



JOURNAL OF THE PHILIPPINE MEDICAL ASSOCIATION

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Ages 12 To 18 Years Old At The East Avenue Medical Center**

**Effect of using Electronic Versus Printed Media on the GWA of 1st – 3rd Year Medical Students at Centro
Escolar University Manila, Semester 1, A.Y. 2021–2022: A comparative study**

**The Effect of Clonidine on Onset of Action of Levobupivacaine Epidural Anesthesia Among Patients
undergoing Elective Lower Limb Orthopedic Surgery**

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with Imperforate Anus For an Emergency Procedure: A Case Report**

Triple Valve Surgery in a Patient with Rheumatoid Arthritis

Tenacious Tumors: basal cell nevus syndrome in a 50-year-old Filipina

**A Case of Pemphigus Foliaceus in a 40-Year-Old Female Successfully Treated with Doxycycline
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Epidermolysis Bullosa Pruriginosa in a 12-Year-Old Male: A Case Report

Guttate Morphea in a 31-Year-Old Filipino Female: A Diagnostic Challenge in its Early Stage

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**A Rare Enigmatic Case of a 24-Year Old Female with cutaneous Tuberculosis (Lupus Vulgaris)
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Spontaneous Remission of Classic Kaposi Sarcoma in an Elderly Filipino Female

Pregnancy in a Case of Chronic Myeloid Leukemia: A Case Report

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

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

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

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

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

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

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

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Editor's Note:

Albert Szent-Györgi, a Hungarian Biochemist, a 1937 Nobel Prize winner in Medicine, once said, "Research is to see what everybody else has seen, and to think what nobody else has thought."

This is exactly the idea behind the first medical journals were first published in the 18th century. It provided a place to share important research and studies.

With this idea also in mind, the Philippine Medical Association (PMA) thought to put together various researches and studies done by our fellow doctors and publish them in this very first medical journal of the PMA.

After reading through various articles and studies, we chose a variety of a subjects from this different fields. There is one about Another proves that Yet, there is piece on An interesting brief on concludes that...

With that, we welcome everyone to enjoy our premiere edition of the PMA Medical Journal, which is the first of many.

"Everything is theoretically impossible until it is done." – Robert A Heinlein

MARIANNE L. ORDOÑEZ-DOBLES, MD
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Cybervictimization Experiences, Reactions and Coping Strategies Among Filipino Adolescent Patients Ages 12 to 18 Years Old at the East Avenue Medical Center*

Ellen Grace Joy P. Samaniego, MD

Michelle Anne Noblejas-Mangubat, MD, FPPS, FPSAMS

ABSTRACT

Background: Adolescents are at risk for cybervictimization given their easy access to the internet and their increased engagement in online activities. Screening adolescents for cybervictimization experiences is essential to address possible adverse effects and to implement timely interventions to prevent untoward outcomes.

Objective: To describe the cybervictimization experiences, reactions and coping mechanisms of Filipino adolescent patients ages 12 to 18 years old at the East Avenue Medical Center

Methodology: This is a prospective cross-sectional study that utilized a 4-part questionnaire survey.

Data Analysis: Descriptive and inferential statistics were used to analyze the results of the study.

Results: A total of 72 adolescents were included in the study. Most of the participants were middle adolescents (55.5%), enrolled in junior high school (56%), with a slight female predominance (52.7%). Almost all of the adolescents (98.6%) used the internet and majority (84.72%) had their own mobile phones. Facebook (94.4%), Tiktok (70.8%), Messenger and Instagram (63.8%) were the most commonly used platforms. Cybervictimization experiences within the past 6 months were reported by 31.9%. More males (52.7%) were cyberbullied and cybervictimization was experienced mostly in the seventh grade (30.4%). The

most common forms of cybervictimization experienced were online exclusion and impersonation and were related to visual (mean=8.17, SD=1.94) and written (mean=8.56, SD=2.19) cybervictimization. Most adolescent cybervictims either felt scared (39.1%) or angry (34.8%). Thirty percent (30.4%) claimed not to have been affected while 26% felt embarrassed. Many of the participants either ignored the cyberbullying incidents (60.9%) or cried (47.8%). More than half of the participants disclosed their cybervictimization experiences to others, mostly to their classmates or friends (43.5%). Mobile phone use (p value= 0.021) and a lower grade onset of bullying (p value=0.020) were noted to be statistically significant associated risk factors for cybervictimization. Most adolescents either blocked the bully (52.2%) or asked support from friends (43.5%). The more time the adolescents spent on social media using their mobile phones, the higher the risk of experiencing cybervictimization. Those who experienced cybervictimization earlier may have a higher probability of re-experiencing cyber-victimization and further traumatization.

Conclusion: Different forms of cyberbullying exist and victims may have different reactions and coping strategies towards the experience. Promotion of cybersafety among adolescents and timely psychosocial support and management should be provided to prevent unwanted outcomes.

Keywords: adolescent, cybervictimization, cyberbullying

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

*Department of Pediatrics, East Avenue Medical Center

INTRODUCTION

Background of the Study

The advent of technology including mobile devices and the Internet has brought about numerous advantages for today's youth. However, access to these technological advances has also brought about concomitant risks. Among these is the risk of adolescents falling victim to the cyberworld.

Cybervictimization has been described by del Rey et al in 2012 as a "form of aggression via electronic devices, mostly using mobile phones or the Internet."¹

The four most common types of cybervictimization that adolescents encounter as described by Nocentini et al in 2010 are: (1) visual (2) written-verbal cybervictimization, (3) online exclusion and (4) impersonation.²

Visual cybervictimization involves offensive, harmful, or injurious photos or videos while written-verbal cybervictimization is done by sending annoying, threatening, or offensive calls, messages, or written comments. Online exclusion on the other hand is the non-acceptance or expulsion from a social networking group or an instant messaging program while impersonation is making fun of or getting the victim into trouble by impersonating him or her on the mobile phone or internet.²

According to the Cybersafe Survey done by the Stairway Foundation, Inc. and the Department of Education in the Philippines in 2016, the most common avenue for cyberbullying was social media in both the 7-12 year old (60%) and 13-16 year old (80%) age groups. Other means of cyberbullying reported were through chatting or texting. Thirty percent (30%) of the 7-12 year old age group experienced cyberbullying in the form of threats, while thirty percent (30%) of the 13-16 year old age group experienced cyberbullying through

photo editing. Cyberbullying was also done by exposing one's secret conversation, humiliation, creation of poser accounts, and exclusion. The usual cyberbullies were classmates in both age groups.³

Cybervictimization is becoming an alarming problem among adolescents. An estimated twenty (20) to forty (40) percent of adolescents have become victims of electronic aggression. Cybervictimization has been associated with increased anxiety, low self-esteem, social anxiety, depressive symptoms and suicidal ideations. Academic performance may also be affected due to problems with concentration, poor performance, and truancy.⁴

Hence, screening adolescent patients for cybervictimization experiences is essential in order to be able to address its possible adverse effects and to implement timely interventions to prevent further untoward cybervictimization outcomes.

Significance of the Study

The present generation of adolescents are highly dependent on mobile phones, gadgets, the internet and social media, making them vulnerable to bullying via these digital communication technologies.

Cybervictimization has grave consequences on the mental health of adolescents and may cause low self-esteem, depression, anxiety and suicide.

Screening for cybervictimization in adolescent patients may help in the identification of victims and facilitate timely implementation of interventions that may prevent the unwanted outcomes of victimization experiences.

The results of this study may also augment the few existing local data on cyberbullying among Filipino adolescents.

Review of Related Literature

Cyberbullying, a form of cybervictimization, can be more serious than traditional bullying since online attacks are public, the audience may be unlimited, and it is difficult to escape or control. It may result in psychological impairment and in severe cases, depression and suicidal behavior.⁵

Sampaga-Kayinga and Hamilton in 2015, examined the relationship between the use of social networking sites and cybervictimization among adolescents. Nineteen percent (19%) of the adolescents enrolled in the study were cyberbullied in the last twelve months. There was an increased risk for cyberbullying in younger, female adolescents, those with lower socioeconomic status and those who had alcohol or tobacco usage. The study results confirmed the association between the use of social networking sites and cybervictimization among adolescents regardless of the intensity of use.⁶

According to the study of Alvarez-Garcia et al in 2015, an estimated twenty to fifty percent (20-50%) of adolescents have been victims of electronic peer aggression. Two to seven percent (2-7%) experienced severe cybervictimization which may be a significant contributor to the onset of depressive symptoms and suicidal ideations. Age, off-line school victimization, parental control, risky internet behaviors, online social network use, use of instant messaging applications, frequency of weekend internet use were identified as significant risk factors for both occasional and severe victimization. On the other hand, owning a mobile phone, engaging in online gaming and frequency of weekday internet use were implicated in severe cybervictimization.⁷

Reactions of adolescents who experience cyberbullying may include anger, sadness, anxiety, embarrassment, crying, fear and self-blame. Poor concentration, a decline in academic

performance and absence from school have also been reported.⁷

Victims of cyberbullying may use multiple strategies in order to cope. Responses to cyberbullying can be categorized as follows: 1) targeted towards cyberbullies (retaliation); 2) ignoring the aggressor; 3) seeking instrumental or emotional support from adults, teachers, friends, or external institutions and 4) cyber-specific technical solutions (reporting abuse, blocking the sender).⁵

The findings of the 2014 study of Remond et al on cyberbullying showed that close to thirty five percent (35%) of the students were cybervictims. The mean age of cyberbullying victims was 17.84 ± 5.9 years. The strategies employed by the student cybervictims included coping, disclosing the bullying experience to someone, analyzing the situation and avoidant coping. The study results also showed that victims of cyberbullying recovered longer from a stressful event compared to victims of traditional bullying.⁸

In a 2012 study conducted by Parris et al in Atlanta, three primary cyberbullying coping themes were identified. *Reactive coping* was done through avoidance of the cyberbullying through deleting or ignoring messages. *Preventive coping* consisted of doing face-to-face talks and having increased awareness and security. However, there were also some students who reported that there was "no way to prevent cyberbullying".⁹

OBJECTIVES OF THE STUDY

General Objective

To describe the cybervictimization experiences, reactions and coping mechanisms of Filipino adolescent patients ages 12 to 18 years old at the East Avenue Medical Center

Specific Objectives

1. To determine the socio-demographic characteristics of the adolescents who experienced cybervictimization as to age, sex, current educational status and internet use
2. To determine the prevalence of adolescents with cybervictimization experiences
3. To determine the different types of cybervictimization experienced by the adolescents
4. To determine the adolescents' reactions to their cybervictimization experiences
5. To enumerate the different coping strategies employed by the adolescents who experienced cybervictimization

OPERATIONAL DEFINITIONS OF TERMS AND VARIABLES

Adolescents - are those who belong to the 10-19 year old age group, further subdivided into Early Adolescents (10-13 years old), Middle Adolescents (14-16 years old) and Late Adolescents (17-19 years old)¹⁰

Cyberbullying - a form of cybervictimization; a "collective label used to define electronic forms of bullying to aggressively and intentionally harm someone"¹¹

Cybervictimization - "aggression by means of electronic devices, mainly mobile phones and the Internet"¹

Visual cybervictimization - type of cybervictimization which uses offensive, harmful, or injurious photos or videos taken or disseminated by electronic means²

Written-verbal cybervictimization - receiving annoying, threatening or offensive calls, messages, or written comments through mobile phone or internet²

Online exclusion - non-acceptance or expulsion from a social networking group or an instant messaging program²

Impersonation - making fun of or getting the victim into trouble by impersonating him or her on the mobile phone or Internet²

Coping Strategy - "an individual's behavioral, emotional, and cognitive response to stress which serves to eliminate or modify a problem by neutralizing its negative character; helping the individual regulate his or her emotional response"⁵

METHODOLOGY

I. Research Plan and Design

1. Study Type and Design

This is a prospective cross-sectional study.

2. Sample Size, Statistical Methods and Power Calculation

The minimum sample size of **72** adolescent patients was computed based on the total number of adolescent patients admitted by the department for a period of four months (June to September 2021).

The computation was based on a 95% margin of error and 80% power. The sample size was computed using Statistical Package for Social Sciences (SPSS) version 26 using the formula below:

$$\begin{aligned}
 X &= Z (c/100) 2r(100-r) \\
 n &= Nz / ((N-1)E^2 + x) \\
 E &= \text{Sqrt}[(N-n)x / n (N-1)]
 \end{aligned}$$

Legend:

N= population size

r=fraction of responses

Z(c/100)=critical value

3. Subject Criteria

a. Inclusion Criteria

1. Filipino adolescent patients ages 12 to 18 years old who consulted at the Pediatric OPD clinic or were admitted at the Pediatric wards of the East

Avenue Medical Center from June to September 2021

2. Adolescents who can read, understand and answer the questionnaires

b. Exclusion criteria

1. Adolescents previously diagnosed with a mental health condition (depression, anxiety, post-traumatic stress disorder, mood disorders, etc.)

2. Adolescents with developmental delays or other conditions who cannot read, comprehend or answer the questionnaire on their own

3. Admitted adolescents with unstable or critical conditions

4. Non-Filipino citizens

5. Questionnaires with incomplete answers

c. Withdrawal criteria

Participation in this study was purely voluntary. The parent and/or adolescent was informed that he or she may withdraw his or her consent at any time before, during, or after completion of the survey questionnaire with no negative consequences.

4. Description of the Study Procedure

a. Specific methods and techniques used throughout the study

The protocol was submitted to the Research Committee of the Department of Pediatrics for initial approval. Once approved, it was forwarded to the Technical Review Board, then to the Institutional Ethics Review Board for final review. Once with IERB approval, letters requesting permission to conduct the study at the OPD and at the

Pediatric wards were sent to the Center Chief, the Chair of the Department of Pediatrics, the Head of the Outpatient Department and the Pediatric Ward Nursing Supervisor. Once approved, parental/guardian informed consent and adolescent informed consent/assent were obtained. The purposes and benefits of the study were explained thoroughly by the principal investigator to the parent/guardian and to the adolescent. Questionnaires were self-administered in the presence of the principal investigator and/or a pediatric resident research assistant who were ready to answer any questions or clarifications that the study participants might have about individual items in the questionnaire. The adolescents were given 30-45 minutes to answer the questionnaire. The patients' responses to the questionnaires were encoded in Excel format and sent to a statistician for statistical analysis. The names of the respondents were kept confidential. Codes were used to label the individual questionnaire forms.

b. Location where study was performed

The study was conducted at the East Avenue Medical Center Pediatric Outpatient Clinic and Pediatric ward.

c. Personnel Who Conducted the Study

The primary investigator (PI) administered the survey questionnaires to the adolescents. One (1) pediatric resident assisted the PI in administering the questionnaires. The assisting pediatric resident was briefed about the study procedure and the questionnaire that was utilized in the study.

II. SUBJECT PARTICIPATION

a. Recruitment

All adolescent patients ages 12 to 18 years old who consulted at the Pediatric OPD clinic or were admitted at the pediatric ward of the East Avenue Medical Center during the specified time period and met the inclusion criteria were recruited.

Screening Interview/Questionnaire: A 4-part validated survey questionnaire was administered. The first part contained questions on demographics. The second part included questions on mobile phone and internet use. The third part of the questionnaire contained questions from the *Cybervictimization Questionnaire (CYVIC)*. The last part of the questionnaire was composed of questions on cybervictimization reactions and coping strategies.

The *Cybervictimization Questionnaire (CYVIC)* is a 19-item, Likert type questionnaire that has been validated for use in adolescents ages 12 to 18 years old. It has been found to be a reliable self-report measure of cybervictimization in adolescents.¹

Permission to use the questionnaire and translate it to Filipino for the purposes of this study was obtained from the author through email correspondence. The questionnaire was translated to Filipino by a language specialist and content validation was done by four (4) Adolescent Medicine specialists and one (1) psychologist. The validated translated Filipino version of the CYVIC was pre-tested on 10 randomly selected adolescents prior to the actual administration to the study population.

b. Informed Consent and Informed Assent process and timing of obtaining of consent

The primary investigator gave detailed and comprehensive information about the study to the parents, guardians and adolescents. Informed consent and/or informed assent were obtained prior to the conduct of the study.

c. Costs to Participants

There was no cost to the participants of the study.

d. Compensation

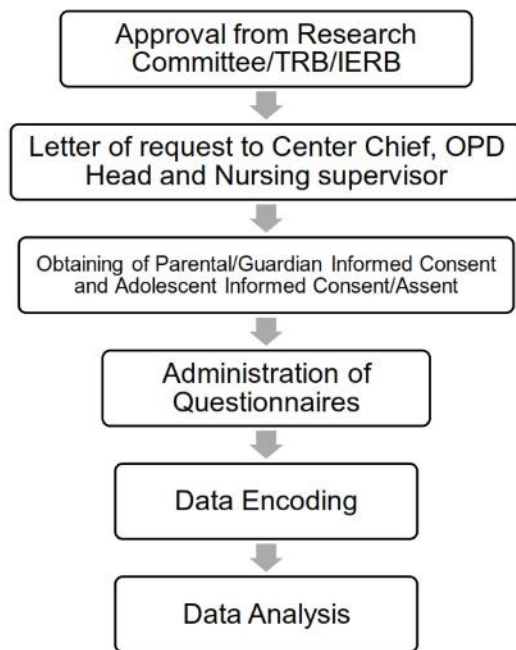
The patients or their parents/guardians did not receive monetary or any other form of compensation for participating in this study.

III. DATA COLLECTION AND PROTECTION

a. Data management and security

All information regarding the study participants was kept strictly confidential. The participants' names were kept in a password-protected database which only the principal investigator had access to. Upon collection, the questionnaires were kept in a sealed envelope that could only be accessed by the principal investigator. The names of the respondents were kept confidential and codes were used to de-identify them. The data will be kept secure by the investigator for a maximum period of 3 years after which it will be discarded.

b. Study Algorithm



IV. DATA ANALYSIS AND REPORTING

Descriptive and inferential statistics were used to analyze the results of the study. Mean, standard deviation, frequency and percentage were used to describe and categorize the cybervictimization experiences, reactions and coping strategies of the adolescents. Chi Square Test of Association was employed to examine the associated risk factors of cybervictimization experiences of adolescents, and their strategies being used as a means to cope with the cyberbullying. Decision to determine relationships and risk factors was set at 95% confidence interval.

V. RESULTS

Table 1. Socio-demographic profile of Adolescents

Variable	No. of Patients (n)	Percentage (%)
Age		
10-13 years	16	22.22%
14-16 years	40	55.55%
17 years and above	16	22.22%

Sex		
Male	34	47.22%
Female	38	52.77%
Educational Status		
Enrolled	63	87.5%
Not enrolled	9	12.5%
Grade		
6	3	4.2%
7	11	15.3%
8	9	12.5%
9	9	12.5%
10	9	12.5%
11	18	25%
12	13	18%
Highest Grade If Not Enrolled		
6	1	1.11%
7	1	1.11%
8	0	0
9	0	0
10	1	1.11%
11	2	22.22%
12	4	44.44%
Has Own Mobile Phone		
Yes	61	84.72%
No	11	15.28%
Uses Internet		
Yes	71	98.61%
No	1	1.39%
Social Media Account		
Facebook	68	94.44%
Twitter	26	36.11%
Instagram	46	63.88%
Tumblr	2	2.77%
Messenger	46	63.88%
Snapchat	25	34.72%
Whatsapp	2	2.77%
Tiktok	51	70.83%
Experienced Cybervictimization		
Yes	23	31.94%
No	49	60.05%

Sex		
Male	12	52.17%
Female	11	47.82%
Grade		
6	1	4.34%
7	7	30.43%
8	3	13.04%
9	3	13.04%
10	2	8.69%
11	3	13.04%
12	4	17.39%
TOTAL	72	100%

A total of **72** adolescents were included in the study. **Table 1** shows the demographic profile of the study participants. There were more female (52.77%) than male (47.22%) respondents. Most were middle adolescents (55%). Majority were currently enrolled in school (87%). Among those enrolled, 56 percent (56%) were in junior high school. For those who were not currently in school, most (44.4%) were able to reach the Grade 12 level.

Of the 72 participants, almost all (98.61%) reported to have used the internet and a majority (84.72%) also had their own mobile phones. The top three platforms used by the participants were Facebook (94.44%), Tiktok (70.83%) and Messenger and Instagram (63.88%).

Among the participants, 31.94% (n=23) reported that they had experienced cybervictimization within the past six months. There were slightly more males (n=12, 52.77%) who were cyberbullied and cybevictimization was experienced mostly in the seventh grade (30.43%).

Table 2. Cybervictimization Experiences of Filipino Adolescents based on CYVIC questionnaire dimensions

Variables	No. of questions	1	2	3	4	Total
Impersonation	1	9	9	4	1	23
	12	19	3	0	1	23
	18	13	8	2	0	23
Visual Cybervictimization	2	21	2	0	0	23
	3	20	3	0	0	23
	6	21	2	0	0	23
	9	22	1	0	0	23
	10	20	3	0	0	23
	14	17	2	1	3	23
	15	20	3	0	0	23
Written-verbal Cybervictimization	5	11	9	3	0	23
	7	14	6	2	1	23
	8	15	7	1	0	23
	11	16	5	1	1	23
	17	21	2	0	0	23
	19	15	7	0	1	23

Table 2 shows the cybervictimization experiences of Filipino adolescents based on the CYVIC questionnaire dimensions. Based on the CYVIC, most of the Filipino Adolescents reported to have experienced **online exclusion** at least two to four times a month, **impersonation** at least one to four times, **written verbal** and **visual cybervictimization** and **general cybervictimization** once a month.

Table 3. Cybervictimization reactions and coping strategies of adolescents

Variables	Total	Percentage
Feelings about cybervictimization experience		
Scared	9	39.1%
Sad	7	30.4%
Angry	8	34.8%
Revengeful	1	4.3%
Embarrassed	6	26%
Not affected	7	30.4%

Reaction to cybervictimization Experience		
Cried	11	47.8%
Told somebody	3	13%
Retaliated	1	4.3%
Ignored	14	60.9%
Did you tell anyone about cybervictimization experience		
Yes	13	56.5%
No	10	43.5%
Person to whom cybervictimization experience was disclosed to		
Friend/classmate	10	43.5%
Brother/sister	2	8.7%
Parents	4	17.4%
Teacher	2	8.7%
Coping strategies		
Avoid using internet	8	34.8%
Avoid using mobile phone	5	21.7%
Blocked the cyberbully	12	52.2%
Changed mobile number	3	13%
Reported the bully to the website Administrator	1	4.3%
Sought help from parents	7	30.4%
Deleted account	4	17.4%
Asked support from friends	10	43.5%
Others:		
Not Affected	1	4.3%

Table 3 shows the adolescents' cybervictimization reactions and coping strategies. Most adolescents who experienced cybervictimization either felt scared (n= 9 , 39.1%) or angry (n=8, 34.8%). Thirty percent (30.4 %) claimed not to have been affected while twenty-six percent (n=6, 26%) felt embarrassed about their experience.

Majority of the participants (n=14, 60.9%) either ignored the cyberbullying incidents or cried in response to the cybervictimization (n=11, 47.8%). More than half of participants (n=13) disclosed their cybervictimization experiences to others, mostly to their classmates or friends (43.5%,n=10). Only a few initially told their parents (17.4%,n=4) or teachers (8.7%, n=2). In order to cope with their cybervictimization experiences, most of the adolescents either blocked the bully (52.2%, n=12), asked support from friends (43.5%, n=10), avoided using the internet (34.8%, n=8) or sought help from their parents (30.4%,n=7). Only four respondents deleted their accounts while one (1) reported the incident to the website administrator.

Table 4. Dimensions of Cybervictimization

	Minimum	Maximum	Mean	Standard Deviation
Impersonation Score	3.00	9.00	4.6522	1.69515
Visual Cybervictimization Score	7.00	13.00	8.1739	1.94591
Written Cybervictimization Score	6.00	14.00	8.5652	2.19143
Online Exclusion Score	3.00	12.00	4.8696	2.36075
General Cybervictimization Score	1.00	4.00	1.4348	.72777

The most common cybervictimization experiences that the participants experienced were related to **visual** (mean=8.17, SD=1.94) and **written** (mean=8.56, SD=2.19) **cybervictimization**. Participants had varying responses with regards to **online exclusion** (mean=4.86, SD=2.36) and **impersonation** (mean=4.65, SD 1.69) making these the least common methods of cybervictimization. **General Interpretation of Cybervictimization** garnered the lowest mean scale score among the dimensions (mean=1.43, SD.727).

Table 5. Risk Factors Associated with Cybervictimization

Profile	Impersonation	Visual Cyber-victimization	Written Cyber-victimization	Online Exclusion	General Cyber-victimization
Age	.361	.265	.386	.287	.328
Educational Level	.705	.069	.533	.519	.302
Grade Level	.188	.288	.190	.242	.371
Use of Mobile Phone	.575	.481	.077	.158	.021*
Social Media Accounts	.915	.723	.535	.745	.711
Grade Level Onset of Bullying	.479	.508	.293	.118	.020*

*significant at .05 level

In **Table 5**, the risk factors for cybervictimization are presented. Based on the study results, age and educational or grade levels were not found to be significant risk factors for cybervictimization. On the contrary, mobile phone use was noted to be a statistically significant associated risk factor for cybervictimization (p value=0.021). The more time the adolescent spends in social media using their mobile phone, the higher the risk of experiencing cybervictimization. A lower grade level onset of bullying was also found to be a significant risk factor for cybervictimization (p value=0.020). Those who experienced cybervictimization earlier on may have a higher probability of re-experiencing cybervictimization and concomitantly, further traumatization.

DISCUSSION

The risk for cyberbullying or electronic bullying (voluntary and repeated actions against one or more individuals through the use of computers and electronic devices) is a reality given the easy access of adolescents to current technological advances, particularly the internet and social media.¹³

Majority of the participants in this study were middle adolescents (55.55%) with a slight female predominance (52.77%). Most were currently enrolled in junior high school (56%) while the highest level attained by most of those who were not enrolled was Grade 12 (44%). Of the 72

participants, almost all (98.61%) reported to have used the internet and a majority (84.72%) also had their own mobile phones. The top three platforms used by the participants were Facebook (94.44%), Tiktok (70.83%) and Messenger and Instagram (63.88%). Patton et al in 2014 also documented that 90% of adolescents reported using the internet on a regular basis and about 70% had at least one user profile on a social networking site. Social media and social networking sites were also used by the youth to bully and harass their peers.¹⁴ Among the participants, 31.94% experienced cybervictimization within the past 6 months. Males (52.77%) were reported to be cyberbullied more than females. The study of Gofin and Avitzour in 2012 likewise showed this male predominance among cybervictims.¹⁵ In addition, UNICEF also reported in 2019 that among 13–17 year old adolescents in the Philippines who experienced cyberbullying, there was a slightly higher number of males affected (44%).¹⁶ Furthermore, Li in 2007 also documented that among 133 seventh grade students who were cyberbullied, 31.2% were male while 26.3% were female.¹⁷

Online exclusion and impersonation were experienced by the study participants one to four times a month. Most adolescents who experienced cybervictimization either felt scared (39.1%) or angry (34.8%). Thirty percent (30.4 %) claimed not to have been affected while twenty-six percent (26%) felt embarrassed about their experience.

Majority of the participants (60.9%) either ignored the cyberbullying incidents or cried (47.8%) in response to the cybervictimization. These reactions to the cybervictimization experiences are similar to those reported by Sahin in 2012, Bauman et al in 2013 and Gimenez in 2015. These authors noted that adolescents who have been victimized by cyberbullying reported feeling sad, feelings of unhappiness, and reported depression more frequently than those who have not been victimized.¹⁸

More than half of the study participants disclosed their cybervictimization experiences to others, mostly to their classmates or friends (43.5%). Only a few initially told their parents (17.4%) or teachers (8.7%). This can be explained by the nature of adolescents who tend to confide more in their peers. Some adolescents might have also been afraid to tell their parents or teachers about the incident. Schenk in 2011 reported similar findings among college students who experienced cyberbullying and coped by talking with friends and getting support from them.¹⁹

On the contrary, Dehue et al in 2008 stated that many adolescents who have been victimized by cyberbullying did not talk to anyone about it or if they did talk to someone it was either with their parents or caregiver.²⁰

In order to cope with their cybervictimization experiences, most of the adolescents either blocked the bully (52.2%), asked support from friends (43.5%) avoided using the internet (34.8%) or sought help from their parents (30.4%, n=7). Only four respondents deleted their accounts while one (1) reported the incident to the website administrator. The findings of a study by Bukowski et al in 2001 showed that friends have a strong influence on students' emotional, behavioral, and affective development and this can explain while many of the cybervictims in this

study sought support from their friends.²¹ Hodges & Perry in 1999 and Jeffrey et al in 2001 also stated that friends helped reduce the cybervictims' anxiety and provided protection and coping advice to victims either in the real world or in cyberspace.²²

In this study, the most common cybervictimization experiences that the participants experienced were related to visual (mean=8.17, SD=1.94) and written (mean=8.56, SD=2.19) cybervictimization. According to Menesini et al in 2011, adolescents reported that the experience of visual cybervictimization (e.g unpleasent photos or videos of oneself distributed online) was more negative than that of written cyberbullying victimization (when one is the recipient of online insults, pranks or flaming).²³

Based on the study results, age and educational or grade levels were not found to be significant risk factors for cybervictimization. On the contrary, mobile phone use was a statistically significant associated risk factor for cybervictimization (p value=0.021). The more time adolescents spend in social media using their mobile phones, the higher the risk of experiencing cybervictimization. Tokunaga in 2010 also reported that age was not significantly associated with cybervictimization.²⁴

CONCLUSION

The risk for cybervictimization is a reality among adolescents today given their easy access to the internet and their increased engagement in online activities. Different forms of cyberbullying exist and efforts should be made in order to promote cybersafety through awareness of these potential risks. Adolescent cyberbullying victims may have different reactions to the experience. Timely psychosocial support and management should be provided to prevent unwanted outcomes.

