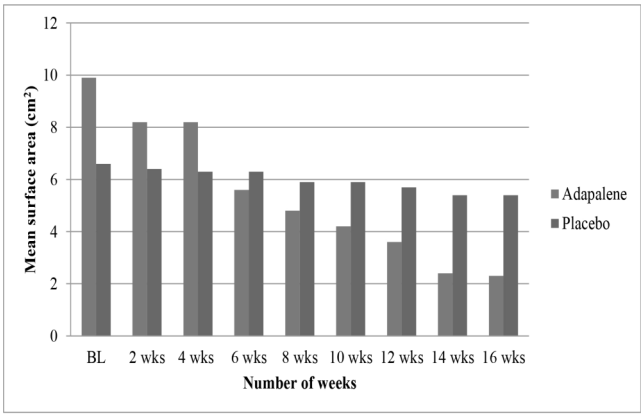

Figure 3. Adapalene group vs. placebo group in the reduction in ulcer

After utilizing ANOVA of repeated measures in the treatment arm, there was a difference in the size of the ulcer from baseline to week 16, as the p value was <0.0005. Since there was a significant difference in the size of the ulcer from the pretreatment to post treatment, a post hoc comparison test was done to assess at which week the size of the ulcer became smaller. The Tukey test determined that on the 12th week, 14th week and 16th week of treatment using adapalene gel, there was a significant difference in ulcer size in between two groups (p values = 0.037, 0.007 and 0.005). Optimal effect of adapalene gel was seen at the 16th week (p = 0.005).

T-test was used to determine if there was difference in the percentage of ulcer surface area after treatment between the treatment and control groups. With a p value of 0.0313, the ulcer size treatment with adapalene gel significantly decreased in comparison with the placebo gel. There were no reported adverse effects such as erythema, pain, nor edema during the 16-week treatment period.

DISCUSSION

This study demonstrated the favorable effect of adapalene 0.1% gel in the closure of neuropathic ulcer among leprosy patients. It showed a more than 50% reduction in almost all the ulcers studied and complete closure at early weeks in a few. There were no adverse effects reported until the end of the study.

Neuropathic ulcer, like most chronic non-healing wounds, result from breakdown of tissue that in turn stimulates the release of enzymes that further enhances connective matrix breakdown and depletion of healing factors. Another feature of these chronic ulcers is an environment containing excessive reactive oxygen species that further damage the cells and healing tissues.

The present study aimed to determine if short -contact application of adapalene 0.1% gel would improve the healing of NU. Through manual planimetry, it was shown that adapalene afforded more than 50% reduction in ulcer surface area, suggesting faster wound healing and granulation tissue formation (**Figures 4 and 5**). Our results also showed that reduction in ulcer size can be observed as early as 12 weeks with optimal results seen at 16 weeks.

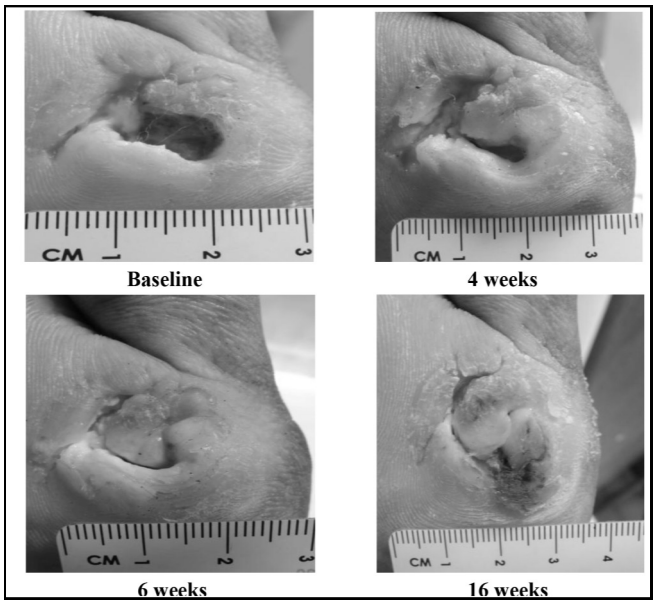

Figure 4. Reduction in ulcer surface area in a representative patient treated with

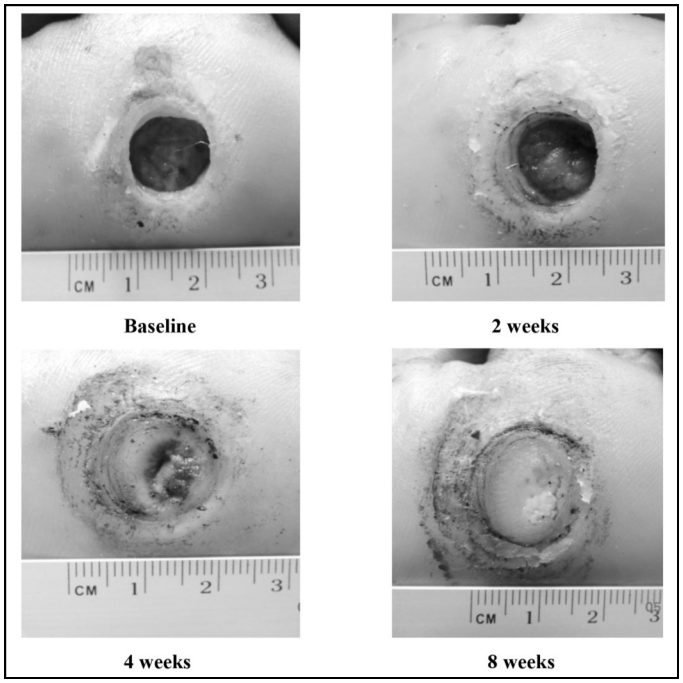

Figure 5. Complete closure of a neuropathic ulcer in another representative patient

Effects of adapalene may be due to the fact that it possesses strong retinoid agonistic properties. It has been reported to produce similar or greater pharmacological activity compared to retinoic acids. Studies on the wound reparative capacity of adapalene reveal that it promotes angiogenesis, enhances collagen synthesis by increasing HP, increases cellular filtration, and stimulates granulation tissue formation. Moreover, collagen, reticular and elastic fibers, which strengthen tension and structural maintenance, are reported to be prominently enhanced.[14] Adapalene is also known to possess anti-inflammatory properties that may be useful in suppressing inflammation associated with chronic non-healing wounds. Its anti-inflammatory action is due to the inhibition of the oxidative metabolism of arachidonic acid via the lipooxygenase pathway. This may contribute to the reduced potential of adapalene to cause erythema and cutaneous irritation.

No adverse effects occurred during the study. However, this is in contrast to the findings in a study done by Basak et al. and Tom et al. which reported more erythema, irritation, and mild pain with tretinoin application.[15,10]

Adapalene is known to behave similarly to tretinoin pharmacologically. This new-generation retinoid addresses many of the problems such as local skin irritation and photoinstability that have limited long-term retinoid use.[17] The biologic effects of retinoids are mediated by two types of receptors: cellular retinoic acid binding protein (CRABP) and nuclear receptors further divided into two: retinoid acid receptors (RARs) and retinoid X receptors (RXR). The development of receptor-specific ligand has been recognized as a way to improve risk-benefit ratio. Adapalene is an example of such as it does not bind to CRABP and has no effect or RXR. The RARs are divided into α, β, and γ subtypes and exhibit distinct affinities for retinoic acid and show characteristic tissue distribution. RAR- γ subtypes are found in the epidermis while RAR- β subtypes are located in the dermis. Tretinoin has a high affinity to all nuclear RARs, whereas adapalene activates RAR- β and RAR- γ only. The unique receptor selectivity of adalapalene offers a clinical advantage over tretinoin, translated into less irritation, more stability, and better tolerance.[18]

Maximum efficacy of a topical drug depends on achieving a high concentration of a drug on the target site while systemic safety relies on minimal passage of the drug to the blood and lymph vessels. Adapalene is characterized by having very low percutaneous absorption once the drug has penetrated the stratum corneum.[18]

One limitation of this study is that ulcer depth was not included in the assessment. As a result, wound healing that may have begun at the ulcer base could not be evaluated and determined.

There is no gold standard in the treatment of NU in leprosy patients. Results were mixed in a systematic review of randomized controlled trials of leprosy with damage to peripheral nerves treated with any measures aimed at healing existing ulcers and prevention of new ones.[6] Eight trials with a total of 557 participants were included. Although three studies that compared zinc tape to more traditional dressings found some benefit, none of these showed a statistically significant effect. One trial indicated that topical ketanserin had a better effect on wound healing than clioquinol cream or zinc paste. Two studies that compared topical phenytoin to saline dressing showed statistically

significant effects in favor of phenytoin for healing of ulcer. Canvas shoes were not much better than polyvinyl chloride (PVC)-boots, and double rocker shoes did not promote healing much more than below-knee plasters.[6] There is an obvious lack of high quality research in the field of ulcer prevention and treatment in leprosy. The success of tretinoin in closure of NU among leprosy patients and diabetic ulcer serves as the basis of selecting adapalene which has similar properties but is more stable, with less adverse effects, less expensive, and better tolerated – features that make it a good alternative in the treatment of foot ulcers in leprosy patients.

CONCLUSION

This randomized controlled study found that compared to placebo, short-contact adapalene 0.1% gel is more effective and generally safe to use in the reduction of surface area of neuropathic ulcer among leprosy patients. It suggests that adapalene may be a novel treatment option for treating neuropathic ulcers.

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Association of Vitamin D Receptor Gene Polymorphisms in the Occurrence and Spectrum of Leprosy in Filipino Patients Seen at Jose R. Reyes Memorial Medical Center

Donn M. Mendoza, M.D.[1]
Zharlah Gulmatico-Flores, M.D., FPDS[2]

Abstract

Introduction / Background: Host genetic factors including major histocompatibility complex (MHC) polymorphisms influence both susceptibility to leprosy and also to leprosy type. Recent studies have implicated variation in the vitamin D receptor (VDR) gene in susceptibility to several diseases, including osteoporosis and pulmonary tuberculosis. Putative polymorphisms at the VDR gene, which potentially modifies VDR mRNA stability and/or activity, have been implicated in susceptibility to intracellular pathogens.

Objectives: The general objectives of the study are to determine the effects of Vitamin D receptor gene polymorphism on the occurrence and spectrum of leprosy among Filipino patients seen at Jose R. Reyes Memorial Medical Center, Department of Dermatology Hospital.

Methods: Five (5) cc of whole blood samples obtained from patients diagnosed with Hansen's disease by smear and histological confirmation as well as healthy controls seen in the outpatient department. DNA was isolated from white blood cells using the phenol/chloroform method and was used for PCR amplification. The primers 5'-CAGAGCATGGACAGGGAGCA-3' and 5'-GGTGGCGGCAGCGGATGTACGT-3' yielding a product of 352 base pairs in the 61675 and 62026 positions of the VDR gene was used (Goulart et al., 2005). The PCR cycle conditions would be 94^{o}C for 20 seconds, 60^{o}C for 30 seconds, and 72^{o}C for 30 seconds (35 cycles), using 2 m*M* MgCl2, 0.2 m*M* dNTPs, 0.009 m*M* of each primer, 100 ng of DNA, and 1 U of Taq polymerase in a 25-µL reaction (Roy et al., 1999).

[1]*Resident, Department of Dermatology, Jose R. Reyes Memorial Medical Center*
[2]*Consultant, Department of Dermatology, Jose R. Reyes Memorial Medical Center*

Results: Sixty (60) subjects were included in the study. A total of 43 (71.67%) patients who were diagnosed case of Leprosy with a spectrum of tuberbuloid and lepromatous type. Fifteen patients (25%) were classified as tubercuoid type and 28 (46.67%) patients were of lepromatous type. Seventeen 17 (28.33%) patients in the control group were composed of healthy volunteers unrelated to patients. The distribution of VDR genotypes at codon 352 in exon 9 was highly significant in between the control and lepromatous, tuberculoid and lepromatous type of Hansen's disease. Heterozygous type of VDR (Tt) were found to be highly significant among controls at 82.35% while 66.67% of tuberculoid has homozygous recessive type (tt) of VDR and 96.43% of lepromatous type has homozygous dominant type VDR (TT) . Significant difference were observed between the HD group (tuberculoid and lepromatous) and control. Fstat = 31.32, ($p < 0.001$). Post-hoc analysis of genotypes between the clinical groups showed that tuberculoid vs lepromatous had significantly different genotypes ($p =< 0.001$) and lepromatous type of HD vs control had significantly different genotypes ($p =< 0.001$).

Conclusion: The polymorphism of VDR genotypes at codon 352 in exon 9 was highly significant in between the control, lepromatous, and tuberculoid type of Hansen's disease. Homozygous TT was highly associated with lepromatous type (odds ratio = 16, $p =< 0.001$), and homozygous tt is highly related to the tuberculoid type (odds ratio = 5.8, $p =< 0.001$).

INTRODUCTION

Leprosy is a chronic, infectious, and slowly progressive disease caused by the bacillus *Mycobacterium leprae* characterized by granulomas and neurotropism with a predilection for the skin and peripheral nerves. The diagnosis of the disease is often delayed and aggravated by subclinical infection, presence of healthy carriers and inconsistent evidence of reduced transmission following multidrug therapy.[1]

Once worldwide in distribution, leprosy is now seen primarily in tropical and subtropical regions of Asia, Africa, and Central and South America. In endemic countries, the vast majority of new cases are in children and young adults who have close relatives with contagious forms of the disease. Elimination of leprosy as a public health problem is defined as a prevalence rate of less than one case per 10 000 persons. Efforts currently focus on eliminating leprosy at a national level in the remaining endemic countries and at a sub-national level from the others. The number of new cases detected in 2008 was 240,007 globally, and has fallen by 9126 (4% decrease) compared with 2007. However, there was a slight increase at the end of 2009 to 244,796.

The National Leprosy Control Program (NLCP) of the Philippines was established in 1986 under the supervision of the National Center for Disease Prevention and Control (NCDPC) of the Department of Health (DOH). Leprosy Control Program envisions to eliminate leprosy as a human disease by 2020. The program thrust is towards finding hidden cases of leprosy and putting them on MDT, emphasizing the completion of treatment within the WHO-prescribed duration.[28] In 1986, there were 38,570 registered patients with leprosy in the Philippines, with a prevalence rate of 7.2 per 10,000 Filipinos. There was a dramatic decrease in prevalence by the end of 1998, to 0.90 per 10,000 population, and leprosy was no longer considered to be a public health problem of the country. In 2004, the prevalence was further reduced to 0.38 per 10,000 population, translating to a total decline of 3,146 from 7,005 in 1998. In 2006, the prevalence of leprosy in the Philippines was more than 3000 cases (0.42%), while the number of new cases detected was 2,517. There was a decrease in the number of patients in 2007. However, an upward trend was observed in 2008 to 3,338 patients (0.35%).

The three requirements for the spread of leprosy are: a contagious patient, a susceptible person, and close or intimate contact. The organism is spread predominantly via nasal and oral droplets from the bacilliferous patient and much less often from eroded skin and even after 1 to 7 days, the bacillus is still viable in dried secretions. Inoculation is via the nasal mucosa or, less commonly, through breaks in the skin barrier. Transmission also depends on the infectivity of the contagious patient.

Leprosy is mainly a clinical diagnosis. Laboratory techniques may serve as adjuncts in the diagnosis. AFB microscopy is still being used in the Philippines; samples for bacilloscopy may be obtained from the earlobes, forehead, chin, extensor forearms, and dorsal fingers, as well as buttocks and trunk. The smear is usually stained by the Fite (or Ziehl-Neelsen) method and a search is made for red rods (against a blue background) at 100x with oil immersion. Routine skin punch biopsy with hematoxylin-eosin stain and Fite-Faraco are also being requested in training institutions in the Philippines but not routinely done in leprosy control programs and rural health centers. In subclinical cases seen in clinics, a clinicopathological correlation may deem necessary. A biopsy specimen of the skin lesions should be obtained, especially in patients with suspected tuberculoid leprosy. There are three basic histopathologic patterns observed in leprosy: lepromatous, tuberculoid and borderline.

Clinical manifestations depend on the relationship of the bacillus and the host immune response. Therefore, patients present a spectrum of clinical and histological characteristics, ranging from multibacillary form, which corresponds to lepromatous leprosy with a high bacillus load in tissues, to the paucibacillary form or tuberculoid leprosy, in which the bacillus is rarely found in skin smears.[2]

Host genetic factors including major histocompatibility complex (MHC) polymorphisms influence both susceptibility to leprosy and also to leprosy type.

Recent studies have implicated variation in the vitamin D receptor (VDR) gene in susceptibility to several diseases, including osteoporosis and pulmonary tuberculosis.[3] Putative polymorphisms at the VDR gene, which potentially modifies VDR mRNA stability and/or activity, have been implicated in susceptibility to intracellular pathogens. The vitamin D receptor (VDR) is traditionally described as responsible for calcium regulation and bone metabolism mediated by 1,25-dihydroxyvitamin D3.[1] Few studies have reported on the interaction between the VDR gene polymorphism and leprosy susceptibility in other countries; however, there are evidence of interpopulation heterogeneity[4] suggesting that variability may also be observed in associations with infectious diseases, perhaps related to variation in calcium intake or other gene-environment interactions,[3] and studies in other populations will be required to determine the generality of these VDR-leprosy associations.

We report herein an analysis of the Vitamin D receptor gene polymorphism on the susceptibility and spectrum of leprosy confirmed by slit-skin smear examination and histopathologically among Filipinos seen at the Department of Dermatology of the Jose R. Reyes Memorial Medical Center. The VDR gene polymorphism can be used as a predicting tool among persons without symptoms or manifestations of leprosy especially those in contact with diagnosed leprosy patients.

MATERIALS AND METHODS

Subjects

An Institutional Review Board / Institutional Ethics Committee of the Jose R. Reyes Memorial Medical Center approved the study prior to its initiation following the guidelines of good clinical practice. Sixty (60) subjects were included in the study. A total of 43 (71.67%) patients who were diagnosed case of leprosy by acid-fast bacilli in slit-skin smear examination with a spectrum of tuberculoid and lepromatous type. Tuberculoid leprosy was defined by the presence of asymmetrical well-defined lesions with a dry surface and the absence of detectable acid-fast bacilli. Lepromatous leprosy was defined by large number of of skin lesions and with numerous acid-fast bacilli in slit-skin smears. Both conditions were confirmed by histopathology and fite-faraco stain. Fifteen (15) patients (25%) were classified as tuberculoid type while 28 (46.67%) patients were of the lepromatous type. A total of 17 (28.33%) patients in the control group composed of healthy volunteers unrelated to patients. The mean age for all the subjects was 34.92 years with a standard deviation of 8.54 years. There were 31 (51.67%) males and 29 (48.33%)were females (Table 1).

Table 1. Demographic data of patients seen at the Jose R. Reyes Memorial Medical Center, 2014.

Subjects (n=60)	Patients	Age (mean years)	Gender M:F
Control	17 (28.33%)	35.58 +/- 8.03	8:9
Hansen's Disease	43 (71.67%)		
Tuberculoid	15 (25%)	36.533 +/- 7.51	7:8
Lepromatous	28 (46.67%)	33.64 +/- 9.42	16:12

Vitamin D Receptor Genotyping

DNA was isolated from white blood cells using the phenol/chloroform method (Sambrook et al., 1989) and was used for PCR amplification. The primers 5′-CAGAGCATGGACAGGGAGCA-3′ and 5′-GGTGGCGGCAGCGGATGTACGT-3′ yielding a product of 352 base pairs in the 61675 and 62026 positions of the VDR gene was used (Goulart et al., 2005). The PCR cycle conditions would be 94^{o}C for 20 seconds, 60^{o}C for 30 seconds, and 72^{o}C for 30 seconds (35 cycles), using 2 m*M* MgCl2, 0.2 m*M* dNTPs, 0.009 m*M* of each primer, 100 ng of DNA, and 1 U of Taq polymerase in a 25-µL reaction (Roy et al., 1999).

