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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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EDITOR'S notes

For this issue, we have selected five research papers and five case reports from the submissions gathered. As in our first issue, we have intended these choices to be representative of various disciplines and various medical institutions. In future volumes, we hope to have a theme for a specific issue. Again, this will be dependent on the number, quality, and commonalities of the material at hand. Moreover, we are promoting our journal as a venue for publication of award-winning studies in PMA competitions, both at the national and local levels. We also strongly encourage contributions from other organizations, particularly papers worthy of note. Certainly, we are not wanting in research fora hosted by the specialty and sub-specialty societies. Hospital also have their own.

Research and publication is the way to go!

AJBAJ, May 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).

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

Ethical Considerations

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

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

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

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

Manuscript Preparation

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

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

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

For the original article, an abstract must be 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 abstract, 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.

Observer Variability in the Diagnosis of ST-Elevation Myocardial Infarction from Emergency Room Electrocardiograms of Patients Presenting with Chest Pain*

Edgardo S. Timbol, MD
Jose Donato A. Magno, MD
Richard Q. Amansec, MD

ABSTRACT

BACKGROUND: The diagnosis of ST-elevation myocardial infarction on standard 12-lead electrocardiography is crucial to the timely institution of appropriate medical therapies and interventions. However, the electrocardiographic diagnosis may be prone to observer variability.

OBJECTIVES: We wanted to determine the 1) inter-observer variability among clinicians from a training hospital in the diagnosis of ST-elevation myocardial infarction (STEMI) from emergency room electrocardiograms (ECG) of patients presenting with chest pain, and 2) the accuracy of clinician readings compared to the final cardiac diagnosis in the official patient records.

METHODS: Forty electrocardiograms were independently interpreted by 40 clinicians which included 10 cardiologists (CC), 5 cardiology fellows (CF), 15 internal medicine (IM), and 10 internal medicine residents (MR), using uniform copies of the standard 12-lead electrocardiogram print-outs. All readers were blinded to the patient's clinical profile. The accuracy of clinician readings (% of tracings correctly identified as STEMI) were compared against a reference standard, which was the final cardiac diagnosis made based on historical, electrocardiographic, biochemical, and angiographic data.

RESULTS: The overall level of agreement among all readers (intergroup variability) was only fair with a kappa of 0.24. The level of agreement within the groups (intra-group variability) was likewise "fair" for the IM (0.35), MR (0.32), and CC (0.30) groups. Agreement was much less (0.18) among the cardiology fellows (0.18) among the cardiology fellows (CF). Accuracy of ECG diagnosis varied among the groups: IM (68%), MR (60%), CF (52%) and CC (50%).

CONCLUSIONS: There is substantial inter-group variability in the electrocardiographic diagnosis of STEMI by clinicians. The accurate diagnosis of STEMI, based on pure electrocardiographic information, varied among readers with different training backgrounds. These findings suggest that the electrocardiographic diagnosis of STEMI may be influenced by training background and experience, as well as presence or absence of supplemental medical information necessary to make a comprehensive and accurate cardiac diagnosis. More importantly, this underscores the need to harmonize electrocardiographic interpretations and recognize the value of reading ECGs in light of pertinent clinical data.

*From the Angeles University Foundation Medical Center (AUFMC), Angeles City, Pampanga

INTRODUCTION

ST elevation myocardial infarction (STEMI) is usually caused by an acute total occlusion of a coronary artery following the rupture of a previously non-obstructing plaque that triggers platelet aggregation and thrombus formation of the site of rupture. On the other hand, non-STEMI (NSTEMI) most commonly results from severe but not total occlusion of a coronary artery due to plaque erosion or progressive arteriosclerosis.

It is generally accepted that patients with typical symptoms presenting with persistent ST elevation in at least two contiguous leads should be accorded prompt reperfusion therapy, either pharmacological or catheter-based. Fibrinolytic therapy is preferred over percutaneous coronary intervention, if it is anticipated that the latter could not be performed within two hours. Patients without ST segment elevations however, are not candidates for thrombolysis but should nevertheless receive anti-ischemic and anti-platelet agents. Thrombolytic therapy reduces mortality among patients with suspected acute myocardial infarction (AMI) and electrocardiogram (ECG) indicators of high risk including acute ST segment elevation of bundle branch block (1-3)

However, the standard electrocardiographic criteria used for triaging patients into STEMI or NSTEMI have not attained the level of specificity and sensitivity in which errors of omission or commission could be avoided upon implementing an intervention that is highly effective but not entirely risk-free. Errors in the identification of potentially eligible thrombolytic candidates occur and can be made in two directions [6-14].

According to the 2014 PHA guidelines on coronary artery disease, it is strongly recommended that a 12-lead ECG be taken within 10 minutes of arrival at the ER. The 12-lead ECG has a pivotal role in the initial evaluation and rapid diagnosis of STEMI patients to determine the patient's eligibility for reperfusion therapy.

Further, it is also recommended that if the initial ECG is not diagnostic and the patient remains asymptomatic, but there is high clinical suspicion for STEMI, serial ECG's at 5 to 10 minute intervals or continuous ST segment monitoring should be done.

In the rural setting, the ECG could be the only available tool in most institutions in the diagnosis of patients suffering from acute myocardial infarction. Oftentimes, it comprises the only basis for treatment of such patients even if the sensitivity and specificity of the ECG in the diagnosis of STEMI is approximately 39% and 69% respectively with inter and intra-observer variability.

This study aims to document the presence and the magnitude of inter-observer variability in the appraisal of ST segment elevations from the ECG of patients with chest pains recorded at the emergency room. The findings of significant inter-observer variability may play an integral role on enhancing the specificity and sensitivity in our flight to help our rural physicians establish a more accurate diagnosis of STEMI thru the 12-lead ECG. state focusing on acne-related QOL in adolescent students.

METHODOLOGY

Trial Design

Forty ECG tracings were selected among patient population presenting as STEMI in the emergency room of the Angeles University Foundation Medical Center. The respondents were made to choose whether or not the ECG tracings presented to them to analyzed were indeed represent a diagnosis of STEMI and for which the respondent is made to choose 'Yes'. On the other hand, if the respondent deems that it is not STEMI, he/she has to check 'No'. The ST-elevation was then confirmed with either the patient's Troponin I, CK-MB, coronary angiography or the presence of subsequent ECG dynamic changes.

Study Setting and Time Frame

The study was conducted from January 2014 to December 2015. The study included 10 cardiologists, 5 cardiology fellows, 15 general internists and 10 medical residents from the Angeles University Foundation Medical Center (AUFMC), Angeles City.

Study Maneuver

Forty electrocardiograms were independently interpreted by 40 clinicians which included 10 cardiologists (CC), 5 cardiology fellows (CF), 15 internal medicine (IM), and 10 internal medicine residents (MR), using uniform copies of the standard 12-lead electrocardiogram print-outs. All readers were blinded to the patient's clinical profile. The accuracy of

clinician readings (% of tracings correctly identified as STEMI) were compared against a reference standard, which was the final cardiac diagnosis made based on historical, electrocardiographic, biochemical, and angiographic data.

Definition of Outcomes or variables measured

Intra-observer and interobserver reliability was then compared among the different subgroups of respondents.

Statistical Analysis

For the statistical analysis, Kappa statistics were used to assess the agreement in ECG interpretation between different physicians. The mean of the correct responses from each group were also computed.

RESULTS

Participants

Forty clinicians which included 10 cardiologists, 5 cardiology fellows, 15 internal medicine specialists and 10 medical residents interpreted 30 12-lead ECG tracings.

Table 1 shows the demographics of the four groups of readers. There were significant gradients in terms of both age since medical school graduation and ECG reading experience favouring CC over trainees.

Table 1. Study Participants

Physician Group	Years since graduation	Average number of ECGs interpreted per week			
		<5	5-9	10-20	>20
Medical Residents (MR)	>3.0	++	+		
Internal Medicine Specialists (IM)	>4.0		++	+	
Cardiology Fellows (CF)	>5.0		+	++	
Cardiology Consultants (CC)	>10.0				+++

Observer variability

The overall level of agreement among all raters was only "fair" with a kappa of 0.24. Similarly, level of agreement within the cardiologist, IM specialist, and IM resident groups were "fair" with

kappa = 0.30, 0.35 and 0.32, respectively. Only slight agreement (kappa = 0.18) was noted among cardiology fellows. Moreover, comparison of the overall number of patients correctly diagnosed with STEMI based on ECG showed significant differences between groups, particularly, between IM specialists and cardiologists with means of 27 and 20 respectively. Mean number of patients correctly diagnosed with STEMI based on ECG by cardiology fellows and medical residents were 21 and 24 respectively.

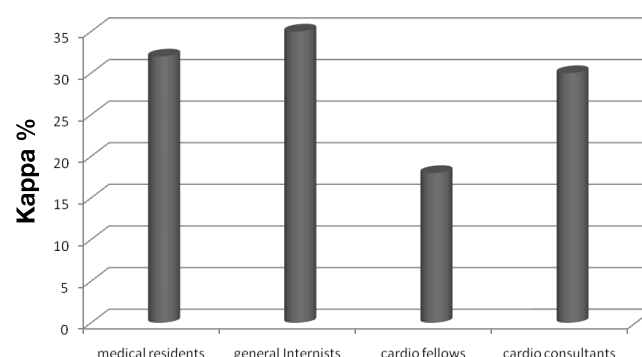


Fig 1. Inter-observer variability among physician groups. Shown are the inter-observer kappa values

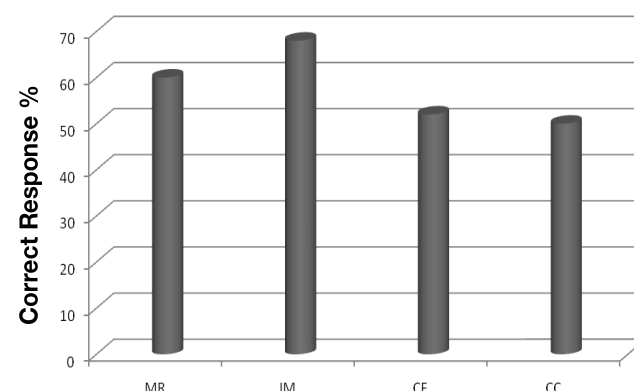


Fig. 2. Accuracy of ECG diagnosis among the physician groups MR- Medical residents; IM - Internal Medicine; CF - Cardiology Fellows

DISCUSSION

Our study has several findings. First, there was significant intergroup variability in the ECG interpretation. The accurate diagnosis of STEMI, based on pure electrocardiographic information varied among readers with different training backgrounds. These findings suggest that the electrocardiographic diagnosis of STEMI may be influenced by training background and experience, as well as the presence

or absence of supplemental medical information necessary to make a comprehensive and accurate cardiac diagnosis.

Unlike other studies, we found out that experience and educational attainment of readers may not be congruent with the accuracy of ECG readings. General internists and medical residents have greater percentages of correct responses identified as to whether a patient has STEMI and thus needs thrombolysis as a revascularization procedure. The correct response is based on cardiac enzymes, result of the coronary angiogram and the 2D echocardiography result.

This study has limited scope and involves only physicians who are active staff of the Angeles University Foundation Medical Centre. Individual patient's setting or clinical background is also not given to the interpreter which is a critical in decision making regarding thrombolysis.

Implications of the Study

Findings in this study would establish that the ECG continues to be an insensitive tool for the diagnosis of AMI and thus the authors would recommend a scoring system that improves the diagnostic sensitivity and specificity of the 12-lead ECG leading to a more determined decision to thrombolysate patients even in the absence of clinical data.

Consequences of variability in electrocardiogram interpretation

This highlights the fact that in the management of our patients, we should not take the diagnostic work-ups done as a standalone basis for our diagnosis. In fact, it is again stressed that the history and physical examination forms the cornerstone for the diagnosis of most if not all of human diseases.

Yet time and again, physicians, especially in the rural areas, may be pushed against the wall in terms of diagnosis of ST-elevation myocardial infarction.

We present in this paper, that 12-leads ECG that may present as STEMI are not actually what they appear to be or those that seems to be rather benign or not classified as STEMI are actually one. This has a big burden on the rural physician since additional diagnostic data are oftentimes not available as a adjunct for the diagnosis of such

time-dependent disease which require one to act within a golden period. As again stressed, "time is myocardium".

Understanding the plight of these physicians, and with the results of this study, we deemed it necessary to improve the sensitivity and specificity of the 12-lead ECG in order that more lives be saved from this silent epidemic. A scoring system could be proposed to be used specially that of ongoing dynamic ECG changes.

In this study, we also emphasized that our training did not made us interpret ST-elevation MI as a definite diagnosis once the ECG is done. But as with all other diagnostics, there is an inter and intra-observer variability which makes it all the more complex for such situations.

Comparison with other studies

Storey and Rowley found considerable variability in the decision to administer thrombolysis based on a typical case history and 30 ECGs, of which 19 were performed on patients in the acute phase of myocardial infarction (17). Thrombolytic therapy was recommended in 75% -100% of cases when the ECG showed unequivocal or strong evidence of acute injury. House officers were more hesitant in deciding to do thrombolysis. On the other hand thrombolysis was advocated in 11-31% of scenarios when the ECG was abnormal but not diagnostic of acute injury. Holmvang and colleagues reported a κ statistics on both intra- and inter-observer variability on ECGs in patients participating in an acute coronary syndrome trial(16).

Intraobserver variability on ST segment elevation was good with a κ of 62%. Agreement between the core laboratory and the local investigators for ST elevation, however, was poor with a κ of only 5%. The latter seems disproportionately poor and may reflect the complexities of including patients in randomized trials. Jayes and colleagues compared ECG interpretations of emergency physicians to expert readers(9). Emergency physicians misinterpreted 7% of ST segments as being abnormal when no abnormalities were seen and 20% of the ST segments as normal when they were not. Moreover, misinterpretation lead to a higher likelihood of inappropriate patient triage. Another study done by Massel D. rating the level of observer variability in ECG interpretation for thrombolysis eligibility with basis of experience and context, shows the overall level of agreement among

all ratters was substantial with a kappa (kappa) of 70.4%. Intra-observer ECG reading reliability was stronger among cardiologists (CC) as compared with cardiology fellows (CF) and medical residents (MR). The reliability of ECG interpretation for deciding to administer thrombolysis was substantial; there was a gradient from lowest to highest commensurate with training and experience. Errors in thrombolysis eligibility are influenced by clinical history and the presence of a computerized ECG interpretation among less experienced clinicians(18).

Palmer and colleagues showed that delays in thrombolysis administration were due to a combination of patient and hospital factors; three are germane to this study: amount of ST segment elevation, an atypical versus typical presenting history, and the grade of doctor who initially assessed the patient in the emergency department (15). The median delays for thrombolysis were 148 and 160 minutes for interns and residents as compared with 65 and 38 minutes for registrars and senior doctors ($p < 0.0001$). In their multivariate analysis the junior grade of doctor remained an important predictor in treatment delay; based on our study this may reflect the inability to identify more subtle ECG changes of acute AMI. It is also interesting to note that senior doctors were more likely to see patients with marked ST abnormalities and urgent triage priorities. This suggests that a visually alarming ECG may well expedite triage and treatment decisions (13).

Limitations of the study

Only ECGs from Angeles University Foundation Medical Center (AUFMC) were included in the study. Adult cardiology consultants, cardiology fellows, internists and medical residents from the same institution were included in the study. Other specialties such as general physicians, ER physicians, family medicine physicians were not included as respondents. The clinical profile of the patients were not given to the reader.

Our study was performed in a tertiary care teaching center and as a result may not be representative of all clinicians who interpret ECGs when assessing patients with chest pain in the emergency department. Moreover, ECG interpretations by emergency department physicians, who provide the initial assessment and triage of patients with acute chest pain, were not included in the study. Notwithstanding, the observation that less experienced

readers may perform less well is an important one as the decision to administer thrombolysis in the vast majority of emergency departments does not hinge on the ECG interpretation of an experienced cardiologist. It does suggest however, that there may be value in seeking an experienced interpretation, possibly by facsimile or other electronic methods, when the decision does not seem to be obvious.

Whether readers would make different interpretations on the same ECGs in 'real life' is speculative. Clinical history was not incorporated during the reading of the ECGs. Readers were also not timed for the whole ECG interpretation. They were allowed to proceed at their own pace. This eliminates the time pressure clinicians feel when using the ECG as one of the clinical tools to help with the decision to administer thrombolysis in a timely fashion.

CONCLUSIONS

There is substantial inter-group variability in the electrocardiographic diagnosis of STEMI by clinicians. The accurate diagnosis of STEMI, based on pure electrocardiographic information, varied among readers with different training backgrounds. These findings suggest that the electrocardiographic diagnosis of STEMI may be influenced by training background and experience, as well as presence or absence of supplemental medical information necessary to make a comprehensive and accurate cardiac diagnosis. More importantly, this underscores the need to harmonize electrocardiographic interpretations and recognize the value of reading ECGs in light of pertinent clinical data.

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Double-Blind Randomized Controlled Trial on the Efficacy and Safety of Metformin as an Adjunct to Doxycycline and Tretinoin 0.025% Cream in the Treatment of Moderate to Severe Acne Vulgaris*

Mary Natalie C Quesada, MD, DPDS¹
Arnelfa C Paliza, MD, FPDS²
Eleanor L Letran, MD, FPDS³

ABSTRACT

Objectives: To evaluate the efficacy and safety of metformin as an adjunct to oral doxycycline and tretinoin 0.025% cream in the treatment of moderate to severe acne vulgaris.

Methods: This is a double blind randomized controlled trial with 17 patients per group, and a study period of 12 weeks. Both groups (Dt group and DtM group) received doxycycline for the first 6 weeks and tretinoin for 12 weeks, while only the DtM group received metformin 1500mg/day for the entire treatment period. Follow up visits were done every 2 weeks from baseline. Non-inflammatory, inflammatory and total acne lesion count, and the modified global severity, subjective patient assessment, and Dermatology Life Quality Index scores, scores of cutaneous adverse events, and incidence and frequency of systemic adverse events were the outcome measures.

Results: The DtM group showed significant statistical benefit for the treatment of noninflammatory lesions (comedones) in the 4th, 6th, 8th and 12th week. Outcome measures of global severity, subjective patient assessment, and DLQI scores, mean reduction rate of inflammatory and total lesion counts, and mean pain, erythema, dryness and scaling counts between groups were comparable. The incidence and frequency of reported systemic adverse events such as diarrhea, nausea and headache, were higher in the DtM group.

Conclusion: The addition of metformin to standard treatment is beneficial in reducing non-inflammatory lesion counts. It offers comparable benefit for inflammatory and total lesion counts. Cutaneous and systemic adverse events in both groups were mild and self-limited, and did not warrant discontinuation of treatment.

Keywords: *metformin, tretinoin, doxycycline, treatment, acne*

*First Place, Residents Category, University of Santo Tomas Annual Scientific Research Forum / Benavides Cancer Institute Auditorium, UST Hospital / December 6, 2012

¹International Global Education Award, XI International Congress of Dermatology and 42nd Annual National Conference of IADVL / New Delhi, India / December 4-7, 2013

²Resident Physician, Department of Dermatology, University of Santo Tomas Hospital, Manila, Philippines

³Professor, Department of Dermatology, University of Santo Tomas, Manila, Philippines

⁴Associate Professor, Department of Dermatology, University of Santo Tomas, Manila, Philippines

INTRODUCTION

Acne vulgaris is a common inflammatory dermatologic condition that afflicts all ages, particularly adolescents and young adults. Its sequela of permanent scarring has its impact on the emotional and psychological well-being of patients. It leads to anxiety, depression, low self-esteem, and withdrawal from society, resulting to a negative impact on the quality of life.¹ Acne vulgaris involves the pathology of the pilosebaceous unit, with pleomorphic manifestations of both inflammatory (papules, pustules, nodules, and cysts) and noninflammatory (comedones) lesions. The primary pathogenic processes are follicular hyperkeratinization, excessive sebum production, hypercolonization of the ducts by *Propionibacterium acnes*, and inflammation.² Agents in different combinations are used to treat acne, to maximize their synergistic and complementary effects through the different pathogenic processes they target.

Systemic antibiotics such as doxycycline, strongly inhibits proliferation of *P. acnes*.³ Topical retinoids, particularly tretinoin, decreases proliferation and differentiation of keratinocytes,⁴ consequently suppressing microcomedo formation. In combination, systemic antibiotics and topical retinoids are a suitable choice of treatment in controlling moderate to severe acne, with a treatment rate ranging from 58.7% to 62.4%.⁵ This is an increase in efficacy with faster therapeutic response when compared to either agent used as monotherapy. However, due to the rising trend of antibiotic resistance, use of antibiotics should be minimized. These should be discontinued once inflammatory lesions begin to resolve, taking effect approximately 6 weeks into treatment.³ Relapse or deterioration, however, is common upon antibiotic discontinuation. There is, therefore, a need for alternatives in the treatment of moderate to severe acne that obviates long-term antibiotic use, and shortens the course of treatment.

Metformin is a well-tolerated drug that has been used in the treatment of Type 2 diabetes. It lowers fasting plasma insulin concentrations by inducing greater peripheral uptake of glucose, and decreasing hepatic glucose output without causing hypoglycemia.⁶ It has been utilized in several studies involving non-diabetic patients^{7,8,9} and for treatment of polycystic ovarian syndrome¹⁰ (PCOS), with no significant untoward decline in blood glucose levels that warranted discontinuation of the study.

The clinical potential of metformin in the treatment of acne in association with PCOS has been well

documented. It has been hypothesized that the effects of Metformin are mediated by a decrease in insulin levels as a result of the reduction in hepatic glucose production. Metformin also reduces androgen production by a direct action on the ovaries.¹¹ Since hyperandrogenemia and increased insulin signaling are involved in the pathogenesis of acne, a reduction in the levels of serum androgens and insulin by metformin, should ameliorate acne and seborrhea.¹²

An uncontrolled study by Kolodziejczyk¹³ addressed acne as a specific endpoint in assessing the response of PCOS to metformin. At a dose of 1500 mg/day for a period of 12 weeks, significant decrease in acne score, as well as other parameters related to hyperandrogenism, was demonstrated.

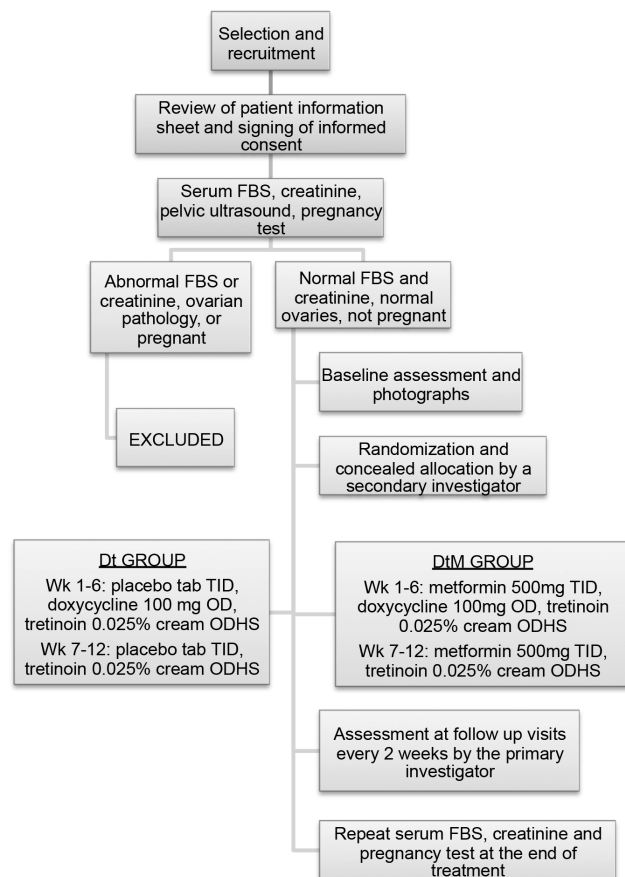
OBJECTIVES

This study compares the efficacy and safety of metformin in combination with doxycycline and tretinoin 0.025% cream vs. doxycycline with tretinoin 0.025% cream in the treatment of moderate to severe acne vulgaris. Specifically, it aims to determine and compare the improvement of acne lesions in both treatment groups through the evaluation of the following:

1. The reduction in number of the non-inflammatory, inflammatory and total lesion count, based on the Leeds Acne Lesion Counting System (Appendix A).
2. The improvement of the modified global severity score (Appendix B)
3. The improvement in severity as reported by the patient during each follow up visit using a subjective self-assessment scale (Appendix C).
4. The improvement in the quality of life as reported by the patient using the Dermatology Life Quality Index or DLQI scores (Appendix D and E), before and after treatment.
5. The grading of cutaneous adverse events on the skin of the face (erythema, pain, scaling and dryness) reported by the patient and/or observed by the investigator.
6. Incidence and frequency of systemic adverse events reported by the patient.

STUDY DESIGN AND METHODOLOGY

Figure 1. Schematic diagram of the study design



This is a phase III clinical trial with a double blind randomized controlled study design (Figure 1). Treatment duration for each patient lasted 12 weeks. Two treatment groups were compared: one group (Dt group) received oral doxycycline and tretinoin 0.025% cream for the first 6 weeks, and tretinoin 0.025% cream alone for the next 6 weeks; the other group (DtM Selection and recruitment Review of patient information sheet and signing of informed consent Serum FBS, creatinine, pelvic ultrasound, pregnancy test Abnormal FBS or creatinine, ovarian pathology, or pregnant EXCLUDED Normal FBS and creatinine, normal ovaries, not pregnant Baseline assessment and photographs Randomization and concealed allocation by a secondary investigator DtM GROUP Wk 1-6: metformin 500mg TID, doxycycline 100mg OD, tretinoin 0.025% cream ODHS Wk 7-12: metformin 500mg TID, tretinoin 0.025% cream ODHS Dt GROUP Wk 1-6: placebo tab TID, doxycycline 100 mg OD, tretinoin 0.025% cream ODHS Wk 7-12: placebo tab TID, tretinoin 0.025% cream ODHS Assessment at follow up visits every 2 weeks by the primary investigator Repeat serum

FBS, creatinine and pregnancy test at the end of treatment 4 of 31 group), received oral metformin and doxycycline, and tretinoin 0.025% cream for the first 6 weeks, and oral metformin and tretinoin 0.025% cream for the next 6 weeks. Oral doxycycline was discontinued 6 weeks into the treatment for both groups, in concordance with the guidelines that recommend that the effects of oral antibiotics in acne vulgaris can usually be observed in 6 weeks.³ Metformin was given at a dose of 1500 mg/day to the DtM group for 12 weeks, the same regimen given in the study by Kolodziejczyk¹³ that achieved significant decrease in acne scores.

Subject Selection and Recruitment

Patients selected for this study were both male and female, aged 16 to 40 years old, diagnosed with moderate to severe acne by the primary investigator, with a global severity score of 2 to 4 (moderate to severe). Recruitment and evaluation of subjects was done at the dermatology outpatient department of a tertiary hospital. It commenced in February 2012, and ended in September 2012. Exclusion criteria were those with history of tetracycline hypersensitivity, diabetes mellitus, renal, cardiac and hepatic disease, alcoholism, serious infection, severe diarrhea or vomiting, fever, poor oral intake, conditions predisposing to tissue anoxia, and females with pregnancy or polycystic ovaries.

Once assessed as suitable to participate in the trial, the patient was asked to read the information sheet (Appendix F) and sign the informed consent (Appendix G). Legal representatives of those aged 18 and below were asked to sign the consent form as well. Baseline fasting blood glucose and serum creatinine were acquired prior to the beginning of treatment. Female patients underwent a pregnancy test, and a transvaginal/transrectal ultrasound done by a licensed OB-Gynecology sonologist, to rule out pregnancy and polycystic ovaries. Patients with abnormal fasting blood glucose or serum creatinine, pregnancy, or polycystic ovaries, were excluded from the study and referred to a medical internist or an obstetrician-gynecologist, respectively, for appropriate management.

Females who fulfilled the inclusion criteria were informed of the harms and risks of pregnancy for the duration of the study. They were advised on the recommended contraception methods (i.e. abstinence, natural rhythm method).

Demographic profiles and the following baseline data were recorded in a data collection sheet (Appendix H):

1. Weight in kg
2. Height in cm
3. Body mass index (BMI)
4. Non-inflammatory, inflammatory and total lesion count using the Leeds' Acne Lesion Count System (Appendix A), and the corresponding modified global severity score (Appendix B)
5. Fasting blood glucose (FBS) level
6. Serum creatinine level
7. For female patients, results of the transvaginal/transrectal ultrasound and pregnancy test.
8. DLQI scores

Study Methods and Data Collection

The sample size was computed based on the mean difference in total number of lesions from a previous study,¹⁴ reported as 0.3014, and a mean difference estimated at 0.55 for the current study. Seventeen (17) subjects were included in each group to detect a statistically significant clinical response between lesion counts, with a power of 80% and $\alpha=0.05$ level of significance. Patients were assigned a study number in the order that they were recruited, and assigned to either of the 2 treatment groups using computerized block randomization (Microsoft Excel Version 12.0: RAND and SORT functions) by a secondary investigator.

Sealed envelopes, prepared and given to the patients by the secondary investigator, were labeled according to the week these were supposed to be opened. Patients were instructed to open a designated envelope for each week, and to take the capsules at bedtime and the tablets 1-2 hours after meals. Metformin 500mg/tablet was titrated in 500 mg increments to the full dose of 1500 mg in the first three days in order to lessen gastrointestinal side effects. The placebo tablets given to the Dt group were titrated the same way.