LIMITATIONS OF STUDY

The study has several limitations. First, only a small sample size was used (72) and the results may not be reflective of the actual prevalence of cybervictimization among Filipino adolescents. Second, the study design is cross-sectional, hence, no direct causative relationships may be derived among the study variables. Also, given the nature of the study and the use of questionnaires, recall bias may have occurred during the time the adolescents were filling out the forms. In addition, the degree of traumatization brought about by the cybervictimization experiences was not measured and the role of the parents in monitoring internet use of the adolescents was not among the variables explored.

RECOMMENDATIONS

A larger sample size is recommended to get a more accurate picture of the prevalence of cybervictimization among Filipino adolescents. A nationwide survey in the school setting involving well adolescents would be ideal to have a point of comparison since this study only included sick adolescents either admitted at the wards or who consulted at the outpatient clinic for acute health concerns. School-based programs addressing the need to educate adolescents on cybersafety are also highly recommended to prevent or decrease the risk for cybervictimization. Follow-up studies that would look into the role of parents and guardians with regards to adolescents' internet use and also those that would quantify the degree of traumatization of the cybervictims are also recommended to help in the prevention and timely management of the negative effects of cybervictimization.

ETHICAL CONSIDERATIONS

IERB approval was sought prior to the conduct of the study. This study was done in compliance with the Data Privacy Act of 2012. Participation was purely voluntary, and the adolescent was allowed to withdraw consent

anytime without any negative consequences on his or her healthcare. Adolescents who were identified to have cybervictimization experiences were referred to an Adolescent Medicine specialist for further evaluation and counseling.

The results of the study will be shared with the medical community, may be presented in local and international conferences or may be submitted for publication in medical journals.

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Effect of Using Electronic Versus Printed Media on the GWA of 1st – 3rd year Medical Students at Centro Escolar University Manila, Semester 1, A.Y. 2021–2022: A Comparative Study*

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ABSTRACT

OBJECTIVE: To compare the effectiveness of the use of electronic media and the use of printed media in obtaining a higher general weighted average (GWA) among 1st to 3rd year medical students at Centro Escolar University (CEU), A.Y. 2021–2022

RESEARCH DESIGN: Cross sectional

SETTING: Centro Escolar University, San Miguel, Manila

PATIENT/SUBJECT SELECTION: The 140 subjects were selected by stratified random sampling design. Those currently enrolled full-time as regular CEU medical students and attending a complete number of units in the year level were included in the selection.

METHODS: The GWA of the participants were obtained from the Administrative Office of CEU–School of Medicine, while data for the independent variables were collected using questionnaires patterned after the Academic Reading Format International Study (ARFIS) and Perceived Stress Scale (PSS). Ethical considerations of the questionnaires were approved prior to the study proper. Both the questionnaires were administered using Google Forms.

OUTCOME MEASURES: Hypothesis testing and RxC contingency table were utilized to determine any significant difference and association among the groups who use printed and electronic on GWA.

KEYWORDS: electronic media, printed media, general weighted average

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

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INTRODUCTION

Background of the Study

Multiple studies have shown that students who use electronic textbooks show higher levels of affective and psychomotor learning than students who use the traditional printed textbook. Still, other references would claim that there is no difference seen in cognitive learning and comprehension. It was further observed that gadgets enable the students to effectively engage in learning activities, boosting their confidence and attention.

Thus, there seems to be equivocal evidence pertaining to the significant differences in studying using electronic media versus printed media. This is particularly true among medical students, for whom there is a dearth of research. The current investigators aimed to add information to this growing body of knowledge, especially geared towards future Filipino students and health practitioners. The researchers also looked at maximizing the target population's learning outcomes and adding knowledge to the efficiency of electronic media usage in the context of the new normal learning environment amidst the pandemic.

Research Problem

Is the use of electronic media more effective than the use of printed media in obtaining a higher GWA among 1st to 3rd year medical students of CEU Manila, 1st semester AY 2021–2022?

Review of Related Literature

Academic performance trends among Philippine medical schools

Students who have fixed their sights on becoming medical doctors (MD) take up medically related undergraduate courses. The belief is that the knowledge and experiences attained in these classes will aid them in future subjects in medical

school. The top five pre-medical courses of students at the University of the Philippines College of Medicine (UPCM) are BS Biology, BS Psychology, BS Public Health, BS Zoology, and BS Molecular Biology and Biotechnology (MBB)⁽¹⁾.

Moreover, there is a significant positive relationship between pre-med GPA and NMAT at the Adventist University of the Philippines (AUP). This is telling of medical schools since both undergraduate grades and NMAT percentile rank are among the foremost qualifiers for admission. NMAT percentile rank of the medicine students in AUP had an average of 72.01, with a Pre-Med GPA of 90.69 and first year Medicine GWA of 84.6. There is a significant positive relationship between NMAT score and Pre-Med grade to the first year Medicine GWA. Regression analysis revealed that Pre-Medicine course GPA and National Medical Admission Test Percentile Rank were both predictors of the first-year medicine GPA among College of Medicine students.⁽²⁾

In addition, apart from pre-med GPA, academic performance of medical students was also discovered to be related to their individual learning styles. Graduates of applied sciences preparatory courses preferred visual, group, and kinesthetic learning styles while they manifest moderate levels of study habits. It was found that these students displayed remarkably good academic performances in their first-year medical classes⁽³⁾.

The summary of a student's grades, or the GWA, has been considered as a crucial boundary in evaluating academic performance. This plays a vital role in evaluating and predicting student performance. However, raw GWA presents a risk of inaccurately assuming grades. In many educational settings, students may have an advantage to take courses which are uncomplicated and in which high grades are easier to achieve. In such cases, the raw GWA

would overlay the performance of a student who chooses a relatively uncomplicated course over another who chooses a more complicated one.

Raw GWA as a previous academic performance gauge is not a perfect indicator of achievement of medical knowledge. Although in undergraduate medical courses, it is said to be the predominant and most consistent independent predictor of success. Since grades and GWAs bring about accountability and constitute the currency of education, lack of accuracy and grade inflation in the grading process can have a profoundly negative impact on higher education.

Proportion of preferences for either electronic or printed media

In interviews conducted among readers, the first segment (aged 18 to 26 years), showed the largest use of digital reading in relation to the rest. Those who use digital formats recognize its practicality. In several cases though, they complain about visual fatigue. In the second segment (aged 27 to 35 years), digital reading is also present, but the traditional format is preferred. Still, people recognize the difficulty of carrying books. On the other hand, all respondents of the third segment (aged 36 to 50 years) preferred to read the traditional way. They preferred this format due to the sense of familiarity in being able to physically hold the material, as well as the sense of owning a library containing stacks of books and reading materials. The fourth segment (aged 51 to 65 years) expressed that they need to touch the pages of books, as well as to smell the ink and own them for keeping in their personal libraries. Interviews with librarians and editors showed that they accept the idea that in a couple of years, libraries will offer electronic services, and the practice of borrowing physical books will eventually become obsolete⁽⁴⁾.

Some students want both formats for their academic studies—and not the complete

obliteration of either one. Most (46.5%) shared the sentiment that electronic books will ultimately cause the disappearance of traditional print books. As for preference, the majority (44%) preferred both print and e-books as compared to print books only (34.5%) or electronic books only (21.5%). It can then be concluded that when students are asked to choose between print books and e-books, they preferred print books. However, if given a third option of the use of both formats, students preferred a combination of the two⁽⁵⁾.

When it comes to the hospital setting, residents and fellows are more likely to use tablet computers several times daily compared to medical students. The most common reported uses were for accessing medical reference applications (46%), reading e-books (45%), and studying for the boards (32%)⁽⁶⁾.

When conducted among 14 Chilean dental schools, students used both electronic and print textbooks. However, four out of five (80%) printed out their electronic texts—mainly female students and those in their first and second years. E-learning has allowed them to have greater access to information using electronic texts—including search and interactivity tools. It was concluded that Chilean dental students prefer print over electronic textbooks despite having access to electronic devices to read them⁽⁷⁾.

With the current pandemic, the use of newer technologies like tablets can be of great help. E-resources such as e-books, e-journals, and other documents are more easily accessible with the help of tablets. The assessment of use of such e-resources at the university library of UPD showed that 53% of respondents were affected considerably. They stated that it made it easier for them to find the materials they needed. However, with regards to the quality of their work, only 37% showed improvement⁽⁸⁾.

Characteristics of the Population that Engages in Electronic Media

Socioeconomic Status

When surveying online students, nearly 100% of them own some form of smartphone. The majority (61.4%) own iPhones; 36.3% own Android phones; and 22.2% own other brands. Laptop ownership outweighs desktop ownership among the respondents. More than half (57.6%) own PC laptops with the rest (41.5%) owning Mac laptops. Overall, 99% of online students own some type of laptop. With regards to preference, students overwhelmingly prefer laptops (73.1%) for accessing their Canvas Learning Management System (LMS) homepages. A total of 19.6% respondents prefer desktop computers, with desktop PCs selected by 16.6% and only 3% preferring desktop Macs. Only 4.3% preferred using their smartphones for accessing the LMS. There were very small numbers of students preferring iPads (1.4%) and other tablets (1.5%) when accessing their LMS course homepages. The survey focused on four main reasons for such: convenience, ease of use, effectiveness for the type of content, and student access to another device. The results showed that overall, regardless of what they chose as a preferred device, –convenience, ease of use, and effectiveness were all important reasons⁽⁹⁾.

There is a “digital divide” which distinguishes the gap between those who have easy and ample access to computers and the internet, and those who do not. This digital divide is highly influenced by the individual’s economic status, which is in direct correlation to income and educational attainment. It can be concluded that there are several sociological factors that drive digital literacy on whether a person engages in digital communications. However, the most pronounced of them all is the person’s socioeconomic status⁽¹⁰⁾.

Furthermore, it was reported that people who belong to the upper income threshold (USD 75,000) have more propensity to use both the internet and their cellphones (95%). By contrast, those below the upper income threshold (70%) use only the internet. Out of these internet users, 99% of the above USD 75,000 income bracket use the internet within the confines of their homes; and 93% of internet users below the threshold use the internet at home. In fact, even among Americans within the lower income level, internet and cellphone usage is quite high. Out of all adults that earn below USD30,000 per annum, close to two-thirds (66.67%) still use the internet. As a corollary, the utilization jumps sharply in the next income bracket for those making income at the range of USD30,000 – 50,000 annually, with 80% regularly using the internet⁽¹¹⁾.

Mental Health

Lifestyle, physical, and mental well-being clearly manifest in an individual’s routines. The interplay between mental health and learning contributes to the exploration of academic performance. It is an essential factor in identifying the effects and underlying events that may be relevant. Adolescents who consume more screen time, or are more emotionally invested in social media, tend to have poorer sleep quality, lower self-esteem and well-being, less curiosity, less self-control, and higher levels of anxiety, depression, and emotional instability⁽¹²⁾. Specifically, the incidence of anxiety and depression among individuals aged 2-17 may rise to twice the normal levels⁽¹³⁾. However, this does not discount the increased incidence of such in adults as well⁽¹⁴⁾.

Venturing into diagnostic medicine, there exists brain-health consequences of digital technology. Attention-Deficit / Hyperactivity Disorder (ADHD) symptoms intensify with continuous use of such, in that there is a decreased chance of interacting with people. Less time is also allowed for the brain to rest in between usage.

Social and emotional intelligence may be impaired. Particularly, a brain still within its course of development is sensitive to long-term exposure. Considering this, the American Academy of Pediatrics (AAP) suggests limiting the screen time of such individuals. With persistent use, social and emotional intelligence are being interfered with. This may lead to addictive behaviors, high risk of social isolation, and restriction of sleep and brain development. Although there still exist some video games, programs, and online educational tools that may impart mental exercises to initiate neural circuitry, enhance cognitive functioning, narrow anxiety, elevate restful sleep, and provide other brain-health benefits ⁽¹⁵⁾.

In contrast, there also exist effects of iPad use in children with autism-spectrum disorder (ASD) in three areas: quality of learning, communication skills, and social skills. It is proven that the iPad aids in communication and learning of children with ASD. The use of breakthrough technology in special education brings significant positive effects into the lives of such children despite its concurrent clear disadvantages ⁽¹⁶⁾.

Family Support

When it comes to factors that influence the adult learners' choice to drop out or persist in online learning, internal factors such as age, gender, or even educational attainment do not have a direct effect on the decision-making process. External factors such as organizational/family support, financial problems, and time constraints were more likely to influence the students' decision making. In conclusion, the lack of family and or organizational support, regardless of the learners' academic preparedness and aspiration, can lead them to drop out ⁽¹⁷⁾.

In conjunction with this, it is important to determine the degree of resilience of students throughout the medical course. It is also necessary to identify underlying mechanisms or processes

and vulnerabilities, as well as coping strategies that contribute to the students' ability to overcome stress. One of the factors that was considered was satisfaction with family and friends' support. Results showed a positive association between the degree of resilience and the students' degree of satisfaction with the social support from their family. High levels of support proved protective against the state of physical and mental exhaustion closely associated with academic life ⁽¹⁸⁾.

An analysis of factors including external environment, school support, and family support were found to have a significant positive relationship with online learning consciousness and behaviors. The study revealed that students who receive more interest and help from family members tend to have a high level of learning engagement. Family support included environmental support in that conducive areas for studying were provided, as well as emotional support and capability support. A healthy and harmonious relationship between students and their family members strengthened online learning engagement ⁽¹⁹⁾.

Factors affecting Academic Performance

Socio-economic Status

There is a moderate correlation between socio-economic status and academic performance. Socio-economic status indirectly predicts academic performance partially through the effect of self-concept. Families with higher socio-economic status help children form and attain positive self-concept, and they anticipate and actualize school performance. Students from low socio-economic status families usually experience more economic hardship, lack of various resources, and higher threats to social identity—which may lead to negative self-concept, stereotypes [regarding their intellectual ability], and lack of social belonging. These threats can undermine students' academic performance ⁽²⁰⁾.

There are positive and negative outcomes in using tablets for students. The use of such is supported by most teachers and students. Much lighter than print textbooks and capable of storing several copies, respondents justify usage because it is favorable especially when individuals need to change locations. Use of such bodes well for the environment, in that there is less waste produced and less use of paper in printing. Pricewise, digital textbooks are much cheaper than prints. Additionally, tablets aid in improvement of standardized test scores, increasing student interactivity and creativity.

When it comes to overall cost, the implementation for e-textbooks on iPad tablets are 552% higher than new prints. The annual cost per student per class with tablets is \$71.55, as compared to only \$14.26 for prints. This is due to costs associated with building wi-fi infrastructure, technological literacy training for teachers and administrators, and annual publishing fees in use of e-textbooks. Print textbook prices nearly tripled from 1986 to 2004, rising at twice the rate of inflation. As such, textbook wholesale prices have risen nearly four and a half times the rate of inflation from 1990–2009⁽²¹⁾.

Family

The family is the basic unit in the community and is the most crucial component in the holistic development of an individual. It is thus a key player in the ability of students to attain a more favorable academic performance.

A good parent–child relationship is a necessary component for healthy physical, mental, and cognitive development. It is therefore an important factor for promoting children’s reading ability. Parents with higher levels of completed education have better parenting styles—and were found to be more knowledgeable on the approaches of addressing problems that arise in their relationships with their children. This

relationship facilitates better academic performance in children⁽²²⁾.

Considering the importance of investing in education, parents of financially challenged families usually are not able to sufficiently provide for their children’s education. This affects the latter’s academic achievements⁽²³⁾.

Social Media

This period being predominantly a digital age, it is unavoidable that connections between the studying generation’s academic performance and their exposure to the various social media platforms will be made. As with any other variable, there will always be positive and negative effects.

Internet use is inevitable and actually essential in a student’s daily routine. The majority report using social media to aid them in their tasks including communication with classmates and organization of their tasks and outputs. Prominently used as an outlet for the students, the internet helps in winding down from academic demands. But just as how use is directly correlated to favorable results, there comes a point where excess becomes negative⁽²⁴⁾. When it comes to the negative aspects, the culprit is addiction to social media, the use of which is indirectly correlated to academic performance. Among students, males are more likely to become addicted to social media than females⁽²⁵⁾.

Considering its effects on the general student population, technology has a positive influence when used in the classroom and other academic settings, especially on school experience and success. It is crucial, however, that teachers be provided with substantial professional development courses and opportunities to deepen their technological literacy. The integration of the devices they have should provide the most appropriate and effective learning experience for students⁽²⁶⁾.

Sleep Habits

Sleep plays an essential role in an individual's cognitive skills. Poor-quality sleep and daytime sleepiness may affect the physical and cognitive health of students and, in extension, the students' academic performance. When adequate, it contributes to efficient learning and memorization skills. Most students who report having bad sleep schedules (less than 5 hours) experience daytime dysfunction almost everyday and have lower GPA ⁽²⁷⁾.

Mental Health

Another predominant factor is mental health, especially risk factors such as anxiety and depression. Medical students are currently seen as a student population under greater stress and heavier physical and emotional demands compared to others. Although symptoms of depression show some association with the students' poor academic performance, it is not yet known how exactly these symptoms cause such. ⁽²⁸⁾.

In contrast, negative correlation of mental illness on academic success and degree completion is well-documented. The mentioned risk factors are mediated by perfectionism; thus, there is an interaction between types of perfectionism, depression, and anxiety. As such, educators should consider how mental health might affect students, and what courses of action to take in response ⁽²⁹⁾.

Relationship between academic performance and preferred learning media

In pursuit of more favorable outcomes, students have their own preferred learning styles and media. With its prevalence, the preference for e-books for both personal and professional development has shown significant increase. Students who use e-books have more developed affective and psychomotor learning ⁽³⁰⁾. However, there is no significant difference in reading speed and comprehension.

Aside from those mentioned above, there is also no difference seen in cognitive learning suggesting that e-books are feasible options in learning ⁽³¹⁾. There are no performance differences for textbook media, computer attitudes, or interaction ⁽³²⁾. Students use textbooks because they believe that it will lead to the level of comprehension that is expected of them ⁽³³⁾. Respondents identified that the disadvantages of e-reading were that large sections of text with hypertexts and skimming techniques pose distractions, impeding digital text comprehension and recall.

To expound on the improvement of students' creativity and outlook, the use of electronic media enables the student to engage in learning activities and gain confidence and attention, thus, producing a positive result on their academic performance ⁽³⁴⁾.

There are also findings that show digital learning has better outcomes and improved motivation ⁽³⁵⁾. Known as the process of applying digital media to learning, it is not limited to digital materials; it includes network- and computer-based learning, virtual classrooms, and digital cooperation. The probable increase in people preferring digital media over traditional prints may be mainly due to format medium, in which it is easier to adjust the visual settings ⁽³⁶⁾.

The patronage of mobile devices such as cellular phones, tablets, and iPads can enhance educational outcomes and serve as better platforms for students ⁽³⁷⁾. Development and innovation of tablets provide a multitude of choices for self-directed learning. Such instances include students who stay engaged in mathematics longer, hence the quicker task execution.

Barriers to adapting are mainly technical, which include errors and delays concerning the device's operating system (OS) and application

updates, software bugs, device management and administration, and internet connectivity ⁽³⁸⁾. Pedagogical issues are also considered. These involve classroom discipline around the devices, budgetary restrictions, training to understand and learn the applications, how to use the devices effectively in lessons, and how to administer the lessons and evaluation methods.

Considering the present trend of online and distance learning, the major contributing factors for the failure of students are the unfamiliarity of the study system and difficulty in the transition from conventional classroom-teaching to self-learning ⁽³⁹⁾. Students are inclined to pursue the proper study program befitting their personalities and habits. Solutions involve educators who can encourage students to have continuous, untiring commitment and self-motivation to arrive at the academic performance they wish to attain.

Mobile learning improves not only academic performance, but also motivation and attitude towards distance learning ⁽⁴⁰⁾. Cognitive overload is only one of the factors that may have a negative effect on academic performance or achievement. There have also been cases documenting that comprehension and assessment is much improved when the materials of instruction are the traditional conventional ones, rather than the digital ⁽⁴¹⁾. As to whether these differences are significant, however, is not yet analyzed.

Kinesthetic feedback generated by book manipulating has an impact on student learning outcomes, although the significance of which is not yet analyzed ⁽⁴²⁾. Reading time, level of engagement, word and sentence recognition scores and recall do not yield differences between media. However, the ability to correctly reconstruct temporal and chronological aspects of reading are better in paper readers. Paper readers can localize events in the story and have a more coherent

situation of the chronology of the story. In fact, learning capacities largely depend on the way information is received. Others would maintain that the use of textbooks is associated with better results in many aspects. Paper-readers have better memory function, longer attention span, faster processing speed, and even better mathematical and writing skills.

Despite these assertions, it is emphasized that learning is ever evolving, and further studies should be conducted to ensure that future generations are receiving and utilizing what can positively affect their cognitive skills and their academic performance ⁽⁴³⁾.

As for the neurological effects, brain activations related to memory, visual imagery, and language during the retrieval of specific information—as well as the deeper encoding of that information—are more evident and stronger in participants who take notes on paper than on electronic devices ⁽⁴⁴⁾. The use of a paper notebook affects high-order brain functions which could have important implications for education especially in these times of e-learning.

Questionnaire

PSS-10

The Perceived Stress Scale (PSS) is widely used to assess the degree to which situations in one's life are appraised as stressful ⁽⁴⁵⁾. As a global stress measure, the PSS items are general in nature rather than event specific. They evaluate the extent to which individuals perceive their lives to be "unpredictable, uncontrollable, and overloading". Respondents rate the frequency of their feelings and thoughts about life events and situations over the previous months using a five-point scale ranging from Never (0) to Very Often (4).

Scores on the PSS-10 demonstrate adequate internal consistency reliability ($\alpha = .78$). It also has moderate concurrent criterion validity

with the amount of stress experienced during an average week ($r = .39, p < .001$) and the frequency of stressful life events within the past year ($r = .32, p < .001$); and has adequate convergent validity as evidenced by expected negative associations with perceived health status ($r = -.22, p < .001$), positive associations with psychosomatic symptoms ($r = .28$ to $.34, p < .001$) and health service utilization ($r = .22, p < .001$).

Since then, other studies have similarly reported that the PSS-10 has good internal consistency reliability and adequate convergent validity based on associations with measures of physical and mental health.

Academic Reading Format International Survey

The Academic Reading Format International Survey (ARFIS) was initially developed and used on UCLA undergraduates to determine their reading format preferences. It was developed as an online survey of 22 questions based on student comments and findings by studies done previously by the author. It was piloted, refined, and extended by its authors into 16 Likert-style statements, six demographic questions, and an open-ended qualitative prompt for comments. The questionnaire was used further in a two-stage global survey in 2017 with 10,293 tertiary students in 19 countries as part of the first stage study. It aimed to determine if there are differences between countries that could influence preference for a particular format for academic reading as well as the learning engagement behaviors of students. Subsequently, it was followed by a second stage survey with a combined result of 21,266 students in 33 countries done in 2021.

The questionnaire has three dimensions: (1) format preference, (2) learning engagement, and (3) language. The demographic part asks about origin, gender, age, visual limitations, academic major, and academic rank of the respondent. Each question is offered responses including Strongly

Agree, Agree, Disagree, Strongly Disagree, and Neither Agree nor Disagree and a space for any explanation for the answer. The instrument also includes one statement that allows multiple answers regarding the devices that participants use for electronic academic reading. Opposing questions are written with avoidance of use of double negatives and slightly different terminology that are intended to limit redundancy and length in order to maximize the number of complete answers.

Each item in the scale contributes to a higher Cronbach's alpha for the scale except for one statement: "I like to make digital copies of my printed course materials" which was internally inconsistent ($r = 0.202$). After dropping said item, dimension 1 and 2 (format preference, learning engagement) has an overall alpha scale of 0.882 across 12 items and corrected item-total correlations range from 0.391 to 0.711. For dimension 3 (language), the first two statements do not correlate particularly well with each other so was dropped and the study focused on the third statement ("My preferred reading format. . depends on the language of the reading") instead as a stand-alone indicator⁽⁴⁶⁾.

Conceptual Framework

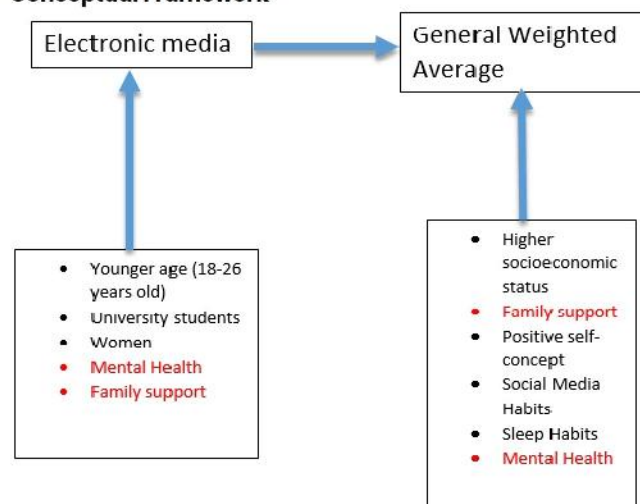


Figure 1. A conceptual framework of the study, depicting the confounding variables possibly affecting the disease (electronic media) and outcome (GWA) variables.

Significance of the Study

The emergence of a new learning set-up prompted the need for changes in medical students' learning styles to adapt. Universities were closed; libraries and possible sources of printed materials were limited. Additionally, technological advancements have led to the versatility of the internet and gadgets when it comes to aiding in education. However, there still exist students whose learning styles dictate their ease with the use of printed materials, as opposed to the digital ones.

Despite this, there exists lacking evidence of the superiority of one mode of learning over the other, especially among medical students. Their source of knowledge comes not only from text but also from visual aids due to their need to develop their clinical skills. For some, descriptive text is more effective; for others, information is better retained when they see the actual methods and procedures.

Considering these, this study aims to provide information as to which mode of learning provides a higher general weighted average (GWA): the use of printed material or electronic material. Specifically, it caters to experiences of 1st to 3rd year medical students of CEU Manila. Only the GWA from the 1st semester AY 2021–2022 will be considered for uniformity of available data.

Research Objectives

General Objective:

To compare the effectiveness of the use of electronic media and printed media in obtaining a higher general weighted average (GWA) among 1st to 3rd year medical students at Centro Escolar University, AY 2021–2022

Specific Objectives:

1. To determine the proportion of 1st to 3rd year medical students who prefer the use of electronic media and printed media in studying

2. To compare the general weighted average of 1st to 3rd year medical students who use
 - a. Printed media
 - b. Electronic media

METHODOLOGY

a. Research Design

The researchers will utilize a cross-sectional research design in which the exposure and disease status occur at one point in time. From the data that will be gathered, a prevalence ratio will be computed and will be expressed in percentage. The independent variables include electronic media and printed media, the dependent variable will be the GWA, and the confounders will be mental health problems and family support.

b. Schematic Diagram

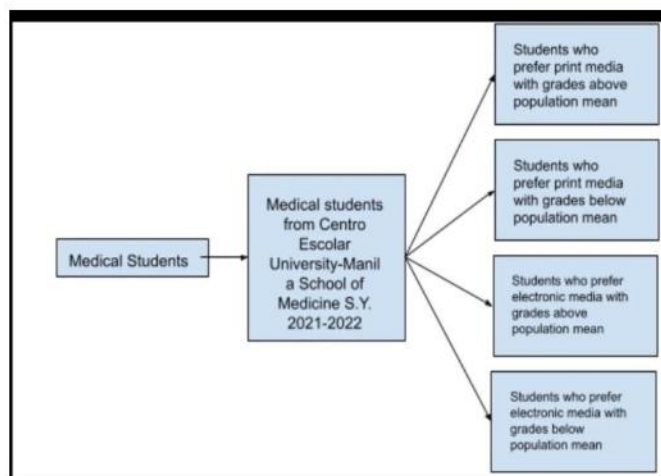


Figure 2. A schematic diagram of the study indicating a visual representation of its proposed methods.

c. Study Population

i. Source

Medical students of Centro Escolar University

ii. Selection Criteria

a. Inclusion Criteria

CEU-SOM students currently enrolled full-time as regular

attendees of A.Y. 2021–2022 will be included in the study. They should have the complete number of units for the year level they are in—YL1 = 40 units; YL2 = 40 units; and YL3 = 40 units.

b. Exclusion Criteria

Excluded from the study are students who cannot be categorized into print or electronic media users or those who use both types of study formats equally. Furthermore, students who acquire a score of 35 and above on the PSS-10 questionnaire and students with part-time jobs are also excluded from this study.

iii. Sampling design

Stratified Random Sampling

This sampling design will be utilized to ensure that the sample is evenly distributed among year levels, opting to arrange the stratum by year level. Age is also a factor that influences the type of media being used, and it is assumed that age increases with year level. The researchers chose probability sampling to ensure that any unknown or undefined confounding variables' influence on the outcome can be reduced.

iv. Sample Size

The researchers used the finite equation to compute the sample size. The total population of CEU-SOM first year students to third year students is 187. From the total population, the total sample size calculated was 127.42. The researchers added 10% more to the sample size, arriving at the final sample size of 140. 25 participants will be taken from the first-year students, 58 from the second-year students, and 57 from the third-year students.

D. Variables and Measurements

i. Operational definitions of variables

Dependent/Disease Variable: General Weighted Average (GWA)

It is a numerical representation of the overall scholastic standing of students and is used for evaluation. It is based on the grades in all subjects taken, whether passed or failed at a particular level, and the corresponding number of units of each class. It serves as the indicator of a student's academic performance in a given semester or school year. Educators typically measure academic performance based on a student's achievement in the classroom, including results from standardized examinations.