VDR gene with the restriction fragment length polymorphism (RFLP) technique was used in genotyping. In the RFLP procedure, PCR amplicons was submitted to TaqI enzyme digestion according to the manufacturer's recommendations. The results was ascertained according to the presence or absence of specific bands visualized after agarose gel electrophoresis (1.5%), ethidium bromide staining, and UV transillumination (Martinez et al., 2006).

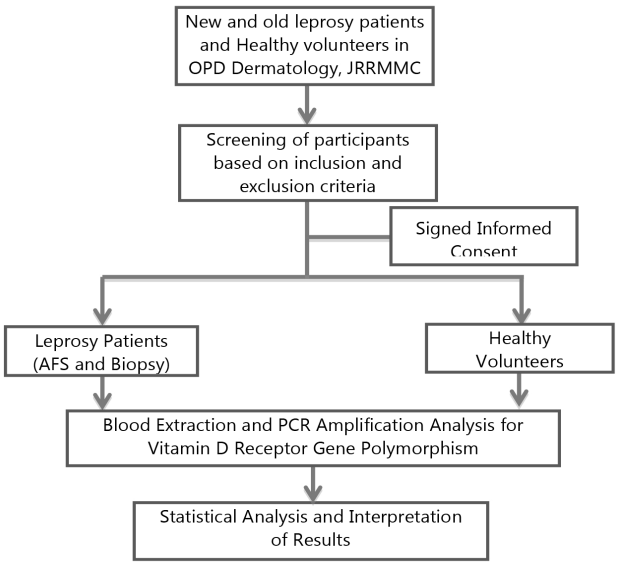
For the primers, it was ordered directly from IDT Tehcnologies which provides primers/ oligonucleotide synthesis for PCR. The PCR was done at the Philippine Genome Center DNA Sequecing Core Facility (DSCF) which is based at the New NIMBB Building, University of the Philippines, Diliman and offers both the extraction of blood and as well as the testing of the gene polymorphism.

To assure the validity of RFLP method, 75 random samples / each sample would be tested twice, and the read-out could be given (98% agreement between the tests). When results for the same sample will be different, a third PCR with that sample will be performed for confirmation.

Statistical Analysis

The raw data obtained was processed using the STATA software version 12. Descriptive analysis of the continuous data was done by getting the mean with standard deviation to describe the demographic profile of all the subjects while proportions was used for the categorical data.

Because the aim of the study was to identify the association between the Taq 1 polymorphisms and Hansen's Disease susceptibility, Chi-square test was used to determine the association of the gene polymorphism with the presence of disease. Also, the strength of association was estimated by crude odds ratios (OR), with 95% confidence interval (95% CI). The statistical significance was accepted if values are $p<0.05$.



RESULTS

The distribution of VDR genotypes at codon 352 in exon 9 is highly significant in between the control, lepromatous, and tuberculoid types of Hansen's disease. 82.35% of the control has heterozygous type (Tt) of VDR while 66.67% of tuberculoid has homozygous recessive type (tt) of VDR and 96.43% of lepromatous type has homozygous dominant type VDR (TT) . Chi-square was done and showed that there was a significant difference in between the control and cases *(X2* = 41.6564, p =<0.0001) while the the tuberculoid and lepromatous showed a significant difference in the VDR genotype (*X2* = 72.2468, p =<0.0001) with odds ratio = 16, interpreted as TT genotype has 16x increased risk among patients with lepromatous spectrum versus control and tuberculoid type, 95% confidence interval [CI = 2.48-22.76; x2 = 10.61, p=<0.001.] Odds ratio of 5.8 was noted in the tt genotype interpreted as 5.8x increased risk among patients with tuberculoid type versus control and lepromatous type, 95% confidence interval [CI = 1.26-18.55; x2 = 21.72, p=<0.001.] (Table 2)

Table 2. Hansen's Disease and Vitamin D receptor genotype

Group N=60	Genotype			Total	
	TT	**Tt**	**tt**		p-value
Control	2 (11.76%)	14 (82.35%)	1 (5.88%)	17	<0.0001
Tuberculoid	5 (33.33%)	0	10 (66.67%)	15	<0.0001
Lepromatous	27 (96.43%)	1 (3.57%)	0	28	<0.0001

***** *There was significant difference observed between the HD group and control. Fstat = 31.32, p <0.001. Post hoc analysis of genotypes between the clinical groups showed that tuberculoid vs lepromatous had significantly different genotypes (p=< 0.001) and Lepromatous type of HD vs control had significantly different genotypes (p=< 0.001).*

The significant difference in between the VDR genotype among the groups seen in this study provided an evidence that Vitamin D receptor gene plays a role in the immune response and regulates one's immune system in vulnerability to infectious disease

such as Hansen's Disease among Filipino patients. Studies have shown that deficiency in Vitamin D has an association to susceptibility to tuberculosis at low concentrations of 1, 25 hydroxyvitamin D3 as it weakens the human macrophages. Studies from different countries have shown that VDR with leprosy and its type has a controlling effect in the VDR pathway on leprosy. The results in this study showed the same outcomes as done among leprosy patients of the same studies where the genotype homozygous (TT) was highly related among lepromatous type and the heterozygous (Tt) and homozygous (tt) was highly associated with control group and tuberculoid type of Hansen's disease correspondingly.

The polymorphism was located around the ~260th base. The expected frequency of fragment length for all of the sequences were 352 bp. VDR sequence-specific oligonucleotides for T (5′-GCGCTGATTGAGGCCATC-3′) and t (5′-GCGCTGATCGAGGCCATC-3′) alleles were used (Roy, et al 1999). The control group (healthy volunteers) did not show the T (5′-GCGCTGATTGAGGCCATC-3′) and t (5′-GCGCTGATCGAGGCCATC-3′) alleles.

Homozygous (TT) was highly associated with the lepromatous spectrum of leprosy where T (5′-GCGCTGATTGAGGCCATC-3′) was seen but t (5′-GCGCTGATCGAGGCCATC-3′) alleles was not noted (Figure 1). Homozygous (tt) was highly associated with the tuberculoid type of leprosy where T (5′-GCGCTGATTGAGGCCATC-3′) was not seen but t (5′-GCGCTGATCGAGGCCATC-3′) alleles was noted (Figure 2).

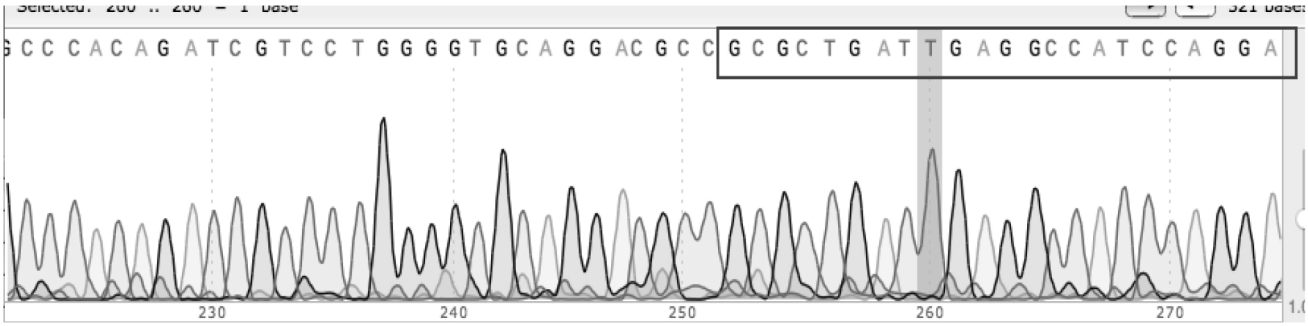


Figure 1: Homozygous TT, T (5'-GCGCTGATTGAGGCCATC-3') was seen and t (5'-GCGCTGATCGAGGCCATC-3') alleles was not seen in this sequence.

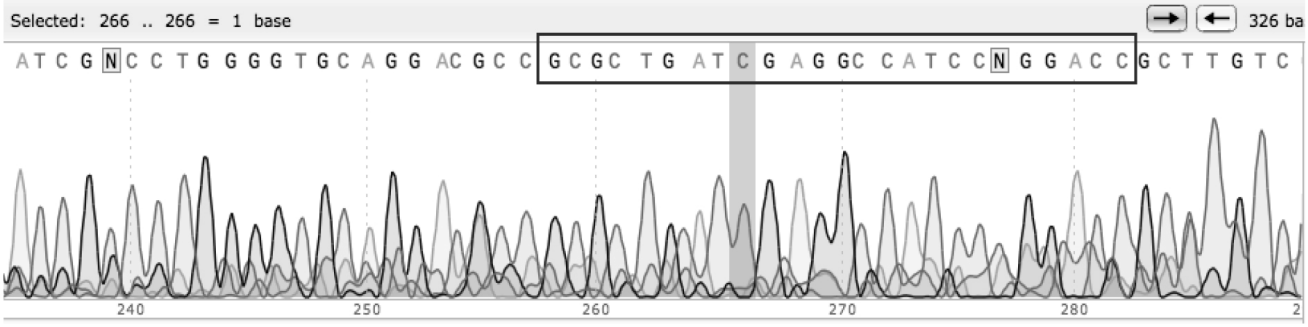


Figure 2: Homozygous tt, t (5'-GCGCTGATCGAGGCCATC-3') alleles was seen and T (5'-GCGCTGATTGAGGCCATC-3') was not seen in this sequence.

DISCUSSION

The association between VDR genotype and susceptibility to leprosy observed in this study provides further evidence for the proposal that the vitamin D receptor may be an immune response gene regulating susceptibility to infectious disease in humans. There is epidemiologic evidence linking vitamin D deficiency and susceptibility to tuberculosis and in vitro data indicating an effect of the active metabolite of vitamin D (1,25 D3), on mycobacterial growth.[3] Addition of physiologic concentrations of 1,25 D3 impairs growth of *Mycobacterium tuberculosis* in human macrophages and monocytic cell lines.[5] Such in vitro studies are not possible for *Mycobacterium leprae,* but early studies of the treatment of leprosy with medications containing vitamin D are consistent with a possible immunomodulatory effect on this bacterium.[6]

This case-control study identifying associations of VDR with leprosy and leprosy type in Filipino patients provides evidence for a modulatory effect of the VDR pathway on leprosy as well as further data supporting the functional relevance of variation in or near the VDR gene. The differential association of VDR genotype with leprosy type is of particular interest in relation to the genetic control of cellular and humoral immune responses.[7] Leprosy provides a model for understanding human immune responses to infection in that the disease presents as a spectrum in which the clinical manifestations correlate with the level of cell-mediated immunity to the bacterial pathogen.[1, 3] Tuberculoid spectrum presents with strong cellular immune response with skin lesions that contain well-organized granulomas with very few bacilli. In contrast, lepromatous leprosy patients have a stronger humoral immune response but a weak cellular response with bacilli-laden macrophages.[8]

Increasing evidence indicates that tuberculoid leprosy is associated with a predominantly Th1-type pattern of cytokine production in T cells from skin and peripheral blood and conversely, lepromatous leprosy is associated with a more Th2-shifted pattern of cytokine production.[9, 10] There is considerable interest in identifying the genetic and other factors that determine whether a Th1- or Th2-type response is made to an antigen or foreign pathogens, as this often correlates with resistance or susceptibility. These leprosy data suggest that one of the genetic factors influencing this Th1-Th2 shift in humans may be VDR genotype, with tt homozygotes tending to produce a TH1-type immune response and TT homozygotes producing a Th2-type response. This possibility is compatible with the observation that tt homozygotes have been found to be strongly correlated with the tuberculoid spectrum of leprosy and TT homozygotes were related to the lepromatous type, as seen in this study. Of interest, in leprosy, the tt genotype is associated with tuberculoid type characterized by a strong cellular response but not with resistance to leprosy per se, which was associated with heterozygosity for VDR genotype.

The role of the VDR gene in regulating the immune response may have a potential application with regard to alternative diagnostics and therapeutics that could solve the public health problem that leprosy still represents. Moreover, the genetic association study of the VDR gene polymorphism with infectious diseases like leprosy and tuberculosis can be a starting point for a better understanding of these diseases.

CONCLUSION

The polymorphism of VDR genotypes at codon 352 in exon 9 was highly significant in between the control, lepromatous, and tuberculoid type of Hansen's disease. Homozygous TT was highly associated with lepromatous type (odds ratio = 16, $p =< 0.001$), and homozygous tt is highly related to the tuberculoid type (odds ratio = 5.8, $p =< 0.001$).

These data suggesting that VDR genotype may influence the Th1-Th2 pattern of immune response in leprosy encourage assessment of the role of this genetic locus in a wide variety of human infectious and autoimmune diseases.

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Patients of Different Body Mass Index Classification and its Effect on Tube Current Time Product, Scanner Radiation Output and Image Quality as Applied in Multidetector Computed Tomography of the Whole Abdomen – A Retrospective Study

Ginalynn Fincale, M.D.[a], and Jackson Dy, M.D.[b]

Abstract

OBJECTIVE: This study aimed to retrospectively determine if there is significant difference in the tube current-time product (mAs) used and radiation output in patients of different BMI classification undergoing CT study, and how this would affect image quality.

METHODS: This study included 144 adult patients who underwent CT of abdomen. Patients were classified according to their BMI. The mAs is set by the CT machine, adjusted according to patient cross section. Radiation output parameters were collected after each study. Qualitative evaluation of images was done based on image noise and effect on diagnostic accuracy.

RESULTS: Correlation Analysis showed significant increase in mAs and radiation output in groups of patient with higher BMI. There is however no significant difference in image quality between BMI groups, such that there is no significant improvement in image quality when mAs is increased.

CONCLUSION: This study reiterates the need for body size-adapted CT protocol in imaging patients since the radiation dose required in patients of higher BMI is increased to maintain diagnostic quality of images.

[a]*CT-MRI Fellow-in-Training, Department of Radiology, Makati Medical Center*
[b]*Chairman, Research Adviser, Department of Radiology, Makati Medical Center*

INTRODUCTION and REVIEW OF RELATED LITERATURE

According to the International Atomic Energy Agency (IAEA), there has been a steady increase in the number of computed tomography (CT) studies performed that on an average, it now contributes 60 to 70% of patient dose for any given center. This is despite the fact that CT only makes up about 15% of all x-ray based imaging studies (16). CT imaging has revolutionized the way clinicians are able to manage their patient that it is not surprising that the number of CT studies is continuously increasing since the inception of the first CT machines in the early 1970s. However, the benefits of CT studies come with risks as expected for an imaging modality using radiation. The American College of Radiology has released a White Paper stating that "medical exposure might be responsible for approximately 1% of the cancer in the United States" (1). The upside with these events is that it has forced the medical community to re-evaluate the risk-benefit of ordering a CT study.

The steady and expected continuous increase in the utilization of CT poses a challenge to the radiologic community to uphold the principle of ALARA (as low as reasonably achievable). A topic associated in CT dose reduction and management is quantifying CT radiation dose. The scanner radiation output is most commonly represented by volume averaged CT dose index (CTDl), a measure of the amount of radiation delivered from a series of contiguous irradiations to standardized acrylic phantoms (10). Thus CTDI is not a reflection of dose for an individual patient, rather represents the dose within the scan volume from a particular scan protocol. The SI unit is milligray (mGy). Dose-Length Product (DLP) on the other hand, is an indicator of the integrated radiation dose of an entire CT examination (8). It is the product of CTDI and scan length (z-extent), and is given in units of milligray-centimeters. DLP better represents the overall energy delivered by a given scan protocol (10). The effective dose (E), is not actually a measurement of dose, but rather reflects the stochastic risk from an exposure to ionizing radiation (14). What it does is it allows an approximate comparison of radiation induced risk among different types of examinations (18). It takes into account the tissue that has absorbed the radiation, and attempts to approximate whole-body radiation, and thus is a weighted average of organ doses (13). Be wary that effective dose should not be used to predict absolute risk for an actual individual patient. Effective dose is measured in millisieverts (mSv). DLP values can be converted from mGy-cm to mSv using a weighting factor (k) coefficient (in mSv/[mGy-cm]) (9, 10, 13).

The benefit of an appropriately indicated CT scan exceeds the associated risk, and it falls on the radiologist to make an accurate diagnosis vis-à-vis using the minimal amount of radiation required to obtain images adequate for evaluating the patient's condition. Reasonably, what radiologists do not want sacrificed in the goal of reducing patient dose is image diagnostic quality. The determination of optimal image quality is a complicated task and is assessed by both objective and subjective measures, the latter affected by inter-observer variation regarding the acceptable image noise. Two of the most commonly used image quality parameters are spatial resolution and low contrast resolution. The former is determined by the number of rays and spacing of the detectors in the CT machine for a projection. Contrast resolution on the other hand is determined solely by noise (6). Noise describes the variation in CT numbers in a physically uniform region. (18). The scan time, tube current and peak kilovoltage, pitch, and slice thickness all affect noise. More importantly, patient size is the lone parameter that cannot be controlled (9).

The tube current-time product with SI unit of milliamperage per second (mAs) is a measure of the photon flux and is the product of the tube current and exposure time. Radiation dose is directly proportional to mAs if all other factors are held constant. One can reduce tube current-time product by either lowering the tube current or increasing the x-ray tube rotation speed (decreasing the rotation time). X-rays are attenuated by soft tissue in an exponential fashion. To maintain a consistent noise level from thin to obese patient, the mAs setting would have to increase exponentially (9).

The relationship between kilovolt peak (kVp) and noise is less direct. Tube potential is defined as the x ray beam energy (5). Radiation dose is

is proportional to kVp raised to an exponential *n*th power, with *n* ranging from 2.49 to 3.12 depending on patient size (9, 17). For example, in a typical abdominal CT phantom, decreasing the peak voltage from 120 to 100 kVp reduces the dose by 28%-40%, and as much as 65% if kVp is further reduced to 80 kVp. The downside of decreasing kVp is an increase in image noise due to reduced photon flux and photon energy (9). The use of iodinated contrast media may further improve image quality, since the attenuation coefficient of iodine increase as photon energy decrease toward the k-edge energy of 33 keV. Thus pathologies that take up contrast are more conspicuous at lower kVp (12). The benefit of lower-kV for non-contrast CT exams is still in question since soft tissue contrast is not highly dependent on tube potential.

Automatic Exposure Control (AEC) systems are now installed in almost all major scanners manufactured in recent years, with the aim of adjusting radiation dose according to the patient's attenuation. It assesses the size of the patient cross-section being scanned and adjusts tube current relative to the reference effective mAs. In turn, the reference mAs is based on an "average size" patient, which is 70-80 kg for adults and 20 kg for pediatric patients. Pre-set peak kVp settings of 80, 100, 120 and 140 are found in the system. With this, image quality is maintained using the minimum required radiation exposure and can reduce dose by as much as 20-44% (8). Even with an existing AEC, the CT user must still be familiar with the parameters employed to ensure correct use. Any type of AEC system is not perfect, since it may not be technically feasible to maintain constant image noise over all patient sizes since it cannot achieve such extremely low and high tube current-time product values (10).

