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MESSAGE

Warm greetings from the Philippine Medical Association!

This Journal features the winning research papers from the Resident's Research Competition for 2017-2018, with the inclusion of other papers which were carefully selected by the Committee on Publications of the PMA.

Resident physicians from healthcare institutions, specialty organizations, medical schools and universities, diligently prepared and completed their papers par excellence. Thus, these research papers are well deserving to be published at this issue of the Journal of the Philippine Medical Association.

PMA strongly supports and promotes the Continuing Professional Development Law or Republic Act 10912 to enhance the practice of the medical profession. In this digital age with rapid advances in technology, our physicians and specialists must have the knowledge and expertise in their respective fields of specialization.

Research has always been an important tool in updating physicians on the current trends and directions in various fields of practice using evidence based medicine. It is one of the components of continuous learning set by Continuing Professional Development which aims to uphold the competencies of clinical practice.

Physicians are strongly encouraged to engage in research and keep abreast with innovations in coming up with valuable research papers. It is our hope that this journal will be a source of valuable pearls of knowledge that will result in high quality healthcare for all Filipinos.

JOSE P. SANTIAGO, JR., MD
President, Philippine Medical Association

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EDITOR'S *notes*

This issue features the winners of both the Original Paper Presentation and the Case Report Category, which the Philippine Medical Association sponsored. The designated Board of Judges for this year selected the winning entries from the various submissions, and came up with the top three placers after a meticulous review and evaluation. We are happy of the outcome, which only goes to show that we are proceeding in the right direction in terms of advancement in research and medical publication. We hope that this trend continues, and we expect an even better reach in subsequent editions.

Also included in this issue are two papers from the Academe, which we deemed worthy to print, as a gauge of the growing interest in the scientific process. May this response generate more participation from other sectors of the medical community, and in turn, elevate the quality of the journal. While progress is indeed noticeable, we still have a long way to go.

AJBAJ

Journal of the
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Instruction for Authors

General Information

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

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

Editorial Policies

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

Ethical Cosiderations

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

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 complaint 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 mush 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 authorsí full names and highest earned academic degrees, and hospital or institutional affiliations. It must also include disclaimer, if any.

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

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

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

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

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Submission

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

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

Comparison of the Anxiety Levels in Children with Acute Lymphoblastic Leukemia and Their Well Siblings Using the Child Drawing: Hospital Manual*

Efraim P. Culminas, MD, Angie Sievert-Fernandez, PhD., CCLS
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ABSTRACT

Objectives. The study aims to determine and compare the anxiety of children with acute lymphoblastic leukemia and their well siblings based on Child drawing: Hospital manual and to identify factors associated with the level of anxiety.

Methods. A prospective cross-sectional study was done in the hematology-oncology outpatient clinic and private clinics of hema-oncology specialist in tertiary pediatric hospitals. The study included children five to eleven years old diagnosed with Acute Lymphoblastic Leukemia (ALL) and their well siblings.

Results. A total of forty dyads of participants were included in the study. ALL patients presented higher anxiety scores than their siblings. However, this was not statistically significant. There is a weak direct correlation between overall anxiety scores of ALL patients and their siblings ($p = 0.017$). There is insufficient evidence to demonstrate an association between select clinical factors with anxiety scores. The linear regression model showed 49.77% in the variation of the anxiety scores.

Conclusions. There is a direct correlation between overall anxiety scores of ALL patients and their siblings. There is a positive association with larger family size and child's response to sibling's illness. A larger families are likely to have a healthier environment. The study showed low to average anxiety levels among participants which may be related to quality of care and support given by the institution and inherent resiliency of the family.

Recommendations. Future research should aim to develop psychological, emotional and behavioral programs in partnerships with families and other social support groups. Future studies should examine other possible cultural and psychodynamic factors prevalent in Filipino Family.

KEYWORDS: *Anxiety, Siblings, Children, Chronic illness, Acute Lymphoblastic Leukemia, Child Drawing: Hospital Manual*

**1st Place, 2018 Philippine Medical Association Original Research Presentation Contest*
***From Philippine Children's Medical Center, Quezon City*

INTRODUCTION

Acute Lymphoblastic leukemia (ALL) is a chronic disease. Leukemia accounted for almost 50% of the total incidence of childhood cancer in the Philippines.[1] The Philippine Cancer facts reported annually that some, 3,500 Filipino children are diagnosed with cancer.[2] These children are at a greater risk of developing mental health or social adjustment problems, resulting in increase in levels of negative affect, higher rates of depression, suicidal behavior and distress.[3,4] Parents become highly distressed and their need to attend to the ill child at the hospital or at home may make them physically and emotionally unable to fully attend to the needs of their healthy children.[5] Siblings of children with cancer experience mental and social adjustments.

Research shows that untreated children with anxiety disorders are at high risk of performing poorly in school; miss out an important social experience; and engage in substance abuse. Determining the degree of anxiety of children with ALL and their sibling will give us an idea of its severity and help to find innovative ways for appropriate interventions that may help to address their psychosocial distress and foster their resilience and mental health. As anxiety disorders can have serious consequences in children/adolescents with chronic and/or life limiting medical illnesses, prompt identification and treatment of these disorders is critical.[6] Currently, there is no specific tool used in measuring anxiety level in children with chronic illness and their siblings, it is then difficult to accurately assess the prevalence rate of anxiety in this population.

This study aims to guide future policy maker to develop programs that will help reduce the burden of cancer for the family and siblings of children with cancer. This paper will help physicians measure and monitor the degree of anxiety experience by the children. This study hopes to add to existing knowledge on the literature on the significance of determining levels of anxiety in children with chronic illnesses as well as their siblings. The general objective of this study is to determine and compare the anxiety level of children with Acute Lymphoblastic Leukemia and their well siblings based on Child Drawing: Hospital manual. The study specifically aims to identify the factors associated with the level of anxiety of Children with Acute Lymphoblastic Leukemia and their well siblings in terms of socioeconomic characteristics, support systems, clinical status and duration of illness from the time of diagnosis. To correlate level of anxiety of children with Acute Lymphoblastic Leukemia and their well siblings with the following demographic features such as age, gender, education (private/public school), socioeconomic status; support systems, clinical status and duration of illness from the time of diagnosis.

OPERATIONAL DEFINITIONS:

- **Child of ALL** – children age 5 to 11 years medically diagnosed with ALL with a duration of 6 months or longer.
- **Siblings** - Children's age ranged between 5 and 11 years with no developmental concerns or delays.
- **Gestalt**- is the overall sense the picture portrays to the scorer.
- **Socioeconomic status**- Classification based on the financial income of the family Pay- monthly per capita income is above 220%

C1 – monthly per capita income is above 180% but not more than 220%

C2 – monthly per capita income is above 140% but not more than 180%

C3 – monthly per capita income is equal to but not more than 140%

METHODOLOGY

Research design

A prospective cross-sectional design was done among chronically ill patients with Acute Lymphoblastic Leukemia and their well siblings. The Child Drawing: Hospital manual by Clatworthy, Simon, and Tiedeman was used to assess the level of anxiety.[7]

Participants

Inclusion criteria

Patient included in this study are children who were diagnosed with Acute Lymphoblastic Leukemia within six months or longer prior to the conduct of the study; with no developmental delays or concerns; child is between 5-11 years old and able to follow instructions; seeking medical consult at the Hematology-Oncology center out-patient unit and private clinic of Hema-oncology specialist of different institutions; the child participates voluntarily; and with informed consent by the parents and assent by the child as deemed necessary. Siblings of children with ALL with no illness and developmental concerns or delays; aged 5-11 years old; able to follow instructions; participates voluntarily; and an informed consent given by the parents and assent was, likewise, given by older children.

Setting

The study was conducted at the out-patient department of Cancer and Hematology Center of a tertiary government hospital and private clinics of Hema-oncology specialist of different institutions.

Sample Size

The sample size was computed based on the study by Myers et at.[8] The level of significance was set at 5%, power of 80% and effective size of 0.4062 as clinically significant anxiety among children with ALL as compared with health siblings. The minimum sample size was 80 participants, composed of 40 ALL patients and their corresponding siblings. The sample size was determined with the following formula:

Legend:

n = computed sample size for children with ALL and their siblings

P0 = proportion of ALL with clinically significant anxiety (SR-ALL) = 25.2%

P1 = proportion of health children with clinically significant anxiety = 12%

zα = 1.96

zβ = 0.842

effect size= 0.4062

Effect size formula:

$$ES = \frac{|P_1 - P_0|}{\sqrt{P_0(1 - P_0)}}$$

Sample Size for Health related Quality of Life type of outcomes[9]

$$n = \frac{4(z_\alpha + z_\beta)^2}{ES^2} + \frac{z^2}{2}$$

$$n = \frac{4(1.96 + 0.842)^2}{0.4062} + \frac{(1.96)^2}{2}$$

$$n = 80$$

Study Procedure

The research protocol was submitted and approved by IRB-EC of a tertiary government hospital prior to study implementation. Research orientation was conducted among members of the research team. An informed consent (Appendix A) was obtained from parents and guardians and assent (Appendix B) from children ages 7-11 years old. Parents or guardians of eligible subjects were fully informed of the nature of the study, and the process of data gathering. A checklist of inclusion and exclusion criteria was also accomplished. Primary information which includes age, gender, socioeconomic status and the duration of illness from the time of diagnosis were obtained by the investigator.

Study Intervention

The study was conducted in a quiet room free from any distractions and medical procedures. Two instruments were used for the study; the Socio-demographic Questionnaire (Appendix D) and the Child Drawing: Hospital manual (Appendix E). The index patient and the corresponding sibling were subjected to the sociodemographic Questionnaire and Child Drawing: Hospital manual.

Demographic Questionnaire. A researcher-made demographic questionnaire was utilized to collect sociodemographic data from their parents or guardians. The information included the name,

address, birth date, age, socioeconomic status and basic psychosocial and medical history of the participants (Appendix D).

Child Drawing: Hospital manual. The CD:H, developed by Clatworthy, Simon, and Tiedeman, was used to measure the participants' level of anxiety. This instrument was specifically made as a means of measuring the emotional status of the hospitalized school-aged child. It was designed to assess hospitalized children's anxiety from the child's point of view. Specifically it was developed as a means to produce an instrument that is nonthreatening to children; with an element of fun; appropriate to the child developmental level; easily administered; and scored with a scientifically sound mechanism. This manual contains three parts: Part A contains 14 items scored on a scale of 1 to 10, with 1 indicating the lowest level of anxiety and 10 the highest level; Part B is an eight items portion presumed to be pathological indices; and Part C is a gestalt rating that calls for an overall response by the scorer to the child's anxiety as expressed in the picture on a 1 to 10 scale. A score of 1 indicates coping or low anxiety, whereas a score of 10 indicates disturbance or high anxiety (Appendix C).[10]

The instrument consisted of an 8.5 x 11-inch blank white sheet of paper and a box of eight crayons (red, purple, blue, green, yellow, orange, black, and brown). The child was asked to "draw a picture of a person in the hospital". The scoring of the tool is based on the theoretical foundations of drawings as a projective measure of children's states of anxiety.[10]

The child doing the drawing was asked to sit on a table of an appropriate height. The researcher then handed the piece of paper to the child at an angle for the child to determine the placement of the drawing on the paper. A box of crayons was opened exposing all of the colors available. The crayons were the only tool allowed to make the drawing (e.g., no pencil was used).

The child was instructed as follows: "Please draw a picture of a person in the hospital." The person administering the CD: H observed the child to be sure that the child was able to attend to the task. In the event that the child becomes distracted, the directions were again repeated and the child was encouraged to participate. Some children asked questions when they were unsure of themselves; when they were suspicious of the situation; or when compulsiveness, neatness, or concreteness interfered with the task of completion. These questions were responded to either with the original instructions or with clarifications that were congruent with the given instructions and have not influenced the child to respond in one way or the other. The children prompted not to add parts or color to the drawing. As the child had indicated verbally or by gesture that he or she is finished, the drawing and crayons were collected. No time limit was given. The drawings were labeled on the backside of the paper with the child's age, gender and birth date.

Data Processing

The drawings of the children, was scored using the CD:H manual, by three raters. The first rater has a doctor's degree in Counseling Psychology, is a Certified Counseling and Developmental Psychologist from the Psychological Association of the Philippines and is a Certified Child Life Specialist from the Child Life Council, USA. The second rater has a master's degree in Family Life and Child Development, with years of experience as a child life specialist. The third rater, is the Executive Director of Kythe Foundation Inc., with a master's degree in psychology and a Certified Child Life Specialist.

The third rater was consulted in the event that the first two raters were unable to determine the score. Inter-rater reliability was determined using Spearman's correlation.

The Children's drawings were interpreted using the CD:H manual, which has acceptable validity and reliability. Using the manual, the drawing is scored in three parts and includes a total score depicting the child's level of anxiety and was analyzed by a Psychologist.

Part A contained 14 items and was scored on a scale of 1 to 10, with 1 indicating the lowest level of anxiety and 10 the highest level. These items were 1. Person: Position 2.Action 3. Length of Person 4. Width of Person 5. Facial Expression 6. Eyes 7. Size of Person to Environment 8. Color: Predominance 9. Color: Number Used 10. Use of Paper 11. Placement 12. Strokes: Quality 13.Hospital Equipment and 14. Developmental Level.

Part B was scored by giving additional points for the presence of any of eight items presumed to be pathological indices. These items included: 1. Omission: 1. Part 2. Exaggeration of a Part 3. Deemphasis of a Part 4. Distortion 5. Omission: 2 or more parts 6. Transparency 7. Mixed Profile and 8. Shading.[11]

Part C was a gestalt rating that called for an overall response by the scorer to the child's anxiety as expressed in the picture on a 1 to 10 scale. A score of 11 indicates coping or low anxiety, whereas a score of 10 indicates disturbance or high anxiety.

A total score was obtained by adding the scores of the three sections, with the range of possible total scores from 15 to 290, with higher numbers indicating more anxiety. Appendix C shows the range of Child Drawing: Hospital manual scores and its corresponding qualitative description on the level of anxiety. Data were checked for completeness, accuracy and consistency. The score of the drawings was encoded and analyzed (Appendix F).

Statistical Analysis

Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion was used for nominal variables. Median and range was used for ordinal variables. Mean and SD for interval/ratio variables. Paired sample t-test and Wilcoxon Signed Ranks test was used to compare item and scale scores. All valid data was included in the analysis. Spearman's correlation coefficient was used to determine the correlation between the patient's and sibling's anxiety scores. Simple and multiple linear regression analyses were performed, after checking that it meant for statistical assumptions required for these analyses. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05 α-level of significance. STATA 15.0 was used for data analysis.

RESULTS

A total of 40 dyads of children with acute lymphoblastic leukemia and their siblings were included in this study. Our patients' socio-demographic profile is presented in Table 1. Majority, eighty eight percent of ALL fathers were employed. In comparison, 75% of ALL, mother were unemployed. The percent of the patients have a monthly per capita income equal to 140% (C3). Forty five percent of the family resides in the National Capital Region.

Table 1. Sociodemographic Profile of Parents of Leukemia Patients and their Siblings

	Frequency (%); Mean ± SD; Median (Range)
Father's occupation	
Employed	35 (87.50)
Unemployed	2 (05.00)
Don't know	2 (05.00)
Deceased	1 (02.50)
Mother's occupation	
Employed	10 (25.00)
Unemployed	30 (75.00)
Socioeconomic status	
C1	0
C2	1 1 (02.50)
C3	29 (72.50)
Indigent	0
Pay	10 (25.00)
Region	
NCR	18 (45.00)
Region 1	1 1 (02.50)
Region 3	8 8 (20.00)
Region 4A	11 (27.50)
Region 5	1 1 (02.50)
Region 6	1 1 (02.50)
Transferred place of Residence	4 4 (10.00)

The ALL patients had a mean age of 7.65 ± 1.94 years. Sixty five percent of ALL were male. The siblings had a mean age of 8.4 ± 1.89 years. Majority, 60% were female (See Table 2).

As seen in table 2, thirty five percent of Leukemia patients are second born, 30% were first born and 17.5% were third born. In Comparison, the well siblings of ALL patients were second born (40%), 38% were first born and 7.50% were third born.

Table 2. Age, Sex and Birth Order of Leukemia Patients and their Siblings

	Patients (n=40)	Siblings (n=40)
	Frequency (%); Mean ± SD; Median (Range)	
Age (years)	7.65 ± 1.94	8.4 ± 1.89
Sex		
Male	26 (65.00)	16 (40.00)
Female	14 (35.00)	24 (60.00)
Birth ordinal position		
1	12 (30.00)	15 (37.50)
2	14 (35.00)	16 (40.00)
3	7 (17.50)	3 (07.50)
4	3 (07.50)	4 (10.00)
5	2 (05.00)	1 (02.50)
6	2 (05.00)	1 (02.50)

There were twenty three percent each of ALL B-cell and ALL standard included in the study. Twenty three percent of the study subjects were in maintenance phase of treatment and three percent were being monitored (See Table 3).

Table 3.Diagnosis and clinical status of 40 leukemia patients

Time since diagnosis (months)	28 (6 – 109)
Diagnosis	
ALL	20 (50)
ALL B-cell	(22950)
ALL isolated CNS	(20150)
ALL Standard	(22950)
ALL T-cell	(02150)
Clinical status	
ALL 4th cycle	(02150)
ALL Bone Marrow relapsed	(02150)
ALL chemo	2 (05.00)
ALL Maintenance	23 (57.50)
ALL consolidation	(02150)
ALL induction	2 (05.00)
ALL intensification	(02150)
ALL Monitoring	(07350)
ALL Relapsed	2 (05.00)
ALL Off-chemo	2 (05.00)
ALL MSK	2 (05.00)

Comparative analysis of the 14 items in Child Drawing: Hospital manual part A showed that the number of color used was significantly higher among ALL patients (P Value 0.029). The other item showed insufficient evidence to demonstrate a difference in scores between ALL patients and their well siblings (See Table 4).

Table 4.Comparative Analysis of Child Drawing: Hospital Manual Part A of 40 dyads of Leukemia Patients and their Siblings

	Patients (n=40)	Siblings (n=40)	*P* value
	Median (Range)		
Person position	2.0 (1–10)	2.0 (1–10)	0.567
Action	5.0 (1–10)	5.0 (1–10)	0.724
Length of person*	3.0 (1–10)	3.0 (1–10)	0.090
Width of person	7.0 (1–10)	6.0 (1–10)	0.383
Facial expression	4.5 (1–10)	4.0 (1–10)	0.552
Eyes	7.0 (1–10)	7.0 (1–10)	0.378
Size of person to environment	2.5 (1–9)	1.0 (1–10)	0.291
Color predominance	6.0 (1–10)	8.0 (1–10)	0.548
Color number used	3.0 (1–10)	2.0 (1–10)	0.029
Use of paper	2.0 (1–9)	1.5 (1–9)	0.287
Placement	1.0 (1–8)	1.0 (1–10)	0.371
Stroke quality	3.0 (1–7)	3.0 (1–7)	0.474
Hospital equipment	3.0 (1–10)	3.0 (1–6)	0.161
Developmental level	5.0 (2–10)	5.0 (1–10)	0.502

Statistical test used: Wilcoxon Sign Rank Test

Comparative analysis of Child drawing: Hospital manual Part B score between ALL patients and their siblings showed no significant difference (P Value >0.05). However it was noted that shading, omission of 2 or more parts, omission of one body part, and exaggeration are observed in both ALL patients and their siblings (See Table 5).

Table 5. Child Drawing: Hospital Manual Part B Scores of 40 dyads of Leukemia Patients and their Siblings

	Patients (n=40)	Siblings (n=40)	*P* value
	Median* (Range), [number of children]		
Omission: 1 part	5 [n=12]	5 [n=13]	-
Exaggeration of a part	5 [n= 8]	5 [n=10]	-
De-emphasis of a part	5 [n=5]	5 [n=1]	-
Distortion	10 (5–10) [n=7]	10 [n=2]	-
Omission: 2 or more parts	10, [n=20]	10 [n=	-
Transparency	0	0	-
Mixed profile	10 [n=1]	0	-
Shading	10 [n=35]	10 [n=35]	-

Comparative analysis of child's drawing: Hospital manual Part C showed no significant difference (P value 0.084) (See Table 6).

Table 6. Comparative Analysis of Child Drawing: Hospital Manual Part C Scores of 40 dyads of Leukemia Patients and their Siblings

	Patients (n=40)	Siblings (n=40)	
	Frequency (%); Mean ± SD; Median (Range)		*P* value
Gestalt of picture	5.83 ± 1.71	5.18 ± 2.06	0.084

Statistical test used: Paired sample t test

Table 7 outline the overall anxiety scores based on the Child Drawing: Hospital Manual. ALL patients have a mean score higher than the well siblings in all part of the manual. However, the result is not significantly different between the two groups with P value of 0.062.

Table 7. Overall Anxiety Scores based on the Child Drawing: Hospital Manual of 40 dyads of Leukemia patients and their Siblings

	Patients (n=40)	Siblings (n=40)	*P* value
	Frequency (%); Mean ± SD; Median (Range)		
Part A (highest possible score is 140)	62.68 ± 18.53	57.68 ± 17.26	0.137‡
Part B (additional scores for pathologic items)	18.75 ± 06.86	16.50 ± 05.80	0.068‡
Part C (Gestalt, overall responses of scorer to the child's anxiety; highest possible score is10)	05.83 ± 01.71	05.18 ± 02.06	0.084‡
Overall score	87.25 ± 22.19	79.35 ± 21.11	0.062‡
Interpretation			0.115⁂
Very low	0	0	
Low	18 (45.00)	26 (65.00)	
Average	21 (52.50)	14 (35.00)	
Above average	1 (02.50)	0	
Very high	0	0	

Statistical tests used: ‡ - Paired sample t test; ⁂ - Fisher's exact test

Table 8 showed that There is a weak but direct correlation between the overall anxiety scores of the ALL patients and their siblings (p = 0.017). This means that a high anxiety score of ALL patients, a high anxiety score on the well sibling. Similarly low anxiety score of ALL patients, a low anxiety score on the well sibling.

Table 8. Spearman's Correlation between Patients score and Siblings Score

	Correlation Coefficient	Interpretation	P-value
Overall anxiety score	0.377	Direct, Weak	0.017
Patient versus siblings		Relationship	

Statistical analysis was done to determine any association of ALL patient's anxiety score with selected clinical factors. Simple linear regression analysis showed insufficient evidence to demonstrate an association between select clinical factors (P value 0.05) (See Table 9).