Independent/Exposure Variable: Electronic Media, Printed Media

Electronic Media

It refers to the type of media that utilizes electromechanical devices to access and view content. This type of media comprises aural and visual signals that are converted into electrical impulses. Electronic media includes screen-based activities such as computer, tablet, and smartphone use, electronic video games, and television viewing. Based on the scoring of the ARFIS questionnaire, a median of 1, 1.5, 2, and 2.5, will fall under electronic media preference of studying.

Printed Media

This is any written or pictorial form of communication produced through printing, photocopying, or digital methods from which multiple copies can be made through automated processes. More strictly, it is any form of 'ink and paper' communication that may be hand-written or reproduced—including handwritten lecture notes, books, circulars, journals, lithographs, memos, magazines, newspapers, pamphlets, and periodicals. Based on the scoring of the ARFIS questionnaire, a median of 3.5, 4, 4.5, and 5 will fall under printed media preference of studying.

Confounding Variables

Mental Health Problem

This refers to conditions that impact a student's thinking, emotions, and mood such that it interferes with memory and concentration or interferes with daily functioning at home and school. Perceived symptoms such as lowered mood, reduced cognitive function, lack of a sense of coping, lack of communication or interest in others, as well as lack of energy will be considered indicators of a mental health problem. Participants who have a total score of 35 and above in the PSS-10 will be considered as having a mental state that can predispose them to mental health problems and will be excluded from the study.

Family Support

This refers to the environmental, material, and emotional support that parents provide to their children. Environmental support includes creating a household environment conducive to learning by providing a quiet area and a clean, comfortable study space. Material support includes the provision of learning materials that the student needs and prefers, examples of which are books, printing machines, internet connection, and electronic media such as phones, tablets, laptops, and the like. Family members provide emotional support by verbal affirmations and encouragement, participating in solving learning difficulties, and allowing their children to freely express their negative and positive emotional experiences. Participants who have a total score of 35 and above in the PSS-10 will be considered as not having enough family support that can predispose them to problems in their academic performance.

ii. Data Collection Methods

a. Identified Data Collection Method

Records review will be the method to be used for the collection of GWA (General

Weighted Average). The researchers will procure the individual data sets, the GWA, from the existing database, the office of CEU School of Medicine. A school record review will allow the researchers to countercheck the information needed for the dependent variable of the research against the GWA of the respondents.

Preferred Medium

The self-administered questionnaire will be disseminated to conduct a survey and collect data on the independent variable which is the respondent's preferred medium of either electronic or printed medium. The questionnaire is patterned after ARFIS, initially developed, and used on UCLA undergraduates to determine their reading format preferences.

Mental Health and Family Support

The self-administered questionnaire will include the PSS-10 scale in consideration of the mental health and family support being received by each participant of the study. According to Baik et al. (2019), the PSS-10 scale is widely used to assess the degree to which situations in one's life are appraised as stressful. It also demonstrates psychometric properties which will serve as the basis for the exclusion criteria.

1. Formulation of pertinent documents for data collection

The questionnaire will be patterned after the PSS-10 and ARFIS. The technicalities, layout, and design of the Google Forms webpage will also be done during this phase. The email composition that will be sent out to the respondents will be formulated, as well as the consent forms that will

be filled out prior to the administration of the questionnaire.

Data collection tool

Preferred Medium

The Academic Reading Format International Study (ARFIS) questionnaire was developed, piloted, and validated in 2014. It has the objective of achieving a wider, more comparable, and more consistent data gathering method that pertains to learner reading format preferences among different contexts and over time. It will be used to classify the respondent's preferred medium. As stated, the preferred medium is considered as the study's independent variable.

Response choices to the Likert-style statements of the survey range from 5 (strongly agree) to 1 (strongly disagree). Median scores were calculated to categorize respondents' format preference. Statements that prefer print readings are scored as: Strongly Agree = 5; Agree = 4; Neither Agree nor Disagree = 3; Disagree = 2; Strongly Disagree = 1. For statements that inquire on how well they like or prefer e-readings, statements were reverse-scored.

Mental Health and Family Support

The Perceived Stress Scale (PSS) is a widely used measure that assesses the degree to which situations in one's life are evaluated as stressful. A shorter version, PSS-10, which will be used in this study, is derived from the original questionnaire without the items with the lowest factor loadings (items 4, 5, 12, 13). This questionnaire will be used to measure confounding variables identified by the researchers.

Respondents rate the frequency of their feelings and thoughts about life events and situations over previous months using a five-point scale ranging from Never (0) to Very Often (4) on a 10-item self-report measure of global perceived stress. A total score ranging from 0 to 40 is

computed by reverse scoring the four positively worded items and then summing all the scale items. Higher scores indicate greater levels of perceived stress. Subscale scores are computed by summing the six negatively worded items (Items 1, 2, 3, 6, 8, and 10) for Factor 1 (Negative) and the four positively worded items (Items 4, 5, 7, and 8) for Factor 2 (Positive), with higher scores indicating greater negative distress/stress feelings and greater positive stress feelings and coping abilities, respectively.

Type of Questions

Preferred Medium

The ARFIS questionnaire consists of 16 Likert-style statements, six demographic questions, and one multiple choice question. The Likert-style questions will also comprise a field for further comments or optional explanations of their response. The ARFIS questionnaire is utilized to investigate a particular type of reader with his or her own preferred engagement and preferences in academic reading. The questionnaire, however, will not only cater to items that focus on format preferences; some questions will ask regarding text engagement behaviors such as highlighting and annotating. It also consists of close-ended types of statements and added extra space in the event that the participants will provide qualitative answers. It also has one statement that allows multiple answers to choose from.

Mental Health and Family Support

The PSS-10 questionnaire is general in nature rather than event-specific. This 10-item instrument evaluates the extent to which an individual perceives his life to be "unpredictable, uncontrollable, and overloading" (Baik, 2017). There are two factors that have been identified in the questionnaire: the positive and the negative. This led to the proposal of a bifactor model of PSS-10 consisting of a single underlying general factor of perceived stress and two domain-specific factors

composed of negatively (Factor 1) and positively (Factor 2) worded items. It also consists of a Likert-style close-ended type of statements.

Mental health and family support being received by each participant of the study are the core information that will aid in generating the PSS-10 questionnaire. In this study, PSS-10 items will come first in the sequence of questions, followed by ARFIS items. This is done so that the flow of the questions will be from more general to more specific types.

Computer Software Used

The researchers will use Microsoft Excel, a spreadsheet program, to sort and calculate the data accurately. The measure of association between the research variables will be analyzed using the RxC contingency table run in the Statistical Package for Social Sciences (SPSS).

Ethical Considerations

Ethical Issues

The information and identities of the participants will not be disclosed to others outside the research team. Pre-selected members of the team will assign a control number to the participants and only they will have access to their name, student number, GWA, and answers, which will constitute the database available only in their personal Google drives. The participant's information will be kept private and deleted by June 2022.

The first part of the questionnaire requires the participants to answer questions relating to their important profile information relevant to the study. The researchers will then sort out the inclusion and exclusion criteria.

PSS 10 and ARFIS will comprise the second and third part respectively.

Should there be any specific questions that are too sensitive and personal for the participants to answer, such may be skipped.

This research study will benefit both the researchers and the participants. The participants will obtain a better understanding of their perceived stress level for the past month. This would likely affect their academic performance. Additionally, this study will shed light on the effectiveness and efficiency of their preferred reading format when studying as reflected by their academic performance.

This research is unfunded and will not provide any reimbursement or incentive for taking part in it. Further, the study design is such that there are no vulnerable populations involved.

The informed consent form (ICF) will be given to all participants in the selection process, and only those who will provide consent will be included. The inclusion and exclusion criteria that have been set will also be applied.

The researchers have no conflict of interest in any form (financial, proprietary, professional).

RESULTS

The researchers used Google forms to administer the questionnaires. Microsoft Excel and Google Sheets were used to accurately sort, tabulate, and calculate the data. The measure of association between the variables were analyzed using the RxC contingency table run in the Statistical Package for Social Sciences (SPSS).

A total number of 127 responses were calculated as an appropriate sample size for the study. The researchers added an extra 13 respondents to be recruited for a total of 140 CEU-SOM students. Of the 140, only 129 participated. 24 out of 25 students responded from YL1; 55 out of 58 students responded from YL2, and 50 out of 57

students responded from YL3. One respondent was excluded from the study because she exceeded a cut off-score of 35 on the Perceived Stress Scale (PSS-10).

Descriptive Statistics

Gender

Among 128 respondents, the majority were female (76.56%) (**Table 1**).

Table 1. Number (n) and percentage distribution among respondents based on gender.

	No. of respondents	Percentage, %
Female	98	76.56
Male	30	23.44

Age

In terms of age, as shown on **Table 2**, the majority of the respondents came from the 22-24 age group (n=85), followed by the 25-27 age group (n=35), and fewest from the age group 28-34 (n=7). The mean age is 24.4 with a standard deviation of 1.81. The median is 24, which means that half of the population is below 24. The most common occurring age is 23, which serves as the mode of the population.

Table 2. The number of respondents (n) corresponding to each age group. Also listed are the mean, standard deviation, median, and mode.

Age	n	Mean Age	SD	Median	Mode
22 – 24	85	24.4	1.81	24	23
25 – 27	35				
28 – 34	7				

Year Level

Students from YL2 composed the greatest number of participants. The least were from YL1. (**Table 3**)

Table 3. Number (n) and percentage distribution among respondents per year level

	n	Percentage, %
YL1	24	18.75
YL2	55	42.97
YL3	49	38.28
Total	128	100

Visual Impairment

Cases of visual impairment were reported by the respondents, as listed in **Table 4**. A total of 27 (21.09%) respondents reported visual impairments. As the year level increased, the number of respondents with visual impairments also increased. 5 were from YL1; 10 from YL2; and 12 from YL3. The most common complaints were astigmatism and eye strain.

Table 4. The types of visual impairments experienced and the number of respondents (n) experiencing such per YL.

	n	Types of visual impairments
YL1	5	- Astigmatism
YL2	10	- Eye Strain
YL3	12	- Others
Total	27	• Retinal Detachment • Myopia • Poor Eyesight • Visual Limitation/Disability

Commonly used Electronic Gadgets

Table 5 below gives details on the preferred medium for study. More respondents in both YL1 and YL2 preferred using laptops, followed by iPads/tablets, and phones. Electronic readers are seldom used.

On the other hand, the predominant gadget among YL3 students are iPads/tablets, followed by laptops, and phones. Media with audio are the least preferred. Additionally, only individuals belonging to YL3 answered none/never.

Taking the data as a whole, iPads/tablets (n=100) were the most used gadget among the 128 respondents. This was followed by laptops (n=97), phones (n=66), and electronic readers (n=7).

Table 5. Distribution of preferred digital medium per year level.

GADGET	YL1	YL2	YL3	TOTAL
Laptop	19	44	34	97
Desktop	7	12	7	26
iPad/Tablet	17	41	42	100
E-reader	3	0	4	7
Phone	15	30	21	66
Audio	4	6	3	13
Never/none	0	0	5	5

Preferred Medium

Gender

Out of the 128 respondents, 98 were females and 30 males. Out of the 98 females, 63 preferred using printed materials for studying, while only 35 used electronic materials. As for the male respondents, 18 used printed materials, while only 12 used electronic media (See **Figure 1** below). For both genders, printed material was the predominant preference.

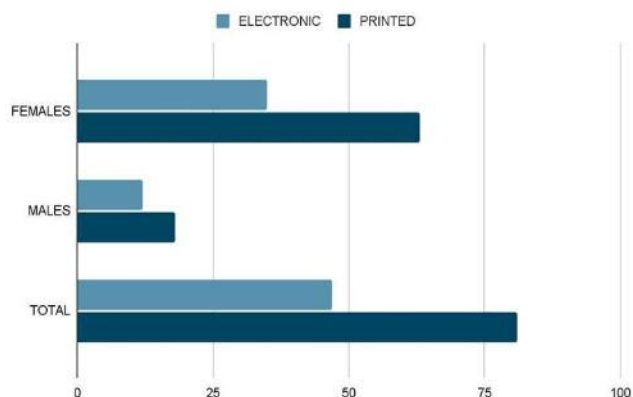


Figure 1. Preferred medium for study, for both genders.

Relationship of Gender and Preferred Medium

Based on the contingency table (**Figure 2**), the p-value=0.670, which is greater than the alpha value ($\alpha=0.05$) implies that the null hypothesis (H_0) was accepted, indicating that there was no significant difference between the gender of the student and their preferred medium when studying.

This was further supported by the $\chi^2=0.182$, which was less than the critical value of 3.841 (df=1), again indicating that the gender of the student and the preferred medium are independent of each other.

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	.182 ^a	1	.670
Continuity Correction ^b	.044	1	.834
Likelihood Ratio	.180	1	.671
Fisher's Exact Test			
Linear-by-Linear Association	.180	1	.671
N of Valid Cases	128		

Figure 2. A generated Chi-square test of independence (SPSS) between gender and preferred medium.

Age

Participants who are below median age (24) preferred printed media. This was also observed in participants who are above the median age. The mode in the ARFIS scale for both subgroups was 4, indicating preference for printed media.

Relationship of Age and Preferred Medium

Based on the contingency table (**Figure 3**), the p-value=0.778 is greater than the alpha value ($\alpha=0.05$), meaning H_0 is thus accepted, indicating that there is no significant difference between the age of the student and their preferred medium for studying.

Likewise, this is supported by the $\chi^2=6.427$ which is less than the critical value of 18.307 (df=10), so that the age of the student and the preferred medium for studying are independent of each other.

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	6.427 ^a	10	.778
Likelihood Ratio	7.675	10	.661
Linear-by-Linear Association	1.381	1	.240
N of Valid Cases	128		

a. 15 cells (68.2%) have expected count less than 5. The minimum expected count is .36.

Figure 3. A generated Chi-square test of independence between age and preferred medium.

Year Level

Figure 4 below explains the distribution of the respondents per year level and their corresponding preferred medium. 14 out of 24 respondents of YL1, 34 out of 55 respondents of YL2, and 34 out of 49 respondents of YL3 claim they prefer printed media. On the other hand, 10 out of 24 respondents of YL1, 21 out of 55 respondents of YL2, and 15 out of 49 respondents of YL3 stated that they preferred electronic media. As a whole, more respondents from each year level preferred printed media. A total of 82 out of 128 of the respondents prefer printed media against a total of 46 chose electronic media as their preference.

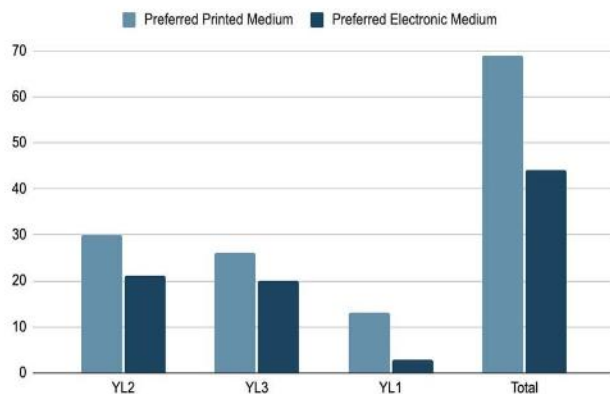


Figure 4. Bar graph plotting the distribution of respondents per year level and preferred medium

Relationship of Year Level and Preferred Medium

Based on the contingency table (**Figure 5**), we see that the p-value=0.587 is greater than the alpha value ($\alpha=0.05$). Hence, H_0 is accepted, indicating that there is no significant difference between year level and medium of preference when studying. H_0 is further supported by the $\chi^2=1.066$ which is less than the critical value of 5.991 (df=1). This is consistent with the finding that the YL of the student and the preferred medium for studying are independent of each other.

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	1.066 ^a	2	.587
Likelihood Ratio	1.073	2	.585
Linear-by-Linear Association	1.004	1	.316
N of Valid Cases	128		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 8.63.

Figure 5. A generated Chi-square test of independence (SPSS) between Year Level and Preferred Medium

Characteristics of participants who preferred electronic media

Out of 128 respondents, 46 (35.93%) had a median scale of 2.5 or less in ARFIS, pointing to a preference for electronic devices while studying. The median score of this subgroup is 2. The 41 (32.03%) respondents from this subgroup had a score of 2 to 2.5, slightly leaning to neutrality, while 5 (3.91%) scored 1, suggesting a firm preference for electronic media.

Of this subgroup, 6 (4.69%) reported having visual impairment (versus 21.09% from the whole sample).

In terms of gadget preference, iPads/Tablets are the most preferred of this subgroup, which is the same as the most popular gadget from the whole dataset. Laptops also tied

with iPads/Tablets, followed by Phones in the electronic media subgroup.

Characteristics of participants who preferred printed media

In general, majority of the respondents preferred printed media for academic purposes. Out of 128 respondents, 82 (64.06%) had a median score of 3.5 or more in the ARFIS scale, which denoted printed media preference (**Figure 6**). To further describe the respondents who belong to the printed media group, the median scores of the whole subgroup was 4. There were 47 (36.71%) individuals who scored 4 or less, showing slight neutrality to their preferred media. 35 (27.34%) respondents scored 4.5 or more, showing firm preference for printed media. **Table 7** lists the breakdown of the median scores of the full subset.

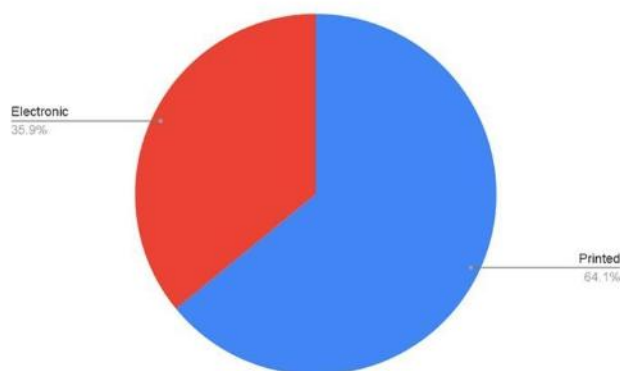


Figure 6. Distribution of Preferred Medium (n=128)

Table 7. ARFIS scores of respondents.

Median Scores	n	Frequency, %
1-1.5	5	3.91
2- 2.5	41	32.03
3.5-4	47	36.71
4.5-5	35	27.34
Total	128	100

Of this subgroup, 21 (16.41%) reported having visual impairment (versus 21.09% of the whole sample).

Gadgets used in this subgroup differed slightly from the full dataset. In the full dataset, the most popular devices were iPads/tablets, followed closely by laptops. This is also the trend in the printed subgroup. **Table 8** shows the reported gadgets used compared with the full subset.

Table 8. Gadget usage by preferred medium.

Gadget	All (n=128)	Electronic (n=46)	Printed (n=82)
Laptop	97	40	50
Desktop	26	10	16
iPad/Tablet	100	40	60
E-reader	7	2	5
Phone	66	25	41
Audio	13	8	5
Never/none	5	1	4

Academic Performance

Table 9 shows that out of the 128 respondents, 4 (3%) had 6 academic subjects with unsatisfactory grades. Going down the line, 5 students had 5 subjects with unsatisfactory grades, which comprised 4% of the total respondents. Those who had 4 subjects with unsatisfactory grades comprised 6% of the total respondents, numbering 8 students. For those who had a better academic performance, having less unsatisfactory grades, there are 7 (5%) that had 3 subjects with unsatisfactory marks. The total number of students who had only 2 unsatisfactory grades increased to 16 (13%). And following the same pattern, there are 31 students (24%) with only one unsatisfactory mark. Lastly, there are 57 students with no unsatisfactory grades, comprising 45% of the total number of respondents, a reflection of their school performance

Table 9. Distribution of number of subjects with unsatisfactory grade (Subjects with UNSATs)

Subjects with UNSATs	# of students	Frequency, %
6	4	3
5	5	4
4	8	6
3	7	5
2	16	13
1	31	24
0	57	45
Total	128	100

Measures of Association

Chi-square test for Independence

Figure 7 shows the distribution of grades relative to the preferred medium. Out of 57 students who did not incur any unsatisfactory grades, 21 (16.40%) of them are electronic media users while 36 (28.15%) are printed media users. For students who had incurred 1-2 unsatisfactory grades, 18 (14.06%) are electronic media users, while 29 (22.65%) students are printed media users. Further, for students with 3 or more unsatisfactory grades, 7 (5.46%) are electronic media users while 17 (13.28%) are printed media users.

Grade		Preference		Total
		Electronic	Printed	
0 Unsat		21	36	57
1 Unsat		10	21	31
2 Unsat		8	8	16
3 Unsat		2	5	7
4 Unsat		2	6	8
5 Unsat		1	4	5
6 Unsat		2	2	4
Total		46	82	128

Figure 7: Distribution of grades relative to preferred medium in crosstabulation (crosstabs) form.

Chi-square test for independence (SPSS) was applied to determine the relationship of these two variables. Based on **Figure 8**, with p-value=0.802 greater than the alpha value ($\alpha=0.05$), H_0 is accepted. This suggests that there is no significant difference between the use of electronic and printed media in obtaining a higher general weighted average among 1st to 3rd year medical students of Centro Escolar University - Manila, 1st semester, AY 2021-2022.

This is further supported by the $\chi^2=3.053$ which is less than the critical value of 12.592 (df=6), more proof that academic performance and the preferred medium for studying are independent of each other.

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	3.053 ^a	6	.802
Likelihood Ratio	3.070	6	.800
Linear-by-Linear Association	.066	1	.797
N of Valid Cases	128		

a. 7 cells (50.0%) have expected count less than 5. The minimum expected count is 1.44.

Figure 8: Relationship of academic performance and preferred medium in Chi-square test for independence (SPSS).

Prevalence Ratio

Table 10 shows the distribution of the exposure relative to the outcome(or "disease") among the respondents. Exposure represented electronic media preference: the "without exposure" subgroup was printed media users. Outcome represented the presence of unsatisfactory grades regardless of number; those "without outcome" were respondents who did not incur a single unsatisfactory grade.

A prevalence ratio of 0.97 was interpreted as having no association between the outcome and exposure. This finding is similar to the previous chi-square test mentioned above, revealing that

preferred medium and academic performance have no association with each other.

Table 10. Distribution of respondents in relation to exposure and outcome

		Outcome		Total	Ratio
		With	Without		
Exposure	With	25	21	46	0.543478
	Without	46	36	82	0.560976
Total		71	57	128	0.968809

DISCUSSION

The literature involving the dichotomy of electronic versus printed media in so far as academic performance is concerned has conflicting results. Studies in relation to such showed no significant difference in academic performance among those using electronic media and those using the printed version. This suggests that electronic media can be a feasible option in learning. These studies were conducted with similar study populations, but were held in various foreign settings^(31, 32, 46).

By way of contrast, there are findings suggesting that electronic media produced better effects on learning motivation and outcome. However, these studies did not specify the demographic information of the respondents. Dissimilar sample populations may strikingly produce variations with the results⁽³⁵⁾. Moreover, one study presented a systematic critical review of papers concerned with digital text use in education. Results showed positive results on academic performance. However, since the electronic media was not juxtaposed with printed media, it was not established which among the two yielded a more significant impact on academic performance⁽³⁴⁾.

Another noteworthy information in previous literature is that results verified a relationship between age and preferred medium. However, it is possible that the differences observed between age and preferred medium were brought about by the variations in the study population and their motive for reading. Digital format understandably appears to be widely accepted by the younger segments, while printed formats are preferred more by the older population. However, the setting of the study was done in the context of reading for leisure and not for academic purposes⁽⁴⁾. This is in contrast with our study which focuses more on the latter and consists primarily of students wherein age had no effect on the preferred medium of reading materials.

The aim of this study is to determine the proportion of medical students who prefer using printed as against electronic media while studying. Studies have already been done to investigate the preference for utilizing a specific instructional medium while studying. This present study shows that 35.93% of the participants preferred the use of electronic media, which is higher compared to the original study of ARFIS, which revealed 10.04% of the same subgroup only⁽⁴⁶⁾. Conversely, a study showed 61% of the student participants perceived the use of e-books as an easier medium to use for research than printed materials⁽⁵⁾. In the same study, however, the preference of using both media when gathering information is the highest (44%) while the use of printed media only (34.5%) scored higher than the use of e-books only (21.5%).

Parallel to the results of this study, a research regarding Indonesian education concluded that electronic media has begun to take over printed media. Nevertheless, the role of printed media continues to dominate their education system given the situation in geographically remote areas of their country⁽⁴⁷⁾.

Possible explanations for printed media preference had been explored by other studies; It was stated that the lack of awareness on the availability of e-books affected the results of higher printed media preference ⁽⁴⁸⁾. While this may still be acceptable, with continuous technological developments and access to information, such is less likely to be a factor in the near future. In the same study, readability, ease of use, and portability were the top reasons for the students' preference of printed materials, and these may also be the same factors that could influence the outcome of this current study.

Other features may also be relevant regarding the effect of instructional media preference on academic performance. One study suggested that "the use of paper notebook promoted the acquisition of rich encoding information and/or spatial information of real papers", the reason why the duration is shorter, and accuracy is higher in writing down schedules using paper notebook compared to electronic tablet or smartphone ⁽⁴⁴⁾. Another explanation regarding the preference for printed media stated a higher risk of gadget addiction which may disrupt the process of getting higher academic grades ⁽⁴⁹⁾. Despite these reports, the results of this present study showed that academic performance and the preferred medium for studying are still independent of each other.

Although electronic media has its practicality and ease of use, it has been emphasized that respondents may still prefer the traditional way of studying due to a sense of familiarity in being able to hold the material. The use of textbooks to provide kinesthetic feedback is thought to be associated with better studying results with details like better memory function, longer attention span, faster processing speed, and even improved mathematical and writing skills⁽⁴³⁾.

Most of the hindrances to adopting electronic media may also have to do with technical aspects in their use, such as navigating the device's operating system, management, applications, bugs, and internet connectivity. Pedagogical issues such as discipline around devices, training to operate and learn the applications, and utilizing devices in lessons are also of concern ⁽³⁸⁾. Another explanation states that even with the present trend of online learning, students are unfamiliar with the study system and have difficulties in transitioning from traditional learning ⁽³⁹⁾. As high as 64% of subjects have also reported that they perceived the attention to and retention of information better in printed media.

The COVID-19 pandemic may have also influenced increasing gadget use today. In one study, students in higher education consider social media as useful for collaborative learning during this period ⁽⁵⁰⁾. Even with the above-mentioned studies, an increasing trend with electronic media use cannot be determined accurately, but it is still remarkable that the proportion of electronic media users of this study is higher than that of the pioneer research that used ARFIS.

Practical implications of academic performance and preferred medium occurring independently on shifting to an online or blended academic set-up, which relies on electronic media, should be studied more in depth. The researchers maintain that learning is ever evolving and further studies should be conducted to ensure that future generations are receiving and utilizing what can positively affect their individual cognitive skills and hence, their scholastic achievements ⁽⁴³⁾. Competing concerns such as comfort, readability, usability, and perceived learning and focus, versus the costs and convenience of e-formats, demonstrate that neither medium is categorically superior in all contexts ⁽⁵¹⁾.

Although the preferred medium has no influence on academic performance, several factors may be considered to have a direct relationship with the latter –such as socio-economic status, family, sleep habits, and mental health.

As regards socio-economic status, families with a higher socio-economic level help children attain a positive self-concept, which in turn leads to enhanced academic performance ⁽²⁰⁾. Families with parents belonging to higher levels of completed education have progressive parenting styles and are found to be more knowledgeable on approaching and addressing problems that arise in their relationships with their children, who then are able to have more significant accomplishments.⁽²²⁾

Adequate sleep habits also contribute to efficient learning and memorization skills ⁽²⁷⁾. Added to this, mental health seems to have a bearing on this notion. Symptoms of depression show some association with the student's poor academic performance, although, it is not yet known how exactly these can be quantified ⁽²⁸⁾. Despite these factors being mentioned, they were not substantially explored in the study.

Even with the overwhelming preference for printed media in various papers, one must not discount the advantages of using online learning. This was identified by Filipino medical students in a separate study, which enumerated improved accessibility of information, ease of standardizing and updating content, cost-effectiveness, accountability, and enhancement of the learning process ⁽⁵²⁾. Besides, a study conducted with Filipino senior high students as respondents concluded that the use of electronic gadgets were “very effective” and that the study habits of those who participated in the study were deemed to be “very good” ⁽⁵³⁾.

With all that said, one must not ignore the barriers of online learning in the Philippines. Filipino medical students encountered problems with poor internet connection, limited access to gadgets, and lack of study space. Students also experienced low morale, difficulty in concentrating, and other socioeconomic factors ⁽⁵²⁾.

Limitations of the Study

This study only covered the preferences of CEU-SOM students from YL1 to YL3. Additionally, only regular students enrolled with the standard number of units per year level were considered, so that academic requirements remain constant. This kept the sample population at a modest number of 128 students.

The study was conducted over the period of January to June 2022, during the online set-up because of the COVID-19 pandemic. The respondents adhered to this arrangement, attending classes in the safety of their homes.

While the results of this study may be construed as true, its reliability would be better established had triangulation been performed along with other populations of similar characteristics. This should further strengthen the outcomes and assure the repeatability of the methods ⁽⁵⁴⁾. Given this, the results cannot be readily extended to a broader cohort of medical students.

In the process of determining relationships, it was found out that there was no significance between the variable components considered (age, gender, year level) and the study medium of preference. This could be correlated to the limited sample pool and the differences in individual set-ups when it comes to online classes. Aside from this, the study does not claim to be exhaustive when it comes to other underlying factors that may play a role.