STUDY OBJECTIVES

1. To determine if there is significant difference in the value of the tube current-time product (mAs) among patients of different body mass index (BMI) classification.
2. To determine if the radiation output, measured as CT dose index (CTDI), Dose-Length Product (DLP) and effective dose (E), in patients of higher BMI classification is significantly increased due to increased tube current-time product (mAs).
3. To determine if the difference in tube current-time product (mAs) among patients of different BMI classification would significantly affect image quality.

Research hypothesis:

Null Hypothesis: Significant increase in tube current-time product (mAs) and thus radiation output is needed in patients of higher BMI classification to maintain image quality.

Alternate Hypothesis: Significant increase in tube current-time product (mAs) and thus radiation output is not needed in patients of higher BMI classification to maintain image quality.

METHODOLOGY

A. Justification of Study Design

A retrospective, cross sectional study was conducted. This was a cross sectional study because of the following factors: body mass index (BMI), tube current-time product (mAs), CT dose index (CTDI), Dose-Length Product (DLP) and effective does (E) were ascertained simultaneously within a defined time period.

B. Study Duration and Location.

The study was conducted in the Department of Radiology, Makati Medical Center. Included data were of patients who underwent CT of the abdomen following the inclusion criteria from April 2014 to July 2014.

C. Inclusion and Exclusion Criteria

Inclusion criteria:

1. Male and female adult patients ages 18 years old and above.
2. Studies requested for out-patients only.
3. CT whole abdomen with intravenous (IV) contrast which will include:

a. CT whole abdomen with intravenous (IV) contrast.
b. CT chest and whole abdomen with IV contrast.
c. CT whole abdomen with intravenous (IV) contrast, oral and/or rectal contrast.
d. CT chest and whole abdomen with intravenous (IV) contrast, oral and/or rectal contrast.

Exclusion criteria:

1. Pediatric patients/patients below 18 years old.
2. Patients without available height measurement needed for BMI measurement (e.g. wheelchair bound patients).
3. CT whole abdomen without IV contrast to eliminate discrepancy in image quality assessment between plain and contrast enhanced studies.

D. CT system and scanning protocol

The scanner used in this study was the Siemens Somatom Definition 128 MDCT machine. Patients were scanned using the available online tube current modulation software. The CT scanner Siemens Somatom has a reference milliamperage-based AEC system called CARE Dose. In this system, the peak kilovoltage setting in the CT console is set automatically to 120 kVp. Tube current-time product (mAs) is then set by Care Dose based on the patient cross-section measured from the initial tomogram scanning. The parameters set by the AEC system for each scanned patient including kVP and mAs, are seen in the CT scanner console and sent in the PACS file of each patient for reference. (Appendix 1).

The other components of the scanning protocol were the same as per usual in the department: single breath hold, 0.5 second rotation time, 0.6 pitch, individually adapted field of view, and a B20f smooth software reconstruction kernel. Images were reconstructed as 2 mm. thick sections with an increment of 2 mm. The contrast enhanced CT whole abdominal protocol in the department has three phases; arterial, portal venous and delayed. The amount of intravenous iodinated contrast (370 mg iodine/ml) given is 115 to 120 mL., administered at a rate of 2.5 to 3.0 mL/sec, depending on patient weight and catheter size.

E. Data Collection

Patient:

All out patients undergoing a diagnostic exam in the department have their gender, age, height (cm2) and weight (kg) obtained and recorded as part of completion of patient chart. Access to patient records was facilitated by the CT unit manager Joel Molina, RRT (Registered Radiologic Technologists) who is in charge of safe keeping of said records. Permission to access these records were given by the department chair, Jackson Dy MD. The patients were categorized according to their BMI based on the World Health Organization BMI classification: underweight (< 18.5 kg/m2), normal (18.5 – 24. 99), overweight (25 – 29.99), obese class I (30 – 34.99), obese class II (35 – 39.99) and obese class III (>/= 40).

Dose measurement:

Dose values based on the CT dose index (CTDl), dose length product (DLP) computed by the CT system were collected as seen in the CT scanner console and sent in the PACS file of each patient. The DLP values were then converted to effective dose (E) using the region specific coefficient for the abdomen (k = 0.015 mSc/mGy x cm.) as set by the International Commission on Radiation Protection (ICRP 60).

The acquired patient information and dose measurements were tabulated on a standard data collection template.

F. Image Quality Evaluation

Qualitative evaluation of images was done by two CT consultants from the Department of Radiology. Both were blinded as to the BMI of each patient. The images only from the portal venous phase of the

scan were included. Classification scheme used was based on another study (3). Images with distinct anatomic detail, sharp vessel edges was classified as 1 (excellent). Examinations with clear anatomic detail and mild to moderate increase in noise without impairment of diagnostic accuracy was rated as 2 (good). If with further increase of noise without impairment of diagnostic accuracy was rated as 3 (fair). A distinct increase in noise and extensive blurring, not sufficient for diagnosis were classified as 4 (nondiagnostic). Patients were assigned in an alternating basis to each consultant. Evaluations were conducted using digital picture archiving and communication system diagnostic workstation (NovaPACS). Quality scores were then tabulated on a standard data collection template.

ETHICAL CONSIDERATION

The investigators of this research study complied with the statement of agreement with the ethical principles set out in relevant guidelines (Declaration of Helsinki 2008, WHO Operational Guidelines, ICH-GCP, National Ethics Guidelines for Health Research, and FDA Policies on Drug Registration).

All identifiable data gathered during data collection were kept confidential, and known only to the principal author and radiologists assigned to participate in the image quality evaluation. Specific names of the patient were included in the data collection form for ease of retrieval of the images during qualitative evaluation of the images. Included patients were then assigned a number that was used during encoding for data analysis so that no patient name was used during statistical analysis part of the study. Specific names did not appear on the documents or spreadsheets for data analysis, and in the final paper. Used data collection forms were shredded after all data have been encoded in Excel spread sheet.

RESULT AND STATISTICAL ANALYSIS

Descriptive Statistics

A total of 144 patients were included in the study. As shown in the table below, age of patients ranged from 20 to 88 years old, with average age at 52.71 (SD of 7.16). BMI average is 24.19 (SD of 4.02), which is categorically "normal". In terms of radiation; average mAs is at 174.58 (SD of 68.27), average CTDI is at 11.81 (SD of 4.60), average DLP is at 620.31 (SD of 282.18), and average ED is at 9.26 (SD of 4.15).

TABLE 1. Descriptive Statistics

	N	Mean	Std. Error of Mean	Median	Mode	Std. Deviation	Minimum	Maximum
Age	144	52.71	1.430	53.50	34.00	17.161	20.00	88.00
Weight	144	64.58	1.129	61.00	60.00	13.550	40.00	95.00
Height	144	163.12	0.901	164.79	152.00	10.811	122.00	183.00
BMI	144	24.19	0.335	23.88	20.56	4.016	16.02	36.79
mAs	144	174.58	5.689	156.00	148.00	68.266	103.00	491.00
CTDI	144	11.81	0.341	10.57	10.01	4.604	6.95	33.17
DLP	144	620.31	23.515	543.00	452.60	282.180	295.00	1,692.20
ED	144	9.26	0.346	8.15	6.19	4.150	4.42	25.38

Majority of patients are females (55.6%), while only 44.4% are males.

TABLE 2. Gender

	Frequency	Percent
Female	80	55.6
Male	64	44.4
Total	**144**	**100.0**

In terms of BMI group, more than half of patients are "normal" (60.4%), while more than one-third (34.7%) are overweight/obese, and only 5% are underweight.

TABLE 3. BMI Group

	Frequency	Percent
Underweight	7	4.9
Normal	87	60.4
Overweight	36	25.0
Obese 1	13	9.0
Obese 2	1	0.7
Total	**144**	**100.0**

Almost half (47.9%) of the samples got "2" image quality score, while 40.3% got the score of "3", and only 11.8% got the score of "1".

TABLE 4. Image Quality Score

	Frequency	Percent
1	17	11.8
2	69	47.9
3	58	40.3
Total	**144**	**100.0**

B. Hypothesis Testing – mAs and radiation output versus BMI

Ho: Tube current-time product (mAs) and radiation output are equal among BMI classification.

HA: Tube current-time product (mAs) and radiation output differs among BMI classification.

Using Pearson Correlation Analysis at 5% level of significance, results reveal that mAs and radiation output variables (CTDI, DLP, and ED) are **significantly** and positively related with BMI score. Hence, as BMI increases, mAs and radiation output variables also increases.

TABLE 5. Correlation Analysis

		BMI	mAs	CTDI	DLP	ED
BMI	Pearson Correlation	1	0.355**	0.357**	0.368**	0.351**
	P-Value (2-tailed)		0.000	0.000	0.000	0.000
	N	144	144	144	144	144

**. Correlation is significant at the 0.01 level (2-tailed).

One Way Analysis of Variance (ANOVA) was used to determine if means of mAs and radiation output variables significantly differ among BMI group, at 5% level of significance. As shown below, means of mAs and radiation output variables increases as BMI group goes from underweight to obese (except for Obese 2 which is negligible because it only has 1 patient).

TABLE 6. Descriptive Statistics - per BMI Group

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval		Minimum	Maximum
						Lower	Upper		
mAs	Underweight	7	135.57	24.227	9.157	113.17	157.98	103.00	162.00
	Normal	87	165.23	75.736	8.120	149.09	181.37	105.00	491.00
	Overweight	36	176.50	28.629	4.772	166.81	186.19	119.00	234.00
	Obese 1	13	250.62	62.254	17.266	213.00	288.24	186.00	395.00
	Obese 2	1	204.00	.	.	.	.	204.00	204.00
	Total	**144**	**174.58**	**68.266**	**5.689**	**163.34**	**185.83**	**103.00**	**491.00**
CTDI	Underweight	7	9.17	1.626	0.615	7.67	10.68	6.95	10.95
	Normal	87	11.17	5.112	0.548	10.08	12.26	7.08	33.17
	Overweight	36	11.98	1.883	0.314	11.34	12.61	8.04	15.80
	Obese 1	13	16.94	4.203	1.166	14.41	19.48	12.59	26.71
	Obese 2	1	13.78	.	.	.	.	13.78	13.78
	Total	**144**	**11.81**	**4.604**	**0.384**	**11.05**	**12.57**	**6.95**	**33.17**
DLP	Underweight	7	491.29	137.030	51.793	364.55	618.02	355.70	681.00
	Normal	87	577.61	309.527	33.185	511.64	643.58	312.30	1,692.20
	Overweight	36	632.18	149.947	24.991	581.45	682.92	295.00	970.60
	Obese 1	13	929.32	240.775	66.779	783.82	1074.81	584.20	1,403.90
	Obese 2	1	794.30	.	.	.	.	794.30	794.30
	Total	**144**	**620.31**	**282.180**	**23.515**	**573.83**	**666.79**	**295.00**	**1,692.20**
ED	Underweight	7	7.37	2.055	0.777	5.46	9.27	5.33	10.21
	Normal	87	8.66	4.643	0.498	7.67	9.65	4.68	25.38
	Overweight	36	9.48	2.249	0.375	8.72	10.24	4.42	14.56
	Obese 1	13	13.52	2.978	0.826	11.72	15.32	8.76	16.72
	Obese 2	1	11.91	.	.	.	.	11.91	11.91
	Total	**144**	**9.26**	**4.150**	**0.346**	**8.58**	**9.95**	**4.42**	**25.38**

It can be seen in the table below that mAs and radiation output variables (CTDI, DLP, and ED) were all found to be **significant** at 5% level of significance. This means that mean values in at least one (1) BMI group significantly differs from other BMI groups.

TABLE 7. ANOVA table for mAs and Radiation output variables

		Sum of Squares	df	Mean Square	F	P-Value
mAs	Between Groups	94,413.806	4	23,603.452	5.736	**0.000****
	Within Groups	572,007.194	139	4,115.160		
	Total	666,421.000	143			
CTDI	Between Groups	432.179	4	108.045	5.777	**0.000****
	Within Groups	2,599.593	139	18.702		
	Total	3,031.772	143			
DLP	Between Groups	1,551,787.535	4	387,946.884	5.483	**0.000****
	Within Groups	9,834,694.250	139	70,753.196		
	Total	11,386,481.785	143			
ED	Between Groups	300.874	4	75.218	4.835	**0.001****
	Within Groups	2,162.473	139	15.557		
	Total	2,463.347	143			

**. Relationship is significant at the 0.01.

C. Hypothesis Testing – Image Quality Score vs. BMI Group

Ho: Image Quality Score is the same among BMI classification / mAs.

HA: Image Quality Score differs among BMI classification. / mAs.

Correlation Analysis results show that Image Quality Score is **not significantly correlated** with mAs and BMI scores.

TABLE 8. Correlation Analysis

		Quality	mAs	BMI
Quality Score	Pearson Correlation	1	-0.030^{ns}	0.117^{ns}
	P-Value (2-tailed)		0.724	0.163
	N	144	144	144

**. Correlation is significant at the 0.01 level (2-tailed).

One Way Analysis of Variance (ANOVA) was used at 5% level of significance. As shown below, mean BMI score and mAs score appear to be equal among 3 image quality scores. This was confirmed to be **not significant** as shown in the ANOVA Table wherein p-value is 0.124 and 0.122, respectively.

TABLE 9. Descriptive statistics – per Image Quality Score

	Score	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval		Minimum	Maximum
						Lower	Upper		
BMI	1	17	24.24	4.875	1.182	21.74	26.75	18.64	32.56
	2	69	23.51	3.837	0.462	22.59	24.43	16.02	32.81
	3	58	24.97	3.879	0.509	23.95	25.99	16.02	36.79
	Total	**144**	**24.19**	**4.016**	**0.335**	**23.53**	**24.85**	**16.02**	**36.79**
mAs	1	17	200.65	81.936	19.872	158.52	242.77	112.00	329.00
	2	69	164.54	38.613	4.648	155.26	173.81	114.00	294.00
	3	58	178.90	87.662	11.511	155.85	201.95	103.00	491.00
	Total	**144**	**174.58**	**68.266**	**5.689**	**163.34**	**185.83**	**103.00**	**491.00**

TABLE 10. ANOVA Table – per Image Quality Score

		Sum of Squares	df	Mean Square	F	P-Value
BMI	Between Groups	67.398	2	33.699	2.122	**0 .124^{ns}**
	Within Groups	2,239.192	141	15.881		
	Total	2,306.590	143			
mAs	Between Groups	19,592.579	2	9,796.289	2.135	**0.122^{ns}**
	Within Groups	646,828.421	141	4,587.436		
	Total	666,421.000	143			

In terms of BMI group, below is the cross-tabulation of BMI Group with Image Quality Score. It can be noticed that there is no "pattern" established as to its relationship with each other. At 5% level of significance, both Pearson Chi-Square Analysis and Spearman Rank Correlation Analysis yield a **not significant** result, which means that there is no significant difference in image quality as BMI increases. Also, since as BMI is increased, mAs also is increased; it can be said that there is **no significant improvement** in image quality when mAs is increased.

TABLE 11. Crosstabulation – Image Quality Score per BMI Group

BMI vs. Quality	1	2	3	Total
Underweight	0	6	1	**7**
Normal	12	40	35	**87**
Overweight	2	18	16	**36**
Obese 1	3	5	5	**13**
Obese 2	0	0	1	**1**
Total	**17**	**69**	**58**	**144**
Pearson Chi-Square	**8.961, 0.346^{ns}**			
Correlation Coefficient	**0.065, 0.437^{ns}**			

ns. - not significant.

DISCUSSION and RECOMMENDATION

This research aimed to determine whether there is significant difference in tube current-time product (mAs) and radiation output in patients of different BMI classification. Pearson Correlation Analysis and ANOVA showed there is indeed significant increase in mAs as BMI increased (Table 5 and 6). As expected, there is corresponding increase in all radiation dose parameters, namely CTDI, DLP and effective dose (E), as BMI increased (Table 6 and 7). An increase in radiation dose with increasing BMI was observed even if the same peak kilovoltage (kVp = 120) was used in all BMI groups. This is due to the use of the Automatic Exposure Control (AEC) system in place in the CT scanner which adjusts the mAs to the size of the patient based on the initial topogram.

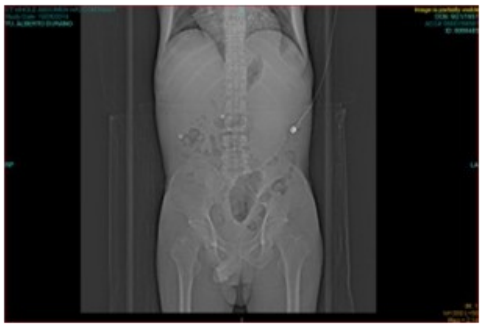
Another question asked by this study was whether there is a difference in the image quality of CT images of patients of different BMI classification due to differences in mAs. The most frequent score given across all BMI groups was 2 or "good", were in the images obtained had "clear anatomic detail with mild to moderate increase in noise but without impairment of diagnostic accuracy" (3). No score of 4 or a non-diagnostic image was obtained during the study. Correlation analysis showed that there is no significant correlation of image quality score with mAs and BMI (Table 8). Using ANOVA at 5% level of significance, the mean of the BMI and mAs among the three quality scores given – namely excellent (1), good (2) and fair (3), did not differ significantly (Table 9 and 10). This indicates that there is no significant difference in image quality with increasing mAs and BMI. In underweight, normal and overweight BMI groups, the most frequent quality score were all 2, while in the Obese 1 group, there is equal number of patients with scores of 2 and 3 (Table 10).

This study reiterates the need for body size-adapted CT protocol in imaging patients since the minimal radiation dose required would be varied even at the same diagnostic task. Several strategies have been proposed to modulate radiation dose. One modulation technique is to lower kilovoltage (kV) that allows reduction of radiation dose (8). However, an ideal balance between lowering the kV with corresponding increase in tube current time product (mAs) should be achieved since lowering the mAs simultaneously would increase contrast to noise ratio, and thus reduce image quality. Scan range should also be carefully planned considering the patient's body habitus to avoid exposure of any regions of the body that are not necessary for diagnosis (18). In this study, there is maintenance of diagnostic image quality even with increasing BMI due to increase in mAs. As reiterated by another study, this is the correct strategy since higher tube current is used at lower tube potential to compensate for the expected increase in noise (5). In particular in larger-sized patients, the use of lower tube potentials tends to increase noise due to higher absorption of lower-energy photons by the patient (17). However, even with an AEC system in place to limit radiation dose, the AEC system would still have to increase exponentially the mAs to achieve ideal contrast to noise ratio. The limitation of an AEC system is highlighted in this study since there is significant increase in radiation dose with higher BMI groups.

The author recommends future studies that will evaluate several protocols that may reduce radiation dose used in CT studies not just of the abdomen, but in evaluation of other body parts. This may be done by manipulating several scanning parameters such as kilovoltage, tube current, scan time and range. A more statistically sound method of evaluating quality is to compare quality between a control group and a group undergoing a reduced dose protocol. Patient safety without compromising image diagnostic quality should always be the primary aim of these studies.