Table 9. Simple Linear Regression of Patient's Anxiety Score and Select Clinical Factors (n = 40)

	Crude Beta coefficient	95% Confidence Interval	P-value
Age	0.650	-02.96 - 04.26	0.718
Time diagnosis (months)	0.096	-00.21 - 00.41	0.532
Sex (Female)	-0.933	-15.79 - 03.92	0.899
Birth ordinal position			
1	(reference)	-	-
2	0.452	-17.30 - 18.27	0.959
3	-07.476	-29.01 - 14.06	0.485
4	-04.333	-33.56 - 24.90	0.765
5	-27.8333	-62.42 - 06.75	0.111
6	15.667	-18.92 - 50.25	0.364
Father's occupation			
Employed	(reference)	-	-
Unemployed	18.414	-15.24 - 52.07	0.274
Mother's occupation			
Employed	(reference)	-	-
Unemployed	-6.333	-22.82 - 10.15	0.442
Socioeconomic status			
C2	-41.70	-87.18 - 03.78	0.071
C3	-12.98	-28.88 - 02.92	0.107
Pay	(reference)	-	-
Region			
NCR	(reference)	-	-
Region 1	02.333	-44.07 - 48.74	0.919
Region 3	13.083	-06.11 - 32.28	0.175
Region 4A	03.970	-13.31 - 21.26	0.644
Region 5	-23.667	-70.07 - 22.74	0.307
Region 6	-23.667	-70.07 - 22.74	0.307
Transferred place of residence	-14.167	-37.69 - 09.36	0.230
Sibling's Total anxiety Score	0.297	-00.35 - 00.63	0.078

Multiple linear regression, evidence demonstrate showed insufficient to an association between ALL patient anxiety score and select clinical factors (P Value >0.005) with anxiety scores. However, compared to first born, those who were born fifth have associated lower anxiety score. The model explained 50.28% in the variation of the anxiety scores, but was not statistically significant (p = 0.586) (See Table 10)

Table 10. Multiple Linear Regression of ALL Patient's Anxiety Score and Select Clinical Factors (n = 40)

	Adjusted Beta coefficient	95% Confidence Interval	P-value
Age	-02.311	-09.47 – 04.85	0.505
Time diagnosis (months)	0.002	-0.58 – 0.58	0.994
Sex (Female)	05.925	-15.49 – 27.34	0.567
Birth ordinal position			
1	(reference)	-	-
2	-05.159	-32.72 – 22.40	0.698
3	-02.615	-40.49 – 35.26	0.886
4	-16.417	-71.71 – 38.87	0.539
5	-50.669	-99.71 – 01.63	0.044
6	-29.491	-13.61 – 72.60	0.167
Father's occupation			
Employed	(reference)	-	-
Unemployed	12.050	-42.93 – 67.03	0.650
Mother's occupation			
Employed	(reference)	-	-
Unemployed	-12.822	-45.06 – 19.42	0.413
Socioeconomic status			
C2	-05.822	-88.37 – 76.73	0.883
C3	-04.428	-31.88 – 23.02	0.738
Pay	(reference)	-	-
Region			
NCR	(reference)	-	-
Region 1	01.680	-82.56 – 85.92	0.967
Region 3	11.042	-19.10 – 42.08	0.463
Region 4A	22.368	-04.81 – 49.54	0.101
Region 5	0.370	-82.73 – 83.47	0.993
Region 6	02.690	-76.03 – 81.41	0.943
Transferred place of residence	-16.785	-86.08 – 52.51	0.616
Sibling's Total anxiety Score	0.494	-0.17 – 01.16	0.134
Constant	0.494	-0.17 – 01.16	-

R^2 = 50.28%; p-value =

Analysis of siblings' anxiety score and selected clinical factors was determined through simple linear regression. There is insufficient evidence to demonstrate an association between select clinical factors with anxiety scores (P value >0.05) (See Table 11).

Table 11. Simple Linear Regression of Sibling's Anxiety Score and Select Clinical Factors (n = 40)

	Crude Beta coefficient	95% Confidence Interval	P-value
Sibling's Age	-2.527	-6.21 – 01.15	0.173
Sibling's sex (Female)	-2.899	-16.63 – 10.83	0.671
Birth ordinal position			
1	(reference)	–	-
2	03.857	-13.31 – 21.03	0.651
3	-9.214	-29.97 – 11.54	0.373
4	-14.17	-42.34 – 14.00	0.314
5	-1.00	-34.33 – 32.33	-.952
6	-15.50	-48.83 – 17.83	0.351
Father's occupation			
Employed	(reference)	–	-
Unemployed	-9.857	-41.10 – 21.38	0.526
Mother's occupation			
Employed	(reference)		-
Unemployed	4.333	-11.41 – 20.08	0.581
Socioeconomic status			
C2	-27.30	-71.84 – 17.24	0.222
C3	-10.02	-25.60 – 05.55	0.200
Pay	(reference)	–	-
Region			
NCR	(reference)	–	-
Region 1	34.278	-08.72 – 77.28	0.114
Region 3	13.903	-03.88 – 31.69	0.121
Region 4A	-0.995	-17.01 – 15.02	0.900
Region 5	-20.722	-63.72 – 22.28	0.334
Region 6	-08.722	-51.72 – 34.28	0.683
Transferred place of residence	09.611	-12.99 – 34.21	0.395
Patient's total anxiety Score	0.268	-00.03 – 00.57	0.078

Table 12. Multiple Linear Regression of Siblings' Anxiety Score and Select Clinical Factors (n = 40)

	Adjusted Beta Coefficient	95% Confidence Interval	P-value
Sibling's Age	-2.309	-9.93 – 05.31	0.532
Sibling's sex (Female)	3.378	-17.73 – 24.49	0.741
Birth ordinal position			
1	(reference)	–	–
2	6.855	-22.63 – 36.34	0.631
3	-13.025	-48.74 – 22.69	0.454
4	10.379	-37.05 – 57.81	0.651
5	19.329	-24.89 – 63.55	0.371
6	-15.418	-73.21 – 42.48	0.583
Father's occupation			
Employed	(reference)	–	–
Unemployed	-21.175	-73.46 – 31.11	0.406
Mother's occupation			
Employed	(reference)	–	–
Unemployed	11.390	-18.01 – 40.79	0.426
Socioeconomic status			
C2	-24.036	-99.52 – 51.45	0.512
C3	-9.600	-34.36 – 15.16	0.426
Pay	(reference)	–	–
Region			
NCR	(reference)	–	–
Region 1	-18.787	-105.12 – 67.54	0.065
Region 3	10.077	-18.97 – 39.13	0.475
Region 4A	-4.427	-34.05 – 25.20	0.757
Region 5	-47.653	-119.22 – 23.91	0.179
Region 6	-29.967	-106.67 – 46.74	0.423
Transferred of place	47.836	-16.65–112.22	0.137
Patient's total anxiety score	0.282	-0.17 – 00.73	0.207
Constant	67.276	-17.80–152.35	–

R^2 = 49.77%; p-value = 0.508

Analysis was performed to determine any association between siblings' anxiety score and selected clinical factors (See Table 12). The result showed insufficient evidence to demonstrate an association between select clinical factors with anxiety scores (P Value >0.05). The model explained 49.77% in the variation of the anxiety scores, but was not statistically significant (p = 0.508).

DISCUSSION

Sibling relationships are intense, complex and of infinite variety. It is widely accepted that siblings contribute enormously to family life. Unfortunately, children as siblings have largely been overlooked in most family health research in favor of the mother-child dyad. The resultant lack of understanding of the world of siblings becomes

especially problematic when health professionals attempt to deliver true family-centered care to families with a chronically ill or disabled child.[27] Bank and Kahn highlighted the importance of the sibling relationship by asserting that siblings spent much more time together than any other family subsystem and that they are striking empathic with one another.[12]

This study compared the level of anxiety of children with ALL versus their well siblings using the Child Drawing: Hospital Manual. The result shows that on the average, ALL patients present higher scores than their well siblings. These however, were not statistically significant. Childhood chronic illness has long been thought to have a negative impact on the psychological functioning and behavior of the ill child that compared with healthy peers.[13]

Childhood chronic illness, affect not only the sick child but all the family members.[14] Coddington, in a survey of life events as etiology factors in childhood disease, found that sibling illness ranked as among the most stressful.[15] In several studies they concluded that these siblings were a "population at risk to experience psychological difficulties". [16,17,18] Similarly, the results of our study shows that there is a direct correlation between the overall anxiety scores of the ALL patients and their siblings. This means that the higher the score of the patients, the higher it is as well for the siblings. Similarly, a lower anxiety score of ALL patients, a lower anxiety score on the well siblings. This is parallel to the result of the study done by Minuchin *et al* which showed that siblings usually share a common environment as well as their parents' attention.[19] The study also showed that siblings serve an important functions as socializers to one another, forming cohesive groups and reciprocating behavior on one another. In a study by Spinetta and Deasy-Spinetta, they concluded that siblings live through the experience with the same intensity as the patient.[20]

It was noted in this study that a lower anxiety level of ALL patient who were born fifth compared to those who were born first. This in relation to the family size wherein previous studies have shown that larger families is likely to have a healthier family environment as the burden of care is dispersed among several children.[20,21,22]

Studies have shown that anxiety levels are significantly affected by factors such as socioeconomic status, transfer of residence, educational attainment of the parents and the patients.[16,22,23] Farber suggested that a child's general life opportunities and social mobility are affected by having a chronically ill sibling.[38] Cairns et al., noted that the financial stress of having a child with cancer, may deprived parents and siblings to fulfill their basic needs as well as the luxuries of life.[24] They also suggested that the long-term needs of siblings may be slighted as parents focus on the draining tasks of the present. Moreover, it is interesting to note that a child's health problem may directly influence where the family will live. Families often move to be closer to treatment center or to find a better climate for the sick child.[25] Moving involves both financial and psychological stress that clearly affects healthy siblings.[15] However, this is not congruent in this study it showed that there is no significant correlations to selected clinical factors in relation to level of anxiety of children with ALL and their well siblings.

CONCLUSION

The Family is the primary social support system for children; however, childhood cancer disrupts family pattern and may interfere substantially with the family-based support that healthy siblings typically receive.[26] Parents of children with cancer report difficulty in attending to the needs of both their sick and healthy children.[4]

This study showed there is a direct correlation between the overall anxiety scores of the ALL patients and their siblings. This means that the higher the score of the patients, the higher it is as well for the siblings. Similarly, a lower anxiety score of ALL patients, a lower anxiety score on the well siblings. Moreover there is a positive association with larger family size and the child's response to a sibling's illness. The larger families is likely to have a healthier environment mainly because the burden of care is dispersed among several children.[20,21]

The study also showed low to average anxiety levels among the participants which may be related to the quality of care and support given by the institution and inherent resiliency of the families included in the study.

LIMITATIONS OF CURRENT RESEARCH

It is recommended that a bigger sample be considered. We did not have a comparison group so we cannot determine if the absolute levels of anxiety experience by the siblings is significant compared to other general population. Furthermore, since we do not have longitudinal data, we cannot determine if patterns in degree of anxiety level as the disease condition progresses. Thus, future research may confirm a longitudinal relationship between social support and better functioning for siblings of children with cancer. Lastly we did not present variation in our finding as a function of age or gender and other selected clinical factors, despite our sample size. These are important questions that may help guide future intervention or prevention programs to help support siblings of children with cancer.

RECOMMENDATIONS

Health care professionals must be proactive in providing psychological and emotional care for the siblings of patient with ALL. It is necessary that emphasis be placed on helping the healthy children to develop their own identities and better understand the differences and similarities between themselves and their sick siblings. Psychological, emotional and behavioral programs must be expanded to the siblings and families of children with chronic illness as well.

Health professionals should ensure that the siblings are not bereft of realistic, age-appropriate information related to the disease and its treatment. It is imperative that siblings are equipped with explanations and are kept updated with age-appropriate disease-related information. Sibling visiting privileges should be open and encouraged to facilitate the maintenance of this important and complex relationship between children. Health professionals must systematically and routinely make inquiries into the repercussion the illness may have on the family life. Specific information should be sought from parents about siblings regarding academic progress, peer relationships, health, appetite, sleep patterns and general mood.

The family and members from the medical community can team together to create an environment that is welcoming and reassuring for the siblings of children with cancer. Parents or guardians should be appropriately educated about cancer that may dispel others' misconceptions and effectively answers any medical questions that may arise from the siblings. Information sessions and support groups must be organized to enhance children's psychological state, their knowledge of disabilities, and their understanding of the family situation.

Child life services should also be considered an integral part of quality pediatric health care and essential in family-centered care and best-practice models of health care delivery for children.

Future research should aim to develop programs and pilot test in partnerships with families and other social support groups. Future research should explore the effectiveness of these interventions to assist the siblings of children with chronic illness. Future researchers should investigate further the impact of disease factors on psychological functioning of siblings. Further exploratory studies can be conducted in the future to examine other possible cultural and psychodynamics prevalent in the Filipino Family.

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APPENDIX A. Range of Child Drawing: Hospital Manual score and corresponding level of anxiety

CD:H Total Score	Level of Anxiety
< 43	Very Low
44-83	Low
84-129	Average
130-167	Above Average
> 168	Very High

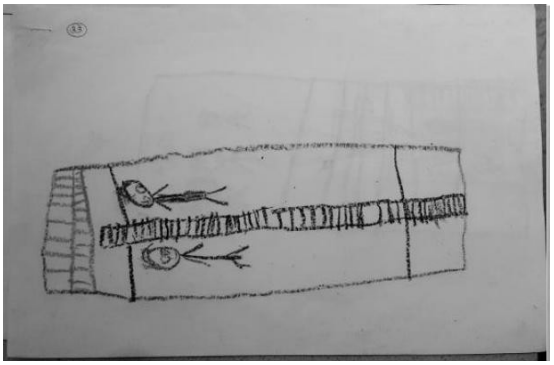
APPENDIX B.

Child Hospital Drawing	
Family Name	
Number	
Age/Gender	
Diagnosis	
Part A	
1. Person: Position	
2. Action	
3. Length of Person	
4. Width of Person	
5. Facial Expression	
6. Eyes	
7. Size of Person to Environment	
8. Color: Predominance	
9. Color: Number Used	
10. Use of Paper	
11. Placement	
12. Strokes: Quality	
13. Hospital Equipment	
14. Developmental Level	
TOTAL PART A	
Part B	
Add 5 points for each	
15. Omission: 1 Part	
16. Exaggeration of a Part	
17. Deemphasis of a Part	
18. Distortion	
19. Omission: 2 or more Parts	
20. Transparency	
21. Mixed Profile	
22. Shading	
TOTAL PART B	
Part C	
Gestalt of Picture	
TOTAL SCORE CH:D	
Interpretation	

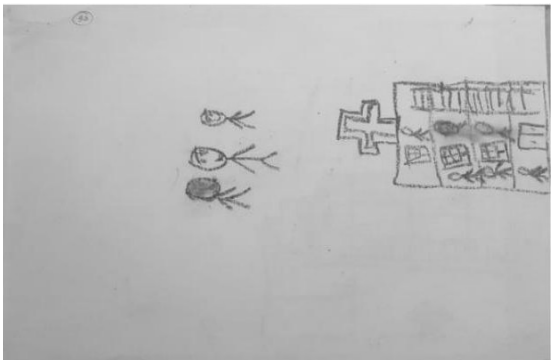
Appendix C. Sample Drawing of patients and siblings

#11. Patient 7yo/F

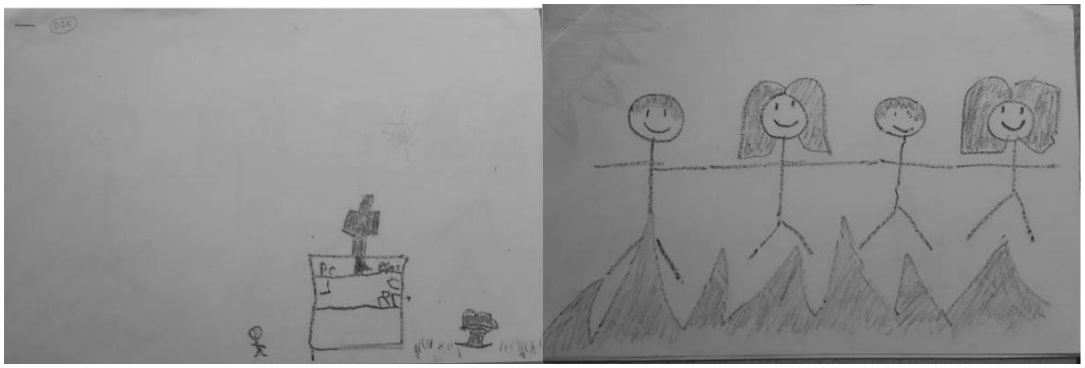
#11. Sibling 8yo/F



#33. Patient 5yo/M



#33. Sibling 6yo/M



#25. Patient 10yo/M **#25. Sibling 11yo/F**

Appendix D. Total Anxiety Scores Based on the Child Drawing: Hospital Manual

Number	Age	Gender	Final Score	Interpretation	Number	Age	Gender	Final Score
1	5	M	125	average	22	8	F	71
1	9	F	65	low	22	7	M	79
2	11	M	94	average	23	10	F	75
2	6	M	92	average	23	6	F	74
3	6	F	100	average	24	9	F	85
3	11	F	68	low	24	7	M	67
4	10	M	83	low	25	10	M	144
4	8	M	79	low	25	11	F	77
5	6	F	66	low	26	10	F	46
5	9	F	72	low	26	7	F	104
6	9	M	76	low	27	6	M	105
6	11	F	44	low	27	9	F	83
7					28	7	M	124
7					28	11	M	79
8	9	M	85	average	29	10	M	103
8	8	F	59	low	29	9	F	88
9	6	M	70	low	30	10	M	79
9	10	M	101	average	30	11	F	99
10	6	M	61	low	31	8	M	114
10	9	M	68	low	31	7	F	84
11	7	F	56	low	32	9	M	79
11	8	F	60	low	32	8	F	54
12	10	M	83	low	33	5	M	101
12	6	F	97	average	33	6	M	106
13	6	M	90	average	34	8	M	104
13	8	F	74	low	34	11	F	110
14	6	F	53	low	35	9	M	89
14	10	M	60	low	35	5	F	117
15	5	F	84	average	36	5	M	97
15	10	F	46	low	36	8	M	125
16	7	M	61	low	37	10	F	65
16	5	F	56	low	37	10	F	71
17	5	M	68	low	38	6	F	57
17	11	F	70	low	38	8	M	45
18	8	M	96	average	39	5	F	105
18	6	M	48	low	39	8	M	78
19	6	M	117	average	40	5	F	87
19	9	M	108	average	40	8	F	111
20	10	F	114	average	41			
20	9	M	83	low	41			

Comparison of the Risk of Depression and Anxiety Between Adolescent and Adult Patients Diagnosed with Acne Vulgaris in a Tertiary Government Hospital*

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ABSTRACT

Background: Acne vulgaris is a common condition, affecting at least 80% of adolescents and adults aged 11-30. In a on fourth of the adolescents affected, it is moderate to severe. Once considered a disease occurring in puberty, studies have shown the prevalence of acne occurring up to the 5th decade. Many studies have shown the relationship between skin disease and mental health. And among acne vulgaris patients, there are reports of psychological disorders and negative quality of life. Many studies have been done about the risk of anxiety and depression among adolescents. However, because acne is more common among adolescents, limited studies have been done regarding the psychological impact of acne among adults.

Objectives: To compare the proportion of risk of anxiety and depression between adolescent and adult acne vulgaris patients in a tertiary government hospital OPD and Skin Center using the Hospital Anxiety and Depression Scale in English and Pilipino (HADS/HADS-P).

Materials and Methods: A cross-sectional study design was used. Forty-six subjects (23 adolescent and 23 adult) diagnosed with acne vulgaris were included in the study. Eligible subjects underwent a thorough dermatologic evaluation. The Global Acne Grading System (GAGS) was used to evaluate the severity of acne. The validated HADS/HADS-P questionnaire was used to assess the risk of anxiety and depression. Independent Students t-test was used to compare means between the groups. Chi-square test was used to compare proportions. Statistical significance was based on p-values ≤0.05.

Results: Among the adolescents included, 56.5% were female and 43.5% were male ranging from 13-24 years old. The adult subjects were consisted of 87% females and 13% males ranging from 25-47 years old. The most frequent age of onset of acne was between 11 to 19 years among adolescents and 12 to 18 years among adults (91.3% vs 56.5%; p=0.017). Duration of acne among adolescents was 4.4 ± 3.0 years and 10.3 ± 6.4 years among adults (p<0.0001). In the adolescent group, subjects had moderate (56.5%) or mild (43.5%) acne. Adults had mild (60.5%), moderate (30.4%) or severe (8.7%) acne. There was a significant difference in the risk of anxiety and depression between adolescents and adults (p=0.007). There were 21 adolescents (93%) and 12 adults (52.2%) who were at risk. Of the subjects included in the study, adolescents were approximately 10 times more likely to be at risk of anxiety and depression (OR=9.625, 95% CI: 1.821, 50.866).

Conclusion: Acne vulgaris is associated with negative psychosocial effects on both adolescent and adult patients. The results of this study are consistent with previous findings across cultures. Because acne is not just a physical problem for many patients, it is important for healthcare practitioners, especially dermatologists to be able to see the red flags for psychological comorbidities among patients. The Hospital Anxiety and Depression Scale is a quick and simple tool to use for physicians for risk assessment that can be done in the clinics and can aid in providing a more holistic treatment for patients.

**2nd Place, 2018 Philippine Medical Association Original Research Presentation Contest*
***From Department of Dermatology, East Avenue Medical Society, Quezon City*

INTRODUCTION

Acne is a disease of the pilosebaceous unit characterized by polymorphic lesions[14]. These may include comedones, macules, papules, pustules, nodules, and pseudocysts. It is frequently seen on the face and trunk. Acne is a chronic condition and may cause severe scarring. It is a common skin condition that affects at least 80% of adolescents and adults aged 11-30[8] and in 20-25% of adolescents, acne is moderate to severe[14]. It is noted to have the greatest severity between 16-19[6] years and usually starts earlier and lasts longer in females. However, in males, more severe disease is frequently seen.

Once considered to be a condition generally occurring during puberty which regresses in the 2nd decade, studies have shown the prevalence of acne among adults up to the 5th decade of life. Adult acne vulgaris is defined as acne occurring in individuals beyond 25 years of age. Two forms of adult acne have been identified: 1) persistent acne, wherein acne persists from adolescence, and 2) late-onset acne, wherein acne presents first beyond the age of 25. Little studies have delved into the epidemiology of adult acne. A study in Germany found that 64% of those aged 20-29 and 43% of those aged 30-39 have visible acne[15.] Most cases have been found to occur among females.

Reports have shown a relationship between skin diseases and mental health. In patients with acne, there are reports of psychological disorders including anxiety, depression, aggression, low self-esteem, suicidal ideation and attempts[2,4,5]. It was also found that acne is associated with a negative impact in social interactions, job-seeking, and overall quality of life[14]. Once thought to be merely a physiological condition, it is well-reported that acne may cause significant morbidity.

REVIEW OF RELATED LITERATURE

Numerous literature regarding acne vulgaris have mainly focused on epidemiology and treatment. However, the psychosocial impact on patients has not been extensively studied and addressed. It was previously found in studies that acne is associated with several psychological disorders especially among adolescents. The physical effects of acne such as scarring may have profound psychological and social effects[6]. Approximately 30-50% of individuals aged 12 and 20 years with acne was found to have lowered self-esteem, lack of confidence, perceived social rejection, anxiety, and depression in several surveys[6]. Studies show that acne severity is positively correlated with depression.