The envelopes given to the DtM group contained the following:

Weeks 1-6:

Day 1: 1 tablet of metformin 500mg/tab, 1 capsule of doxycycline 100mg/cap

Day 2: 2 tablets of metformin 500mg/tab, 1 capsule of doxycycline 100mg/cap

Days 3-42: 3 tablets of metformin 500mg/tab, 1 capsule of doxycycline 100mg/cap

Weeks 7-12:

Days 43-84: 3 tablets of metformin 500mg/tab

The envelopes given to the Dt group contained the following:

Weeks 1-6:

Day 1: 1 capsule of doxycycline 100mg/tab, 1 placebo tablet

Day 2: 1 capsule of doxycycline 100mg/tab, 2 placebo tablets

Days 3-42: 1 capsule of doxycycline 100mg/tab, 3 placebo tablets

Weeks 7-12:

Days 43-84: 3 placebo tablets

In addition, for both treatment groups, tretinoin 0.025% cream was applied thinly over the entire face nightly, and a mild facial soap was used twice daily. The patients, as well as the primary investigator who assessed them at baseline and during their follow up visits, were blinded to the treatment being given. The following data were recorded at every follow up visit, scheduled at week 2, 4, 6, 8, 10 and 12 from the beginning of treatment:

1. Weight in kg
2. BMI
3. Non-inflammatory, inflammatory and total lesion count using the Leeds' Acne Lesion Count System (Appendix A), and the corresponding modified global severity score (Appendix B).
4. Subjective Self-Assessment Score of Change in Acne Severity (Appendix C) as reported by the patient, to be graded (0) worsened, (1) no change, (2) mild improvement, (3) moderate improvement, or (4) marked improvement
5. Systemic adverse events to treatment as reported by the patient.
6. Cutaneous adverse events of erythema, pain, scaling and dryness of the skin over the face, reported by the patient and observed by the clinical investigator, assessed as none (0), mild (1), moderate (2), and severe (3)
7. DLQI score on the 12th week of treatment.

Photographs were taken at baseline and at every follow up visit, 1 foot away from the subject, using a Panasonic Lumix camera (Model DMC-LX3, macro mode setting, ISO 100). Full anterior, right and left views of the face were photographed. Patients were instructed to contact the primary investigator immediately if any adverse events are experienced during the course of treatment. Serum fasting blood sugar and creatinine, and pregnancy test for females, were repeated upon completion of the treatment. Data collected were securely recorded, filed, and protected from inadvertent or inappropriate access by the primary investigator.

Statistical Analysis

Descriptive analysis for continuous variables (age and body mass index), were performed using central tendency measures of mean and standard deviation. For bivariate analysis of categorical variables such as gender, Fisher's exact test was used.

Shapiro-Wilk test for normality was done to determine if parametric or non-parametric tests are indicated for each variable.

The Student's t-test was used to analyze the difference between groups for age and FBS at baseline and at the end of treatment. The Mann-Whitney U test was used to determine the difference between groups for BMI and DLQI at baseline and at the end of treatment. The mean reduction rates from baseline to each follow up visit of non-inflammatory, inflammatory, and total lesion counts for each group were compared using the Mann-Whitney U test to determine if a statistically significant difference would be demonstrated. The mean scores for every follow-up visit of global severity and subjective self assessment, and the mean DLQI scores at baseline and at the end of treatment, were compared using the Mann-Whitney U test as well.

For cutaneous adverse events, the grading of erythema, pain, scaling and dryness, between the two groups were compared using the Mann-Whitney U test. Incidence and frequency of systemic adverse events between the two groups were determined, and the Mann-Whitney U test was again used to compare the frequency of systemic adverse events per follow-up visit between the two groups.

Unless otherwise noted, all results are expressed as the mean $\pm$ standard deviation. For all parameters, a p-value of <0.05 was deemed statistically significant.

An intent-to-treat analysis was performed, with the study population defined as those assigned to their respective treatment arms and received the dispensed medications, regardless of outcome, whether the subjects completed the study or not. For missing data and withdrawals, it was assumed that there was no change or improvement in the variable of interest after the period of non-compliance.

All data were analyzed using Stata Version 10.0.

Efficacy end points

Primary efficacy end points were the mean reduction rates of non-inflammatory, inflammatory and total acne lesion counts at each follow up visit until the end of treatment. Secondary efficacy end points were the modified global severity score, subjective self-assessment score, and the DLQI, on the 12th week of treatment.

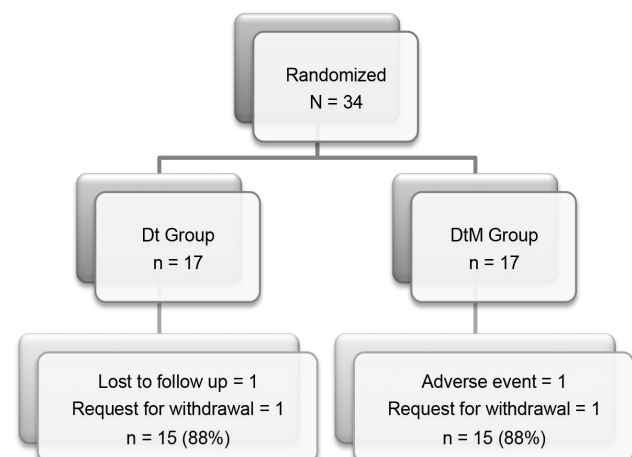
Safety end points

Safety end points were the comparison between the two treatment groups of the following parameters: (1) mean grades of erythema, pain, scaling and dryness at each follow-up visit, as a result of topical application of tretinoin cream; and (2) the incidence and frequency of systemic adverse events as reported by the patient (e.g. diarrhea, nausea, vomiting, abdominal pain)

RESULTS

Subjects

Figure 2. Summary of subject disposition



A total of 35 patients were recruited in this study, but one female patient was excluded due to high fasting blood sugar, and was referred to Endocrine Medicine. None of the female patients had pregnancy or polycystic ovaries. The intent-to-treat population included all the randomized subjects who were dispensed the study medication.

The remaining 34 patients were randomized into two groups (Figure 2): 17 subjects in the DtM group, and 17 subjects in the Dt group.

In the DtM group, only 15 patients (88%) completed the study. One patient acquired furunculosis on the face during the 8th week of treatment. The patient admitted to have been habitually picking on his lesions. Culture of wound discharge showed heavy growth of *Staphylococcus epidermidis*. The patient was treated with first generation cephalosporins for a week, which resolved the condition. The second patient dropped out after the 4th week of treatment because of time conflict with school.

In the Dt group, only 15 patients (88%) completed the study. One patient had to go home to the province, and requested to be pulled out of the study after the second week of treatment. The second patient was lost to follow-up after baseline assessment, and could not be contacted.

Discontinuation rates between the DtM group and the Dt group had no statistical difference, having the same number of patients completing the study.

Both treatment groups were comparable as to their demographic characteristics of age and gender, with no statistically significant difference (Table 1).

Table 1. Demographic characteristics of the study population treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt)

Parameter	DtM group (N=15)	Dt group (N=15)	p value
Age in yrs (mean ± SD)	19.65 ± 4.09	19.82 ± 3.94	0.8989 ^a
Gender			
Female [n (%)]	8 (47.06)	6 (35.29)	0.364 ^b
Male [n (%)]	9 (52.94)	11 (64.71)	

^aStudent's t-test; ^bFisher's exact test

Baseline and final scores of body mass index and fasting blood sugar between the two groups (Table 2) showed no statistical difference as well.

Table 2. Mean baseline and final body mass index, fasting blood sugar, and serum creatinine of study populations treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt)

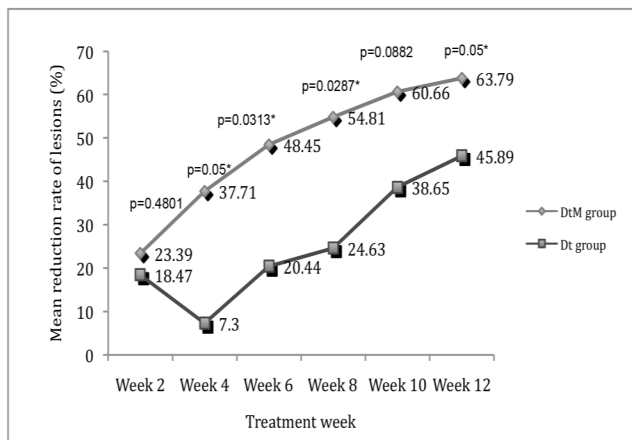
Parameter	DtM group (mean ± SD)	Dt group (mean ± SD)	p value
Baseline body mass index (kg/m ²)	20.27 ± 2.43	19.16 ± 2.30	0.1431 ^a
Final body mass index (kg/m ²)	19.15 ± 5.49	19.18 ± 2.58	0.3262 ^a
Baseline fasting blood sugar (mmol/L)	4.99 ± 0.35	4.85 ± 0.39	0.2700 ^b
Final fasting blood sugar (mmol/L)	4.79 ± 0.49	4.69 ± 0.50	0.6192 ^b

^aMann-Whitney U test; ^bStudent's t-test

Efficacy Outcomes

The mean reduction rate of non-inflammatory (comedonal) lesions at each follow up visit (Figure 3), showed consistent improvement when compared to baseline. For the 4th week of treatment, there was a statistically significant difference in the mean reduction rate between the DtM (37.71%) and the Dt (7.30%) group, with a p-value of 0.05. On the 6th treatment week, the DtM group showed a statistically significant higher mean reduction rate as well (48.45%) compared to the Dt group (20.44%) with a p-value of 0.0313. A statistically significant benefit was still demonstrated in the 8th treatment week in the DtM group (54.81%) over the Dt group (24.63%) with a p-value of 0.0287. On the 12th week of treatment, the DtM group again showed a significant statistical benefit (63.79%) compared to the Dt group (45.89%) with a p-value of 0.05.

Figure 3. Mean reduction rate of non-inflammatory (comedonal) lesions in patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at baseline and treatment weeks 2, 4, 6, 8, 10 and 12



*p-value ≤ 0.05

Both treatment groups showed improvement in the mean reduction rate of inflammatory and total lesion counts on all follow up visits compared to baseline. There was no statistically significant difference in the reduction rates of both treatment groups during all follow up visits with p-values greater than 0.05 (Figure 4 and 5).

Figure 4. Mean reduction rate of inflammatory lesions in patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at baseline and treatment weeks 2, 4, 6, 8, 10 and 12

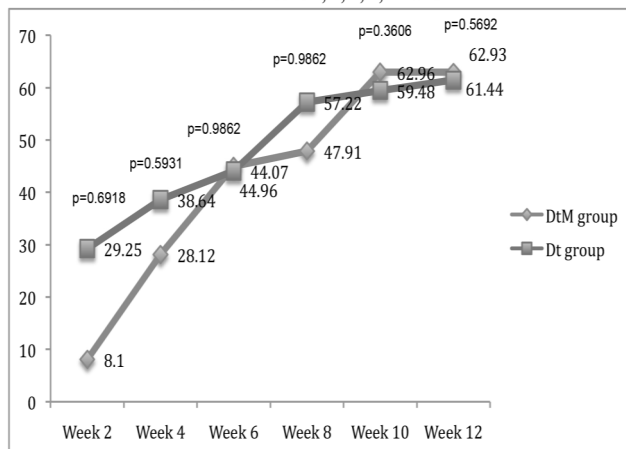
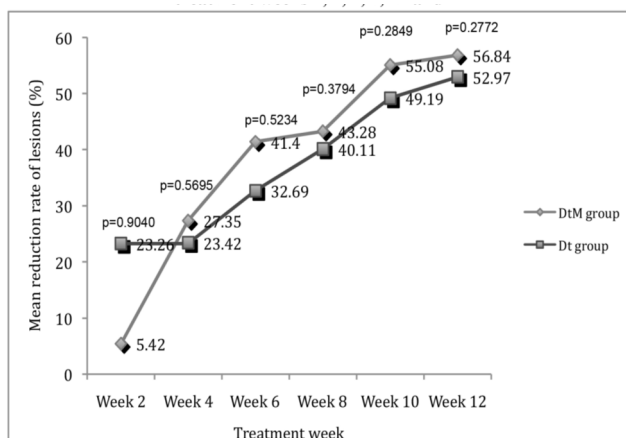


Figure 5. Mean reduction rate of total acne lesions in patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at baseline and treatment weeks 2, 4, 6, 8, 10 and 12



Both groups showed improvement in their modified global severity and subjective self-assessment scores (Figure 6 and 7) at each follow up visit and their DLQI (Table 3) at the end of treatment. Comparison of the two treatment groups showed no statistical difference.

Figure 6. Mean global severity score for patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at baseline and treatment weeks 2, 4, 6, 8, 10 and 12

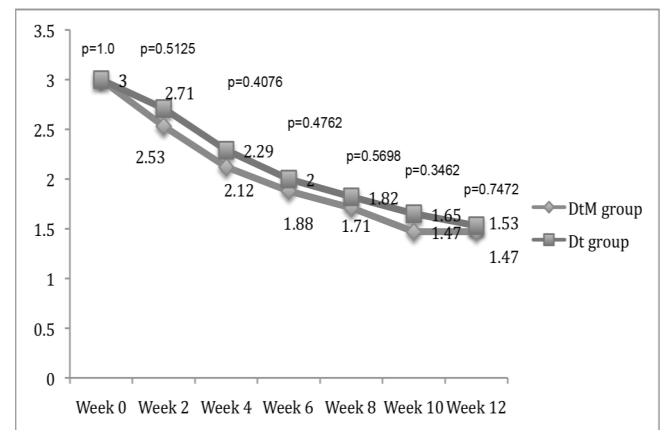


Figure 7. Mean subjective self-assessment score for patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at baseline and treatment weeks 2, 4, 6, 8, 10 and 12

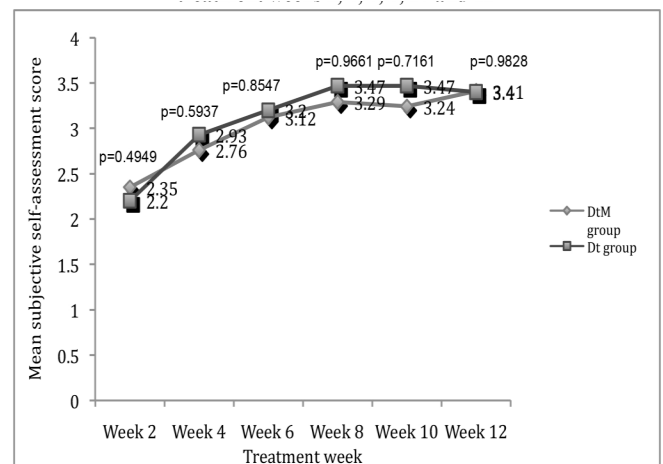


Table 3. Mean DLQI scores of patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at baseline and at the end of treatment

Parameter	DtM group (mean ± SD)	Dt group (mean ± SD)	p value ^a
Baseline DLQI score	12.76 ± 5.76	9.88 ± 6.29	0.1662
Final DLQI score	2.33 ± 1.84	3.13 ± 2.42	0.3762

^aMann Whitney U test

Safety Outcomes

Erythema scores (Table 4) for the DtM group showed a decreasing trend from the 2nd (1.0) to the 12th week (0.38) of treatment. The Dt group, on the other hand, showed a fluctuating but a general decrease in trend of erythema scores, increasing from the 2nd week (0.75) to the 4th week (0.81) of treatment, going back down on the 6th week (0.75), further decreasing up to the 10th week (0.44), and increasing on the 12th week (0.69). Between the two treatment groups, there was no observed statistical difference in erythema scores for all follow-up visits.

Pain scores (Table 4) also showed a decreasing trend in both groups. The DtM group score decreased from the 2nd week (0.38) to the 8th week (0.06). The Dt group pain scores decreased from the 2nd week (0.19) to 4th week (0.13), and maintained scores until the 8th week of treatment. There was no report of pain in all subjects beginning at the 10th week of treatment. No statistical difference was observed in the pain scores between the DtM and Dt groups for all follow-up visits.

Table 4. Mean erythema and pain count of patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at treatment weeks 2, 4, 6, 8, 10 and 12

	Mean erythema count			Mean pain count		
	DtM Group (mean ± SD)	Dt Group (mean ± SD)	p value ^a	DtM Group (mean ± SD)	Dt Group (mean ± SD)	p value ^a
Week 2	1.0 ± 0.63	0.75 ± 0.93	0.2961	0.38 ± 0.62	0.19 ± 0.40	0.3816
Week 4	0.81 ± 0.40	0.81 ± 0.91	0.7566	0.19 ± 0.40	0.13 ± 0.34	0.6318
Week 6	0.63 ± 0.62	0.75 ± 0.86	0.8053	0.13 ± 0.34	0.13 ± 0.34	1.0
Week 8	0.50 ± 0.63	0.56 ± 0.73	0.8814	0.06 ± 0.25	0.13 ± 0.34	0.5506
Week 10	0.38 ± 0.50	0.44 ± 0.73	0.9280	0	0	-
Week 12	0.38 ± 0.13	0.69 ± 0.95	0.5117	0	0	-

^aMann-Whitney U test

The mean scaling count (Table 5) in the DtM group showed a decreasing trend from the 2nd (0.56) to the 10th week (0.138), maintaining values up to the 12th week (0.138) of treatment. The Dt group showed decreasing scores from the 2nd week (0.25) to the 6th week (0.06), increasing on the 8th week (0.25), decreasing on the 10th week (0.13) and maintaining the same 13 of 31 score on the end of treatment (0.13). Between the two groups, no significant statistical difference was observed.

For the DtM group, the mean dryness count (Table 5) showed a decreasing trend until the end of treatment. For the Dt group, mean scores showed a decreasing trend until the 6th week of treatment. There was an increase in the mean dryness score on the 8th week of treatment, and the mean score went back to baseline on the 12th week of treatment. Comparing the mean dryness count between the DtM and Dt group showed no statistically significant difference.

Table 5. Mean scaling and dryness count of patients treated with doxycycline+tretinoin+metformin (DtM) and doxycycline+tretinoin (Dt) at treatment weeks 2, 4, 6, 8, 10 and 12

	Mean scaling count			Mean dryness count		
	DtM Group (mean ± SD)	Dt Group (mean ± SD)	p value ^a	DtM Group (mean ± SD)	Dt Group (mean ± SD)	p value ^a
Week 2	0.56 ± 0.73	0.25 ± 0.45	0.2058	0.38 ± 0.62	0.25 ± 0.45	0.6304
Week 4	0.38 ± 0.50	0.19 ± 0.54	0.1471	0.38 ± 0.50	0.25 ± 0.58	0.3123
Week 6	0.19 ± 0.40	0.06 ± 0.25	0.2927	0.31 ± 0.48	0.06 ± 0.25	0.0746
Week 8	0.19 ± 0.40	0.25 ± 0.45	0.6738	0.13 ± 0.34	0.31 ± 0.60	0.3449
Week 10	0.138 ± 0.34	0.13 ± 0.34	1.0	0.19 ± 0.54	0.31 ± 0.60	0.4055
Week 12	0.138 ± 0.34	0.13 ± 0.34	1.0	0.06 ± 0.25	0.25 ± 0.45	0.1506

^aMann-Whitney U test

The most frequent systemic adverse event noted (Table 6) in the DtM group was diarrhea, reported by 10.64% of patients. Nausea was experienced by 8.51% of patients in the DtM group, and in 1.20% in the Dt group. Diarrhea, headache, vomiting and abdominal pain were adverse events found only in the DtM group.

Loss of appetite (4.40%) was the most frequent systemic adverse event noted in the Dt group. None of the patients in the DtM group complained of this.

Table 6. Incidence of systemic adverse events reported per treatment group

Adverse effect	DtM group [n(%)]	Dt group [n(%)]
Diarrhea	10 (10.64)	0 (0)
Nausea	8 (8.51)	1 (1.20)
Vomiting	3 (3.19)	0 (0)
Headache	4 (4.26)	0 (0)
Dizziness	2 (2.13)	2 (2.20)
Loss of appetite	0 (0)	4 (4.40)
Heartburn	2 (2.13)	1 (1.20)
Abdominal pain	2 (2.13)	0 (0)

The frequency of systemic adverse events (Table 7) on the 2nd week of treatment was statistically higher in the DtM group (68.75%) compared to the Dt group (18.75%), with a p-value of 0.006. On the 4th week of treatment, the DtM group still showed a statistically higher frequency (50%) of systemic adverse events, while the Dt group demonstrated no systemic adverse events (0%), with a p-value of 0.001. On the other hand, there was no statistical difference demonstrated between the two groups for the 6th (DtM group 33.33% vs. Dt group 6.25%) and 8th (DtM group 13.33% vs. Dt group 0%) weeks of treatment with p-values greater than 0.05. No adverse events were reported during the 10th and 12th week for both groups.

Table 7. Frequency of systemic adverse events per follow up visit

Week	DtM group [n(%)]	Dt group [n(%)]	p value
2	11 (68.75)	3 (18.75)	0.006 ^a
4	8 (50)	0 (0)	0.001 ^a
6	5 (33.33)	1 (6.25)	0.072
8	2 (13.33)	0 (0)	0.226
10	- ^b	- ^b	-
12	- ^b	- ^b	-

^ap-value ≤ 0.05 ; ^bno reported systemic adverse events

DISCUSSION

Acne occurs in the pilosebaceous unit, composed of the sebaceous glands, rudimentary hair and a wide follicular canal lined by the stratified squamous epithelium.³ For years, the four key pathogenetic factors that have been recognized include follicular epithelial hyperproliferation and resultant follicular plugging; excess sebum; inflammation; and the presence and activity of *Propionibacterium acnes*.¹⁵ Follicular epithelial hyperproliferation and follicular plugging leads to formation of non-inflammatory lesions known as comedones. Excessive sebum production and chemotaxis triggered by hypercolonization of sebaceous ducts by *Propionibacterium acnes*, stimulate inflammation of the pilosebaceous unit, producing the inflammatory lesions of papules, pustules, nodules, and cysts.¹⁵

The pathogenesis of acne involves complex and multifactorial processes. Despite many research studies done on acne, its exact pathogenesis is still not completely understood. New developments in its pathogenesis are continuously being discovered to develop better treatment strategies.

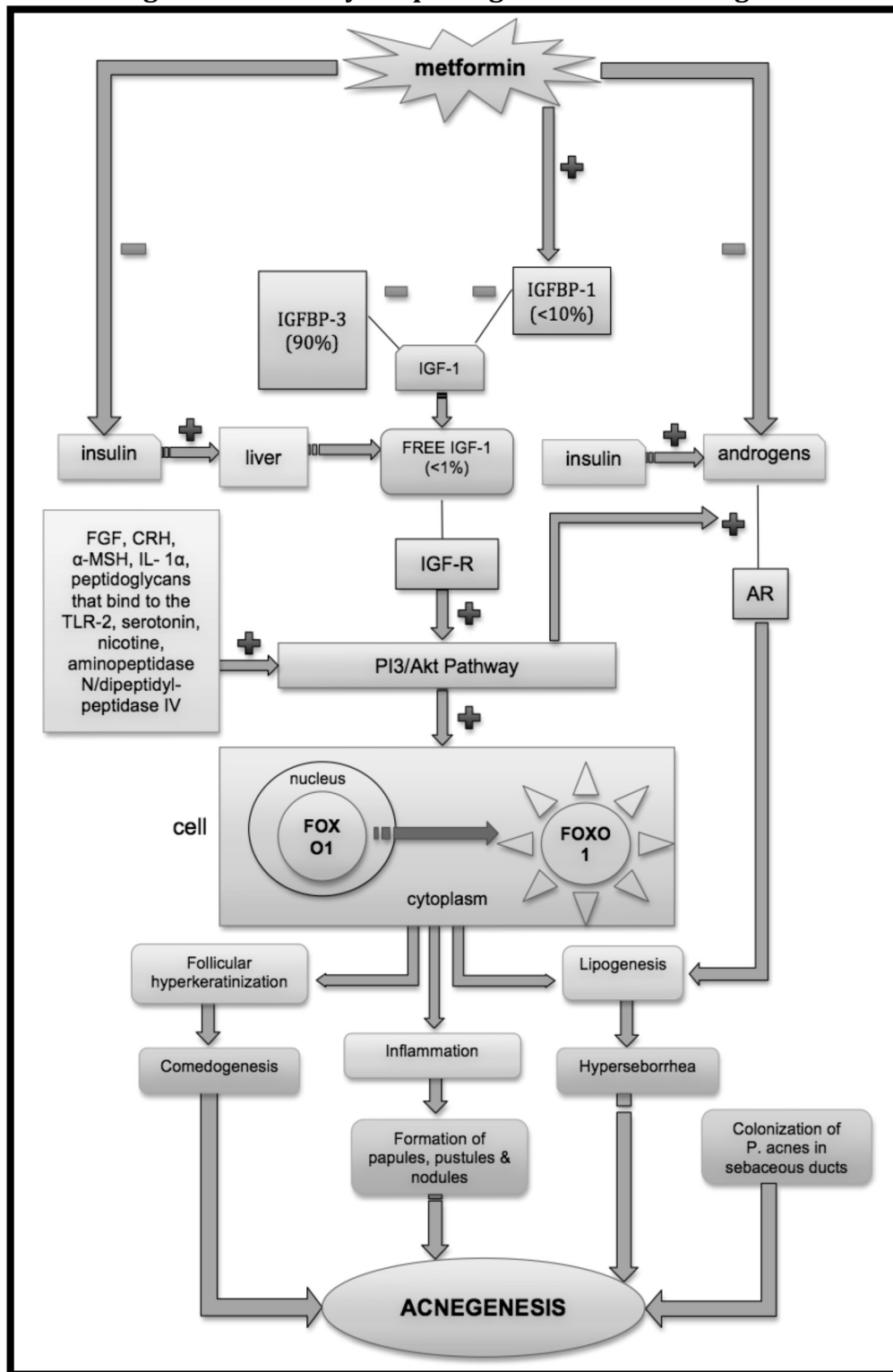
Androgen plays a crucial role in the pathogenesis of acne. The interaction of androgen other biological factors, including growth factors, are

required for the normal development, growth and differentiation of the pilosebaceous unit.¹⁶ The sebaceous gland has been shown to express the necessary enzymes for the biosynthesis of testosterone from circulating dehydroepiandrosterone sulfate (DHEA-S) and subsequent conversion of testosterone to 5 α -dihydrotestosterone (DHT).¹⁷ Testosterone and DHT form complexes with the nuclear androgen receptors, which are expressed in the basal cell layer of the sebaceous glands and in the keratinocytes lining the outer root sheath of hair follicles. The androgen-receptor complex then interacts with DNA in the nuclei of sebaceous gland cells to regulate genes involved in cell growth and lipid production.¹⁸ Increased DHT may act on infundibular keratinocytes, leading to abnormal hyperkeratinization,¹⁹ which is the most crucial initial event in the development of acne lesions. The retention hyperkeratosis in the follicular infundibulum and sebaceous duct leads to occlusion, blocking the outward flow of sebum secretion, resulting in the formation of non-inflammatory micro-comedo which is the initial lesion seen in acne. The trapped sebum and shed cells promote bacterial proliferation, immune reactions and inflammation, resulting in the development of inflammatory lesions.³

Several studies have shown that metformin treatment decreases androgen levels,²⁰ or levels of DHEA-S and testosterone.²¹ The decrease in the androgen levels, the crucial hormone for the hyperkeratosis and lipogenesis, may, therefore, explain the beneficial effect of metformin in decreasing the manifestation of the non-inflammatory lesions of acne, which are the comedones.²¹

The complex pathogenesis of acne may also be explained at the level of genomic regulation (Figure 8). Recent studies by Melnik^{22,23} claim that acneigenic stimuli converge in the phosphoinositol-3 kinase (PI3K)/Akt/FoxO1 signal pathway. Various growth factors and acneigenic stimuli activate the PI3K/Akt signal transduction. Activated kinase Akt triggers phosphorylation of FoxO1, promoting export into the cytoplasm from the nucleus. It is hypothesized that the deficiency of transcription factor FoxO1 in the nucleus underlies all pathogenic pathways of acne. This results to derepression of target genes and activation of nuclear receptors that trigger acneigenesis by 3 pathways: First is by activating androgen receptors located on sebaceous glands and ducts, leading to hyperseborrhea. Second is by activating antimicrobial peptides, matrix metalloproteinases, & other inflammatory mediators, resulting to formation of papules, pustules and nodules. Third is by regulating key genes of cell cycle control, triggering follicular hyperkeratinization and comedogenesis.

Figure 8. Pathways of pathogenesis of acne vulgaris



(IGFBP-3, insulin-like growth factor binding protein-3; IGFBP-1, insulin-like growth factor binding protein-1; IGF-1, insulin-like growth factor-1; IGF-R, insulin-like growth factor receptor; AR, androgen receptor; PI3/Akt, phosphoinositol-3/Akt kinase; P. acnes, Propionibacterium acnes; FGF, fibroblast growth factor; CRH, corticotrophin releasing hormone; α -MSH, α -melanocyte-stimulating hormone; IL-1 α)

Insulin and insulin-like growth factor-1 (IGF-1) are some of the acneogenic stimuli that upregulate P13K/Akt signaling. The homology of insulin and IGF-1 allows one to bind to the receptor of the other. Insulin, therefore, also binds to the insulin-like growth factor-1 receptor (IGF-1R), explaining the significant overlap in signal transduction. Insulin also directly stimulates hepatic secretion of IGF-1 by the liver, and increases serum androgens¹⁶ through biosynthesis. IGF-1 and its receptors are strongly expressed in the epidermis, sebocytes and suprabasal cells of sebaceous ducts.^{24,25} IGF-1 thereby directly regulates seborrhea and lipogenesis, and cell differentiation that facilitates follicular hyperkeratinization. Interestingly, a study by Rebecca et al²⁶ found higher glucose levels in acne patients compared to healthy controls. This relative hyperglycemia may also stimulate secretion of insulin.