APPENDIX I

CT SCAN ABDOMEN PROTOCOL



Activation of automatic exposure control (AEC)

Tube current-time product (mAs) is set by the AEC. AEC adjusts the mAS based on patient cross-section, which is based on initial topogram

Peak kilovoltage (kVp) set at 120 for all patients

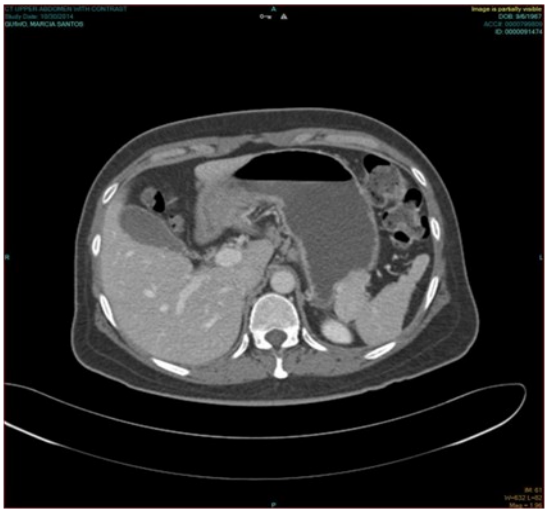
CT scan of abdomen conducted

CT scanning done, patient escorted out of CT machine suite

CT software system computes dose length product (DLP).

DLP, mAs, kVp and other CT parameters used for a patient's scan is displayed in CT monitor and sent to PACS for reference

Images sent to PACS for interpretation



INDEX OF ABBREVIATIONS and DEFINITIONS

Absorbed radiation dose:
Describes the amount of energy absorbed per unit mass at a specific point (13).

AEC: Automatic Exposure Control
Software installed in CT machines that are designed to reduce the radiation dose by altering the tube current as the x-ray tube rotates around the patient during multidetector CT scanning (17).

CTDI: Computed Tomography Dose Index
A measure of the amount of radiation delivered from a series of contiguous irradiations to standardized acrylic phantoms (10). It is a measure of the intensity of radiation directed at a given patient by the CT scanner (17). SI unit is milligray (mGy).

DLP: Dose-Length Product
CTDI multiplied by the length of the scan (in centimeters). SI unit is is milligray-centimeters (mGy-cm).

E: Effective dose
Sum of equivalent doses to organs and tissues exposed. It attempts to reflect the equivalent whole-body dose that results in a stochastic risk that is equivalent to the stochastic risk from the actual absorbed dose. It is a weighted average of organ doses (13). SI unit is millisieverts (mSv).

kVp: peak kilovoltage
SI unit for electric potential. It is the peak voltage applied to the X-ray tube and determines the highest energy of X-ray photon.

mAs: milliamperage per second
SI unit for electrical current or flow of electric charge in a defined boundary per second.

mGy: milligray
SI unit for absorbed dose. 1 Gray is equivalent to 1 Joule per kilogram (1 Gy = 1 J/kg).

mSv: millisieverts
SI unit for effective dose. 1 mSv is the dose produced by exposure to 1 milligray (mG) of radiation.

MDCT: Multi-Detector Computed Tomography
A form of CT technology that uses multiple arrays of detector which enables to acquire multiple slices simultaneously and greatly increases speed of image acquisition.

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Acral Lentiginous Melanoma in Filipinos: Report of Two Cases

Luella Joy A. Escueta, MD
Ana Maria O. de la Serna-Mah, MD, DPDS
Johannes F. Dayrit, MD, FPDS

Abstract

Introduction: Acral Lentiginous Melanoma is a clinicopathologic subtype of malignant melanoma. It is the most common expression among the four variants in Asian population. Its prognosis is generally poorer than the other subtypes. Hence, early diagnosis and surgical excision is the key in management.

Case Summaries:
A 65-year-old male presented with a 10-year history of patch on the second digit of the right hand. There was history of trauma to the finger where subungual hematoma developed. Five years after the injury, a black macule was noted on the previously bruised area. The lesion increased in size involving the periungual area with destruction of the nail plate. Biopsy showed acanthosis and basal layer hyperpigmentation. Intra-epidermal and dermal vacuolated melanocytes were seen. The patient was referred to an oncologist and orthopedic surgeon for management. An 88-year-old male had a 2-year history of black patch on the interdigital area between the 4th and 5th digits of the left foot. No history of trauma was reported prior to the appearance of the lesion. Biopsy showed lentiginous proliferation of atypical melanocytes in the epidermis. Referral to an oncologist and orthopedic surgeon for treatment was made.

Conclusion:
Clinical management of ALM begins with an accurate diagnosis. Therefore it is important to remain vigilant and where there is clinical suspicion, patients should be referred for a dermatological opinion. A typical patient profile, which includes age of onset, location of the lesion, prior trauma, and its relatively high incidence in the Asian population must be borne in mind.

Department of Dermatology, Research Institute for Tropical Medicine

INTRODUCTION

Cutaneous malignant melanoma is the most common cause of mortality from skin cancers in Caucasian populations. The incidence rate continues to rise in the UK and Australia. Currently there are around 8,500 new cases annually in the UK. In 2003, there were 9,534 new cases of melanoma reported in Australia.[1] In contrast, a significantly lower incidence rate has been reported in Asian populations with rates of 0.65-1/100,000.[2]

There are four distinct categories of melanoma based on histological features. These are superficial spreading (SSM), nodular (NM), lentigo maligna (LMM), and acral lentiginous (ALM).[1-4] The incidence rates of SSM, NM, LMM and ALM In the United States are approximately 70%, 15%, 13% and 2-3% respectively. However, ALM is the most common expression in Asian and Black populations, the rate of ALM is 41% in Japan, 65% in Korea and 62% in the American Blacks.[2]

The prognosis of ALM is generally poorer than the other subtypes. Patients likely overlook the lesion, especially on soles and nail beds. Moreover, ALM may mimic benign morphologies. Hence early diagnosis and surgical excision is the key in management. We report herein two cases of ALM seen in our institution.

Case 1

A 65-year-old male presented with a 10-year history of a black patch on the second digit of the right hand. There was history of trauma to the finger where subungual hematoma developed. The hematoma spontaneously resolved. Five years after the injury, a solitary black macule was noted on the previously bruised area. The lesion increased in size involving the periungual area with destruction of the nail plate. (Figure 1A) Biopsy showed acanthosis and and basal layer hyperpigmentation due to increased melanocytic activity. There was elongation and broadening of the rete pegs. Intra-epidermal and dermal singly scattered vacuolated melanocytes that form intraepithelial theques were seen. There was also pigmented parakeratosis accompanied by moderate numbers of lymphocytic infiltrates. (Figure 1B) Diagnosis of acral lentiginous melanoma was made. The patient was then referred to an oncologist and orthopedic surgeon for management.

Case 2

An 88-year-old male had a 2-year history of black patch on the interdigital area between the 4th and 5th digits and medial aspect of the 5th digit of the left foot. (Figure 2A) No history of trauma was reported prior to the appearance of the lesion. Skin biopsy confirmed the diagnosis of acral lentiginous melanoma. Marked acanthosis, elongation of rete ridges and lentiginous proliferation of atypical melanocytes in the epidermis were present. (Figures 2B-D) Referral to an oncologist and orthopedic surgeon for treatment was made.

DISCUSSION

Acral Lentiginous Melanoma accounts for 2-3% of all melanomas.[5] Overall incidence of melanoma is less in dark skinned individuals. However, ALM makes up a much higher proportion in Asian and Black populations.[2-3] Furthermore, ALM has a very poor prognosis. In Reed's study, patients with ALM had a mean 3-year survival rate of 11%.6 The poor survival rate of these patients may have been due in part to delay in diagnosis. Metzger et al also found that ALM had a high probability of being clinically misdiagnosed as benign melanocytic lesion, which defers the initiation of treatment.[7]

The mean age at diagnosis for ALM was 62.8 years. Our patients were diagnosed at age 65 and 88 years. Bradford et al conducted a study, which stated that the lower extremity was most commonly involved than the upper extremity.[6] Similarly, Kai and Fujiwara reported that ALM occurs more frequently on lower extremities. The soles of the feet are the most frequent sites of ALM, where 56% of ALM on lower extremities occurred. In contrast, most frequent sites on upper extremities are fingernails, where 45% of ALM on upper extremities appeared[2], which is the case in our first patient.

Green et al did a case control study of 275 melanomas diagnosed on the soles and palms to look into the risk factors. Interestingly, they found that sun exposure was an important risk factor in the development of ALM despite their plantar and nail bed location.

Both patients however, did not have significant sun exposure. Trauma has also been proposed as a possible risk factor for the development of ALM.8 Likewise, our first patient had a history of trauma prior to the appearance of the lesion.

Clinically, ALMs begin with pale brown macules, enlarge slowly and form irregularly pigmented, asymmetric macular lesions. Nodules may appear on the pigmented lesion and form ulceration. Both of our patients presented with a hyperpigmented patch, which enlarged slowly. Bristow and Acland stated that the most common symptom among the 21 patients in their study was a change in size of lesion. This is followed by bleeding, change in color, and change in lesion form. A case series by Soon et al reported that atypical presentations of acral melanoma include wart, callus, keratoacanthoma, non-healing ulcer, non-healing traumatic wound, subungual hematoma, and onychomycosis.[9] Other studies confirm that acral melanoma may assume benign morphologies consistent with benign nevus, ulcers, bacterial and mycotic infections, chronic paronychia, pyogenic granuloma, plantar wart, ganglion cyst, blister, ischemic toe, and traumatic lesion.[10-12] Hence, misdiagnosis and delay in diagnosis are particularly likely in ALM. Both of our patients deferred their consult for years which maybe due to the assumption of a benign lesion.

Histopathology of ALM shows acanthosis, spindled melanocytes, and lentiginous elongation of rete ridges. Cytologic atypia and lymphocytic infiltration are present. Marked hyperpigmentation is seen because of the melanophages in the upper dermis and aggregates of melanin in the stratum corneum. ALM usually appears thick due to its glabrous skin location.[13]

Clinical management of ALM begins with an accurate diagnosis. Therefore it is important to remain watchful. If there is clinical suspicion, patients should be referred for a prompt dermatological opinion. A typical patient profile, which includes age of onset, form and location of the lesion, prior trauma, and its relatively high incidence in the Asian and Black populations must be borne in mind. Patient awareness should be strengthened as well.

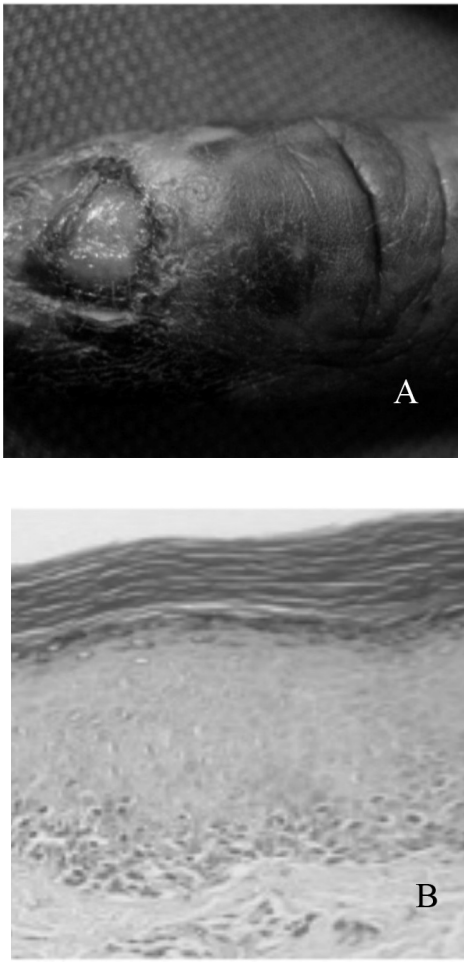

Figure 1. A. Solitary well-defined black patch with nail involvement on the right index finger of an 88-year-old male

B. Singly scattered melanocytes in the epidermis (10x, Hematoxylin & Eosin stain)

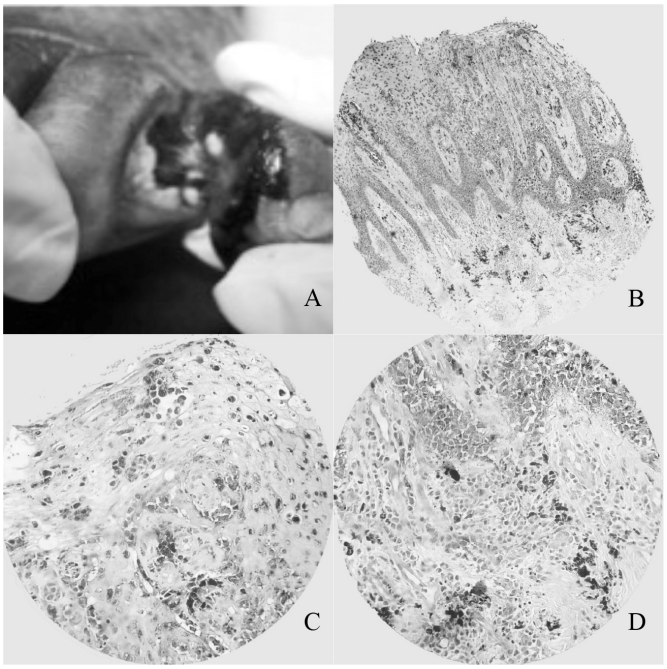

Figure 2. A. Solitary well-defined black patch with areas of depigmentation on the medial aspect of the 5th digit and interdigital area between the 4th and 5th digits of the left foot of an 88-year-old male

B. Elongation of rete ridges, lentiginous proliferation, and melanophages (10x, S100 stain)

C. Upward migration of melanocytes (40x, S100 stain)

D. Melanocytic nests at the tip of rete ridges, pigment incontinence and plasma cells (40x, S100 stain)

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Cavernous Lymphangioma of the Thigh in a 4-Year Old Boy Treated by Excision: A Case report

Josephine P. Nario-Manalo, M.D.[a]
Elizabeth Amelia V. Tianco, M.D.[b]

INTRODUCTION

Lymphangiomas are uncommon, hamartomatous, congenital malformations of the lymphatic system that involve the skin and subcutaneous tissues. They usually occur in children before the age of two years. We are reporting here a rare case of a gradually enlarging cavernous lymphangioma that arose at birth in a Filipino boy.

The objective of this paper is to create increased awareness of the clinical and histological characteristics of cavernous lymphangioma in order to enhance its diagnosis, thereby avoiding confusion with other disease entities. It is also its objective to discuss potential treatment options.

CASE REPORT

This is the case of a 4-year-old Filipino boy who presented with a gradually enlarging right thigh since birth with no accompanying symptoms. The patient's right thigh at birth was noted to be slightly enlarged as compared to the left thigh. X-ray and ultrasound were done at Tondo General Hospital, which revealed a huge tissue mass, probably an inflammatory process. The right thigh gradually enlarged as the child grew. At the age of one year, the patient was brought to the Pediatric Surgery Service of Philippine General Hospital where a diagnosis of lymphangioma was made. Complete blood count and X-ray of the right thigh were done. Surgical excision was advised but due to unavailability of bed, the patient was not admitted. He was then lost to follow-up.

Thirty-six months prior to referral, the patient's right thigh was noted to be erythematous and continuously enlarging. This time, there were intermittent bouts of high-grade fever. He was brought to the Pediatric Service of this institution and was admitted with a diagnosis of lymphangioma with cellulitis. The patient was given intravenous oxacillin 100 mg/kg/day, chloramphenicol 100 mg/kg/day and paracetamol 10 mg/kg/dose which provided relief of the fever and improvement of the cellulitis. He was then referred to the Surgery Service whose assessment was a tissue mass of the right thigh. Ultrasound and x-ray were requested which were not done. He was discharged improved and was lost to follow-up.

Fifteen months prior to referral, the patient had low to moderate grade fever accompanied by cough and colds. His enlarged right thigh was noted again to be erythematous. He was brought to the Pediatric Service of this institution and was admitted with the diagnosis of infected lymphangioma. He was given a course of antibiotic and was referred to the Pediatric Surgery Service. Ultrasound of the right thigh was done which revealed an inflammatory process; differential diagnoses were cellulitis, abscess, lipoma and lymphangioma. The Pediatric Surgery Service advised follow-up on an out-patient basis. He was discharged after 11 days with resolution of fever, cough, colds and improvement of the cellulitis.

Two weeks prior to referral, the patient's mother noted multiple minute vesicles on the affected thigh which was erythematous and tender and associated with moderate grade fever. The boy was again admitted at this institution with a diagnosis of infected lymphangioma. He was then given a course of antibiotics. Repeat ultrasound was done which

[a] - *Primary Investigator* [b] - *Adviser*

revealed a huge tissue mass. Considerations included hemangioma and lymphangioma. A malignant soft tissue neoplasm could not be excluded. He was also referred to the Otolaryngology Service for evaluation of decreased hearing ability. Play Audiometry was recommended. He was then referred to the Dermatology Service for further evaluation and management.

Skin examination revealed an enlarged, fluctuant right thigh with girth at mid thigh measuring 52 cm, with erythematous to hyperpigmented verrucous plaques on the surface. The girth of the left thigh was 27 cm.

The skin punch biopsy of the hyperpigmented verrucous plaques of the right thigh showed a hyperplastic epidermis with focal thinning and marked spongiosis. In the upper and lower dermis were numerous dilated cystic spaces, lymphatic channels lined with flat endothelial cells, with proteinaceous material seen inside some of the cystic spaces. There were moderate superficial and deep infiltrates of lymphocytes and histiocytes and numerous neutrophils and plasma cells. The report was signed out as cavernous lymphangioma.

The patient was referred to the Vascular and Plastic Surgery Service of this institution for possible resection of the mass. He was also referred to Pediatric Service for complete immunization and to the Otolaryngology Service for evaluation of his hearing impairment.

After the patient was assessed as having cavernous lymphangioma, the Vascular and Plastic Surgery Service suggested a CT scan of the thigh to determine the extent of the lesion prior to excision of the mass. The gross operational findings were a 17 cm mass in its widest diameter on the antero-lateral aspect of the right thigh, extending from the inguinal area up to the knee. On opening, the mass was noted to be fibromuscular with small vacuoles containing serous fluid. The mass was adjacent to the muscle and fascia. Neuromuscular structures were not involved. The microscopic pathological finding was lymphangioma with no evidence of malignancy.

The patient was given intravenous ampicillin 100 mg/kg/day and ketorolac 0.5 mg/kg/day. He was discharged improved after 10 days and was given cefalexin 50 mg/kg/day and paracetamol 10 mg/kg/dose as home medications.

Figure 1

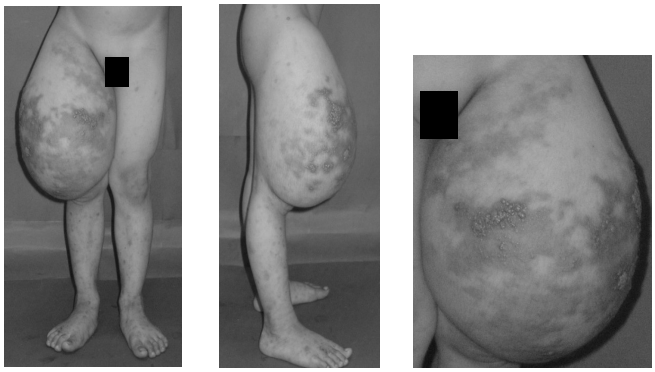

Figure 1A *Figure 1B* *Figure 1C*

Figure 1: Enlarged, fluctuant right thigh with girth at mid thigh measuring 52 cm (A) front view (B) side view (C)erythematous to hyperpigmented verrucous plaques on the surface.