However, a few reports show otherwise. It was suggested that negative self-image contribute to the incidence or severity of depression. Other studies have established suicidal ideation among adolescents and young adults. In study conducted among 9398 secondary school students in New Zealand with acne, 2185 (23.6%) reported having suicidal thoughts.

Because acne is predominantly found among adolescents, there are limited studies reporting on the psychosocial impact of acne among adults. It was found that adult acne was more prevalent among females and also seek consult twice a much as men[8]. Higher rates of depression were also found among females. Because acne is perceived to be a disease among adolescents, patient with adult acne experience increased anxiety. Higher risk for depression was found may be due to additional stresses on motherhood, adult sexuality, career demands, and aging[8].

The Global Acne Grading System is an acne severity scale that includes six locations on the face and chest/upper back. A factor is provided for each of the six locations to get a local score with the maximum global score of 44. Acne severity is rated as none, mild, moderate, severe, and very severe with corresponding cut-off scores.

The Hospital Anxiety and Depression Scale was developed as a reliable screening tool for anxiety and depression in the hospital, out-patient, and community setting. The 14-item self-administered questionnaire is divided into an Anxiety subscale (HADS-A) and a Depression subscale (HADS-D) with 7 items each. Responses are rated 0-3, with the highest score of 21 for each subscale. A score of 8 has been validated to be a reliable cut-off score for identifying risk for anxiety and depression. In the Philippines, De Guzman conducted a validation of the Tagalog version of the HADS among patients seen in the University of the

Philippines – Philippine General Hospital (UP-PGH). The optimal score found to be the most sensitive and specific is 11.

SIGNIFICANCE OF THE STUDY

Acne vulgaris does not only significantly impact physical appearance of patients, but also the psychosocial aspects of their lives. According to the World Health Organization, depression is a leading cause of disability worldwide. In the past, dermatologists have underestimated the prevalence of psychiatric disorders and have poor sensitivity in recognizing red flags. One study found that dermatologists only discussed psychological issues in 39% of acne visits with no further action taken[8]. It has been established in numerous studies that acne among adolescents and even adults is associated with anxiety and depression. Given this, it is not enough for dermatologists to address just the cutaneous problem. It is important to take a holistic approach and probe deeper into the potential negative impact on the overall well being of the patients.

No previous studies have been done in the Philippine setting that assesses the risk for anxiety and depression among adolescent and adult acne vulgaris patients. By doing so, we can address the psychosocial effects of Acne Vulgaris among patients across different age groups in the Filipino population. Consequently,

1. The dermatologists and the patients can work better in formulating treatment strategies and plans. By having realistic and achievable goals in acne treatment, patient and doctor dissatisfaction and frustration can be avoided. Addressing the psychosocial issues of patients will help facilitate a deeper relationship between doctors and patients. In turn, this can decrease incidences of "doctor shopping" and poor continuity of care.

2. By assessing the risk of anxiety and depression of acne patients, the dermatologists may be able to discern the need for referring patients to a psychologist or psychiatrist for further evaluation.

By identifying and acknowledging the negative psychosocial effects of chronic and disfiguring dermatologic diseases, we will be able to provide more comprehensive and holistic care for our patients.

RESEARCH QUESTION

Among patients with acne vulgaris, how do the adolescents and adults differ in their risk of anxiety and depression using the Hospital Anxiety and Depression Scale/ Hospital Anxiety and Depression Scale – Pilipino (HADS/HADS-P)?

OBJECTIVES OF THE STUDY

General Objective

- To compare the proportion of risk of anxiety and depression between adolescent and adult acne vulgaris patients in a tertiary government hospital OPD and Skin Center using the Hospital Anxiety and Depression Scale in English and Pilipino (HADS/HADS-P).

Specific Objective

- To determine the demographic characteristics of acne vulgaris patients seen at the OPD and Skin Center of a tertiary government hospital.
- To assess the severity of acne vulgaris in patients using the Global Acne Grading System (GAGS)
- To determine the risk of anxiety and depression among acne vulgaris patients, using Hospital Anxiety and Depression Scale/ Hospital Anxiety and Depression Scale – Pilipino (HADS/HADS-P)
- To compare the proportions of adolescent and adult acne vulgaris patients with the risk of anxiety and depression according to
    - Sex
    - Severity of acne

METHODOLOGY

Study Design

A cross-sectional study design was utilized for this study which was conducted from October 2016 to March 2017.

Ethical Considerations

Informed Consent

The study was initiated upon the approval of the Institutional Ethics and Review Board (IERB). Subjects were duly informed regarding the nature and purpose of the study. Before initiating data collection, all subjects were informed of the purpose and methods of the study. Consent was obtained using a standard consent form.

Confidentiality and Security of Information

All information gathered was kept confidential and used solely for the purpose of the study.

Non-maleficence

Non-maleficence was practiced throughout the course of the study. All subjects were duly informed of the study design and were given the option not to participate in the study if they deemed any activity or process to be offensive.

Beneficence

All the data that was gathered from the study may be used to improve management and intervention among patients with Acne vulgaris.

Plagiarism

All materials that were used in the study were properly cited.

Study Setting

The study was conducted at the clinics of a tertiary government hospital

Study Population

The subjects of the study included patients clinically diagnosed with acne vulgaris, aged 13-50 years of age.

Inclusion Criteria:

- Filipino patients who are aged 13-50 years old;
- Able to read and write in English and/or Tagalog;
- Diagnosis of Acne Vulgaris;
- Seen at the clinics of a tertiary government hospital;

Exclusion Criteria:

- Patients with history of other chronic dermatoses
- Diagnosed psychiatric disorder
- History of oral tretinoin treatment

Sample Size

A sample size of 92 patients diagnosed with Acne Vulgaris (46 adolescent and 46 adult), satisfying the inclusion/exclusion criteria was needed based on a 5% significance level, 80% power and observed proportions. The average number of newly diagnosed Acne Vulgaris patients seen at clinics of a tertiary government hospital in 6 months is, however, only approximately 90. Hence, the adjusted total sample size was at least 46 patients (at least 23 per group).

Study Protocol

Recruitment of Subjects

Acne vulgaris patients who were eligible for inclusion in the study using a checklist was referred by the residents in the clinics to the principal investigator. Those who did not fulfill all the inclusion criteria will not be included. And those who fulfilled at least one exclusion criterion were not included.

Phase I: Obtaining Consent and Assent

Patients who have been assessed to be eligible subjects in the study were given a consent form by the principal investigator which they read themselves. Individuals aged 13-17 were given an

assent form which they signed, in addition to the consent form which was signed by the parent/legal guardian. The principal investigator was present during this time to answer question regarding the study. Patients who voluntarily gave their consent were examined further.

Phase II: Dermatologic Assessment

A more comprehensive history regarding the subject's acne was done by the principal investigator. A case report form was used. The subjects were assigned a subject identification number to maintain confidentiality during the study. They subsequently underwent a dermatologic evaluation using the Global Acne Grading System. All subjects were recorded in the Subject Enrollment Log form.

Phase III: Administration of HADS/HADS-P

After comprehensive dermatologic evaluation, the subjects were asked by the co-investigator to choose between the English and Filipino version of the Hospital Anxiety and Depression Scale which they completed. The test was self-administered and the subjects were given five minutes to complete the questionnaire. The co-investigator was present oversee and time the process. Scores were calculated by the co-investigator using the HADS scoring guide.

Phase IV: Disclosure of HADS/HADS-P Result to the Subject

After calculation of the HADS/HADS-P scores, the results were relayed by the co-investigator to the subject. Those with scores equal to or more than 11 were given the option to seek consult with a psychiatrist for further evaluation.

Operational Definitions

1. Adolescent acne – Acne occurring in individuals less than 25 years old
2. Adult acne – Acne occurring in individuals 25 years old and older

Variables

Independent Variables

- Age – chronological age in years
- Sex – male or female
- Age of onset – age in years when acne first occurred
- Duration of Acne – number of years of patient has had acne
- Previous treatment – over-the-counter medications, whether topical or oral that have been previously tried without a dermatologist's prescription. This excludes oral tretinoin which is part of the exclusion criteria.
- Acne Severity – severity of acne based on the Global Acne Grading System (GAGS)

Dependent Variable

- Risk of Anxiety and Depression – Numerical score of the answers from the Hospital Anxiety and Depression Scale/ Hospital Anxiety and Depression Scale-Pilipino (HADS/HADS-P)

Data Analysis

All forms and questionnaires were checked for completion and accuracy by the co-investigator immediately after the subjects have answered the HADS/HADS-P. All valid data from the subjects were included in the analysis. Missing values were not replaced or estimated during the statistical analysis. Checks for homogeneity of sample population and normality assumption of quantitative patient demographic and clinical characteristics were done. Summary statistics were presented in tables or graphs as mean $\pm$ SD or median (range) for quantitative characteristics (age, age of onset, duration of acne) and as n (%) for qualitative outcome measures (gender, previous treatment, acne severity, risk of anxiety and depression. Independent Students *t*-test was used to compare two means between the adolescent and adult acne patients. Chi-square test, Fisher's exact test, or Yates' chi-square test was used to compare proportions. The chi-square test of

association was done to compare the risk of anxiety and depression between adolescent and adult subjects. Odds ratio and a 95% confidence interval were computed. A p-value of ≤0.05 was used to assess for statistical significance. Stata v13 was used to analyze the data.

RESULTS

In this study, 23 adolescent and 23 adult patients diagnosed with acne vulgaris seen in the outpatient clinic and Skin Center in a tertiary government hospital were examined. Among the adolescents included, 56.5% were female and 43.5% were male with an average age of 19.9 ± 3.3 years, ranging from 13-24 years old. The adult subjects were consisted of 87% females and 13% males with an average age of 30.5 ± 5.8 years, ranging from 25-47 years old. The most frequent age of onset of acne was between 11 to 19 years among adolescents and 12 to 18 years among adults (91.3% vs 56.5%; p=0.017). Duration of acne among adolescents was 4.4 ± 3.0 years and 10.3 ± 6.4 years among adults (p<0.0001). Approximately 47.8% of adolescents and 52.5% of adults had previous treatment (p=0.768). There were statistically significant differences in the age (p<0.0001), gender (p=0.047), age of onset of acne (p=0.020), and duration of acne (p<0.0001) between the adolescents and adults. Both groups were comparable with respect to previous treatment (p=0.078).

Table 1: Demographic profile of adolescent and adult Acne vulgaris patients

Demographic Characteristics	Adolescent	Adult	*p*-value
	n = 23	n = 23	
Age in years, mean ± SD	19.9 ± 3.3	30.5 ± 5.8	0.000*
Age in years, n (%)			
<10	9 (39.1%)	-	0.000*
10-19	14 (60.9%)	4 (17.4%)	
20-25	-	16 (69.6%)	
26-35	-	2 (8.7%)	
36-45	-	1 (4.3%)	
Gender, n (%)			
Female	13 (56.5%)	20 (87.0%)	0.047*
Male	10 (43.5%)	3 (13.0%)	
Age of onset in years, mean ± SD	15.7 ± 2.8	18.9 ± 5.6	0.020*
Age of onset in years, n (%)			
10-19	21 (91.3%)	13 (56.5%)	0.017*
20-25	2 (8.7%)	9 (39.1%)	
26-35	-	1 (4.3%)	
Duration of acne in years, mean ± SD	4.4 ± 3.0	10.3 ± 6.4	0.000*
Previous treatment, n (%)			
Yes	11 (47.8%)	12 (52.2%)	0.768
No	12 (52.2%)	11 (47.8%)	

** Significant at 5% level*

In the adolescent group, subjects had moderate (56.5%) or mild (43.5%) acne. Adults had mild (60.5%), moderate (30.4%) or severe (8.7%) acne. No significant differences in the severity were found in both groups (p=0.346).

Table 2: Acne severity grading of adolescent and adult patients in the GAGS score

GAGS Score	Adolescent	Adult	*p*-value
	n = 23	n = 23	
31 – 38 (Severe)	-	2 (8.7%)	0.346
19 – 30 (Moderate)	13 (56.5%)	7 (30.4%)	
1 – 18 (Mild)	10 (43.5%)	14 (60.9%)	

There was a significant difference in the risk of anxiety and depression between adolescents and adults (p=0.007). There were 21 adolescents (93%) and 12 adults (52.2%) who were at risk. Of the subjects included in the study, adolescents were approximately 10 times more likely to be at risk of anxiety and depression (OR=9.625, 95% CI: 1.821, 50.866).

Table 3: Risk of anxiety and depression of adolescent and adult acne vulgaris patients

HADS/HADS-P Score	Adolescent	Adult	*p*-value
	n = 23	n = 23	
≥11	21 (91.3%)	12 (52.2%)	0.007*
<11	2 (8.7%)	11 (47.8%)	

** Significant at 5% level*

Among those who had a risk of anxiety and depression, majority were female (52.4% adolescent and 91.7% adult; p=0.027). Of the 21 adolescents, acne was graded as moderate (57.1) or mild (42.9%). Of the 12 adults, acne was severe (8.3%), moderate (25%), or mild (66.7%). However, there was insufficient evidence to show a significant difference in the severity of acne between the two groups (p=0.444).

Table 4: Risk of anxiety and depression (HADS ≥ 11) of adolescent and adult acne vulgaris patients by gender and acne severity (GAGS grading)

	Adolescent	Adult	*p*-value
	n = 21	n = 12	
Gender, n (%)			
Female	11 (52.4%)	11 (91.7%)	0.027*
Male	10 (47.6%)	1 (8.3%)	
Severity, n (%)			
Severe	-	1 (8.3%)	0.444
Moderate	12 (57.1%)	3 (25.0%)	
Mild	9 (42.9%)	8 (66.7%)	

** Significant at 5% level*

DISCUSSION

The association of acne with psychological problems such as low self esteem, anxiety, depression, and suicidal ideation has been documented in several studies across different cultures[1,2,4,6,8]. However, since most of these studies focus on the adolescent population, not much is known about the psychosocial impact on acne on adult patients.

In this study, majority of the subjects in both groups were female. Among the adolescents, more than half were female. According to previous studies, more adolescent males are affected with acne vulgaris and have more severe disease compared to females[8,18]. However, it was also found that females are more affected psychosocially, hence, seek consult twice as much as males[8]. In adults, the prevalence of acne is higher among women[18,19]. While most males will have improvement and resolution of symptoms by their mid-twenties, females may continue to have acne even beyond 40 years of age[19]. Studies have cited that acne among the older female age group may be attributed to several factors such as hormonal imbalances, use of cosmetic products, and drugs[10,11,19].

Age on onset of acne among the majority of the subjects is between 11 to 19 which is consistent with previous studies done[20-21]. A minority of adult subjects had later onset acne. Studies show that among those with adult acne, most cases are ersistent (i.e. progressing from adolescence) while a smaller percentage experience late onset acne[10,11,18].

Among the study subjects for both groups, there was no significant difference in having previous treatments, including both physician-prescribed and over the counter medications. However, previous studies showed significant differences between adolescents and adults with regards to seeking treatment. Law et al (2009), found that less than 40% of adolescents sought treatment for acne. In a study by Poli et al (2001), they found that only 22% of adults were undergoing treatment. Differences may be attributed to perception of acne and it's effects on self-image. Due to significant negative psychosocial effects of acne on adolescents, they may be more likely to seek treatment.

Severity of acne did not show any significant differences between the study groups. In a study done by Shen et al (2012), they showed that severity of acne was similar between adolescent and persistent acne, with late-onset acne having milder severity. In other studies, it has been found that adolescent acne presents with mostly comedonal lesions while adult acne is characterized by more inflammatory lesions[11,18,19]. However, severity grading using standardized assessment tools were not employed.

A significant difference was found between adults and adolescents in their risk of anxiety and depression. In this study, adolescent acne patients had higher risk and were about 10 times more likely to be at risk. Findings were consistent with previous studies documenting the association of negative psychological effects for both groups. Majority of these studies on the psychosocial effects of acne have focused on the adolescent age group because adolescence is the stage of maximal development physically, psychologically, and socially. Thus, any perceived flaw in the physical appearance may have a significant impact on the self-image of the adolescent. Consequently, this may leads to decreased self-esteem, body image problems, and social withdrawal. This is consistent with a study by Shakoor et al (2012), which found that anxiety and depressive symptoms were most prevalent in the 10 to 19 years old age group and had a decreasing trend as age progresses. In contrast, one study showed increasing trend of depression, with the age group of 36 to 64 years old having the highest prevalence[8]. Negative effects of body dissatisfaction were seen as additional stress to the demands of adulthood. But limited studies have been done regarding adult acne. This may be due to the traditional notion that acne is only prevalent in the adolescent age group. In the recent years, more studies have been done on the epidemiology of adult acne but more research on the psychosocial impact of acne is needed.

Among the subjects who had a risk of anxiety and depression, majority were female in both groups. However more males in the adolescent group were at risk. This is due to the number of adolescent males included in the study. Compared to the 10 males in the adolescent group, only 3 of the

adult group were males. This is consistent with previous findings that adolescent acne in males is more prevalent during adolescence with a decline in the mid-twenties. While in females, acne may be prevalent up to the 4th and 5th decades. Severity of acne among the patients at risk for anxiety and depression were comparable. But among the adolescents, most of those who were at risk had moderate acne while in the adult group, most of those at risk had mild acne. Studies show that severity of acne does not have a linear relationship with severity of anxiety and depression[1,4,8]. However, this is beyond the scope of this study.

CONCLUSION

Acne vulgaris is associated with negative psychosocial effects on both adolescent and adult patients. The results of this study are consistent with previous findings across cultures. Because acne is not just a physical problem for many patients, it is important for healthcare practitioners, especially dermatologists to be able to see the red flags for psychological comorbidities among patients. The Hospital Anxiety and Depression Scale is a quick and simple tool to use for physicians for risk assessment that can be done in the clinics and can aid in providing a more holistic treatment for patients.

RECOMMENDATION

To make the study more conclusive, a larger sample size is needed.

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Preoperative Hemoglobin A1C level and Preoperative Capillary Blood Glucose Level as Predictors of Clinical Outcomes of Patients who Underwent Low to Intermediate Risk, Non- Cardiovascular Surgical Procedures*

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ABSTRACT

Background: Hyperglycemia has been associated with poor clinical outcomes in both diabetic and non-diabetic patients. The aim of this study is to determine if preoperative hemoglobin A1C level and capillary blood glucose level can be used as predictors of clinical outcomes of patients who underwent low to intermediate risk, non-cardiovascular surgical procedures.

Methodology: A Single Center Cohort Retrospective Study was conducted and data were obtained from lists of patients who underwent low to intermediate risk, non-cardiovascular surgical procedures admitted for more than one day from January 2016 to December 2016. Chart review was done and provided information on demographics, presence and status of co-morbidities, availability of hemoglobin A1C ninety days prior to surgery or pre-operative capillary blood sugar, and surgical outcomes (length of hospital stay, surgical site infection, postoperative sepsis, acute renal failure or mortality). Comparison of outcomes among different levels of A1C was analyzed using Analysis of Variance and Fisher's exact test. Comparison of outcomes between normal and elevated CBG was analyzed using independent t-test and Fisher's exact test. The level of significance was set at 5%.

Results: A total of one hundred forty five patients were included in the final analysis. Of which, 69 patients had an HbA1C available within 90 days prior to surgery with the mean A1C at 8.04% ± 2.48%, and 93 patients had pre-operative capillary blood glucose with a mean value of 125.16 ± 55.94. Longer hospital stay was shown in patients with A1C level of 8-10% (4.7 ± 5.16 days). However, the association is insignificant with a *P* value of 0.1412. There were no significant difference in the length of hospital stay in patients with CBG level of <140mg/dL and ≥140mg/dL, with a mean value of 2.9014 ± 1.7167 days and 2.8636 ± 1.2834 days, respectively. (*P* = 0.9244) .There were too few events to meaningfully evaluate for secondary outcomes.

Conclusion: Our study suggests that neither preoperative capillary blood glucose level nor hemoglobin A1C is significantly associated with longer hospital stay. But the findings on patients with hemoglobin A1C values of 8.0% - 10% warrants further investigation. Providing a preoperative intervention to improve glycemic control in individuals with hemoglobin A1C values of 8.0% - 10% may improve surgical outcomes, but prospective studies are needed.

**3rd Place, 2018 Philippine Medical Association Original Research Presentation Contest*

***From Mary Mediatrix Medical Center, Lipa City, Batangas*

INTRODUCTION

Several parameters are included in the pre-operative evaluation of patients who will undergo surgical procedures, which includes assessment of co-morbidities, such as diabetes, and laboratory workups such as fasting blood sugar. Diabetes Mellitus, in particular, is a known risk factor for postoperative complications including infection and mortality primarily because uncontrolled hyperglycemia is associated with factors that can potentially affect the healing process of the surgical patients. In the review of literature, it has been shown that inadequate glycemic control increases morbidity and mortality. However, not all patients that will undergo low and intermediate risk surgical procedures have measures of glycemic control, especially if they are not known diabetic or do not have risk factors to develop diabetes.

The underlying mechanisms relating hyperglycemia to adverse clinical outcomes postoperatively is not completely understood. It has been suggested that elevated blood glucose levels may lead to vascular and immune system dysfunctions by impairing the neutrophil function and causing an overproduction of reactive oxygen species and inflammatory mediators, which contribute to direct cellular damage.

In the review of studies done on pre-operative hyperglycemia, it has been suggested that acute hyperglycemia, measured by random capillary blood glucose, is associated with poor clinical outcomes in patients with and without diabetes. However, there were few studies which examined the relationship between chronic hyperglycemia represented by pre-operative Hemoglobin A1C level and surgical outcomes. The American Diabetes Association has not provided recommendation for the optimal A1C in patients undergoing elective surgery but generally recommends an A1C less than 7% to avoid long term complications especially in patients with diabetes. Current evidence points toward a recommended preoperative A1C between 7% and 8.5%. Length of hospital stay postoperatively is a relative indicator of both patient morbidity and cost of care as each additional day in the hospital costs more than 2,000 pesos in our institution. This study was conducted to evaluate whether preoperative hemoglobin A1C level and capillary blood glucose level can be used as predictors of clinical outcomes of patients, who underwent low to intermediate risk, non-cardiovascular surgical procedures. The primary outcome is the length of hospital stay.

Research Question

Can preoperative hemoglobin A1C level and preoperative capillary blood glucose level be used as predictors of clinical outcomes of patients who underwent low to intermediate risk, non-cardiovascular surgical procedures?