Metformin treatment has been shown to decrease serum levels of IGF-1 and insulin.^{20,21} This in turn, also decreases the hyperandrogenemia that results from the action of insulin on androgen biosynthesis (Figure 8). These findings elucidate further the regulatory effect of metformin in the process of lipogenesis, seborrhea and hyperkeratinization. This is an additional explanation for the decrease in the non-inflammatory lesions noted in this study.

The free or unbound IGF-1 is the active component involve in the P13K/Akt pathway. Only less than 1% of IGF-1 circulates unbound in the serum. Ninety percent is bound to insulinlike growth factor binding protein-3 (IGFBP-3), and less than 10% is bound to IGFBP-1, -2, -4, -5 and -6.²⁴ Any factor that would increase serum IGFBPs would then decrease circulating IGF-1, the magnitude of which will be dependent on the type of IGFBP that is increased. Metformin has been shown to increase IGFBP1 levels, decreasing free circulating IGF-1, and downgrading acneogenesis.²⁷

The role of *Propionibacterium acnes*, the predominant microorganism in acne, in the transformation of non-inflammatory acne lesions to inflammatory ones, is well recognized. Studies have suggested that sebum represents a growth substrate for *P. acnes* proliferation.²⁸ The microcomedo with its trapped sebum becomes filled with *P. acnes*, whose cell wall and biological byproducts are chemoattractant and proinflammatory. Cell-mediated immune responses and activation of the complement system and humoral responses have been shown to be involved in the process.³ As a result, inflammatory

cells surround the follicle, diffuse through the follicular wall, and produce enzymes that disrupt the follicular wall.¹⁴ The movement of sebum into the dermis is also highly inflammatory.³

Systemic antibiotics such as the tetracyclines (tetracycline, minocycline, doxycycline and lymecycline) suppress the growth of *P. acnes* and have been widely used for the treatment of moderate to severe inflammatory acne.³ In this study, doxycycline was used for both treatment groups, Dt and DtM. It is expected, therefore, that both treatment groups will show decrease in the inflammatory lesions due to the suppression of *P. acnes* colonization. Metformin does not have antibacterial effects and its beneficial effects in the management of acne, as explained previously, involve a different pathway. This may explain why there was no statistically significant difference in the reduction of inflammatory lesions, as shown in this study.

At the level of genomic regulation as explained by Melnik²², there are other growth factors and acneogenic stimuli that activate the P13k/Akt/FOXO1 signaling pathway which can lead to inflammation. Among these factors are fibroblast growth factor, corticotrophin releasing hormone, α -melanocyte-stimulating hormone, interleukin 1 α , peptidoglycans that bind to the toll-like receptors 2, serotonin, nicotine, and aminopeptidase N/dipeptidylpeptidase IV. The binding of these factors is not inhibited by metformin, thus explaining the absence of its additional benefit in decreasing the inflammatory lesions.

Another explanation is that several external and uncontrolled environmental factors may influence the inflammatory pathway. Recently, it has been shown that hyperglycemic food and milk consumption, smoking, and stress,²⁶ may also trigger insulin/IGF-1 signaling or the phosphorylation of FoxO1 itself.

In this study the group that received metformin also had the standard treatment of doxycycline and tretinoin. It was not compared to a placebo but to a group that received the standard treatment as well. This may explain why both groups had improvement in patient's subjective self-assessment score of change in acne severity and DLQI scores with no statistical difference.

The pathophysiology of acne indicates that inflammatory lesions originate from comedones or non-inflammatory lesions. Therefore, the positive

effect of metformin in decreasing the non-inflammatory lesions should ultimately have an appreciable benefit on inflammatory lesions as well. It is possible that a longer treatment duration may have provided better results.

Adverse Events of Treatment

In this study, mild to moderate erythema, scaling, and dryness were noted during the entire treatment duration for both groups, but with a general trend of decreasing severity upon continued use. These manifestations, together with pain, are known common cutaneous adverse effects of tretinoin, which was part of the treatment regimen of both groups. Interestingly, pain was not reported by any of the subjects in both treatment groups at the 10th and 12th weeks of treatment. These findings support general observations that these predictable side effects of topical retinoids are temporary, peaking within the first month of use and diminishing thereafter.²⁹

The group that received metformin significantly had a higher incidence and frequency of systemic adverse events, with diarrhea, nausea and headache being the most common. Although diarrhea has been reported as a common side effect upon intake of doxycycline³⁰, the lack of subjects reporting diarrhea in the Dt group suggests that there is no additive side effect from doxycycline in this study. On the other hand, nausea, headache and heartburn have also been reported as common side effects of doxycycline³⁰. Therefore, an additive effect by doxycycline cannot be ruled out.

Gastrointestinal side effects of metformin may be addressed by intake of the drug after meals and by slower titration of dose. The patients who reported these symptoms claimed that they were not consistent or persistent, resolving spontaneously within the first month without need for treatment. The levels of fasting blood sugar of all subjects who received metformin remained normal by the end of treatment. Metformin is thus a well-tolerated and safe oral medication that can be used in the treatment of moderate to severe acne.

Limitations and Recommendations

The primary limitation of this study is its short treatment duration. For future studies, a longer treatment time might be able to detect a statistically significant difference in the reduction of inflammatory and total lesion counts, and improvement of subjective and objective scores.

Other variables, proven or anecdotal, that have been reported to affect the course and severity of acne, such as smoking, psychosocial stress, hours of sleep, and diet in relation to glycemic index, may also be considered in the assessment of baseline characteristics.

CONCLUSION

In the treatment of moderate to severe acne vulgaris, the addition of metformin to oral doxycycline and tretinoin 0.025% cream, offers significant additional benefit in the reduction of non-inflammatory acne lesions.

The inflammatory and total acne lesion counts, and scores of global severity, subjective self-assessment, and DLQI improved in both treatment groups, with no significant difference at the end of the 12-week period.

The cutaneous side effects of erythema, pain, scaling, and dryness of the skin, attributed to be due to tretinoin cream, were noted in both treatment groups, but were self-limited. The metformin-treated group had more non-cutaneous side effects of diarrhea, nausea, and headache, but these were mild, and likewise self-limited. These adverse effects did not warrant the discontinuation of treatment.

DISCLOSURE

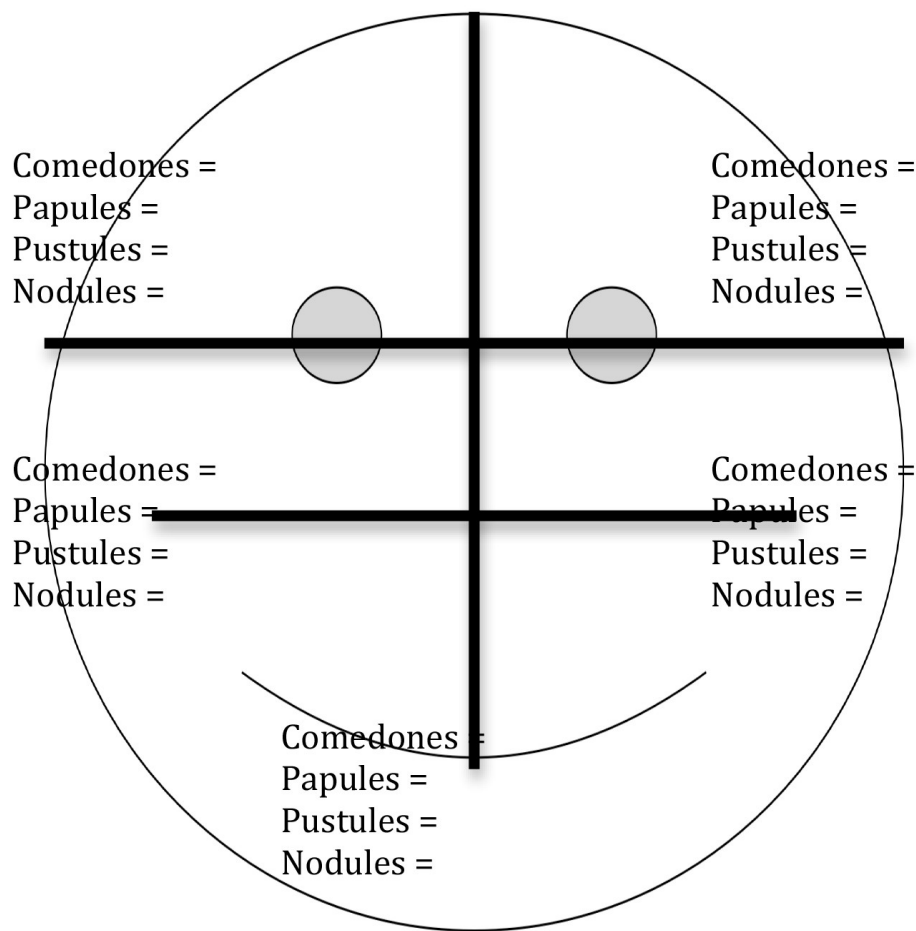
This is an investigator-initiated, self-funded research trial. There is no potential conflict of interest.

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Appendix A
Leeds Acne Lesion Counting System



Area	Lesion Type			
	Comedones	Papules	Pustules	Nodules
Right forehead				
Left forehead				
Right cheek				
Left cheek				
Chin				
Total lesions				

Appendix B
Modified Global Severity Score

Global Severity Score	Description	Simplified Classification
1	Comedones are the main lesions. < 10 papules and pustules $\pm$ < 6 nodules	Mild
2	<10 papules & pustules $\pm$ $\geq$ 6 nodules or 10-40 papules & pustules $\pm$ < 6 nodules	Moderate
3	10-40 papules & pustules $\pm$ $\geq$ 6 nodules or 40-100 papules & pustules $\pm$ < 6 nodules	Moderately Severe
4	40-100 papules & pustules $\pm$ $\geq$ 6 nodules or >100 papules & pustules or Nodulocystic	Severe

Appendix C
Subjective Self-Assessment Score of Change in Acne Severity

0	Worsened <i>Lumala</i>
1	No change <i>Walang pagbabago</i>
2	Mild improvement <i>May konting pagbabago</i>
3	Moderate improvement <i>May katamtamang pagbabago</i>
4	Marked improvement <i>Malaki ang pagbabago</i>

APPENDIX D
Dermatology Life Quality Index (DLQI)

Indeks sa kalidad ng Pamumuhay sa may Sakit sa Balat (IKPAS)
DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Layunin ng pagtatanong ito na masukat ang epekto ng sakit sa balat sa iyong pamumuhay sa **NAKARAANG LINGGO**. Paki-tsek (✓) ang isang sagot sa bawat tanong. Anumang impormasyong nakalathala rito ay mananatiling lihim at ang iyong duktore lamang ang nakaaalam.

The Aim of this questionnaire is to measure how much your skin problems has affected your life **OVER THE LAST WEEK**. Please tick ☐ box for each question.

1. *Sa nakaraang linggo, gaano **kakati, kahapdi o kasakit** ang iyong balat?*
Over the last week, how **itchy, sore, painful or stinging** has your skin been?
☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala
☐ Very much ☐ A lot ☐ A little ☐ Not at all
2. *Sa nakaraang linggo, **nahihiya** ka ba dahil sa iyong balat?*
Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?
☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala
☐ Very much ☐ A lot ☐ A little ☐ Not at all
3. *Sa nakaraang linggo, gaanong abala ito sa iyong pag-**shopping** o **pamamalengke** o **gawaing bahay**?*
Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home or garden**?
☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala
☐ Very much ☐ A lot ☐ A little ☐ Not at all
4. *Sa nakaraang linggo, naaapektuhan ba ang iyong **pananamit** nito?*
Over the last week, how much has your skin influenced the **clothes** you wear?
☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala ☐ Walang kinalaman
☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant
5. *Sa nakaraang linggo, paano naapektuhan ang iyong gawaing **pansosyal** o **panlibangan** (halimbawa, panunood ng sine) ng dahil sa iyong sakit sa balat?*
Over the last week, how much has your skin affected any **social** or **leisure** activities?
☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala ☐ Walang kinalaman
☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant
6. *Sa nakaraang linggo, paano ka nahirapan sa paglaro ng anumang **isport** o pag-gawa ng anumang **ehersisyo** ng dahil sa iyong sakit sa balat?*
Over the last week, how much has your skin made it difficult for you to do any **sport**?
☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala ☐ Walang kinalaman
☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant
7. *Sa nakaraang linggo, napigilan ka bang makapag**trabaho** o makapag **aral** ng dahil sa iyong sakit sa balat?*
Over the last week, has your skin prevented you from **working** or **studying**?
☐ Oo ☐ Hindi ☐ Walang kinalaman
☐ Yes ☐ No ☐ Not relevant

Kung “Hindi” ang sagot, sa nakaraang linggo, paano nakaapekto sa iyong **trabaho** o **pag-aaral** ang iyong sakit sa balat?

If no, over the last week how much has your skin been a problem at **work** or **studying**?

- ☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala ☐ Walang kinalaman
☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

8. Sa nakaraang linggo, paano naging problema sa iyong **partner** o matalik na **kaibigan** o **kamag-anak** ang iyong sakit sa balat?

Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?

- ☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala ☐ Walang kinalaman
☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

9. Sa nakaraang linggo, paano nagpahirap sa pakikipagtalik (**sex**) ang iyong sakit sa balat?

Over the last week, how much has your skin caused any **sexual difficulties**?

- ☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala ☐ Walang kinalaman
☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

10. Sa nakaraang linggo, paano naging problema ang **paggamot** ng iyong sakit sa balat, halimbawa, dahil sa idimulot nitong kalat sa bahay o sa pagkaubos ng iyong oras na iyong inuukol dito?

Over the last week, how much of a problem has the **treatment** for your skin been, for example, by making your home **messy**, or by taking up your time?

- ☐ Sobra-sobra ☐ Sobra ☐ Medyo ☐ Wala ☐ Walang kinalaman
☐ Very much ☐ A lot ☐ A little ☐ Not at all ☐ Not relevant

Paki-tsek kung nasagot mo ang lahat ng tanong. Maraming salamat!

Please check your have answered EVERY question. Thank you.

Appendix E Dermatology Life Quality Index Scoring System

The scoring of each question is as follows:

Very much / <i>Sobra-sobra</i>	Scored 3
A lot / <i>Sobra</i>	Scored 2
A little / <i>Medyo</i>	Scored 1
Not at all / <i>Wala</i>	Scored 0
Question unanswered / <i>Walang kinalaman</i>	Scored 0
Question 7: “prevented work or studying” / “nakaapekto sa iyong trabaho o pag-aaral”	Scored 3

The sum of the score of each question results to a DLQI maximum score of 30 and a minimum of 0. A higher score means there is more impairment of the quality of life.

Interpretation of DLQI Scores

0-1 = no effect at all on patient's life

2-5 = small effect on patient's life

6-10 = moderate effect on patient's life

11-20 = very large effect on patient's life

21-31 = extremely large effect on patient's life

Correlation of Sterno-Aortic Distance with FEV1/FVC and FEV1 in Patients with COPD*

Regina Cristina Q. Mangada, M.D.¹

Alfredo F. Villarosa, M.D.²

Carolina A. Drilon, M.D.³

ABSTRACT

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is defined by the Global Initiative for Chronic Obstructive Lung Disease as "a disease state characterized by airflow limitation that is not fully reversible". Several qualitative and quantitative CT parameters have been studied in diagnosing patients with COPD. The clinical application of CT scan in quantitative assessment of the morphologic features of airways in patients with COPD has been subjects of numerous investigations. However, studies on sterno-aortic distance as a parameter in assessing morphologic feature of COPD in CT scan has been rare. Hence, this study aims to find a correlation of sterno-aortic distance with pulmonary function test in patients with COPD.

Methods: Eighty-one patients diagnosed with COPD who underwent chest CT scan and PFT within the period of one year were included. Sterno-aortic distance were measured and correlated with PFT results and severity of COPD.

Results: Most patients enrolled were males with average age of 64 ± 11 years old. Most of these patients are categorized as mild COPD with 38 % and severe COPD with 38% of the total population. Patients classified as moderate COPD comprise 24 % of the total population. There is significant weak inverse correlation between sterno-aortic distance and PFT results, FEV1 ($r = -0.419$, $p < 0.001$) and FEV1/FVC ($r = -0.322$, p value of 0.003). There is a significant correlation derived between sterno aortic distance and severity of COPD ($\rho = 0.88$, p -value of <0.001).

Conclusions: Sterno-aortic distance is a valuable parameter in patients with COPD as well as its severity.

Keywords: chronic obstructive pulmonary disease, COPD, sterno-aortic distance, chest CT scan

*From the Department of Education, Training and Research, Philippine Heart Center

¹ - Investigator

² - Adviser

³ - Chairman, Division of CV Radiological Sciences

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined by the Global Initiative for Chronic Obstructive Lung Disease as "a disease state characterized by airflow limitation that is not fully reversible". The airflow limitation is caused by a combination of small airway remodeling and emphysema with varying distribution and severity (1). COPD is characterized by decreased maximal expiratory airflow, hyperinflation, and gas trapping. The physiologic abnormalities are caused by a combination of loss of elastic recoil and narrowing of small airways (2).

COPD consist of heterogenous group of disorders i.e. chronic bronchitis, emphysema and peripheral airway disease. The diagnosis of COPD is conventionally based upon spirometry (3). Spirometry (meaning the measuring of breath) is the most common of the pulmonary function tests (PFTs), measuring lung function, specifically the amount (volume) and/or speed (flow) of air that can be inhaled and exhaled. Spirometry is an important tool used for generating pneumatographs, which are helpful in assessing conditions such as asthma, pulmonary fibrosis, cystic fibrosis, and COPD (4). Total lung capacity is the amount of air that remains in the lungs at the end of maximal inspiration. In patients with COPD, the greatest increase in total lung capacity is seen in patients with severe emphysema.

Several qualitative and quantitative CT parameters have been studied in diagnosing patients with COPD. In a study done by Arakawa et al., parameters such as tracheal index, thoracic cage ratio, thoracic cross sectional area and sterno-aortic distance were used in patient with COPD. Their study showed that these parameters are significantly correlated with FEV1/FVC ratio.

The clinical application of CT scan in in quantitative assessment of the morphologic features of airways in persons with COPD has been subjects of numerous investigations. Some imaging indices used are wall area, percentage, luminal area, and bronchial wall attenuation (5). It has been said that patients with COPD develop an increase in their thoracic cage diameter as the disease progresses. Parameters such as thoracic cage ratio and tracheal index have been studied in the past. However, studies on sterno-aortic distance as a parameter in assessing morphologic feature of COPD in CT scan has been rare. Hence, this study aims to find a correlation of

sterno-aortic distance with pulmonary function test in patients with COPD.

RESEARCH QUESTION

What is the diagnostic value of sterno-aortic distance in the diagnosis of COPD?

OBJECTIVES

General Objective:

1. To determine the correlation between sterno-aortic distance with FEV1/FVC and FEV1 in patients with COPD.

Specific Objectives:

1. To determine the sterno-aortic distance of patients with COPD.
2. To determine the FEV1/FVC and FEV1 among patients with COPD.
3. To determine the correlation between sterno-aortic distance with FEV1/FVC and FEV1 among patients with COPD.

HYPOTHESIS

Null:

There is no correlation between sterno-aortic distance and with FEV1/FVC and FEV1 in patients with COPD.

Alternative:

There is a correlation between sterno-aortic distance FEV1/FVC and FEV1 in patients with COPD.

METHODOLOGY

1. Study Design

This study is a cross-sectional study of cases of patents diagnosed with COPD and underwent CT scan and pulmonary function test.

2. Time Frame/Setting

This study was conducted at the Philippine Heart Center, enrolled subjects are those who have chest CT scan and PFT from January 2007 to December 2014.

3. Study Population

a. Inclusion Criteria

1. 40 years old and above
2. Patients who are diagnosed with COPD who underwent both CT scan and PFT with a maximum interval of one year

b. Exclusion Criteria

1. Patients whose CT scan was done outside the PHC
2. Clinically unstable patient
3. Patients with other chest CT scan findings i.e bullae, mass, pleural effusion
4. Patients with CT scan findings involving both upper lungs
5. patients with coexisting bronchiectasis, asthma, PTB, and bronchogenic cancer

c. Sample Size

Using NCSS-PASS 13 software, the minimum sample size requirement was estimated to be at least 61 patients base on the following parameter: Alpha = 5%, Power = 80%. Correlation coefficient between sterno-aortic distance and pulmonary function test in patients with COPD is -0.351 based on the paper of Arakawa et al (6).

4. Study Maneuver

Patients who fulfilled the inclusion criteria were included in this study. Patient's age, gender, height, and weight were recorded. The sterno-aortic distance was obtained thru their CT scan. The sterno-aortic distance was measured from the posterior surface of the sternum to the anterior margin of the aorta at the level of the carina (Appendix A). Two radiologists reviewed the CT scan images independently. These radiologists were blinded to the results of the pulmonary function tests (FEV1/FVC and FEV1). Measurements obtained by these radiologists were analyzed using t-test to check for interobserver variability. These measurements were correlated with the FEV1/FVC and FEV1 of patients who underwent pulmonary function tests results using Pearson correlation. These measurements were correlated with the severity of COPD according to the GOLD criteria.

Description of Data Collection

The results of chest Computed Tomography scan and pulmonary function test of patients diagnosed with COPD were reviewed. Eighty-one patients from January 2007 to December 2014 who qualify the inclusion criteria were included.

Inter-observer Variability

Two trained radiologists reviewed the Computed Tomography images. They were blinded to the pulmonary function test results. The data was then analyzed using t-test to check for interobserver variability.

Measurement of sterno-aortic distance

Coronal and sagittal images of chest CT scan were used. The steno-aortic distance was measured from the posterior surface of the sternum to the aorta at the level of the carina (Appendix A).

Pulmonary function test

The pulmonary function test results of patients who qualify in this study were reviewed. The presence of COPD was confirmed using FEV1/FVC ratio while the severity of COPD was measured using FEV1. These values were correlated and used to stratify the patients according to the GOLD criteria of COPD.

Description of Outcomes

The outcome of this study is to determine the correlation of sterno-aortic distance with severity of COPD.

5. Data Analysis

Data analysis will be done using Strata SE version 13. Quantitative variables were summarized and presented as mean and SD while qualitative variables were tabulated and presented as frequency and percent distribution. Correlation between sterno-aortic distance and pulmonary function test (FEV1 and FEV1/FVC) in patients with COPD were determined and tested using Pearson's product moment correlation and was graphically presented in a scatter plot. A p-value Of 0.05 was considered statistically significant.

WAIVER OF CONSENT

This study was conducted in compliance with the ethical principles of Declaration of Helsinki. Prior to the study invitation, the protocol was reviewed and approved by the Philippine Heart Center Ethics Review Board (PHC IERB). The investigator requested for the waiver of consent for the following reasons: difficulty of obtaining individual authorization since the last contact with research subjects.

The risk to the subject's privacy is minimal and no sensitive information was obtained. The investigator ensured that the subject's anonymity is maintained. The data were obtained by review of PFT records from the Pulmonary Department and CT scan images from the Radiology Department. There was no patient data that revealed.

DEFINITION OF TERMS

- 1. COPD** - chronic obstructive pulmonary disease
- 2. Sterno-aortic distance** - distance from the posterior surface of the sternum to the anterior margin of the aorta at the level of the carina.
- 3. FEV1** - volume of air exhaled in one second after full inspiration
- 4. FEV1/FVC**- the percentage of the vital capacity which is expired in the first second of maximal expiration

REVIEW OF RELATED LITERATURE

Chronic obstructive pulmonary disease (COPD) is one of the leading most common cause of morbidity and mortality worldwide. The increasing incidence of exposure to its risk factors has placed a burden on our society and economy.

COPD is defined by the American Thoracic Society as an abnormal permanent enlargement of the air spaces distal to the terminal bronchioles with destruction of their walls. COPD is a heterogeneous group of disorders including emphysema, peripheral airways disease and chronic bronchitis. In the past, diagnosis of COPD has been greatly dependent on spirometry. However, In the recent years, with the advent of computed tomography (CT), there has been increasing interest in diagnosing patients with COPD using computed tomography parameters.

Several qualitative and quantitative CT parameters have been studied in diagnosing patients with COPD. In a study done by Arakawa et al., parameters such as tracheal index, thoracic cage ratio, thoracic cross sectional area and sterno-aortic distance are used in patients with COPD. Their study showed that these parameters are significantly correlated with FEV1/FVC ratio.

This study aims to determine if there is a significant correlation between sterno-aortic distance and COPD. Sterno-aortic distance is the distance between the posterior surface of the sternum to the anterior margin of the aorta at the level of the carina. Even though sterno-aortic distance has been used in some study, studies on this parameters has yet to show any finite correlation. In a study by Gupta et al., which included 40 patients with COPD, various quantitative parameters were used. These include tracheal index, sterno-aortic distance, thoracic cage ration and thoracic cross sectional area, which are said to be suggestive of hyperinflation in COPD. Their study showed that sterno-aortic distance greater than 4 cm were found in 5 patients with COPD. The same study also showed that these parameters had significant correlation with age, duration of illness, pack years of smoking and dyspnea scale, as well as with FEV1 and FEV1/FVC ratio.

The use of CT scan recently has been the pivot point in assessment of airway morphologic features in patients with COPD. A study by Yamashiro et al., showed that bronchial peak wall attenuation in CT correlates with significantly with expiratory air-flow obstruction in patients with COPD. The change in airway characteristic is believed to be due to chronic remodeling. This is one parameter in which the use of CT scan was used in determining the presence of COPD, by using bronchial wall attenuation.

In diagnosing patients with COPD, CT scan is an important and indispensable tool for its evaluation. COPD patients with emphysema on CT scan have a higher BODE index (body mass index, airflow obstruction, dyspnea and exercise performance) while they have lower inspiratory capacity to total lung capacity than those without emphysema. Hence the addition of CT scan in to pulmonary function tests serves as a valuable tool in obtaining the diagnosis.

Another study done by Mostafa and Mostafa, 50 male patients with average age of 40 to 60 years old were examined for COPD using HRCT. Male subjects were included in accordance to a study done by Wang et al., which showed that the prevalence of emphysema is higher in man than in woman. Their study showed that 33 out of 50 patients (66%) were found to have a sterno-aortic distance of 4 cm or more.

Heagan and Kolbenstvedt also reported that sterno-aortic distance was measured in CT sections at the carinal level if 4 cm or more is characteristic for emphysema.

Amidst all the data collected from different studies, reports on correlations between the sterno-aortic distance to COPD have been rare. Since COPD patients usually presents with emphysematous changes such as increase in AP diameter of the thorax, degree of hyperinflation, or changes in lung attenuation, the increase in sterno-aortic distance is said to be present in patients with COPD.

RESULTS

TABLE 1. Demographics of patients with COPD included in this study.

Characteristics n=81	Mean $\pm$ SD or n(%)
Age	64.42 $\pm$ 11.19
Gender	M= 62 (77) F= 19 (23)
Height (cm)	163.19 $\pm$ 7.71
Weight (kg)	62.83 $\pm$ 15.07
COPD	
Mild	31 (38)
Moderate	19 (24)
Severe	31 (38)

The demographic characteristics of patients with COPD included in this study is shown in Table 1. In this study, 81 records of patients who are diagnosed with COPD and underwent chest CT scan within one year interval were included and reviewed. There were 62 (77 %) male subjects and 19 (23 %) females. Most patients have an average age of 64 years old. The subjects have a mean height of 163.19 cm and mean weight of 62.83 kg. Most of these patients are categorized as mild COPD with 38 % and severe COPD with 38% of the total population. Patients classified as moderate

COPD comprise 24 % of the total population. Two radiologists reviewed the records of these 81 patients.

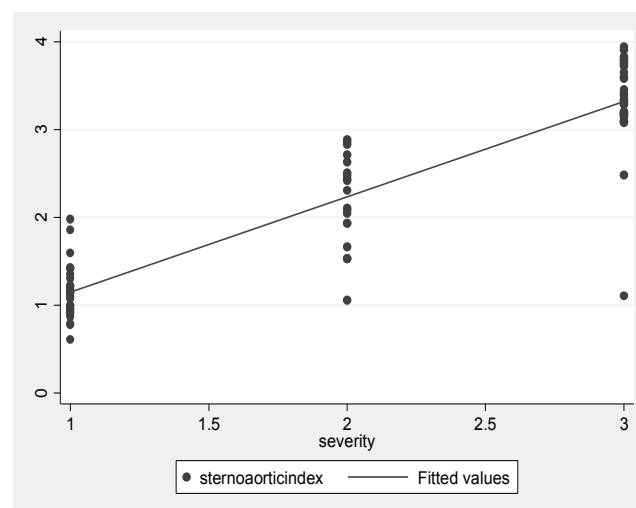


Figure 1 shows that sterno-aortic distance have a significant correlation with the severity grading of COPD by GOLD criteria (r of 0.3 - 0.4). The greater is the sterno-aortic distance, the more severe is the obstructive process.

TABLE 2. Correlation coefficient of sterno-aortic distance in CT scan with PFT

PFT Parameters	Sterno-aortic Distance	
	r	p
FEV1/FVC	-0.322	0.003
FEV1	-0.419	< 0.001

$P = < 0.05$ will be considered significant

r = Pearson's correlation

Table 2 shows that there is significant weak inverse correlation between sterno-aortic distance and FEV1 ($r = -0.419$, p value of <0.001). There is likewise a significant weak inverse correlation between sterno-aortic distance and FEV1/FVC ($r = -0.322$, p value of 0.003).