Figure 2

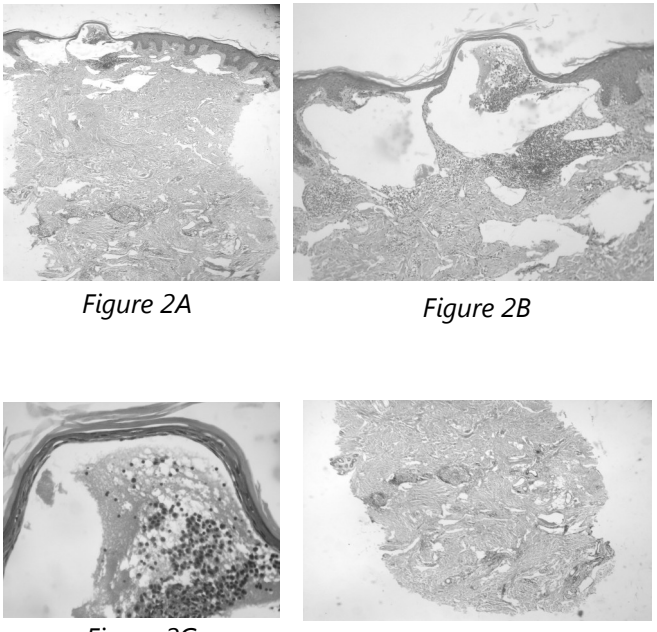

Figure 2A *Figure 2B*

Figure 2C *Figure 2D*

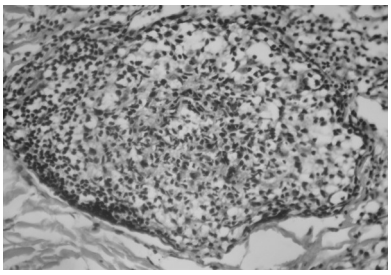

Figure 2E

Figure 2: (A) Scanning view: hyperplastic epidermis with focal thinning and marked spongiosis. (B)Low power: In the upper and lower dermis were numerous dilated cystic spaces, lymphatic channels lined with flat endothelial cells, with proteinaceous material seen inside some of the cystic spaces (C) High power (D) Scanning view: There were moderate superficial and deep infiltrates of lymphocytes and histiocytes and numerous neutrophils and plasma cells (E) High power

Figure 3

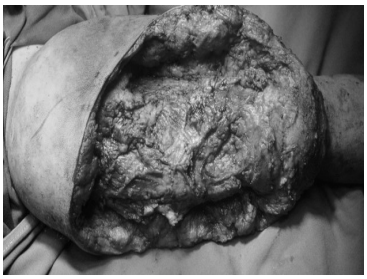

Figure 3A

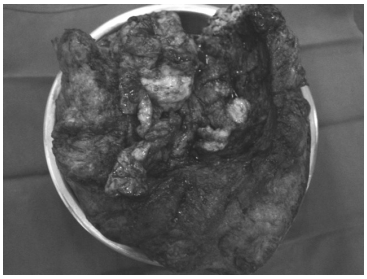

Figure 3B

Figure 3 (A) gross operational findings were a 17 cm mass in its widest diameter on the antero-lateral aspect of the right thigh, extending from the inguinal area up to the knee (B) specimen for pathology

Figure 4

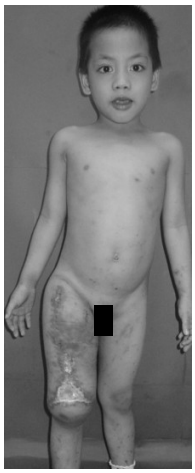

Figure 4A

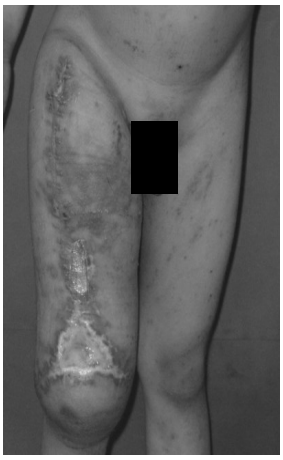

Figure 4B

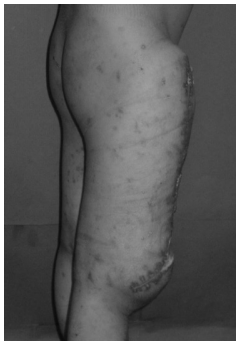

Figure 4C

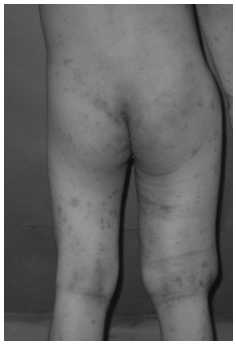

Figure 4D

Figure 4:Post-operational pictures(A) full view (B) front view (C) side view (D) back view

DISCUSSION

The lymphatic system is an extensive unidirectional system of blunt-ending vessels that retrieve excess fluid from the interstitium, transport it to regional lymph nodes, and return it to the venous system by way of the thoracic duct. The lymphatics absorb protein and lipid from the liver and small intestine.

Redenbacher was cited as first describing lymphatic malformation in the European literature in 1828.[1] The lesion is thought to represent a failure of the primitive lymph sac to connect to the venous system during embryogenesis. In 1938 Goetsch noted

that this sequestered lymphatic tissue forms cysts and that endothelial sprouts projected from the walls of the cysts which produce spaces.[1] The enlargement of the cyst is due to the accumulation of lymph. These sprouts may surround and destroy tissue and force the lesion into areas of least resistance between muscles and vessels, invading tissue planes. This invasion of local structures causes atrophy, fibrosis and hyalinization of the engulfed tissue.

Lymphangiomas, also known as lymphatic malformations are categorized into four types of lymphangiomas (lymphangioma circumscriptum, cavernous lymphangioma, cystic hygroma and diffuse lymphangiectasia.)

Cavernous lymphangioma is a rare benign proliferation of the lymphatic vessels that usually arises at birth in 50-60% of cases with equal sex indices. It usually involves the limbs. These lesions are deep seated in the dermis, forming a painless swelling or thickening of the skin, mucous membranes and subcutaneous tissue.

The diagnosis of lymphangiomas rests mainly on the clinical history and findings from physical examination and conventional light microscopy. In some infants with atypical lesions, observation of change over time or radiologic investigation is necessary to confirm the diagnosis. Ultrasonography is a useful and cost-effective diagnostic method but does not portray the extent of the lesion or its relation to adjacent structures. MRI can define the degree of involvement and the entire anatomy of the lesion. It can also help prevent unnecessary extensive and incomplete surgical resection.

Histological examination reveals large, irregular channels in the reticular dermis and subcutaneous tissue that are lined by a single layer of endothelial cells. An incomplete layer of smooth muscle often lines the walls of these malformed channels. The surrounding stroma consists of loose or fibrotic connective tissue with a number of inflammatory cells. As previously described, the histopathological result of the patient was consistent with cavernous lymphangioma.

Immunohistochemical studies may be useful in differentiating lymphangiomas from hemangiomas in difficult cases. Immunohistochemical studies for laminin may differentiate a normal blood vessel from a lymphangioma. High endothelial reactivity for the erythrocyte-type glucose transporter protein GLUT 1 is observed in hemangiomas and may provide a diagnostic tool to differentiate it from vascular malformation.

Typically, cavernous lymphangiomas appear as subcutaneous nodules with a rubbery consistency. They may have large dimensions. The area of involvement varies, ranging from lesions smaller than 1 cm in diameter to larger lesions that involve an entire limb.

The patient's clinical presentation as an enlarging fluctuant mass on the right thigh at birth is consistent with cavernous lymphangioma. This is further supported by the CT-scan showing a bulging, slightly hypodense soft tissue mass with cleavage between the mass and the muscular compartment seen except at its inferior portion. Haziness and slight decrease in density were also noted in the vastus lateralis and a portion of the vastus intermedius with no evidence of neurovascular or osseus involvement.

The major indications for treatment include life or function threatening lesions, those that tend to leave disfiguring scars or deformities, facial lesions, and those lesions that are exposed such as the extremities. Therapeutic decisions should be tailor-made to each individual lesion, and should always take into account psychosocial factors, including the emotional well being of both the child and parents. Because no treatment is without risks, all potential complications should be detailed prior to initiation of therapy.

Treatment of lymphatic malformations can be challenging and various approaches have been attempted. The most appropriate management of cavernous lymphangioma at any site is conservative surgical therapy with preservation of all important neurovascular structures.

Another option for cavernous lymphangioma is injection of sclerosing agents such as alcohol, steroids, bleomycin sulfate, tetracycline and OK-432 (picibanil).

Qin et al[2] described 200 patients with various types of head and neck lymphangiomas who were treated by inratumorous injection of bleomycin-A5. All 200 cases were followed from 2 to 10 years; 95 cases were followed for more than 5 years. The effective rate was 97% and the curative rate was 86.5%. No pulmofibrosis or other serious complications were found.

In a study made by Kobayashi et al[3], three patients with cavernous lymphangioma of the legs were treated. The suggested guidelines for treatment are extensive surgical resection of the mass and approximately two weeks after the operation, aspiration of serous fluid which has accumulated at the operation site. This is then followed by injection of OK-432 at the resected area.

Side effects include pyrexia and focal inflammation for several days, but the accumulation of serous fluid disappeared after the injection. There were no complications with any recurrence, joint contracture, or pain during a mean follow-up of 48 months.

Recurrence of larger lymphomas after surgical excision is common because the tumor closely involves important nerves and vessels. Saijo et al[4] reported that tumor resection recurred in one third of operations that were only partially successful. Patients who have grossly or microscopically infiltrative lesions should be counseled about the increased likelihood of recurrence, even if resection is thought to be complete. In our patient's case, the neurovascular structures were not involved and the likehood of recurrence is less.

The prognosis of cavernous lymphangioma heavily depends on early diagnosis with definitive surgical treatment. Full recovery is possible in patients whose lesions are completely resected.

CONCLUSION

Cavernous lymphangioma is a rare clinical entity that is defined as a congenital malformation of the lymphatic system that involves the skin and subcutaneous tissues.

A keen awareness of the clinical and histological features of cavernous lymphangioma can alert physicians to early detection and proper management. Several treatment options are available but the patient should be aware of the risk of recurrence with this disease.

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Submandibular Extraskeletal Osteosarcoma: A Case Report

Christian Joseph Z. Tagal, MD [a]
Lorelei L. Chavez, MD, FPROS [b]

ABSTRACT

Extraskeletal Osteosarcoma (ESOS) is an extremely rare subtype of osteosarcoma accounting for about 1% of all soft tissue sarcomas1. It is a malignancy capable of osteoid, bone, or chondroid matrix production, located in the soft tissues, and does not have any attachment to bone or periosteum. As a rare entity, there have only been three cases reported to be found in the submandibular area.7,9,10 Review of literature did not reveal any reported cases of head and neck ESOS in the Philippines. We report a case of 70/M diagnosed with ESOS presenting with a gradually enlarging right submandibular mass. He was initially managed by the Otorhinolaryngology and Head and Neck Surgery Service. They performed wide excision of the said mass, the largest dimension of which was approximately 7.5 cm. Histopathology report revealed ESOS with close margins, with no perineural nor lymphovascular space invasion seen. On the basis of its size, its close margins, and its high-grade histology, we irradiated the face and neck (fascio-cervical field) of the patient to 44 Gy, then cone-down to 50 Gy to the low-risk areas, then boost to the gross tumor volume (GTV) with 2 cm margins all around to reach 66 Gy. Expected radiation therapy toxicities such as xerostomia and dermatitis were seen in the patient and managed accordingly. We plan to follow the patient up every three to six months for the next two years, and annually thereafter.

INTRODUCTION

Extraskeletal Osteosarcoma (ESOS) is an extremely rare subtype of osteosarcoma accounting for about 1% of all soft tissue sarcomas.[a] It is a malignancy capable of osteoid, bone, or chondroid matrix production, located in the soft tissues, and does not have any attachment to bone or periosteum. They have a histologic appearance that is hard to distinguish from that of primary osteogenic sarcoma of bone.[b,c]

Several studies have found a male predominance with a degree of 2:1, but some authors have failed to affirm this difference.[d,e,f,g] In a retrospective study of 88 patients, the median and mean age for its prevalence was 59 and 54.6, respectively.[h]

People with ESOS usually present with a gradually enlarging mass, but they can also be asymptomatic. Pain or tenderness has been found in as many as 19% of cases, and duration of symptoms have been found to range from two weeks to twenty-five years, with a median of six months, in a landmark study done by Chung and his colleagues in 1987.[h] They also described the three most common locations for these neoplasms – lower extremities (46.6%), upper extremities (20.5%), and the retroperitoneum (17%). Among all the specific sites, the thigh was the most commonly involved (27.3%), followed by the trunk (11.4%)[d,e,h] Other than their rarity, these tumors have the predilection to be deep-seated, large, and of high grade.[b]

a - Primary Investigator *b - Adviser*
Section of Radiation Oncology, Department of Radiology - Philippine General Hospital

It has a wide spectrum of histologic features, but the variable amounts of neoplastic osteoid and bone that it contains is the common denominator in this subset of sarcoma. This forms the basis why it can often be confused with several other tumors like malignant fibrous histiocytoma, myositis ossificans, fibrosarcoma, malignant schwannoma, oseteoblastic osteosarcoma, and chondroblastic osteosarcoma.[b,h]

In the same study by Chung et al, two main factors have been implicated in its pathogenesis – history of trauma or injury (12.5%) and prior radiation exposure (5.7%). The main mechanism why or how this is so remains unknown.

Studies on ESOS are mainly retrospective except for that from the Memorial SloanKettering Group, in which the followed up fifteen patients prospectively[b.]

As a rare entity, interesting reported cases include one found in the esophagus[i], and another in the greater omentum[j]. Cases in the head and neck have also been reported[g,k,l,m], but only three have been found in the submandibular area - one in a radiation-exposed human patient[m], another in a young Japanese patient[g], and lastly, in a canine subject[l]. Review of literature did not reveal any reported cases of head and neck ESOS in the Philippines.

CASE REPORT

We report of a 70/M from the Philippines who is known to have Parkinson's Disease (on Levodopa with erratic compliance), controlled asthma (uses Salbutamol inhaler as needed), and has been treated for Pulmonary Tuberculosis 22 years ago. He used to work as a driver and a welder, used to smoke one pack per day, and is an occasional alcoholic beverage drinker. He presented with a gradually enlarging right submandibular mass noted initially when some teeth were extracted for application of dentures. At this point, it was estimated to be approximately 1 x 1 cm in size. A few weeks after, the mass was noted to be enlarging with concomitant pain. His dentist gave him NSAIDS, relieving him of pain, but the mass continued to grow. The patient did not experience any dysphagia or dyspnea. He only reported of undocumented weight loss.

For the next eight months, several doctors were consulted for subsequent opinions. He was advised surgery, but declined due to financial constraints. He was subsequently referred to our institution for further management and was initially received by the Otorhinolaryngology – Head and Neck Surgery Service. *Figures 1 and 2 depict the status of the patient when he was initially received.*

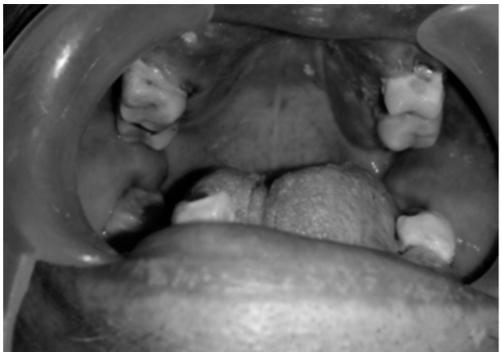

Figure 1. Oral cavity examination of the patient *(Photo courtesy of UP-PGH Department of ORL-HNS)*

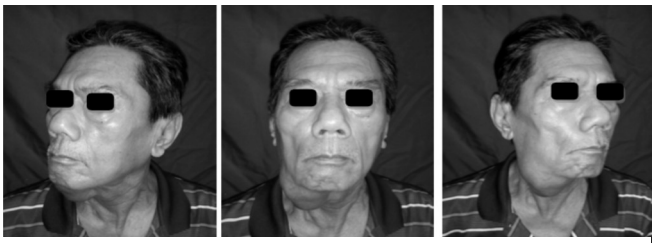

Figure 2. Patient when originally seen by the ORL-HNS Service (*Photo courtesy of UPPGH Department of ORL-HNS)*

CT-scan imaging was done revealing a fairly defined, heterogeneously enhancing soft tissue mass with calcifications and areas of necrosis in the submandibular area extending to the right masticator space measuring 6.5 x 4.3 x 5.6 cm (CC x W x AP), with no involvement of the other neck spaces, vascular structures, and lymph nodes (See *Figure 3).*

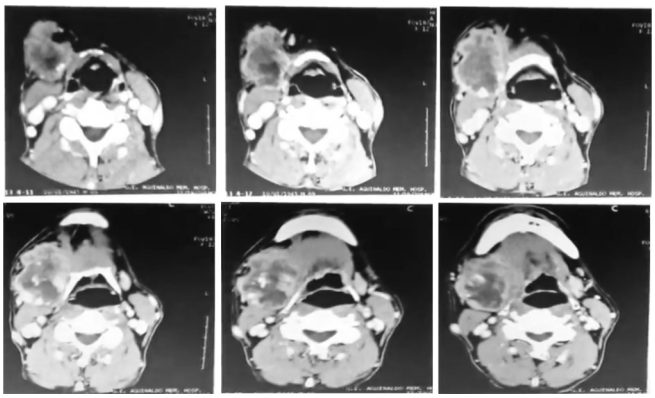

Figure 3. Representative CT Scan images of the patient from inferior to superior

Other metastatic work-up turned out to be negative. At this point, primary differentials were pleomorphic adenoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, and squamous cell carcinoma. Several biopsies were done which revealed inconclusive findings. The ORLHNS service then decided to do wide excision of the mass (*Figure 4), and histopathologic study of the specimen revealed extraskeletal osteosarcoma (Figure 5) with close margins (1.5 mm away from the nearest excision margin), with no perineural nor lymphovacular space invasion seen*.

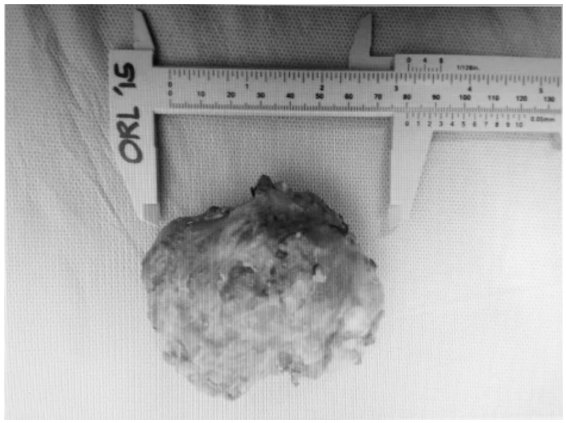

Figure 4. Gross specimen (tumor) removed during wide excision *(Photo courtesy of UPPGH Department of ORL-HNS)*

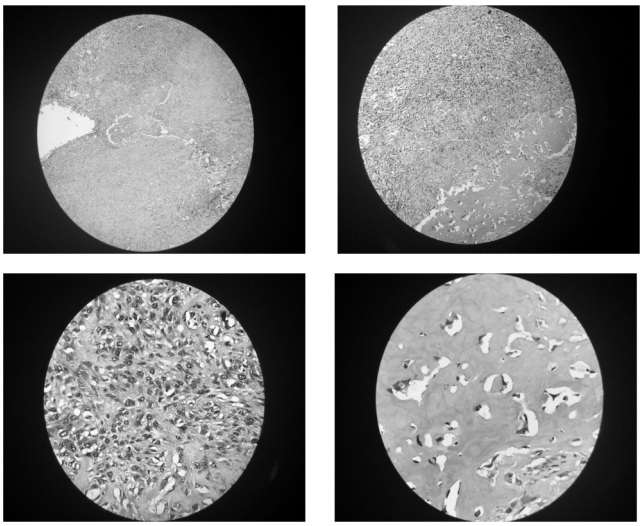

Figure 5. Histopathologic images of the specimen *(Photo courtesy of the UP-PGH Department of Laboratories)*

The patient was then referred to the Radiation Oncology service for adjuvant radiotherapy. We irradiated the fascio-cervical field using a Cobalt-60 machine with opposing lateral beams to a total of 66Gy, keeping the spinal cord dose to a maximum of 44 Gy, and low-risk areas to a maximum of 50 Gy. Radiation was delivered using conventional fractionation (2 Gy per fraction). *Figure 6 shows the x-ray treatment plan for the patient*.