The initial plan for this study was to use the numerical grades of the students acquired within the 1st Sem S.Y. 2021-2022. Since such was not yet available as of this writing, the data gathered were limited to the qualitative report of partial grades (either Satisfactory or Unsatisfactory). If ordinal values (GWA) had been used instead, the researchers could have been better able to distinguish the variability among the respondents' performances. This would improve the reliability of Pearson correlation-derived analyses ⁽⁵⁵⁾.

Conclusion

The transition from traditional learning to online learning was abrupt and unprecedented. Before the pandemic, very rarely were medical schools in the Philippines reliant on online learning methods and materials. There was a growing concern among medical students regarding the challenges that come with virtual or remote modalities. These concerns ranged from a simple technical navigation and usage of electronic media to the more pedagogical aspects, such as exercising discipline around gadgets and educators incorporating online teaching methods. One of the components of online learning explored in this study was the use of electronic media (e.g., audio, phones, and laptops) as an alternative to the more familiar printed media (e.g., textbooks) used in the academic setting.

The study's general objective was achieved as results have shown that the preference of one medium does not show any academic advantages among YL1 to YL3 medical students. Other factors that could have an impact were not determined in this study. This finding can serve as an understanding that learners are able to adapt and shift to online mode which relies on gadgets to achieve learning outcomes. This type of learning comes with advantages such as time management, comfort, and accessibility. Educators and institutions should incorporate

electronic media and subsequently online learning to develop practicable teaching strategies as an alternative or adjunct to traditional learning to maximize the advantages of both learning modalities.

The specific objectives were also achieved as the demographic profile of the medical students in the context of preferred medium was ascertained. The study results were congruent with results from the Academic Reading Format International Study, the largest investigation of university students' behaviors towards preferred format of academic materials. Both studies showed that respondents were predominantly printed media users.

Recommendations

This study may be considered preliminary and introductory which, eventually, may be expanded to several more advanced phases. Given current physical distancing measures imposed during the pandemic when the study was being developed, there were limitations with recruitment and thus, a relatively small sample of medical students available for the survey. A comprehensive dataset in the future can involve multiple medical schools as study sites in order to capture a wider and broader representation of the Filipino medical students' preferences and its relationship with academic performance.

Controlled academic settings such as a subgroup of students strictly enrolled solely in online learning and a counterpart subgroup strictly enrolled solely in traditional learning, could also serve as a more precise estimation of correlation. This may be more conclusive in terms of determining actual effectiveness of online learning in achieving successful outcomes.

Lastly, the use of GWA as an evaluation for academic performance could be implemented in

future studies to reflect a quantitative analysis of the effectiveness of the preferred medium or academic setting.

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The Effect of Clonidine as an Adjuvant on Onset of Action of Levobupivacaine Epidural Anesthesia among Patients Undergoing Elective Lower Limb Orthopedic Surgery*

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ABSTRACT

Background: Epidural anesthesia is a widely used anesthesia technique commonly for surgeries involving the lower extremities up to the abdomen. It is beneficial for long duration surgeries because the epidural catheter in place allows additional of local anesthetic as needed. However, this technique has a slower onset of action and requires a larger volume of local anesthetic compared with spinal anesthesia. This study aims to determine if clonidine when used as an adjuvant can hasten the onset of action of levobupivacaine epidural anesthesia thus allowing the early commencement of surgery.

Methodology: This is a double blind randomized controlled trial. After approval from the institution's research ethics and review committee, a total of 36 patients of American Society of Anesthesiologist Classification I or II for elective lower limb orthopedic surgery under levobupivacaine epidural anesthesia were purposively enrolled in this study and randomly assigned by match pairing of characteristics to two groups: Group A-Clonidine and Group B- plain normal saline solution. Group A were given 0.5% levobupivacaine 15cc with 30 µg (0.2cc) clonidine and group B were given 0.5% levobupivacaine 15cc with 0.2cc plain normal saline solution. In both groups the onset of levobupivacaine epidural anesthesia (sensory block at T10 dermatomal level/

Bromage 1) were observed. Side effects such as hypotension, decreased in respiratory rate, oxygen saturation, and any untoward incidence were noted. All data gathered: statistical mean, median, standard deviation, and T test were analyzed using the SPSS software at 5% significance level.

Results: The mean onset of action of group A- Clonidine group (5.62 minutes) was faster compared to group B-control (11.33 minutes), which was statistically significant ($P<0.05$). The highest dermatomal level for the clonidine group was at T6 and T7 for the control group. Two segments regression was at 180 minutes for the Clonidine group while 60 minutes for the control group. The patients given clonidine experienced side effects such as sedation, bradycardia (20% decrease in cardiac rate from baseline), and shivering. Hypotension was not observed in both clonidine and control groups.

Conclusion: Clonidine at a dose of 30 µg when used as an adjuvant to levobupivacaine epidural anesthesia can hasten its onset of action among patients undergoing elective lower limb orthopedic surgery.

Keywords: *epidural anesthesia, clonidine, adjuvant*

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

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INTRODUCTION

Background of the Study

Anesthesiology is the practice of medicine that provides insensibility to pain during surgical, obstetric, therapeutic and diagnostic procedures. It has become progressively safe due to the availability of advance patient monitoring devices and delivery technology.¹ One such anesthetic technique is epidural anesthesia. In a skilled anesthesiologist it is easy to learn and safe to perform. Epidural is useful for surgical anesthesia of different specialties such as orthopedic, obstetric, gynecologic, general surgery, cardiothoracic, among others.² It is also useful for pain management both intraoperatively and postoperatively. Furthermore it has also been shown to decrease the surgical risk and morbidity of patients such as those with cardiac diseases.³

Epidural anesthesia involves the insertion of a hollow needle in the epidural space. This is a potential space located between the dura mater and the vertebrae spine.⁴ Its contents are the lymphatics, spinal nerve roots, loose connective tissues, adipose tissue, small arteries and a network of internal vertebral venous plexuses.⁵ A small, flexible catheter inserted into epidural space in the lumbar, thoracic, or cervical level. The anesthetic agent is injected into the catheter. It then diffuses into the epidural space and coat the dural sac while partly passing through the foramina before it is able to cause motor and sensory blockade).⁶

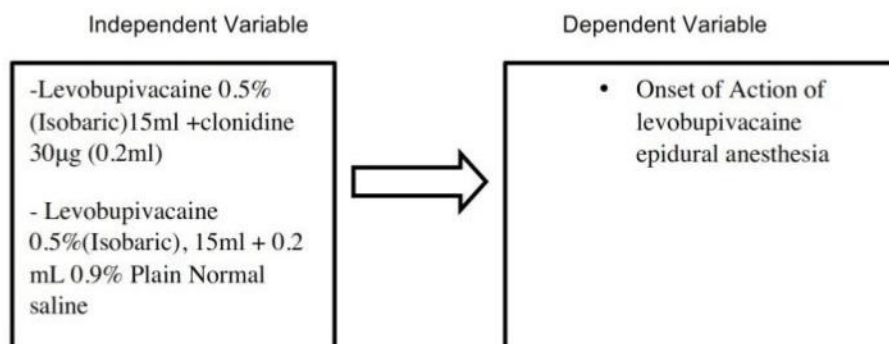
On the other hand, in spinal anesthesia, the anesthetic agent is directly injected into the cerebrospinal fluid into the subarachnoid space. This direct bathing of the nerve root with a local anesthetic agent allows a relatively small dose and volume of local anesthetic to attain a dense sensory and motor blockade.

For epidural anesthesia to achieve the same local anesthetic effect with spinal anesthesia, a larger volume of local anesthetic is given. Adults require 1-2 ml of local anesthetic per spinal segment to be blocked. For instance, to achieve a T4 sensory level blockade from an L4-L5 injection would require about 12-24 ml of local anesthetic. Furthermore, epidural anesthesia has a slower onset of action at around 10-20 minutes and may not be as dense as spinal anesthesia.⁷

Because epidural anesthesia requires larger volume of local anesthetic and a slower onset of action, it is imperative to find an adjuvant that will help to hasten the onset and prolong the duration of action of levobupivacaine epidural anesthesia. This will allow the early commencement of the surgery and use of lower volume of local anesthetic.

One such adjuvant is clonidine. It is a derivative of imidazoline and exerts its action on the alpha 2 adrenergic receptor as an agonist. Once this receptor is activated it can lead to inhibition of excitatory cardiovascular neurons and a reduced sympathetic outflow from the central nervous system. It can also decrease transmission of pain, hence producing analgesia. If added as an adjuvant to epidural, aside from reducing pain transmission in the dorsal horn, it can also cause vasoconstriction of the blood vessels, which slows the removal of local anesthetics. Lastly, there is an additive effect when it is combined with other adjuvants such as opioids leading to a reduced dose of each component by as much as 60% for postoperative analgesia.⁸

Conceptual framework



Objectives

General Objective

To determine the effect of clonidine as an adjuvant on levobupivacaine epidural anesthesia

Specific Objectives

- To determine the effect of clonidine on the onset of sensory blockade and motor blockade of levobupivacaine epidural anesthesia
- To determine if there is significant difference on onset of action of levobupivacaine epidural anesthesia with clonidine adjuvant versus levobupivacaine alone

Definition of Terms

Levobupivacaine - a local anesthetic belonging to the amino amide group and the S enantiomer of bupivacaine. Indicated for infiltration, nerve block, ophthalmic, epidural, and intrathecal anesthesia

Epidural anesthesia - a local anesthetic is injected into the epidural space around the spinal cord using an epidural catheter, the injection can result in a loss of pain sensation by blocking the transmission of signals through nerve fibers in or near the spinal cord

Dermatome - an area of skin that is mainly supplied by afferent nerve fibers from a single dorsal root of spinal nerve, which forms a part of a spinal nerve.

Pinprick test- a gross test to check the actual ability to feel a pinprick and the ability to determine the difference between sharp and dull

Bromage scoring- measures the intensity of motor block by assessing the patient's ability to move their lower extremities: Grade I (complete block-100%)-unable to move feet or ankle, Grade II-(Almost Complete-66%)-able to move feet only, Grade III (Partial-33%)- just able to flex/move the knee, IV (NONE-0%) full flexion of knee and feet

Onset of action- - inability to feel pinprick at T10 dermatome and Bromage I or unable to move feet or legs

Top-up- the addition of anesthetics via epidural route to maintain anesthesia at the desired dermatomal level

Scope and Limitation of the Study

This study is limited to patients admitted at a tertiary level hospital undergoing an elective lower limb orthopedic surgery who are ASA (American Society of Anesthesiologist) I-II, aged 19-50 years old.

Significance of the Study

The result of this study will benefit anesthesiologists for they will be given a possible adjuvant to hasten the onset of sensory and motor blockade of levobupivacaine epidural anesthesia. For the surgical team, because faster onset of epidural anesthesia means early commencement of surgery thus saving time. For the patients, this will help lessen the risk of local anesthetic systemic toxicity. For the “tertiary level hospital”, more patients will be catered because of the faster transit time at the operating room and this will serve as a baseline study for future researchers.

MATERIALS AND METHODS

Research Design

This was a double blind randomized controlled trial. An experimental form of research in which the population receiving the intervention was chosen at random from the eligible population, and a control group was also chosen from the same eligible population.

Participants

Thirty-six participants scheduled for elective orthopedic surgery under epidural anesthesia were included in this study.

Sample Size and Randomization Technique

The 36 recruited subjects were purposively enrolled in this study and randomly assigned by match pairing of characteristics to groups two groups (Group A and Group B).

Sample size computation

The result of the study was recorded in “minutes”. This was a continuous variable, with a minimum and maximum value; hence this formula for continuous variable was used for the sampling size computation:

$$N = 2 \times \left(\frac{z_{1-\frac{\alpha}{2}} + z_{1-\beta}}{\delta} \right)^2 \times s^2$$

Parameter definitions

N=sample size; p=the response rate of standard treatment group; p₀= the response rate of new drug treatment group; z_x= the standard normal deviate for a one or two sided x; d= the real difference between two treatment effect; δ₀= a clinically acceptable margin; S²= Polled standard deviation of both comparison groups.

$$N_{\text{statistical superiority}} = 2 \times \left(\frac{1.96 + 0.845}{4} \right)^2 \times 6^2 = 36$$

COVID 19 Precautions and Protocols

The safety of both the patient and the researcher was the utmost priority of this study. The hospital's existing COVID 19 guidelines were strictly followed. Patients who were scheduled for operation underwent a preoperative risk assessment. This was a screening form from the Infection and Prevention and Control unit of the “tertiary level hospital” which was adapted from the Philippine Society for Microbiology and Infectious Diseases and Philippine Hospital Infection Control Society. The following details were obtained from the patient: signs and symptoms, history of travel, preexisting medical conditions, physical examination, vital signs, laboratory including COVID 19 RT PCR result. From these, the patients were then classified as either low risk or high risk for COVID 19 transmission.

Based on the risk for COVID-19 transmission during surgery, there was a minimum recommended personal protective equipment to be used by the anesthesiologist and the surgeon. For low risk for transmission, the following were the recommended personal

protective equipment: Fit tested N95 mask and goggles/face shield.

At the wards, patients were placed in isolated cubicles and were mandated to wear facemask at all times.

For this study, only patients who were classified as low risk for COVID-19 transmission were included. The use of appropriate personal protective equipment was observed during preoperative visit, recruitment process, and operation proper. The patient at the operating room was required to wear facemask at all times.

Recruitment

The Department of Orthopedics submitted a list of patients for elective surgery a day before their scheduled operation. Hence, the recruitment was done a day before the scheduled elective surgery. The principal investigator did the recruitment process and this was done at their respective wards. Those who were eligible to become a participant of the study were visited and recruited. During the recruitment process it was ensured that the participant was in a quiet room or surrounding.

COVID 19 safety protocols such as wearing of proper protective equipment were strictly observed during recruitment process.

Inclusion criteria

- Patients admitted for elective orthopedic lower limb surgery
- Patients who were assessed as low risk for COVID 19 transmission during operation
- ASA (American Society of Anesthesiologists) I-II patient
- Ages 19-50 years old
- Voluntary with written informed consent

Exclusion criteria

- Pregnancy
- Unsuitable condition for lumbar puncture/epidural anesthesia such as: patient refusal, severe coagulation abnormalities, sepsis, elevated intracranial pressure, anticoagulant use, thrombocytopenia, other bleeding diathesis, preexisting central nervous system disorder such as multiple sclerosis, infection at lumbar function site, previous back surgery, preexisting neurologic injury, back pain, placement in anesthetized adult, needle placement through tattoo
- Untreated psychiatric disorder, preexisting psychotic disorder and non compliance to psychiatric medications and no follow-up
- Those who had sedative or analgesic medications 24 hours prior to surgery
- Epidural block failure (unable to reach sensory block at T10 and motor block-Bromage grade I) after 30 minutes of epidural injection
- Allergy to local anesthetic

Withdrawal criteria:

- Request of patient to withdraw from the study
- COVID positive/exposure to COVID 19 positive patients while at the wards
- Cancellation of surgery
- Change in anesthetic technique

Risk

The level of risk in this study was more than minimal because of the use of an adjuvant drug. Expected side effects were the following: hypotension, sedation, bradycardia, with little effect on respiratory drive. The risks were assessed by the use of standard monitors recommended by the American Society of Anesthesiologists such as pulse oximeter,

electrocardiography, noninvasive blood pressure device, and a temperature probe. These monitors were used during the operation and at the post anesthesia care unit until full recovery from anesthesia was attained. Emergency drugs were made available at all times in order to address these possible side effects.

Benefit

Surgeons and anesthesiologists – faster onset of epidural anesthesia is equivalent to faster commencement of surgery.

Patient – clonidine is known to prolong the duration of action of local anesthetics, lower amount of local anesthetic was given to the patient hence lessening the risk of local anesthetic systemic toxicity. Furthermore, it can also reduce the cost of surgery

The Tertiary Level Training Hospital – a baseline for future researchers. Furthermore, the institution's operating room could cater more patients due to faster transit time of patients.

Study Setting

This study was conducted at the operating room of a tertiary hospital.

Duration of the Study

This study was conducted for over 20 weeks.

Research Team Members

The following were the research team members with their respective roles and responsibilities:

Principal investigator – supervised all aspects of the study including the development of the concept of the study, writing of the protocol, submission of the protocol to the Institutional Review Board approval, direction of the

recruitment of participants, manages the informed consent process, and supervising the data collection, preparation of summaries, final data analysis, interpretation, and presentation.

Anesthesia residents:

Anesthesiologist A – a member of the team of anesthesiologists assigned for the elective cases for the day. His sole responsibility was the preparation of the sterile solution to be given to the patient. He labelled these with unique codes. Furthermore, he has the sole knowledge with regards to the composition of the solution (either it contains clonidine adjuvant or the control plain normal saline solution). He was also responsible for the distribution of these solutions.

Anesthesiologist B – another member of the team of anesthesiologists assigned for the elective cases for the day. His responsibilities were the following: inserted the epidural catheter, administered the prepared solution, assessed the level of the motor and sensory block, timed the onset of action of levobupivacaine epidural anesthesia, and monitored the patient during the operation.

It was made sure that the anesthesiologist who prepared the solution was different from the anesthesiologist who performed the lumbar puncture/ epidural catheter insertion and administered the prepared solution.

Instrument and Intervention

Group A received 15 ml 0.5% levobupivacaine mixed with 30-µg clonidine (0.2 ml), and group B received 15 ml 0.5% levobupivacaine mixed with 0.2ml 0.9% plain normal saline solution by epidural route. Both preparations were placed in a 20 ml syringe. The prepared solution was given as a bolus to the patient at a rate of 1ml/second and with 1- minute pause for every 5 ml delivered to observe for any

untoward signs and symptoms. The anesthesiologist who administered the prepared solution was blinded. Everything else was kept constant in both groups.

Procedure

COVID 19 PROTOCOLS

This study strictly adhered to the COVID 19 protocols provided by the Infection Prevention and Control Unit of the "Tertiary Level Hospital". Minimum recommended personal protective equipment for low risk transmission surgery were followed. For the anesthesiologist, this included a fit tested N95 mask and goggles. Patients were asked to wear surgical facemask at all times during the surgical procedure.

PREINDUCTION

The patient from the ward was brought to the exchange area of the operating room. He was then transferred to the operating room's transport stretcher. At the exchange area, a review of patient's history and physical examination were done. The patient was given sedative/anxiolytic and was transferred to the main operating theater where the patient was assigned.

Once transferred to the main operating theater, the patient was moved from the transport stretcher to the operating table. The patient was hooked to oxygen via nasal cannula at 3 liters per minute. Then was attached to American Society of Anesthesiologist Standard monitors such as: non-invasive blood pressure monitor, cardiac monitor, pulse oximeter, and temperature probe. Baseline vital signs were determined.

Prior to induction of anesthesia, the patient was hydrated with plain lactated ringer's solution at a rate of 10 ml per kilogram. Once hydration has been done, he was positioned for the insertion of the epidural catheter.

It was made sure that the levobupivacaine solution to be given to the patient was already prepared before the induction process. The patients were randomly assigned to either group A or group B. Group A received 15 ml 0.5% levobupivacaine mixed with 30 µg clonidine (0.2ml), and group B received 15 ml 0.5% levobupivacaine mixed with 0.2ml 0.9% plain normal saline.

INDUCTION

The patient was positioned for lumbar puncture insertion: lateral decubitus or sitting position. The lumbar puncture area was cleaned with povidone-iodine solution and infiltrated with 2% lidocaine. Lumbar puncture was done using Tuohy needle gauge 18. Epidural space was identified using lost of resistance to air technique. About 4 centimeters of epidural catheter was left in the epidural space. Proper placement of the catheter at the epidural space was verified using a test dose of 3ml, 1.5% lidocaine with epinephrine 0.2mg (1:200,000). After insertion, the patient was then placed in supine position and dermatomal mapping was done. Once the desired dermatomal level was attained, the patient was positioned optimized for the surgical procedure.

Procedure/Maneuvers:

The patient either received the prepared solution containing 15 ml levobupivacaine 0.5% Isobaric mixed with 30 µg (0.2ml) clonidine which were given simultaneously or 0.2 ml plain normal saline which was also given simultaneously. The solution was placed in a 20 cc syringe labeled with a code composed of four characters, which was a combination of numbers and letters. The code was generated using random code generator software.

This was followed by the assessment of the onset of epidural anesthesia using the Bromage and pinprick testing. Bromage scoring is

a grading system based on the patient's ability to move their lower extremities and signifies the intensity of the anesthetic block. The Bromage scoring system is as follows: grade I - unable to move feet or knees, grade II- able to move feet only, grade III-just able to move knees, IV- full flexion of feet and knees. The anesthesiologist administering the solution was blinded. Once the block was considered adequate: inability to feel pinprick at T10 dermatomal level and attainment of Bromage score of I, the surgery was allowed to commence.

The following data were collected: the time taken for onset of epidural anesthesia which was sensory block at T10 and Bromage I; the highest dermatomal level of sensory analgesia; the time to two segment regressions. All recorded in minutes.

A Casio digital HS-70W-1D timer was used in this study and the same model was used in all patients during data collection.

Intraoperative monitoring

Vital signs were monitored every minute for 15 minutes and every 5 minutes thereafter until the surgery ended. Any untoward side effects such as: hypotension, bradycardia, and respiratory depression were closely monitored. Emergency medications were made available at all times. Regression of sensory block was assessed using pinprick test. Once sensory block regressed to T12, top up with 5ml (0.5% isobaric) levobupivacaine was done.

At the end of the surgery, the patient was transferred to the post anesthesia care unit and was kept attached to non invasive blood pressure monitor, cardiac monitor, pulse oximeter, and temperature probe. Vital signs were monitored every 15 minutes until the patient was suitable for transout.

Post Operative Care

An anesthesiologist assessed the patient prior to transfer back to the ward. The Bromage scoring and Aldrete Scoring were used in determining the patient's readiness for transfer out of the post anesthesia care unit.

Aldrete Scoring

Activity

- 2 Able to move spontaneously on command four extremities
- 1 Able to move voluntarily or on command two extremities
- 0 Unable to move any extremities

Respiration

- 2 Able to deep breath and cough freely
- 1 Dyspnea, shallow or limited breathing
- 0 Apneic

Circulation

- 2 BP +20mmHg of premedication level
- 1 BP+ 20-50mmHg of premedication level
- 0 BP + 50 mmHg of premedication level

Consciousness

- 2 Fully awake
- 1 Arousable on calling
- 0 Not responding

Skin color

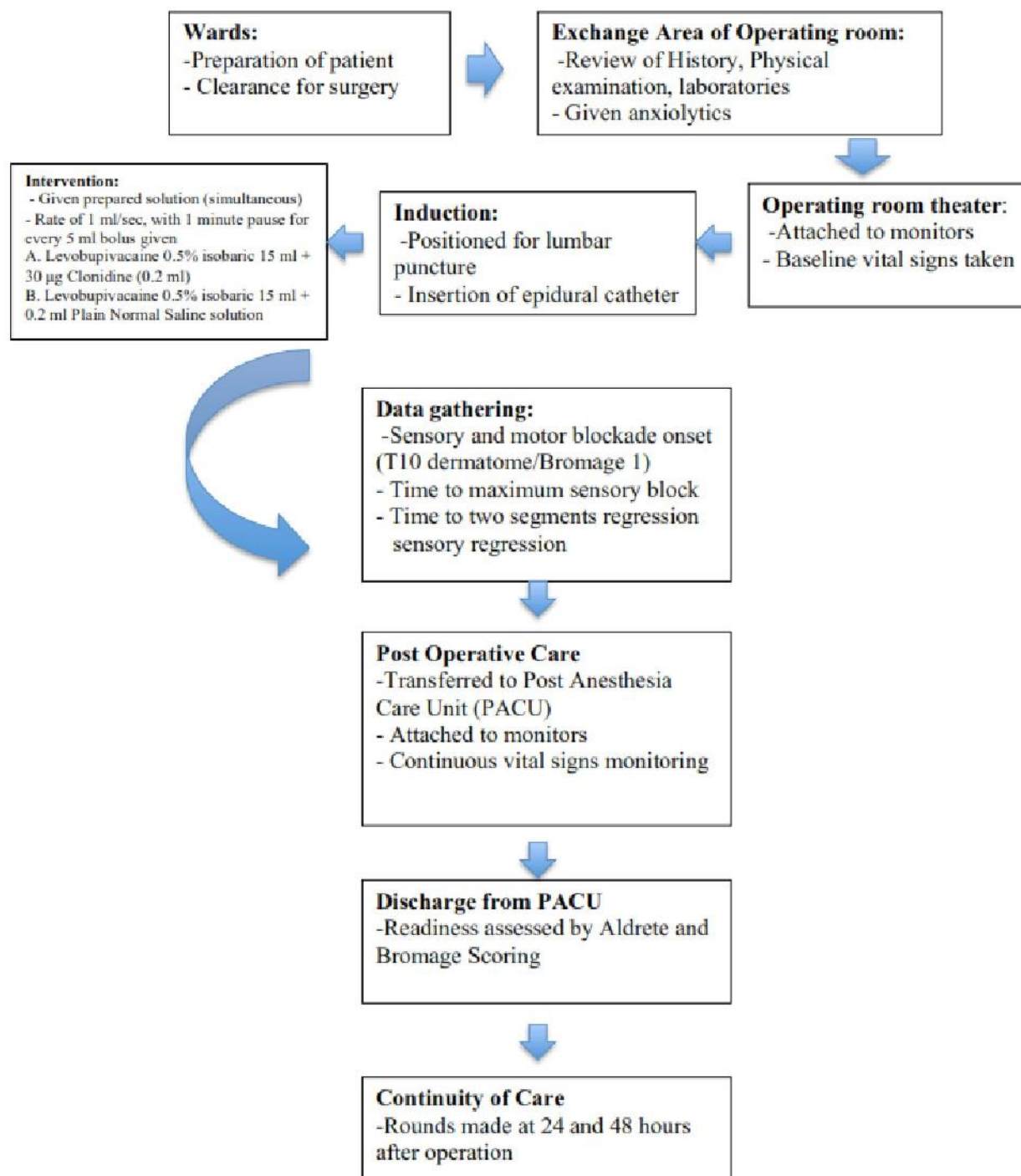
- 2 Normal
- 1 Pale, dusky, blotchy, jaundiced, other
- 0 Cyanotic

Bromage (Assessment of Intensity of Block)

- I- Complete - Unable to move feet or knees
- II- Almost complete - Able to move feet only
- III- Partial - Just able to move knees
- IV-None - Full flexion of Knees and Feet

The patient was discharged from the Post Anesthesia Care Unit when Aldrete score was at least 8 and a Bromage score of IV. Rounds were done to the patient 24 and 48 hours after the operation.

Procedure Flow Chart



Ethical Consideration

Ethical issues concerning research participants were mainly privacy, anonymity, voluntary and informed consent. The privacy of information obtained from the participants as well as their anonymity were respected. The participants voluntarily participated and at no one time coerced. The anonymity of the participants was adhered to as no personal information, such as names, were collected. However, it is not only the researcher who had the knowledge of the participant's information but also the entire research team. The researcher assured that all collected data from this research project was kept in a metal box with a lock. Such metal box was kept inside the storage room in the office of the Department of Anesthesia. Information and data in electronic form were kept in a password-protected personal computer in the department's desktop. All data was kept for five (5) years and disposed by shredding for printed documents and deletion of electronic copies from the computer. No one but the researcher had the access to it. This approach was considered once approved and supported by the Western Visayas Medical Center Research Ethics Committee.

Data Analysis Procedure

SPSS software was used to analyze all the data gathered. Descriptive analysis was used in the subject's characteristic. The parametric test of difference used in the data analysis was justified by Shapiro-Wilkman test of normality. The data that were obtained were processed using statistical mean, standard deviation, and T-test for independent sample and effect size and hypothesis was tested at 5% significance level.

Results

The present investigation determined the effect of clonidine as an adjuvant to levobupivacaine anesthesia on the onset of sensory and motor blockade and if there is a

significant difference on the onset of action sensory and motor blockade between the experimental and control groups among 36 patients scheduled for elective orthopedic surgery under epidural anesthesia at a tertiary hospital using double-blind randomized controlled trial research design. Data obtained were all analyzed at 5% significance level using the independent t-test since the data distribution was observed to be normally distributed as revealed by Shapiro-Wilk test of normality for the experimental group ($p = .405$) and control group ($p = .408$)

Effect of Clonidine Adjuvant and Control on the Onset of Levobupivacaine Anesthesia in Experimental and Control Groups

Groups	N	Mean	SD
Clonidine	18	5.62	1.14
Control	18	11.33	1.22

Table 1 shows the average time of onset of levobupivacaine anesthesia in experimental and control groups among 36 patients scheduled for elective orthopedic surgery under epidural anesthesia at a tertiary hospital

The descriptive data in table 1 shows the average onset time of levobupivacaine anesthesia in two groups of patients scheduled for elective orthopedic surgery under epidural anesthesia. The experimental group received 15 mL of 0.5% levobupivacaine (Isobaric) with 0.2 mL (30 µg) clonidine as adjuvant while the control group received 15 mL of 0.5% levobupivacaine (Isobaric) with 0.2 mL of 0.9% plain normal saline solution as control. The introduction of 15 mL of 0.5% levobupivacaine among patients in both experimental and control groups has taken effect but the 15 mL of 0.5% levobupivacaine with clonidine as adjuvant showed faster onset time ($M = 5.62$, $SD = 1.14$) than the 15 mL of 0.5% levobupivacaine with 0.2 mL of 0.9% saline solution as control ($M = 11.33$, $SD = 1.22$).