RESEARCH OBJECTIVES

General Objectives

- To determine if preoperative hemoglobin A1C level and preoperative capillary blood glucose level can be used as predictors of clinical outcomes of patients who underwent low to intermediate risk, non-cardiovascular surgical procedures

Specific Objectives

- To determine the HbA1C level of patients who underwent low to intermediate risk, non-cardiovascular surgical procedures
- To determine the preoperative capillary blood glucose level of patients who underwent low to intermediate risk, non-cardiovascular surgical procedures
- To determine the association between hemoglobin A1C and capillary blood glucose levels of patients with length of hospital stay, surgical site infections, postoperative sepsis, renal failure and mortality

SIGNIFICANCE OF THE STUDY

According to some literature, more severe and prolonged hyperglycemia is likely to cause more severe damage than acute hyperglycemia alone. Other studies said otherwise. Given the conflicting results, with the increasing number of patients undergoing surgical procedures, it is timely and relevant to do this study to know if glycemic control, whether it is acute or chronic, is adequately addressed in our institution. The data that were gathered from this study were important because they will serve as a guide in the improvement of management of hyperglycemia preoperatively. Given the higher probability of postoperative complications in hyperglycemic patients, possible interventions targeted toward decreasing these complications may lead to improved surgical outcomes and minimize health care costs.

Definition of Terms

Low Risk Non-vascular Surgeries: procedures that have reported cardiac risk generally <1% which include endoscopic procedures, superficial procedures, cataract surgery, breast surgery.

Intermediate Risk Non-vascular Surgeries: procedures that have reported cardiac risk generally <5% which include intraperitoneal and intrathoracic surgery, head and neck surgery, orthopaedic surgery, prostate surgery.

High Risk Surgeries: procedures that have reported cardiac risk of >5% which include emergent major operations, particularly in the elderly, aortic and other major vascular surgery, peripheral vascular surgery, anticipated prolonged surgical procedures associated with large fluid shifts and/or blood loss.

Pre-operative Hemoglobin A1C: Hemoglobin A1C level that was done within 90 days prior to surgical procedure.

Pre-operative Capillary Blood Glucose: Random Capillary Blood Glucose that was done on the day of surgical procedure.

Postoperative Renal Failure: A 0.3 mg/dL or 50% or higher change in serum creatinine from baseline or a reduction on urine output of less than 0.5mL/kg/hr over a six-hour interval, within a 48-hour postoperative period.

Hospital Length of Stay: The number of days the patient stayed in the hospital postoperatively.

REVIEW OF RELATED LITERATURE

Hyperglycemia is associated with impaired neutrophil phagocytic activity, increased inflammation and oxidative stress, and poor endothelial function. These factors can potentially affect the healing process after surgical procedures. According to the study done by Raju, et.al, hyperglycemia has been associated with poor clinical outcomes in both diabetes and nondiabetes patients. Diabetes patients are more likely to present as surgical patients with glycemic control challenges. (Raju, 2009).

In diabetic and nondiabetic patients, the stress of the surgery causes a hyperglycemic response characterized by increased catecholamines, growth hormones, glucagon, and cortisol levels, with a concomittant depression in insulin levels. Hepatic glycogenolysis and gluconeogenesis, along with reduced insulin secretion and tissue insulin resistance, further contribute to the hyperglycemia. Surgical stress also increases the prothrombotic state, which may present issue in patients with diabetes; thus diabetes is an important risk factor for perioperative cardiac complications and death. (Raju, 2009).

Diabetes mellitus is rapidly increasing worldwide but the greatest increase is expected in developing countries including the Philippines, which is one of the world's emerging diabetes hotspots, ranked in the top 15 in the world for diabetes prevalence. According to the International Diabetes Federation Western Pacific, 415 million people have diabetes in the world and almost 153 million people in the Western Pacific region, and by 2040 this will rise to 215 million. According to data lifted from the WHO Western Pacific Region, the prevalence of diabetes in the Philippines reached to a total of 2,770,000 cases reported last 2000 and by the 2030, it is expected to rise to 7,798,000. There were 3.5 million cases of diabetes in the Philippines in 2015. With a 6.1% prevalence of diabetes in adults aged 20-79 years, approximately 204.2 USD cost per person with diabetes, total of 51,127 number of deaths in adults due to diabetes, and 1,840.6 number of cases of diabetes in adults that are undiagnosed.

In the study done by Underwood, et. al, acute hyperglycemia during the perioperative period, noted on the day of surgery, within 24 - 48 hours of surgery and during the entire hospital stay, is also associated with poor clinical outcomes in patients with and without diabetes (Underwood, et.al, 2014).

It was noted in the 2014 ESC-ESA Guidelines on Non-Cardiac Surgery: Cardiovascular Assessment and Management, a significant number of surgical patients will have previously undiagnosed pre-diabetes, and are at increased risk of unrecognized peri-operative hyperglycemia and the attendant adverse outcomes. Although there is no evidence that screening low- or moderate-risk adults for diabetes improves outcomes, it may reduce complications in high-risk adults.

Chronic hyperglycemia noted with high hemoglobin A1C is a clear predictor of long term complications of diabetes and is the main target for glycemic control in diabetes but it is unclear whether it has an adverse effect on surgical outcomes over and above acute perioperative and whether standards of care that address elevated A1C levels prior to surgery would improve clinical outcomes. Few studies have examined the relationship between preoperative A1C level and surgical outcomes. A study in patients undergoing coronary artery bypass surgery showed an association between high A1C values and surgical complications, including mortality, cerebrovascular accidents, and deep sternal wound infection. However, high A1C values in cardiac surgery patients may be associated with more severe primary cardiac disease; therefore, these data are probably not applicable to non-cardiac surgery patients. (Underwood, et.al, 2014)

In the review of related literature of the study done by Raju, a recent retrospective analysis showed that diabetic patients with elevated HbA1c had an augmented adverse event rate and higher 30-d mortality after cardiac procedures. In another small cohort of presumably non-diabetic patients, elevated HgbA1c concentrations were associated with an increased risk of complications after vascular surgery. If it holds true that poor preoperative glycemic control adversely affects outcomes of diabetic patients, it remains to be studied whether the timely improvement of glycemic control before surgery reduces complications seen in medical patient population. (Raju,et.al, 2009)

A high blood glucose level is one component of the anesthetic care that may need more stringent control, as evidence by many studies, but tight control may also have negative outcomes as shown in the data from the Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR) Study. It has been suggested that a blood glucose of <150mg/dL is generally considered clinically acceptable, although not always easily achieved, this is explained by the many factors that can lead to hyperglycemia or hypoglycemia. (Raju,et.al, 2009)

Furthermore, the risk of postoperative infection was found to be directly related to the perioperative blood glucose values rather than hemoglobin A1C. Postoperative hyperglycemia in diabetes or nondiabetes patients has been associated with an increased risk of 30 day postoperative infectious complications and a longer hospital stay. Every 40mg/dL increase in postoperative glucose led to a 30% increase in risk of postoperative infection. (Raju,et.al, 2009)

According to the 2014 ESC-ESA Guidelines on Non-Cardiac Surgery: Cardiovascular Assessment and Management, it is well established that surgery in patients with diabetes is associated with longer hospital stay, greater use of healthcare resources and higher perioperative mortality. Elevated levels of glycosylated hemoglobin - a marker of poor glycemic control- are associated with worse outcomes in surgical and critical care patients. More recently, the emphasis has shifted from diabetes to hyperglycemia, where new-onset hyperglycemia, compared with hyperglycemia in known diabetics, may hold a much higher risk of adverse outcome. Oxidative stress, a major cause of macrovascular disease, is triggered by swings in blood glucose, more than by sustained and persistent hyperglycemia. Minimization of the degree of glucose variability may be cardioprotective, and mortality may correlate more closely with blood glucose variability than mean blood glucose per se.

According to the recent recommendations of 2014 ESC-ESA Guidelines on Non-Cardiac Surgery: Cardiovascular Assessment and Management, post operative prevention of hyperglycemia with the targeting levels at least <180mg/dL by intravenous insulin therapy is recommended in adults after high risk surgery that requires admission to the intensive care unit, and was given Class 1b recommendations. It is further recommended that, in patients at high surgical risk, clinicians should consider screening for elevated HbA1C before major surgery and improving pre-operative glucose control, and intraoperative prevention of hyperglycemia with insulin may be considered, with Class IIa level C and Class IIb level C recommendations, respectively. Postoperative targets of <110mg/dL are not recommended with Class III recommendation.

RESEARCH METHODOLOGY

Study Design: This is a Retrospective Cohort Study of patients who underwent low to intermediate non-cardiovascular surgeries from January 2016 to December 2016. Charts and recorded data of patients were reviewed.

Study Setting: The study was conducted at a tertiary care hospital, at Mary Mediatrix Medical Center.

Time Frame: 1 year

Study Duration: Chart review covered patients who underwent surgical procedures admitted on January 2016 to December 2016. The study were conducted for 6 months, 3 months were allotted for data gathering and 3 months for the analysis of the data.

Study Population:

Inclusion Criteria

1. Patients, 18 years old and above, that were admitted for more than 1 day at Mary Mediatrix Medical Center from January 2016 to December 2016 who underwent low and intermediate risk surgical procedures. Subjects were identified and filtered using the Hospital Bizbox System ver. 7.0
2. All individuals with an HgbA1c measurement within 90 days before surgery were included in the analysis.
3. Randomly selected patients with pre-operative capillary blood glucose level were also included.

Exclusion Criteria:

1. Patients who underwent cardiovascular surgical cases and high risk cases
2. Individuals undergoing same day surgeries
3. If an individual underwent multiple surgeries, only the first surgery was taken into account.
4. Individuals who underwent endoscopic and ophthalmologic surgeries

Study Maneuver

Patients that are included in the study were patients that were admitted for more than one day at Mary Mediatrix Medical Center from January 2016 to December 2016 who underwent low to intermediate risk procedures. Lists of patients were obtained from the General Database provided by the Insitution's IT Department. Subjects were filtered using the Hospital Bizbox System ver. 7.0.

Data for this study were obtained from the Medical Records Department. Chart review of patients' demographics, co-morbidities, types of surgery, level of HgbA1C and preoperative capillary blood glucose, were done. Patients' study data were coded and a unique code number were given to each chart that was reviewed in the study. More specifically, personal identifying information, including hospital unit numbers, subject names/initials, phone numbers, and addresses were removed. (*See Appendix A for the Data Collection Form*)

All individuals with an HgbA1c measurement within 90 days before surgery were included in the study. Randomly selected patients with pre-operative capillary blood glucose level were also included.

Upon identification of patients with hemoglobin A1C, they were placed on four categories, namely: patients with HgbA1C <6.5%; patients with HgbA1C ≥6.5% - <8%; patients with HgbA1C 8-10%; patients with HgbA1C >10% for comparison of clinical outcomes. Patients with pre-operative capillary blood glucose were grouped into: patients with CBG <140mg/dL and patients with CBG ≥140mg/dL. Hospital length of stay was designated as the primary outcome thus, patients undergoing same day surgery were excluded. Other secondary outcomes such as surgical site infection, postoperative sepsis, renal failure, death during hospitalization were noted.

Statistical Analysis:

Data analysis was performed in Stata SE version 13. Quantitative variables were summarized as mean and standard deviation, while qualitative variables were tabulated as frequency and percentage. Comparison of outcomes among different levels of A1C was analyzed using Analysis of Variance for quantitative variables while Fisher's exact test for qualitative variables. Comparison of outcomes between normal and elevated CBG was analyzed using independent t-test for quantitative variables while Fisher's exact test for qualitative variables. The level of significance was set at 5%.

Ethical Considerations:

All data that were used for the study were obtained after the Institutional Review Board approved the protocol. (*See Appendix C for the copy of Certificate of Approval*). All study data regarding the patients were coded and a unique code number were given to each patient's chart that was reviewed in the study. More specifically, personal identifying information, including hospital unit numbers, subject names/initials, phone numbers, and addresses were removed. The requirement for written informed consent was waived.

Results

Excluding same day surgeries, high risk, cardiovascular, and endoscopic surgeries, there were a total of eight hundred ten patients who underwent low to intermediate risk procedures from January 2016 to December 2016. Patients were randomized and a total of 145 patients were included in the final analysis. There were 56 (38.62%) patients who underwent low risk procedures and 89 (61.38%) patients who underwent intermediate risk procedures (*see Figure 1*). Of which, 69 patients had an HbA1C available within 90 days prior to surgery with the mean A1C at 8.04% ± 2.48%, and 93 patients had pre-operative capillary blood glucose with a mean value of 125.16 ± 55.94mg/dL. Majority of patients underwent laparoscopic cholecystectomy and wound debridement. (*see Figure 2*)

Baseline characteristics of patients are shown in Table 1. The mean age was 53 years old, 63(43.45%) are males, 82 (56.55%) are females. Mean body mass index is 25.23kg/m2. Co-morbidities are as follows, diabetes mellitus type 2 (42.07%), hypertension (36.55%), bronchial asthma (2.76%), thyroid disease (4.83%), malignancy (0.69%) and others (6.21%). Only 26.90% were smokers and 22.07% were alcoholic beverage drinkers. Based on the data gathered, most of the diabetic patients underwent wound debridement and majority of non-diabetic patients underwent laparoscopic cholecystectomy.

Table 1: Patients' Baseline Characteristics and Surgical Outcomes

Baseline Characteristics (N = 145)	**Mean ± Standard Deviation or n (%)**
Age (years)	53.83 ± 15.68
Sex	
Male	63 (43.45%)
Female	82 (56.55%)
Body Mass Index (in kg/m2)	25.23 ± 4.04
Co-Morbidities	
Hypertension	53 (36.55%)
Diabetes Mellitus Type 2	61 (42.07%)
Chronic Obstructive Pulmonary Disease	0
Bronchial Asthma	4 (02.76%)
Malignancy	1 (00.69%)
Thyroid Disease	7 (04.83%)
Others	9 (06.21%)
Smoker	39 (26.90%)
Alcoholic Drinker	32 (22.07%)
Low Risk Procedures	56 (38.62%)
Intermediate Risk Procedures	89 (61.38%)
Capillary Blood Glucose Pre-operative (mg/dL) (n = 93)	125.16 ± 55.94
Hemoglobin A1C levels (%) (n = 69)	8.04% ± 2.48%

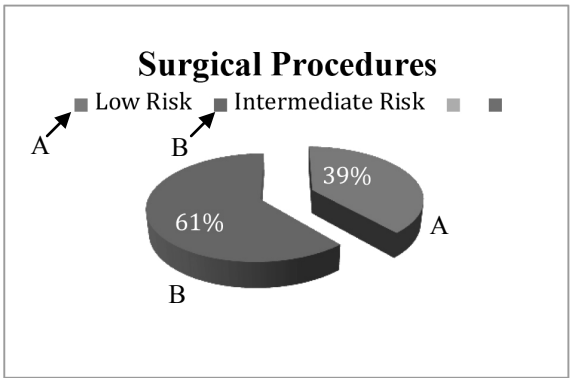

Figure 1: Percentage of Patients who Underwent Surgical Procedures

Breakdown of Surgical Procedures

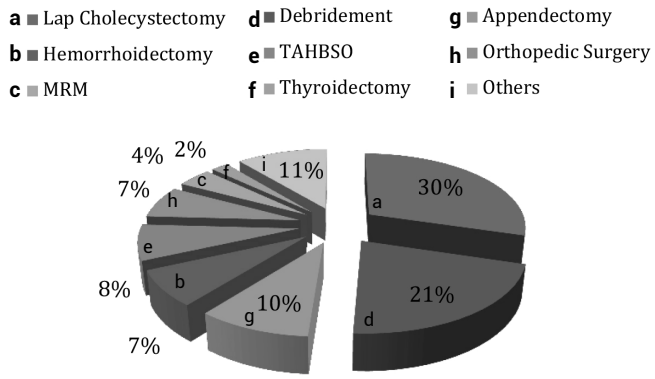

Figure 2. Breakdown of Surgical Procedures by Percentage

Comparisons among hemoglobin A1C categories with surgical outcomes, primarily length of hospital stay post-op, are shown in Table 2. Comparison of outcomes among different levels of A1C was analyzed using Analysis of Variance for quantitative variables while Fisher's exact test for qualitative variables. Among patients with A1C level ≥6.5% - <8%, the mean LOS was at 2.07 ± 1.07 days. Longer hospital stay was shown in patients with A1C level of 8-10% (4.7 ± 5.16 days). Even in patients with controlled A1C (<6.5%), the mean LOS was at 4.0 ± 3.0 days in comparison with patients with A1C level ≥6.5% - <8% (2.07 ± 1.07 days) and A1C >10% (3.588 ± 2.063 days). However, the association is insignificant with a P value of 0.1412. Surgical site infection (3.57%) and Sepsis (3.57%) were noted at A1C category of <6.5%, and Sepsis (11.76%) at A1C level of >10%, however these findings were not significant. There were no significant differences among other surgical outcomes (surgical site infection, sepsis, postoperative renal failure, and mortality).

Table 2: Surgical Outcomes by Hemoglobin A1C Category

Surgical Outcomes	A1C <6.5%	A1C ≥6.5% - <8% (n = 14)	A1C 8-10% (n = 10)	A1C >10% (n = 17)	*P* value
Length of Hospital Stay (days)	4.0 ± 3.0	2.07 ± 1.07	4.7 ± 5.16	3.588 ± 2.063	0.1412
Surgical Site Infection	3.57%	0	0	0	1.0000
Sepsis	3.57%	0	0	11.76%	0.483
Postoperative Renal Failure	0	0	0	0	0
Mortality	0	0	0	0	0

Comparison among Pre-operative Capillary Blood sugar level categories with surgical outcomes are shown in Table 3. Comparison of outcomes between normal and elevated CBG was analyzed using independent t-test for quantitative variables while Fisher's exact test for qualitative variables. Cut-off value of 140mg/dL was set because this was the level of CBG wherein interventions to control the blood sugar in non-critical patients are given. There were no significant difference in the length of hospital stay in individuals with CBG level of <140mg/dL with a mean value of 2.90 ± 1.71 days, and in individuals with CBG level of ≥140mg/dL with a mean value of 2.86 ±1.28 days (*P = 0.9244, 95% C.I = 2.5591 -3.2257*). No other outcomes were noted in CBG group.

Table 3: Surgical Outcomes by Capillary Blood Glucose Preoperatively

Surgical Outcomes	CBG <140mg/dL (n= 71) (mean ±	CBG ≥140mg/dL (n= 22) (mean ± SD)	*P* value	95% Confidence Interval
Length of Hospital Stay	2.90 ± 1.71	2.86 ±1.28	0.9244	2.5591 – 3.2257
Surgical Site Infection	0	0	0	0
Sepsis	0	0	0	0
Postoperative Renal Failure	0	0	0	0
Mortality	0	0	0	0

DISCUSSION

Patients at risk for perioperative hyperglycemia, whether they are diabetic or non-diabetic, deserve special consideration before surgery. But identifying patients at risk upon admission is difficult, especially patients with no previous consultations. Currently, data are limited to suggest that significant preoperative interventions aimed at controlling blood sugar have an impact on outcome and if such interventions are applicable to all patients who will undergo low and intermediate risk procedures, especially in non-diabetic patients wherein probability of hypoglycemia is a consideration. Majority of low and intermediate risk procedures are elective surgeries. In the review of literature, there are no guidelines that suggest delaying surgery until specific level of glycemic control is reached.

There are studies that evaluate the relationship of A1C and hospital length of stay in diabetic patients. Some studies evaluate the relationship between pre-operative, peri-operative and post-operative capillary blood glucose levels with surgical outcomes in diabetic patients also. Our study is different because we looked into both hemoglobin A1C and pre-operative capillary blood glucose level as possible predictors of clinical outcomes in all patients who underwent low and intermediate, non-cardiovascular procedures. We did not limit the study on diabetic patients only because we considered the possibility of undiagnosed diabetes in the said surgical patients.

According to the study done by Underwood, et. al., more severe and prolonged hyperglycemia represented by hemoglobin A1C level is likely to cause more damage than acute hyperglycemia (preoperative capillary blood sugar) alone. We evaluated the association of preoperative Hemoglobin A1C and preoperative capillary blood glucose with surgical outcomes, primarily hospital length of stay preoperatively, and other secondary outcomes in one hundred forty five diabetic and non-diabetic patients who underwent low and intermediate risk procedures. Primary outcome was length of hospital stay postoperatively, thus same day surgeries, endoscopic and cataract surgeries were excluded.

Baseline characteristics of Filipino patients included in our study are different from the baseline characteristics of subjects of the studies done in the literature which includes Caucasians and African Americans. In the study done by Underwood, et.al, they suggested that an A1C level of >8% may have an effect on surgical outcomes, increased length of hospital stay. The finding is consistent in our study wherein a hemoglobin A1C level of 8% - <10% showed increased hospital length of stay but results were insignificant due to the limited number of patients with hemoglobin A1C. However, there were noted differences in the baseline characteristics in between studies (BMI 34.8 ± 9.9 kg/m2 in their study, 25.23 ± 4.04 kg/m2 in our study) which could have an effect on the results that we have. Both studies have almost the same mean age at 53.83 ± 15.68 years and majority of subjects are females. Only 42.07% of subjects were diabetic and 36.55% were hypertensive.

The American Diabetes Association (ADA) has not provided recommendation for the optimal A1C in patients undergoing elective surgery but generally recommends an A1C less than 7% to avoid long term complications especially in patients with diabetes. Current evidence points toward a recommended preoperative A1C somewhere between 7% and 8.5%. Based on the data that we gathered, there is no significant association between the level of hemoglobin A1C and hospital length of stay postoperatively. In our study, longer hospital stay was noted at A1C levels of 8.0% - 10%. Worth noting in the results of the data was a longer hospital stay in individuals with HbA1C level of <6.5% than in patients with HbA1C >10% and A1C levels of ≥6.5% - <8.0%. Patients with HbA1C <6.5% may have had a higher incidence of hypoglycemia before hospital admission or may be related to severity of underlying illness which could also explain the occurrence of surgical site infections and sepsis in this A1C level category compared to the others. However, due to the limited number of patients with available A1C, the association is not significant and warrants further investigation. 11.76% of patients with hemoglobin A1C >10% had sepsis but the result was not significant. Occurrence of other secondary outcomes was also not significant. According to the American Diabetes Association, perioperative glycemic control between

80 – 180 mg/dL is recommended and advises against intensive insulin therapy due to lack of benefit and potential for increased hypoglycemic episodes. Based on the data gathered, there were no significant difference in the length of hospital stay in individuals with CBG level of <140mg/dL with a mean value of 2.90 ± 1.71 days, and in individuals with CBG level of ≥140mg/dL with a mean value of 2.86 ±1.28 days (*P = 0.9244, 95% C.I = 2.5591 -3.2257*). It has been shown in the results that only 42.07% of subjects are diabetics therefore preoperative hyperglycemia might not be totally related to diabetes per se but instead may also be a response to acute illness or injury. In line with this, a postoperative blood glucose monitoring should have also been done and management of hyperglycemia should have been taken into account. But the data were available for only a limited number of patients and it was difficult to obtain in retrospect.

Our results suggest that neither acute glycemic nor chronic glycemic control can be used as predictors of clinical outcomes of patients who underwent low to intermediate non-cardiovascular surgical procedures. However, the data in hemoglobin A1C categories showed promising results but due to the unavailability of hemoglobin A1C in majority of surgical patients, the above findings warrant further investigation.