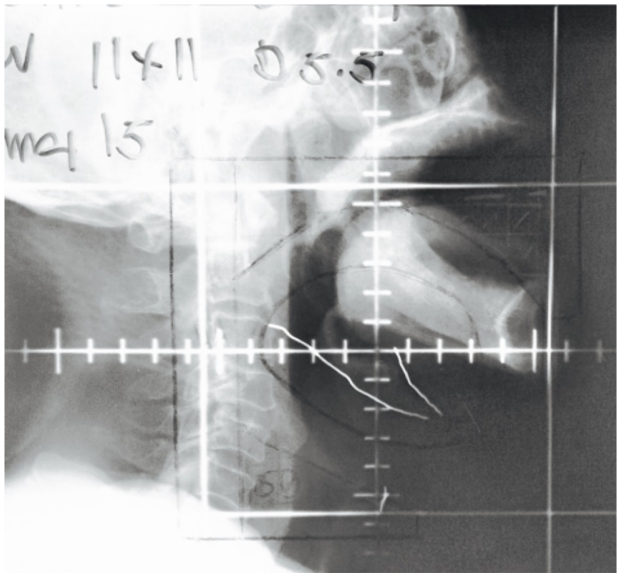

Figure 6. *X-Ray simulation and planning film*

The patient was followed-up once a week, and no significant morbidity was seen. Usual radiation toxicities such as dermatitis, xerostomia, mucositis, and dysphagia were observed, and managed accordingly, based on existing treatment guidelines. The patient was sent home, and was instructed to follow-up after three months. *Figure 7 shows the patient, after Radiation Therapy*.

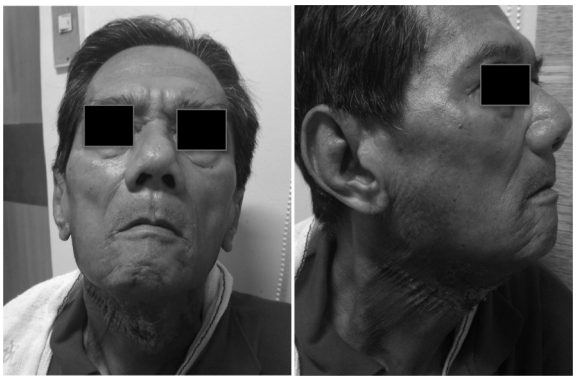

Figure 7. Patient on his last day of Radiation Therapy.

DISCUSSION

Treatment

Researchers from the Memorial Sloan-Kettering Cancer Center have recommended that treatment of ESOS should adhere to currently established guidelines in the treatment of soft tissue sarcomas.[b] The use of adjuvant therapy (chemotherapy or radiation therapy) should be individualized, based on independent risk factors, such as incomplete resections, large tumors (>5cm), or high-grade lesions. Chemotherapy and RT did not appear to affect or influence survival, but this may be attributed to the low number of patients in their study (fifteen pathologically-confirmed ESOS in a 17-year period from 1982-1999).

Ahmad and his colleagues from MD Anderson Cancer Center have supported this claim on the value of adjuvant therapy.[n] In their institutional experience, an overall response rate of 19% (two complete and three partial responses) was seen for Doxorubicin-based systemic therapy, which they deemed as a low response rate. They then insisted that ESOS should be viewed as clinically and therapeutically distinct from osseous osteosarcoma.

Though no clear survival or local control benefit when giving adjuvant radiotherapy have been established for ESOS as of the moment, the patient was irradiated on the basis of its very close margins on histopathology (1.5mm), and its size (>5 cm) preoperatively. Upon consultation with the Medical Oncology service, adjuvant chemotherapy is not warranted since there are no adverse features seen, but close follow-up was advised.

Prognosis

ESOS has an exceptionally poor prognosis which can partially be attributed to the limited clinical information about its natural course.[c,d,e,o] Researchers have set the estimated mortality to be between 70 to 80%, and overall disease-specific survival at 5 years at 50% (with a median follow-up of 35 months).[b]

The MD Anderson experience cited earliern revealed their statistics to be 82% (95% CI, 70-98), 64% (95% CI, 43-93%), 47% (95% CI, 30-70%), and 46% (95% CI, 26-80%) for the 5-year actuarial local recurrence-free survival, distant recurrence-free survival, event-free survival, and disease-specific survival, respectively.

Of the 88 patients in the landmark study by Chung[h], 65 had follow-up data. Twentyfive (38.5%) were alive, eight of whom were well, while 17 had recurrence or metastasis. The remaining 40 (61.5%) died, 4 of whom attributable to other causes not connected to the malignancy. Median follow-up for this study was 2.4 years, ranging from one to 22 years.

We plan to follow the patient up every three to six months for two to three years, then every six months for the next two years, then annually thereafter. Though limited data has shown poor prognosis for this kind of malignancy, compliance to follow-up and other medications was advised and reiterated, as he has a really good performance status at baseline.

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Adverse Drug Reaction to Nevirapine in an Immuno-Compromised Patient: A Case Report

Lei Anne Michelle R. Hernandez MD, DPDS
Lonabel A. Encarnacion MD,FPDS

Abstract

Adverse drug reaction in an immuno-compromised patient is a common condition brought about by poly-pharmacy, and notably due to the use of antiretroviral medications. We present a case of a 35 year old male, who initially presented with a morbilliform rash.. The patient was treated initially as a case of drug hypersensitivity reaction who did not respond to regular course of intravenous corticosteroid. After revealing his sero-positive human immunodeficiency virus (HIV) status, corticosteroid was discontinued and the patient responded with conservative management.

Key words: nevirapine, drug hypersensitivity reaction, adverse drug reaction

Department of Dermatology, St. Luke's Medical Center, Quezon City

INTRODUCTION

Cutaneous adverse drug reactions are quite common especially among patients taking multiple medication. Among immuno-compromised patients, the initiation of anti-retroviral medications and concomitant treatment of their associated diseases may compound and increase their risk of developing hypersensitivity reaction. Hence, complete history taking and adequate physical examination are important steps in the correct diagnosis and management of such patients.

CASE REPORT

A 35-year old Filipino male presented with morbilliform rash of 2 day duration. Eight weeks prior to consult, he was diagnosed to be seropositive with HIV with no medications started. At 6 weeks prior to consult, he had concomittant ill-defined, dry, slightly scaly plaques on the forehead and malar area accompanied by mild pruritus, nonspecific symptoms of cough, colds and malaise. He was started on Cotrimoxazole 800mg tab OD, Isoniazid 400mg tab OD and Clarithromycin 500mg tab BID on follow up when his CD4 count was noted to be 23cells/mm3. There were no noted lesions after starting these medications. He noted gradual progression of scaling and erythema over the next 6 weeks but claims no associated skin lesions.

At 4 weeks prior to consult, he was subsequently started on anti-retrovirals: Stavudine 40mg +Lamivudine 150mg tab twice daily and Nevirapine 200mg tab once daily for the first 2 weeks. The dose of nevirapine was then increased to twice daily on the succeeding 2 weeks. During these times, there were no noted skin lesions.

At 2 days prior to consult, the patient still had persistence of erythematous scaly plaques on the face but he claimed gradual onset of multiple and generalized, erythematous, blanching, pruritic morbilliform rash on the chest, back, arms, legs and palms and soles. This was associated with odynophagia, described as difficulty swallowing solid food, and bilateral periorbital edema. He also claimed development of undocumented fever. This was accompanied by oral ulcers. The patient had malaise, fever, associated undocumented weight-loss, weakness and odynophagia. He also claims easy fatiguability. The patient is a known diabetic since 2010 maintained on metformin. He also withheld at the time of interview that he had 2 male sexual partners in the last 5 years and practices unprotected sex. He is in a male monogamous relationship.

On examination, the patient had multiple, scattered, blanching, erythematous macules, papules and plaques on the trunk, arms and legs. Very prominent localized, ill-defined, dry, moderately erythematous patches with adherent scales on the forehead, nose, malar areas and ears were seen. He also had mild bilateral periorbital edema, with conjunctival suffusion accompanied by labial swelling and tender ulcers on the buccal mucosa (Figure 1A-C).

Upon admission, skin punch biopsy showed interface dermatitis, most probably drug hypersensitivity reaction or early erythema multiforme (Figure2). He was started on intravenous hydrocortisone 100 mg every 6 hours. We started him on a mouthwash consisting of sucralfate, diphenhydramine and aluminum chloride and twice daily 50mg intravenous diphenhydramine. After four doses of 100mg intravenous hydrocortisone were given, there was progression of lesions. It was only during this time that the patient revealed that he was previously diagnosed with HIV hence, intravenous hydrocortisone was discontinued. The patient was shifted to Levocetirizine 5mg twice daily due to persistent pruritus. Oral thrush was treated with Nystatin 5ml twice daily. Treatment of seborrheic dermatitis with ketoconazole cream and desonide cream twice daily was started. During interim, there was gradual improvement of the skin lesions. On the 6th hospital day, the patient was discharged with improvement of seborrheic dermatitis and mostly hyperpigmented patches on the body.

DISCUSSION

Adverse drug reaction (ADR) was defined by the world health organization (WHO) as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnoses or therapy of disease, or for the modification of

physiologic function" [1]. Among the manifestations of adverse drug reactions are cutaneous and are caused by immune and non-immune mechanisms [2-9]. The mechanism of drug reactions may be attributed to one or a combination of the following [10]: drug overdose, cumulative toxicity, drug interactions, exacerbation of preexisting skin disease, ecologic disturbances of skin flora, nonimmune activation of effect or pathways, metabolic changes and secondary to or side effects of the normal pharmaceutical action of the drug .

In a study conducted at the Harvard Community Health Plan involving 684 HIV infected individuals, about 8.2% of dermatologic consults showed drug-related cutaneous manifestation, while 1/3 of the admitted patients with skin diseases were being admitted due to this cause[11].

The presence of more cutaneous adverse drug reactions among HIV infected individuals may be attributed to multi-factorial theories, directly and indirectly. HIV infection may affect through active viral infection, immune dysregulation/stimulation. Indirectly, factors such as diet deficiency, co-morbidities, associated cutaneous diseases, polypharmacy, or exposure to high-risk medications may play a role for drug reactions [12]. In fact, other studies suggest that decreased CD4 count, older age, concomitant dermatologic conditions, and associated acute or reactivation Epstein-Barr virus and cytomegalovirus [13] can also contribute to the increased incidence of drug-related adverse reaction. Medications that account for drug reactions include antibiotics such as sulfonamides, sulfones and penicillin [11,13] and non-nucleoside reverse transcriptase inhibitors (NNRTI) [14]. Other explanations are regional differences in drug prescription, genetic background of patients and coexisting diseases [15, 16, 17]. Factors that may also increase the incidence of adverse drug reactions among patients taking NNRTI are female gender, CD4 cell count of less than 100 cells/ml, age above 40 years old [14]. In our case, our patient's immune status could have contributed to the development of the cutaneous drug reaction.

Typical presentation of drug reactions involving NNRTI is a rash in 10-17%, ranging from urticaria to morbillifom rash. Other lesions may show erythema multiforme major, vasculitis, exfoliative dermatitis, and photodermatitis [11]. To diagnose drug-related adverse effects, it is important to take note of the temporal relation of the symptoms to the initiation of the drug, symptomatic picture of the patient and role of history taking. Among NNRTI reactions, symptoms present within the first 6 weeks of treatment, development of rash such as morbilliform to Stevens-Johnson's syndrome and involvement of mucosal areas, and hypotoxicity together with the rash. Patients may also develop fulminant liver failure with or without systemic hypersensitivity symptoms or signs [18]. Our patient presented with morbilliform rash 2 weeks after intake of nevirapine and lamivudine. He did not have any systemic symptoms upon presentation.

A patient suspected to have an adverse drug reaction may undergo liver and renal function testing and complete blood count. For severe symptoms such as fever, urticaria, wheezing, clinical hepatitis, muscle/joint pains, desquamation, mucosal involvement, conjunctivitis, aminotransferase or aspartate aminotransferase 5 times more that the normal limit, eosinophilia, granulocytopenia or renal dysfunction warrant discontinuation of the medications. In nevirapine-associated drug hypersensitivity, screening for hepatitis B and C and normal liver function test monitoring is recommended prior to initiating treatment. A dose escalation protocol, which involves administration of nevirapine at 200mg once daily for the first 2 weeks and increase to twice daily dosing in the next 2 weeks is also advised to prevent drug reactions[18]. Our patient followed such protocol but still developed the hypersensitivity reaction.

Among patients developing adverse drug reactions, medication must be discontinued until the lesions disappear. Immediate discontinuation of the offending agent in this case was done. Our patient's non-response to corticosteroids and persistence of pruritus even after giving antihistamines may be explained by the lack of role of prednisone and antihistamines during the initial phase of the disease[19,20]. Administration of both did not prevent the further development of skin lesions in this patient.

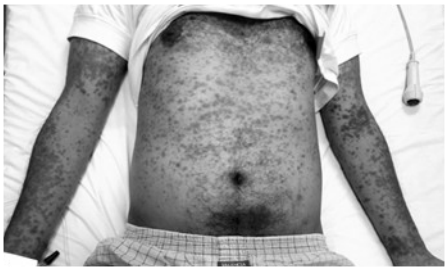

Figure 1A. Anterior trunk

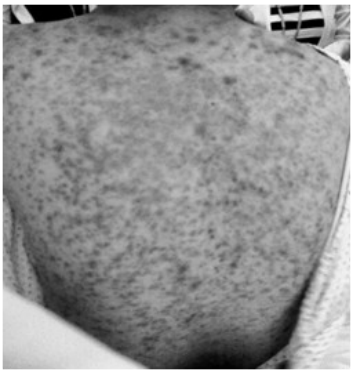

Figure 1B. Posterior trunk

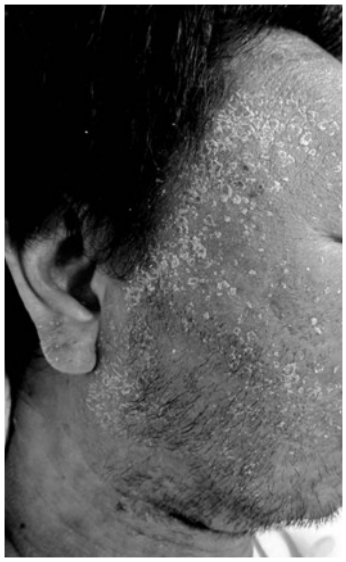

Figure 1C. Right lateral aspect of face

Figure 1(A-B). Physical exam showed multiple, scattered, blanching, erythematous macules, papules and plaques on the trunk, arms and legs. (C). Prominent localized, ill-defined, dry, moderately erythematous patches with adherent scales on the forehead, malar areas and ears.

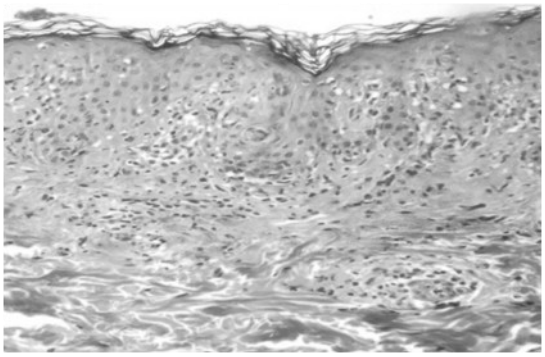

Figure 2. (HPO) Skin punch biopsy revealed basket-weave stratum corneum, spongiosis, and dermal melanophages. There were occasional necrotic keratinocytes in the epidermis with basal vacuolar alteration. Superficial perivascular to patchy band-like infiltrate of lymphocytes with eosinophils were seen in the dermis.

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Stage III Eumycetoma successfully treated with Ketoconazole and Surgical Debulking

Aileene I. Peña-Dumdum, MD
Geraldine O. Banate-Gulfan, MD
Therese Giannine V. Ledesma, MD
Ma. Teresita G. Gabriel, MD, FPDS
Leilani R. Senador, MD, FPDS

Abstract

Mycetoma is a chronic, debilitating, granulomatous disease affecting the subcutaneous tissue, fascia, muscle, bone and adjacent organs characterised by triad of tumefaction, draining sinus, and grains. Ten-year incidence at our institution is 3/81,015. We present a 33-year old male with a 9-year history of painless nodules with draining sinuses on the left foot unresponsive to oral antibiotics and topical antifungals. Biopsy of the nodule was consistent with mycetoma. Fungal culture revealed Madurella mycetomatis growth. Xray of the left foot showed poorly marginated lucencies on the calcaneus. Ultrasound of the left foot revealed mixed hyper reflective echoes and multiple small cavities. Diagnosis was Stage III Eumycetoma. Ketoconazole 200mg twice daily was given for 9 months achieving 50-60% decrease in lesion size. Surgical debunking was done and Ketoconazole continued for 9 months. There was good granulation tissue formation and no appearance of new lesions.

Research Institute for Tropical Medicine

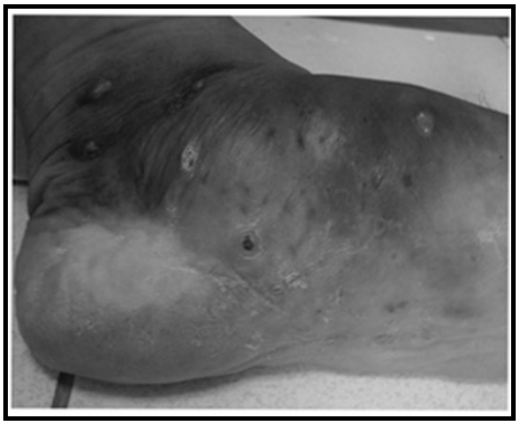
INTRODUCTION

Eumycetoma is a chronic, granulomatous disease involving the skin, subcutaneous tissue, fascia, muscle, bone and adjacent organs. Lesions evolve over months to years and may spread to involve deeper structures resulting in destruction, deformity, loss of function and even amputation.

CASE REPORT

We present a 33-year old male with a 9-year history of painless nodules with draining sinuses on the left foot. Lesion started as a solitary erythematous, pruritic nodules on the sole of the left foot after walking barefoot in the rice fields. It developed draining sinus tracts with black grains and purulent discharge. Patient applied topical anti fungal and took Cloxacillin 500mg four times for 2 weeks with no improvement. The lesions continued to spread to the dorsum and lateral aspect of the left foot, hence consult. On dermatologic examination, there were multiple ill-defined hyper pigmented and skin-colorer nodules and sinuses with erosions and scales on the medial and plantar area of the left foot. Some areas of scarring and localised edema surrounded the nodules. On the dorsal aspect, there was a well-defined hyper pigmented, hypertrophic plaque with few skin-colorer nodules with sinuses. On the lateral aspect, there were some erosions, scarring and scales.