TABLE 3. Correlation of sterno-aortic distance by CT scan with severity of COPD

COPD	ρ	p
Severity	0.88	<0.001

$p = < 0.05$ will be considered significant

r = Spearman's rho correlation

Table 3 shows that there is a strong direct significant correlation between sterno-aortic distance and severity of COPD ($\rho = 0.88$, p-value of <0.001).

Table 4. Interobserver variability of the sterno-aortic distance measured by the two radiologists.

	Radio 1 Mean $\pm$ SD	Radio 2 Mean $\pm$ SD	p - value
Sterno-aortic distance	2.24 $\pm$ 1.06	2.23 $\pm$ 1.05	0.316

In assessing for interobserver variability between the two radiologists who reviewed the chest CT scan of the subjects, a t-test was done (Table 3). A value of 0.316 was obtained indicating that there is no significant variability between the measurements of the two observers.

DISCUSSION

This study showed that measurement of the sterno-aortic distance could be potentially used as a quantitative CT index in patients with COPD. It showed significant weak inverse correlation with FEV1 ($r = -0.419$, $p < 0.001$) and FEV1/FVC ($r = -0.322$, $p < 0.003$), which are parameters of obstructive pulmonary disease in pulmonary function test. These findings showed that as we observe an increase in the sterno-aortic distance, there is likewise a corresponding decrease in the FEV1 and FEV1/FVC values, which are measures of an obstructive process. This is in congruent with the study of Gupta et al., that various CT parameters such as tracheal index, sterno-aortic distance, thoracic cage ratio and thoracic cross sectional area are said to be suggestive of hyperinflation in COPD. (3) These findings are also in agreement with the paper done by Arakawa et al., which showed that parameters such as tracheal index, thoracic cage ratio, thoracic cross sectional area and sterno-aortic distance are used in patient with COPD. However, their study showed that these parameters are significantly correlated with FEV1/FVC ratio. (6)

This study also showed a strong direct significant correlation between sterno-aortic distance and severity of COPD ($\rho = 0.88$, p-value of <0.001). The study Mostafa and Mostafa showed a correlation between HRCT and spirometry in patients for early diagnosis of emphysema, however, their study revealed moderate correlation. (7) Nakano, et al., made an attempt to correlate HRCT of emphysema and spirometry that with moderate and showed significant correlation. (7)

These findings can be explained by the fact that changes in the thoracic diameter were observed in patients with chronic obstructive disease of the airways. This can be attributed to the fact that as an increase in the severity of the obstructive disease, an increase in the degree of hyperinflation of the thorax is likewise noted. (3)

Emphysema causes abnormal enlargement of the airspaces distal to the terminal bronchiole, hence, airway wall obstruction is evident. This causes air trapping and subsequent hyperinflation of the lungs. (7)

In addition, this study was able to establish the range of sterno-aortic distance of patients with COPD. As shown in Figure 1, the higher the severity of COPD, the wider is range of sterno-aortic distance. This can be attributed to a relatively difference in the degree of compensation of the thorax to the degree of air trapping in hyperinflation.

The subjects in this study were those patients who underwent chest CT scan and pulmonary function test within one year period from 2007 to 2014. One of the limitations in this study would be the fact that the CT images from this period would be compressed and reconstructed, hence, this would limit the radiologist from obtaining optimal sterno-aortic distance measurement. Also the distribution of patients should be more equal and groups the severity should be well-represented since in this study most patients included were patients with mild and severe COPD, both occupying 38% of the entire population of subjects. A follow up should have been also done in these patients so the progression of the disease can be evaluated. This can give a stronger and more predictive diagnostic value.

In order to obtain a more specific CT parameter that can give predictive value to COPD, a comparison with sterno-aortic distance and other CT parameters such as tracheal index, thoracic cage ratio and bronchial wall attenuation can be an area for further research.

CONCLUSION

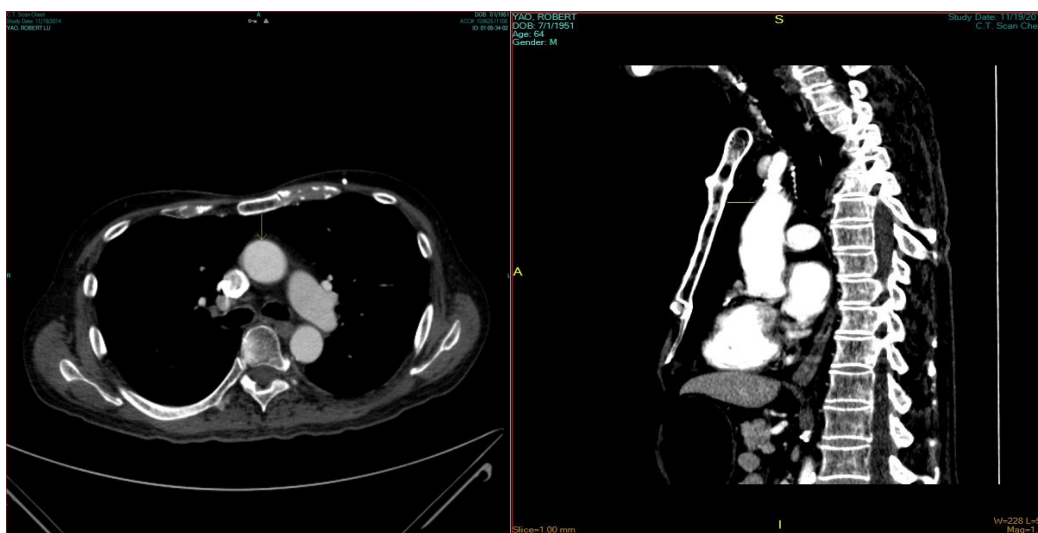
This study shows that sterno-aortic distance is a valuable index in evaluating patients with COPD. The sterno-aortic distance measured in chest CT scan showed significant weak inverse correlation when correlated with FEV1 and FEV1/FVC, and that there is a strong direct significant relationship between sterno-aortic distance and severity of COPD.

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APPENDIX

APPENDIX A. MEASUREMENT OF THE STERNO-AORTIC DISTANCE AT THE LEVEL BEFORE THE FIRST BRANCH OF THE AORTIC ARCH.



A Double-Blind Randomized Controlled Trial of the Efficacy of 5% Tea Tree Oil Cleanser versus Mild Cleanser in the Treatment of Mild-Moderate Facial Seborrheic Dermatitis

Catherine C. Mendoza, MD¹
Deanna Moreno, MD²
Ma. Luisa Cuizon, MD²
Ma. Angela M. Lavadia, MD, FPDS³

ABSTRACT

Background: Seborrheic dermatitis is a chronic, relapsing, inflammatory disease characterized by erythema, scaling, pruritus over the areas of the scalp, face, ears, sternum and upper back. Tea tree oil is rich in terpene alcohols such as terpinen-4-ol which is thought to be the active germicidal component.

Objective: To determine the efficacy of 5% tea tree oil cleanser in the treatment of mild-moderate facial seborrheic dermatitis and to determine the adverse side effects.

Methods: Forty-five patients with clinical signs of seborrheic dermatitis were randomly assigned to one of the two treatment groups: mild cleanser and the 5% tea tree oil group. This study was done as a double-blind randomized controlled trial for 4 weeks. The parameters – area involved, erythema, scaling, and Seborrhea Area and Severity Index were taken at baseline and weekly for 4 weeks. At the end of 4 weeks, the difference of the two groups were compared using paired t-test.

Results: After 4 weeks, significant clinical improvement of the area involved, erythema, and scaling and the reduction of Seborrhea Area and Severity

Conclusion: The use of 5% tea tree oil cleanser provides significant improvement in the treatment of mild-moderate facial seborrheic dermatitis with no adverse side effects.

*From the Angeles University Foundation Medical Center (AUFMC), Angeles City, Pampanga

¹Primary Investigator

²Co-authors

³Adviser

Clinical Question

Is 5% tea tree oil cleanser effective in the treatment of mild-moderate facial seborrheic dermatitis?

Tea tree oil, an essential oil, which is clear to pale yellow in color, is distilled from the leaves and terminal branches of *Malaleuca alternifolia*, an Australian tree. Traditionally, it has a wide range of topical applications and is commonly used to treat skin and respiratory infections.

Among the 100 components of tea tree oil, *terpinen-4-ol*, α -pinene and β -pinene, and 1,8-cineol showed the most activity, with minimum inhibitory concentrations and minimum fungicidal concentrations. An in vitro antifungal activity of tea tree oil against 26 strains of dermatophyte species, 54 yeasts, and 22 different *Malassezia furfur* strains, showed that the lipophilic yeast, *M. Furfur* seemed to be most susceptible to tea tree oil. MIC values between 556.2 and 4,450.0 $\mu\text{g/ml}$ (geometric mean 1,261.5 $\mu\text{g/ml}$) were found against the tested *M. furfur* strains, corresponding to 0.5-0.44% tea tree oil content. These values are far below the usual relatively high therapeutic concentrations of the agent; approximately 5-10% solution or even the concentrated essential oil are used for external treatment.

Seborrheic dermatitis is a chronic, relapsing inflammation of sebum-rich areas of the scalp, face, and trunk. It is commonly aggravated by changes in humidity, changes in seasons, trauma, or emotional stress. The severity varies from mild dandruff to exfoliative erythroderma.

This condition is associated with normal levels of *Malassezia* but an abnormal immune response. Helper T cells, phytohemagglutinin and concanavalin stimulation, and antibody titers are depressed compared with those of control subjects. There is increased sebum production, which may come from its lipase activity—releasing inflammatory free fatty acids—and from its ability to activate the alternative complement pathway. Persons prone to this dermatitis also may have a skin-barrier dysfunction. Various medications may flare or induce seborrheic dermatitis.

The prevalence rate of seborrheic dermatitis is 3-5%, with a worldwide distribution. Dandruff, the mildest form of this dermatitis, is probably far more common and is present in an estimated 15-20% of

the population. It occurs in persons of all races and affects more males than females. It has two peak periods – infancy and adulthood. The adult type is chronic and peaks during the fourth to sixth decade of life.

Clinically, facial seborrheic dermatitis manifests as erythematous, inflamed skin topped with branny or greasy scales. There is accompanying pruritus of variable degree. Distribution follows the oily and hair-bearing areas of the face, such as the forehead, the eyebrows, the lash line, the nasolabial folds, the beard, and the postauricular skin. An extension to submental skin can occur.

The use of mild topical corticosteroids +/- antifungal is still the gold standard. Mild cleanser, an adjuvant to the treatment regimen helps decrease inflammation and helps veer away from the vicious cycle of seborrhoea elicited by the use of harsh soaps commonly used by patients with seborrheic dermatitis. The objective of this study was to determine the efficacy and safety of 5% tea tree oil cleanser in the treatment of mild-moderate facial seborrheic dermatitis compared with mild cleanser as to improvement of area involved, erythema, and scaling and the reduction of the seborrhea area and severity index.

METHODOLOGY

The ethics committee approved the study. Patients were diagnosed clinically based on the location of the lesions, the erythema, scaling, and pruritus. All patients, male and female, twelve years and older, who were systematically well, with no known allergies to tea tree oil and were not taking arsenic, gold, methyldopa, cimetidine, and neuroleptics were invited to enter the study and informed consent was obtained. (*Appendix A*)

Randomization was made through the Research Randomizer. The total number of subjects intended for the study was entered and was divided into 2. Subject was asked to pick a number from 1-140 and was assigned to the set where his/her preferred number fell. The subjects were randomly assigned to receive either 5% tea tree oil cleanser or the vehicle mild cleanser. Subjects were then given their treatment sample by the secondary investigator.

Patients were instructed to wash their face twice a day for 3 minutes before rinsing off with tap water. Male subjects were free to shave but were prohibited

the use of shaving cream, after-shave lotion, toner, or astringents. Female subjects were free to use face powder but were likewise prohibited the use of toner or astringents. The primary investigator and an assistant (blinded) assessed the patients (blinded) at baseline and weekly for 4 weeks based on the Seborrhea Area and Severity Index. (*Appendix B*). Photographic documentations on selected patients were done baseline, and weekly until week 4. (*Appendix D*)

It was determined that a sample size of 45 patients per treatment group would be required to detect a difference of 30% in the proportion of clearance of symptoms and 80% clearance in the 5% Tea Tree Oil Cleanser and 50% clearance in cleanser alone. (Using a power of 80% and $\alpha = 0.05$)

Paired T-test was used to determine the difference between baseline and week 4 of the areas involved, erythema, scaling, and SASI for the 5% tea tree oil and mild cleanser.

Independent T-test was used to determine mean difference in area involved, erythema, scaling and SASI scores between the 5% tea tree oil cleanser and mild cleanser

RESULTS

A total of ninety-five subjects were enrolled in the study, ninety of which finished the four-week period. Sixty-three males and twenty-seven females ranging from 18 to 68 years entered the study. Forty-eight subjects were randomly assigned to the mild cleanser group (A) while forty-seven were randomly assigned to the 5% tea tree oil (B). The mild cleanser group had thirty-five males and ten females. While, the 5% tea tree oil cleanser had twenty-eight males and seventeen females. There were three drop-outs for the mild cleanser group and two for the 5% tea tree oil group. The drop-outs were lost to follow-up. Demographic data are shown in Table I.

Statistically significant improvements were observed in the area involved, erythema and scaling and Seborrhoea Area and Severity Index for both groups.

For the 45 patients using the mild cleanser, the area involved was 3.2 at baseline, and 2.24 after 4 weeks, a 30% reduction. In the 45 patients using the 5% tea tree oil cleanser, the score for the area involved fell from an average of 3.36 at baseline to

1.62 after 4 weeks, a 52% drop in the mean score. (Graph A)

The score for the erythema for the mild cleanser group fell from 3.04 at baseline to 1.96 at week 4. A 36% drop in the mean score. The score for the erythema for the patients using the 5% tea tree oil fell from an average of 3.13 at baseline to 1.02 after 4 weeks. A 67% improvement in the mean score. (Graph B)

In the mild cleanser group, the score was 2.955 at baseline and 1.84 at week 4, while in the 5% tea tree oil, the score for the scaling at baseline was 3.07 and 0.73 at the end of 4-weeks, 38% and 76% drop in the mean score respectively. (Graph C)

The primary objective efficacy variable was the improvement in Seborrhea Area and Severity Index (SASI), the SASI rates both the degree of involvement and severity.

The scores for the Seborrhea Area and the Severity Index were significantly improved in both the mild cleanser and the tea tree oil groups. The score for the mild cleanser at baseline was 10.13 and at week 4 – 4.93, a 51% improvement. The tea tree oil score fell from an average of 10.8 baseline to 1.61 at week 4, an improvement of 85% in the Seborrhea Area and Severity Index. (Graph D)

The difference were likewise calculated to show the mean percentage improvement from the baseline to week 4 for the mild cleanser group and the 5% tea tree oil cleanser group.

The *independent group T-Test for means* was used to test the means of the two independent groups – the mild cleanser and the 5% tea tree oil cleanser, to determine if they are significantly different from one another.

The differences between the mean percentage change, 22.0 for the area involved, 31.0 for the erythema, 38.0 for the scaling and 34.0 for the seborrhoea area and severity index, were statistically significant with 95% confidence level and a P value of less than 0.05. (Table 2)

Tolerance of the 5% tea tree oil was excellent, no adverse reactions were reported by the subjects during the treatment period. No cutaneous adverse reactions were observed during the subsequent follow-ups after the study period.

DISCUSSION

Tea Tree Oil is a distillate, colorless to pale yellow in color with a characteristic strong fragrance attributed to *1,8-cineol* (eucalyptol). It is a complex mixture of over 100 different components, most of which being monoterpenes and sesquiterpene hydrocarbons and their alcohols. *Terpinen-4-ol* is thought to be the active germicidal component. Traditionally, the Bundjalung Aborigines of northern New South Wales were the first to use the leaves of this tree. Tea Tree Oil was named by Captain James Cook when he first visited Australia in the 18th century. In 1923, Dr. Penfold proved that tea tree oil was 13 times stronger than the antiseptic of that time carbolic acid and that it did not burn the skin. And during WW II, tea tree oil was issued to Australian soldiers for use as antiseptics.

Tea tree oil is active against all three categories of infectious organisms: bacteria, viruses and fungi.

A study by KA Hammer et al, published in 2003 investigated the *in vitro* antifungal activity of tea tree oil. It was shown that among the 100 components of tea tree oil, *terpinen-4-ol*, α -*terpineol*, *linalool*, α -*pinene* and β -*pinene*, and *1,8-cineole* showed the most activity, with minimum inhibitory concentrations and minimum fungicidal concentrations. It was concluded that all tea tree oil components, except β -*myrcene*, had antifungal activity.

Another paper by the same authors showed that tea tree oil has both inhibitory and fungicidal properties. Tea tree oil MICs for all fungi ranged from 0.004% to 0.25% and minimum fungicidal concentrations (MFCs) ranged from <0.03% to 8.0%. Time-kill experiments with 1-4 x MFC demonstrated that 3 out of 4 test organisms were still detected 8 hrs post treatment, but not after 24 hours.

With the antifungal evidences of tea tree oil, a randomized, placebo-controlled, double-blinded study was done for the treatment of interdigital tinea pedis with 25% and 50% tea tree oil solution. One hundred fifty-eight patients with tinea pedis were randomized to received either the placebo, 25% or 50% tea tree oil solution. Patients were instructed to apply the solution twice a day for 4 weeks. A marked clinical response was seen in 68% of the 50% tea tree oil group, 72% of the 25% tea tree oil group, and 39% in the placebo group. Mycological cure rate was 64% in the 50% tea tree oil compared to 31% in

the placebo group. Four patients developed moderate-severe dermatitis that improved on stopping the study medication.

Locally, a randomized double blind clinical trial on the efficacy and safety of tea tree oil in the treatment of tinea corporis by Drs. P Nagbuya-Cebrian, E. Morales, J. Dizon showed that tea tree oil 2% cream is effective and safe for the treatment of tinea corporis. It has a comparable efficacy and safety with miconazole 2% cream.

In the study by Satchell AC et al, one hundred twenty-six subjects with mild to moderate dandruff were randomly distributed to receive either the placebo or the 5% tea tree oil shampoo. They were assessed after a four-week period. Those using the 5% tea tree oil shampoo significantly improved. 5% tea tree oil: baseline score 91.0; down to 53.0 after 4 weeks versus placebo: baseline score of 99.7; down to 88.2 after 4 weeks; $P < .001$. Unfortunately, this study was not double-blind.

The antifungal activity of tea tree oil against yeasts (*Candida spp.*) and dermatophytes (*Microsporum spp.* And *Trichophyton spp.*) is reported in the study of KA Hammer et al.. This study documented the ability of tea tree oil to inhibit *Candida albicans* conversion from yeast form to the pathogenic mycelial form. These results, along with the lipophilic nature of the tea tree oil, which enables it to penetrate the skin, makes it suitable for topical use for the treatment of fungal mucocutaneous infections.

The adverse side effects of the use of tea tree oil were mostly of the allergic contact dermatitis. This reaction is a well-documented phenomenon and has been described in several reports since the early 1990's. In a paper published by The University of Western Australia Tea Tree Oil Research Group, they found that "*1,8-cineol* (eucalyptol) which gives eucalypts their characteristic strong fragrance and medicinal properties, was the allergen.". "*Aromadendrene*, α -*terpinene*, *d-limonene*, and *eucalyptol* have been all suggested as primary sensitizers" in a case presented by YM Monthrope and JC Shaw in 2004. In the study done by Cebrian et al, they note "worsening of erythema and pruritus and hyperpigmentation" which "upon discontinuation of the given medicines, reactions spontaneously resolved".

CONCLUSION

This study has shown that 5% tea tree oil cleanser is an effective and safe treatment for mild-moderate facial seborrheic dermatitis.

It is recommended that for the succeeding study, a larger sample population and longer follow-up period for at least 12 months to determine the incidence of recurrence and to determine the mean period of remission.

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TABLES AND GRAPH

Table 1. Demographic Data of the 5% Tea Tree Oil and Mild Cleanser Groups

	MILD CLEANSER	5% TEA TREE OIL CLEANSER
Gender		
Male	35	28
Female	10	17
Age	39.31±9.73	41.02±13.40

Graph A. Change in Area Involved

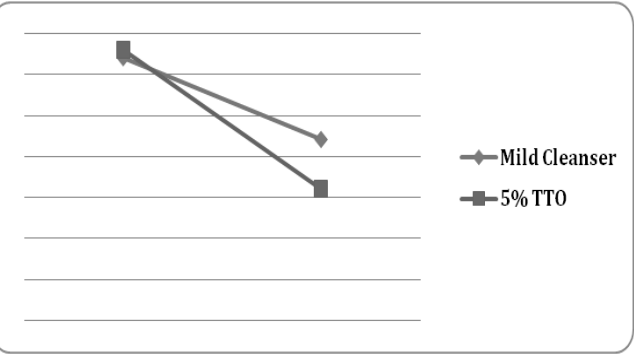


Table A

	MILD CLEANSER	5% TEA TREE OIL CLEANSER
Baseline	3.2±1.32	3.35±1.13
Week 4	2.24±1.22	1.62±0.88
Percentage Mean Score	30%	52%

Graph B. Change in Erythema

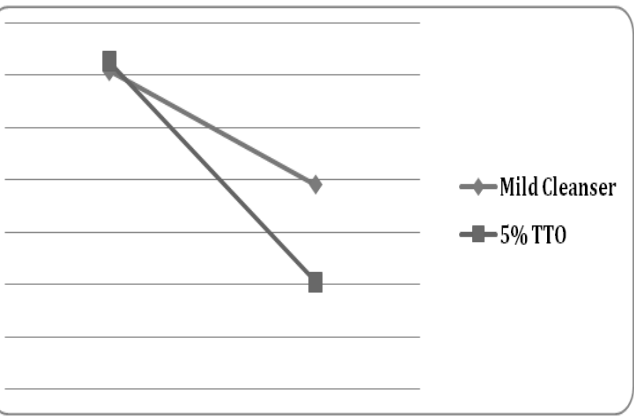


Table B

	MILD CLEANSER	5% TEA TREE OIL CLEANSER
Baseline	3.04±0.63	3.13±0.63
Week 4	1.95±0.74	1.02±0.45
Percentage Mean Score	36%	67%

Graph C. Change in Scaling

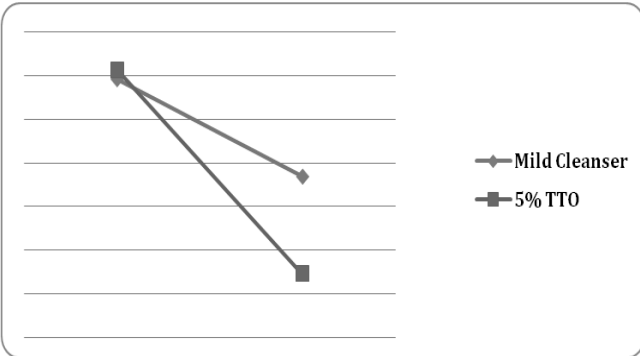


Table C

	MILD CLEANSER	5% TEA TREE OIL CLEANSER
Baseline	2.95±0.74	3.07±0.54
Week 4	1.84±0.90	0.73±0.45
Percentage Mean Score	38%	76%

Graph D. Change in SASI

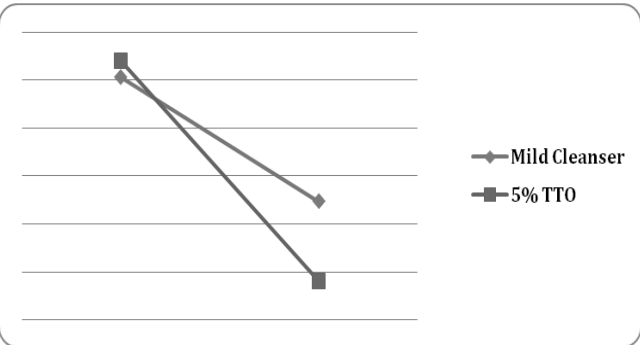


Table D

	MILD CLEANSER	5% TEA TREE OIL CLEANSER
Baseline	10.13±5.34	10.8±4.76
Week 4	4.93±3.40	1.61±1.07
Percentage Mean Score	51%	85%

Mean Difference**Table 2. Percent Improvement in Mean Difference in 5% Tea Tree Oil and Mild Cleanser**

	MILD CLEANSER	5% TEA TREE OIL CLEANSER	DIFFERENCE BETWEEN MEAN PERCENTAGE CHANGE	P-VALUE
Parameters				
Area	30%	52%	22%	.000025
Erythema	36%	67%	31%	.000001
Scaling	38%	76%	38%	.000001
SASI	51%	85%	34%	.000003

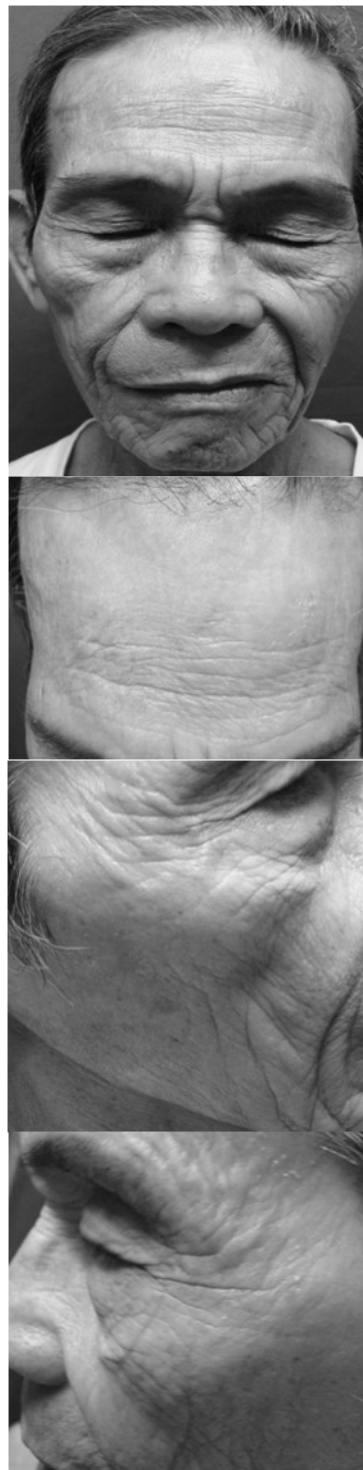
Significant Difference p: < 0.05

APPENDIX A

MILD CLEANSER



BASELINE



WEEK 4

5% TEA TREE



BASELINE



WEEK 4

A Randomized, Double-blind, Controlled Trial on the Efficacy and Safety of 1.5% Carica Papaya Latex Cream Compared to 1% Terbinafine Cream in the Treatment of Localized Tinea Corporis and/or Tinea Cruris*

Marisel P. Abejo, M.D.¹
Vesna Castillo-Yapinchay, M.D., FPDS²
Jesusa Barcelona-Tan, M.D., FPDS²

ABSTRACT

Background: Tinea corporis and cruris are superficial fungal infections mainly caused by dermatophytes. The antifungal effect of carica papaya latex cream has been demonstrated in clinical studies, however, larger population and comparative studies to standard antifungal agents are needed to further strengthen this conclusion. This study determined the efficacy and safety of 1.5% carica papaya latex in cream base as treatment for tinea corporis and/or cruris compared to 1% terbinafine cream.

Methods: This is a randomized, double-blind controlled trial wherein subjects with a clinical diagnosis of tinea corporis or cruris confirmed by microscopy applied terbinafine or carica papaya latex cream twice daily for 6 weeks. The efficacy and safety were assessed 2, 4, and 6 weeks using clinical and mycological cure parameters. The incidence of adverse effects was likewise evaluated.

Results: 90 subjects were randomized, 45 in carica papaya group and 45 in the terbinafine group. Both groups had statistically comparable improvements based on symptoms and mycological cure rates. Adverse events are significantly higher in the papaya latex cream group.

Conclusion: Carica papaya latex cream is as effective as terbinafine cream in the treatment of tinea corporis and/or cruris, but it has a higher incidence of adverse events.

Key words: tinea corporis, tinea cruris, carica papaya latex cream, terbinafine cream

^{*}From the Department of Dermatology, Jose R. Reyes Memorial Medical Center, Manila, Philippines

¹ Resident, Department of Dermatology, Jose R. Reyes Memorial Medical Center

²Consultant, Department of Dermatology, Jose R. Reyes Memorial Medical Center

INTRODUCTION

“Tinea” refers exclusively to dermatophyte infections and are among the most common skin diseases affecting millions of people throughout the world. It is seen commonly in typically hot humid climates and the classic presentation also known as “ringworm” is a lesion with central clearing surrounded by an advancing, red, scaly, elevated border. Its estimated lifetime risk is between 10 and 20 percent. In the epidemiologic surveillance of cutaneous fungal infections in the United States from 1999 to 2002, dermatophytes remain the most commonly isolated fungal organisms.¹ A local study in 2005 revealed that fungal infections ranked as the second leading cause of consultation with a prevalence of 12.98% and among these, tinea corporis comprised 22.63%.² From 1995 to 2004, an analysis of a cross sectional study revealed an estimated 51 million visits for superficial fungal infections of the skin, of which tinea corporis represented 17.4% of the total cases.³ In our institution (Jose R. Reyes Memorial Medical Center, Department of Dermatology), tinea corporis together with tinea cruris consistently played part of the top 15 most common dermatologic diseases from 2001-2012 with an average incidence of 7.6%.