Because of the retrospective nature of our study, it has several limitations. Our data had only one year coverage and with small sample size that limits the number of outcomes that we could evaluate. In the study, we excluded patients with unavailable preoperative hemoglobin A1C and preoperative capillary blood sugar levels which may have introduced selection bias. We did not also include in our study the interventions made in response to elevated CBGs preoperatively which could have an effect in the length of hospital stay. We, therefore recommend that a follow up study be done prospectively and in a longer time frame to evaluate the secondary outcomes. Further research is required to confirm the above findings and determine whether a preoperative glucose management strategy can improve outcomes after low to intermediate non-cardiovascular surgery in patients with and without diabetes mellitus.

CONCLUSION

Preoperative glucose control is important to maximize patient outcomes and reduce costs of care. Our study suggests that neither acute glycemic (CBG) nor chronic glycemic control (HbA1C), both done preoperatively, is significantly associated with the primary outcome, length of hospital stay. There were too few events to meaningfully evaluate for secondary outcomes. The findings on patients with hemoglobin A1C values of 8.0% - 10% warrants further investigation. Providing a preoperative intervention to improve glycemic control in individuals with hemoglobin A1C values of 8.0% - 10% may improve surgical outcomes, lessen hospital length of stay and reduce costs of care, but prospective studies are needed.

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Congenital Methemoglobinemia*

Elaine Diane G. Santos, MD**

ABSTRACT

This report a case of a ten-year-old female with progressive cyanosis and dyspnea on exertion. Clinical and laboratory work up ruled out a cardiac and pulmonary pathology warranting further investigation for possible hemoglobinopathies. Enzyme assay showed deficiency in cytochrome b5 reductase seen in patients with congenital methemoglobinemia. Ascorbic acid at 200mg daily afforded gradual improvement in cyanosis.

Keywords: *methemoglobinemia, cytochrome b5 reductase, cyanosis, ascorbic acid, child*

INTRODUCTION

Congenital methemoglobinemia is a rare autosomal recessive condition that is secondary to a cytochrome b5 reductase deficiency. This report aims to present and discuss the clinical presentation, pathophysiology, diagnosis, and management of congenital methemoglobinemia.

CASE REPORT

E.A., a 10-year old female, Filipino, Roman Catholic from Novaliches, Quezon City who was brought in for consult in a tertiary institution due to cyanosis.

The patient was born to a then 32-year old G3P3 (3003) mother with no exposure to chemicals, teratogens, radiation or viral exanthem. The patient was noted to be dusky at birth, which persisted throughout infancy. The patient had regular well baby check-ups with a private physician. No intervention or work-up was done. On the interim, there was progressive cyanosis *(Figures 1, 2, 3, 4 - see appendix)*, easy fatigability and dyspnea on exertion.

Two months prior to consultation, there was persistence of the symptoms. The patient had ten episodes of non-projectile, non-bilious vomiting consisting of previously ingested food approximately ½ cup per bout. Complete blood count showed polycythemia. She was referred to a hematologist and a cardiologist. ECG showed sinus tachycardia while echocardiogram result was normal. A hemoglobin electrophoresis showed an equivocal result. She was referred to a tertiary center for further work-up hence the consultation.

There was no history of hematologic or cardiac disease in the family. The patient denied exposure to any chemical, pesticide or toxin. There was no history of recent travel. The past medical, nutritional, immunization and psychosocial histories were non-contributory.

Pertinent physical examination revealed a blood pressure of 100/70 mmHg. She was tachycardic at 118 beats per minute. The respiratory rate was 18 cycles per minute and the temperature was 36.8 °C. The anthropometric measurements were normal for age. The patient had dusky skin, cyanotic mucosa and nail beds. (Figure 5 - *see appendix*) There was no murmur, organomegaly or clubbing of the fingernails. The neurological examination was unremarkable.

The patient was seen by a hematologist and a pulmonologist. Chest x-ray showed normal result. Baseline oxygen saturation was 89% at room air. Oxygen supplementation was given with no improvement in saturation. (Table 1) Pulmonary pathology was unlikely at this time. Congenital methemoglobinemia was considered hence serum analysis for cytochrome b5 reductase enzyme activity was done, which showed a low enzyme level. (Table 2)

**1st Place, 2018 Philippine Medical Association Case Report Contest*
***From Philippine Children's Medical Center, Quezon City*

Table 1: Oxygen Saturations in Percentage, Heart rate in Cycles per minute And Different Oxygen Flow Rates

Date/Time	Device	Flow rate	O2 sat	Heart rate
9/24/2017 9AM	Room air		87-88%	120
	O2 prong	4lpm	89-90%	101
	O2 mask	5lpm	89%	101
	O2 mask	6lpm	89%	101
	O2 mask	7lpm	89%	103
	O2 mask	10lpm	89%	105-108

Table 2: Result of Cytochrome b5 reductase enzyme in Uh/ Hb with accompanying Reference Value

	Value	Unit	Reference Value
Methemoglobin Reductase, B (cytochrome b5 reductase)	1.4	U/g Hb	6.6-13.3

Ascorbic acid at 200 mg per day was started with gradual resolution of cyanosis *(Figures 6 and 7 - see appendix)* and improvement in oxygen saturation.

CASE DISCUSSION

We are presented with a 10-year old female with progressive cyanosis since birth. Cyanosis is a blue or purple appearance of the skin or mucous membranes caused by inadequately oxygenated blood that perfuse peripheral tissues. Cyanosis can also result from the presence of abnormal hemoglobin forms that are unable to bind oxygen to supply end organs and tissues.[1] Outlined in Table 3 are the differential diagnoses of cyanosis.

Part of the initial assessment of cyanosis is the initiation of oxygen therapy. Clinical improvement with oxygen therapy suggests diffusion impairment whereas non-improvement with high-concentration oxygen is suggestive of ventilation-perfusion mismatch, such as shunting from a consolidated pulmonary lobule or congenital heart disease with right to left shunting. Our patient did not respond to high-concentration oxygen support.[2]

The non-improvement of cyanosis of our patient with high concentration oxygen therapy warrants reassessment of the respiratory status. The absence of fever, respiratory distress and a normal chest and lung examination make pulmonary pathology a least likely cause of cyanosis in our patient. An unremarkable chest x-ray findings further strengthen a non-pulmonary pathology.[1,3]

Cardiac pathology may also be considered in patients with central cyanosis. Our patient did not present with easy fatigability, growth retardation and other findings suggestive of a cardiac disease. Cardiac examination was essentially normal. Radiologic and echocardiographic findings are unremarkable. Hence, in a patient presenting with persistent cyanosis in the absence of significant pulmonary or cardiac disease, the rare possibility of an abnormality in hemoglobin structure or disorders of oxygen affinity was entertained.[3,4,5]

It is imperative to discuss hemoglobin structure and synthesis. Hemoglobin is a tetrameric protein composed of 2 pairs of globin chains. Each globin chain, or subunit, is associated with a heme group in its center. The dominant form of adult hemoglobin is hemoglobin A (HbA), which is made up of 2 α chains and 2 β chains. The synthesis and structure of the different globin chains is under tight genetic control. Defects in these genes can cause the abnormal production of hemoglobin and anemias, a disorder called hemoglobinopathies. These genetic defects can result in structural defects in the hemoglobin molecule, diminished production of the hemoglobin subunits, or abnormal association of subunits.[6]

Hemoglobinopathies are classified according to the (I) qualitative nature of the resultant hemoglobin wherein there is production of structurally abnormal globin chains (ie, sickle cell disease) and the (II) quantitative amount of hemoglobin produced wherein there is structurally normal but decreased amount of globin chains (ie, thalassemia).[6,7] Most hemoglobinopathies are not clinically apparent, while others produce abnormal laboratory findings and a few cause serious disease.[6]

As enumerated in table 4, quantitative disorders of globin chain synthesis such as thalassemia in infants and children usually presents with pallor and does not present with cyanosis. Patients with thalassemia show a variable quantity of HbA_2 in haemoglobin electrophoresis. Our index patient presented with a normal hemoglobin electrophoresis which rule out quantitative disorders of globin chain synthesis.[8]

Qualitative disorders of globin structure produce mutations or alterations of the globin protein producing pronounced changes in the functional property of the hemoglobin specifically oxygen affinity and solubility. Structural hemoglobinopathies presenting with cyanosis include those with abnormalities with oxygen binding such as those with low oxygen affinity mutants (Hemoglobin M) and methemoglobinemia.[7] These are abnormalities that result from a change of its iron from the Ferrous form to its Ferric state which is unable to carry oxygen.[9]

Hemoglobin M is an autosomal dominant hemoglobin variant that causes cyanosis as a result of structural changes in the alpha or beta chains that stabilize the hemoglobin in the ferric state. In such cases, hemoglobin M may be differentiated from methemoglobin by its corresponding absorption spectrum in hemoglobin electrophoresis.[10] A normal hemoglobin electrophoresis in our index patient excludes hemoglobin M as the possible cause of cyanosis.

Congenital methemoglobinemia was considered in our patient due to the presence of central cyanosis and low oxygen saturations, which were unresponsive to oxygen therapy. Hence, serum analysis for cytochrome b5 reductase enzyme activity was done, which showed a low enzyme level.

To elucidate the importance of cytochrome b5 reductase enzyme in central cyanosis, let us discuss the role of this enzyme. Cytochrome b5 reductase, an enzyme system present within the RBCs, converts methemoglobin to hemoglobin. It maintains intracellular methemoglobin to less than 1%. Decreased activity of this enzyme promotes the accumulation of methemoglobin leading to central cyanosis and symptoms related to hypoxia. An alternative pathway that is not physiologically active utilizes nicotinamide adenine dinucleotide phosphate (NADPH) generated by glucose-6-phosphate dehydrogenase (G6PD) in the hexose monophosphate shunt. However, there is normally no electron carrier present in the red blood cells to interact with NADPH-methemoglobin reductase. Exogenously administered electron acceptors such as methylene blue are required for this pathway to be activated. This non-physiologic pathway becomes clinically important for the treatment of methemoglobinemia.[4]

Methemoglobinemia results from an oxidation-reduction imbalance, either due to (I) excessive oxidation of hemoglobin (increased production of methemoglobin) following exposure to various oxidant drugs/toxins or (II) decreased in the activity of reducing enzymes secondary to a genetic defect in red blood cell metabolism or hemoglobin structure. The newly formed methemoglobin causes an increase in its oxygen affinity, but a functional decrease in its oxygen binding capacity shifting the oxygen dissociation curve of the oxidized hemoglobin to the left which hinders the release of oxygen in the tissues. This now leads to tissue hypoxia and a relative or functional anemia (i.e., the amount of functional hemoglobin is less than the measured level of total hemoglobin) due to the reduction of free hemoglobin to transport oxygen to the tissues. Clinically, these two mechanisms will produce central cyanosis which is unresponsive to oxygen therapy.[10,11,12]

Methemoglobinemia can be congenital or acquired. Acute or acquired methemoglobinemia results from exposure to several oxidizing agents. (Table 5) There is no exact prevalence of methemoglobinemia but studies have shown that acquired methemoglobinemia are more frequent than congenital types. Symptoms in patients with acquired methemoglobinemia tend to be more severe than in patients with congenital methemoglobinemia.

Acquired methemoglobinemia is life-threatening when methemoglobin comprises more than 40% of total hemoglobin.[4] The diagnosis of acute methemoglobinemia is least likely in this case due to the chronic presentation of the symptoms and the absence of exposure to oxidizing agents, hence, congenital methemoglobinemia was considered.

Congenital methemoglobinemia results from either cytochrome b5 deficiency, cytochrome b5 reductase deficiency or hemoglobin M.[1] The gene regulating the synthesis of cytochrome b5 reductase has been localized to chromosome 22q13qter. A number of mutations have been identified.[13]

In our patient, a deficiency of the cytochrome b5 reductase is the cause of cyanosis as evidenced by a low enzyme level.

Clinical manifestations of methemoglobinemia reflect the reduction in oxygen-carrying capacity. The clinical hallmark is unexplained cyanosis and decreased oxygen saturation via pulse oximetry despite adequate ventilation and increased inspired oxygen concentration.[12,14] This manifestation was seen in our patient. The spectrum of skin pigmentation depends on the level of methemoglobin in the blood, the higher the methemoglobin level the more expressive the cyanosis.[12] In general, a fraction of methemoglobin fewer than 15% causes only a pale, grayish or bluish pigmentation of the skin which is frequently overlooked.[12]

An additional clinical sign among patients with methemoglobinemia is the presence of dark brown colored blood. Varying degrees of brownish discoloration of the blood occurs depending on the levels of methemoglobin.[12,14] As levels of methemoglobin increase, the patient evolves with a reduction in the level of consciousness, respiratory depression, shock, and death. Levels of methemoglobin above 70% are usually fatal.[12] Table 6 shows the correlation of methemoglobin and its clinical manifestations.

At birth, our patient manifested with dusky skin complexion. Based on the table, it is estimated that she has a 3-15% methemoglobin level. On consult, the patient manifested with visible cyanosis and dark colored blood associated with dyspnea on exertion. A 30% fractional methemoglobin level may be present. [13]

Several methods are available for detecting the presence of methemoglobinemia and assessing the severity of the disease. Arterial blood gas paired with oxygen saturation by pulse oximetry and serum methemoglobin levels are clinically utilized to make a diagnosis. In methemoglobinemia, arterial blood gas will show a high partial pressure of O2 (PaO2) with normal hemoglobin saturation (SaO2), with values well above those indicated by pulse oximetry.[12] In comparison, children with cyanotic heart disease who receive supplemental oxygen have a low partial pressure of oxygen and low calculated oxygen saturation. Methemoglobinemia is strongly suggested when there is clinical cyanosis in the presence of calculated normal arterial PaO2 as obtained by arterial blood gases.[4]

The gold standard in the diagnosis of methemoglobinemia is the use of a pulse co-oximeter[11] Unlike a pulse oximeter, which measures light absorbance at two wavelengths (oxyhemoglobin and deoxyhemoglobin), a co-oximeter measures light absorbance at four different wavelengths which correspond to the absorption characteristics of deoxyhemoglobin, oxyhemoglobin, carboxyhemoglobin, and methemoglobin. In patients presenting with cyanosis of uncertain cause, co-oximetry measurements are a valuable diagnostic tool.[15] The high cost of these machines is a hindrance to its availability. [11]

Measurement of the level of cytochrome b5 reductase activity or cytochrome b5 is recommended to distinguish cytochrome b5 reductase deficiency from cytochrome b5 deficiency.[4] These assays are not available in the local market. The author was able to coordinate to an international institution to determine the enzyme assay of our patient. The cytochrome b5 reductase enzyme level of our patient is 1.4 U/g Hb which is low compared to the reference value of 6.6-13.3 U/g Hb. This result is consistent with cytochrome b5 reductase deficiency.

Congenital methemoglobinemia secondary to NADH-cytochrome b5 reductase deficiency is usually benign and does not necessitate any treatment. However, for cosmetic reasons, treatment might be necessary.[1,4,5] Treatment options include methylene blue and ascorbic acid.[1,5,16]

Ascorbic acid is a potent antioxidant and reducing agent. It has direct reducing action on methemoglobin rather than restoration of the normal enzymatic reduction mechanism.[5] Daily oral treatment with ascorbic acid (200-500 mg/day in divided doses) gradually reduces the methemoglobin to

approximately 10% of the total pigment and alleviates cyanosis as long as therapy is continued. Some studies recommended the use of 300 to 600 mg of ascorbic acid given orally three times a day.[4,11,15] In this case report, our patient was started on ascorbic acid at 200 mg daily. There was improvement in skin discoloration and oxygen saturation measured via pulse oximetry from 89% pre-treatment to 90- 92%.

The use of ascorbic acid to treat toxic methemoglobinemia is not recommended. Some studies suggested that high dose ascorbic acid may be used at 10 grams intravenously every 6 hours for the treatment of symptomatic methemoglobinemia in patients without renal insufficiency when methylene blue is not available.[4] A retrospective chart review done in a large tertiary care pediatric hospital in Argentina involving 5 patients less than 18 years of age with confirmed methemoglobinemia significant enough to cause cyanosis and functional hypoxia. These patients were treated with 100% oxygen and high dose intravenous ascorbic acid. There were no side effects noted in all patients. There was marked improvement within 24 hours. None of the patients had any additional episodes of cyanosis. This retrospective study concludes that ascorbic acid can be used in the absence of methylene blue.[17] Concerns about kidney stone formation with ascorbic acid therapy remain unproven, although high-dose therapy may be associated with some risk. [4]

In case of life-threatening and toxic methemoglobinemia, definitive treatment is methylene blue through intravenous route. Methylene blue is a thiazine dye which has dose-dependent antiseptic and oxidizing properties. It serves as a cofactor for the enzyme NADPH-methemoglobin reductase utilized by the body when normal physiologic reductive pathways are overwhelmed. Methylene blue is administered intravenously initially at 1-2 mg/kg to treat toxic methemoglobinemia. It is administered as one percent solution over a five-minute interval and should not exceed 7mg/kg. It is in itself toxic and can cause dyspnea, chest pain, and hemolysis. This dose may be repeated at 1mg/kg every 30 minutes as necessary. An oral dose can be administered at 100-300 mg orally per day as maintenance therapy.[11] Methylene blue is not devoid of toxicity and its chronic administration can cause urinary tract irritation. It also colors the urine blue or green.[18] However, methylene blue may not always be accessible in our setting.

A treatment option for methemoglobinemia is the administration of riboflavin at a dose of 400mg once daily. Riboflavin utilizes the alternate pathway of methemoglobin reduction. The clinical experience with the use of Riboflavin in the management of methemoglobinemia is very limited. [4,16]

In patients with severe methemoglobinemia unresponsive to methylene blue, hyperbaric oxygen therapy and exchange-transfusion are recommended.[5]

Patients with hereditary methemoglobinemia like our patient are advised to avoid exposure to oxidizing agents that induce methemoglobinemia. Any further increase in their baseline methemoglobin level may be life-threatening.[4]

The prognosis of patients with congenital methemoglobinemia depends on the type of the disorder. Type I recessive congenital methemoglobinemia is a benign condition and is the most common form.[4,12,18,19]The life expectancy in this type is not lower than the general population. Pregnancies may develop normally and have not been complicated due to the disorder. Type II is much less common. It is associated with neurological manifestations that would usually begin in infancy. 11 Due to the benign nature of symptoms and the absence of any neurological manifestations, our patient has type I recessive congenital methemoglobinemia.

It is recommended that families of an affected child undergo enzymatic and molecular genetic testing. Prenatal diagnosis of type II disease has been performed successfully in some cases. It has a recurrence rate of 25%. [20] It is necessary to emphasize the importance of family counselling and referral to support groups or organizations to uphold the primary concerns and welfare of individuals with rare disorders. [21,22]

SUMMARY, CONCLUSION AND RECOMMENDATION

We reported a case of a ten year old female with progressive cyanosis unresponsive to oxygen supplementation. A low cytochrome b5 reductase assay confirmed the diagnosis of congenital methemoglobinemia. Ascorbic acid treatment at 200mg daily gradually improved clinical manifestations and oxygen saturation. Prevention of exposure to oxidizing agents is warranted to prevent life-threatening complications. The importance of history, clinical clues and a high index of suspicion are indispensable in arriving to a correct diagnosis even in a limited setting.

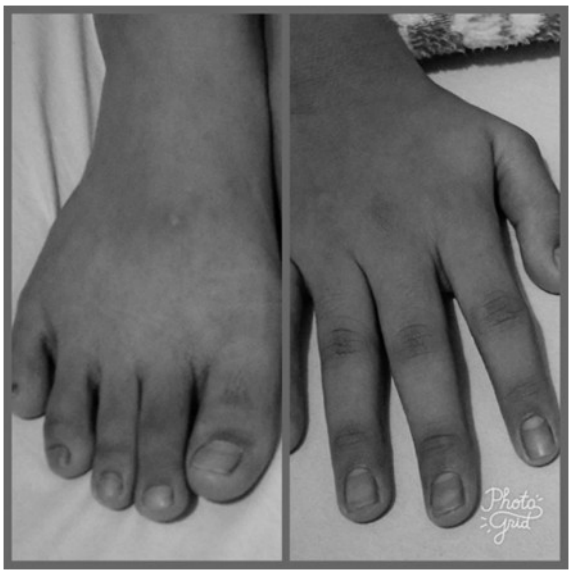
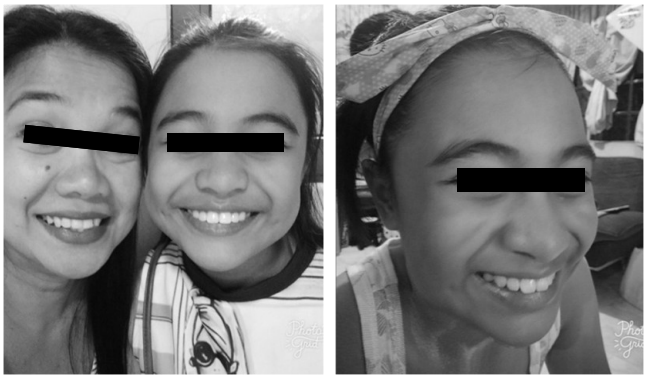


Figure 5: Picture of the right foot and hand of the patient presenting with cyanoitc nailbeds, absence of clubbing with a note of dusky skin complexion

APPENDIX

Figures 1,2,3,4: Pictures of the patient from infancy to childhood showing the progression of dusky skin complexion



Figures 6 and 7: Picture of the patient showing the gradual resolution of cyanosis

Table 3: Differential Diagnoses of Cyanosis as to Peripheral Cyanosis and Central Cyanosis

Peripheral Cyanosis	Central Cyanosis
Low cardiac output states Shock Left ventricular failure Hypovolemia	A. Decreased arterial oxygen saturation 1. High altitude (> 8000ft) 2. Impaired pulmonary function a. Hypoventilation b. Impaired oxygen diffusion c. Ventilation-perfusion mismatching - Pulmonary embolism - Acute respiratory distress syndrome - Pulmonary hypertension d. Respiratory compromise - upper airway obstruction - pneumonia
Environmental exposure (cold) Arterial occlusion Thrombosis Embolism Vasospasm (Raynaud's phenomenon) Peripheral Vascular Disease	B. Anatomic shunts 1. Pulmonary arteriovenous fistula and intrapulmonary shunts 2. Cerebral, hepatic, peripheral arteriovenous fistula 3. Cyanotic congenital heart disease
Venous Obstruction Redistribution of blood flow from extremities	C. Abnormal hemoglobin 1. Methemoglobinemia a. Hereditary b. Acquired 2. Sulfhemoglobinemia 3. Mutant hemoglobin with low oxygen affinity

Table 4: Classification of Hemoglobin Disorders

Quantitative Disorders of Globin Chain Synthesis	Qualitative disorders of globin structure: structural variants of hemoglobin
A. Beta Thalassemia B. Alpha Thalassemia C. De novo and acquired a-thalassemia	Sickle cell disorders Hemoglobin with decreased stability (unstable hemoglobin variants) Mutants causing congenita Heinz body hemolytic anemia Acquired instability—oxidant hemolysis: Drug induced, G6PD deficiency Hemoglobin with altered oxygen affinity High/ increased oxygen affinity states: - Fetal red cells - Decreased RBC 2,3 BPG - Carboxyhemoglobinemia - Structural variants Low/ decreased oxygen affinity states: Increased RBC 2,3 BPG Structural variants Methemoglobinemia Congenital methemoglobinemia Structural variants Cytochrome b5 reductase deficiency 2. Acquired (toxic) methemoglobinemia E. Posttranslational modifications Nonenzymatic glycosylation Amino-terminal acetylation Deamination Amino-terminal carbamylation

Table 5: Different Drugs and Chemical Capable of Inducing Methemoglobinemia

Drugs capable of Inducing Methemoglobinemia		Chemical Agents Capable of Inducing Methemoglobinemia	
Acetaminophen	Phenacetins	Acetanilide	Automobile exhaust fumes
p-Aminosalicylic acid	Oral hypoglycemics	Alloxan	Burning wood and plastic
local anesthetics	Metoclopromide	Anilines	Nitrates
Benzocaine	Nitrates	Aminophenol	Potassium nitrate
Bupivacaine	Silver nitrate	Benzene	Sodium nitrate
Lidocaine	Nitroglycerine	Bivalent copper	Nitrites
Prilocaine	Nitroprusside	Chlorates	Naphthalene
EMLA	Nitrites	Chromates	Nitrophenol
Anticonvulsants	Nitrofurantoin	Dimethyl sulfoxide	Nitrobenzene
Valproic acid	Nitric oxide	Dinitrophenol	Toluidine
Phenytoin	Nitrous oxide	Phenol	
Antimalarial drugs	Piperazine	Fumes	
Chloroquine	Rifampin		
Primaquine	Sulfonamides		
Quinacrine	Sulfasalazine		
Methylene blue	Sulfamethoxazole		
Dapsone	Sulfadiazine		

Table 6: Percentage of Methemoglobin level with Associated Signs and Symptoms

Fractional Methemoglobin level (%)	Signs and symptoms
<3 (normal)	None
3-15	Frequently none Grayish skin
15-30	Cyanosis Chocolate-brown blood
30-50	Dyspnea Headache Fatigue, weakness Diziness, syncope SpO_2 ~85%
50-70	Tachypnea Metabolic acidosis Cardiac arrythmias Seizures CNS depression Coma
>70	Death

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Aggressive Angiomyxoma of the Vulva: A Case Report*

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ABSTRACT

Aggressive Angiomyxoma is a rare, slow growing, benign mesenchymal tumor arising from the pelvis and perineum which commonly affects women in the reproductive age group. Though benign, it is locally infiltrative with a marked tendency for local recurrence. We report a case of aggressive angiomyxoma of the vulva with translevator extension into the pelvic cavity in a 33 year old G2P2(2002). She presented with a left labial mass that recurred two years after excision was done. Debulking of the mass was carried out by abdominal and perineal approach. Histopathologic studies of the mass confirmed aggressive angiomyxoma. Long-term periodic follow-up with imaging studies was advised because of its high rate of recurrence in spite of negative tumor margins after wide excision.