Independent t-Test Result for the Difference in the Mean Onset Time Between the Experimental and Control Groups

	N	t	p
Clonidine	36	14.51	.000
Control Group	18	11.33	1.22

Table 2 shows the difference in the average onset time of levobupivacaine anesthesia between experimental and control groups, $p < 0.05$.

Table 2 reveals the difference in the average onset time of levobupivacaine anesthesia between experimental and control groups. The t-test for the independent samples generated a p-value less than 0.05, hence, statistically, there is a significant difference in the onset time between the experimental and control groups, $t(33.86) = 14.51$, $p = .000$ with an effect size of 4. This suggests that clonidine as an adjuvant hastens the onset time of the 15 mL of 0.5% levobupivacaine anesthesia as compared to the 15 mL of 0.5% levobupivacaine anesthesia with the 0.9% plain normal saline solution as a control.

Effect of Clonidine Adjuvant and Control on the highest sensory block, time of maximum sensory block, two segment regression, and regression to T12 of Levobupivacaine Anesthesia in Experimental and Control Groups

	Highest dermatomal level (Thoracic)	Mean Time to maximum sensory block (Minutes)	Mean Time to two segment regression (Minutes)	Mean Time to sensory regression to T12 (Minutes)
Clonidine group	6	10	176.67	0
Control group	7	17.05	60	60

Table 3 shows the highest dermatomal level and the average times of: maximum sensory block, two segment regression, and sensory regression to T12 of levobupivacaine anesthesia in experimental and control groups among 36 patients scheduled for elective orthopedic surgery under epidural anesthesia at a tertiary level hospital.

Based on this table it can be seen that that clonidine and control group both reached a higher than desired dermatomal level (T10) at T6 and T7 respectively. Furthermore, the time to maximum sensory block was also faster in the Clonidine group. The mean time to two segments regression of the Clonidine group was also longer at 176.67 minutes compared with the control group which was at 60 minutes.

Side Effects Experienced

	Bradycardia (%)	Shivering (%)	Sedation (%)	Hypotension (%)
Clonidine	33.3	11	33.3	0
Control	0	33.3	0	0

Table 4 shows the side effects experienced of patients in the clonidine group vs control group

It can be seen on this table that the most common side effect of clonidine are bradycardia and sedation (assessed by the Ramsay Agitation and Sedation Scale) both at 33.3% and this was followed by shivering at 11%. None of the participants experienced hypotension. However, shivering has a higher incidence in the control group.

Discussion

Onset of Action of Levobupivacaine

Levobupivacaine is the S enantiomer of the widely used Bupivacaine. It has a safer pharmacologic profile with less cardiac and neurotoxic effects. It is considered as long acting with dose-dependent duration of anesthesia. For a 15 ml 0.5% solution, the onset of sensory block is noted at 8-30 minutes. The maximum cephalad

spread is at T7-T8 dermatomal level and duration of analgesia at 4-6 hours.⁹

In this study the mean onset time of levobupivacaine was noted to be 11.33 minutes. The result of this study was faster compared to a study done by Casati, et al.¹⁰ where the onset of action of levobupivacaine, bupivacaine and ropivacaine were compared. Results showed that for a 15 ml of 0.5% levobupivacaine, the onset of sensory block was at 31 +/- 16 minutes, while for 0.5% bupivacaine and 0.5% ropivacaine were at 25 +/- 19 minutes and 30 +/- 24 minutes, respectively.

In another comparative study done by Koch, et al,¹¹ 0.5% bupivacaine and 0.75% ropivacaine, and 0.5% levobupivacaine showed clinically significant equivalent profiles. However, the levobupivacaine group showed more frequent top ups.

CLONIDINE PROPERTIES AS ADJUVANT

The addition of adjunctive agents (epinephrine, opioids or clonidine) to levobupivacaine in epidural anesthesia and analgesia may increase the duration and quality of analgesia, and decrease the volume of local anesthesia.¹²

Clonidine is part of the Philippine National Drug Formulary, hence widely available. It was first used in epidural block in the year 1984.¹³ It is a mixed agonist that stimulates α_1 , α_2 and imidazoline receptors while it has agonistic effects on α_2 receptor.¹⁴ It stimulates α_2 adrenergic inhibitory neurons in the medullary center decreasing the sympathetic outflow from central nervous system to peripheral tissue, and the decrease in the sympathetic outflow causes decrease in blood pressure, heart rate and cardiac output. On spinal cord the activation of postganglionic α_2 receptors in the substantia gelatinosa produces analgesia. Neuraxial

placement of clonidine inhibits the spinal substance P release and the nociceptive neuron firing produced by noxious stimulation. The sedative and anxiolytic effects may be mediated by the postsynaptic α_2 subtype adrenoreceptors located in the locus coeruleus.¹⁵

In this study, the side effects noted with Clonidine were both sedation and bradycardia (20% decrease in the baseline cardiac rate) both recorded at 33.3%. Hypotension was not noted in both groups.

In addition, clonidine also potentiates sensory and motor blockade of epidural and peripheral nerve block administered local anesthetics. Different reasons have been given. First, clonidine has intrinsic ability to block conduction in C and A δ fibers and will intensify conduction block of local anesthetics. Second, clonidine may cause local vasoconstriction and thus impair vascular removal of epidural local anesthetics, and lastly it has been shown that any analgesic, whether neuraxial or systemic, will augment peripheral or spinal blockade. Clonidine also enhances neuraxial opioids, with epidural clonidine and fentanyl interacting in an additive manner.¹⁶

After epidural administration, clonidine is rapidly and extensively absorbed into the cerebrospinal fluid, the concentration peaking at 30-60 minutes after injection. It produces peak concentration in arterial blood within 10 minutes and venous blood within 30-45 minutes.¹⁷

The potentiating effect of clonidine was demonstrated in this study; the clonidine group's highest sensory block was at T6 while that of the control group was at T7. Mean time to maximum sensory block was also faster in the clonidine group 10 minutes while 17.05 minutes in the control group.

Clonidine's Effect on Duration of action

The result of this study showed that there was a longer decrease in two segments dermatomal regression of sensory block in the clonidine group when compared with the control group. The mean time to two-segment dermatomal regression in the clonidine group was 176.7 minutes compared to the 60 minutes in the control group.

Several studies support these findings. In a study done by Arumugan, et al,¹⁹ clonidine at a dose of 2 µg/kg prolonged the duration of epidural analgesia. Pain scale was assessed using the visual analog scale, and result showed that clonidine group had lower pain scale than the control group. The same result was supported by a study done by Prasad, et al¹⁷ the use of 150 µg of clonidine using the epidural route showed a prolonged duration of analgesia as compared to the control group at 299 min vs 152 minutes, respectively. Arumugan, et al¹⁹

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group (P=0.0001). This result is similar to a study done by Alves, et al,²⁰ clonidine 300 micrograms was used as an adjuvant to 0.75% ropivacaine (150mg) and they found out that there was a significant prolongation in sensory and motor block duration (P<0.0001).

This slower regression of the Clonidine group can be explained the clonidine's ability to cause local vasoconstriction and thus slowing the vascular removal of local anesthetics leading to a prolonged duration of action of the local anesthetic.⁸ Slower regression of local anesthetic would imply a less frequent "top up" or addition of local anesthetic, hence lowering the chances of local anesthetic systemic toxicity, and on the economic side a lower cost of operation for the patient.

In this study, no "top up" was done on any patients belonging to the clonidine group until the end of the surgical procedure because the sensory analgesia did not regress to T12 dermatome. Thus, the minimal volume utilization of the local anesthetic.

Clonidine's Effect On Onset of Action

The dosage of Clonidine based on the patient's weight as adjuvant on epidural anesthesia has been studied. In a study done by Gupta, et al,¹⁸ clonidine was used an adjuvant to bupivacaine epidural anesthesia at a dose of 1 µg /kg among patients undergoing total knee replacement surgery, and compared with the control group, the result of their study showed that the clonidine group had faster onset of sensory and motor blockade at 8.23 and 10.26 minutes respectively when compared with the control group, where the onset of sensory and motor blockade was noted at 11.4 minutes and 13.4 minutes, respectively.

This study also showed that there was a statistically significant difference in mean arterial

pressure between the clonidine and control group with the clonidine group having a lower mean arterial pressure. However there were no significant differences in oxygen saturation, respiratory rate and sedation score between the two groups.

In another study done by Arumugan, et al,¹⁹, the dose of clonidine was at 2 µg/kg. The onset of sensory blockade was at 7.8 minutes, while the motor blockade was 10.9 minutes.

A fixed dose of Clonidine regardless of the patient's weight was also investigated. The result of the study done by Prasad, et al²⁶, the use of 150 µg of clonidine showed faster onset of action when added as adjuvant. Hazarika, et al,²¹ did a study using 100 µg clonidine as an adjuvant to 20 ml of 0.5% levobupivacaine anesthesia. This study showed that the onset of sensory blockade and motor block was at 12 minutes versus the control group which was at 26 minutes.

In these studies the onset time of clonidine as an adjuvant to levobupivacaine epidural anesthesia was statistically significant when compared to levobupivacaine alone regardless of the dose given.

In this study, a lower dose of Clonidine was used at 30 µg. It was able to hasten the onset of action of the epidural anesthesia, prolonging its duration of action with minimal side effects comparable to other studies with higher fixed dose and patient's weight-based dosages.

Clonidine versus dexmedetomidine

Clonidine was compared with the newer alpha 2 adrenergic agonist dexmedetomidine. Results showed that both adjuvants have the ability to hasten the onset and prolong the duration of action of levobupivacaine epidural anesthesia. In a study done by Hazarika, et. al,²¹ patients received epidural levobupivacaine 0.5%

20 ml with 100 µg clonidine as an adjuvant. The result showed that the onset of sensory blockade was at 12 minutes, while the onset of motor block was at 26 minutes. This was compared with dexmedetomidine, at a dose of 50 µg added to levobupivacaine 0.5% 20 ml. The result showed that dexmedetomidine had a faster onset of sensory and motor blockade compared with clonidine. The result of this study is further supported by another study done by Bajwa, et al,²² where clonidine at 2 µg/kg was compared with dexmedetomidine at 1.5 µg/kg, dexmedetomidine showed a faster onset of action compared with clonidine. This faster in onset of action of dexmedetomidine is attributed to its greater affinity to alpha 2 receptor.

However, there was higher incidence of nausea, dry mouth, and sedation in the dexmedetomidine group. In terms of cost, dexmedetomidine is significantly more expensive at 2100 PHP per vial compared with clonidine at 104 pesos per ampoule.

Summary, Conclusion, and Recommendations

Summary

The present investigation determined the effect of clonidine as an adjuvant to the onset of action of levobupivacaine epidural anesthesia and if there is a significant difference on the onset of sensory and motor blockade between the experimental and control groups among 36 patients scheduled for elective lower limb orthopedic surgery under epidural anesthesia in a tertiary level hospital using double-blind randomized controlled trial research design. Results showed that the experimental group that has received 15 mL of 0.5% levobupivacaine (Isobaric) with 0.2 mL (30 µg) clonidine as an adjuvant has a faster onset time than the group that received 15 mL of 0.5% levobupivacaine (Isobaric) with 0.2 mL of 0.9%

plain normal saline solution. Furthermore, there is a significant statistical difference in the onset time of levobupivacaine anesthesia between experimental and control groups.

Conclusion

The present investigation proved that clonidine as an adjuvant leads to a significant faster onset time of 15 mL of 0.5% levobupivacaine epidural anesthesia than without an adjuvant. This can allow early commencement of surgery and more patients can be served due faster turnover time at the operating room.

Recommendations

Based on the aforementioned findings, the following recommendations are hereby advanced:

1. Clonidine may be used as an adjuvant for faster onset of action of 15 mL of 0.5% levobupivacaine epidural anesthesia for patients undergoing elective lower limb orthopedic surgery.
2. Clonidine's use as an adjuvant may be investigated in other surgical cases such as those involving the lower abdomen.
3. Other local anesthetic agent such as Ropivacaine and Bupivacaine may be explored
4. Adjuvants other than clonidine may also be investigated such as dexmedetomidine and epinephrine

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Anesthetic Considerations for a Preterm Two-Day Old Omphalopagus Conjoined Twins with Imperforate Anus For an Emergency Procedure: A Case Report*

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ABSTRACT

Conjoined twins are one of the most intriguing malformations in human beings. This report describes the anesthetic management of a two-day-old preterm omphalopagus conjoined twins posted for an emergency diverting colostomy for imperforate anus. These conjoined twins were born to a primigravid via cesarean section for fetal indication. They were born preterm at 36 weeks age of gestation with a collective birth weight of 4.1 kg and an APGAR score 8,9. Computerized tomography scan of the chest and abdomen revealed Omphalopagus twins with left lower lobe atelectasis for Twin 2, fused liver, separate stomach and small intestines with distal fusion, imperforate anus, horseshoe kidney, bladder fistula, and the shared lower extremity appears to derive its blood supply from Twin 1. Evaluation of cross-circulation between the twins was done pre-induction by giving atropine IV to Twin 1. Atropine flush and increase in heart rate were noted in Twin 1, however, were not appreciated in Twin 2. Anesthesia for conjoined twins can be the most daunting and intimidating procedure that an anesthesiologist can handle in his lifetime. We highlight the challenges encountered with anesthesia preparation, preoperative planning, positioning, airway management, preservation of hemodynamic stability, as well as monitoring in an emergency setting.

Keywords: conjoined twins, atropine flush, omphalopagus, cross circulation

INTRODUCTION

Conjoined twins are an uncommon phenomenon worldwide ranging from 1 in 50,000 to 1 in 200,000 live births, with a somewhat higher incidence in Southwest Asia and Africa¹. This condition is more frequently found among females with a ratio of 3:1². About 40% are still born and 60% liveborn, although only about 25% of those that survived to birth lived long enough to be candidates for separation surgery¹. One third of live births who die within the first few days are usually associated with complex anatomical conjunction, multiple congenital anomalies, and different degrees of cross circulation³. In some local context, giving birth to conjoined twins puts a social stigma giving the mother the perception that she delivered monster kids⁴. The occurrence of conjoined twins was initially explained by the fission theory arising from a partial / incomplete separation of the zygote around the 20th gestational day. More recently, the fusion theory has been proposed and is now more generally accepted. During fusion, stem cells find a like stem cells in the other twin and cause them to fuse together. The union of the embryos occurs around the 4th gestational week^{5,2}. Conjoined twins are classified according to the anatomical site of conjunction: 40% for thorax (thoracopagus), 30% for abdomen (xiphopagus and omphalopagus), 18% for sacrum (pygopagus), 6% for pelvis (ischiopagus), and 1-2% for the head (craniopagus)⁵. Thoracopagus, thoraco-

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omphalopagus, and omphalopagus comprise approximately 70% of all conjoined twins². Detailed evaluation of shared organs and associated anomalies is significant for anesthetic management. Here, we describe our experience regarding the successful anesthetic management of omphalopagus conjoined twins posted for emergency colostomy.

Case Description

Two-day-old preterm 36 weeks AOG conjoined twins, Twin FFA boy and Twin FFC boy, born to a 32-year old primigravid via primary cesarean section secondary to fetal indication, with a collective birthweight of 4.1 kg and Apgar Score of 8,9 was posted for an emergency diverting colostomy for an imperforate anus.

Antenatal history showed complete prenatal checkups from the first month of pregnancy up to delivery. 4 months age of, On prenatal check up, the parents were informed of fetal conjunction through an ultrasound. Upon admission for birth, the Main Service informed the Section of Pediatric Surgery for co-management of conjoined twins based on prenatal ultrasound. Immediately after birth, the diagnosis of an imperforate anus was made. The conjoined twins were then formally referred to Pediatric surgery service. Seen by Pediatric surgery service on the 3rd hour of life, Assessment made was complete colonic obstruction secondary to absent fecal outlet. Hence, an emergency diverting colostomy was called. Further diagnostics were ordered which included cranialultraz, baby gram and ct scan of the chest and abdomen. The conjoined twins were also referred to the Anesthesia service for evaluation and anesthetic management.

Physical examination by the Anesthesia service was done on the 17th hour of life. The conjoined twins were noted to be active, with good cry and appeared to be well-hydrated. Vital signs range for Twin 1 – 70/50 mmhg, 140 bpm, 40 cpm,

98% O₂ sat; Twin 2 – 70/45 mmhg, 140 sbpm, 40cpm, 100% O₂ sat. An OGT French 8 was noted to be in place for each twin, no fluid was seen draining from it. The chests were not shared and were noted to have adequate expansion. The lungs had good air entry and with clear breath sounds. Cardiac sounds were distinct, no murmurs were appreciated. The abdomen was noted to be slightly distended, the conjunction was observed to be just above the umbilicus up to the pelvis. There was a single genitalia that was ambiguous, and a shared imperforate anus. Twins have complete upper limbs with no distal limb deformities of the fingers and toes however, one twin has a pair of lower limbs and the other has a fused lower limb located posteriorly.

Assigning which of the twins was Twin 1 and which one was Twin 2, was based on taking the reference of the anesthetist's position on the head part of the operating table. Twin FFA (Twin1) was identified as the one on the left lying laterally on his right side, while Twin FFC (Twin2) was the one on the right lying supine. There was enough space between their faces to allow for intubation.

Umbilical catheter was in place and hooked to D51MB with calcium gluconate. Separate gauge 26 intravenous line was also cited on the upper extremity of each twin and attached to hepllock. No urinary catheter was attached because of ambiguous genitalia. Urine output was assessed by weighing the diaper and approximated at 1cc/kg/hr. There were no episodes of hypoglycemia and cyanosis at the NICU. Due to the urgency of the procedure, both twins were only partially evaluated for the extent of organ sharing as well as the presence of other associated anomalies. Based on perinatal workup, the pedia service assumed a shared circulation between the twins hence only one set of labs was taken. Laboratory results showed acceptable limits for preterm neonates except for leukopenia. Cranial ultrasound was unremarkable. Baby gram result showed a singular

abdominal cavity, while CT scan of the chest and abdomen revealed Omphalopagus twin with left lowerlobe atelectasis for twin 2, fused liver, separate stomach and small intestines with distal fusion, imperforate anus, horse shoe kidney, bladder fistula, and the shared lower extremity appears to derive its blood supply from Twin 1. No angiogram was done.

The twins were then prepared for surgery. Parents' consent was obtained for the surgical and anesthetic plan. The twins were maintained on NPO. One aliquot of 100mL cross matched maternal blood group-packed red blood cells was requested. They were given Ampicillin at 100 mg/kg, Gentamicin at 4 mg/kg and Metronidazole at 0mg/kg. Given the limited time for preparation, the two Anesthesia teams were immediately organized and planned. A dedicated anesthesia team was assigned for each of the twins. Each team consisted of 1 senior resident and 1 junior resident. The two teams were oriented and primed as to the plan and what to anticipate. In addition to the 2 teams, there was a single Team Captain (a pediatric anesthesiologist) who served as the central analyst and integrator of all of the data of the two patients. The monitors and anesthesia workstations were also designated for each twin. Infusion pumps, syringe pumps, as well as suction machines were positioned separately; anesthetic drugs were drawn and aspirated accurately, while emergency drugs were kept readily available. The operating room, the bed, as well as the fluids were warmed. The Pediatric Surgery team was also consulted for their site of incision in order to guide the Anesthetists' positioning of their workstations, for a more fluid flow during the time of operation.

The twins were received at the prewarmed operating room on the 28th hour of life and hooked to standard monitors as per American Society of Anesthesiologists' Basic Anesthetic Monitoring⁶. Even though the monitors and tubings were not color-coded, care was made sure to avoid

entanglement. Vital signs were within normal limits. Peripheral line was patent on the upper extremity of each twin, as well as a central umbilical catheter hooked to a dextrose-containing intravenous fluid with calcium gluconate incorporation. Patency of all indwelling catheters and lines were checked prior to induction. The anesthetic plan was general endotracheal anesthesia. The twins were preoxygenated using Jackson Rees modification of the Ayre's T-piece. Since both twins were similar in size, for estimation of fluid and blood replacement as well as calculation of drug dosage to be given, the weight used for Twin 1 was 2kg, similar to Twin 2. Evaluation of the extent of cross-circulation between the twins was assessed by giving atropine 0.1mg IV to Twin 1 via the umbilical catheter. Atropine flush and increase in heart rate were noted in Twin 1, however, were not appreciated in Twin 2, partially ruling out cross-circulation but still on continued vigilance for unexpected depression of Twin 2. Hence, a sequential general endotracheal anesthesia induction was planned. Umbilical catheter was removed, main lines shifted to peripheral line for each twin and hooked to D5IMB with calcium gluconate incorporation. Twin 1 was then positioned for induction by placing a shoulder roll and the body shifted slightly to the left for better ventilation, while Twin 2 was supported with linen paddings. After positioning, Twin 1 was given fentanyl at 2mcg/kg IV, then sevoflurane was started at 1-2 MAC. Preparation for muscle paralysis of Twin 1 was facilitated upon an N-PASS (Neonatal Pain, Agitation, Sedation Scale) of -2 and after confirmation of ease of gentle manual ventilation, atracurium 0.5mg/kg IV was given thereafter. During intubation, Twin 2 was lifted a little higher over Twin 1 for better airway access. Intubation of Twin 1 was uneventful. Sequential induction of Twin 2 proceeded at the same doses of drugs as Twin 1. Intubation of Twin 2 did not need Twin 1 to be lifted because the former was already positioned supine. However, care was taken not to accidentally extubate Twin 1 while attempting to intubate Twin 2. Two attempts were made on

intubation of Twin 2 because of a change to a smaller uncuffed endotracheal tube size from 3.5 to 3. No desaturation, cyanosis, hypotension, nor bradycardia was observed during induction of both twins. Thereafter, Ultrasound-guided central venous access was performed on both twins – Left internal jugular vein for Twin 1, and the Right internal jugular vein for Twin 2. This was hooked to Sterofundin for fluid shift replacement.

Maintenance of anesthesia was carried out using 50% oxygen, 50% medical air, and 1-2 MAC sevoflurane. Intraoperative Vital signs range of both twins were as follows: Twin 1 70/40 mmhg, 145 bpm, 35 cpm and 100% O₂ sat; Twin 2 65/40 mmhg, 149bpm, 35 cpm, 95% O₂ sat. The twins were kept warm all throughout the procedure. Active forms of heat transfer were applied. Blood glucose was monitored hourly intraoperatively and showed normal results. The monitoring of urine output was not really accurate because no urinary catheter was inserted due to the ambiguous genitalia. However, urine output was estimated based on the spillage on the under pad.

Surgery was uneventful and was concluded after two hours. On discontinuation of sevoflurane, the twins were later noted to have active movement of extremities, with good respiratory effort and volume. There was good air entry and breath sounds were clear. They were eventually safely extubated. Total duration of surgery was 2 hours, while total anesthesia time lasted 4 hours. Blood loss was estimated to be less than 5mL. Total amount of fluids given for Twin 1 was 100cc (12.5cc/kg/hr) and for Twin 2 was 80 cc (10cc/kg/hr). Total urine output was estimated at 1.3cc/kg/hr. They were transported back to NICU after the procedure, both were stable and with maintenance of thermo regulation on transport. They were given paracetamol IV at 7.5 mg/kg/dose each and were continued every six hours for two days. Rescue dose of nalbuphine at 0.2mg/kg IV as needed every 6 hours was ordered for each

twin for restlessness and incessant crying. The final procedure done was Exploratory laparotomy, ileostomy with distal mucus fistula, ultrasound-guided central venous access left internal jugular vein, Twin 1, and right internal jugular vein, Twin 2.

Monitoring for desaturation, hemodynamic instability and hypothermia were continued in NICU. Blood sugar was checked periodically. Hypoxemia, electrolyte imbalance, and acidosis were evaluated through serial blood gas. Describe the stay in NICU – Was nalbuphine rescue given, how many doses? How long was NICU stay, were there any problems encountered in NICU? What were the labs requested in NICU? How many days did the twins stay in the ward? On what postoperative day were the twins started on feeding? On what postop day were they finally sent home?)

DISCUSSION

Anesthetizing conjoined twins present several challenges to the anesthesiologists. While there is a number of data regarding the management of conjoined twins for elective surgery, we found paucity of literature of conjoined twins for an emergency procedure. Our case is one of emergent non-separation surgery.

The preparation of conjoined twins for an emergency procedure is nothing different from that for an elective. Because of the rarity and complexity of the case, an elaborate understanding of its pathophysiology should be obtained in order to anticipate potential problems, and prepare for its management. Additional pressure is put on the needs of not only one, but two neonates who are especially preterms, just like in our case. They are often delivered preterms because obstetric intervention is planned around the 36-38 weeks of gestation, once the pulmonary maturity has already been achieved, avoiding a complicated vaginal delivery or an emergency cesarean section. Emergency cesarean

procedures have a mortality rate of 70% versus 20% of the electives^{5,7}.

Careful and meticulous planning is vital because of the complexity associated with organ sharing, cross-circulation, as well as the presence of other congenital anomalies. In our case, time constraint was a limiting factor - The work-up was limited, the planning was short, and no practice rehearsal was done before the procedure. However, it did not affect the outcome of the procedure. As per The American Society of Anesthesiologists, the Risk Classification for these preterm conjoined twins were 4E, which means an absolute mortality rate of 7.8-25.9% plus 0.001-0.026% risk for postoperative complications for an emergency surgery⁸.

Cardiorespiratory insufficiency is the main cause of immediate death⁵. Thus, Anesthesia preparation is indispensable. A duplicated supply of equipment such as anesthesia machines, medical air, suctioning and scavenging systems, and monitors should be available. The anesthesiologist should be prepared for multiple changes in positions, ET tube must be secured as well as arterial and venous lines for large fluid shift procedures. Care should be taken to avoid disconnection of monitoring lines as well as entanglement of IV lines leading to cross-dosing of drugs-which is why color-coding of tubings and monitors is ideal. We were not able to do this, however, we made sure that all the lines were fixed and organized in reference to the patient's body. Analgesics, anesthetic agents, muscle relaxants as well as emergency drugs should be prepared for each twin. Operating room should be arranged based on the type of conjoined twins to be operated on. In our case, two anesthesia machines were arranged on the head part of the twins, one on each side of the operating room table. Lastly, controlling the environment of the operating room is essential, noise and congestion should be limited both for the patients and the medical team's

interest. Room temperature should also be regulated between 24-26C⁵. These challenges should be discussed with pediatric surgeons and with the neonatologist^{5,6}.

Difficult airway management is one of the anticipated potential problems encountered during the perioperative period. In non separation procedure, airway difficulties are more common in twins who are conjoined high on the chest, when their faces are facing each other or when there is hyper extension of the head and neck with exaggerated lordosis. In ample time such as in elective procedure, a mock drill and simulation is usually done a day ahead of surgery which involves stitching two dolls at the same site of conjunction seen in the conjoined twins. This is in order to increase the confidence of the anesthetist, and to avoid confusion and mismanagement on the day of surgery³. We were not able to do this because of the emergency nature of surgery. However, we did not encounter extreme difficulty during ventilation and intubation because their chests were not fused, so there was enough space in between their faces to maneuver. Access to their airway was also improved when proper positioning was done. Caution for auto transfusion was performed during lifting of Twin 2 over Twin1⁵. Signs of hypo volemia in Twin 2 such as increase in heart rate and poor pulses were, however, not observed.

As to blood loss, the type of fusion that is commonly associated with extensive blood loss is the thoraco pagus or ischiopagus twins. They require blood transfusion between 10% and 450% of estimated blood volume especially in separation surgery involving hepatic fusion⁵. There is more extensive blood loss when there is greater fusion of organs. Cross matching of blood products is vital especially for separation surgery. Maintaining hemodynamic stability is essential during the surgical procedure. Blood loss assessment can be done by aspirating the volume of the operative field, checking for hematocrit variation, and

weighing of surgical gauzes. When there is circulatory communication there is no need to separately estimate the blood loss of each twin, as the volume and hematologic variation are shared⁵. Cross circulation is seen more often in craniopagus and thoracopagus twins^{9,10}. Drug pharmacokinetics and pharmacodynamics are dependent on cross circulation¹⁰. This can be seen when an anesthetic agent administered in Twin 1 may have altered and unpredictable response in Twin 2^{3,11}. Cross circulation also poses a risk of major bleeding during separation surgery¹⁰. In our case, there was no large fluid shift because our omphalopagus twins underwent a non-separation surgery and blood loss was only less than 5 mL.

Normothermia is another challenge in large neonatal surgeries. Drop in central temperature is expected because of the thermal self-regulation breakdown caused by the anesthesia, especially in the first hours due to heat redistribution. The unique physiology of these neonates pose additional clinical implications and challenges to the anesthesiologist: they have thin skin with large surface area which predispose them to rapid heat loss and hypothermia. In addition, a cephalic and more anterior glottis, poorly compliant lung, easy fatigability of the respiratory muscles, heart rate-dependent cardiac output, as well as hepatic and renal immaturity. The organ systems are not mature, the heart is not prepared for hypervolemia or hypovolemia. The kidney has difficulty retaining sodium under stress and there is tubuloglomerular imbalance, with urine concentration difficulty. The liver has not yet developed mechanisms for drug metabolism. The concentration of albumin and alpha1-acid glycol protein that bind to drugs is small which predisposes to a higher percentage of free drugs⁵. All these complicate the management of neonates, more so preterm conjoined twins.

In our case, we attribute the success to multiple factors: 1. The good medical status of the twins apart from the fact that they were conjoined,

however, they had no congenital cardiac lesions which could pose additional problems hemodynamically; 2. The surgery was straightforward, it did not take long, and did not require changes in positions, which could otherwise have clinical implications in terms of monitoring, airway maintenance, and blood loss; 3. The knowledge and skill of the team captain pediatric anesthesiologist having had clinical experience with two separation surgeries in the past and one of which involved hepatic fusion with a good outcome; 4. The skill, vigilance, and coordination within the team and between the teams of the two anesthesia teams in handling neonates.