Topical antifungals in the treatment of tinea corporis include most commonly the imidazoles, allylmines and the benzylamines. Terbinafine 1% cream is an antimycotic with a broad-spectrum of anti-fungal activity belonging to the allylamine group. This product interferes with fungal sterol biosynthesis by the inhibition of squalene epoxidase in the fungal cell membrane, which leads to an intracellular accumulation of squalene, resulting in fungal cell death. Twice daily applications of terbinafine 1% cream for one week (followed by three weeks of placebo) was significantly superior, both in terms of mycological cure and effective treatment, to twice daily applications for four weeks of clotrimazole 1% cream when compared six weeks after starting treatment. The cure rates with terbinafine 1% cream were high, with 97% of patients mycologically cured and 90% of patients effectively treated.⁴

Carica papaya tree (from the family *Caricaceae*) have shown great potential against a number of health problems. A study in 2009 demonstrated that treatment with papaya preparation accelerated wound healing and reduced the severity of local inflammation in rats with burn wounds.⁵ The fungistatic effect is the result of degradation of the

polysaccharide constituents of the fungal cell walls. It is the latex from unripe fruits that showed full activity towards both proteins and peptones.⁶⁻⁷

Two years ago, a randomized, double-blind, controlled trial in the efficacy and safety of 1.5% *carica papaya* latex cream compared to 2% ketoconazole cream and vehicle in the treatment of tinea corporis revealed complete resolution which occurred within 14 days with the *carica papaya* group compared to 21 and 28 days for the ketoconazole and placebo group, respectively⁸. A hundred percent therapeutic response (or treatment success) was achieved. A quasi-experiment also revealed that *carica papaya* latex cream exhibits antifungal properties and is a safe and cost-effective alternative as treatment for tinea corporis and/or cruris.

Carica papaya is used as food in most parts of the world. No health hazards have been noted in conjunction with designated therapeutic dosages. The leaves contains tannins and both leaves and roots contain cyanogenic glucosides which form cyanide. Together, at high concentration can cause adverse reactions. Allergic reaction have also been documented. However, in this study latex was extracted from the stems and the fruit itself.⁹⁻¹⁴

The general objective of this study is to evaluate the efficacy and safety of 1.5% *carica papaya* latex cream compared to 1% terbinafine cream in patients with tinea corporis and/or cruris. Specifically, it determined the differences in clinical and mycological cure, incidence of adverse effects and overall efficacy of both topical antifungal medications in comparison.

METHODOLOGY

Patient and Study Design

This study was a randomized, double-blind controlled trial conducted at Jose R. Reyes Memorial Medical Center Department of Dermatology from July 2012 to August 2013. The Institutional Review Board of the hospital approved the trial protocol prior to commencement. This clinical trial was conducted in compliance with Good Clinical Practice and in accordance with the ethical principles of the Declaration of Helsinki.

Eligible patients included male or female aged 18 years old and above with clinical diagnosis of tinea corporis and/or cruris confirmed by microscopy

detection of fungal hyphae on potassium hydroxide (KOH) smear. A clinical diagnosis of tinea corporis was based on the presence of pruritic annular patch with erythematous border, may be topped with scales, papules, pustules and or vesicles. The lesions were localized on areas of the body except the scalp, palms and soles.

The following criteria excluded patients from the study (1) Subjects who took systemic antifungals or corticosteroid therapy during the past month (2) Subjects who applied topical antifungals and corticosteroids during the past 2 weeks (3) Subjects who took or applied other medications like antibacterial and antiviral agents within the past 2 weeks (4) Subjects with associated dermatophytosis of hands, feet, scalp and nails (5) Subjects with extensive lesions not suitable for topical treatment (6) Subjects with known hypersensitivity reactions to carica papaya or allyamines (7) Pregnant or lactating women (8) Immunocompromised patients (9) Unreliable subjects as assessed by the investigator (10) Patients participating in any other investigational drug study during the 4 weeks before the trial begun.

The subjects were oriented and primed on the study's objectives, procedures and outcome measures. Written informed consent forms were provided and signed by the subjects before admission to the study. Appropriate measures were done in taking photographs to conceal patients' identities.

Study Medications

The carica papaya latex creams were prepared at the Department of Industrial Pharmacy, College of Pharmacy, University of the Philippines, Manila. (Appendix 5) The test creams [1.5% carica papaya latex cream and 1% terbinafine cream were stored in identical opaque 15 g containers. The containers are of the same size, color and shape. The creams are also of the same color and consistency without any pertinent, characteristic smell. The containers were labeled A or B by the pharmacist. The same mild soaps were provided by the investigator and were the only ones used by the subjects throughout the duration of the study. Instructions were given to all patients not to apply any other creams, lotions or powder to areas under active treatment and not to use any oral antifungal medications and antihistamines.

Randomization, treatment allocation and blinding

The primary investigator provided a computer generated table of random numbers. The second investigator (a resident doctor) who was blinded to the codes allocated the labeled creams randomly. All were blinded to the treatment allocations.

Clinical Assessment

Demographic data (Appendix 1) were collected and clinical examinations of the patients were done by the primary investigator. The location and size of each lesion were noted and photographs were taken. From the border of each test site, skin scrapings were obtained for potassium hydroxide (KOH) examination. Patients were instructed to apply the cream twice daily for 6 weeks. They were asked to follow up after every 2 weeks for 6 weeks, and were required to bring the container on each follow up visit to check for compliance. During every visit, photographs were taken under standardized settings, skin scrapings were obtained for KOH examination and the patients were assessed by the third investigator (another resident doctor) blinded to the treatment allocation. Adverse reactions such as erythema, burning sensation, stinging or pain, exacerbation of pruritus were recorded by investigators. The codes were only disclosed to the investigators at the end of the study

The primary outcome in this study were the therapeutic response rate at six weeks based on clinical and mycologic scores. Clinical assessment scores were based on the following clinical parameters: scaling, erythema, and pruritus. (Appendix 2) Mycologic scores were based on mycological examination (KOH) done at baseline, every 2 weeks and follow up. Scales were obtained using the blunt side of a blade from an advancing border of the lesion. Ten percent (10%) KOH was used to determine the presence or absence of branched, septated hyphae. (Appendix 3)

Secondary outcomes measured were the patient's assessment of efficacy and adverse events. The efficacy of study medication at the end of the study were assessed by each patient and was scored 0-3, 0 = not effective, 1 = slightly effective, 2 = moderately effective, 3 = markedly effective (Appendix 4). The ultimate response or complete resolution of tinea corporis/cruris was based on the complete mycological clearance until the disappearance of hyphae on repeat KOH examination.

Stopping guidelines

The study was stopped in patients who experienced adverse reactions to the test creams, who had worsening of the skin lesions, if the patient became pregnant, or if the patient voluntarily withdrew from the study. These patients were considered as withdrawals from the study. Those who did not comply to the twice-daily application of the test creams, or those who used other topical or oral medications were also withdrawn from the study. Likewise, both test creams were given 2 weeks maximum for the observation of improvement on the lesions for the study to continue. Dropouts 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

The sample size was computed based on frequency in a population. Population size (for finite population correction factor or fpc) (N):3000. Hypothesized % frequency of outcome factor in the population (p):7.5% $\pm$ 5 and design effect (for cluster surveys-DEFF):1. We aimed at 45 study patients per arm to achieve at least 80% confidence interval.

Data processing and analysis

Statistical analysis was done using Stata v10. Descriptive analysis was done by computing the frequency and central tendency measures of the demographic variables. The association between the proportion of “improved” tests was analyzed using Pearson chi-squared test and Fisher’s exact test. Comparison of means using Student’s t-test and paired t test were also used for the comparisons of results between monitoring. Tests below 0.05 were regarded as statistically significant.

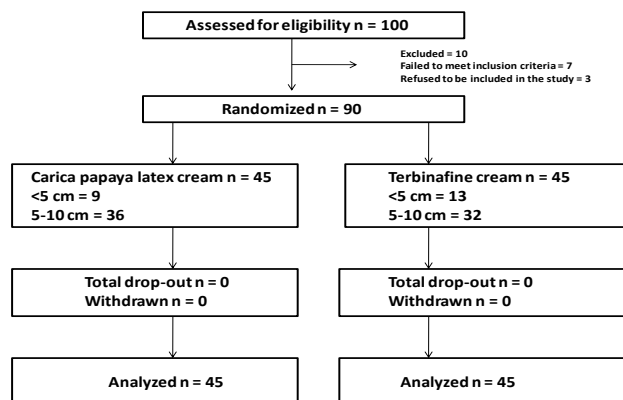


Figure 1. Trial profile showing patient populations

RESULTS

Study Population

One hundred patients were screened and 90 met the inclusion criteria. They were randomized to treatment (carica papaya, n=45) and (terbinafine, n=45) groups. (Figure 1) There were no dropouts nor withdrawals in the study. All 90 patients were included in the full analysis. The baseline characteristics showed no statistically significant differences between the 2 groups based on gender, duration, location and size of lesions. A difference was noted based on age. (Table 1)

There is an increase in reduction rates of all clinical parameters of carica papaya group and terbinafine group throughout 6 weeks of treatment. (Table 2) The adverse events of carica papaya group are higher than terbinafine group. (Table 3) Overall efficacy was shown after 6 weeks of treatment. (Table 4)

Table 1. Demographic profile

VARIABLE	CARICA PAPAYA (N=45)	TERBINAFINE (N=45)	P-VALUE
Age in years (mean $\pm$ sd)	40.73 $\pm$ 13.78	29.27 $\pm$ 13.62	P=0.0001
Sex			
Female	31 (68.89%)	26 (57.78%)	P=0.105
Male	14 (31.11%)	19(42.22%)	
Duration of lesions in months	4.98 $\pm$ 3.50	4.94 $\pm$ 5.18	P= 0.9673
Number of lesions	2.20 $\pm$ 1.47	2.31 $\pm$ 0.70	P=0.6485
Widest diameter in cm			
< 5 cm	9 (20%)	13 (28.89%)	P = 0.327
5 – 10 cm	36 (80%)	32 (71.11%)	
Positive koh	45 (100%)	45 (100%)	P= 1
Baseline scaling	2.18 $\pm$ 0.72	2.44 $\pm$ 0.50	p=0.0439
Baseline erythema	2.18 $\pm$ 0.58	2.07 $\pm$ 0.54	p=0.3473
Baseline pruritus	1.96 $\pm$ 0.74	2.51 $\pm$ 0.55	p=0.0001

Table 2. Reduction rates throughout 6 weeks of treatment between both groups

Clinical Parameters	Mean Carica papaya	Mean Terbinafine	P value
Scaling			
2 weeks	26±55.15 %	41.10±55.15 %	p<0.0001
4 weeks	44.08±44.97 %	74.45±22.36%	p=0.0001
6 weeks	90.37±23.97 %	100±0 %	p=.0084
Erythema			
2 weeks	20.36±48.31 %	55.18±31.35%	p=0.0001
4 weeks	48.52±50.98 %	88.52±22.42%	p<0.0001
6 weeks	91.48±20.61 %	100.0±0%	p=0.0068
Pruritus			
2 weeks	37.40±39.11 %	79.63±27.51%	p<0.0001
4 weeks	45.93±60.53 %	100±0%	p<0.0001
6 weeks	77.78±34.08 %	100±0%	p<0.0001

Table 3. Adverse events throughout 6 weeks of treatment

Adverse events	Mean Carica papaya	Mean Terbinafine	P value
Pruritus			
2 weeks	1.47±0.84	1.29±0.76	p=0.2953
4 weeks	1.33±0.90	1.53±0.16	p=0.2953
6 weeks	0.23±0.52	0	p=0.0045
Burning			
2 weeks	1.16±0.93	0.60±0.69	p=0.0018
4 weeks	0.96±0.90	0.84±0.77	p=0.5311
6 weeks	0.2±0.59	0	p=0.0249
Erythema			
2 weeks	1.40±0.99	0.76±1.03	p=0.0031
4 weeks	1.07±0.81	0.38±0.53	p<0.0001
6 weeks	0.15±0.52	0	p=0.0480

Table 4. Efficacy scoring by patients after 6 weeks of treatment

Efficacy scoring	Mean Carica papaya	Mean Terbinafine	P value
6 weeks	2.71±0.63	2.84±0.37	p=0.2209

Both groups showed decline in the mean scaling scores post treatment but the terbinafine reduction rate (100%) is statistically higher (p=.0084) than the carica papaya group (90.37±23.97 %). (Figure 2)

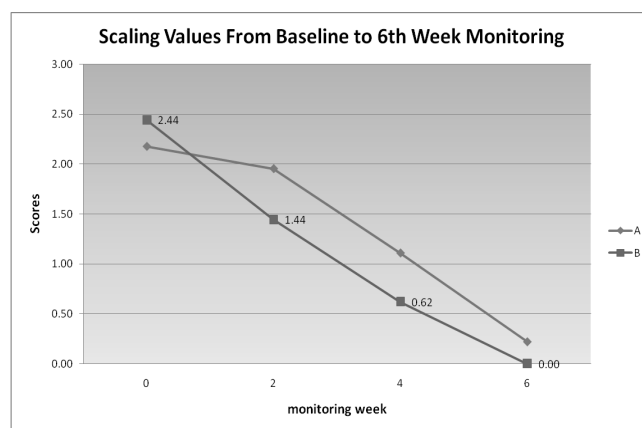


Figure 2. Comparison of changes in mean score for scaling for carica papaya and terbinafine group from baseline to week 6

Similarly, both groups showed decline in the mean erythema scores post treatment but the terbinafine reduction rate (100%) is statistically higher (p=0.0068) than the carica papaya group (91.48±20.61 %). (Figure 3)

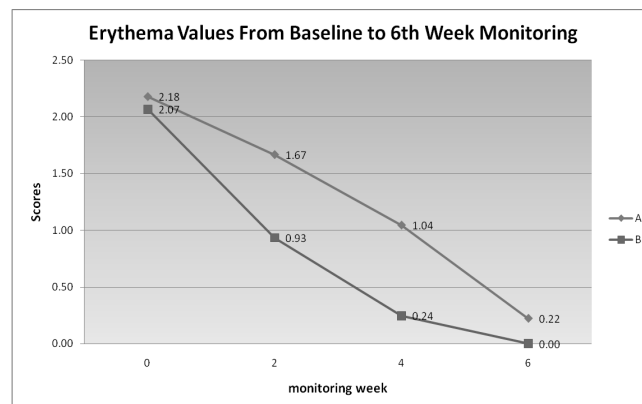


Figure 3. Comparison of changes in mean score for erythema for carica papaya and terbinafine group from baseline to week 6

Both groups showed decline in the mean pruritus scores post treatment but the terbinafine reduction rate (100%) is statistically higher ($p<0.0001$) than the carica papaya group ($77.78\pm34.08\%$). (Figure 4)

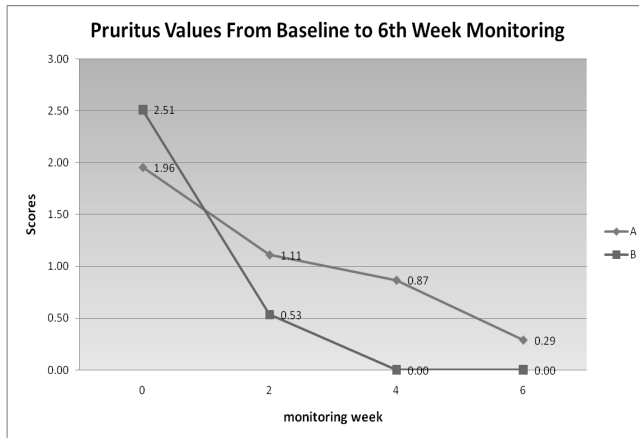


Figure 4. Comparison of changes in mean score for pruritus for carica papaya and terbinafine group from baseline to week 6

Post treatment, mycological cure rates are comparable ($p=0.315$) in both groups. (Figure 5)

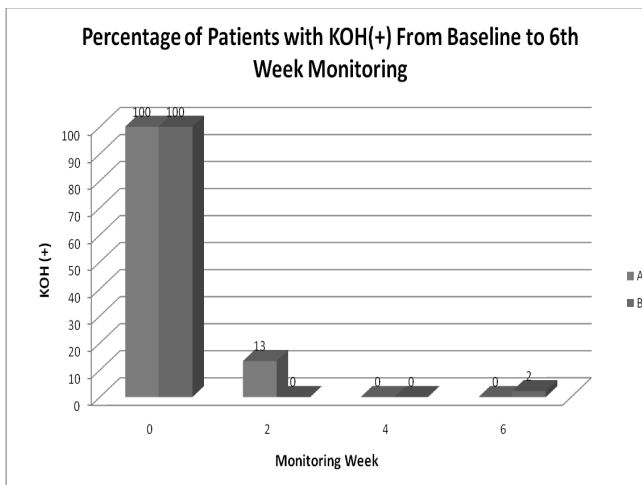


Figure 5. Mycological cure rates for both groups characterized by a negative KOH smear.

The mean scores of adverse events (pruritus, burning and erythema) after 6 weeks of treatment showed statistically higher in the carica papaya group. ($p=0.0045$, $p=0.0249$, $p=0.0480$, respectively). (Figure 6, 7, 8)

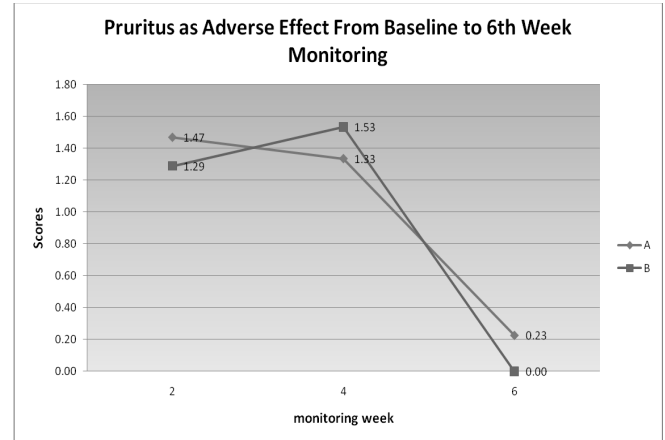


Figure 6. Incidence of adverse effect, specifically pruritus from both groups.

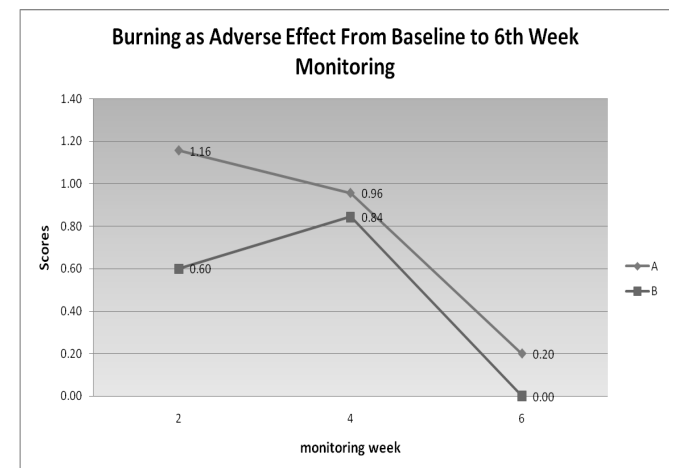


Figure 7. Incidence of adverse effect, specifically burning from both groups.

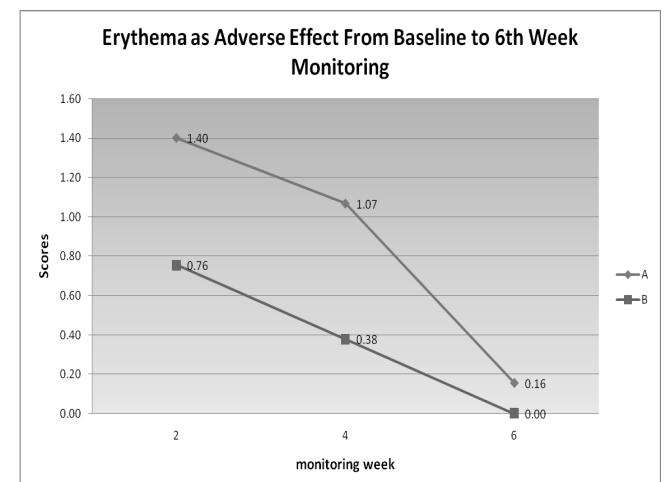


Figure 8. Incidence of adverse effect, specifically erythema from both groups.

DISCUSSION

Mycological cure rates are comparable for both groups, but clinical parameters of improvement were significantly better in the terbinafine group. The terbinafine group showed significant decreases in scaling, erythema and pruritus at two and four weeks, however the carica papaya group achieved maximal and almost comparable improvement of these parameters at the sixth week of treatment. This suggests that terbinafine has a faster onset of action, and better clinical cure which may be attributed to its fungicidal action and inherent anti-inflammatory actions, as compared to carica papaya having more of a fungistatic effect. The decrease in these clinical parameters may be attributable not only to carica papaya latex' ability to degrade polysaccharide component of the fungal cell wall (fungistatic effect) but also to its inhibitory effect on chronic inflammation.⁶⁻⁸ Also, the adverse effects of erythema, burning and pruritus were significantly higher in the carica papaya group, which may mask the clinical improvement of this intervention. These events are attributable to the tannin and cyanogenic glucoside contents of papaya that were reduced in this study by using the stems and fruit itself compared to the leaves and roots which contains more of those harmful elements.⁹⁻¹⁴ After 6 weeks, mycological cure rates are comparable and clinical parameters of improvement more similar, suggesting that the adverse effects have resolved and the anti-mycotic activity of carica papaya becomes more obvious.

Limitations of the study are the locations of lesions that should be more uniform in both groups for better comparison in future studies. The difference in age as baseline characteristic was noted. However, this may not be a confounding variable because the efficacy of topical antifungals is not influenced by age. In this study, mycological cure based on the KOH results was used as the primary outcome efficacy measure instead of clinical cure. Fungal culture is the undisputable gold standard of diagnosis but the discordance between fungal culture and KOH examination results is too great.¹⁵ KOH examinations were true positives in spite of negative culture. It was found that the a low percentage of patients presenting with a clinical diagnosis of tinea that had skin cultures positive for fungus, raising a question as to whether culture is the optimal gold standard by which to evaluate diagnostic tests for tinea infections. It concluded that clinical tinea infection with positive KOH is equivalent to clinical tinea with positive fungal culture in accurately diagnosing fungal infections. Examples

of how culture may miss a diagnosis include sampling error from the affected area, using defective culture medium, and mishandling of the culture medium.¹⁶⁻¹⁸

Recurrence rates were not investigated after discontinuation of treatment, thereby recommending considerations of prolonged investigations should this study be done in the future. A decrease in the concentration of carica papaya latex cream, a change of vehicle used and a longer time of treatment and observation should likewise be considered.

CONCLUSION

Carica papaya latex cream has comparable mycological cure rates as terbinafine cream in the treatment of tinea corporis and/or cruris. However, clinical improvement is significantly faster in the terbinafine group, and higher incidence of adverse events is seen with carica papaya latex cream use.

Appendix 1 : Demographic data of study patients

Characteristics	Carica Papaya	Terbinafine 1% cream	P value
Age			
Sex			
Duration of lesions			
Number of lesions			
Size of lesions			

Appendix 2: Clinical assessment score based on degree of scaling, erythema, and pruritus

Score	Scaling	Erythema	Pruritus
0	none	none	none
1	minimal scaling	slightly erythematous	1-3
2	moderate scaling	erythematous	4-6
3	severe scaling	Brightly erythematous	7-10

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One Mistake, One Life at Stake: A Case of Methotrexate Toxicity in A 57-Year Old Male Presenting with Painful Plaques with Erosions*

**Maria Franchesca S. Quinio, MD
Elizabeth P. Prieto, MD, FPDS**

Abstract

Introduction: Methotrexate is being given by dermatologists in only extreme cases of skin disorders such as in severe Psoriasis Vulgaris. Strict precautionary measures are done to avoid its well-known adverse effects. An early but less common sign of its toxicity are painful erosions on plaques. Methotrexate is an effective but potentially toxic treatment for different severe dermatologic disorders such as in severe Psoriasis Vulgaris. Meticulous and complete history-taking, physical examination and laboratory work-up to come up with a correct diagnosis as well as, knowledge of indications for treatment, proper dosing, folate supplementation, monitoring, proper referral and early detection of its toxicity are important in order to avoid cutaneous and systemic adverse effects including death.

Case Report: A case of a 57-year old male with a 2-day history of painful erosions on plaques on both upper and lower extremities after eleven days of taking Methotrexate 2.5mg/tablet one tablet three times a day without folate supplementation. He was then being treated by a general physician as a case of Psoriasis Vulgaris. He was subsequently admitted under the Internal Medicine service due to epigastric pain, nausea, anorexia, generalized body weakness and passage of black tarry stools. He was referred to the Department of Dermatology for the painful erosions on plaques. He expired two days after admission due to Acute Respiratory Failure. Post-mortem Skin punch biopsy was done and revealed chronic eczematous dermatitis consistent with Lichen Simplex Chronicus with superimposed drug induced hypersensitivity reaction.

Keywords: Methotrexate toxicity, painful erosions on plaques, Lichen Simplex Chronicus, Psoriasis Vulgaris, folate supplementation

**From the Department of Dermatology, East Avenue Medical Center, Quezon City, Philippines*

INTRODUCTION

Methotrexate is being given by dermatologists in only extreme cases of skin disorders such as in severe Psoriasis Vulgaris. Strict adherence to proper guidelines with regards to the indications and proper dosing of this potentially toxic drug is definitely a must in order to avoid its adverse effects. Although the incidence of this condition is unknown, a study by Olsen, Elise, et al in 1991 reported that in Duke University Medical Center, they have recorded 64 cases from 1951 to 1991¹. In our department, this was the first case seen and managed. An early but less common sign of methotrexate toxicity are painful erosions on plaques. In this report, we present a case of a 57-year old male who was referred to the Dermatology Service of a tertiary training institution due to painful erosions on plaques over both upper and lower extremities as well as on the abdominal area while taking 120 mgs worth of prescribed oral methotrexate by a general physician in a span of 16 days. This case report stresses the importance of doing complete history-taking, physical examination and laboratory work-up in order to obtain the correct diagnosis as well as the adherence to the proper guidelines to avoid methotrexate's toxic effects. Furthermore, it also aims to increase awareness of the different clinical manifestations of its toxicity in order to have early detection and prevent further deterioration of the patient's health and ultimately, demise.

CASE REPORT

The patient is F.V., 57 year old male, Filipino, from Quezon City, Philippines was referred to our service due to painful erosions on plaques. One year and four months prior to referral, he noted the appearance of these pruritic thin erythematous plaques over the lower third of both legs extending down to the dorsum of the feet associated with pruritus. Consult was done to his company physician wherein assessment was not disclosed. Sessions with intralesional triamcinolone injection was done and Betamethasone valerate with occlusion at night was started. The patient noted flattening of lesions and relief of pruritus after only two months of compliance with medications. He was not able to follow-up due to financial constraints.

On interval history, the patient noted recurrence of pruritic plaques over both upper extremities. Patient self-medicated with topical Fluocinonide cream which provided temporary improvement but lesions would eventually recur few weeks after the

discontinuation of the topical medications.

Three weeks prior to referral, the patient noted progression of erythematous thick plaques with minimal whitish fine scales over both upper extremities now with new hyperpigmented patches over the abdomen. Consult was done to a private physician wherein assessment was Psoriasis Vulgaris. No skin punch biopsy was done on patient. He was then started on Methotrexate 2.5mg per tablet, three times a day which the patient continuously took for sixteen (16) days.

On the second day of intake of methotrexate, (cumulative dose of 15 mg) the patient noted generalized dryness of the skin. While on the third day of intake of Methotrexate (cumulative dose of 22.5 mg), the patient noted plaques which became more erythematous to violaceous while some forming moist blackish central eschars and crusts associated with pain over both upper and lower extremities. At this point, there were no consults done, no pain relievers nor other medications taken or applied.

Two days prior to referral (16th day of methotrexate treatment with a cumulative dose of 120 mg), persistence of lesions now accompanied by epigastric pain, nausea, anorexia, fever, generalized body weakness, and passage of black tarry stools prompted consult at the emergency room and subsequently referred by the primary service (Internal Medicine) to the Dermatology service for further evaluation and management.

The patient is hypertensive for already three years and is maintained with on Amlodipine 10mg/tab once a day. He had no history of allergies, asthma, previous surgeries or hospitalizations as well as other systemic diseases such as lung, kidney, and liver diseases. He noted that his father also had hypertension but did not note any other diseases in the family. There was no note of Psoriasis Vulgaris in the patient's family history. The patient is a 25-pack year smoker and an occasional alcoholic beverage drinker. He noted drinking only during special occasions like office parties or holidays at least once a week. He said he can consume three bottles of beer. He denied illicit drug use. The patient worked as a supervisor at a local newspaper company.

Upon seeing the patient, we noted that the patient is awake alert, speaks in phrases and is stretcher-borne. He was normotensive, with regular heart rate and rhythm, afebrile but tachypneic (respiratory rate at 30 breaths per minute). Others

systemic findings were unremarkable although we noted crackles over both lung fields. On cutaneous examination, we noted, multiple, ill-defined, irregularly shaped erythematous to violaceous patches and hyperpigmented lichenified plaques with central blackish eschars and areas of erosions over the upper and lower extremities as well as in the extremities (Figures 1). The initial consideration for this case was 1) Multiple organ methotrexate toxicity 2) Lichen simplex chronicus vs. Psoriasis Vulgaris For the initial workup for the following diagnosis, we requested for: Complete Blood Count, Urinalysis, BUN/creatinine, SGOT, SGPT, PTT, aPTT, Clotting time and bleeding time, Chest X-ray and Skin punch biopsy (once with normal blood parameters). The laboratory results revealed pancytopenia with a very low WBC ($1.3 \times 10^9/L$), hemoglobin 75 g/L, hematocrit (0.221) as well as the platelet count ($25 \times 10^9/L$) although her peripheral blood smear results revealed normocytic and normochromic red blood cells which helped us ruled out anaplastic anemia. He has also prolonged prothrombin time (21) increased BUN (10.4 mmol/L), with a decreased creatinine clearance (74.2 ml/min), hyponatremia (121 mmol/L) and slightly increased AST (36 U/L) and ALT (69 U/L). Upper endoscopy report done by gastroenterology service revealed erosive esophagitis and multiple gastric as well as duodenal ulcers.