Biopsy showed sulfur granules demonstrating Splendore-Hoeppli phenomenon with hyphae-like structures positive with Periodic Acid Schiff stain. Fungal culture revealed Madurella mycetomatis growth. Xray showed poorly marginated licences on the calcaneus and navicular bones. Ultrasound revealed mixed hyper reflective echoes and multiple small cavities. Diagnosis is Stage III Eumycetoma.



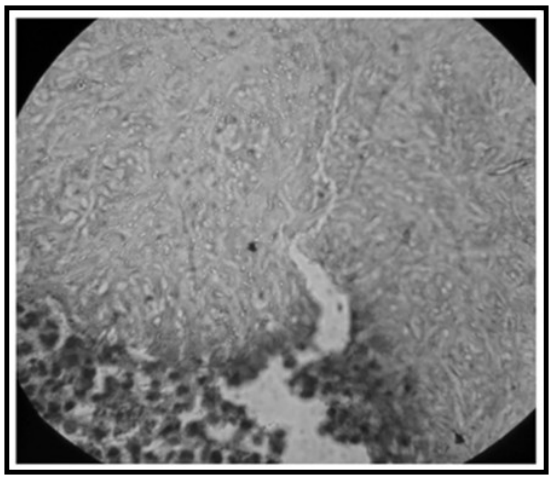


Figure 2: Hyphae-like structures in the granules (H&E, HPO x 40)

Ketoconazole 200mg twice daily was given for 9 months achieving 50-60% decrease in lesion size after which surgical debulking by wide excision of the nodules was done. Ketoconazole was continued for another 9 months. There was good granulation tissue formation and no appearance of new lesions.

DISCUSSION

Eumycetoma occurs in the tropics with low annual rainfall and relative humidity. It is common in males during the 2nd-4th decades, agricultural workers, or those who walk barefoot in dry, dusty condition. Minor trauma allows pathogens to enter the skin, which are then implanted into the hist tissue. Most common site is the dorsal aspect of the foot (79.2%) similar to that of our patient.[2]

Early stages are manifested by firm, painless nodules that spread slowly with development of draining sinus tracts over the surface. Grains discharged from sinuses vary in size, color and consistency. Lesions painlessly burrow deeply until it reaches the bone.[4]

New Radiographic classification of bone involvement in pedal mycetoma

PATTERN OF SPREAD	STAGE	EFFECT	FINDINGS
Limited to entry site	0	Soft-tissue swelling	No bone involvement
Expanding granuloma	I	Extrinsic pressure	Displacement or scalloping
Impending bone invasion	II	Bone irritation	Periosteal reaction or reactive sclerosis
Localized bone invasion	III	Erosion or cavitation	Solitary bone involvement
Longitudinal spread	IV	Joint involvement	Localized along single ray
Horizontal spread	V	Invasion of adjacent structures	Localized to forefoot, midfoot or hindfoot
Multidirectional spread	VI	Total disruption	Multiple rays and multiple rows involved

Figure 3: New radiographic Classification in bone involvement in pedal mycetoma.

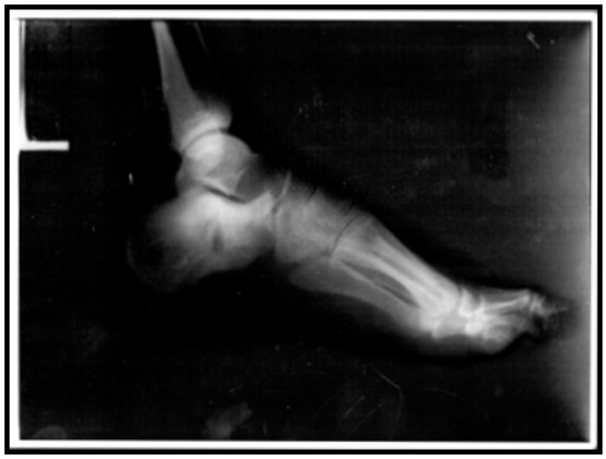


Figure 4: Radiographic imaging.

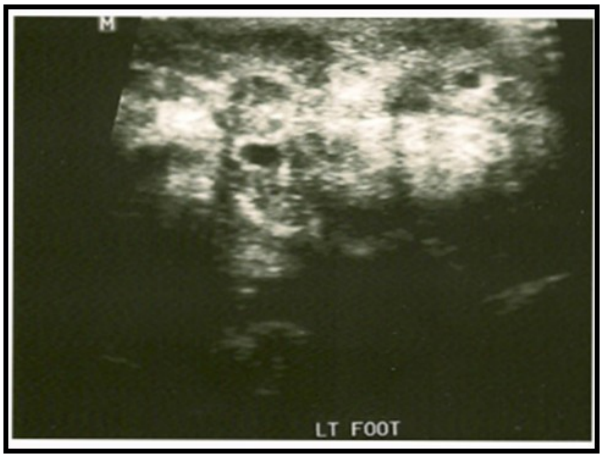


Figure 5: Ultrasonic imaging.

Clinical features do not always provide reliable measure of the extent and spread of disease. Diagnosis of Eumycetoma may be made through clinical findings, histology, mycology, radiology and ultrasonic imaging.[5]

It is necessary to determine the extent and severity of bone involvement through radiography since all mycetoma agents are osteophilic. This can aid the clinician decide the proper treatment in order to halt the progression of the disease and prevent recurrence. The radiographic parameters include the type of bone involvement, direction and pattern of spread and location of bone lesion in the foot. Based on the radiographic classification of bone involvement in pedal mycetoma, our patient belongs to Stage III (localized bone involvement) with note of cavitation on the calcaneus and navicular bones.[1]

Ultrasound imaging can differentiate between eumycetoma and actinomycetoma and between mycetoma and other non-mycetoma lesions. In eumycetoma, there are numerous, isolated sharp bright hyperreflective echoes corresponding to the grains in the lesion which was the finding in our case. Single or multiple thick-walled cavities with no acoustic enhancement are commonly identified and the cavities may contain debris and filaments. In actinomycetoma, the findings are similar but the grains are less distinct.[1]

The goals of treatment are to eradicate infection, to slow the course of the disease thereby halting the progression of deformity and preventing untoward amputation. Ketoconazole is given at a dose of 400 to 800mg daily. It has better coverage against organisms producing black grains than white or pale grains. Treatment may continue for periods ranging from months to years. It is usually stopped with clinical, mycological, radiological and ultrasonic cure.[3]

Eumycetoma are only partially responsive to anti-fungal therapy but can be reared by surgical debunking due to their normally well-circumscribed nature.[5]

Our patient successfully responded to oral Ketoconazole at 200mg twice daily for 18 months and

surgical debulking. There was no appearance of new lesions. Repeat culture was negative. Repeat X-ray of the left foot showed on the calcaneus and navicular bones and ultrasound revealed absence of hyperreflective echoes and cavities.

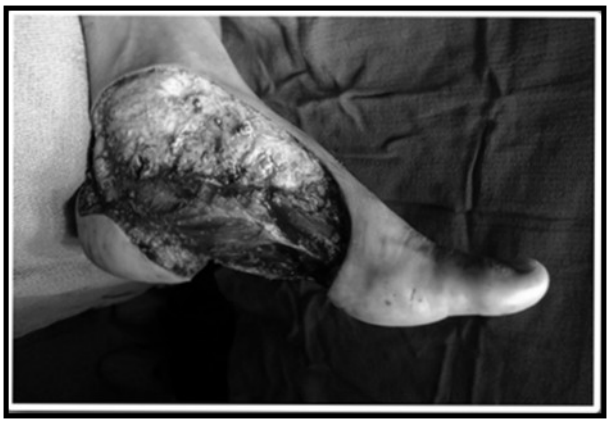


Figure 6: Immediately after surgical debulking.

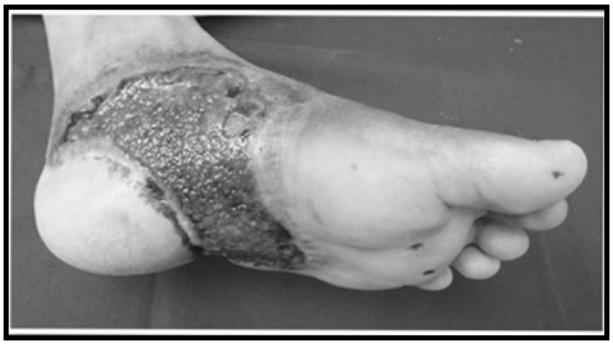


Figure 7: Two months after surgical debulking.

CONCLUSION

Our patient is a confirmed case of Stage III Eumycetoma through clinical findings, histology, mycology, radiology and ultrasonic imaging. Eumycetoma must be considered when confronted with persistent nodules on the foot and if not treated appropriately can lead to unwanted deformities and even amputation. Institution of medical treatment and surgical debunking in this case was curative and has improved our patient's quality of life.

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Case Report: X-linked Dystonia Parkinsonism - Bridging Cultural Beliefs with Medical Practice

Trisha Mae C. Mendoza, M.D. [a]

Abstract

Dystonia is often ascribed by common folk to supernatural causes rather than to a treatable medical condition. Such is what happened in this case of a 24 year-old male who presented with involuntary opening and closing of the mouth and writhing movements of the extremities, and who was eventually diagnosed with X-linked Dystonia Parkinsonism, endemic in males from Panay Island in the Philippines. A biopsychosocial approach on the management of the patient included symptom relief with an atypical antipsychotic, neuroleptics, and botulinum toxin injection, CEA, and risk assessment evaluation for prevention of long term complications and death.

[a]*Resident Physician, Department of Family and Community Medicine, UP-PGH Medical Center*
Paper selected for presentation, Interesting Case Competition, Philippine Academy of Family Physicians - Manila Chapter

INTRODUCTION

Dystonia is often ascribed by common folk to supernatural causes rather than to a treatable medical condition, especially in our country that is rich in culture and folklore. X-linked Dystonia Parkinsonism (XDP), a progressive, debilitating, adult-onset movement disorder first described in Filipino males from Panay Island is highlighted in this rare case. The number of existing cases of primary dystonia in the population is not precisely known, but the condition is probably much more frequent than reported. The prevalence of Primary Dystonia is at 16.43/100,000 while as of January 2010, 505 cases of XDP (500 males, 5 females) have been identified in the updated XDP Philippine registry.

CASE DISCUSSION

The patient is a 24 year-old male, single, Filipino, Roman Catholic, right-handed, born and raised in Cajidiocan, Romblon. He was previously well, with no known previous hospitalization or surgeries, and no history of encephalitis or trauma. He first exhibited jaw stiffening, accompanied by involuntary opening and closing of the mouth and temporomandibular joint pain, 1 year prior to consult. There was no history of animal bite, excessive drooling, dysphagia, restlessness or hydrophobia. Consult was done with a private doctor and he was prescribed a muscle relaxant and analgesics which afforded temporary relief. Nine months prior to consult, he started having involuntary writhing movements of the right upper and lower extremity. Contractions would persist throughout the day accompanied by periods of relaxation. The patient was still able to perform activities of daily living until 7 months prior to consult, when the involuntary writhing movements progressed to the abdomen and left upper and lower extremities. There was noted difficulty in ambulation. Spasms would cease when patient was asleep. There was no fever, pain, dyspnea, dysphagia, upward rolling of eyeballs, loss of consciousness, numbness, weakness or bladder and bowel changes. In the interim, there was progression in severity of patient's symptoms. The sustained contractions would occur more often and the intervals of relaxation were shorter. A consult to a faith healer was done and he was made to drink a bitter concoction which did not afford any relief. Persistence of symptoms prompted consult at a tertiary hospital in Manila, and the patient was subsequently decked to Family Medicine at the Emergency Room.

Review of Systems

There was noted weight loss, from 55kg to 51 kg. Otherwise, the review of systems was unremarkable.

Past Medical History.

There were no known co-morbidities, allergies, previous hospitalizations, surgeries or blood transfusions. The patient had completed the recommended Expanded Program of Immunization vaccines. He has also received a tetanus booster in 2012.

Family History.

The maternal great grandfather also had symptoms similar to the patient's. (*Figure 1. Genogram*). There was a family history of pulmonary tuberculosis and hepatitis B in the maternal side; while there was arthritis in the paternal side of the family.

Personal and Social History.

Patient had a 1.25 pack-years smoking history. He was an occasional alcohol beverage drinker and he denied illicit drug use. The patient also denies sexual activity. At that time, was residing in a dormitory close to school and used purified water as water source. He was taking a BS Customs Administration course and was on his last year when the involuntary movements began as a result of which he had to stop his studies. He was born and raised in Romblon but moved to Subic in 2008 to study.

Physical Examination.

The patient was wheel-chair borne, well-kempt, conscious, coherent, cooperative with stable vital signs. His weighed 51 kg (ideal body weight should have been 72 kg), and had a height of 5 feet and 8 inches, with a calculated BMI of 16.28 kg/m^2. There was no

noted temporomandibular joint tenderness or stiffness. The abdomen was flat with no visible pulsations. There was 2cm x 3cm birthmark on the left lower quadrant of the abdomen. There were intermittent involuntary contractions of abdominal muscles. There was no organomegaly of costovertebral angle tenderness. Direct rectal examination revealed no skin tags, and intact rectal vault, tight sphincter tone, non-bloody brown stools on the examining finger. Pulses were full and equal. There was no edema, cyanosis, or tenderness. Neurologic findings revealed an awake, conversant patient who was oriented to person, place and time, and was able to follow commands. The pupils were 2 to 3 mm in size and were equally and briskly reactive to light. There were no visual field deficits. There was no weakness of the extra-ocular muscles. There were no sensory deficits on the face. There was no weakness of the temporalis and masseter muscles, there was no facial asymmetry, gross hearing was intact, the tongue was midline, and the gag reflex was good. The spatula test was negative, there was good shoulder shrug, no resistance on turning the head. There was no dysmetria or dysdiadochokinesia, and the patient maintained good balance with eyes closed. There was no nuchal rigidity, and Kernig's and Brudzinski's signs were absent. There was good muscle bulk and tone, and motor strength was 5/5 on all extremities. Writhing movements were noted on legs and there was involuntary lifting of the hip while lying down. Pinprick, light touch, position and vibration senses were intact. Reflexes were symmetric and there was no Babinski's sign or clonus. There were no joint deformities and there was good range of motion in the joints of the hands, wrists, elbows, shoulders, spine, hips, knees, ankles. There were tremors at rest on the right hand. There were intermittent, involuntary contractions of the muscles of the right arm, and both legs with intermittent involuntary extension of feet and toes. Gait was normal. The other systems were unremarkable.

Movement disorders commonly encountered at the clinic may be essential tremors, chorea, dystonia, myoclonus or a combination of any of these. Essential tremors are involuntary, rhythmic alternating movements of one or more body parts. Chorea are involuntary movements that are abrupt, unpredictable and non-rhythmic, resulting from a continuous random flow of muscle contractions. Dystonia is an involuntary abnormal co-contraction of antagonistic muscles, which may cause sustained abnormal postures or twisting repetitive movements. Myoclonus is a sudden, brief, shock-like involuntary movement, which is usually caused by muscle contraction but can sometimes be due to inhibition of muscular tone.

The patient presented with intermittent flexion of abdominal muscles, writhing movements noted on legs, and involuntary lifting of hip while lying down, with tremors at rest on the right hand, intermittent, involuntary contraction of the muscles of the right arm, and both legs, as well as involuntary extension of feet and toes. These symptoms were characteristic of dystonia.

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both. It is typically patterned, twisting, and may be tremulous, often initiated or worsened by voluntary action and associated with overflow muscle activation. The underlying neurochemistry of dystonia is not known, but dopaminergic and cholinergic neurotransmitters may be involved.

Dystonia may be classified by clinical characteristics and by etiology. By clinical characteristics, the classification may be further divided into age of onset, body distribution, temporal pattern and associated features. (Appendix A)

The patient manifested generalized, persistent and progressive dystonia in his early adulthood, with associated Parkinsonism. The laboratories done so far, were all unremarkable. *(Appendix B)* Ideally, genetic testing should be done to confirm the diagnosis however, due to financial constraints, the patient opted not to have it done immediately.

Along with a family history of a similar symptom in the maternal great grandfather, our final diagnosis for the patient was Dystonia, probably genetic in origin, probably X-linked Dystonia Parkinsonism, Underweight.

Dubbed as the Panay dystonia, or *Lubag* in the native tongue which means "musically out of sync", X-linked dystonia parkinsonism was popularly known as the "aswang of Panay". In 1975, the existence of a severe and progressive movement disorder called XDP was discovered, which is a form of Parkinson's with dystonic features. In 1968, an independent study by the Roxas Memorial Provincial Hospital, pointed to a physical aberration that is believed to explain the aswang myth and the reason why the province of Capiz is singled out in all the folklores. The affected gene is the DYT3, mapped to a 350 kb locus in the DXS 7117-DX 559 region. Females are rarely affected, most of them are carriers, and the disease may hide in families until there is an affected male. Symptoms begin as focal dystonia, often becoming generalized by 4 years, commonly manifesting as twisting or dragging a foot, repeated jaw opening and closing, abnormal turning of the neck. In the next 7-15 years of illness, dystonia and Parkinsonism manifest together until after 15 years, when Parkinsonism predominates. By then, the writhing movements are very minimal. Neuropathology studies revealed marked atrophy of the caudate and putamen while the cerebral cortices, thalamus, subthalamic nuclei, substancia nigra and pons were unremarkable.

The diagnosis of dystonia is clinical, based on the recognition of specific features. It is highly relevant for providing appropriate management, prognostic information and genetic counselling. Certain laboratory examinations are requested depending on the etiology that the clinician has in mind. As for the patient in this case, a XDP gene test was requested.

Treatment involves symptom relief of dystonia and parkinsonism with anticholinergics, benzodiazepines or neuroleptics. In this case, Clonazepam 2mg/tab ½- ½ - 1xxx and Baclofen 10mg/tab ½ tab TID were prescribed. Also, Botulinum toxin injections are the first line treatment for dystonia affecting the face and neck, provided the patient does not have pre-existing dysphagia. However, for symptomatic improvement in individuals with XDP with advanced disease and medically refractory dystonia may be best treated with bilateral pallidal stimulation according to a study by *Wadia et al 2010, Aguilar et al 2011, Patel et al 2014.*

To prevent disease complications, diet modification and other techniques to reduce the risk of aspiration by doing a swallow evaluation is suggested. Physical and occupational therapy may also be done to improve mobility and assistive devices. This may prevent the formation of contractures and delay bedbound state. Prolonged sitting or lying down is discouraged to avoid pressure sores.

In dealing with these cases, the family physician must understand the cultural context of the patient and his family. In this case, the patient was born and raised in a small town in Panay and their family and ancestors have their own health beliefs, one of them being that these symptoms were a "sumpa" in the family spread through generations. This explains why the patient went home when his disease couldn't be treated with the medicines prescribed to him. Faith healers were consulted, but because their interventions were not helpful, one of their relatives suggested that a consult to a tertiary hospital must be done to put an end to their belief that the patient had indeed become a victim of the "sumpa".

Helping the patient and his family understand the true biomedical context of this chronic, familial disease will help them come to an acceptance of the disease so that the patient will agree to the major therapeutic efforts that the physician will suggest.

Because dystonia influences various aspects of quality of life, particularly those related to physical and social functioning, it is important that the patient is educated about his disease. Functional disability, body concept and depression are important predictors of quality of life in dystonia. In a study conducted by *Jamora et al, Suicidality among patients with sex-linked Dystonia Parkinsonism*, about 10.8% deaths in XDP are attributed to suicide, with hanging as the number one method used, followed by starvation organophosphate poisoning non-accidental and self-mutilation. Mean age at suicide was between 32 – 75 years of age, at an average of 5.8 years from diagnosis. Majority were in the generalized stage of the disease. This may be due

to poor functional capacity, disfigurement and perhaps, abandonment. Screening for depression is highly recommended for patients with XDP, as well as counselling of their caregiver to promote better care for the patient, prevent abandonment, as well as, care-giver strain.