Key words: Aggressive angiomyxoma, vulvar tumor

INTRODUCTION

Aggressive angiomyxoma is an uncommon, slow growing, benign,locally infiltrative mesenchymal tumor of the pelvic region. Since 2010, only less than 250 cases were reported worldwide (3) and this is the first reported case in our institution in the last 20 years. This paper will be discussing a case of aggressive angiomyxoma in a 33 year old, who presented with a vulvar mass that extended in the pelvic cavity.

CASE REPORT

H.A., 33 year old, G2P2(2002), sought consult at the gynecology outpatient department complaining of an enlarging vulvar mass. Four years prior patient underwent excision of a left labial mass at a district hospital; however histopathology of the mass was unknown. Two years prior to consult, patient noted recurrence of the left labial mass with associated increasing abdominal fullness and pelvic heaviness. There was no history of vaginal bleeding, vulvar pain nor changes in bowel and bladder habits. The patient's menstrual cycles ccurred regularly with a normal flow. There was no history of papsmear or oral contraceptive pills used. The patient denied any family history of malignancy or other heredofamilial diseases. She is a non-smoker and non alcoholic beverage drinker. Upon physical examination of the abdomen, there was palpable mass measuring 20 cm x 20 cm, cystic, movable, non tender from the hypogastrium to the left upper quadrant and the subxiphoid area. Genital examination revealed a well circumscribed left labial mass, soft, nontender with spongy consistency measuring 18 cm x 25 cm extending to the crural fold laterally; compressing the vaginal cavity medially and cephalad; with extension to the left gluteal fold presenting as a 10 cm by 10 cm soft non tender mass (Figure 1). The inguinal lymph nodes were not enlarged bilaterally. The initial impression was a pelvoabdominal mass with possible perineal extension/herniation.

Ultrasound of the abdomen revealed an isoechoic mass measuring 20 cm x 15 cm x 15 cm anterior to the uterus, extending to the vulvovaginal area. Contrast enhanced computed tomography (CT) of the abdomen revealed an enhancing mass within

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the left ischioanal fossa that extended through the pelvic floor musculature into the pelvis (Figure 2). The soft tissue mass is seen predominantly on the left side of the vaginal region extending inferiorly to the vulva and superiorly to the uterus at the level of L5 vertebra. The mass displaced and compressed the adjacent rectum and sigmoid colon to the right. This mass measured approximately 33cm x 10 cm x 17 cm (CC x W x AP). Another intraabdominal mass was seen in the region of the left upper abdominal quadrant and was noted to be predominantly cystic with enhancing septations. The lower portion of the mass was solid and measured 28 cm x 20 cm x 12 cm causing mass effect to the adjacent bowels displacing them to the right side.

Tumor debulking was done by abdominal and perineal approach. Intraoperative findings revealed a large tumor occupying almost the entire abdomen displaced to the left, on top of the intestines. The superior borders of the mass was noted to be just below the stomach and adjacent to the left lobe of the liver. Inferiorly, the mass was densely adherent to the left lateral border of the uterus, cervix and the bladder. The mass also had dense infiltration into retroperitoneum and was adherent to the rectum. The tumor was excised securing the integrity of the bowels, bladder and ureters. The surgical specimen was a soft, gelatinous mass with a glistening pink outer surface measuring 65 cm x 38.5 cm x 8.5 cm (Figure 3). Cut sections showed smooth, solid, tan to yellow soft fatty surface. Along with the tumor, the uterus with the left ovary and fallopian tube were removed. A 2 cm x 3cm submucous myoma was seen on cut section of the uterus (Figure 4). Upon closure of the abdomen, surgical drains were placed.

Excision of the vulvar mass was carried out by sharp dissection and electrocautery. Surgical specimen was an irregularly-shaped tan to brown rubbery tissue measuring 30 x 19 x 8.5 cm with portion of her labial skin (Figure 5). Cut sections showed smooth, solid, tan to yellow soft surface similar to the abdominal mass (Figure 6). Vulvar defect was approximated after placing a surgical drain which was removed on the 5th post operative day (Figure7).

The histopathological exam of the abdominal and vulvar specimens showed aggressive angiomyxoma. Histopathologic reports showed small, uniform, spindle shaped cells with poorly defined, pale eosinophilic cytoplasm and vesicular nuclei in a myxoid background. There are small thin walled capillaries showing perivascular hyalinization (Figure 8).

During follow-up 4 months postoperatively, the patient did not show any sign of recurrence (Figure 9). Yearly follow-up with physical examination was advised to the patient to monitor recurrence.

DISCUSSION

Aggressive angiomyxoma (AA) is a benign mesenchymal tumor of premenopausal women with peak incidence between 30 and 50 years (6). Classic presentation of the said tumor is a painless mass that has indolent growth. It has variable presentation involving the vulva, perianal region, buttock or pelvis. The greatest clinical dilemma of AA is high predisposition for local recurrence. Recurrence is local and reported in 36-72% of cases and usually manifests within 2 to 10 years. As to the patient, the vulvar mass recurred 2 years after excision was done.

Up to 80% of cases are wrongly diagnosed (7). Clinically, AA may be misdiagnosed as Bartholin cyst, lipoma, labial cyst, Gartner duct cyst, levator hernia or sarcoma. Smooth muscle tumors, canal of Nuck hernia, pelvic floor hernia, and vaginal prolapse also need to be considered in the differential diagnoses of a mass in the perineum. Histologically AA may mimic the following entities: angiomyofibroblastoma, fibroma, myxofibrosarcoma, myxoid leiomyoma, lymphangioma, neurofibroma, malignant mesenchymoma, malignant fibrous histiocytoma, myxolipoma, sclerosing mesodermal tumor, leiomyosarcoma, and embyonal rhabdomyosarcomas (4).

There is no agreement regarding the pathogenesis of aggressive angiomyxoma. This hormonally responsive tumor is thought to arise from primitive multipotent perivascular progenitor cells of the female lower genital tract display variable myofibroblastic and fibroblastic features (1). The tumor expresses desmin and smooth muscle actin

which are characteristic of myofibroblasts (9). A gene in the 12q12-15 region of chromosome 12, called high-mobility group protein isoform I-C (HMGIC), encodes proteins involved in the transcriptional regulation that renders the specialized mesenchymal cells of the pelvic-perineal region to display myofibroblastic features (9). The term "aggressive angiomyxoma" is due to the high local recurrence and its nature to infiltrate adjacent organs (2). These lesions can grow slowly into enormous sizes and infiltrate surrounding perivaginal and perirectal tissues (8). The neoplasm in this case grew into a large mass almost occupying the whole abdominal and pelvic cavity with infiltration to the retroperitoneum, uterus and rectum.

Aggressive angiomyxoma exhibits unusual growth patterns of translevator extension with growth around perineal structures (4). Extension from the perineum into the pelvis is common and often clinically unsuspected. The tumor tends to grow around the structures of the pelvic floor without penetrating the muscularis of the vagina or the rectum. These tumors have the tendency to displace rather than invade perineal structures (10). The hypothesis for the translevator extension of the mass in this case was through the round ligament. The mass from the labia majora passed through the deep inguinal ring entering the pelvis through the inguinal canal and continuing on to the pelvic cavity. CT and MR imaging can accurately reveal whether a tumor traverses the pelvic diaphragm. This determination is critical to choosing the surgical approach –either perineal, abdominal, or both – comprehensive enough to avoid leaving residual tumor. Imaging studies are important in preoperative evaluation since the tumor extension is often underestimated by physical examination (7).

Grossly, AA is a soft, well defined, sometimes polypoid mass, ranging in size from a few centimeters to 20cm or even more. The main feature is a shiny, homogenous, gelatinous appearance on cut sections (8). Microscopically the tumor is composed of widely scattered spindled to stellate-shaped cells with ill-defined cytoplasm and small round to oval hyperchromic nuclei with small centrally located nucleoli, embedded in a myxoid stroma. A significant special feature is the presence of variably sized vessels that range from small thin walled capillaries to large vessels with secondary changes including perivascular hyalinization and medial hypertrophy (8).

Several imaging modalities have been used to describe AA. On sonographic imaging, it appears as a hypoechoic or cystic mass. Computed Tomography scan typically demonstrates a mass with well-defined margins, slightly hypodense to muscle. This is due to loose myxoid stroma and high aqueous content of such tumor (7). On MRI, these neoplasms are usually hyperintense on T2 weighted images, likely related to high water content and loose myxoid matrix (9). On T1-weighted images, the tumors are isointense to muscle. Characteristically, the mass will have internal areas of swirled linear low-intensity signal on both T1-weighted and T-2 weighted images, thought to be related to fibrovascular stroma. Aggressive angiomyxomas demonstrate significant contrast enhancement, likely due to the high internal vascularity (6).

The first line of treatment for aggressive angiomyxoma is wide surgical excision, although achieving negative resection margins is difficult because of the infiltrative nature of the tumor and the absence of a well defined capsule (4). Organs such as the rectum and bladder to which the tumor may be attached are spared (9). Partial excision can be acceptable when high surgical morbidity is anticipated. Unfortunately recurrences can occur, even with negative surgical margins (7). Recurrences are reported from months to several years after excision. Local recurrences are treated with reoperation when possible and cannot be anticipated from tumor size nor cellularity (8).

Most of angiomyxomas show positivity to receptors of estrogen and progesterone. For this reason, hormonal treatment is believed to be a possible option for treatment. GnRH analogs have been used in some few cases of premenopausal women, but this tumor can regrow once the therapy is discontinued. The pre-operative reduction of tumors using analogs of GnRH can increase the chances of complete excision and reduce the morbidity of the surgical procedure. The length of GnRH agonist treatment is unknown at the moment, whether a short course or intermittent treatments are necessary (4). Our patient was not able to afford

the cost of treatment with GnRH analogs. Adjuvant hormonal treatment has also been described with Tamoxifen and Raloxifene with several degrees of success –from no response to complete remission of primary or recurrence of aggressive angiomyxoma. Radiotherapy and chemotherapy are poor treatment options because the tumor has low mitotic activity (6). Angiographic embolization may also help in subsequent resection by shrinking the tumor as well as making it easier to identify if from surrounding normal tissues (9). Generally, it is not conducted, as the tumors frequently have numerous feeding vessels. The role of biopsy of sentinel lymph nodes and lymphadenectomy is still unclear. Although there various treatment options, the recurrence rate is higher than 72% (7).

Currently there are no guidelines on the postoperative management of aggressive angiomyxoma. Because of high recurrence rate and potential morbidity associated with non-diagnosed recurrences, several authors have recommended periodic evaluations with physical exam and magnetic resonance for up to 15 years after the treatment (7). Early detection of recurrences can also be improved by inclusion of imaging studies in the follow-up protocol (7). Our patient was advised yearly follow-up at the outpatient department for 2 years and every 5 years thereafter. Prognosis is very good though some literature reported metastatic potential of aggressive angiomyxoma. Only two cases with metastatic disease have been reported. The first case occurred in a 63-year-old woman who presented with nonspecific abdominal symptoms and was found to have a pelvic AA with abdominal and lung metastasis. The second case occurred in a 27-year-old woman who developed several local recurrences after primary resection of an AA and subsequently died of multiple lung metastases (2).

By reviewing this case together with other reported cases, many physicians can gain better understanding of aggressive angiomyxoma. It is important to keep aggressive angiomyxoma as part of the differential diagnosis when patients present with painless vulvar mass. High index of suspicion is needed to make a clinical diagnosis.Current literature supports the current recommendations for treatment of angiomyxoma with a surgical resection and GnRH agonist treatment following resection. It is important to advise the patient for close follow-up with imaging of MRI or ultrasound since aggressive angiomyxoma has a high recurrence rate.

SUMMARY

This is a case of aggressive angiomyxoma in a 33 year old G2P2(2002) which presented as recurring left labial mass that extended in the abdominal cavity measuring 65 cm x 38 cm x 18cm. Wide excision of the mass was done by abdominal and perineal approaches. Histopathologic examination of the mass revealed an aggressive angiomyxoma. Periodic follow-up is warranted to monitor recurrence since aggressive angiomyxoma is known for its high propensity for tumor recurrence.

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APPENDIX

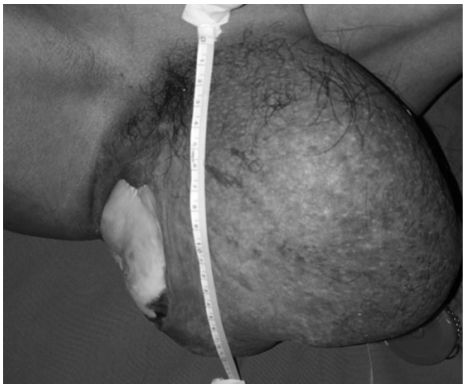

Figure 1. Preoperative appearance. Large mass located on the perineal and vulvar region

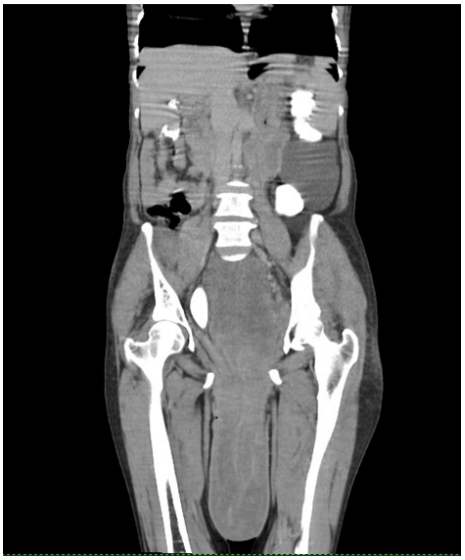

Figure 2. Contrast enhanced coronal CT scan image of abdomen and pelvis shows a large hypodense mass lesion herniating into the perineum.

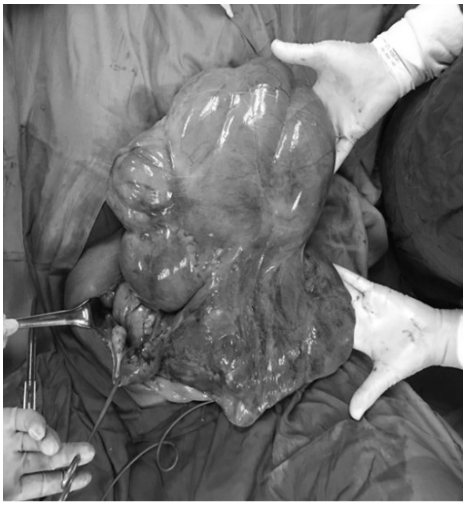

Figure 3. A 33 year old female with an enlarged vulvar mass diagnosed with aggressive angiomyxoma. Intra-operative photograph shows highly vascular fleshy mass.

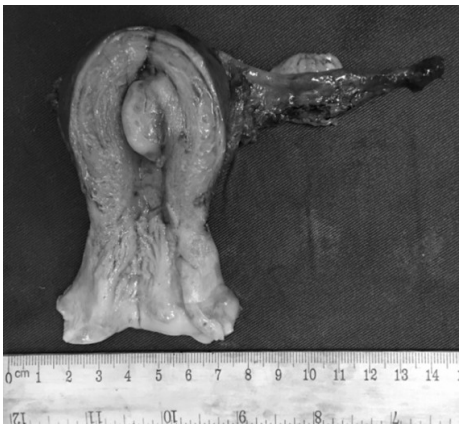

Figure 4. Cut section of the uterus showed posterofundalsubmucous myoma. Cervix, the myometrium, left ovary and fallopian tube were grossly normal.

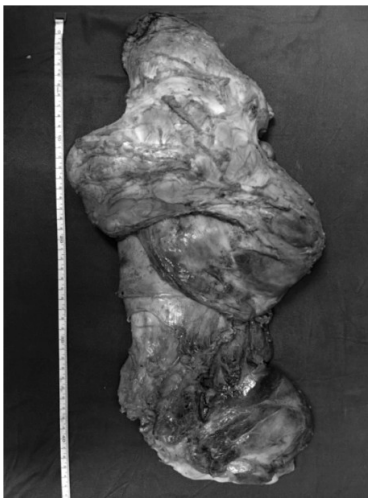

Figure 5. Gross appearance of the tumor, which measured 45cm x 30 cm x 13 cm with irregular external surface

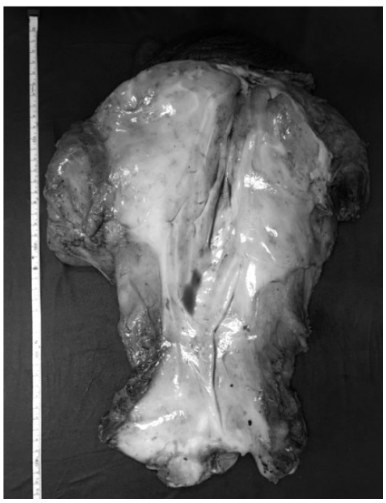

Figure 6. Cut section of the vulvar mass showed glistening gelatinous surface.

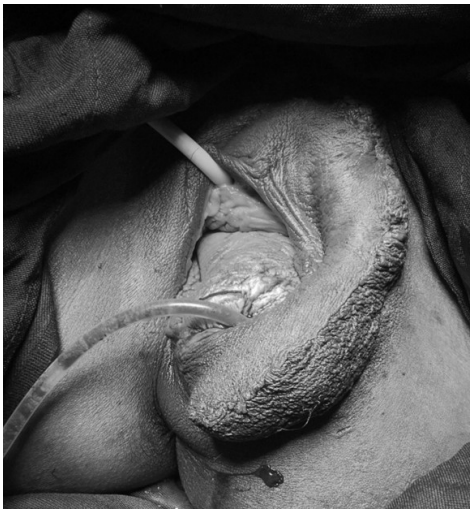

Figure 7. Post operative appearance. Approximation and suturing of the vulvoperineal region with application of suction drain

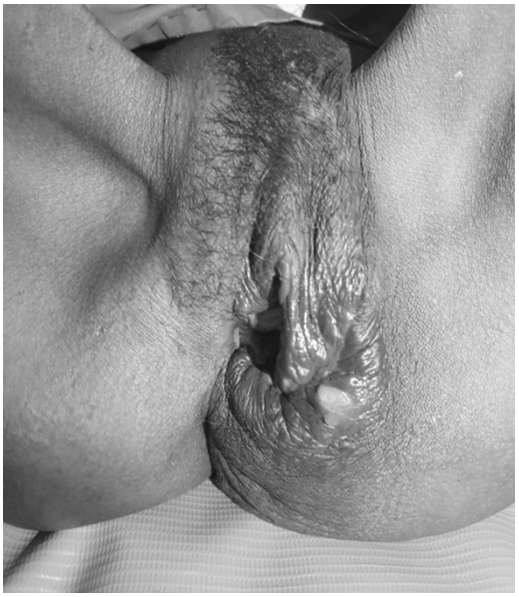

Figure 9. Four months postoperative appearance.

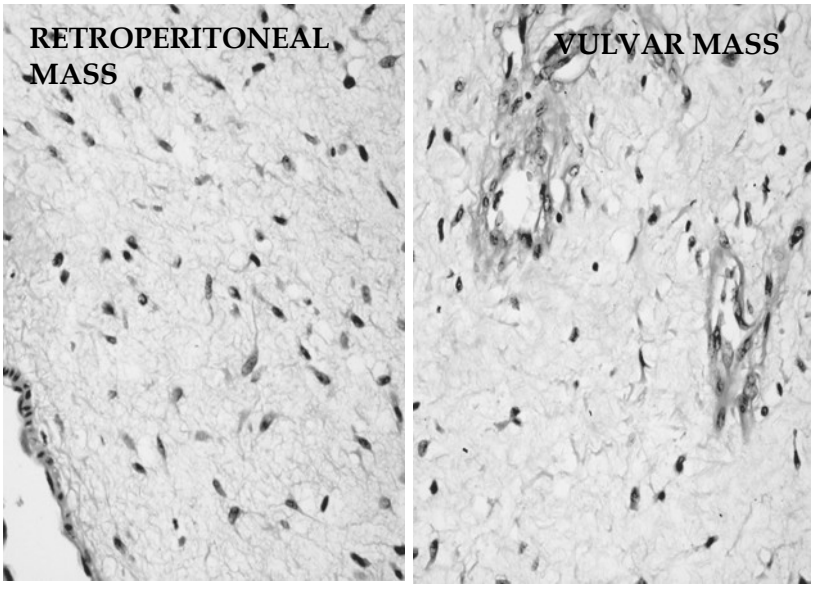

Figure 8. High power magnification showed small, uniform, spindle shaped to stellate with poorly defined, pale eosinophilic cytoplasm and bland, often vesicular nuclei in a myxoid background.