The Dermatology Service suggested Folic acid supplementation. Also, Clobetasol propionate ointment + vaselina blanca, mix well (1:1), and apply over the lesions 2x a day (trunk and four extremities), Mupirocin ointment, apply over the eroded areas 2x/day and PNSS compress 2x a day for 20 minutes over moist eroded areas, Chlorphenamine maleate, 4mg/tab, 1 tab 3x a day as needed for itch and advised mild soap for bathing. Gastroenterology, Hematology, and Toxicology referrals were also done for further evaluation and management.

On the second day referral day the patient was noted to have desaturations, and progressive dyspnea and decrease in sensorium. The patient expired and the Internal Medicine service made their final working impression as: 1) Acute Respiratory Failure 2) Hospital Acquired Pneumonia, early onset, and immunosuppression secondary to methotrexate toxicity. Skin punch biopsy by the Dermatology service on the left forearm on post mortem which revealed chronic eczematous dermatitis such as Lichen simplex Chronicus. The possibility of superimposed drug induced hypersensitivity reaction cannot be entirely excluded. The final diagnosis of our service is 1) Multiple Organ Methotrexate Toxicity 2) Lichen Simplex Chronicus.

DISCUSSION

Although the incidence of methotrexate toxicity is unknown Olsen, Elise, et al in 1991 reported that in Duke University Medical Center, they have recorded 64 cases from 1951 to 1991¹. In our records at the East Avenue Medical Center Department of dermatology, this is the first case of methotrexate toxicity. Although, according to the census, there were five cases of hypersensitivity reaction from methotrexate. There are cases from the Obstetrics and Gynecology service whose patients were undertaking methotrexate therapy for Hydatidiform Mole and other gynecologic related malignancies.

Methotrexate is an analog of folate that competitively and irreversibly inhibits dihydrofolate reductase. It also inhibits thymidylate synthetase. Through the inhibition of these processes, methotrexate decreased the availability of reduced folate and thymidilate necessary for RNA as well as DNA synthesis. Furthermore. Methotrexate-polyglutamate increases the local tissue concentration of adenosine, which has potent anti-inflammatory action².

Oral methotrexate is absorbed rapidly through the gastrointestinal tract. The mean bioavailability is 67%. While the Peak Plasma Levels occur 1-3 hours after administration. The half-life of methotrexate is Half-life: 4-5 hours. It is important to note that dosages of greater 25mg/week of methotrexate makes the gastrointestinal absorption erratic and recommends intramuscular dosing. Elimination of methotrexate is primarily done by the kidneys. Therefore, Decrease in Glomerular filtration Rate leads to Methotrexate toxicity.³

Since methotrexate is primarily given to cancer patients especially those suffering from Acute Lymphoblastic Anemia (ALL), Oncologic doses (100-250 mg/m²/week) for these usual cases.² On the other hand, in Dermatology, Methotrexate are only used in cases of, Severe psoriasis +/- psoriatic arthritis and Mycosis fungoides +/- advanced disease but there are also "Off-label" uses such as Dermatomyositis, Cutaneous lupus erythematosus, Scleroderma, Pemphigus vulgaris, Bullous pemphigoid, Sarcoidosis, Severe atopic dermatitis, PLEVA and Pityriasis Rubra Pilaris Immunomodulatory dose will be (7.5- 25 mg/week)³. It is important to note that in our market, methotrexate is available at Preparation: 2.5mg/tab and methotrexate liquid (25mg/ml)⁴. According to Ahmed et. Al (2013), it is better to give Single weekly dose or in divided doses (usually 3 divided doses separated by

12 hours)⁵. Although it is much better to give equal efficacy but split dose since it may increase tolerance by minimizing gastrointestinal upset. It is important to take note, that methotrexate should never be given on a daily dose basis because it promotes toxicity such as in the case of our patient. It is important to remember that before initiating methotrexate therapy, it is important to have a thorough history and physical examination, have exclusion criteria and equip oneself with proper knowledge of the indications as well as the exclusion criteria.²

Laboratory Monitoring:

CBC with platelet count as well as liver function should be done weekly for 2 to 4 weeks gradually increase to every 3-4 months with time and perform 5-6 days after any dose escalation. Renal function should be done once or twice a year or if suspicion of renal problems are at hand. Liver biopsy should also be performed after 1.5 g (cumulative dose) if there are no risk factors and then repeat biopsy every 1 g thereafter. One can perform pre-treatment if there are risk factors involved in our patient. In the case of our patient, no pre-treatment laboratory work-up were done.^{6,9}

Initiating Therapy

If all laboratory results showed normal results and the patient does not have any risk factors for toxicity, then we could start with Single 5-10 mg test dose, after which, Repeat laboratory studies, skin examination and review of systems after 1 week. The dose may be increased to 2.5-5.0 mg every 2-4 weeks and taper at the same dose depending on the response. If there is no response in 20-25mg/week, the dermatologist might as well open its options to UVB Phototherapy or Oral retinoids.⁶

Indications

Since methotrexate is prone to toxicities here are the absolute as well as the relative contraindications:

Absolute: Pregnant and lactating women. Methotrexate is a known teratogen that causes oligospermia, although it is not a mutagen, current recommendations are that both women and men take measures to avoid either pregnant or impregnating their partner during therapy and 3 months for women and 1 month for men after discontinuation.

Relative: Renal dysfunction, hematologic diseases, hepatic diseases such as hepatitis, excessive alcohol intake diabetes mellitus or obesity, active infection, HIV-VIRUS- Men or women contemplating or impending conception.⁵

Adverse Effects:

BONE marrow, gastrointestinal mucosa, hair and skin are vulnerable to adverse effects of methotrexate secondary to their high rate of turn over

GI: Nausea, vomiting and mucositis, hepatotoxicity,

Bone Marrow: Myelosuppression

SKIN: alopecia; painful skin eruptions

Kidney: decreased creatinine clearance

Lung: non-productive cough, fever, malaise and dyspnea.

Nervous: Intrathecal administration (headache, meningeal signs)

Eye: Ocular burning

In the case of our patient, he experienced mucositis, hepatotoxicity, myelosuppression, painful skin eruptions, decreased creatinine clearance, and dyspnea.^{7,8}

In one case report on the erosion of psoriatic plaques as an early sign of methotrexate toxicity by Hannah Pearce MD (1996), noted two cases of methotrexate toxicity which manifested as bone marrow suppressions, gastrointestinal ulceration and painful erosions of psoriatic plaque which were also experienced by our case index.⁸ Like our patient, they weren't able to administer folinic acid as antidote for the said toxicity because the golden period of 24-36 hours after the administration of methotrexate toxicity.

According to Review of the prevention and management of high dose methotrexate toxicity by Ahmed Yasar et al (2013) and Folate supplementation during methotrexate therapy for patient with psoriasis article on by Strober BE, MD (2005) Folic acid is used as a Daily supplementation with 1-5mg/folate reduces nausea, vomiting, stomatitis, ulceration, elevated AST, and mild myelosuppression.^{5,6} It can be taken with methotrexate without decreasing its efficacy and

it's considered as a 1st line folate supplement: Lower cost and comparable efficacy with folinic acid, while folinic acid (Leucovorin) should be given 1st 24-36 hours after overdose, which prevents myelosuppression, gastrointestinal toxicity and neurotoxicity. This should not be given on same days as methotrexate dosing because it competes with Methotrexate for cellular uptake. Usual dosing will be 15-25mg of folinic acid by mouth every 6 hours for 6-10 doses and is considered first choice of treatment of methotrexate overdose.

In summary, methotrexate can be used not only in severe cases of skin problems but also in other systemic diseases. What important is to know the right indication, the complete and proper management and monitoring as well as having folic acid supplementation. Early detection of its toxicity is important in order to give the rescue dose of folinic acid to prevent further deterioration and demise.

CONCLUSION

This case report is done to increase awareness of the importance of strict adherence of proper guidelines in prescribing medications. Methotrexate is an effective but potentially toxic treatment for different severe dermatologic disorders such as in severe Psoriasis Vulgaris. Meticulous and complete history-taking, physical examination and laboratory work-up to come up with a correct diagnosis as well as, knowledge of indications for treatment, proper dosing, folate supplementation, monitoring, proper referral and early detection of its toxicity are important in order to avoid cutaneous and systemic adverse effects including death.

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FIGURES



Figure 1

Multiple erythematous to violaceous patches and hyperpigmented lichenified plaques with central blackish eschars and areas of erosions over the a) upper extremities, b) lower extremities, c) abdomen

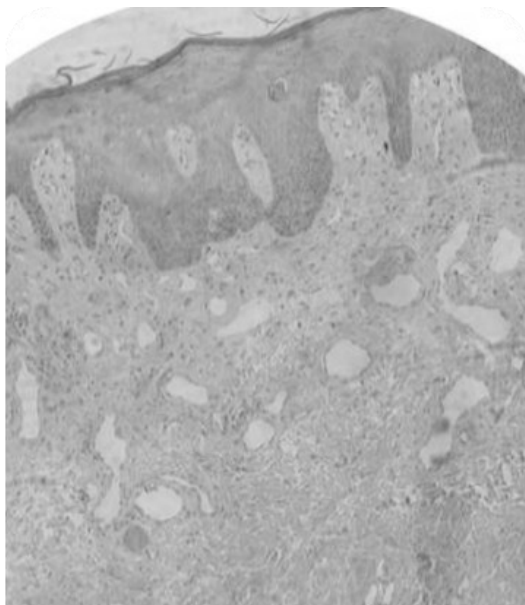


FIGURE 2:

Section from the right leg revealed **psoriasiform dermatitis**. This is more consistent with chronic eczematous dermatitis such as **LICHEN SIMPLEX CHRONICUS**

Dermatofibrosarcoma Protuberans of the Hand*

Sarah V. Velasquez, MD¹
Ma. Flordeliz Abad-Casintahan, MD, FPDS²

ABSTRACT

Dermatofibrosarcoma protuberans (DFSP) is a rare, locally aggressive dermal and subcutaneous mesenchymal neoplasm that often presents as a slow-growing lesion on the trunk, proximal extremities, head and neck. We report a rare case of DFSP arising on the dorsum of the left hand. A 35-year-old male, who presented with a solitary verrucous nodule on the dorsum of the left hand and had experienced two recurrences of the lesion following local excision and electrocautery. Histopathologic examination was consistent with DFSP. CD34 immunostain was positive. Wide surgical excision with a three centimeter margin and direct skin closure was done. Although metastasis is rare, DFSP is associated with marked tendency towards local recurrence after surgery hence patient is for follow-up every six to twelve months post operatively.

Keywords: dermatofibrosarcoma protuberans, CD34 immunostain, wide surgical excision

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

¹Resident, Department of Dermatology, Jose R. Reyes Memorial Medical Center (JRRMMC)

²Consultant Staff, Department of Dermatology, Jose R. Reyes Memorial Medical Center (JRRMMC)

INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is a locally aggressive sarcoma arising from the skin. It is relatively rare and accounts for approximately 4% of all soft tissue sarcomas.¹ It typically arises on the chest, back, head and neck and proximal parts of the extremities. DFSP arising on the hand is rarely reported in literature.² Worldwide, there are only 8 reported cases of DFSP of the hand from 1977 to the present.^{2,8-14} Locally, there have been no published reports of DFSP of the hand. We report a case of a 35-year-old male with recurrent DFSP occurring on the hand treated with wide excision.

CASE

A 35-year-old male policeman from Tondo, Manila, Philippines presented with a nodule on the dorsum of the left hand, in between the proximal portion of the 4th and 5th digit.

Approximately fifteen years prior to consultation, he noted a slightly pruritic erythematous papule on the dorsum of the left hand, in between the proximal portion of the 4th and 5th digit. The lesion was noted to gradually increase in size from pinpoint to about 1 x 1 cm. No consultation was done and no medications were applied or taken.

Ten years prior to consultation, the lesion then measured approximately 1.5 x 1.5 cm with no accompanying symptoms. Excision was done during a medical mission. Post-operative course was unremarkable. Five months later, he noted recurrence of the lesion on the previous site. The lesion gradually increased in size evolving into a nodule. There was also noted pain with trauma.

Six years prior to consultation, still with increasing size of the lesion, he consulted with a surgeon at a private hospital where electrocautery of the lesion was done. Post-operative course was unremarkable.

5 years prior to consultation, recurrence of the lesion was noted at the same area. Lesion was brownish with a verrucous surface. There was gradual increase in the size of the lesion to more than 1.5 cm in diameter. No pain was noted however, there was minimal bleeding with trauma. No change in color as well as ulceration observed.

4 months prior to consultation, there was noted rapid growth of the lesion to about 3 x 2.5 cm. There was no fever, no weight loss at that time.

Due to persistence of the lesion, patient sought consult at our institution.

The systems review was unremarkable. The patient was non-hypertensive and non-diabetic. He was a non-smoker and an occasional alcoholic beverage drinker. Family history revealed no similar illness and no known malignancies.

The patient came in conscious, coherent, not in cardiorespiratory distress with the following vital signs: blood pressure of 130/80, heart rate of 88 beats/min, respiratory rate of 16 cycles/min, and a temperature of 36.5 °C. No axillary lymphadenopathy noted. On dermatological examination, he had a solitary, firm, nontender, brownish, verrucous nodule with an eroded ulcerated surface measuring approximately 3 x 2.5 cm in size (**Figure 1**).

An incision biopsy was done on the nodule of the left hand. The epidermis showed acanthosis. (**Figure 2**). The dermis showed closely spaced spindle cells with pleomorphic nuclei and few mitotic figures in a storiform pattern extending to the subcutis (**Figure 3**). CD34 immunostain done was positive (**Figure 4**). With clinicopathologic correlation, the case was signed out as dermatofibrosarcoma protuberans.

The patient was referred to orthopedic surgery for management of the lesion. They planned to do wide excision of the lesion with possible grafting. However, he opted to have surgery done with a general surgeon at a Chinese General Hospital and Medical Center. Wide excision with a 3 cm margin and direct skin closure was done (**Figure 5**). Histopathology of the lesion confirmed the diagnosis of dermatofibrosarcoma protuberans. No adjuvant treatment was given. Patient was advised regular self-examination and follow up every six months to check for possible recurrence and metastasis of the lesion.



Figure 1. Solitary, firm, nontender, brownish, verrucous nodule with an eroded ulcerated surface measuring approximately 3.5 x 2 cm in size located on the dorsum of the left hand.

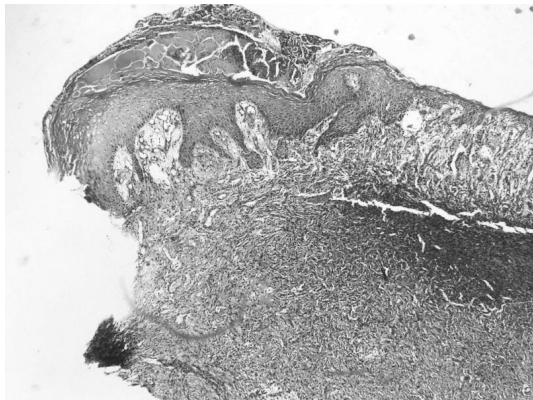


Figure 2. Incision biopsy done on the nodule at the left hand showed acanthotic epidermis on low power (10x) magnification view (hematoxylin and eosin stain)

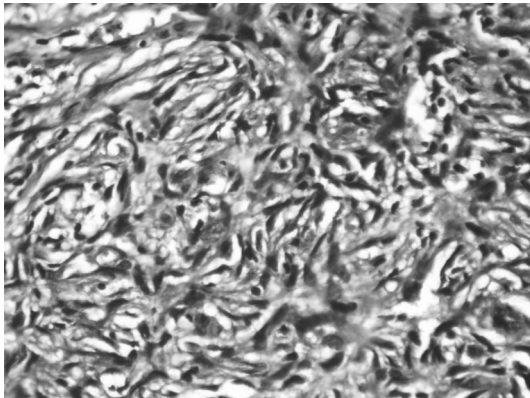


Figure 3. Oil immersion field (400x) showed presence of closely spaced spindle cells with pleomorphic nuclei and mitotic figures in a storiform pattern in the dermis (hematoxylin and eosin stain)

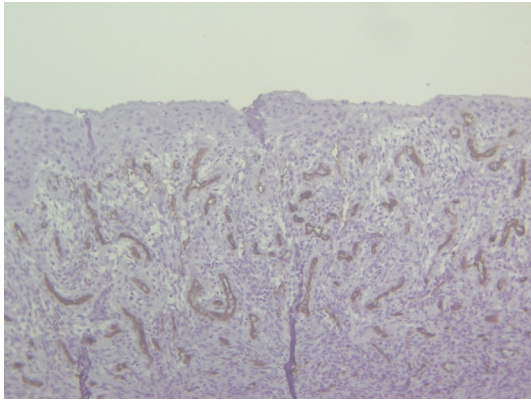


Figure 4. CD34 Immunostaining is positive on low power (10x) magnification view



Figure 5. Post-operative photo after wide surgical excision was done.

Table I. Summary of Immunohistochemical staining of DFSP and other spindle cell dermal tumors

	CD34	Factor XIIIa	S-100	Actin	Desmin	Vimentin
DFSP	+	-	-	-	-	+
Dermatofibroma	-	+	-	+	-	+
Nerve Sheath tumors	+/-	-	+	-	-	-
Fibrosarcoma	-	-	-	+	-	+
Malignant Fibrous histiocytoma	+/-	-	-	-	+/-	+

+, More than 80% of cases staining; -, less than 20% of cases staining; +/-, variable staining.

DISCUSSION

Before 1924, several authors independently described DFSP, but it was the description of “progressive and recurrent dermatofibroma” by Darier and Ferrand that established it as a distinct clinicopathologic entity. In 1925, Hoffmann proposed the descriptive term dermatofibrosarcoma protuberans. Taylor and Helwig, later in 1962, emphasized the microscopic findings of a spindle-cell proliferation arranged in a cartwheel or whorligig pattern.³

DFSP is a rare tumor that constitutes less than 0.1% of all malignancies. The incidence in the United States has been estimated at 4.2 million cases per million population per year.⁴ Data from the Jose R. Reyes Memorial Medical Center Dermatology Department showed 6 reported cases of DFSP from year 2000 up to present time. DFSP occurs in early to middle adult life between 20 and 50 years of age, although its range of occurrence is from birth through the 80s. An almost equal sex distribution with a slight male predominance was seen in literature.⁵

DFSP arises from the rearrangement of chromosomes 17 and 22 such that the collagen Type I α 1 gene (COL1A1) becomes fused to the platelet-derived growth factor (PDGF) β -chain gene (PDGFB). This rearrangement results in the deregulation of PDGF β -chain expression and leads to continuous activation of the PDGF receptor β (PDGFR β) protein tyrosine kinase, which promotes DFSP cell growth.⁶

DFSP presents most commonly on the trunk (47%), followed by the lower extremity (20%), upper extremity (18%) and finally head and neck (14%).⁷ It initially appears as an asymptomatic, indurated plaque that may be violaceous, red-brown or flesh-colored. It slowly and relentlessly enlarges and develops protuberant nodules within the plaque.⁵

On routine hematoxylin-eosin-stained sections DFSP is characterized by a distinct storiform pattern, created by spindle-shaped cells arranged in an irregularly whorled pattern. The cells have been described as arranged in cartwheel-like arrays around collagenous centers. There may be only slight to moderate nuclear atypia, although mitoses can be present.¹⁶ However, DFSP may sometimes be difficult to differentiate histologically from other fibrohistiocytic tumors such as dermatofibroma, fibromatosis and malignant fibrous histiocytoma.

It is important to differentiate DFSP from dermatofibroma because their biological behaviour differs greatly.¹⁷ Immunohistochemical stains can be used to augment routine histologic examination to aid in differentiation DFSP from other dermal spindle cell tumors. The immunohistochemical profile of DFSP as well as tumors often considered in the differential diagnosis is summarized in Table I. Many recent studies have shown the usefulness of CD34 in distinguishing DFSP from other dermal tumors, particularly dermatofibroma.¹⁶ The human progenitor cell antigen CD34 is a surface antigen expressed on normal hematopoietic stem cells and in a significant proportion of acute leukemias. It is a single-chain transmembrane glycoprotein which seems to be involved in the process of leukocyte adhesion to vascular endothelium and may participate in acute and chronic inflammatory responses.¹⁶ CD34 reactivity in DFSP was first reported in 1990 by Ramani, Bradley and Fletcher.¹⁸ Thereafter, other studies have surfaced and most of them documented the sensitivity of CD34 staining in DFSP as ranging from 84% to 100%. CD34 was found to be strongly positive in the plaque areas where the neoplastic cells were slender and arranged in fascicles parallel to the skin surface. However, in nodular areas with a typical storiform pattern, the staining was uneven with strong to moderate staining in early nodular areas but weaker staining in fully developed nodules as seen in our case.¹⁶

DFSP of the hand is a rare condition with approximately only 8 cases reported in world literature since 1977 to 2009.^{2,8-14} In the Philippines, no case reports of DFSP of the hand have been published from local journals, specifically from the Journal of the Philippine Dermatologic Society from 1990-2009.

Schvarcz LW presented a case of congenital DFSP on the dorsum of the hand treated by local radical surgical excision and skin closure. The function of the hand remained normal and no signs of recurrence were noted six months post-operatively.⁸ Wirman et al. presented a case of a DFSP arising on the back of the hand, that was widely excised and the defect closed with a split thickness skin graft. There were no details regarding the follow-up of the patient.⁹ Coles et al. reported a case of DFSP involving the thumb that was treated by excision biopsy. No evidence of tumour or lymphadenopathy is reported at six-month follow-up.¹¹ A case similar to the patient was reported by Demiri et al in 2006. They presented a 51-year-old woman with DFSP on the dorsum of the left hand and had experienced four recurrences of the

tumor following local excisions. Radical surgical excision with distal ulnar artery skin island flap was done as well as adjuvant radiation therapy following surgery. Forty months post-operatively, the patient had a functional hand without signs of recurrence and no evidence of disease.² Although DFSP is locally aggressive, no evidence of nerve involvement was noted in similar case reports of DFSP of the hand.

As with other sites of predilection of DFSP, DFSP of the hand is considered to be an intermediate malignant tumor with a high tendency to recur repeatedly if precedent management is not adequate.¹⁵ The optimal treatment option is resection with wide margins, typically 2-4 cm. The likelihood of local recurrence after the procedure is less than 10%.⁶ Relative 5-year survival rate of DFSP is 99.2%. It very rarely metastasizes to regional lymph nodes or distant sites, mainly the lungs.² Although our patient presented with recurrent DFSP, does not show findings in the review of systems and physical examination that would lead us to suspect metastatic disease. Hence, extensive evaluations with chest x-ray, computed tomographic scans, liver function tests, complete blood counts are not indicated at this time. Local recurrences are noted within 3 years of excision, but late recurrence of greater than 10 years has been reported.⁵ Hence, patient is to be followed up every 6 months during the first 3 postoperative years and annually thereafter. Particular attention must be paid to careful inspection and palpation of the original excision site and regional lymph nodes on subsequent follow-ups.

CONCLUSION

Dermatofibrosarcoma protuberans is a rare soft tissue neoplasm with intermediate to low-grade malignancy. It presents as a large indurated plaque but may also exhibit a nodular pattern late in its course, similar to our case. Sites of predilection are the trunk, extremities, head and neck. DFSP of the hand can occur rarely. Although it is locally aggressive, there have been no reports of nerve involvement that would impede function of the hand in similar studies. Wide excision with 2-4 cm margin is warranted and recurrences after surgery have been minimal. Metastasis in DFSP is rare and it has a very high survival rate.

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"Expecting" A Family Case Discussion*

Katrina Lenora Villarante, MD¹

INTRODUCTION

The practice of family medicine extends from womb to tomb and provides opportunities to care for not just one but all members of the family. Regardless of the complaint that brings a patient to the clinic, a family physician's role is to provide comprehensive care for the patient, the family, to go beyond the biomedical approach, not just to treat the disease but also to address the impact of the illness, and to have a continuing plan for promoting the family's wellness.

Families are greatly affected by the presence of chronic illnesses in any of its members. How then does a family physician address the potential problems of a chronic disease in the family especially if the sick member is one of the parents, with an unborn child? This paper aims to discuss the circumstances and situational relationships of a family with pregnant mother with a newly diagnosed kidney disease that would require hemodialysis.

INDEX PATIENT

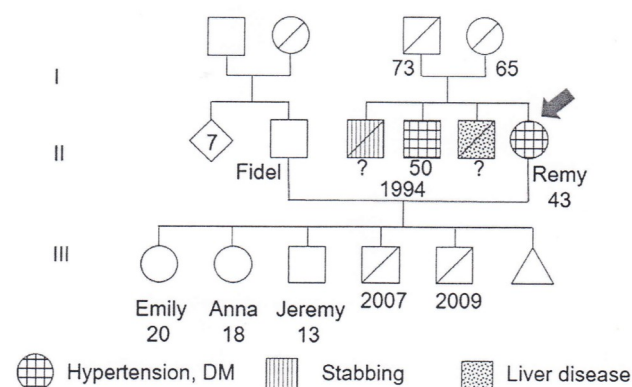
Remy, 43, is the mother of a family of five in Caloocan City. She is a known hypertensive and diabetic. Remy and her husband, Fidel, learned of the present pregnancy at two months age of gestation. She had four prenatal checkups since then. Despite having minimal bipedal edema, Remy had good baseline functional capacity and was independent in activities of daily living. She was admitted on August 15, 2015 at the OB Admitting Section of Philippine General Hospital for the complaint of dyspnea.

Two weeks prior to admission, the patient started to experience increasing shortness of breath related to exertion. This was associated with generalized weakness, anorexia, nausea, occasional vomiting, and orthopnea. She was also noted to be pale and had frothy urine. Progression of the symptoms

prompted the patient and her husband to seek consult at a local clinic. Initial laboratory findings revealed a high serum creatinine and she was referred to a government tertiary hospital for hemodialysis.

The patient was maintained on metoprolol and metformin, both taken with poor compliance. Highest blood pressure was at 160/90 mmHg, with a usual range of 110-120/70-80 mmHg. The medications were discontinued at two months age of gestation upon knowledge of the pregnancy. The patient was hospitalized for excision of a pancreatic cyst in the past

A review of the family history reveals that hypertension and diabetes ran in Remy's family. One brother died from complications of an unspecified liver disease. There was no PTB, bronchial asthma, cardiac, renal, or thyroid disease in the family.



Remy had four pregnancies prior to the present one. She delivered her firstborn when she was 23 years old. Their fourth child died three days after birth while the fifth died in utero. No symptoms of hypertension or other similar illnesses were noted during the previous pregnancies. Remy's LMP was on March 12, 2015. The couple had been practicing withdrawal method as contraception for the past few years.

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¹Resident Graduate, Department of Family and Community Medicine, UP-PGH Medical Center

The patient is a non-smoker but has had previous exposure of secondhand smoke from her husband. She had occasional alcohol intake but she denies any illicit drug use. There was no history of domestic abuse.

Remy was received tachypneic and with an elevated BP of 140/90 mmHg. Remy had grade II bipedal edema. The rest of the systemic physical examination was normal. Fundic height was 20 cm, with fetal weight estimated to be less than 500 g and fetal heart tones at 145 bpm. Pelvic exam revealed a closed cervix, parous vagina, no adnexal masses/tenderness, and an enlarged uterus. The capillary blood glucose on admission was 253 mg/dL.

The admitting impression at the time was: (1) pregnancy uterine, 22 2/7 weeks AOG by LMP, G6P5 (5003), (2) pregestational diabetes mellitus, type 2, uncontrolled, (3) chronic hypertension, and (4) s/p excision of pancreatic cyst (2000, PGH).

Laboratory workup was done which revealed anemia with a hemoglobin of 60 mg/dL, elevated BUN and creatinine, with an eGFR of 3.2 mL/min/1.73 m², and glucosuria (+2), albuminuria (+2) and negative ketones on urinalysis. Arterial blood gas showed metabolic acidosis. Biometry showed a single live intrauterine pregnancy with good cardiac and somatic activities, 17 2/7 weeks AOG by composite aging, with an estimated fetal weight of 179 grams.

Working impression was then revised to: (1) chronic kidney disease, stage V, in uremia, secondary to hypertensive/diabetic kidney disease, with secondary anemia, (2) pregestational diabetes mellitus, type 2, (3) chronic hypertension, stage II, (4) pregnancy uterine, 22 2/7 weeks AOG by LMP, (5) s/p excision of pancreatic cyst.

Remy's biomedical problems were identified as follows: (1) newly diagnosed deteriorating renal function from hypertension and diabetes, two chronic conditions complicating her current pregnancy: (2) pregestational diabetes and (3) chronic hypertension, and lastly, (4) her current pregnancy. Goals for Remy were (1) renal replacement therapy, (2) blood sugar control, (3) blood pressure control, (4) maintenance of the pregnancy, and lastly, (5) to manage new problems as they arise. During the course of her admission, Remy was also seen and co-managed by the following services: Renal, Endocrinology, Perinatology, Ophthalmology, Cardiology, and Dietary.

There were 12 sessions of hemodialysis during the admission, with a decreasing creatinine trend from 1,101 pmol/L on admission to 385 pmol/L. Remy received blood transfusions with three units packed RBC and was prescribed with sodium bicarbonate, ferrous sulfate and folic acid, calcium carbonate and vitamin D, furosemide, and erythropoietin.