All these cumulative factors have played significantly toward the success of the procedure. Therefore, it cannot be over emphasized that the key factor in the success of surgery for conjoined twins lies in the multidisciplinary team approach with meticulous preoperative planning, perioperative vigilance, and interdisciplinary communication.

CONCLUSION

Anesthetizing conjoined twins is demanding and complex. Hence, it cannot be overemphasized, that the key factors in success lies in the multidisciplinary team approach with meticulous preoperative planning, perioperative vigilance and interdisciplinary communication.

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Table and Figures

Figure 1: Conjoined twins at the Operating Room



Figure 2: Double setup prepared for the operation of the conjoined twins



Figure 3: Preoperative laboratory results

CBC	
HEMOGLOBIN	153g/l
HEMATOCRIT	0.46
WBC	5.61x 10 ³ /ul
PLATELET	140
PT	22.5
INR	1.7
%ACT	47%
APTT	75.5
CHEMISTRY	
NA	142g/l
K	3.6 mmol/l
CA	1.8 mmol/l
MG	0.56 mmol/l
CREATININE	44 umol/l

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Triple Valve Surgery in a Patient with Rheumatoid Arthritis*

Cassandra P. Lao, MD¹

ABSTRACT

Rheumatoid arthritis is a multisystem disorder that affects not only the musculoskeletal system but also other vital organ systems. This report tackles a case of a Filipino adult female with a 28-year history of rheumatoid arthritis on chronic DMARD and steroid use who developed symptoms of heart failure. This report will review the perioperative implications of a patient with rheumatoid arthritis for triple valve surgery.

Keywords

Triple Valve Surgery, Rheumatoid Arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a multi-system autoimmune disease characterized initially as an erosive, symmetrical polyarthropathy which may also affect the function of other organs in the body.¹ The prevalence of RA in industrialized countries is 0.5-1%.⁷ In a state of chronic systemic inflammation, patients with rheumatoid arthritis are predisposed to the development of heart disease including accelerated atherosclerotic disease and valvular lesions.⁷ Compared with persons without RA, those with RA have twice the risk of developing heart failure not explained by traditional cardiovascular risk factors and ischemic heart disease.²

We present a case of a Filipino adult female with RA who presented with symptoms of heart failure and was assessed with severe mitral and aortic regurgitation and moderate tricuspid regurgitation who underwent aortic and mitral valve replacement with tricuspid valve annuloplasty.

In RA patients undergoing surgery, multiple perioperative concerns are taken into consideration when planning for anesthetic management.

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

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¹3rd Place, PSA Interesting Case Oral Presentation 2023

OBJECTIVES

In presenting this case, we aim to discuss the preoperative preparation, intraoperative and postoperative management of an RA patient with multivalvular heart disease.

CASE DESCRIPTION

Background

The patient is a 47-year old female known to have rheumatoid arthritis since 1995, initially presenting as hand and joint pains. She has been on treatment since then, and has regular consults with her rheumatologist. She was maintained on Prednisone, Methotrexate, Paracetamol and Celecoxib as needed for pain. She underwent bilateral hip and knee arthroplasty due to avascular necrosis and knee contractures. Atorvastatin was being given for atherosclerotic heart disease, coronary artery disease, while Losartan was given for hypertension.

Two months prior to admission, the patient experienced progressive bipedal edema, with exertional dyspnea, three pillow orthopnea, and decreased appetite.

One month prior to admission, she was diagnosed with cellulitis on the right thigh, with progression of bipedal edema. Further workup was done which lead to the diagnosis of heart failure with preserved ejection fraction, severe mitral and aortic regurgitation. The patient was admitted for treatment of cellulitis and during the same admission, was advised to undergo valvular repair or replacement.

On admission, examination revealed moon facies, limited extension, flexion and rotation of the neck, mouth opening measuring less than 3 fingerbreadths, Boutonniere deformity of the second to fifth digits of the hands, inability to extend wrists, limited lower extremity movement with muscle atrophy.



She weighed 48 kg with a BMI of 18. A circumscribed erythematous lesion over the right medial thigh was seen.

Preoperative Tests

CBC was normal. Serum sodium was 134 and potassium was 3.15. ESR was 14. Prothrombin Time was 14.3, INR was 1.2, and aPTT was 34.8.

2D Echo showed an ejection fraction of 56%, mitral valve prolapse, anterior mitral valve leaflets with severe mitral regurgitation, concentric left ventricular hypertrophy with adequate wall motion and contractility and preserved systolic function with Gr. 3 diastolic dysfunction, normal resting ventricular systolic function, biatrial dilatation with no evidence of thrombus, aortic sclerosis with moderate to severe aortic regurgitation, dilated mitral annulus with severe mitral regurgitation, moderate tricuspid regurgitation, mild pulmonic regurgitation, high probability of pulmonary artery hypertension.

12 lead ECG showed sinus rhythm, left axis deviation, left ventricular hypertrophy with strain or ischemia, and lateral wall ischemia.

Coronary angiogram revealed normal coronary arteries.

Preoperative Preparation

Prior to the day of surgery, the patient's condition was optimized to decrease the risk of morbidity and mortality perioperatively. Multidisciplinary juntas were conducted. Cellulitis on the right thigh caused by MRSA was treated with Clindamycin prior to surgery. The patient underwent dental extraction and clearance due to multiple infected teeth. Electrolyte imbalances were corrected accordingly. The patient was started on Enoxaparin while Prednisone, Atorvastatin and Losartan were continued. She was assessed then to have RA with low disease activity.

The patient was eventually given the following risk stratification: high risk for perioperative cardiovascular events, low risk from dental standpoint, no objection from Infectious Diseases and Rheumatology. For anesthesia, the patient was identified to have a difficult airway and invasive line insertion is expected to be difficult due to her deformities.

Preoperatively, the patient was kept on NPO for 8 hours prior to surgery. Enoxaparin and losartan were discontinued 24 hours prior. Omeprazole 40mg tablet was given prior to NPO status. Two units pRBC, 2u FFP, 4u PC, and 4u cryoprecipitate were reserved for intraoperative use. The anesthesia plan was combined general endotracheal anesthesia with intravenous anesthesia.

Intraoperative Course

Pre-Induction:

The patient was wheeled in with oxygen support and was hooked to standard ASA monitors. Cerebral oximetry and BIS monitors were placed prior to invasive line insertion. After adequate sedation with Midazolam, Nalbuphine and Fentanyl, invasive lines and monitors were inserted with ultrasound guidance. Large bore IV catheters were not placed on the extremities due to thin, fragile

skin and vasculitis. Due to hand deformities, the radial arteries were inaccessible for arterial line placement. The arterial line was placed at the right femoral artery. A central line was placed on the right femoral vein while a right IJ vein catheter with pulmonary artery catheter was inserted for pulmonary artery pressure monitoring. Patient had moderate PAP with initial mean reading of 36 mmHg. During placement of these lines, vital signs were maintained as follows: BP was 120-130/45-55, HR was 75-80, and RR 16-20. Dexamethasone 10mg/IV was given to prevent post-operative nausea and vomiting.

Induction:

Midazolam 4 mg/IV, Nalbuphine 8 mg/IV, Tranexamic acid 1 g/IV, and Fentanyl 400mcg/IV were given for induction of anesthesia. Induction medications were titrated carefully with guidance of BIS monitor to achieve adequate level of anesthesia while avoiding severe bradycardia and hypotension. Endotracheal intubation using a 7.0mm cuffed tube was performed smoothly under videolaryngoscopy using D-blade on first attempt while avoiding external manipulation of the neck.

Intraoperative Course:

A combination of Sevoflurane and Propofol infusion were used as maintenance while an infusion of Rocuronium was used. Tranexamic Acid infusion was also started prior cutting. TEE assessment was done prior to heparinization and initiation of CPB, which was uneventful. Aortic valve replacement, mitral valve replacement, tricuspid valve annuloplasty, and closure of patent foramen ovale were done. Total bypass time was 3 hours and 48 minutes, and aortic cross clamp time was 3 hours and 24 minutes.

Post valve replacement intraoperative TEE showed an EF of 55%, hypokinetic septum, base to apex, MV and AV were noted to have good opening and closing and without paravalvular leak.

Weaning off bypass was smooth and was unremarkable with titration of Dobutamine, Milrinone, and Norepinephrine. Heparin reversal was done with protamine and transfusion of the following were given: 1 packed RBC, 4 units of cryoprecipitate, and 4 units of platelet concentrate. After the surgery, the patient was given a bilateral parasternal and serratus anterior plane block with Bupivacaine 0.125% 20 mL per site of injection for pain management.

Postoperative Course:

Postoperatively, the patient was monitored at the ICU and was successfully extubated on day 1 post op. Her postoperative course was complicated by HAP which was successfully treated with antibiotics. Three weeks after the surgery, patient was eventually discharged stable.

DISCUSSION

Rheumatoid arthritis is a chronic, autoimmune, and inflammatory disease characterized by symmetric polyarthropathy and diverse systemic effects³ affecting approximately one percent of the population.⁴ Several factors should be considered to ensure safe and effective perioperative management.

Comprehensive preoperative assessment is crucial in patients with RA. It should include documentation of symptoms related to organ systems involved with detailed examination of the neurologic, airway, pulmonary and cardiovascular systems. Baseline level of function, disease severity and associated complications should be determined. A review of medications is done to determine possible interactions with anesthetic drugs. It may be necessary to withhold drugs prior to surgery including immunosuppressants like biologic DMARDs and TNF inhibitors, B cell inhibitors, and IL-6 inhibitors which predispose patients to infections.⁵ All possible sources of infection were controlled including dental infection. Psychological

preparation was done by explaining in detail what to anticipate intraoperatively and postoperatively, including invasive monitors, planned extubation, risks and possible complications. Questions were encouraged to promote understanding of the procedure.

Several potential complications may be seen in RA. Cardiovascular involvement may present with atherosclerotic disease, coronary artery disease and myocardial infarction, pericarditis, and valvular heart disease.⁶ If indicated, coronary angiography may be done in addition to ECG and echocardiography such as in the case presented.

Pulmonary manifestations include restrictive disorders and pulmonary fibrosis which can reduce forced vital capacity and forced expiratory volume. With progressive lung injury, hypoxemia and reduction in gas exchange can be seen.⁶ In this patient, incentive spirometry was started preoperatively to prevent postoperative pulmonary complications.

In the absence of nephrotoxic medications, more than 40% of RA patients have renal dysfunction. Significant renal disease is more common in those undergoing therapy with nephrotoxic effects.⁶ Determination of renal function allows for adjustment of anesthetic medication doses. The patient had a normal level of creatinine and eGFR.

RA may involve the temporomandibular joints and cricoarytenoid cartilage leading to limited mouth opening and hoarseness. Spine involvement can lead to cervical instability.¹ RA affects the atlanto-axial joint due to attenuation of the transverse ligament and erosion of the odontoid peg hence patients may present with a difficult airway.⁸ When acute subluxation occurs due to improper handling of the patient, spinal

cord and vertebral artery compression may occur leading to quadriparesis or death. Induction of anesthesia must be properly planned, with preparation of materials for difficult airway intubation. During induction of anesthesia in this patient who had inadequate thyromental distance and mandibular length, Mallampati score of 3, and limited neck mobility, careful intubation with a videolaryngoscope was done with the head in the neutral position, with a fiberoptic endoscope on standby. Common positioning techniques for intubation such as the sniffing position were not done.

Positioning of the patient during surgery should be done carefully to prevent joint and nerve injury. Pressure points were padded.

Cardiopulmonary bypass can cause an acute inflammatory response leading to significant morbidity and mortality due to contact activation of blood by surgical wounds, and synthetic perfusion circuits.⁹ In a state of chronic inflammation, a short bypass time is required to prevent the development of SIRS.

The goals of anesthesia are to maintain contractility, reduce afterload, maintain normal volume, and reduce pulmonary artery pressures because severe MR and AR with moderate TR patients cannot tolerate bradycardia, high afterload, reduced preload and increased pulmonary pressures.

Postoperatively, observation of the airway and breathing are required after extubation due to possible airway obstruction from unrecognized glottic stenosis. Adequate pain control prevents delayed mobilization, thromboembolism, and infections.¹ In this case, a peripheral nerve block was done to reduce the need for multiple systemic pain medications.

Considering all these, tailoring the anesthetic perioperative plan to the patient's needs, disease severity and complications is crucial for achieving favorable surgical outcomes.

CONCLUSION

Rheumatoid arthritis puts the patient at higher risk for morbidity and complications perioperatively. Anesthesiologists must aim for patient optimization achieved with multidisciplinary teamwork before surgery in RA patients, whose primary disease has multi organ effects. Due to multiple musculoskeletal deformities, the anesthesiologist must be careful to prevent further insult in a patient undergoing major surgery, especially during anesthesia induction, airway management, introduction of invasive lines. All medications must also be reviewed to determine whether they may be continued intraoperatively and whether these medications may have interactions with anesthesia management.

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Tenacious Tumors: Basal Cell Nevus Syndrome in a 50-Year-Old Filipina*

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INTRODUCTION

Basal cell nevus syndrome is a rare autosomal dominant disorder with a prevalence of between 1 in 60,000 to 1 in 120,000. This disorder is associated with a panoply of phenotypic abnormalities that includes developmental anomalies and tumors particularly basal cell carcinoma. The genetic abnormality in almost all known cases is a mutation in the *PATCHED1* gene which is essential for normal body and limb patterning.^{1,2}

We report a 50-year-old Filipina who suffered from multiple recurrent pigmented papules, plaques, nodules, and tumors on the face with the first tumor appearing at age 20.

Case Presentation:

This is a 50-year-old Filipino female who presented with multiple tumors on her face. Thirty years prior to consult, at age 20, a black "mole" appeared on her right cheek. Initially marble-sized, it continued to enlarge for 3 years. Attributing its growth to sun exposure and manipulation, she would notice some scaling and bleeding on some occasions. An excision biopsy of the mass revealed basal cell carcinoma. The wound defect would require skin grafting.

Nine years prior to consult, gradually enlarging "moles" arose on her left cheek and forehead. After a year, these tumors grew with radial enlargement and increase in height. She underwent another skin excision and grafting. The biopsy had the same finding.

Two years prior to consult, she grew "moles" on her nose and left upper lip which both had a ring of redness. These eventually drained purulent discharge and had some crusting. A year prior to consult, multiple "moles" grew on her face, including the left lower eyelid. This eyelid tumor would cause her pain whenever she would open her eye.

Except for her mother who was diagnosed with basal cell carcinoma, she had an unremarkable medical history.

Examination revealed multiple black, variously-sized papules, plaques, nodules and tumors on the face with some lesions forming crusts (Fig. 1). Both hands showed palmar pits (Fig. 2). Dermoscopy of the lesions displayed blue-gray non-aggregated globules, large blue-gray ovoid nests, and arborizing telangiectasias (Fig. 3). The skin punch biopsy revealed findings consistent with basal cell carcinoma (Fig. 4). Chest x-ray (Fig. 5) showed a bifid left 3rd rib.

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

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Figure 1. (a) and (b) Multiple, black, firm, shiny, smooth, and round papules, plaques, and tumors with measurements ranging from 0.5 x 0.5 cm to 1.5 x 1.5 cm scattered over the face; (c) Solitary black, firm, and dome-shaped tumor measuring 3 x 4 cm on the left upper lip, with a crater and yellowish crusts

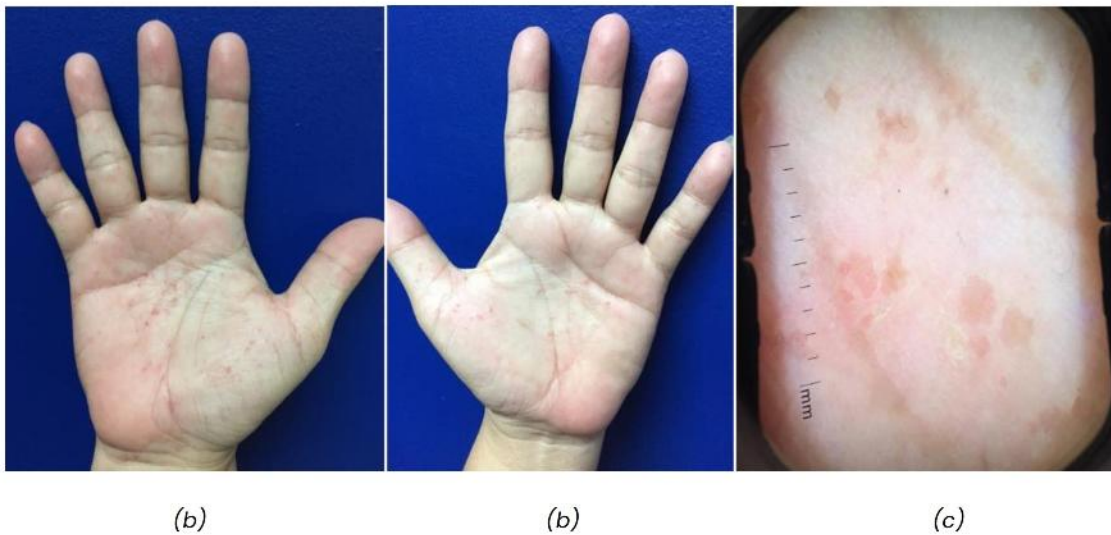


Figure 2. (a) and (b) Florid palmar pits; (c) Dermoscopy of palmar pits

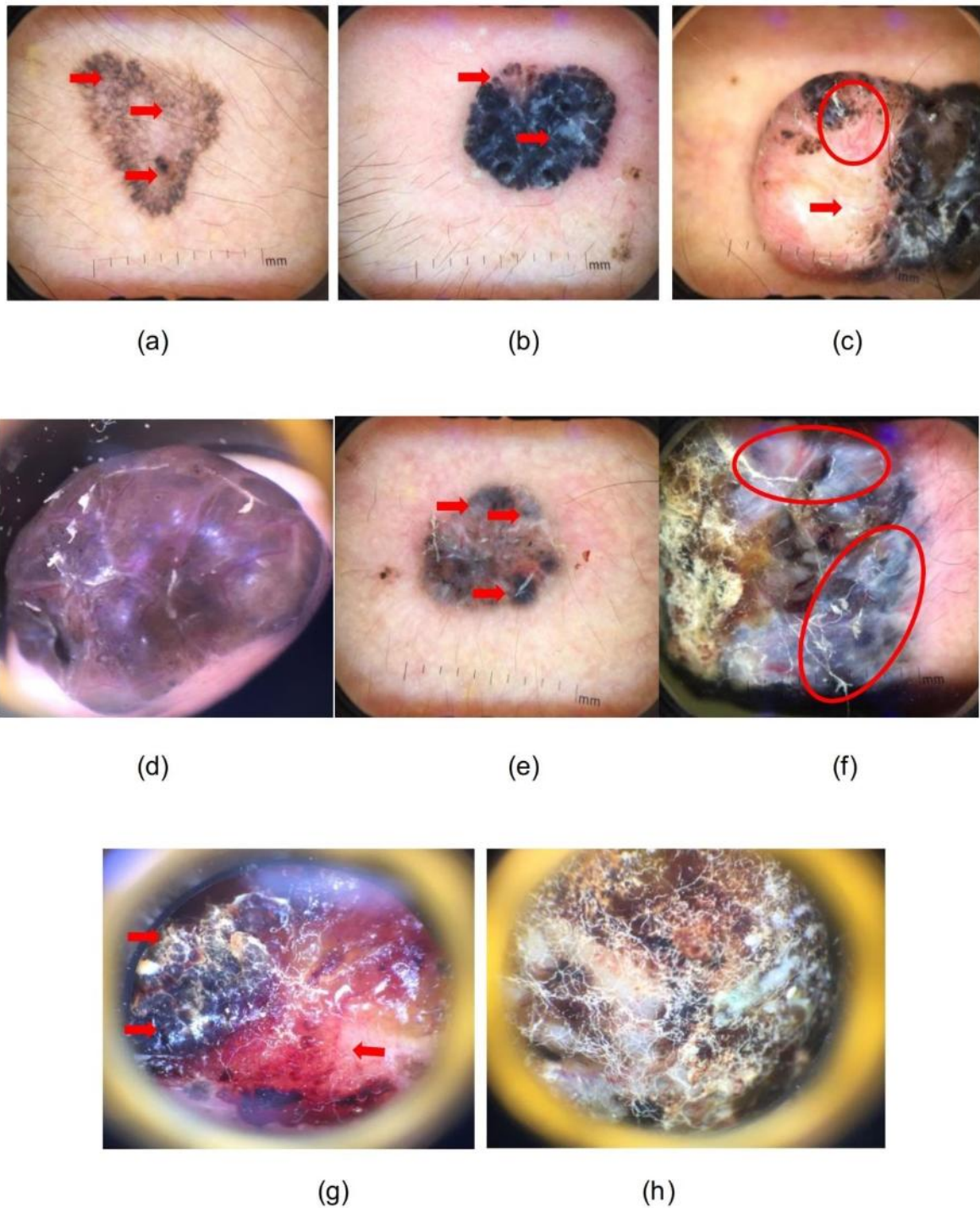


Figure 3. Dermoscopy of the lesions: (a) and (b) blue-gray non-aggregated globules and large blue-gray ovoid nests; (c) arborizing telangiectasias; (d) and (e) blue-gray ovoid nests; (f) blue-white veil; (g) and (h) ulceration and crusts

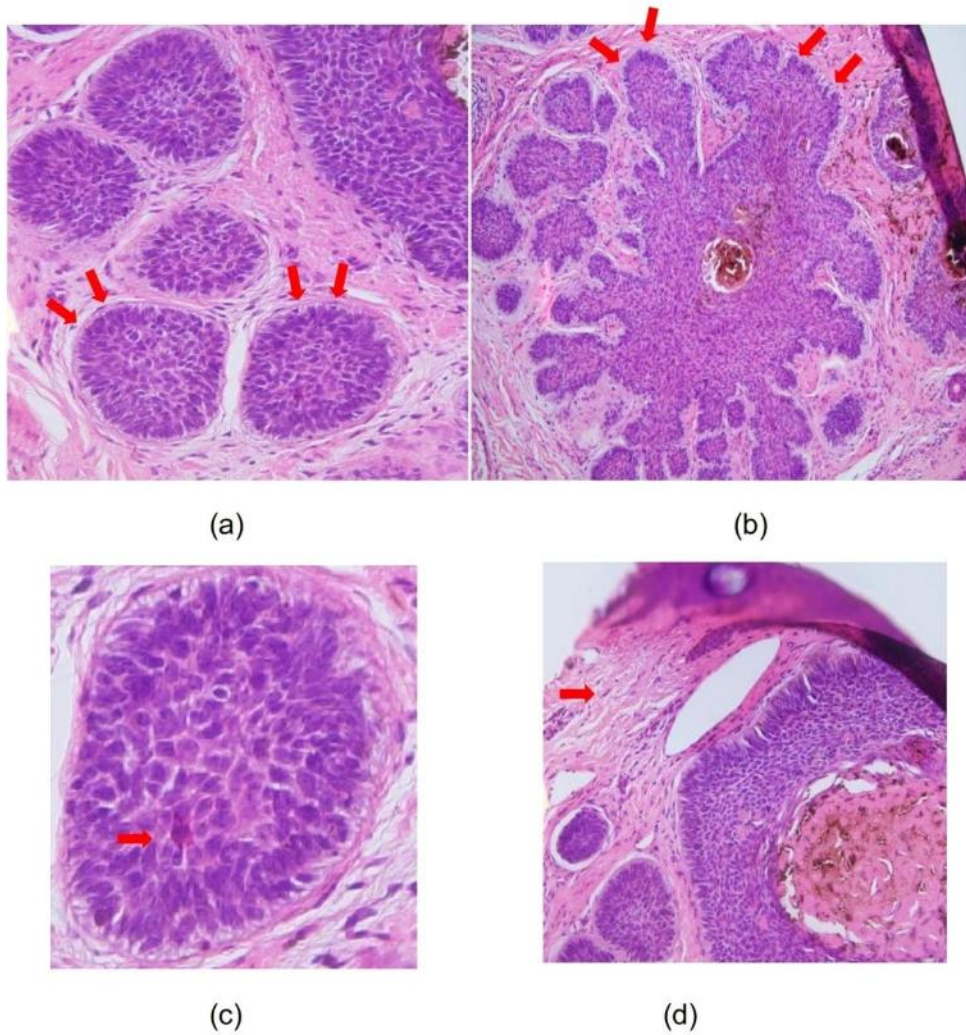


Figure 4. Histopathology: (a) and (b) islands of tumor cells showing peripheral palisading; (c) mitotic figures and (d) clefting artifact between the epithelium and the stroma



Figure 5. Chest X-ray: bifid 3rd rib, left.

She was referred to the ophthalmology service and subsequently underwent excision of the left lower lid tumor with complex reconstruction and skin grafting (Fig. 6a). Four months

after, she underwent excision (Fig. 6b) of the remaining tumors on her face done by otorhinolaryngology-head and neck surgery service. She had an uneventful recovery.



(a)



(b)

Figure 6. Post-operative photos showing: (a) The patient after undergoing excision of left lower lid tumor with complex reconstruction and skin grafting and; (b) post- excision of multiple basal cell carcinomas on the face still covered with gauze.

DISCUSSION

Basal cell nevus syndrome (BCNS) is a rare autosomal dominant disorder showing high penetrance and variable expressivity. It is caused by a mutation of the *PATCHED1* tumor suppressor gene resulting in uncontrolled upregulation of the Sonic Hedgehog pathway and carcinogenesis.⁷

The disease is characterized by multiple basal cell carcinomas (BCC) of the skin, skeletal abnormalities, palmar and/or plantar pits, bifid ribs, ectopic calcification of the falx cerebri, and multiple keratocystic odontogenic tumors in the jaw. The last two that were mentioned were not seen in our patient. Because of the variety of systemic symptoms, early diagnosis in most cases may be difficult.⁴

The Philippine Dermatological Society reported only 9 cases of BCNS in the Philippines from

a 7-year registry (2011-2017).⁶

Eyelid BCCs are the most common ocular finding in BCNS. Aside from eyelid BCCs, these tumors may arise on the neck, chest, back, arms and elsewhere on the face. Eyelid lesions are often multiple and generally start to appear in the post-pubertal period, usually by age 35. However, their indolent nature can result in considerable delay in diagnosis and local recurrences are common.³

BCC subtypes share common histologic characteristics: malignant basal cells with large nuclei and relatively little cytoplasm, absence of mitotic figures, and a slit-like retraction of the stroma from tumor islands, creating peritumoral lacunae.² Our patient's biopsy showed islands of tumor cells with prominent palisading pattern.

Evans and Kimonis et al formulated the criteria for diagnosing BCNS. The major criteria are the following: 2 or more BCCs, keratocystic odontogenic tumors in the jaw, 3 or more palmar and/or plantar pits, bi-lamellar calcification of the falx cerebri, and family history. The minor criteria are bifid ribs and various skeletal abnormalities. To diagnose BCNS, 2 major criteria or 1 major and 2 minor criteria must be present.⁴ Our patient had multiple BCCs, a parent with BCC, palmar pits, and a bifid rib satisfying the diagnosis of BCNS.

The burden of BCNS lies with the recurrent nature of BCCs on the face and/or odontogenic tumors and its impact on quality of life.⁵

Vismodegib is an oral sonic hedgehog pathway antagonist approved in 2012 by the US Food and Drug Administration for metastatic, locally advanced, or inoperable BCC.⁷ Its high cost made it inaccessible for our patient.

The BCC's anatomic location determines the approach to therapy. Treatment includes standard surgical excision, Mohs micrographic surgery, destruction by various modalities, and topical chemotherapy. The best chance to achieve cure is to adequately remove the primary tumor. Surgery and radiotherapy appear to be the most effective treatments with surgery having the lowest failure rate. Standard surgical excision offers the advantage of histologic evaluation of the removed specimen compared to non-surgical techniques. Our patient underwent standard surgical excision.

Non-surgical approaches may be aggressively pursued in a BCNS patient. The key is to convince the patient to accept frequent treatments. Minimization of discomfort and prevention of scarring are major goals.¹

CONCLUSION

This rare case illustrates how a case of BCNS was diagnosed through the recognition of distinctive clinical, histopathologic, and radiologic

findings: BCCs at a young age, a parent with BCC, biopsy findings, palmar pits, and a bifid rib. BCNS should be suspected in a patient who has multiple and recurrent BCCs starting at a young age

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A Case of Pemphigus Foliaceus in a 40-Year-Old Female Successfully Treated with Doxycycline and Prednisone Combination Therapy*

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Mae Ramirez-Quizon, MD, FPDS²

Here, we present a 40-year-old female with multiple pruritic occasionally painful vesicles, papules, and plaques in a circinate pattern on seborrheic areas, progressing to erosions and scales. Clinical findings led to the diagnosis of pemphigus foliaceus (PF). Initial treatment with prednisone and clobetasol ointment, however, did not fully suppress blister formation and healing of erosions. Skin punch biopsy revealed a subcorneal split and intracorneal neutrophilic infiltrates, while enzyme-linked immunoassay (ELISA) revealed elevated anti-desmoglein 1 (Dsg1), consistent with PF. Doxycycline was then added to the previous regimen, resulting in remission. We discuss the role of doxycycline as a cost-effective adjunctive treatment in patients with refractory PF.

INTRODUCTION

Pemphigus foliaceus (PF) is an autoimmune blistering disease (AIBD) mediated by autoantibodies targeting Dsg1 responsible for cell-to-cell adhesion of keratinocytes in the upper epidermis [1,2].