A Case Of A 32-Year-Old Male With Rare Presentation of Secondary Syphilis*

Ruby Ann B. Imson, MD**

ABSTRACT

Nodular secondary syphilis is a rare condition with only 12 cases reported from 1980 to 2005[5]. Cutaneous nodular granulomatous lesions, a positive serologic test for syphilis, and rapid resolution of symptoms with administration of Benzathine Penicillin are usually seen in previous cases [3,4,5,6]. We report a case of a 32-year old male with clinical manifestations and laboratory findings consistent with nodular secondary syphilis, and concurrent manifestations of primary and secondary stages. This is the first documented case in East Avenue Medical Center and possibly in the Philippines, highlighting the need for meticulous historytaking, physical examination and laboratory work-up to determine the correct diagnosis.

Keywords: Secondary syphilis, nodules, HIV, sexually transmitted disease

INTRODUCTION

Syphilis is a sexually transmitted infection characterized by a variety of clinical manifestations depending on the stage of the disease. Mucocutaneous manifestations vary from genital ulcers to widespread papulosquamous eruptions to granulomatous nodules. We report a rare case of a 32-year old male with clinical manifestations and laboratory findings consistent with nodular secondary syphilis, and concurrent manifestations of primary and secondary stages.

CASE REPORT

A 32 year old man, Filipino, from Quezon City was seen at the dermatology out patient department of East Avenue Medical Center for evaluation of nodular skin lesions on his face, trunk, genitalia, upper and lower extremities.

History of present illness started one month prior to consult when he noted an asymptomatic papule on his glans penis. No pain, pruritus nor urethral discharge were noted. This was followed by the appearance of bilateral, non-tender, inguinal lymphadenopathy with the left side more grossly enlarged. No medications were taken and no consult was done at this time.

One week prior to consult, the patient noted sudden eruption of pinkish papules and nodules on his face accompanied by non-tender bilateral cervical lymphadenopathy. He initially thought that these papules were pimples. However, he noted increase in size of the lesions, spreading to the scalp, trunk, genital area, and extremities. Persistence of symptoms prompted consult.

Review of systems showed no pertinent systemic findings aside from loss of appetite. He denies weight loss, body weakness, eye pain or redness, changes in vision, and any history of mouth sores or thrush. Past medical history was unremarkable. Patient denies similar lesions among other members of the family. He works as a sales clerk in a grocery store. He is a non-smoker and occasional alcoholic beverage drinker. For the sexual history, his first contact was at 15 years of age and he claims to have had approximately 30 male sexual partners, most of which were casual encounters. He denies use of condoms and contact with prostitutes.

*3rd Place, 2018 Philippine Medical Association Case Report Contest
**From Department of Dermatology, East Avenue Medical Center, Quezon City

On cutaneous examination, there were numerous well defined, round, pink erythematous to hyperpigmented papules and nodules, some with erosions on the face, nape, trunk, upper and lower extremities sparing the mucous membranes, palms and soles (see figure 1). There was also a solitary, well-defined, round, pink, eroded papule on the glans penis (see figure 2). On physical examination, there were bilateral non-tender, firm, movable cervical lymph nodes along with a grossly enlarged matted lymph node on the left inguinal area *(buboe).* Cardiac and neurological examination was unremarkable.

A working diagnosis of syphilis, rule out other sexually transmitted infection was made based on the patient's sexual activity profile and clinical picture. Skin biopsy was taken on a new lesion on the left arm which revealed an ulcer surmounted by a crust and fibrin with a zone of neutrophils at the base. The adjacent epidermis showed spongiosis, subcorneal pustule, irregular acanthosis and a foci of slight basal layer vacuolization. There is also a superficial and deep perivascular moderately dense mixed- cell infiltrate consisting of lymphocytes, histiocytes, neutrophils, and numerous plasma cells forming nodular aggregates in the upper dermis. There was exocytosis of lymphocytes and neutrophils into the dermis. Endothelial swelling was noted. The overall findings were consistent with *secondary syphilis*.

Laboratory tests showed that complete blood count, urinalysis, Chest X-ray, Anti-HIV, Anti-HCV, Anti-HBV antibodies were normal. There was also a highly reactive rapid plasma regain test (RPR) strengthening the diagnosis of secondary syphilis. One dose of Benzathine Penicillin G 2.4 million units was administered via intramuscular injection. Antihistamine was given for pruritus and patient was advised to apply a skin barrier repair cream on lesions. He was advised to abstain from any form of sexual activity, to contact all sexual partners for the past six months, and to use protection on future sexual contacts.

Upon follow up, we noted resolution of lesions with post-inflammatory hyperpigmentation of the papules. Lymphadenopathies were no longer palpable. Repeat HIV test was requested despite the initial negative result in order to remove the potential false negative result in a patient that was tested within the window period. The window period is a 3-4 week delay between a newly acquired HIV-1 infection and development of antibodies to HIV. During the window period a person can be infected with HIV and be very infectious but still test HIV negative.

DISCUSSION

Syphilis dates back to the time of Columbus, when pandemics of the disease were first documented. Since then, syphilis remained prevalent until the discovery of Penicillin in 1928, which became widely available for the treatment of syphilis during the postwar era[1]. In the United States, the Center for Disease Control (CDC) reports that in 2000 and 2001, the national rate of reported primary and secondary cases of syphilis was 2.1 cases per 100,000 population which is the lowest rate since reporting began in 1941. After being on the verge of elimination in 2000, syphilis cases have rebounded which is attributed to the increase in cases primarily among men, and particularly among men who have sex with men (MSM). The increase in syphilis cases among MSM is a major public health concern, particularly because syphilis and the behaviors associated with acquiring it increase the likelihood of acquiring and transmitting human immunodeficiency virus (HIV)[8]. In the Philippines, the exact prevalence and incidence of syphilis is lacking although 589 new cases of syphilis were reported in the Philippine Dermatological Society Health Information System Database (PDS- HIS) from 2011 to 2017.

Syphilis is a disease caused by the spirochete *Treponema pallidum.* It is most commonly acquired sexually when a person comes in contact with infectious lesions of syphilis on another person. Syphilis can also be acquired through nonsexual contact such as blood transfusion, accidental inoculation in an occupational setting, or through exposure in utero [1]. According to CDC, it has been observed historically that increase in the number of cases of congenital syphilis paralleled the increase in primary and secondary cases among women in 2014 –2015 (27.3%) and during 2011–2015 (55.6%)[8]. This is of particular importance because early diagnosis and treatment would prevent the devastating effects of syphilis.

Most of the manifestations of syphilis are cutaneous, making it of particular interest to dermatologists. Persons infected with syphilis pass through four distinct clinical phases. The primary lesion develops 10-90 days after infection and classically presents with a painless chancre at the site of inoculation. In 60-70% of cases of *primary syphilis*, painless regional lymphadenopathy arises which is usually unilateral early in the in the course of the disease, with bilateral involvement later in the course. The chancre heals in 3-6 weeks without treatment, and within 1-2 weeks with treatment[1]. The lesions of *secondary syphilis*, corresponds to a phase of infection characterized by widespread dissemination of spirochetes. Clinical manifestations are famously varied, reinforcing the reputation of this infection as "The Great Imitator"[3]. The cutaneous lesions of secondary syphilis are diverse, while the most being macular, maculopapular, papulosquamous, and annular often located on the palms and soles, sometimes accompanied by fever, lymphadenopathy, weight loss, arthralgias and myalgias[4]. A *latent period* of varied duration is characterized by the absence of signs or symptoms of disease, with only serologic tests as evidence of infection. The *tertiary stage* is characterized by the presence of a small number of organisms and a high cellular immune reactivity against the organisms. The microorganisms may invade the central nervous and cardiovascular systems as well as the skin, leading to delayed type hypersensitivity responses which produce local inflammation and gummas in affected tissues [2].

Serology is the most reliable method for laboratory diagnosis of syphilis, regardless of the stage of infection[9]. According to the CDC, a presumptive diagnosis of syphilis requires use of two tests: a nontreponemal test (i.e., Venereal Disease Research Laboratory [VDRL] or Rapid Plasma Reagin [RPR]) and a treponemal test (i.e., fluorescent treponemal antibody absorbed [FTA-ABS] tests, the *T. pallidum* passive particle agglutination [TP-PA] assay, various enzyme immunoassays [EIAs], chemiluminescence immunoassays, immunoblots, or rapid treponemal assays). The traditional algorithm for the diagnosis of syphilis recommends the use of nontreponemal test to screen for syphilis. Once positive, diagnosis is confirmed by treponemal tests[12].

The recommended treatment for most types of syphilis is benzathine penicillin G, with dose and administration schedule determined by disease stage. Treatment success is generally defined as clinical improvement accompanied by a fourfold decline in serologic nontreponemal titer within a specified timeframe depending on the stage of infection and HIV status of the infected person[1].

This case is noteworthy because lesions of primary and secondary syphilis are concurrently present. As mentioned, syphilis goes through several stages, often described in time intervals that come one after another, but the presence of two stages is not usually seen. Are these two stages present at the same time? Did we catch the patient during the transition of primary and secondary stages? According to literature, simultaneous presentation of primary and secondary syphilis has been reported and that chancre can persist into the secondary stage especially in HIV positive patients[7]. In fact, HIV infected persons are more likely to present with secondary syphilis with a primary chancre[1]. Hence, retesting for HIV as done in this case is even more necessary because of the patient's clinical presentation. Our patient shows us that the clinical manifestations of syphilis, which are classically divided in literature according to stages, may not appear in the orderly manner as we thought and may occur simultaneously.

Aside from the simultaneous occurrence of primary and secondary syphilis, our patient's manifestation of secondary syphilis was very unusual. He presented with few papules accompanied by nodules. There were no lesions on the palmoplantar areas, which are usually involved in secondary syphilis. Nodular lesions are rare in secondary syphilis. In fact, only 12 cases of nodular secondary syphilis have been reported from 1980 to 2005[5]. The most commonly reported histological patterns in nodular secondary syphilis are mainly diffuse dermal infiltrates and a granulomatous inflammation[5]. The pathogenetic interpretation of nodular granulomatous lesions in secondary syphilis is not clear. Some authors suggest that this kind of lesion represents a reaction of specific hypersensitivity to treponemal infection, while others believe that the formation of dermal granulomata should be correlated with the duration of the disease, representing a transition

eruption to the tertiary phase[6]. This becomes especially important because nodular secondary syphilis could be a precursor of tertiary syphilis, a potentially morbid condition. A high degree of clinical suspicion, a careful sexual history and thorough physical examination, followed by serological testing permits accurate diagnosis, thus facilitating prompt treatment of these cases[11]. The response to treatment was the same as in the typical secondary syphilis[5].

Comparing the above mentioned information on secondary nodular syphilis with the clinical and histopathologic findings seen in our patient, we can say that almost all characteristic findings of nodular secondary syphilis is evident in our patient, except for the histopathologic finding of granuloma formation. The question now is, is this a case of the rare nodular secondary syphilis?

Except for the histopathologic findings described above, there are no guidelines described in literature on how to accurately give a diagnosis of nodular secondary syphilis because very few cases have been reported. A possible explanation why granuloma formation is not appreciated in this case is because skin biopsy was taken from a fairly new lesion on the right arm. Granuloma may not have developed yet, but the true etiology of the condition which is secondary syphilis is persistently evident. The authors are postulating that if biopsy was taken from the old nodular lesions, granuloma formation might have been appreciated. This also emphasizes the importance of clinicohistopathologic correlation in the diagnosis of syphilis. Although granuloma formation was not evident in histopathology, the clinical presentation and laboratory findings still points to a diagnosis of nodular secondary syphilis.

CONCLUSION

Syphilis remains a public health concern. Syphilis is curable at any stage of the disease with devastating effects if left untreated. This case report outlines the diagnosis and management of a patient with a rare condition of nodular type of secondary syphilis. Although patients with this condition are not frequently seen in general practice, physicians must be made aware to avoid misdiagnosis and incorrect treatment. Aside from administration of curative drug, supportive treatment such as patient education, counselling, and contact tracing is just as important. This case report stresses the importance of meticulous historytaking, physical examination and laboratory work-up to come up with the correct diagnosis when presented with a patient with a rare condition. Furthermore, a thorough review of the literature especially existing case reports and case series is essential.

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APPENDIX

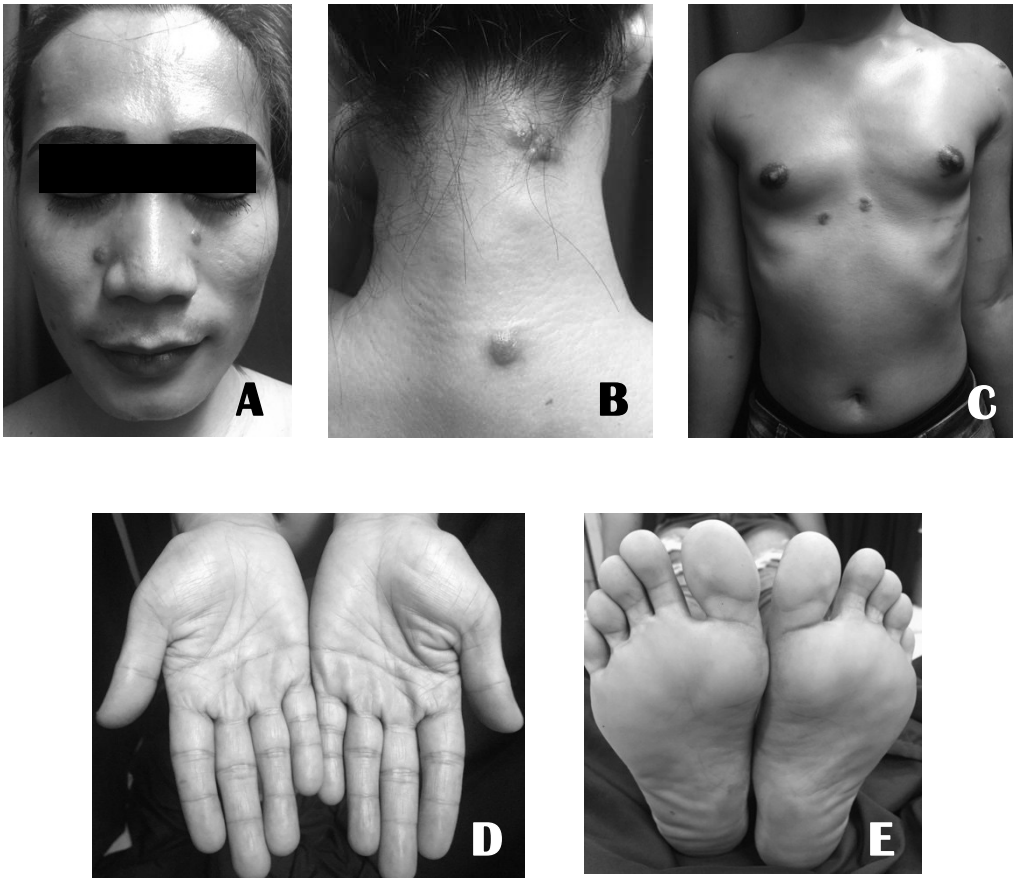

Figure 1. Multiple, well defined, round, pink erythematous papules and nodules, some with central erosion distributed on the face, nape, trunk (A,B,C), upper and lower extremities sparing the palms and soles (D,E).

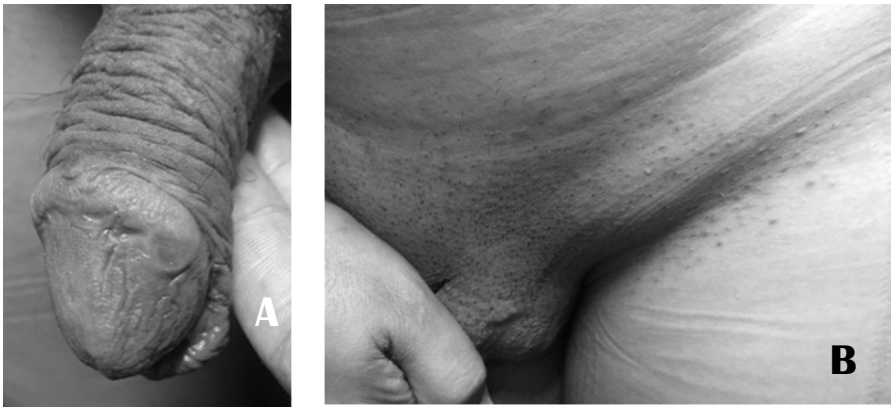

Figure 2. Nodular lesion on the glans penis where chancre was previously located (A). Grossly enlarged lymph node on the left inguinal area or *Buboe* (B).

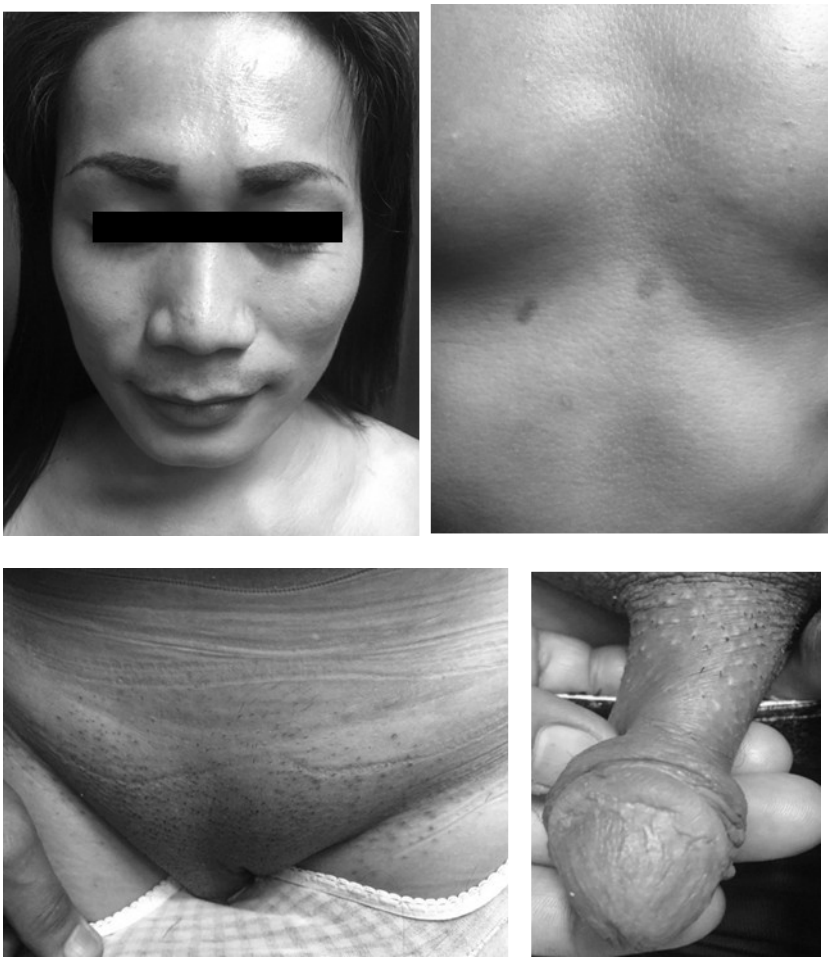

Figure 3. Resolution of erythematous nodules and lymphadenopathies of secondary syphilis three months' post treatment with Benzathine Penicillin G.

Advances in the Treatment and Management of Filipino Patients with Multiple Myeloma: From Deadly to Chronic Disease with Possibility of Remission

Erwin G. Benedicto, MD, MPH[1], Kristine Joy L. Tomanan, RN[2]
Marvin P. Angeles, RN[1], Carl Abelardo T. Antonio, MD, MPH[3]

Abstract

Background: Multiple myeloma is a malignant proliferation of plasma cells that accumulate in the bone marrow and results in several organ dysfunctions that are debilitating and fatal. For the past 20 years, advances in the understanding of genetic abnormalities, interactions in the bone marrow microenvironment, developments in the diagnosis and staging in myeloma and introduction and incorporation of novel agents early in the disease course have been pivotal in the clinical treatment and management of patients with multiple myeloma. However, the burden associated with the disease, including treatment costs, is significant for Filipino patients as it is still incurable. In the Philippines, the introduction of bortezomib in the market in the last decade have brought hope to many patients by expanding the availability of treatment options, improving quality of life and extending survival.

Methods: This paper documents the proceedings of a forum on multiple myeloma conducted last March 2018 at Makati City. The purpose of the forum was to discuss the major clinical presentations of the disease as well as treatment and management of selected patients. Speakers were hematology and medical oncology experts in the Philippines.

Results: Five cases of multiple myeloma with different clinical presentations and management were discussed: (1) renal insufficiency, (2) easy fatigability, (3) bone pain, (4) autologous stem cell/bone marrow transplantation and (5) coagulopathy. Short videos of selected patients (or their family members) after each presentation was showed, describing their treatment journey with myeloma. Other patients with multiple myeloma who were treated with bortezomib were present in the forum and briefly shared their experiences.

Conclusion: As multiple myeloma is a highly heterogeneous molecular disease, approaches and provision of care will need to be individualized for each patient. Because of its impressive performance, bortezomib is likely to continue being an important part of the clinical treatment and management of Filipino patients with myeloma.

Keywords: multiple myeloma, plasma cell disorders, monoclonal gammopathies, targeted therapy, bortezomib

INTRODUCTION

Multiple myeloma is a malignant proliferation of plasma cells that accumulate in the bone marrow and results in several organ dysfunctions and symptoms[1-3] that are debilitating and fatal.[4] The most prominent clinical features are bone pain or fracture, renal failure, anemia, infections, hypercalcemia and occasionally clotting abnormalities, neurologic symptoms and problems related to hyperviscosity.[3] Myeloma commonly affects the elderly, aged 65-74 years, with 69 years as median age.[5]

Globally, multiple myeloma accounts for around 1% of all cancer cases and 10-15% of hematologic cancers.[1,5] On the other hand, the incidence of multiple myeloma in the Philippines is considered low at 1.1-1.2 per 100,000 compared to the United States (particularly of African American origin), New Zealand, Martinique and Britain.[5,6] In 2015, for both sexes, new cases in the country were estimated at 395 while deaths were recorded at 266.[7] However, the burden associated with the disease, including treatment costs, is significant for Filipino patients as multiple myeloma is still an incurable disease.