Insulin was started, blood sugar levels were monitoring regularly, and doses of insulin titrated. Metformin could have been continued during the pregnancy until insulin was started, as hyperglycemia is a potential teratogen. However, clinical trials are still needed before this can become a formal recommendation (Feig & Moses, 2011).

Hypertension was treated with methyldopa and nifedipine, with regular monitoring of Remy's blood pressure. Blood pressure spikes were addressed with nicardipine and titration of doses of anti-hypertensive medications. For pregnant hypertensive patients with chronic kidney disease, target BP is from 120/80 mmHg to less than 140/90 mmHg (Task Force on Hypertension in Pregnancy, 2013). The use of most beta-blockers, ACE-inhibitors, angiotensin receptor blockers and diuretics are recommended against in pregnancy (Kjeldsen et al., 2014).

Progress of the pregnancy was monitored through fetal movement and biometry. A congenital anomaly screening was planned and medications known to be safe during pregnancy were given. Remy was prescribed a diet tailored for a pregnant patient with diabetes ongoing dialysis. Intensive hemodialysis, feto-maternal monitoring, avoiding protein restriction and ensuring that the mother reaches target weight gain have been shown to improve pregnancy outcomes, (Hladunewich et al., 2014; Manisco et al., 2015).

Risks of future pregnancies were discussed with Remy and Fidel. The couple planned for Remy to undergo ligation after the current pregnancy. The option of vasectomy was also offered to Fidel.

New problems such as recurrence of dyspnea and the onset of cough and dysuria were investigated and managed. A hospital-acquired pneumonia was ruled out and Remy was started treatment for heart failure from hypertensive heart disease. Appropriate antibiotics were also started for a urinary tract infection.

Remy went home on methyldopa, nifedipine, insulin and prenatal supplements, with blood pressure and blood sugar monitoring, and with plans of continued outpatient dialysis.

After her discharge, Remy was refused dialysis by the outpatient centers they went to since the centers are ill-equipped to handle a pregnant patient. Thus, she again became weak and dyspneic.

Eventually, Remy was readmitted and was able to undergo three sessions of hemodialysis. With improving symptoms, plans were made for Remy's discharge. The plan was to continue hemodialysis in PGFI on an outpatient basis due to the special circumstances during the remaining weeks of the pregnancy.

Remy began to experience episodes of vaginal spotting and medical management for threatened abortion was started. Repeat biometry at this time showed that the baby still had not reached viable age.

Shortly prior to her planned discharge, Remy went into premature labor. She delivered a live but very small baby weighing only 360 grams. The neonate was 27 3/7 weeks AOG at this time. Remy and Felix refused aggressive neonatal resuscitation and the baby was given direct skin-to-skin contact with Remy until he died after a few hours.

Remy was discharged to continue hemodialysis with a local dialysis center. Medications were shifted to losartan, carvedilol, amlodipine, and aspirin and simvastatin were started. Follow-ups with the different services were scheduled.

On OPD follow up, Remy had decreased orthopnea, weakness, edema, improved sleep and increased urine output. She was compliant with medications, blood pressure and blood sugar monitoring, and was able to undergo outpatient hemodialysis. Remy was now independent in activities of daily living from previously needing assistance.

DESCRIPTION OF THE FAMILY

The Perez family is a family of five based in Caloocan City. Remy, the index patient, is the mother. The household is composed of the immediate family except for the middle child who already lived with her own family. The family lived in an

owned house in a compound with the father's family of origin.

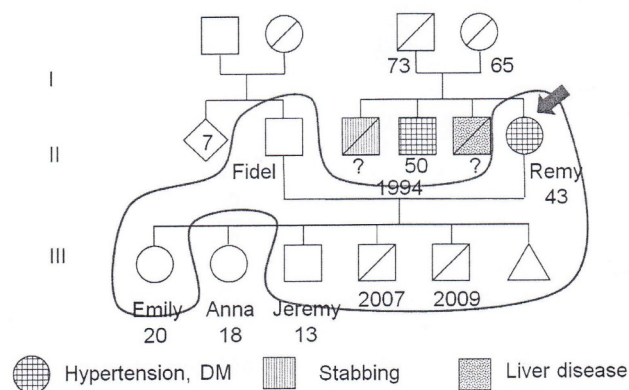


FIGURE 1. Perez Family Genogram (September 2015, Philippine General Hospital)

The family is in launching stage in the life cycle and is nuclear in structure with three children 13, 17 and 20 years of age. The key principle of this stage is accepting entries and exits into the family system (Alip, Jr., 2014). Family life cycle stages that are supposed to launch members outside the system can be a difficult time for a family to cope with, especially if there's a severe illness in the family.

Remy was a housewife while Fidel was a fisherman. Prior to the onset of symptoms, the index patient took care of most of the household tasks while the father, Fidel, and the eldest child, Emily, both worked to finance the needs of the family. Emily has been working for three years, most recently as a saleslady at a mall in Divisoria. The middle child, Anna, already lived separately with her own family. Jeremy, the youngest child, was still attending school.

CASE ANALYSIS

Having a member with chronic kidney disease has consequences on the family. Issues that arise include the inability of the sick parent to fulfill gender-specific parental roles (Smith, & Soliday, 2001). Mothers such as Remy become less able to do housework and take care of children. For parents with chronic kidney disease, the time spent together by the family becomes less because of the illness. While dialysis and hospitalization take the patient away from the family, the fatigue that is a common symptom in chronic kidney disease also prevent patients from spending as much time with the family as before (Smith, & Soliday, 2001).

Another concern of renal patients who are parents is how it causes the children to worry (Smith, & Soliday, 2001). Aside from missing having their mother at home, Remy's three children were scared by their mother's illness and worried about their future sibling's condition.

The patient's prolonged admission and subsequent readmission allow a family physician to observe and assist the Perez family in going from one stage of the illness trajectory to another. The disclosure of the diagnosis of chronic kidney disease and the knowledge of the possible consequences comprise the impact phase. It is understandable that the family's initial reaction was that of anxiety and being overwhelmed.

After all family members understood Remy's condition and the treatment plan, the next step was to guide them through major therapeutic efforts. An important part in the management of Remy's illness was the assurance that regular hemodialysis would be done. Financial difficulties is another problem identified by parents with chronic kidney disease, due to the cost of treatment (Smith, & Soliday, 2001). Early into the admission, it was evident that the financial resources of the family was limited and would not be able to sustain the cost of her treatment. The present income of the family was substantially less than what Fidel had earned before.

Three things were salient from reviewing the family lifeline: that previously, the family's income was sufficient to cover previous medical expenses; that the family had coped well with two previous negative pregnancy outcomes; and that this was the first pregnancy they would experience that would be complicated by diabetes, hypertension, and now, chronic kidney disease that required hemodialysis. Remy found it hard especially since she could compare this pregnancy to the relatively uneventful course of the previous ones. Like all expecting parents, the couple wanted to deliver a healthy baby once term. However, the couple have been advised of the uncertainty of the outcome of the pregnancy given Remy's comorbid illnesses. Thus, the couple's anticipation has been overshadowed by other concerns--the need to control Remy's blood sugar and blood pressure, and the need to find funds so that Remy gets regular hemodialysis.

A shift in family roles is expected as a response of the family to the illness (Smith, & Soliday, 2001). With Remy in the hospital and unable to fulfill

her role in taking care of the household, readjustment in roles in the family took place. Fidel and Emily needed to leave work to assume the role of watchers. Anna, although already with her own family, came home often to take care of the household while their mother was in the hospital.

When Remy began to show signs of improvement, the family began to enter the phase of early adjustments to outcomes. Continuation of the treatment plan once at home was ensured. Readjustment in roles at home continued, with all three children and Fidel pitching in with housework that Remy used to do.

Family function was assessed using APGAR which yielded a score of 10 from Remy and a score of 8 from Emily. The score may be indicative of a highly functional family, the characteristics of which enable families to cope well with illness in a family member.

The resources of the family were assessed using the SCREAM tool. Aside from showing the problem of meeting the financial demands of the current illness, it reflected the family's difficulty in accessing medical care in their community. The family was unaware of the medical resources available nearby, aside from not being able to easily afford these medical services. Although they had a relative who initially helped out with medical expenses, the family would be unable to sustain dialysis out of pocket with the family's income and lack of savings. Philhealth coverage could not be utilized during the admission due to incomplete contributions. It would have allowed Remy with 45 sessions of dialysis as an inpatient and another 45 sessions on an outpatient basis in one year.

At P4,500 per session, the family would spend P13,500 per week at the recommended frequency of dialysis while still getting their Philhealth coverage in order. The couple was promised financial assistance from the local church but also knew not to rely solely on that. They were yet to approach PCSO for assistance. The family found out that a dialysis center was planned to be built in the local area that would be able provide dialysis services at a lower cost.

When Remy's continued dialysis and improvement were unexpectedly sidetracked, it was understandable that the family, especially Emily, felt frustration and helplessness.

Pregnancy loss entails the loss of the future of the child, and may result in a loss of sense of self and a sense of inadequacy in fulfilling the role of procreation. It is considered a form of disenfranchised grief or mourning that is complicated by the lack of societal norms (Van Dinter M., & Graves L., 2012).

Guilt may be felt over what may have been done to cause or to prevent it, and symptoms of anxiety and depression may appear. Other family members may have their own reactions to the pregnancy loss. Fathers may feel self-blame, a sense loss of identity as a father, and a need to hide feelings. The children may make conclusions about the cause of the pregnancy loss, at times blaming themselves or the parents (Van Dinter M., & Graves L., 2012).

Physicians may also grieve for a patient's pregnancy loss, may question own actions or feel some responsibility for the outcome. Difficulty in providing support to the family may result (Van Dinter M., & Graves L., 2012).

The couple felt prepared for the turn of events since the prognosis of the pregnancy was already known to them. Remy and Fidel were against aggressive neonatal resuscitation to spare the baby from further suffering, knowing the small odds he had of survival. While Remy could talk about her feelings, Fidel was not ready to talk about how he felt after losing the baby.

The couple reported that faith has helped them during this difficult time. The major difficulty the family had was still in finding funds to sustain regular hemodialysis.

The changes in the family can also be viewed in a positive light since the index patient found her husband and children as a source of strength, owing to the open communication among the family members during this time and their sharing responsibility with the housework. While Emily was scared for her mother and the baby, she also became afraid for her own health, which resulted in a decision to take better care of herself.

INTERVENTIONS

The family was assisted as they went through the phases from the impact phase up to early adjustment to outcome. The disease and

treatment plan were explained in simple terms in an effort to dispel the anxiety that the patient and the family members felt and to avoid creating confusion. This would ensure that the family can absorb essential medical information and to establish open lines of communication between the doctors and the patient and the family. Coordination of the treatment plan with the other doctors on board was also done.

Assistance in mobilizing economic resources was done by referring the family to the Medical Social Service for access to the DOH-Medical Assistance Fund. The family was encouraged to apply for assistance from PCSO for Remy's hemodialysis. The couple was also advised by the service to complete their Philhealth contributions to be able to use the coverage during succeeding hospitalizations and/or during the birth. To help the family access medical services in the community, a list of outpatient hemodialysis centers close to their home was provided by the Renal service, to continue dialysis sessions.

Remy's status after the first hospital discharge was followed through SMS, with updates being received from the eldest daughter which revealed the problem encountered in undergoing outpatient hemodialysis. Communication with the eldest daughter and coordination with the other services resulted in eventual readmission for the hemodialysis that Remy needed.

Psychosocial support was provided to the index patient and the other family members with her in the hospital by allowing them to ventilate emotions.

A brief bereavement interview was conducted and the couple both reported feelings of hurting and sadness after losing the baby. However, the couple said they had already accepted the prognosis of the pregnancy as it was explained to them early on. There were no symptoms present that could be problematic manifestations of grief for either one of them at that time.

The following measures have been recommended when confronted with a patient dealing with pregnancy loss and applied: (1) assess the level of grief and individualize counseling accordingly, (2) acknowledge and try to dispel guilt if present, (3) acknowledge the grief, (4) include the father in the counseling, (5) provide comfort, empathy and

and support. Other measures include (6) guiding on how to share the news, (7) reassuring them about the future, and lastly, (8) anticipating grief on its anniversary (Griebel, Halvorsen, Golemon, & Day, 2005; Van Dinter M., & Graves L., 2012).

In general, while the couple was experiencing grief in response to pregnancy loss, at this time, they were more preoccupied with Remy's illness and treatment.

Plans for Remy's case was as follow: (1) to follow up the family's Philhealth coverage, (2) to apply for assistance from PCSO, (3) to be able to have the requested labs done for follow-up check-ups, (4) to ensure continued intake of prescribed medications, (5) to continue following the prescribed diet for her conditions, (6) to follow-up as scheduled with the other clinics, (6) to follow up for AV fistula creation and tubal ligation.

Long-term plans for the family's wellness include ensuring continued open communication among family members. Second, the family needs to be ensured that the family transitions through the family life cycle changes expected during the launching family stage. Third, adjustment of the whole family to the "new normal" needs to be ensured as Remy gets better and becomes able to assume her previous role in the household. Another goal was to make sure that Fidel would be able to return to work in the near future.

The individual wellness plans for the members of the family include exercise, dietary prescription, dental exam and annual chest x-rays, vaccinations for all members, and breast exams for Remy, Emily and Anna. Individual wellness plans specific for each family member are as follows: for Felix, maintenance of smoking cessation and abstinence from alcohol; for Jeremy, anticipatory advice on the avoidance of vices; for Anna, birth spacing.

PERSONAL INSIGHTS

The family physician has an under-appreciated role in the coordination of care of patients requiring multidisciplinary care. Knowledge in the care of a pregnant patient, beyond providing prenatal care, should also be part of the experience of a family medicine trainee.

Assessing the impact of illness and the factors that affect the ability of families to cope with illness in a family member is a skill that should be applied to patients with potentially serious or chronic conditions.

Prognosticating patients to prepare families for possible bad outcomes is a skill that is necessary in family medicine

Lastly, patient care does not end upon patient's discharge or at the end of their outpatient consults until we see them again for follow-up. Certain situations call for a doctor to follow up patients through other means such SMS and phone calls, and to make arrangements for their behalf.

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A Case of Nevus Lipomatosus Superficialis in a 14-year-old Filipino Female*

Ana Aurelia M. Santos, MD
Karen M. Prieto, MD, DPDS
Charlene U. Ang-Tiu, MD, DPDS
Milali T. Torres, MD, DPDS

Abstract

Introduction: Nevus lipomatosus superficialis is a rare benign hamartomatous skin lesion. It is classified into 2 types: solitary and multiple. Lesions consist of multiple, flesh-colored or yellow papules and/or nodules in a segmental pattern, with a linear, zosteriform, or along the lines of skin folds distribution. Surfaces are smooth, but may also have verrucous or cerebriform appearance. Pathogenesis is unknown, but there is speculation that precursor cells around dermal blood vessels give rise to mature fat cells in a mosaic pattern. Incidence is presently unknown, but this is the first reported case in this institution. Histopathology reveals presence of aggregates of mature adipose tissue among the collagen bundles of the dermis.

Case Summary: DF is a 14-year-old, Filipino, female, who consulted due to multiple, pedunculated, soft papules over the right lower back, and extending to the right flank, with a clustered arrangement. There was no history of trauma or manipulation, nor was there pain, pruritus, or other associated symptoms. Past medical, family, and social history were non-contributory. Initial impression was acrochordon. Excision biopsy revealed mature adipose tissue in the dermis, which is diagnostic for nevus lipomatosus superficialis. Serial excision was done.

CONCLUSION: Excision is the treatment of choice. Other treatment options that can be explored are CO₂ laser, cryotherapy, and intralesional injection of phosphatidylcholine, which yield promising results recommended by other studies. Dermatopathology plays a vital role in the diagnosis of this condition. A high index of suspicion, a good clinical eye, and dermatopathologic analysis are essential tools in clinching the diagnosis.

**From the Department of Dermatology, East Avenue Medical Center, Quezon City, Philippines*

INTRODUCTION

Nevus lipomatosus superficialis, also known as nevus lipomatosus superficialis of Hoffman and Zurhelle, is a rare benign hamartomatous skin lesion. It is divided into 2 subtypes: solitary and multiple. The solitary type presents as a single, soft, pedunculated papule located in any part of the body. The multiple type appears within the first 2 decades of life, where lesions consist of multiple, grouped, flesh-colored or yellow papule and/or nodules in a segmental pattern. In this report, we describe the first known case of nevus lipomatosus superficialis in a 14-year Filipino female, which was managed by excision of lesions.

CASE REPORT

This is a case of a 14-year-old Filipino female from Quezon City who sought consult due to appearance of pedunculated papules over the right lower back.

Two years prior to consult, patient noted appearance of skin-colored papules associated with intermittent pruritus starting on the right lower back, which later involved the right flank. Papules were gradually noted to increase in number and size, with a clustered arrangement. There was neither history of trauma, manipulation, pain, loss of sensation, nor other associated symptoms. No intervention or consult done. Lesions persisted, hence consult.

The review of systems, past medical history, and family history were unremarkable.

Physical examination was unremarkable. Cutaneous examination showed multiple, ill-defined, clusters of linearly arranged, round to irregularly-shaped, soft, skin-colored papules and nodules over the right flank.

The initial working impression was acrochordon. Differential diagnoses include linear verrucous epidermal nevus, neurofibromas, and nevus lipomatosus superficialis.

The plan was to do excision of the lesions, and was explained thoroughly to the patient and her mother. Informed consent was obtained prior to the procedure. Excision site was marked with a pen. Skin surface was cleansed using povidone-iodine solution, which has a broad antimicrobial spectrum, including fungi. The sterile area was covered with a drape, followed by local instillation of anesthetic agent (lidocaine-epinephrine). A fusiform incision was done,

and excision of lesions done. Specimen was sent out for histopathology reading. Subepidermal layers were closed with interrupted dermal stitch using vicryl 4-0, and epidermal layers were closed with prolene 4-0 using running stitch. She was prescribed with Cefalexin 500mg/tablet, 1 tablet every 4 hours for 7 days, Mefenamic acid 500mg/tablet, 1 tablet every 8 hours as needed for pain. She was also advised proper daily wound care and to come back after 1 week for removal of sutures.

On third consult, patient came in for follow-up. She was conscious, coherent, ambulatory, and was compliant with prescribed medications and instructions. Cutaneous examination revealed a solitary, well-defined, linearly-shaped, surgical wound over right flank. Wound dehiscence was noted. Histopathologic examination of the excised specimen revealed an exophytic polyphoid structure with papillomatosis and deposition of mature adipose tissue in the dermis. These features are consistent with a diagnosis of nevus lipomatosus superficialis. It is a benign condition, and treatment was done for cosmetic purposes. Removal of sutures was done. Na fusidate 250mg/tablet, 1 tablet 2x a day for 7 days was prescribed, as well as compression dressing. She was advised to come back after 1 week for follow-up.

DISCUSSION

Nevus lipomatosus superficialis, also known as nevus lipomatosus superficialis of Hoffman and Zurhelle, is a rare benign hamartomatous skin lesion¹. It is divided into 2 subtypes: solitary and multiple. The solitary type presents as a single, soft, pedunculated papule that may be located in any part of the body, and is usually seen in individuals in the 3rd-6th decade of life. The multiple type appears within the first 2 decades of life, and consists of multiple, grouped, flesh-colored or yellow papule and/or nodules in a segmental pattern. Distribution of the lesions is usually linear, zosteriform, or along the lines of the skin folds. Surfaces are smooth, but may also have verrucous or cerebriform appearance. Pathogenesis is unknown, but there is speculation that precursor cells around dermal blood vessels give rise to mature fat cells in a mosaic pattern¹. Ectopic fat cells in dermis are derived from perivascular mesenchymal tissue. Histopathology reveals presence of aggregates of mature adipose tissue among the collagen bundles of the dermis². Nevus lipomatosus superficialis is a benign condition, and management is done for cosmetic purposes³. Excision is the treatment of choice¹. Since the patient is female and an adolescent, she is

conscious of the unsightly appearance of the lesions, hence she opted for excision. The plan is to do serial excisions because of the number of lesions. Excision biopsy was done on the first session, which was both diagnostic and therapeutic. Subepidermal layers were closed with interrupted dermal stitch using vicryl 4-0, and epidermal layers were closed with prolene 4-0 using running stitch. Polyglactin 910, also known as vicryl, is a synthetic braided copolymer of glycolide and L-lactide and is absorbable. It has good ease of handling, fair knot security, and low tissue reactivity that makes it a good choice for subcutaneous closures¹. Polypropylene (prolene) is a non-absorbable suture that has high plasticity and stretches with tissue swelling, which reduces the likelihood of postoperative track marks¹.

Patient came back for consult three weeks after the scheduled follow-up. Upon physical examination, there was a solitary, well-defined, irregularly-shaped surgical wound over right flank. Wound dehiscence was noted. There were no symptoms of bleeding, pain or fever noted. Wound dehiscence may be caused by location of the excision site in the body, infection, pressure on sutures, injury to the affected area, weak tissue or muscle at the wound area⁴. In the patient's case, this may be due to the location of the excision site on a highly mobile area of the body, which is the right flank.

Nevus lipomatosus superficialis can also present in a variety of ways. Brasanac et al (2005) reported a case of a 47-year-old female from England that had a history of skin-colored papules and nodules in the sacral region since birth, associated with pain. Resection of lesion was done. Histology showed infiltration of fat cells in dermis with multiple folliculosebaceous cystic hamartomas and dermoid cysts⁵. Kwon et al (2002) reported a case of a 72-year-old male from South Korea with chief complaint of left nasal obstruction of 10 years. On physical examination, there was a round, fleshy, skin-colored mass connected to skin of left nasal vestibule. Excision was done. Histopathology revealed presence of mature ectopic fat tissues embedded in dermis. There was no recurrence of the lesion after 10 months of follow-up⁶.

Other treatment options that can be offered to patients who are unable to undergo surgery are CO₂ laser, cryotherapy, and intralesional injection of phosphatidylcholine. In a study by Jung et al (2007), they treated affected patients with CO₂ laser with staged excisions and covered with local

advancement flaps. Patients were reported to be satisfied with the results, and recurrence was not observed⁷. Cryotherapy was used by Al-Mutairi et al (2005) in a case of a 43-year-old male diagnosed with nevus lipomatosus superficialis. Liquid nitrogen cryotherapy was administered by spray method at 2-week intervals, and after 3 sessions, there was considerable size reduction of lesions⁸. Another treatment option, which is not available in the Philippines, is the use of intralesional phosphatidylcholine. Phosphatidylcholine is a class of phospholipids that incorporate choline. It is a major component of biological membranes, and can be obtained from a variety of sources, such as egg yolk and soybeans. Intralesional injection with phosphatidylcholine has been initially used in the treatment of atheroma plaques in cardiac diseases. Hexsel and Serra (2003) reported their experience on the use of 250mg/mL phosphatidylcholine injections in the treatment of localized fat deposits among patients with a minimum interval of 1 week and mean interval of 15 days between injections. Results showed that phosphatidylcholine was effective in reduction of fatty areas⁹. Similar studies done by Kim et al (2011), Rittes (2009) and De Paula et al (2009) also showed promising results of with intralesional injection of phosphatidylcholine^{9,10,11}. These treatment options can be fully explored provide alternative treatment options for patients who are hesitant to undergo excision, and for those with large areas of affectation.



Figure 1. A 14-year-old Filipino female presented with multiple, ill-defined, clusters of linearly arranged, round to irregularly-shaped, soft, skin-colored papules and nodules over the right flank



Figure 2: Excision, which is both diagnostic and therapeutic, was done



Figure 3. Surgical site closed with prolene 4-0

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Hyper Immunoglobulin E Syndrome with Concomitant Folliculotropic Mycosis Fungoides in a Filipino Child Treated with Narrowband UVB Phototherapy: A Case Report*

Ma. Criselda M. Rescober, MD¹
Ma. Luisa Abad-Venida²

Abstract

Hyper Immunoglobulin E Syndrome (HIES) is a primary immunodeficiency disorder characterized by the classic triad of recurrent staphylococcal abscesses, frequent airway infections, and increased serum immunoglobulin E. It is now widely accepted as a multisystem disorder with involvement of the skeletal, connective tissue, dental, and vascular systems. Lymphoma has been reported to occur at an increased frequency. Folliculotropic mycosis fungoides (FMF) is a rare variant of cutaneous T-cell lymphoma in which the neoplastic T lymphocytes display tropism for the follicular epithelium. We report a case of a 14-year old Filipino male with the classic type of HIES presenting with severe eczema associated with intractable pruritus, recurrent respiratory tract infections, cold abscesses, and a serum IgE of 9,350 IU/ml. Skin biopsy also revealed findings consistent with FMF. Narrowband UVB (NB-UVB) phototherapy was initiated three times a week with continuation of supportive medication. Patient reported significant relief of pruritus and gradual improvement of eczematous lesions after one month.

Keywords: Hyper IgE syndrome, Job's syndrome, Folliculotropic mycosis fungoides, narrowband UVB phototherapy

OBJECTIVES

To present the first documented case of Hyper Immunoglobulin E syndrome in Jose R. Reyes Memorial Medical Center

To present the first documented case of Hyper Immunoglobulin E syndrome with concomitant Folliculotropic Mycosis fungoides in the Philippines

To present the first case of Hyper Immunoglobulin E syndrome with concomitant Folliculotropic Mycosis fungoides treated with Narrowband UVB phototherapy

SIGNIFICANCE

Hyper Immunoglobulin E syndrome is a primary immunodeficiency disorder presenting with recurrent abscesses, pneumonia, and elevated serum IgE levels. In patients presenting with chronic relapsing eczema with recurrent skin infections, it is important that clinicians learn to recognize, or at least, think of HIES as a differential diagnosis. It is also imperative to recognize symptoms that may already be part of a syndrome. HIES is related to an increased risk of lymphoproliferative malignancies such as mycosis fungoides. Knowledge on the clinical spectrum of HIES will aid in the early diagnosis and prediction of the course and prognosis of this disease, thereby prolonging life.

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

¹Resident, Department of Dermatology, Jose. R. Reyes Memorial Medical Center, Philippines

²Consultant, Department of Dermatology, Jose R. Reyes Memorial Medical Center, Philippines

INTRODUCTION

Hyperimmunoglobulin E Syndrome (HIES) is a rare, complex primary immunodeficiency disorder with a worldwide prevalence of 1 in 1,000,000 persons with approximately 250 cases reported in literature.¹ Two distinct entities have been recognized – autosomal dominant HIES (AD-HIES) and autosomal recessive HIES (AR-HIES). However, most cases are considered sporadic.² Both types are characterized by the triad of recurrent staphylococcal abscesses, respiratory infections, and elevated serum IgE. In AD-HIES, there is also involvement of the skeletal, dental, connective tissue, and vascular systems, which is absent in AR-HIES. In patients with HIES, an increased incidence of lymphoproliferative disorders have been noted, particularly non-Hodgkin's lymphomas.³ Cutaneous T-cell lymphomas are non-Hodgkin's lymphoma characterized by malignant T cells, with mycosis fungoides (MF) being the most common form. Folliculotropic mycosis fungoides (FMF) represents a distinct variant of MF that shows infiltrates of neoplastic T-helper cells that involve the follicular epithelium, with minimal or no involvement of the overlying epidermis. Patients present with alopecia and acneiform lesions such as pustules, milia, and clustered comedones involving most commonly the head and neck.⁴ Only one case report of HIES with concomitant MF in literature exists. Narrowband UVB therapy is currently used for pruritic dermatoses such as atopic dermatitis and is the standard treatment in managing MF in children. No case reports have been presented in literature of HIES with MF treated with NB-UVB. This is a case of a 14-year-old Filipino male with HIES and concomitant FMF treated with NB-UVB for the relief of pruritus and improvement of lesions.

CASE REPORT

A 14-year-old male from Quezon City, Philippines, sought consult at the outpatient department due to generalized lichenified papules and pustules on severely dry skin.

Three years prior to consult, patient noted multiple skin-colored papules on the dorsa of both hands associated with intractable pruritus. Lesions gradually evolved into vesicles and pustules and later became lichenified. He sought consult at a dermatologist and was prescribed Cetirizine 10mg/tablet OD and emollient which gave temporary relief. Pruritus would abate but would recur, hence, oral anti-histamine was shifted to Chlorphenamine maleate 4mg/tablet TID and then to Loratadine 10mg/tablet

OD. Same lesions developed on the upper and lower extremities. Patient was then lost to follow-up.

Two years prior to consult, with the persistence of lesions and spread to the trunk, he was brought to a government pediatric hospital where an initial impression of lichen planus vs. acquired perforating disease was made. Clobetasol propionate 0.05% ointment BID was advised. A 4mm skin punch biopsy from the left elbow and leg revealed findings consistent with psoriasiform dermatitis. He was then referred to a dermatological institute where he was managed as a case of chronic eczema. Patient was subsequently treated with shifting topical corticosteroids, oral anti-histamines and emollients. Lesions and pruritus would be alleviated but would recur. Patient also reported developing multiple abscesses on the extremities with no associated tenderness, warmth, erythema, and fever. Due to financial constraints, patient was not able to come back for consult.

One year prior to consult, pruritic papules and pustules were observed to be spreading to his face. He also noted gradual hair loss and excoriations starting from the parietal scalp. Due to the increase in the number of lesions and persistence of pruritus, patient came back to his previous doctor. Skin punch biopsy of the scalp showed scarring alopecia with eosinophilic spongiosis. He was then prescribed Minoxidil 5% lotion BID, Betamethasone dipropionate 0.05% ointment for the scalp and lichenified lesions, Prednisone 30mg/day, and oral anti-histamines. He was also instructed to apply Erythromycin 4% cream BID on infected lesions. Patient reported 50% improvement of his eczema and sparse growth of hair. However, symptoms persistently recurred. Total serum IgE was requested and was markedly elevated at 9,350 IU/ml. He was then advised referral to Allergy-Immunology service but was lost to follow-up. Persistence of symptoms subsequently prompted consult at our institution.