PF is characterized by flaccid vesicles on seborrheic areas. However, examination more often reveals scaly or crusty erythematous

patches, plaques, and erosions with cornflake scales. The lack of blisters and mucosal involvement lead to diagnostic delay as this may be misdiagnosed as eczema, seborrheic dermatitis, or psoriasis [2]. Histologic examination may not be enough and DIF, ELISA, and/or indirect immunofluorescence (IIF) may be used to aid diagnosis.

No optimal therapeutic approach has been established for pemphigus. Glucocorticoids remain as cornerstone in treatment, and may be used in combination with other immunomodulatory therapies such as rituximab, azathioprine, or mycophenolate mofetil. However, present literature supports that combined therapies have not been shown to be more effective than glucocorticoids alone. Unfortunately, as therapy is prolonged, numerous drug-induced side effects can occur, many of which are serious. Moreover, most steroid-sparing agents available are expensive and not widely available especially in third world countries like the Philippines [1,3,5].

Contrary to present evidence-based data, this case initially did not have complete remission to monotherapy with prednisone but responded well with the addition of doxycycline.

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

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CASE REPORT

A 40-year-old Filipino female presented with a 2-year history of multiple flaccid vesicles, erythematous papules, plaques, patches, erosions as well as whitish scales on the trunk, face and extremities. This was perceived by the patient to be exacerbated by stress and not triggered by sun exposure and medications. Past medical, family, and social history were all unremarkable. She consulted a dermatologist and was clinically diagnosed as pemphigus. She was initially given prednisone 60 mg per day tapered weekly to 5mg per day, clobetasol 0.05% ointment applied twice a day on the body, and hydrocortisone 1% cream applied twice a day on the face, that all afforded temporary minimal decrease in thickness but did not result in complete resolution despite compliance to treatment. A re-appearance of new lesions on the trunk after 3 months, prompted consultation at our institution. Routine histology showed subcorneal splitting and intracorneal neutrophilic infiltrates, DIF revealed intercellular IgG deposition, and ELISA showed elevated anti-desmoglein 1 levels, all of which were consistent with the initial clinical diagnosis of PF.

The lack of response to prednisone, as well as the limited availability of other steroid-sparing medications posed a challenge in the management of the case. Doxycycline 100 mg twice a day was then added to the treatment plan and resulted in gradual decrease in the thickness, number and erythema of the lesions. With clinical improvement, prednisone was tapered gradually for 2 months until zero with no flaring of lesions. Our patient did not experience any side effects with intake of doxycycline.

CASE DISCUSSION

Pemphigus foliaceus (PF) is a rare autoimmune disorder that typically occurs in patients aged 40 to 60 years and affects

males and females equally. Clinically, it is characterized by an often thick keratotic scale on an erythematous base in a "seborrheic" distribution. PF patients are rarely ill. Further diagnostic tests reveal subcorneal acantholysis mediated by IgG anti-desmoglein-1 (DSG1) antibodies [1,2,5,8]

A number of studies confirm the efficacy of doxycycline in conjunction with topical steroids as a first treatment strategy in bullous pemphigoid. The Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) study revealed favorable results in patients given 0.5mg/kg body weight prednisolone or 200mg doxycycline daily and 30g steroid cream applied as needed for 3 weeks [3]. The British Association of Dermatologists 2012 guideline recommends use of systemic and topical steroids along with doxycycline may be used in BP. However, this treatment regimen and its use with pemphigus foliaceus is less documented [6,7].

In this case, we present doxycycline as a treatment for PF that can be used in conjunction with prednisone and clobetasol ointment. Doxycycline is a tetracycline antibiotic which acts via the inhibition of bacterial ribosomes. It also has useful anti-inflammatory properties which make it useful in blistering diseases. Unlike other non-steroidal adjuncts, doxycycline is widely available and affordable, which may prove to be a promising management in patients with PF.

CONCLUSION

This study provides evidence that the use of doxycycline, in conjunction with oral and topical steroids may be effective in the management of PF and adds to the list of medications that may be used as a steroid-sparing agent in PF.



Figure 1-A



Figure 1-B



Figure 1-C



Figure 1-D



Figure 2-A

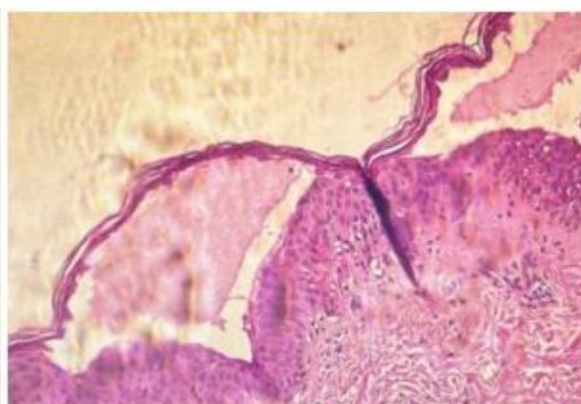


Figure 2-B

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Epidermolysis Bullosa Pruriginosa in a 12-Year-Old Male: A Case Report*

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ABSTRACT

Introduction: Epidermolysis Bullosa Pruriginosa (EBP) is a rare subtype of the inherited Dystrophic Epidermolysis Bullosa spectrum of diseases and results from a gene mutation in COL7A1. Though predominantly an autosomal dominant disease, autosomal recessive and even sporadic mutations have been reported.

Case Summary: We report a case of a 12-year-old Filipino male presenting with a chronic history of numerous scratching-induced blisters predominantly distributed on the extensor aspect of his arms and legs without concomitant oral lesions, nail dystrophy, or hair findings, and without a family history of similar lesions. Histopathologic assessment, Direct Immunofluorescence (DIF), and Indirect Immunofluorescence (IIF) showed a subepidermal split with scant inflammatory infiltrates, no immunofluorescence, and absent u-serrated linear immunofluorescence at the dermal-side of the Salt Split Skin slide, respectively, which were all consistent with EBP. Enzyme-Linked Immunosorbent Assay (ELISA) for Anti-Collagen VII antibodies was slightly elevated, which may suggest an alternative diagnosis of Epidermolysis Bullosa Acquisita (EBA). This slight elevation may be due to the mutated Collagen VII protein becoming antigenic and therefore provoking an

immune response. To conclusively distinguish EBP from EBA, a COL7A1 gene mutation analysis was recommended. With a diagnosis of EBP cannot totally rule out EBA, the patient was initially managed with dapsone monotherapy, counseled regarding behavioral modification to reduce scratching and trauma, advised wound care and close monitoring for the development of oropharyngeal lesions, and recommended for COL7A1 genetic mutation analysis.

Conclusion: This report demonstrates a case of EBP with elevated Anti-Collagen VII antibodies. The distinction between EBP and EBA is important because this changes the management: EBP is largely supportive, while EBA may benefit from immunosuppressive therapy.

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

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INTRODUCTION

Epidermolysis Bullosa Pruriginosa (EBP) is a subtype of the inherited Dystrophic Epidermolysis Bullosa spectrum of disease, resulting from a gene mutation in COL7A1 leading to a glycine substitution within the triple helical collagen domain of the type VII collagen, which is a component of the anchoring fibrils that attach the dermis to the epidermis, rendering it dysfunctional. This is in contrast to Epidermolysis Bullosa Acquisita (EBA), which is an acquired autoimmune blistering disease where a breakdown in immune tolerance results in the production of IgG antibodies against Collagen VII. Both diseases result in skin fragility, wherein tense blisters form in response to trauma. The distinction between both diseases is important in the management and prognosis: EBA benefits from immunosuppressive therapy while the management of EBP is largely supportive.

In this paper, we present a case of a 12-year-old Filipino male that that appeared as a straightforward case of EBP, but Anti-Collagen VII IgG antibodies were found to be elevated through ELISA, and may point towards a diagnosis of EBA.

CASE

A 12-year-old male, Filipino, from Quezon City, Philippines, consulted for multiple blisters on the legs and arms after scratching.

2 years prior to consult, the patient's family noted first-onset erythematous to purplish plaques with tense blister formation after the patient scratches his lower legs. The patient was noted to have a history of habitual scratching of his legs in response to his emotional state, as well as rubbing and pinching the lesions on his feet. Prior to the onset of the skin lesions, there was no drug, vitamin, or food supplement intake, without history of blister formation in response to insect bites, intake of gluten-containing food, or sun exposure.

At this time, consult with a dermatologist was sought. The patient was clinically assessed to have a probable blistering disease. Over the course of 2 years, the patient was managed with courses

of topical corticosteroids ranging from hydrocortisone to mometasone, wound care with normal saline solution and sterile aspiration of the tense blisters, short courses each of betamethasone + loratadine (Claricort) and betamethasone + dexchlorpheniramine (Celestamine), and antibiotics as needed for wound infection. There was no noted improvement or worsening of the blisters.

In the interim, new blisters would continue to form on the patient's legs and feet after scratching, which were managed with steroids and sterile aspiration, leaving behind hyperpigmented patches once healed. There was no development of dysphagia, odynophagia, ocular complaints, lesions on the genital or oral mucosa, nail dystrophy or hair loss.

1 week prior to consult, the patient suffered a bicycle accident, with tense blister formation on his forearms. This prompted consult with their dermatologist, who urged the patient to undergo further investigation to identify the specific blistering disease, prompting consult at this institution. At the time of consult, the patient's father denies any topical application or oral intake of corticosteroids within 2 weeks of the consult.

The patient was noted to have a history of asthma, well-controlled, and allergic rhinitis, mild, intermittent. He has no history of gastrointestinal disease or intolerance to wheat, bread, or rice. There was no family history of blistering disease, nail dystrophy or discoloration, alopecia, or chronic pruritus.

During consult, the patient was noted to have multiple approximately 0.1 x 0.1 cm at the smallest, faintly erythematous to violaceous plaques with tense bullae showing confluence and erosions without active discharge, clustered on the extensor surface of the bilateral legs, with few blisters scattered across the bilateral arms, in the background of hyperpigmented patches, and no visible milia or scar formation. There was no observed nail dystrophy nor lesions on the oral mucosa.

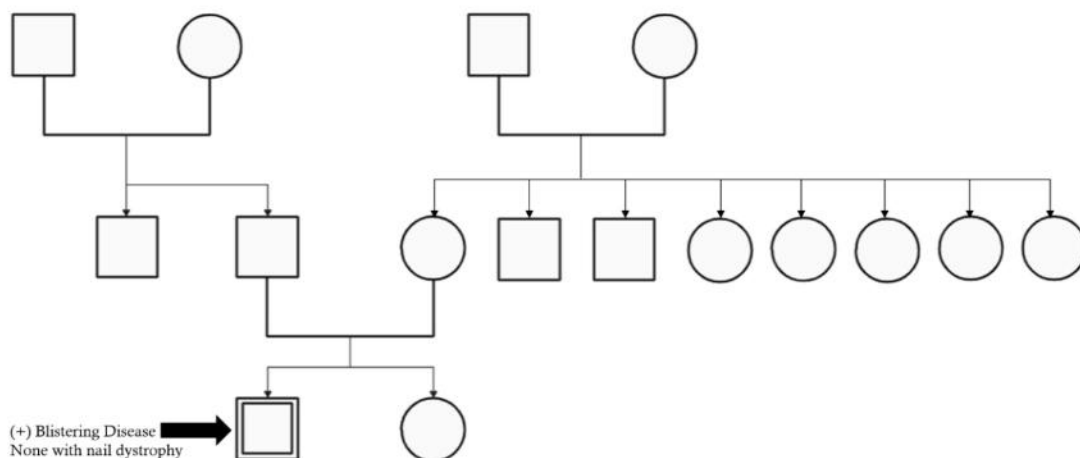


Figure 1: Genogram showing the patient's family tree. The black arrow points towards the patient. There were no relatives within three degrees of relations with blistering disease or nail dystrophy.





Figure 2: The patient's lesions. Note the numerous blisters, some with confluence, in the background of hyperpigmentation. No obvious milium-like scarring, oral mucosa involvement or nail dystrophy were present.

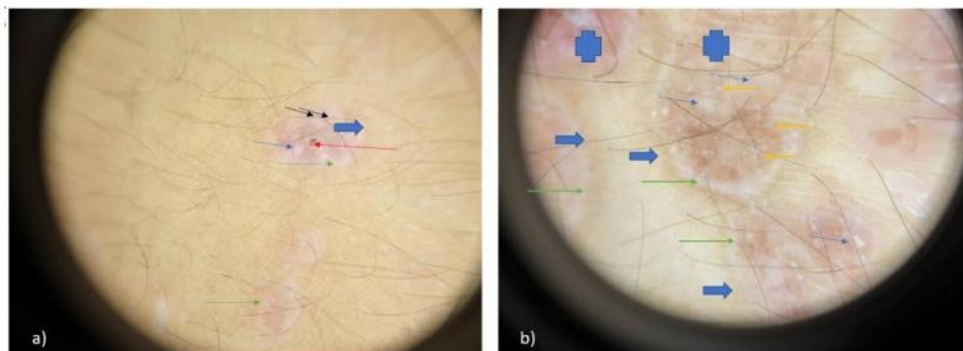


Figure 3: Dermoscopic findings of the a) arm and b) leg lesions, showing an erythematous to pink structureless background (blue cross) suggestive of an inflammatory process, with white globules (thin blue arrows), perilesional halo (thin green arrow), and white streaks (thin black arrow) suggestive of a vesiculation. Several lesions show prominent perilesional brown zone (thick blue arrow) akin to post-inflammatory pigment deposition. White dot-like areas (thin yellow arrow) can be seen, that may either be milium-like cysts or perifollicular openings. Some areas also show erosions (red arrow).

Three skin punch biopsy specimens were taken: one lesional biopsy each from the arm and leg for histopathologic examination and one perilesional biopsy for Direct Immunofluorescence (DIF) examination. In both lesional skin specimens, a subepidermal split in the background of scant inflammatory infiltrates was observed. DIF examination, however, showed no fluorescence for IgG, IgA, IgM, C3, and Fibrinogen. Indirect Immunofluorescence (IIF) using EUORIMMUN BIOCHIP MOSAIC showed inconclusive – to – negative results, owing to a negative result in the positive control. Enzyme-Linked Immunosorbent Assay (ELISA) showed normal ranged Anti-BP180 and Anti-BP230, but a slightly elevated Anti-Collagen VII with a result of 30.8 IU and a normal range of < 20 IU.

Due to these laboratory findings, the patient was assessed as a case of Epidermolysis Pruriginosa cannot totally rule out Epidermolysis Bullosa Acquisita. The patient was then worked up for baseline laboratory parameters to initiate oral dapsone monotherapy, advised wound care and to avoid trauma to the skin, strongly advised for regular monitoring for flares of the disease, and advised to undergo *COL7A1* gene mutation analysis.

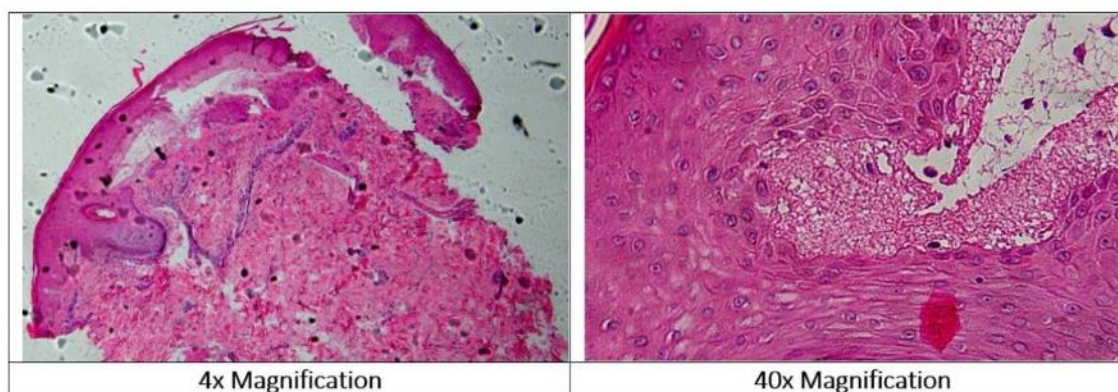


Figure 4. Histopathologic examination of lesional skin on the leg shows a subepidermal split with scant to almost absent inflammatory infiltrates composed of lymphocytes, neutrophils, eosinophils, and prominent subepidermal edema. Acantholysis is seen at the split.

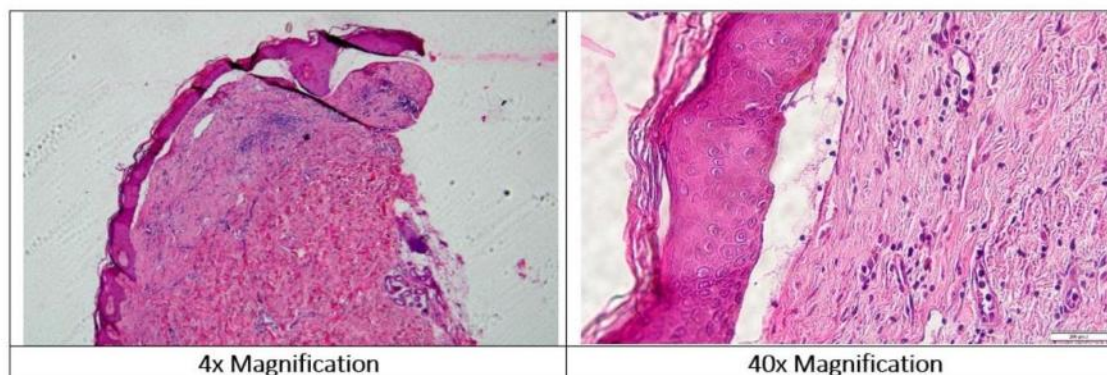


Figure 5. Histopathologic examination of lesional skin on the arm likewise shows a subepidermal split with scant to mild superficial infiltrates of lymphocytes, neutrophils, and eosinophils, with few to almost absent eosinophils and neutrophils within the blister.

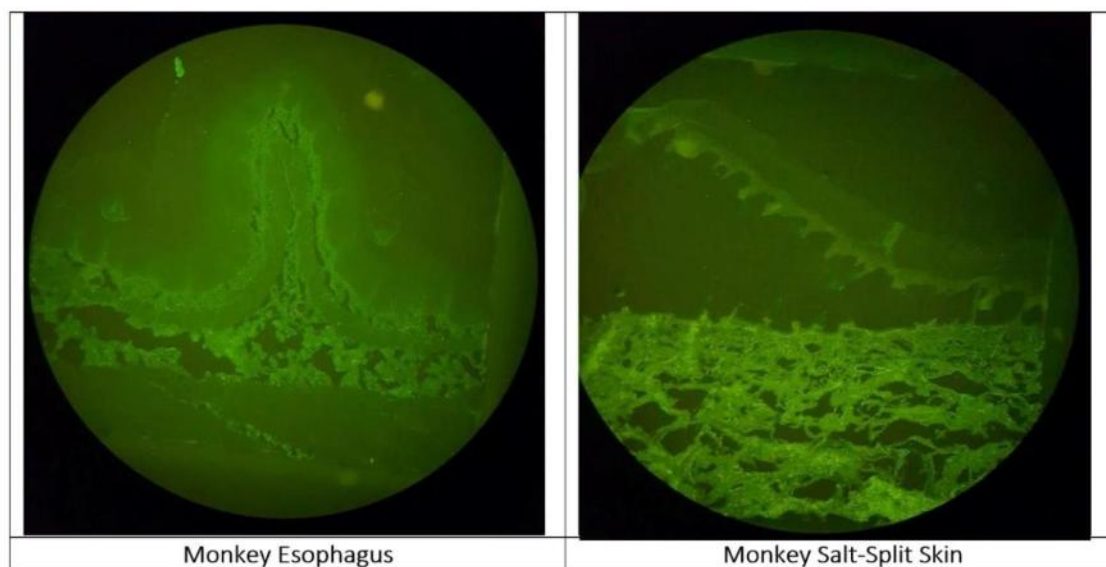


Figure 6. IIF using the EUROIMMUN BIOCHIP Mosaic does not display the expected fluorescence at the level of the basement membrane on the Monkey Esophagus slide, nor an n-serrated or u-serrated pattern expected of Bullous Pemphigoid or Epidermolysis Bullosa Acquisita, respectively, on the Monkey Salt-Split Skin slide.

DISCUSSION

EBP is a rare disease that is typically autosomal dominant in inheritance, but reports of autosomal recessive and even sporadic mutations have been published. This is a subtype of inherited Dystrophic EB, where a mutation in COL7A1 occurs, leading to a glycine substitution within the triple helical collagen domain of the type VII collagen molecule. This disease is characterized by intense pruritus, excoriations, skin fragility, nail dystrophy, milia-like or violaceous linear scarring, and nodular prurigo-like lesions. While the exact cause of pruritus is unknown, it is suggested that the exposure of mutated Type VII collagen activates a kinin cascade, leading to bradykinin release. This pruritus then gives the clinical findings of prurigo-like lesions commonly associated with nail dystrophy.

This is in contrast to EBA. This is an acquired autoimmune blistering disease where a breakdown in immune tolerance results in the production of IgG antibodies against Collagen VII, which is a component of the anchoring fibrils that attach the dermis to the epidermis.

Simply, EBA is an autoimmune disease against Collagen VII while EBP is a mutation of collagen VII. Both diseases result in skin fragility, wherein tense blisters form in response to trauma. The distinction between both diseases is important in the management and prognosis: EBA benefits from immunosuppressive therapy while the management of EBP is largely supportive.

EBA exists as a spectrum of diseases divided into classical / mechanobullous / non-inflammatory and non-classical / non-mechanobullous / inflammatory subtypes. The non-classical subtype is further subdivided into Bullous Pemphigoid-Like EBA, Mucous Membrane-EBA, Brunsting-Perry-Type EBA, and IgA-EBA.

Should our patient be a case of EBA, the presence of skin-fragility, bullous lesions and erosions, encompassed by non-inflamed skin in trauma-prone sites and the extensor skin surface, as well as the scant inflammatory infiltrates in histology, point towards the Classic Subtype. However, scant inflammatory infiltrates associated

with a subepidermal blister have also been described in case reports of EBP.

Moving on to the DIF and IIF findings, it is first important to understand the mechanism behind each test. DIF subjects the patient tissue to fluorochromes bound to an antibody that attaches to the molecule under question. In our case, perilesional skin was assessed for IgG, IgA, IgM, C3, and Fibrinogen, yielding a negative result, thus showing no activity from the aforementioned molecules.

In a similar vein, IIF subjects the antibodies within patient sera to known tissue specimens. Thus, should patients have active Anti-Collagen VII antibodies such as in EBA, then IIF findings should show the characteristic linear basement membrane deposition on the Monkey Esophagus slide, and u-serrated dermal-side deposition in the Salt – Split Skin slide, both of which were not seen in our patient.

Thus, our patient presenting with negative DIF results and a possibly-negative IIF result raises the suspicion that an autoimmune process may not be involved as the underlying mechanism to his lesions. The normal-range Anti-BP180 and Anti-BP230 autoantibodies also rules out Bullous Pemphigoid as a diagnosis. In the background of an absent family history of blistering disease or nail dystrophy, our patient, therefore, is more likely to be a sporadic case of EBP.

However, for this to be a true case of EBP, the conundrum behind our patient's elevated IgG autoantibodies against Collagen VII, as documented by ELISA, is raised. A literature search revealed a case report published in 2012 of a 50-year-old woman with similar skin lesions to our patient, albeit with personal and family history of onychodystrophy, negative IIF studies, and elevated IgG antibodies against the NC1 domain of

Collagen VII measured using immunoblot studies. This patient was managed with methylprednisolone and azathioprine, with her skin lesions healing after 15 months of maintenance therapy. However, the patient had unexpected flares of her blisters, prompting COL7A1 mutation search, showing the glycine substitution mutation in the triple helix domain of COL7A1, leading to the final diagnosis of EBP. The author of this case report explains that the presence of autoantibodies against Collagen VII in EBP can be as a result of an autoimmune reaction against Collagen VII.

CONCLUSION

In conclusion, given these clinical, laboratory, and literature evidence, our patient is therefore assessed as a case of EBP, and cannot totally rule out EBA. The one test that will be able to conclusively differentiate the former from the latter would be a COL7A1 assay.

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Guttate Morphea in a 31-Year-Old Filipino Female: A Diagnostic Challenge in its Early Stage*

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Cindy Jao Tan, MD, FPDS, Camille B. Angeles, MD, FPDS

ABSTRACT

Introduction: Morphea, also known as localized scleroderma, describes a distinctive inflammatory skin disorder that ultimately leads to sclerosis. It is differentiated from systemic scleroderma by the absence of vasculopathy and organ involvement. Initial erythema may precede the sclerotic stage by a few months causing initial diagnostic confusion. High index of suspicion and knowledge of disease evolution are essential. We report a case of morphea and its progression, the diagnostic approach and the importance of early treatment and long-term monitoring.

Case summary: A 31-year-old Filipino female who presented with multiple erythematous plaques on the trunk and extremities and arthralgia was initially diagnosed with cutaneous drug reaction. Prompt treatment led to partial relief of symptoms. However, two months later, eruption of multiple ivory-white small patches and plaques were noted on the same affected areas prompting an impression of morphea. Serum markers revealed elevated antinuclear antibody levels and negative anti-Scl70/anti-centromere serum autoantibodies. Skin biopsy showed homogenized thick dermal collagen bundles confirming the diagnosis of morphea. Topical therapy with calcipotriol + betamethasone dipropionate ointment showed

remarkable improvement with decrease in erythema and softening of the lesions while adjunct narrowband-UVB phototherapy also provided relief due to its ability to reduce collagen synthesis and cytokine production.

Conclusion: Morphea may be easily misdiagnosed during the early stages especially if sclerosis ensues late in the disease. Characteristic clinical appearance of erythematous plaques with violaceous borders may not always be present. Histologic examination and serum autoantibodies help exclude other disorders with the same clinical and histopathological spectrum. Treatment is individualized depending on the severity and depth of skin involvement, early treatment and monitoring should be initiated before complications arise.

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Keywords: *guttate morphea, localized scleroderma, cutaneous sclerosis, fibrosis*

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CASE REPORT

INTRODUCTION

Morphea also known as localized scleroderma refers to a distinctive inflammatory disease that primarily affects the skin and underlying tissues that ultimately leads to sclerosis. It is differentiated from the systemic form of the disease by the absence of sclerodactyly, Raynaud phenomenon, abnormalities of the nail-bed capillaries, or internal organ involvement.¹ Both have a different clinical expression but they share a common pathologic and pathogenetic mechanism leading to vascular damage, immune activation, and excessive deposition of collagen. The cause is unknown however genetic background in association with exogenous triggers such as viral (EBV, varicella) and bacterial (*Borrelia burgdorferi*) infections, local trauma, surgical operations and vaccinations (BCG) has been suggested to play a role in morphea.²

CASE

A 31-year-old female sought consult at the University of the East Ramon Magsaysay Memorial Hospital (UERM) dermatology out-patient clinic (OPC) with multiple erythematous, irregularly shaped plaques associated with pruritus on her extremities and trunk of 2-weeks duration (Figure 1). There were no complaints of fever, swelling of eyes and lips, dysphagia, difficulty of breathing, chest pain or vaginal discharge. Medication taken prior to eruption of skin lesions was etoricoxib tablet which the patient takes as needed for her arthralgia. Initial impression was cutaneous drug eruption probably secondary to etoricoxib. A 3-mm skin punch biopsy of the skin on the left arm revealed spongiotic dermatitis with psoriasiform epidermal hyperplasia and focal areas of neutrophils subcorneally overlying parakeratotic stratum corneum (Figure 2) hence a spongiotic reaction to a drug was considered. Clearance of lesions were noted after giving a potent topical corticosteroid

and a sedating antihistamine. Patient was advised to discontinue taking the etoricoxib. Rheumatology work-up revealed (+) antinuclear antibody (ANA), elevated erythrocyte sedimentation rate (ESR) and normal rheumatoid factor (RF) and C3; an inconclusive diagnosis of rheumatoid arthritis was conferred.

One month after discontinuation of previous medication and clearance of lesions, patient consulted again due to progression of previous lesions to multiple ivory-white small patches and plaques on bilateral hips, lower abdomen, back, and gluteal area (Figure 3). There was absence of sclerodactyly, Raynaud phenomenon, abnormalities of the nail-bed capillaries, and internal organ involvement. Patient still reported arthralgia with restricted mobility of the MCP and PIP joints.

Morphea was highly considered due to its limited cutaneous involvement and a negative anti-centromere (ACA) and anti-Sc170 autoantibodies. A 3-mm skin punch biopsy on the left hip confirmed a beginning homogenized thick collagen bundles that are present in the dermis and impinging into the adventitial layer (Figure 4).

Topical therapy with a combination of betamethasone dipropionate and calcipotriol twice daily was initiated to target the early inflammatory phase. Narrowband-UVB phototherapy was also initiated 3-5 times weekly at 200mJ/cm² with weekly increments of 100mJ/cm² on subsequent sessions until a maximum dose of 1,500 mJ/cm² is reached.