In this case, risk assessment was done at the end of the consult. The service recommended genetic screening, depression screening, as well as lifestyle modifications. the service also suggested, if finances allowed, that the patient be vaccinated for Hepatitis B, pneumococcal polysaccharide vaccine, annual influenza vaccine, HPV, Hepatitis A vaccine and meningococcal conjugate vaccine. Anticipatory guidelines for the avoidance of tobacco, alcohol and other substances of abuse were also given. Rehabilitation was suggested and education about the prevention of fals and aspiration was done.

There is no known definitive treatment for X-linked Dystonia Parkinsonism to date. However, in the Filipino community, it is imperative that a rare disease like this be recognized, especially since it is hypothesized to be endemic in the Panay Island in the Philippines. In addition, it is important to be recognized in the primary care setting as the dystonia is associated with the *aswang myth,* a part of the Philippine folklore and has been passed on from generations to generations.

The patients who suffer from X-linked dystonia-parkinsonism are people who need care, and are not supposed to be feared. Perhaps, if the disease becomes common knowledge, the fear will be turned into understanding, the stigma would be abolished, and the patients afflicted with the disease will be given the appropriate management and be given hope.

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End Notes:

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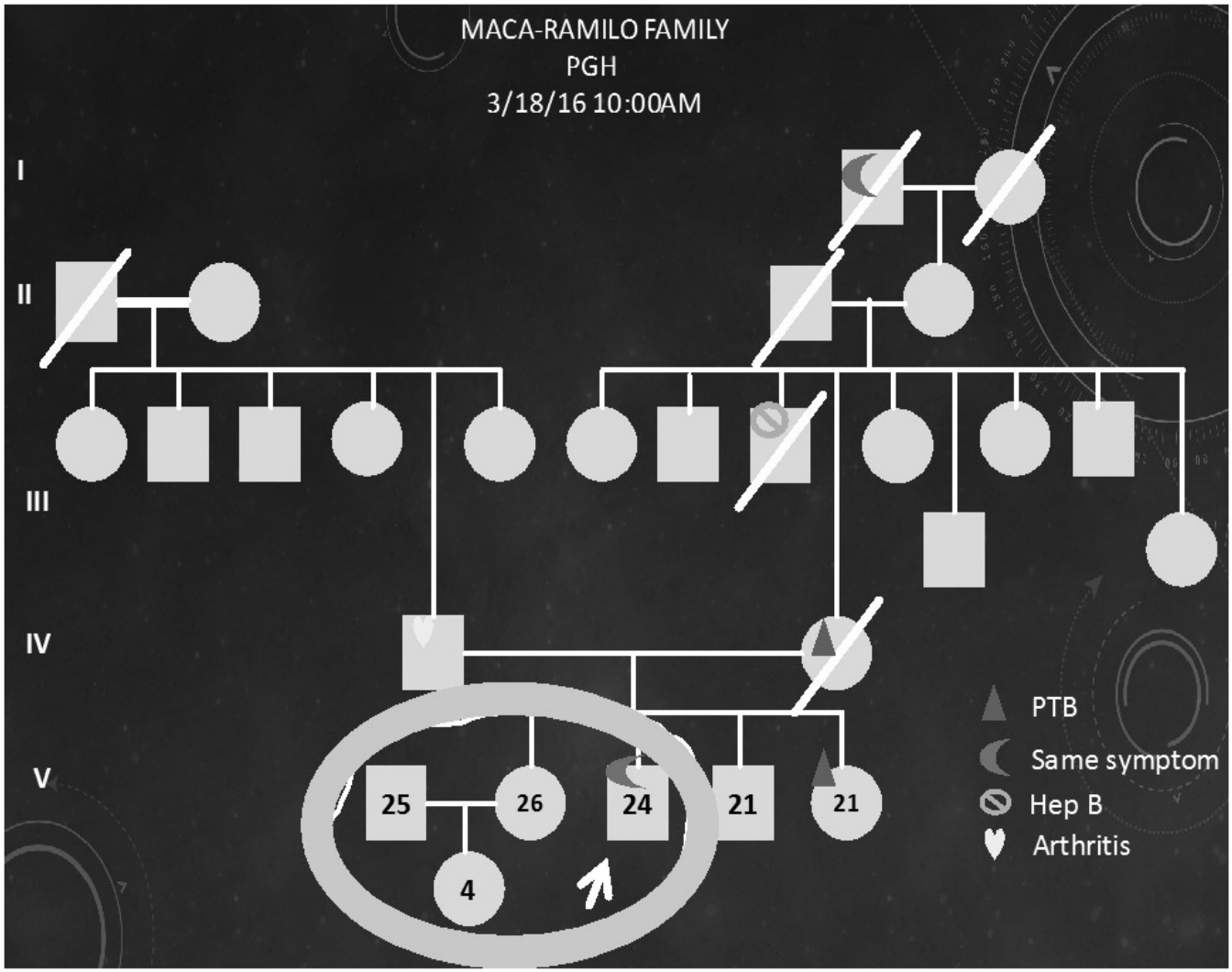


Figure 1. Maca - Ramilo Family Genogram

APPENDIX A

Classification of dystonia by clinical characteristics and etiology

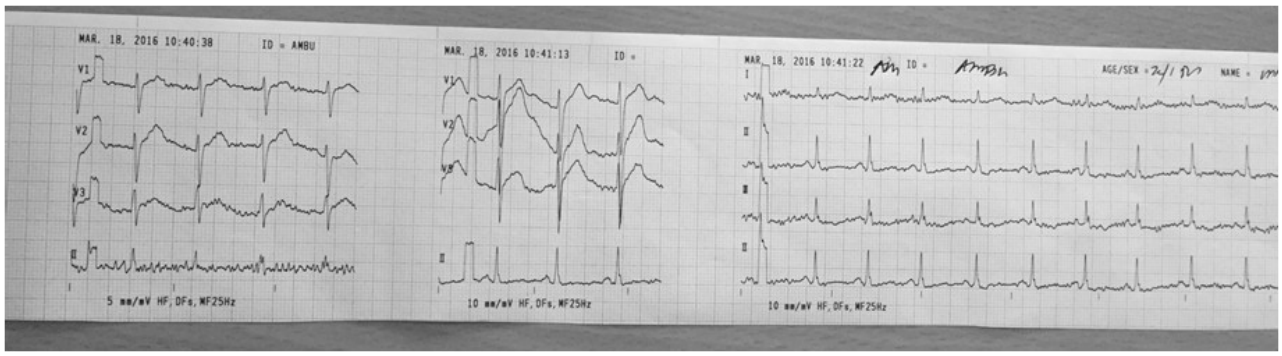
Clinical characteristics	
Age of onset	Infancy: birth to 2 years
	Childhood: 3 to 12 years
	Adolescence: 13 to 20 years
	Early adulthood: 21 to 40 years
	Late adulthood: >40 years
Body distribution	Focal: involving a single body region
	Segmental: involving two or more contiguous body regions
	Multifocal: involving two noncontiguous or more (noncontiguous or not) body regions
	Generalized: involving the trunk and at least two other sites
	Hemidystonia: involving more regions restricted to one body side
Temporal pattern	Disease course:
	Static
	Progressive
	Variability:
	Persistent: dystonia that persists to approximately the same extent throughout the day
	Action-specific: dystonia that occurs only during a particular activity or task
	Diurnal: dystonia fluctuates during the day, with recognizable circadian variations in occurrence, severity and phenomenology
	Paroxysmal: sudden self-limited episodes of dystonia usually induced by a trigger with return to preexisting neurologic state
Associated features	Isolated or combined with another movement disorder:
	Isolated: dystonia is the only motor feature, with the exception of tremor
	Combined: dystonia is combined with other movement disorders (such as myoclonus, parkinsonism, etc)
	Occurrence of other neurologic or systemic manifestations
Etiology	
Nervous system pathology	Evidence of degeneration (progressive structural abnormality, such as neuronal loss)
	Evidence of structural (often static) lesions
	No evidence of degeneration or structural lesion
Inherited or acquired	Inherited (dystonia forms of proven genetic origin):
	Autosomal dominant
	Autosomal recessive
	X-linked recessive
	Mitochondrial
	Acquired (dystonia due to a known specific cause):
	Cerebrovascular (infarction or hemorrhage)
	Perinatal brain injury
	Traumatic brain injury
	Infection
	Drug
	Toxic
	Neoplastic
	Psychogenic
Idiopathic (unknown cause)	Sporadic
	Familial

Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013; 28:863.

Figure 2 Classification of Dystonia by clinical characteristics and etiology

EXAM NAME	RESULTS	UNIT	REFERENCE VALUE
WBC	8.85	X 10^9/L	4.50 – 11.0
RBC	4.57	X 10^9/L	4.6 – 6.2
Hemoglobin	136	g/L	135 – 180
Hematocrit	0.42		0.40 – 0.54
MCV	91.4	fL	80 – 96
MCH	29.8	pg	27.0 – 31.0
MCHC	326	g/L	320 – 360
RDW	13.8		11.0 – 16.0
Platelet count	379	X 10^9/L	150 – 450
Differential Count			
Neutrophil	0.67		
Lymphocyte	0.23		
Monocyte	0.07		
Eosinophil	0.02		
Basophil	0.01		

TEST NAME	RESULT	UNIT	RANGE	RESULT	UNIT	RANGE
Creatinine	57	umol/L	58-110	0.64	mg/dl	0.66-1.15
Calcium	2.29	mmol/L	2.10 – 2.55	9.16	mg/dl	8.4 – 10.2
Mg	0.76	mmol/L	0.7 – 1.00	1.85	mg/dl	1.7 – 2.4
Sodium	142	mmol/L	137 – 145	142	mmol/L	137 - 145



APPENDIX C

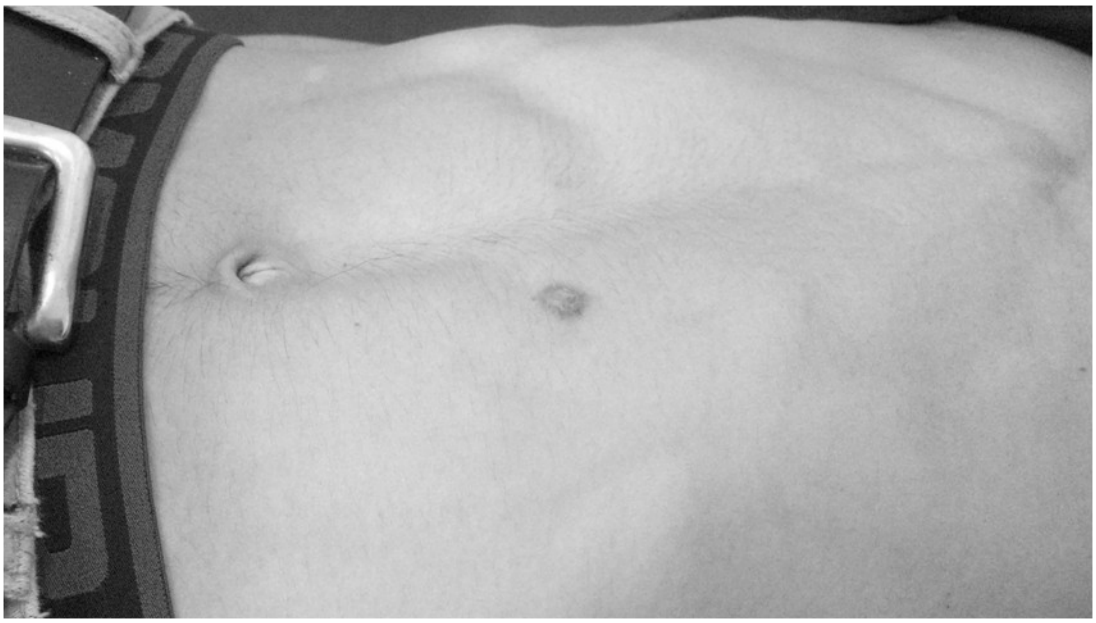


Figure 3 Involuntary flexion of abdominal muscles

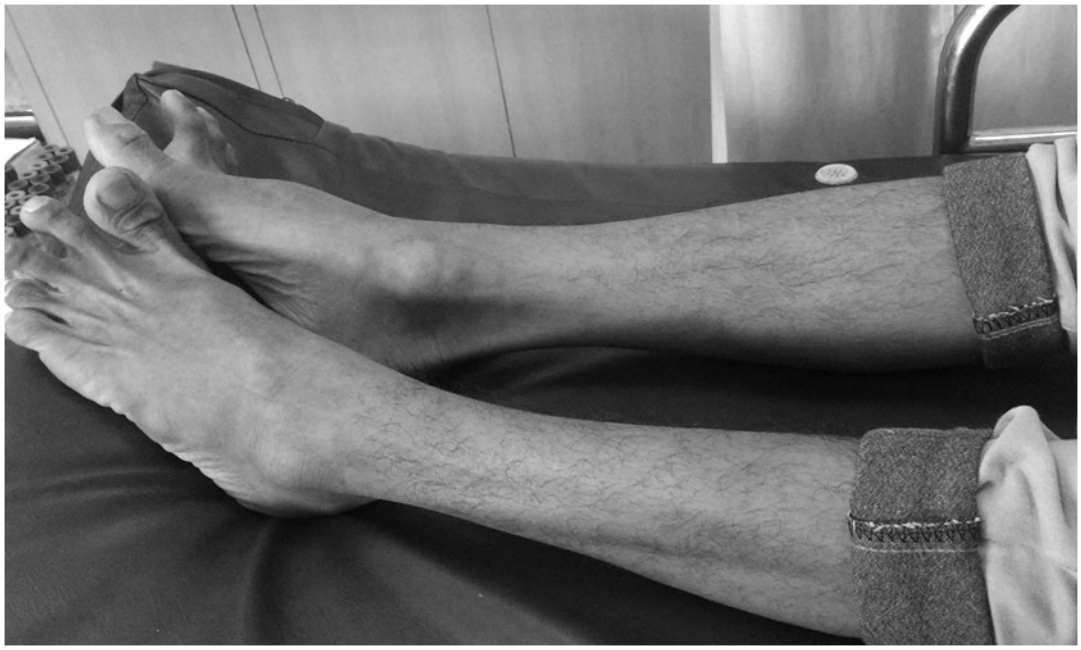


Figure 4 Flexion of leg muscles and extension of toes

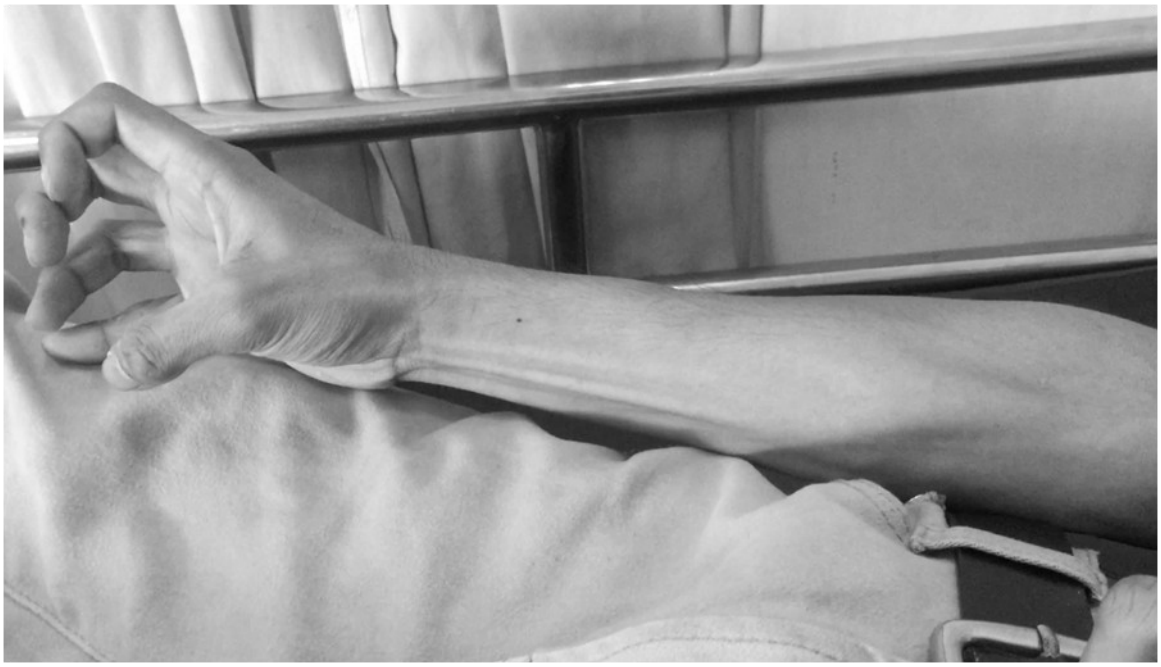


Figure 5 Extension of arm and flexion of phalanges

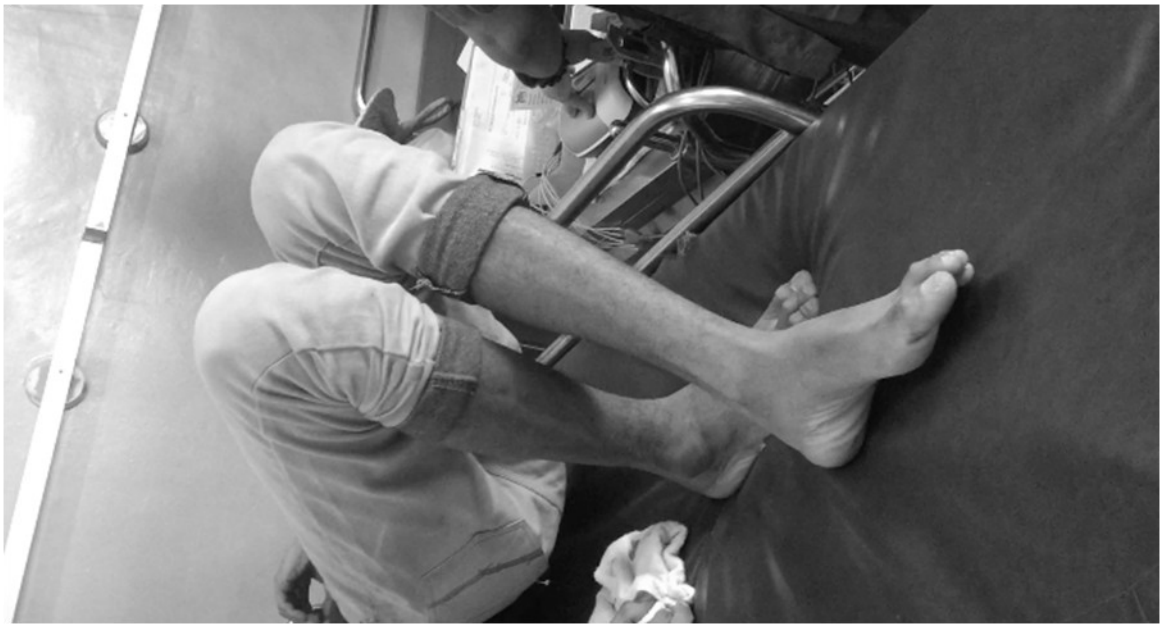


Figure 6 Involuntary lifting of the hip when lying down, giving the patient a bizarre posture