On systems review, patient reported recurrent cough and colds (around 6-8 times a year), occasional ear discharge, and repeated episodes of pustules and abscesses observed not to be associated with cardinal signs of inflammations. Past medical history revealed an undocumented seizure disorder starting at 6 years old. He was maintained on Carbamazepine 200mg/tablet BID. Seizure episodes recurred until he was 9 years old. Electroencephalogram done revealed multifocal epileptiform discharges from the left fronto-centro-parietal area. He had no history of other previous illnesses and hospitalizations. No similar illness and malignancies was reported in the family history.

On initial physical examination, patient had a blood pressure of 110/70, heart rate of 86 bpm, respiratory rate of 18 cpm, and temperature of 36.5°C. Based on the Waterlow classification, patient had moderate wasting (70%) and stunting (86%). Inter-pupillary distance was increased at 60 mm (normal: 41-55 mm) denoting hypertelorism. Dental examination showed retention of primary 2 mandibular and 2 maxillary teeth (Figure 4). The neurologic, cardiovascular, respiratory, gastrointestinal, and musculoskeletal systems were unremarkable. On dermatological examination, he had generalized lichenified hyperpigmented papules and numerous pustules topped with excoriations over very dry skin with accentuated skin markings (Figure 1-2). There were also multiple well-defined alopecic patches topped with excoriations on the scalp (Figure 3.B.). There was absence of the eyebrows, eyelashes, and pubic hair. Multiple milia were noted to be distributed over the head and neck. Distinctive facial features such as a prominent forehead, deep-set eyes, broad nasal bridge, and rough skin with prominent pores were observed. (Figure 3.A.)

Laboratory work-up revealed leukocytosis (18.49×10^9 /L) with eosinophilia of 25% and total eosinophil count of 4,622 cells/ μ L. Serum IgE was elevated at 9,350 IU/ml, a 57-fold increase of the normal value. Urinalysis and fecalysis showed normal results ruling out parasitic infections. Thyroid stimulating hormone and FT₄ were normal and rapid plasma reagin was non-reactive. Chest radiograph and head CT scan were likewise unremarkable. A 4 mm skin punch biopsy done at our institution showed findings consistent with mycosis fungoides. The epidermis showed some epidermotropism with parakeratotic invaginations in dilated follicular structures ("folliculotropism"). The papillary dermis was thickened with lichenoid infiltrates, lymphohistiocytic infiltrates and telangiectatic blood vessels (Figure 5. A-B). Immunohistochemical studies revealed the lymphocytes to be CD3-positive T cells. Rare CD20-positive B cells were identified. Alcian blue stain showed numerous mucin deposits surrounding follicular structures (Figure 6. A-D). A diagnosis of mycosis fungoides, folliculotropic variant, was then made. According to the International Society of Cutaneous Lymphoma (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC), patient is stage IIB (T₃ N₀ M₀B₀). (Table 1)

During regular consults, patient developed difficulty of breathing and cough. Chest xray was

done which revealed pneumonia. He was then admitted at another government-owned hospital.

The National Institute of Health (NIH) Scoring System with Clinical and Laboratory Tests for Related Individuals with HIES (Table 2) was used to diagnose HIES, and revealed a total-point score of 51 (10 points for serum IgE >2,000 IU/ml, 8 points for skin abscesses, 2 points for pneumonia, 8 points for more than 3 retained primary teeth, 6 points for eosinophil count > 800 cells/ μ L, 5 points for characteristic face, 4 points for severe eczema, 4 points for > 6 upper respiratory infections per year, 4 points for the presence of lymphoma). However, his family does not have any history of HIES. Thus, our patient may be a sporadic case but may likely carry the HIES genotype.

Patient was then started with Prednisone 20 mg OD, Cetirizine 10 mg/tablet, Chlorphenamine maleate 4mg/tablet TID, and topical corticosteroids mixed with petroleum jelly (1:10) starting with Clobetasol propionate, Betamethasone dipropionate, Fluocinolone acetonide, and Mometasone furoate at 2-week intervals. He was also prescribed Ranitidine 150 mg/tablet OD, and Vitamin D and Calcium tablet BID. On subsequent follow-ups, Montelukast 10 mg/tablet and Cloxacillin 500mg/tablet QID for impetiginized lesions were added. Frequent application of emollient was strongly advised. He was also put on a hypoallergenic diet. After one month, patient reported diminished pruritus by approximately 50% and decrease in the number of lesions. However, he still complained of on and off stubborn pruritus.

Before initiating narrowband UVB phototherapy, liver and renal profiles were requested which were normal. He was also referred to Ophthalmology service for clearance. On examination, patient had punctate epithelial keratitis, OU. He was then prescribed Tobramycin eye ointment BID for 1 week. NB-UVB phototherapy for Fitzpatrick skin type III following Dr. Vichit's protocol was given 3 times a week beginning with 360 mJ/cm² with regimen following the standard treatment. He was advised to continue present medications and to apply sunblock with SPF > 50. Response to treatment with respect to pruritus was monitored every week. Patient is currently on the 12th session with current dose of 1130 mJ/cm² and a cumulative dose of 7,772 mJ/cm². He reported steady decrease in the pruritus of approximately 10% weekly. Photography was done every 2 weeks which showed lessening of the number of lesions especially at the back (Figure 7. A-B) and smoothening of the facial skin (Figure 8. A-B). During the course of therapy,

patient tolerated the procedure well with no episodes of erythema, burning, and nausea. However, he complained of a “cold” abscess described as localized thickening on the medial aspect of the right leg associated with pain. No erythema, discharge, and fever observed. After 2 days, he noted purulent discharge from the affected area.

DISCUSSION

HIES is a primary immunodeficiency disorder characterized by the triad of recurrent staphylococcal abscesses, frequent respiratory infections, and elevated serum IgE (serum IgE > 2,000 IU/ml). It was first described as Job’s syndrome by Davis et al. in 1996 referring to the biblical character, Job, who was “smote with sore boils”. They reported two girls suffering from recurrent eczema, pneumonia, and recurrent abscesses distinct for their lack of erythema, warmth, or tenderness. In 1972, Buckley et al. further described HIES in two boys who had the same symptoms but with characteristic facial appearance and extremely elevated serum IgE.⁶ Since then, involvement of the skeletal, dental, connective tissue, and vascular system has been documented. It is an extremely rare condition with a worldwide prevalence of 1:100,000 with approximately 250 cases reported in literature.¹ It occurs in equal frequency among males and females.³ Most cases are sporadic, but both AD-HIES and AR-HIES have been recognized.⁵ In the Philippines, no case reports of HIES, more so HIES with MF, have been published from local journals, specifically from the Journal of Philippine Dermatological Society from 1990 to 2012. No cases have been reported from other dermatological institutions in our country. This is the first case of HIES documented in our institution.

AD-HIES or the classic type presents with the typical triad of symptoms but with a wide spectrum of clinical features divided into immunologic and somatic features. Immunologic features and their frequencies include peak serum IgE > 2,000 IU/ml (97%), moderate-severe eczema (95%), eosinophilia (90%), recurrent pneumonia (87%), abscesses (87%), mucocutaneous candidiasis (83%), newborn rash (80%), recurrent sinusitis or otitis (80%), bronchiectasis or pneumatoceles (70%), and lymphoma (5%).⁶ The top 3 most prevalent features are present in our case. Eczema is often worsened by *Staphylococcus aureus* infection. Although frank pus is present on aspiration, cardinal features of inflammation, such as warmth, erythema, and tenderness, are often lacking. These are considered “cold” abscesses

which occasionally occurred in our patient. Presence of cold abscess is pathognomonic for HIES but is not needed for a definitive diagnosis. Recurrent pyogenic pneumonia usually starts in early childhood. *S. aureus* is the most common pathogen, but *Streptococcus pneumoniae* and *Haemophilus influenza* also frequently complicate respiratory infections. Healing of pneumonia often leads to subsequent formation of pneumatoceles and bronchiectasis – parenchymal abnormalities that may be sites of fungal infection caused by *Aspergillus* sp. or gram negative pathogens (*Pseudomonas aeruginosa*). Opportunistic infections are also seen in HIES. Pneumocystis jiroveci pneumonia, cryptococcosis, histoplasmosis, and mucocutaneous candidiasis have been reported.³ Somatic features include characteristic face (85%), hyperextensibility (70%), retained primary teeth (70%), focal hyperintensities on brain MRI (75%), minimal trauma fractures (65%), scoliosis more than 10 degrees (60%), coronary vasculature anomalies (60%), and Arnold Chiari I malformations (40%).⁷ Of these, distinctive facial features and dental abnormalities are observed in our patient.

The majority of cases of AD-HIES are caused by mutation in the signal transducer and activator of transcription 3 (STAT3). STAT3 is involved in the signal transduction of many cytokines and plays a role in wound healing, angiogenesis, cancer, and immunity. STAT3 is integral to Th17 cell differentiation and IL-17 production.⁸ Th17 cells are thought to be important in the host defense through neutrophil recruitment, upregulation of antimicrobial peptides, and anti-fungal protection. Th17 cells are also essential for IL-22 secretion which is critical for beta-defensin production. Lack of beta-defensin is implicated in the susceptibility of HIES patient to *S. aureus* infection. HIES is also thought to result from Th1/Th2 cytokine production imbalance with Th2 predominance. Th1 cytokines activate cellular responses while those of Th2 induce the humoral immune system. A bias towards Th1 is associated with autoimmune diseases while Th2 predominance induces allergic reaction through hypereosinophilia and hyper IgE production. In STAT3 mutation, main Th1 cytokines such as IFN- γ and IL-2 are decreased whereas IL-4 and IL-10, primary Th2 cytokines, are increased.⁹ Experimental studies have observed that decreased IFN- γ and increased IL-4 predispose to IgE production. However, the exact mechanism explaining the elevation of IgE remains poorly understood.⁷ The chief concern of our case is severe pruritus. This is attributed to the increase in mast cells that goes with the elevation of IgE. Another feature of HIES is eosinophilia. Eosinophils play a role in allergic

conditions such as atopic dermatitis, helminthic infection, and drug hypersensitivity. IgE receptors are known to be expressed on eosinophils. Eosinophilia is then related to pronounced expression of IgE, thereby inducing pruritus as mediated by mast cells.¹⁰

Diagnosis of AD-HIES is based on the NIH Scoring System with Clinical and Laboratory Tests for Related Individuals with HIES.³ A score of > 40 is suggestive of AD-HIES, 20-40 indeterminate, and < 20 is unlikely to indicate AD-HIES. The hallmark of this syndrome is an increased concentration of IgE, frequently higher than 5,000 IU/ml, and in some, reaching up to 100,000 IU/ml. A cut-off of 2,000 IU/ml is considered the cut-off point in establishing diagnosis. In adulthood, IgE level normalizes in 20% of cases. The severity of infectious complications do not correlate with serum IgE.³ Eosinophilia is present in 90% of cases and values considered significant wavers within at least 2 SD above the normal range (usually higher than 700 cells/ μ L).

In 2004, Renner et al. reported an autosomal recessive form of HIES, sharing the same triad of recurrent staphylococcal abscesses, recurrent respiratory infections, and elevated IgE, but with the following differences: 1.) increased incidence of neurologic abnormalities, 2.) increased susceptibility to viral infections such as herpes simplex virus and molluscum contagiosum, 3.) absence of somatic features of AD-HIES, 4.) increased risk for malignancy, 5.) extremely elevated eosinophils and IgE, and 6) inability to form pneumatocoles. It is caused by dedicator of cytokinesis 8 gene (DOCK8) mutation which also causes Th17 deficiency.¹² Autosomal recessive pattern is assumed because of consanguinity and multiple affected siblings. This form is more lethal in childhood because of early-onset neurologic complication such as ischemic infarctions, hemiplegia, and subarachnoid hemorrhage.

The mainstay of treatment is prevention and control of infection. Antibiotics directed against *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* are recommended. The use of long-term antibacterial chemotherapy, including trimethoprim/sulfamethoxazole, semisynthetic penicillin, or cephalosporins significantly reduces skin abscesses and staphylococcal pneumonia. Sequelae of pneumonia, such as pneumatocele, lung abscess, and bronchiectasis may require surgical intervention. Patients are advised to apply topical antibacterials on localized infected lesions. Patients

are advised oral anti-histamines and liberal use of emollients for pruritus. Experimental studies about the use of IFN- γ to improve neutrophil chemotactic functions have been undertaken. However, a case of autoimmune thrombocytopenia in one patient has been reported. Monitoring of complications must be undertaken closely by periodic imaging of the bones, chest, and heart. Referral to ophthalmology and dental services are advised.

Prognosis with AD-HIES is good with patients reaching adulthood. However, lifespan is relatively shortened compared to the healthy population. Fatal hemorrhage due to cystic lung disease infected with opportunistic agents, metastatic fungal disease to the brain, and lymphoma are the most common causes of mortality.¹³

Patients with HIES are seen to have 5% increased risk for lymphoma.⁷ Although HIES is a T cell-mediated disorder, the lymphoid malignancies reported in literature are mostly B cell in origin with few reports of cutaneous T cell lymphomas. Mycosis fungoides is the most common type of cutaneous T cell lymphoma in adults with a prevalence of 0.36 per 100,000 persons.²¹ Although, it is rare in children, it happens to be the most common variant of cutaneous T-cell lymphoma in children and adolescents as well. Mycosis fungoides has been reported to start in childhood in around 4% of all MF cases. Limited (involving less than 10% of the total skin surface) or generalized (involving more than 10% of the total skin surface) patch-stage disease without lymph node involvement or with histologically negative nodes are the most common clinical presentations of childhood MF.²² In literature, a single case report exists linking MF and HIES.¹⁹ The association between HIES and, specifically, MF has yet to be elucidated and the mechanism underlying susceptibility to lymphoma remains unclear.

Folliculotropic mycosis fungoides is a rare clinical variant of MF characterized by follicular cysts, or comedo-like lesions with preferential involvement of the head and neck (80%).²⁰ The extremities and trunk can also be involved. Infiltrated plaques (55%), acneiform lesions (comedo-like and epidermal cysts) (45%), and follicular keratosis-pilaris-like lesions (45%) are the more prominent features. These lesions are often accompanied by alopecia and moderate-to-severe pruritus. Our patient presented with multiple alopecic patches topped with excoriations on the scalp, numerous milia on the face and neck, and loss of eyebrows, eyelashes, and pubic hair. Little is known

about the etiology of FMF, although it has been suggested that the epithelium of the hair follicle might express higher levels of skin-selective homing receptors and adhesion molecules than the epidermis leading to preferential tropism of the neoplastic lymphocytes towards the follicle.²³ Diagnosis is made clinically and histopathologically. In addition to the classical findings of MF, emphasis was laid on the following histological features: degree and density of folliculotropism of lymphocytes, presence of follicular mucin (confirmed by Alcian blue - PAS stain), presence and number of eosinophils (< 5, 5–20, > 20 per section), location of folliculotropism (infundibular / isthmic / bulbar), presence of granulomas, and presence of conventional epidermotropism outside the follicles.²⁴ Histopathological findings in our patient's biopsy were consistent with findings in FMF that include selective infiltration of the follicular epithelium by atypical lymphocytes and mucinous degeneration of the follicular epithelium.

Staging of MF is based on skin manifestations, nodal, visceral, and blood involvement. (Table 1) Our patient presented with skin manifestations of more than 10% of body surface area. However, FMF has been shown to be associated with a worse prognosis than expected for clinical stage and is considered equivalent to T₃ tumors.²⁵

Classic MF in children with no extracutaneous involvement has a good prognosis. However, the course of FMF with concurrent HIES is unknown. In the case report of Miyayama et al.¹⁹, the patient died 2 years after the findings of lymph node involvement and extremely elevated serum IgE (536,640 IU/ml).

Recurrent and intractable pruritus is one of the complaints of our patient, hence, addressing it will bring considerable relief and improvement of the quality of life. HIES and atopic dermatitis share common features being both Th2-mediated, with increased IgE levels, and eosinophilia. A recent systematic review concluded that in view of its efficacy, benefit-risk profile, and costs, NB-UVB should be considered as the first-line phototherapeutic option for moderate to severe AD.¹⁴ NB-UVB reduces the production of Th2 chemokines without excess production of proinflammatory cytokines, suggesting its therapeutic effectiveness on Th2-mediated skin disorders such as atopic dermatitis, subacute prurigo, and eosinophilic pustular folliculitis.¹⁵ NB-UVB phototherapy has also been used in the treatment of childhood MF especially for early stages (I-II). However, MF is rarely cured. Instead,

most treatments are aimed at controlling the symptoms, improving the quality of life, and preventing the disease from progressing into later stages. Because of the perifollicular localization of the dermal infiltrates, patients with follicular MF should always be considered to have tumor-stage disease, regardless of the clinical appearance of the skin lesions. UVB irradiation is thought to be therapeutic by suppressing the function of the neoplastic population of clonal T-cells in the skin and around hair follicles, and by serving as an upregulator of the immune system.²⁶ Following this line of thought, the rationale for performing NB-UVB on a patient with HIES and MF is acceptable. NB-UVB was also initiated on a 56-year-old Japanese female with FMF. After 24 (total 12.3 J/cm²) exposures, all of the lesions had completely disappeared.²⁶ On follow-up 3 years after her presentation, there were no new skin lesions. In a case report by Hinrichs et al.¹⁶, a patient with HIES was successfully treated with a 4-month course of UVA irradiation 5 times a week. However, we decided to give NB-UVB because of shorter exposure time, shorter course of therapy, longer periods of remission, and less side effects, making it safer to use in children.¹⁷ The most common adverse effect is erythema followed by a case of painful erythema and reactivation of herpes simplex virus.¹⁴

Patient was put on NB-UVB 3 times a week and was advised to continue other present medications. As relief of pruritus denotes a better prognosis in MF, grading of the severity of pruritus was done weekly. Patient reported 10% improvement each week. Photography was done every 2 weeks and after 1 month of treatment, smoothening of the facial skin and decrease in the number of lesions especially at the back were observed. However, after the 12th session, patient complained of thickening of the skin over the medial aspect of the right leg associated with pain. No fever, erythema, and warmth noted. Purulent discharge was expressed from the area 2 days after. He was then advised to start Cefalexin 500mg/tablet QID for 7 days and to apply cool compress which gave prompt relief.

Aside from the clinical improvement, it is advised that periodic monitoring of the CBC, liver and renal profiles, and chest imaging be done to watch out for complications and to assess for adverse effects of phototherapy.

CONCLUSION

Hyperimmunoglobulin E Syndrome is a rare primary immunodeficiency disorder classically characterized by the triad of recurrent staphylococcal abscesses, frequent respiratory tract infections, and elevated serum IgE. With continuing research, it is now widely accepted as a multisystem disorder involving the skeletal, dental, connective tissue, and vascular systems. Diagnosis is mainly clinical in addition to the hallmark of increased serum IgE and eosinophilia. In patients presenting with chronic relapsing eczema with recurrent skin infections, it is important that clinicians learn to recognize, or at least, think of HIES as a differential diagnosis.

Increased risk of lymphoma such as mycosis fungoides has been reported in HIES which further complicates management of this disorder. However, strength of association and mechanism of susceptibility has yet to be determined.

Confronted with a patient with HIES and MF, narrowband UVB phototherapy may be appropriate for the management of these two disorders. NB-UVB phototherapy acts by reversing Th2 response predominance, subsequently leading to decreased IgE and eosinophils, and restraining the function of neoplastic population of clonal T cells in the skin. Based on the response of our patient to the irradiation, NB-UVB is suggested for the management of pruritus, improvement of skin lesions, and suppression of malignant cells. Close monitoring and early recognition of complications is imperative in order to prolong life.

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Figure 1. Generalized lichenified hyperpigmented papules and some pustules topped with excoriations over very dry skin with accentuated skin markings. Note moderate wasting and stunting.



Figure 2. A. Multiple ill-defined hyperpigmented papules topped with excoriations over the back
B. Lichenified papules and plaques with some pustules on both hands.



Figure 3. A. Distinctive facial features are observed such as prominent forehead, deep-set eyes, broad nasal bridge, and wide and fleshy nasal tip. Facial skin was also noted to be rough with excoriations and prominent pores. There is loss of eyebrows and eyelashes. **B.** Multiple well-defined alopecic patches topped with excoriations.



Figure 4. Retained primary lower maxillary teeth

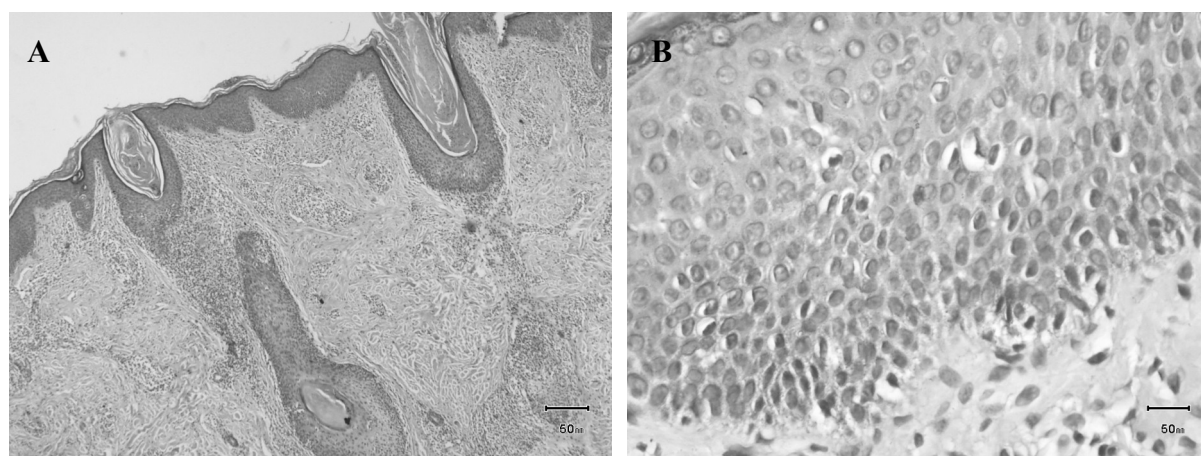


Figure 5. A. Hyperplastic epidermis with parakeratotic invagination in dilated follicular structures. Papillary dermis is thickened with lichenoid infiltrates, patchy dense perifollicular infiltrate of lymphohistiocyte, and telangiectatic blood vessels. **B.** Some epidermotropism.

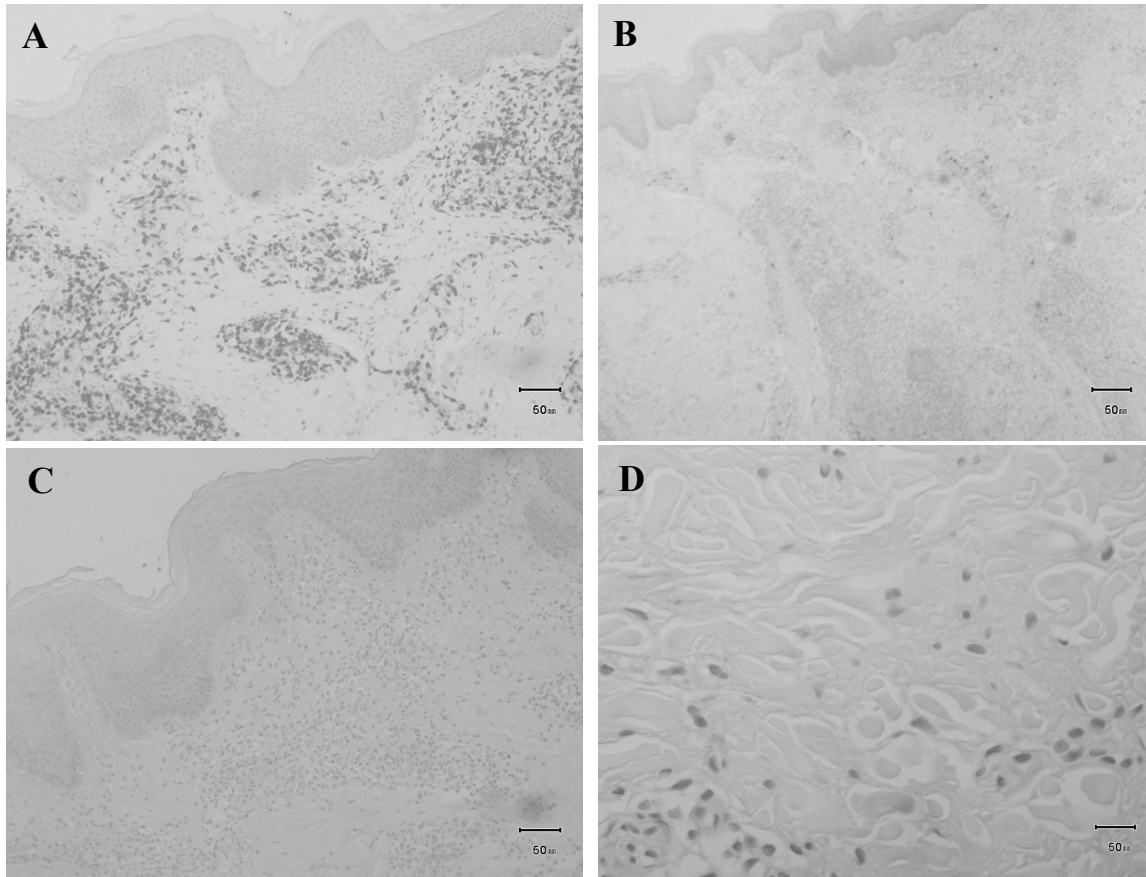


Figure 6. **A.** Immunohistochemical studies revealed the lymphocytes to be CD3-positive T cells. **B.** Rare CD20-positive B cells were identified. **C.** Alcian blue stain showed numerous mucin deposits surrounding follicular structures **D.** Closer look at the mucin deposits.



Figure 7. **A.** Photograph of the back at baseline. **B.** Photography taken at the same area after 12 sessions of NB-UVB phototherapy. Note decrease in the number of lesions.



Figure 8. A. Photograph of the face at baseline. **B.** Photograph taken of the face after 12 session of NB-UVB. Note smoothing of the facial skin and decrease in excoriations.

Table 1 International Society of Cutaneous Lymphoma (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC) Staging of Mycosis

TNMB stages

Skin	
T ₁	Limited patches,* papules, and/or plaques [†] covering < 10% of the skin surface. May further stratify into T _{1a} (patch only) vs T _{1b} (plaque ± patch).
T ₂	Patches, papules or plaques covering ≥10% of the skin surface. May further stratify into T _{2a} (patch only) vs T _{2b} (plaque ± patch).
T ₃	One or more tumors [‡] (≥ 1-cm diameter)
T ₄	Confluence of erythema covering ≥80% body surface area
Node	
N ₀	No clinically abnormal peripheral lymph nodes [§] ; biopsy not required
N ₁	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN ₀₋₂
N _{1a}	Clone negative*
N _{1b}	Clone positive*
N ₂	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN ₃
N _{2a}	Clone negative*
N _{2b}	Clone positive*
N ₃	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN ₄ ; clone positive or negative
N _x	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M ₀	No visceral organ involvement
M ₁	Visceral involvement (must have pathology confirmation [†] and organ involved should be specified)
Blood	
B ₀	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sézary) cells
B _{0a}	Clone negative*
B _{0b}	Clone positive*
B ₁	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B ₂
B _{1a}	Clone negative*
B _{1b}	Clone positive*
B ₂	High blood tumor burden: ≥1000/μL Sézary cells with positive clone*

Table 2. Scoring System with Clinical and Laboratory Tests for Related Individuals with HIES

Clinical Finding	Points ¹									
	0	1	2	3	4	5	6	7	8	10
Highest serum-IgE level (IU/mL) ²	<200	200-500			501-1,000				1,001-2,000	>2,000
Skin abscesses	None		1-2		3-4				>4	
Pneumonia (episodes over lifetime)	None		1		2		3		>3	
Parenchymal lung anomalies	Absent						Bronchiectasis		Pneumato-coele	
Retained primary teeth	None	1	2		3				>3	
Scoliosis, maximum curvature	<10°		10°-14°		15°-20°				>20°	
Fractures with minor trauma	None				1-2				>2	
Highest eosinophil count (cells/ μ L) ³	<700			700-800			>800			
Characteristic face	Absent		Mildly present			Present				
Midline anomaly ⁴	Absent					Present				
Newborn rash	Absent				Present					
Eczema (worst stage)	Absent	Mild	Moderate		Severe					
Upper-respiratory infections per year	1-2	3	4-6		>6					
Candidiasis	None	Oral	Fingernails		Systemic					
Other serious infections	None				Severe					
Fatal infection	Absent				Present					
Hyperextensibility	Absent				Present					
Lymphoma	Absent				Present					
Increased nasal width ⁵	<1 SD	1-2 SD		>2 SD						
High palate	Absent		Present							
Young-age correction	>5 years			2-5 years		1-2 years		$\leq$ 1 year		

Scoring: > 40 Suggestive of AD-HIES
 20-40 Indeterminate
 < 20 Unlikely to indicate AD-HIES

From Grimbacher et al (1999b)

1. The entry in the furthest-right column is assigned the maximum points allowed for each finding.
2. Normal <130 IU/mL
3. 700/ μ L = 1 standard deviation (SD), 800/ μ L = 2 SD above the mean value for normal individuals.
4. For example, cleft palate, cleft tongue, hemivertebrae, other vertebral anomaly, etc.
5. Compared with age- and sex-matched controls