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[3] *From Department of Health Policy and Administration, College of Public Health, University of the Philippines Manila*

Current management of myeloma involves chemotherapy, radiotherapy and bone marrow transplantation, with the goals of controlling disease and striving for deep responses, thereby prolonging patient survival and maximizing quality of life.[8,9]

For the past 20 years, advances in the understanding of genetic abnormalities present in multiple myeloma cells, alongside interactions in the bone marrow microenvironment, have been pivotal in the diversity of available clinical treatment and management of patients with myeloma.[10-12] In addition, developments in the diagnosis and staging of multiple myeloma contributed to the improvement in better provision of care and patient outcomes.[9] Furthermore, the introduction and incorporation of novel agents, particularly early in the disease course, has resulted to a paradigm shift in the treatment of multiple myeloma.[13] Specifically, the entry of immunomodulatory drugs (especially thalidomide and lenalidomide) and proteasome inhibitors (e.g. bortezomib, carfilzomib) in the last 15 years have been pivotal in improving the median overall survival of patients with myeloma.[14]

In the Philippines, the introduction of bortezomib (Velcade®) in the market since 2006 have brought hope to many patients by expanding the availability of treatment options as well as improving quality of life and outcomes. Bortezomib's effectiveness and safety profile in adult Filipino patients with multiple myeloma as well as improvement in activities of daily living have already been established.[8] Common treatment for the disease used to be melphalan-prednisone (MP) combination, vincristine-adriamycin-dexamethasone (VAD) combination, thalidomide and autologous stem cell (bone marrow) transplantation.[8] More than 10 years later, bortezomib has already become an important part of the frontline clinical treatment and management of Filipino patients with myeloma.

METHODS

This paper documents the proceedings of a forum on multiple myeloma treatment and management organized by Johnson & Johnson Philippines, Inc. last 13 March 2018 at Manila Peninsula Hotel, Makati City. The purpose of the forum was to discuss the major clinical presentations of multiple myeloma as well as treatment and management journey of selected patients. There were approximately 70 attendees of this event.

The program consisted of five (5) brief clinical case discussions with an open forum at the end of each case. The five (5) speaker-lecturers were the following: (1) Dr. Marjorie Ferriols Bravo, currently affiliated with Providence Hospital, Marikina Doctors Hospital and St. Luke's College of Medicine; (2) Dr. Pamela Rose Mancio, affiliated with University of Sto. Tomas Hospital and Asahikawa Medical University Hospital; (3) Dr. Maria Clariza Santos, presently affiliated with Manila Doctors Hospital and University of the Philippines (UP) College of Medicine; (4) Dr. Alma Calavera, currently affiliated with University of the East-Ramon Magsaysay (UERM) Memorial Medical Center, UERM College of Medicine and The Medical City; and (5) Dr. Jesus Relos, presently affiliated with UP-Philippine General Hospital, Asian Hospital and Medical Center, Makati Medical Center, St. Dominic Medical Center and University of Perpetual Help Rizal. The moderator of the forum is Dr. Ivy Escasa, currently affiliated with UP-Philippine General Hospital, Adventist Medical Center and St. Luke's Medical Center – Global City.

RESULTS

Each speaker presented one (1) remarkable case of multiple myeloma they encountered during clinical practice. Treatment and management done for the patients were briefly discussed. Short videos of selected patients in the case (or his/her family member) were played after every discussion, describing their treatment journey with myeloma. Other patients present in the forum also briefly shared their experience.

Case 1: Renal insufficiency

The patient is a 65-year old female who reported five (5) months of back pain, easy fatigability and weight loss. Anemia with multiple compression deformities on the thoracic and lumbar vertebrae were seen by the orthopedic specialist. Patient also noted drowsiness, decreasing urine output, anorexia and nausea. Significant laboratory results showed low hemoglobin levels at 6.6 g/dl, hypercellular bone marrow with plasmacytosis at 40%, and monoclonal gammopathy at 21.6% (1.75 g/dl). A decreasing trend

on estimated creatinine clearance (ECC) was noted from May to August (from 53 ml/min to 11ml/min). During the same period, increasing levels of serum K (from 5.71 to 6.00 mmol/L) and creatinine (from 1.1 mg/dl to 4.7 mg/dl) were observed. Treatment plan included administration of bortezomib for one (1) cycle. Progress in patient's condition was then observed, with hemoglobin levels improved to 10.2 g/dl, K at 4.50 mmol/L, creatine at 1.57 mg/dl and ECC at 34 ml/min.

Case 2: Easy fatigability

The patient is a 45-year old male who was admitted for easy fatigability. Notable findings from laboratory diagnostics included rouleaux formation in the peripheral blood smear, monoclonal gammopathy and elevated beta-2 macroglobulin levels (14.9 g/dl). Treatment plan consisted of intensive chemotherapy, bortezomib and dexamethasone. Conservative management was pursued; blood transfusion was restrictive and erythropoietin injections were limited. Administration of bortezomib resulted to gradual improvement in the patient's hemoglobin levels (from 8.4 g/dl to 10.7 g/dl).

Case 3: Bone pain

The patient is a 52-year old male who was admitted for bone pain. He complained of worsening back pain, progressing to debilitating until he was mostly bedbound. Thereafter, he was admitted at a local hospital. Significant laboratory findings included anemia and elevated serum creatinine as well calcium levels, in which the patient was advised work up for possible malignancy. He was transferred to a public tertiary hospital for further management. Notable baseline lab results showed low hemoglobin (7.7 g/dl), elevated serum Ca levels (15 mg/dl), creatinine (4.75 mg/dl), monoclonal gammopathy (3.0 g/dl) and multiple lytic lesions on the ribs, humerus, vertebral bodies and compression deformities on T7, T9 and T12. Interventions done included intravenous hydration plus furosemide, erythropoietin injection, dexamethasone pulsing and chemotherapy (bortezomib, cyclophosphamide and dexamethasone). After 4 cycles of chemotherapy, the patient improved from being mostly bedbound to fully active with no performance restrictions. Moreover, his hemoglobin, creatinine and serum Ca returned to normal levels.

Case 4: Autologous stem cell transplantation (Auto SCT)

Five (5) patients (2 males and 3 females) from ages 45 to 65 were identified as eligible for autologous stem cell (bone marrow) transplant. Prior to transplantation, bortezomib was part of the induction regimen of each patient (from as low as 4 cycles to as high as 9 cycles). Very good partial response to complete response were achieved by the patients before auto SCT. All five (5) were able to tolerate the procedure relatively well, with minor and manageable post-operative complications noted (e.g. fever/chills, infection, weakness, mucositis, hematuria, gastrointestinal problems). Four (4) patients are presently in complete remission (one patient for already 2 years) and one (1) is undergoing consolidation.

Currently, autologous SCT is the standard of care for patients with multiple myeloma. Patients who are eligible for transplantation are offered this option because it mobilizes stem cells early, the procedure is more tolerable and cost-effective in the long run (around Php 700,000 including hospitalization to Php 2 million). However, transplant will not cure myeloma but can help increase patients' survival and lengthen their remission. Complete remission is highly possible with auto SCT up to 10 years. Relapse can occur but can be controlled with alkylating medications.

Especially for younger patients (30 years old and above) with multiple myeloma, allogeneic SCT is a promising option. Nevertheless, stem cells from the umbilical cord blood can be difficult to obtain as there is currently no cord blood bank in the Philippines. Another concern is graft versus host disease that can occur as a complication with allogeneic transplantation. Still, costs and benefits of available treatment options must be carefully considered together with patients and their families.

Case 5: Coagulopathy

The patient is a 63-year old female who was admitted for surgical intervention of compartment syndrome. She was seen at the emergency department with swelling and tenderness of the left forearm, limited range of motion but with intact

sensation and good capillary refill. During surgery, because of the uncontrolled bleeding and impending shock that did not respond to standard measures (e.g. blood transfusion, platelet transfusion), the patient's condition was referred to the hematology department and multiple myeloma was suspected. Plasmapheresis was then initiated and bortezomib was also administered perioperatively. Her status improved, and amputation of the affected limb was avoided. Significant laboratory findings showed low hemoglobin levels (8.4 g/dl), serum creatinine (1.12 mg/dl), monoclonal gammopathy (5.9 g/dl) and lytic change on the superior angle of scapula and degenerative changes in the spine (C3-C4, C5-C6, C6-C7, L5-S1). While recuperating from surgery, long-term management of the patient's myeloma was pursued, with the inclusion of bortezomib among treatment. Currently, the patient can already move her left arm with full range of motion with some but manageable limitations in finger dexterity.

DISCUSSION

Although multiple myeloma remains an incurable disease, advances in drug development and treatment, especially with the introduction of immunomodulatory drugs (especially thalidomide and lenalidomide) and proteasome inhibitors (e.g. bortezomib, carfilzomib) in the last 15 years have improved patients' median overall survival.[14,15] These have also resulted in a paradigm shift in the treatment and management of myeloma, especially when used early in the disease course.[13,16]

As multiple myeloma is not homogenous[17] but a highly heterogeneous molecular disease[18] new treatments and drugs will continue to develop that can selectively target proteins or modify signaling pathways that are relevant in the pathogenesis of individual patients. Several classes of agents currently used in the treatment of myeloma include immunomodulatory drugs, proteasome inhibitors, histone deacetylase inhibitors, monoclonal antibodies, alkylators and steroids.[19] These drugs are often combined as doublets, triplets or multiple drug regimens, which makes choosing the optimal therapy at diagnosis and relapse, challenging.[19] The five cases presented in the forum demonstrates the varying clinical manifestations associated with myeloma, each managed differently.

Since its approval by the US Food and Drug Administration in 2003 and Committee for Proprietary Medicinal Products of the European Union in 2004, bortezomib has been an integral part of multiple myeloma therapy.[20] It is a highly selective, reversible inhibitor of the 26S proteasome that plays a key role in the regulation of protein degradation in the cell (Figure 1).[21] Through proteasome inhibition, bortezomib acts via multiple mechanisms to suppress tumor survival pathways as well as arrest tumor growth, spread and angiogenesis.[22] The drug is the first proteasome inhibitor approved for clinical use in multiple myeloma because of its notable performance and was considered as a major advance in the treatment of this disease.[23] A 2016 Cochrane meta-analysis review of bortezomib found that patients receiving the drug benefited in terms of overall survival (OS), progression free survival (PFS) and response rate compared to those who did not receive bortezomib.[23] This was specifically observed in trials of bortezomib versus no bortezomib with the same background therapy (moderate-quality evidence, prolonged OS: four studies, 1586 patients; Peto OR 0.77, 95% CI 0.65 to 0.92; moderate-quality evidence, prolonged PFS: five studies, 1855 patients; Peto OR 0.65, 95% CI 0.57 to 0.74) and in trials of bortezomib versus no bortezomib with different background therapy in each arm or compared to other agent/s (high-quality evidence, prolonged OS: five studies, 2532 patients; Peto OR 0.76, 95% CI 0.67 to 0.88; low-quality evidence, prolonged PFS: four studies, 2489 patients; Peto OR 0.67, 95% CI 0.61 to 0.75).[23]

In the latest National Comprehensive Cancer Network (NCCN) guidelines,[2,19] bortezomib-based therapy is currently the preferred regimen for transplant candidates as well as non-transplant candidates. On the other hand, for non-transplant candidates, bortezomib is the alternative option after lenalidomide for maintenance therapy. The drug is also part of the preferred regimen for patients previously treated for multiple myeloma.

While the overall safety and effectiveness of bortezomib have already been established by several studies, the disease characteristics of myeloma might predispose certain patients to thrombocytopenia and peripheral neuropathy – and the drug can exacerbate these symptoms. In addition, considering

cost-effectiveness in the Philippine setting, indefinite therapy especially for bortezomib-triplet combination regimens is highly expensive and catastrophic for patients from the lower socioeconomic classes. Overall, medical practitioners must be prudent in considering the optimal treatment and management plan offered to patients.

Nonetheless, based from clinicians' presentations and patient stories shared during the forum, there is reason to consider the substantial impact of bortezomib (Velcade ®) in the treatment and management of myeloma. From renal problems to use in autologous stem cell transplantation, it is evident that bortezomib has significantly contributed to improved clinical outcomes and consequently, better quality of life of these patients despite their differing clinical presentations. Already in its 12 years in the Philippines, bortezomib is expected to remain significant in the clinical armament against multiple myeloma.

CONCLUSION

As multiple myeloma is a highly heterogeneous molecular disease, approaches and provision of care will need to be individualized for each patient. As of this time, considering the improved outcomes, bortezomib is likely to continue being an important part of the clinical treatment and management of Filipino patients with myeloma.

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Childcare Arrangements of Dual-Physician Families With Young Children: A Descriptive Study

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Abstract

Families where both parents are physicians may face greater challenges with regard to childcare due to long and demanding work schedules. This study presents a profile of dual- physician families with young children, describes their childcare arrangements, and examines the effect on their medical practice.

Subjects: Dual-physician families with at least one child aged 7 years and below.

Method: Semi-structured interview was used to determine the participants' age, type of practice, number and age of children, living and childcare arrangements.

Results: Forty physicians, 27 to 39 years (Mean = 34.03 years) were included. Twenty were medical specialists, 18 were in training, and two were general practitioners. Sixteen families had two children each, age ranging from three weeks to seven years (Mean=2.84). Four families had children with special needs, two with autism and two with speech delay.

The number of working hours per week ranged from 11 to 119 hours, with a mean of 56.48 hours. Training physicians had a mean of 76.83 hours while the specialists had a mean of 39.82 hours. Extended family members, especially grandparents, were a major source of childcare support aside from live-in paid caregivers. Thirteen families lived with or near their extended families. In two families, the children lived with the grandparents, away from their parents.

Five physicians, all female, reported decreasing the number of working hours to care for their children while six others, four of them female, did not pursue or delayed pursuit of further training to care for their children.

Conclusion: The study suggests that childcare concerns may affect physicians' practice patterns and may have an impact on healthcare. The provision of quality, on-site childcare services to provide support to dual-physician and other dual-income families is recommended.

Keywords: dual-career families, dual-physician families, childcare arrangements.

INTRODUCTION

Finding reliable childcare is a common concern among young families across societies and socio-economic levels [1,2,3]. For families where both parents are physicians with high-demand and high-stress careers, this may present a greater challenge[4].

REVIEW OF RELATED LITERATURE

Review of literature shows that physicians work longer hours compared to other professions [5,6]. On the other hand, there are studies which showed that having young children heavily influenced the physician's decision to cut down on work, with a higher prevalence among female physicians in particular [7,8,9]. Furthermore, a study has shown that concerns about whether or not their children are getting appropriate care may actually result in stress for the physicians while they are away at work, and may affect the quality of their performance, as well as the quality of healthcare in general [10].

This issue has received attention in certain developed countries such as the United States of America, where it has been suggested that the difficulty of arranging for reliable childcare may have an impact on the number of individuals entering medical educational programs, and ultimately, the number of practicing physicians.

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It was further suggested that the situation may possibly result in a shortage of physicians in the United States within the next decade [10].

In the Philippines, the Department of Health reported a lack of physicians in the country in the year 2016[11]. A review of the literature shows a lack of reports on dual-physician families.

OBJECTIVES

This study aims to describe the profile of Filipino dual-physician families with young children, describe their childcare arrangements, and determine if their social situation has any effect on their medical practice.

METHODS

Subjects: Families where both parents are doctors residing in Metro Manila, who have at least one child aged seven years and below.

Design: Descriptive

study. Methodology:

Respondents were recruited through purposive sampling of couples who met the criteria, supplemented by snowball sampling through referrals of initial respondents. Informed consent was obtained and confidentiality was assured.

A standardized pre-interview survey and semi-structured interview tool for data collection was used. Demographic data were noted including age, sex, workplace, average daily number of working hours, and work schedule. This was followed by a background of the family in terms of the place of residence, other family members living in the same household, age and sex of children, and the presence or absence of household helpers or nannies. Data were made anonymous using code-names. Results were tabulated and analyzed.

RESULTS

A total of 20 dual-physician couples, or 40 individual physicians were included in the study. Participants were 27 to 39 years of age, with a mean of 34.03 years. Of the 40 respondents, 20 were medical specialists, 17 were in training – 11 in specialty residency training, and six in subspecialty fellowship training. Two were general practitioners, and one was a post-graduate intern.

Of the 20 medical specialists, 15 were practicing in private institutions, while five were with government institutions. Of the 17 physicians in training, 15 were in government institutions, with only one resident and one fellow affiliated with private institutions. The lone post-graduate intern was rotating in a public institution while both general practitioners were working in private institution.

The number of working hours per week varied widely with a range of 11 to 119 hours, with a mean of 56.5 working hours per week. There is an observed difference between the mean number of working hours of physicians-in-training, which was 78.8 hours per week versus 38.8 hours for the specialists. The mean number of working hours for the general practitioners was 50 hours per week. The medical specialists reported more free days in a week compared to the physicians who were still in training. (Table 1)

Table 1. Working hours of Dual-physician Families, Metro Manila, 2017

	Range	Mean (SD)
Working hours per week overall	11 to 119 hours	56.48 hours (± 27.07)
Working hours per week, in- training	45 to 119 hours	76.83 hours (± 22.42)
Working hours per week, specialist / GP	11 to 86 hours	39.82 hours (± 17.56)
Working hours per week, male	12 to 94 hours	58.1 hours (± 23.06)
Working hours per week, female	11 to 119 hours	54.85 hours (± 31.10)
Working hours per week, male specialist	12 to 86 hours	45.83 hours (± 18.24)
Working hours per week, female specialist	11 to 50 hours	32.6 hours (± 14.38)
Working hours per week, male in-training	45 to 94 hours	76.5 hours (± 16.58)
Working hours per week, female in-training	40 to 119 hours	77.1 hours (± 27.11)

Twelve out of the 17 physicians in training were required to go on 12-hour and 24-hour duties at regular intervals. Five of the 20 medical specialists also were on-call to render medical services even during their non-working hours. The two general practitioners were found to have more regular working hours with no 24-hour or on call duties.

Sixteen out of the 20 families had two children each, with two mothers pregnant with a third child. Three other families had three children, and one family had one child, with the mother pregnant with her second child. The children's ages ranged from three weeks to seven years, with a mean age of 2.84 years. Four out of the 20 families had a child with special needs; two of these were diagnosed with autism, while the other two had speech delays.

In terms of their childcare arrangements, 16 out of 20 families had at least one stay-in maid to help with both childcare and general household maintenance.

The study documented the major role of the extended family system in the life of dual- physician families. In 17 out of the 20 families (85%) the extended family members were involved in some way in the care of their children. In two of these families, the children lived completely with the maternal grandparents, one set in the province, and the other in the suburbs. The parents lived separately in Metro Manila to pursue further medical training. Eight families lived in the same household as their extended family, while three other families lived adjacent to their homes or nearby. Only seven out of the 20 families lived independently of their extended families, including the two families whose children lived with the grandparents. (Table 2)

Table 2. Living and Childcare Arrangements of Dual-physician Families

	Number of Families	% (Out of 20 families)
Stay-in Maids / Nannies	16 families	80%
Living with Extended Family Members	8 families	40%
Families Adjacent or Nearby	3 families	15%
Children Living with Grandparents	2 families	10%

Six respondents, four of them female, decided to delay or no longer pursue further medical training to take care of their family. Three of these were female physicians who cited pregnancy and childbirth as the reason for postponing their training. One was a male post- graduate intern who only pursued his internship after his wife had finished hers in order to care for their children. The remaining two decided to cease further training altogether.

Five out of the 20 medical specialists (25%), all female, specifically adjusted their working hours in order to attend to their children's needs. Their working hours ranged from 11 to 48 hours weekly, with an average of 28.4 working hours per week.

In addition to decreasing their working hours, four respondents, all female, occasionally brought their children to their place of work. One brought her children with her to work as part of their daily routine due to a lack of reliable paid caregivers. The rest only brought their children to work as the need arose, such as when their children were sick and needed supervision and medical attention, or when there were no available caregivers to stay at home with them.

DISCUSSION

A medical career requires a profound dedication to the profession and a commitment to a lifetime of learning. Several studies have noted that physicians tend to marry co-physicians, thus leading to an increase of so-called dual-physician families [7,8,9]. The study aimed to examine this social situation and determine its possible effect on medical practice.

The Magna Carta for Public Health Workers (RA 7305) prescribes 40 hours of work per week, but the results of this study showed that 27 out of the 40 respondents, or 67.5% worked longer than 40 hours per week, including one respondent who worked up to 119 hours each week, about 297.5% more than the prescribed. Four respondents had exactly 40 hours of work per week, and nine worked for less than 40 hours.

The extensive working hours of the majority of respondents may leave them with less time to spend on family and childcare. This finding was most pronounced among physicians who were still in specialty and subspecialty training. On the other hand, for physicians who were already medical specialists, the working hours were 27.5% lower than the standard 40 hours, with one respondent reporting only 11 working hours per week, in order to actively attend to her children's needs.

High occupational demands and irregular and inflexible working schedules have been shown to increase work-life conflict[6,4,12], particularly if the children are below the age of six and have yet to start regular schooling[13,14,15]. In the case of physicians, this stress may lead them to limit their working hours, or their practice overall even if they have spent many long, difficult years on extensive training.

The results of this study highlighted the major role of extended family members, particularly the grandparents, in providing childcare support to the dual-physician families. The literature reports a similar pattern with a study that showed that among a pool of families, the ones that had physicians for both parents relied on either family members who lived nearby, reliable caregivers or babysitters, or live-in nannies to take care of the housework and childcare since both parents had inflexible schedules [8].

In the present study, two couples had temporarily given the full responsibility over their children to the grandparents who lived in far off and separate households. This arrangement allowed the parents to pursue further training. Eight families lived with the extended family in the same household while an additional three families lived close by or directly adjacent to the homes of the extended family who could thus be regularly relied on for childcare.

Studies have shown that a high degree of confidence in the quality of childcare reduced the anxiety of parents regarding the welfare of their children while they were at work [10,16]. Having extended family in the same household or close by was also cited by several respondents in this study as a factor that helped alleviate some of the worry that they experienced while away at work, as compared to when their children were in the sole care of paid caregivers.

While some respondents reported that their children were enrolled in pre-schools and daycare centers, they also noted that these establishments held sessions for short periods of time only, and therefore these were not considered a form of support for childcare, but more for social development and supplementary learning experiences for their children.

Foreign studies have reported the demand for quality, on-site childcare facilities that can cater specifically to the long working hours of physicians. This was a proposed solution to give physicians, particularly those in training, peace of mind, thus allowing them to "provide unhurried, high-quality patient care"[16].

The results of this study support the same recommendation. There appears to be a need for high quality childcare services with longer hours, preferably in or near the workplace, that may provide childcare support to families with young children.

CONCLUSION

In summary, this descriptive study gave a profile of 20 dual-physician families with young children. The results showed that a majority of the physicians worked longer hours than prescribed, especially while in training. However, after completion of training, there is a trend, especially among the female physicians to cut down on practice hours to take care of their children. The role of the extended family, particularly the grandparents, in providing childcare support to the dual-physician families was documented.

While this study focused on dual-physician families, the results may also be pertinent and the recommendations applicable to other dual-income, dual-career families, which is a growing phenomenon, not only in the Philippines but elsewhere, given the increasing employment of women in the workforce[17].

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