Fig 1. Multiple erythematous, irregularly shaped plaques on face, trunk and extremities on first consult

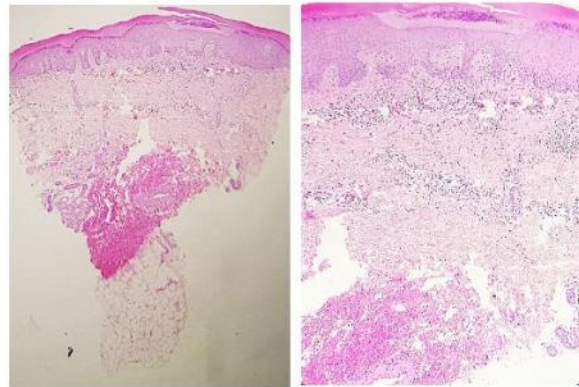


Figure 2. Spongiotic dermatitis with psoriasiform epidermal hyperplasia and focal area of neutrophils subcorneally overlying parakeratotic stratum corneum (H&E stain, 4x and 10x magnification)



Figure 3. Progression of previous lesions to multiple ivory-white patches and plaques on second consult

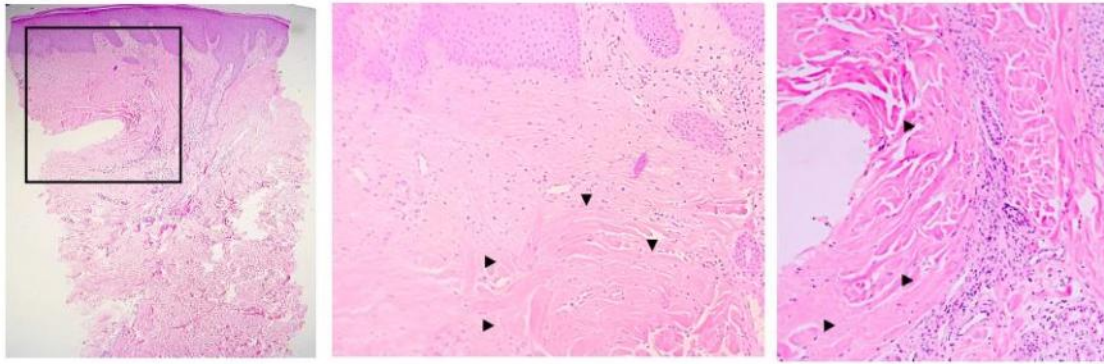


Figure 4. Section shows beginning homogenized thick collagen bundles present in the dermis impinging into the adventitial layer (black arrows) (H&E stain, 4x and 40x magnification)

Scleroderma is a chronic connective tissue disease of unknown etiology that causes widespread microvascular damage and excessive deposition of collagen in the skin and internal organs.² There are two types of scleroderma, a systemic form which is characterized by cutaneous sclerosis and visceral involvement and morphea which classically presents benign and self-limited evolution that is confined only to the skin and/or underlying tissues.³ Morphea is a rare disease with an annual incidence rates between 3.4 and 27 cases per 1,000,000. Females are more frequently affected than males (ratio: 2.4–5.0 to 1).⁶

Subtypes are differentiated based on clinical presentation and depth of skin involvement. It is subdivided into linear scleroderma, plaque morphea, deep morphea, bullous morphea, and generalized morphea.³ The most common subtype is the plaque type.

Three of the following must be established for the diagnosis of morphea: 1) presence of sclerodermatous skin changes, 2) histopathological examination that shows thickened and increased collagen fibers in the dermis and 3) these diseases can be excluded: systemic sclerosis, eosinophilic fasciitis, lichen sclerosus et atrophicus, keloid, (hypertrophic) scars and sclerosing panniculitis.⁴

This case report will highlight the importance of establishing the clinical and histopathologic diagnosis, the stages of its development and the treatment approach.

The patient presented with initial symptoms of recurrent arthralgia occurring for almost a year followed by an eruption of multiple erythematous pruritic plaques on the trunk and extremities. At this stage, the typical clinical and histopathological features of morphea is not yet fully seen therefore being able to identify the different stages of morphea is imperative for the clinician since misdiagnosis may happen.

According to Careta et al., there are stages in the development of sclerosis. In the inflammatory phase or in the early lesions, morphea clinically exhibits an erythematous component (red, erythematous lesions) with a histologic picture that is not characteristic of scleroderma thus making a definitive diagnosis difficult. In the later stage, the presence of denser, homogenized collagen that is a little more eosinophilic, especially around vessels and adnexa is observed.

The patient's skin lesions have progressed to become multiple ivory-white oval plaques measuring 1–2cm on the previous affected areas two months after initial presentation. The size of the

lesions is described as guttate which is a subtype classification of plaque morphea in the Peterson et al. classification. Koebnerization was also observed as the lesions appeared in areas of pressure (hips, around the waist, and around the bra line)¹⁰. Anti-Scl70 and anticentromere serum autoantibodies, specific for systemic scleroderma and Raynaud phenomenon were negative hence a localized form was considered.

Histopathologic examination confirmed beginning homogenized thick collagen bundles that are present in the dermis, impinging into the adventitial layer. This explains that in later lesions, scleroderma can be established and a definitive histological diagnosis is possible. In summary, scleroderma lesions are characterized by an initial inflammatory stage that is followed by a fibrosis stage and results in the replacement of normal dermis and hypodermis structures by abnormal collagen.

Elevated ANA is also seen in the early phases of morphea lesions characterized by the influx of large amounts of mononuclear lymphocytes, plasma cells, and eosinophils because of widespread autoimmune reactivity seen in morphea patients.⁷ Several laboratory tests that can aid in the diagnosis of scleroderma are the serum autoantibodies. They are still of limited use in morphea but they can help in excluding it from the systemic form. In the case of our patient, requested laboratories revealed a positive ANA indicating an early phase of morphea, a negative anti-centromere (ACA) and anti-Scl 70 hence a localized form is now established.

Recommended treatment for morphea should be based on disease activity and damage, depth of involvement, disease progression, systemic involvement and disease subtype. It is also important to differentiate active (new, erythematous, expanding lesions) from inactive or

damaged (pigmentary changes, atrophy, static size) morphea.⁸ Treatment options may be divided into topical and systemic therapy as well as ultraviolet (UV) phototherapy.

Corticosteroids is best used in the most superficial and limited forms of morphea and during the early, most inflammatory phase.¹ Plaque morphea is best treated with topical betamethasone dipropionate and calcipotriol hydrate combination therapy. The mechanism of efficacy for calcipotriol-betamethasone dipropionate is twofold as both components inhibit fibroblast proliferation and act as cytokine immunomodulators to decrease fibrosis and inflammation.¹² Therefore, it is considered suitable for the treatment of active morphea for our patient.

Another treatment option is phototherapy (level 1, randomized controlled trials: broadband ultraviolet (UV) A, narrowband UVB, and UVA-1). NB-UVB is considered for lesions affecting the superficial dermis (relatively thin on palpation or with sclerosis and inflammation in the papillary and superficial reticular dermis).⁴ Based on the histopathologic exam of the patient, thick collagen bundles were seen in the dermis hence NB-UBV is still recommended. Although BB- UVA and UVA1 has greater depth of skin penetration, it is more useful on those types with deeper dermal lesions that are also affecting the subcutaneous, muscular and bone tissues.

Prognosis for morphea may have a remitting and relapsing course with periods of activity and reactivation over several years.¹³ To monitor therapeutic success, disease activity and damage, an outcome measure known as localized scleroderma cutaneous assessment tool (LoSCAT) has been developed.⁷ This tool can be used for my patient to monitor her disease progression and to evaluate clinical improvement after treatment.

Morphea presents a self-limited course with a tendency to spontaneous regression after 3 to 5 years but it may progress and recur especially when the onset of disease occurs in childhood.³

CONCLUSION

Morphea may be easily misdiagnosed during the early stages especially if sclerosis ensues late in the disease. Characteristic clinical appearance of erythematous plaques with violaceous borders may not always be present. Histopathologic examination is used to aid in making therapeutic decisions for the depth of involvement of the disease while autoimmune workup is employed to rule out other conditions with the same clinical spectrum. Treatment is individualized depending on the severity and depth of skin involvement and early treatment and monitoring should be initiated before complications arise.

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Bullous Presentation of Acrodermatitis Enteropathica in Three Female Siblings: A Case Series

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ABSTRACT

Acrodermatitis enteropathica is a rare autosomal recessive disease that results from a defect in zinc metabolism. It is clinically characterized by a phenotypic triad of periorificial and acral dermatitis, diarrhea, and alopecia. Oral zinc therapy gives a rapid excellent clinical response and reduces mortality. We report three female pediatric siblings who presented with periorificial and acral dermatitis, diffuse alopecia, nail dystrophy, irritable mood, and stunted growth. A diagnosis of acrodermatitis enteropathica was confirmed with markedly decreased levels of serum zinc. The patients were successfully treated with oral zinc sulfate at a dose of 5mg/kg/day for the first two weeks then maintained on a dose at 2mg/kg/day.

Keywords: acrodermatitis enteropathica (AE), zinc, bullae, congenital zinc deficiency

OBJECTIVE

To present a case series of three female pediatric siblings with acrodermatitis enteropathica, a rare condition

INTRODUCTION

Zinc is an essential trace element and it plays an important role in growth and development.¹ Deficiency in zinc results to an autosomal recessive disorder called acrodermatitis enteropathica (AE). It is caused by a mutation of the *SLC39A4* gene which encodes the ZIP4 zinc transporter and is located on chromosome 8q24.3.² Clinically, it is characterized by the triad of acral and periorificial dermatitis, alopecia, and diarrhea which can be resolved by oral zinc supplementation.^{1,2,3} This is a case series of three female siblings - a pair of twins and a younger sister who came at our clinic for consultation due to a periorificial and acral eczematous and erosive dermatitis accompanied with thinning of hair and nail dystrophy. History of consanguinity was present in the parents. Serum zinc levels were significantly decreased and patients improved upon oral zinc supplementation.

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

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CASE SERIES

CASE 1

A five-year-old female born normally at full term to healthy, related (second cousins) parents presented with a three-year-history of having bullous lesions over the periorificial and acral areas. Spontaneous rupture of bullae was observed leaving well demarcated erythematous to hyperpigmented plaques with fissures and crusts. Birth history was unremarkable. Milestones were normal. The child was exclusively breastfed since birth up to two months of age and mixed feeding followed. Immunizations were unrecalled but were incomplete. Similar lesions were also evident on her twin sister. The patient had been treated unsuccessfully for presumed atopic dermatitis and bacterial infections with topical steroids and oral and topical antibiotics in the province.

On the day of examination, we saw an afebrile, irritable child weighing 11.7kg, severely of paronychia. Scalp hair was light brown, thin, and sparse. A delay in consultation led to the appearance of painful eroded and fissured plaques over the feet (see figures 1-3).



Figure 1. Before treatment. Profile of the patient (front and back) showing well demarcated erythematous scaly plaques over the periorificial, acral, and flexural areas as well as diffuse alopecia.



Figure 2. Patient 1 with angular cheilitis and scaling around the eyes.



Figure 3. Nail dystrophy: Beau's lines and paronychia.

The patient was initially assessed as a case of epidermolysis bullosa and co-management with pediatric service was ordered. She was given oral antibiotics for pneumonia and topical antibiotics for the crusted lesions. Laboratory work up was done revealing non-contributory results. Wound care and trauma precaution were emphasized to the caregivers. Mechanical induction of vesicle was unsuccessful. A 6mm skin punch biopsy of a fresh pustule on the left thigh was done.

Histopathologic examination revealed a subcorneal separation with neutrophils, hyperkeratosis, and irregular acanthosis in the

epidermis. There were dense infiltrates of lymphocytes with neutrophils in the dermis (refer to figures 4-5). These changes are not specific for an autoimmune blistering disease hence re-assessment was done.

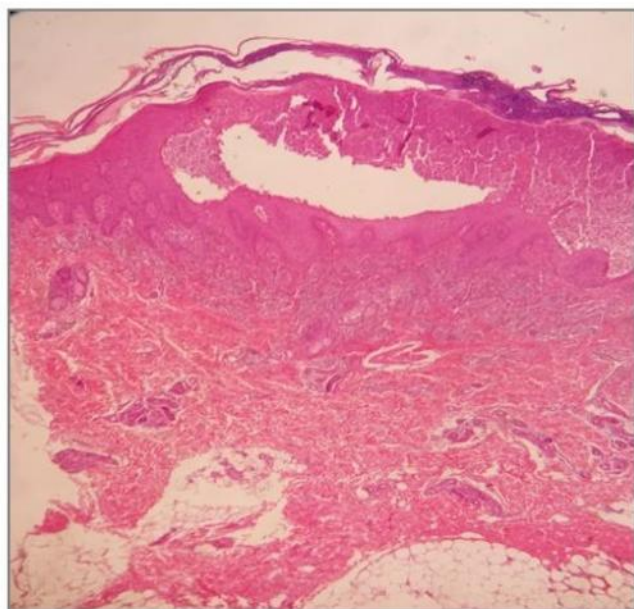


Figure 4. On scanning view, the epidermis showing subcorneal separation and hyperkeratosis.

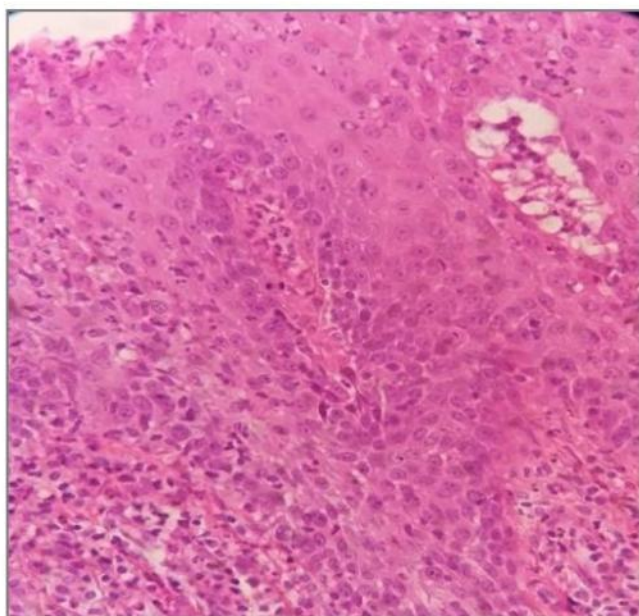


Figure 5. On closer magnification, the dermis is infiltrated with lymphocytes and neutrophils.

Serum zinc determination was ordered and revealed a decreased amount of 52 $\mu\text{g/dL}$ (normal: 70-250 $\mu\text{g/dL}$). Alkaline phosphatase level: 55 U/L (normal: 70 – 160 U/L) was also noted. On the basis of clinical and biochemical findings, we arrived at a diagnosis of acrodermatitis enteropathica. An overall rapid response to treatment of zinc sulfate 5mg/kg/day was seen in one week (see figures 6-8). The incessant crying and whining first disappeared followed by the improvement of the plaques and the hair and nails. The patient is still on zinc maintenance therapy at 2mg/kg/day.



Figure 6. After treatment. Improvement of plaques and growth of hair.



Figure 7. After treatment. Improved periorificial dermatitis



Figure 8. After treatment. Improved nail dystrophy.

CASE 2

A five-year-old female, twin sister of patient 1, was born term via normal spontaneous vaginal delivery to a then 30-year-old gravida 1 mother. Their parents are second cousins. Birth history was unremarkable. Milestones were at par with age. The child was exclusively breastfed since birth up to two months and mixed feeding followed. Immunizations were unrecalled but were incomplete. At the age of two years old, bullae were noted over the inguinal areas. Spontaneous rupture of bullae left well-defined erythematous scaly plaques. Interval history showed progression of lesions particularly seen on the periorificial and acral areas. Similar lesions were also evident on her twin sister. The patient had been treated unsuccessfully for presumed atopic dermatitis and bacterial infections with topical steroids and oral and topical antibiotics in the province.

Examination revealed an afebrile, irritable child weighing 12kg, underweight and severely stunted. Dermatologic findings showed well-defined erythematous to hyperpigmented plaques

with peripheral scaling over the upper extremities particularly the hands, wrists, antecubital fossae and elbows, and over the lower extremities on the inguinal and anogenital areas, anterior and posterior aspects of the legs, and ankles. The back of the trunk was relatively spared. Crusted scaly plaques were seen around the canthi, alar creases, and oral commissures. There were erythema and fissuring at the angles of the mouth. All fingernails were dystrophic showing beau's lines and some degrees of paronychia. Scalp hair was light brown, thin, and sparse. A delay in consultation led to appearance of painful eroded and fissured plaques over the feet (see figures 9-11).



Figure 9. Before treatment. Profile of the patient (front and back) showing well demarcated erythematous scaly plaques over the periorificial, acral, and flexural areas as well as diffuse alopecia.



Figure 10. Patient 2 with angular cheilitis and scaling around the eyes.



Figure 11. Nail dystrophy: Beau's lines and paronychia.

The patient was initially assessed as a case of epidermolysis bullosa and co-management with pediatric service was ordered. She was given oral antibiotics for pneumonia and topical antibiotics for the crusted lesions. Laboratory work up was done revealing non-contributory results. Wound care and trauma precaution were emphasized to the caregivers. The lesions were observed not to be trauma induced hence re-assessment.

Serum zinc determination was ordered and revealed a markedly decreased value of $18\mu\text{g/dL}$

(normal: $70\text{--}250\mu\text{g/dL}$). Alkaline phosphatase level: 43 U/L (normal: $70\text{--}160\text{ U/L}$) was also noted. On the basis of clinical and biochemical findings, we arrived at a diagnosis of acrodermatitis enteropathica.

A 4mm skin punch biopsy was done over the right leg. Histopathology showed hyperkeratosis, irregular acanthosis, and hypogranulosis in the epidermis. There were dilated blood vessels in the upper dermis and moderate superficial perivascular infiltrates of lymphocytes (see figures 12–13). These findings are non-diagnostic but may be consistent with acrodermatitis enteropathica

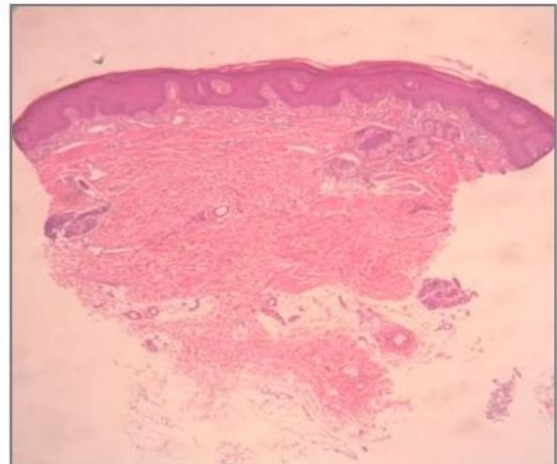


Figure 12. On scanning view, the epidermis shows hyperkeratosis and irregular acanthosis.

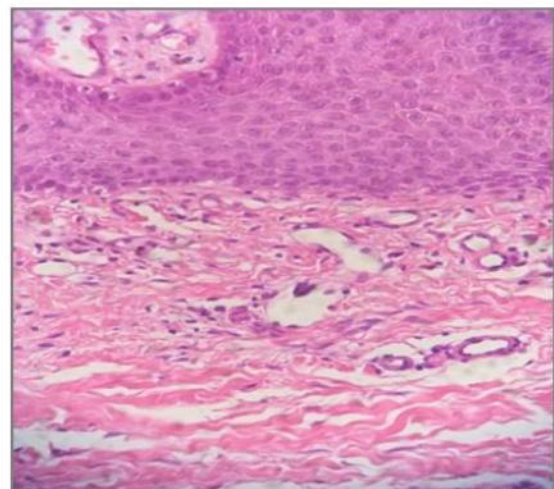


Figure 13. On closer magnification, the dermis is infiltrated with lymphocytes.

An overall rapid dramatic response to treatment of zinc sulfate 5mg/kg/day was seen in one week (see figures 14-16). The incessant crying and whining first disappeared followed by improvement of the plaques and the hair and nails. The patient is still on zinc maintenance therapy at 2mg/kg/day.



Figure 14. After treatment. Improvement of plaques and growth of hair.



Figure 15. After treatment. Improved periorificial dermatitis.



Figure 16. After treatment. Improved nail dystrophy.

CASE 3

This is a case of a two-year-old female who was born term via normal spontaneous vaginal delivery. There is a history of consanguineous marriage of parents. Birth history was unremarkable. Milestones were at par with age. The child was exclusively breastfed since birth up to six months of age and mixed feeding followed. Immunizations were unrecalled but allegedly complete. Six months prior to consult, bullae were noted over both inguinal areas. Spontaneous rupture of bullae left well-defined erythematous scaly plaques. Interval history showed progression of lesions particularly seen on the flexural areas. Similar lesions were also observed in her two older sisters. The patient had been treated unsuccessfully for presumed atopic dermatitis and bacterial infections with topical steroids and oral and topical antibiotics.

Examination revealed an afebrile, irritable child weighing 10.2kg, underweight and stunted. Dermatologic findings showed well-defined erythematous to hyperpigmented plaques with minimal peripheral scaling over the nape, axillary areas, upper extremities particularly the hands, wrists, antecubital fossae and elbows, and over the

lower extremities on the inguinal and anogenital areas, posterior aspect of the legs, ankles and dorsum of feet. There was a solitary hyperpigmented ill-defined patch over the back. Angular cheilitis was mild. There was no nail dystrophy. Scalp hair was thin and sparse (see figures 17-19).



Figure 17. Before treatment. Profile of the patient (front and back) showing well demarcated erythematous scaly plaques over inguinal and flexural areas.



Figure 18. Angular cheilitis, mild.

The patient was initially assessed as a case of epidermolysis bullosa and co-management with pediatric service was ordered. She was given oral antibiotics for pneumonia and topical antibiotics for the crusted lesions. Laboratory work up was done revealing non-contributory results. Wound care and trauma precaution were emphasized to the caregivers. The lesions were observed not to be trauma induced hence re-assessment.

Serum zinc determination was ordered and revealed a markedly decreased value of $0.15\mu\text{g/dL}$ (normal: $70\text{--}250\mu\text{g/dL}$). Alkaline phosphatase level: 51 U/L (normal: $70\text{--}160\text{ U/L}$) was also noted. On the basis of clinical and biochemical findings, we arrived at a diagnosis of acrodermatitis enteropathica.

A 4mm skin punch biopsy was done on the left arm. Histopathology showed hyperkeratosis with scale crust, irregular acanthosis, and hypogranulosis in the epidermis. There were dilated blood vessels in the upper dermis and moderate superficial perivascular infiltrates of lymphocytes. These findings are non-diagnostic but may be consistent with acrodermatitis enteropathica (see figures below).

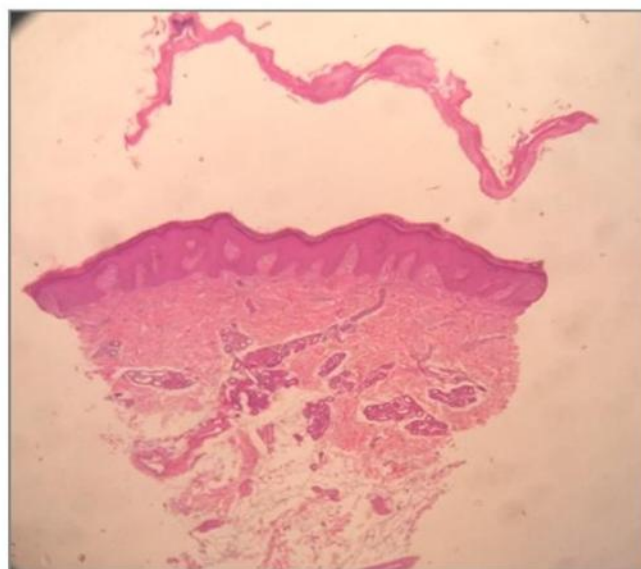


Figure 19. On scanning view, the epidermis shows hyperkeratosis with scale crust, irregular acanthosis.

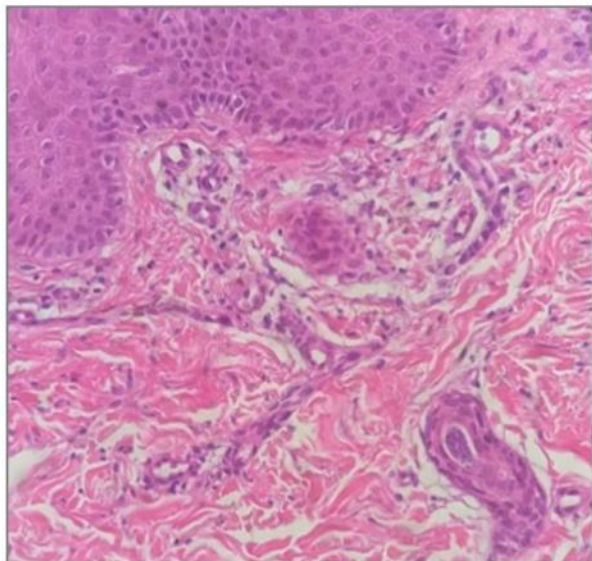


Figure 20. On closer magnification, the dermis is infiltrated with lymphocytes and there are dilated blood vessels.

An overall rapid dramatic response to treatment of zinc sulfate 5mg/kg/day was seen in just one week. The incessant crying and whining first disappeared followed by improvement of the plaques and the hair. The patient is still on zinc maintenance therapy at 2mg/kg/day.



Figure 21. After treatment. Improvement of plaques now seen as patches of hypopigmentation.



Figure 22. After treatment. Improved angular cheilitis.

DISCUSSION

Zinc is an essential trace element required by living organisms for its diverse biochemical and physiologic roles. It has functions in enzyme catalysis, cell signaling and division, and DNA synthesis.^{4,5} It is also vital for growth and development and brain and immune function. Nutritionally, zinc may be found in leafy vegetables, whole grains, nuts, whole wheat bread, beans, cheese, cereals, and animal protein in lean meat and pork.

Deficiency in zinc may be inherited or acquired. It is primarily caused by defective zinc absorption in the duodenum and jejunum resulting in plasma zinc levels below the normal (normal: 70–250 µg/dL). Acquired cases may be due to dietary inadequacy, premature and low birth weight infants, deficient zinc in maternal milk, parenteral nutrition and various malabsorption syndromes such as inflammatory bowel disease, celiac disease, and cystic fibrosis as well as alcoholism, low calcium diet, and kwashiorkor.^{1,6}

The genetic type referred to as acrodermatitis enteropathica (AE) was first

recognized by Swedish dermatologist Thore Brandt in 1936.^{3,7} It is a rare autosomal recessive condition due to a mutation in the *SLC39A4* gene located on chromosome 8q24.3 that encodes the zinc transporter ZIP4. Studies and reports of AE cases with history of consanguineous marriages lead to higher carrier state of the mutation in the said gene.² In fact, the study on the homozygosity mapping of AE gene was tested in consanguineous Jordanian and Egyptian families.⁸ Incidence rate of AE is approximately at 1 per 500,000 children worldwide without predilection for race or gender.^{2,6,7} Population at particular risk are the premature infants due to inadequate zinc stores, suboptimal absorption and high zinc requirement.⁹ Locally, for the past five years, there have been 12 cases diagnosed with pediatric AE according to the health information system task force of the Philippine Dermatologic Society, three of which were from our institution.

AE classically manifests during infancy upon weaning from breast milk to formula or cereal which has lower zinc bioavailability than breast milk. AE usually presents after weaning in affected patients on the fourth to tenth week of life in infants who are not breastfed.¹⁰

The classical triad of AE is clinically characterized by acral and periorificial (perioral, periorcular, anogenital) eczematous and erosive dermatitis, alopecia, and diarrhea. However, this triad only occurs altogether 20% of the time.¹ Cutaneous lesions present with well demarcated erythematous scaly plaques but pustules, blisters, and bullae may also develop.⁷ Other clinical features include angular cheilitis and stomatitis, nail dystrophy, anorexia, neurologic disturbances, growth retardation, failure to thrive, and recurrent infection with *Candida albicans* or *Staphylococcus aureus*.

The diagnosis is mainly based on clinical manifestations and can be confirmed by low

serum zinc levels and a dramatic response upon oral zinc replacement. However, a normal serum zinc level may be observed in approximately 30% of all cases.¹¹ Serum alkaline phosphatase – a zinc-dependent enzyme – may be measured since it may also serve as an indicator of hypozincemia. Histopathologic findings are non-specific and have a little contribution in the diagnosis. Typical features show variable psoriasiform hyperplasia with confluent parakeratosis, spongiosis and pallor of the upper epidermis, focal dyskeratosis, and variable epidermal atrophy.¹⁰

Treatment of AE is simple and is done by giving oral zinc supplementation. Most authors suggest an initial dose of 3–10 mg/kg/day followed by a maintenance dose of 1–2 mg/kg/day. Rapid clinical response is usually seen in a matter of days. Irritability and whining would disappear first followed by improvement of skin lesions. Zinc and copper should be monitored as excess zinc may interfere with copper metabolism. With adherence to life-long zinc substitution, the prognosis is good. Only when infants are left untreated can the disease be fatal.

CONCLUSION

Herein, we present three female siblings aged five, five, and two, seen with periorificial and acral scaly eroded plaques, diffuse alopecia, nail dystrophy, failure to thrive, stunted growth, and irritable mood. An initial presentation of bullae caused diagnostic delay. Markedly reduced serum zinc levels were obtained and patients were diagnosed with acrodermatitis enteropathica, a rare genetic autosomal recessive disorder. Replacement with oral zinc sulfate given at the dose of 5 mg/kg/day led to a rapid clinical improvement. To confirm the diagnosis of congenital zinc deficiency, we recommend molecular genetic studies on these patients by direct sequencing analyses.

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A Rare Enigmatic Case of a 24-Year Old Female with Cutaneous Tuberculosis (Lupus Vulgaris) Arising on Burn Scar Lesion *

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ABSTRACT

Cutaneous tuberculosis, a rare dermatologic condition with a wide spectrum of clinical findings depending on the source and immune status of patient. The common subtype is Lupus Vulgaris which is extremely chronic and progressive type

Objective: To discuss the summary of the case, management options and outcomes of the management options.

Case Summary (Methods): Herein a case of a 24-year-old female presenting with two year history of gradual appearance of pruritic and tender erythematous plaque on the left forearm arising on scald burn lesions sustained twenty years ago. Patient is generally healthy with no history of pulmonary tuberculosis (PTB) nor exposure to close contacts. Skin punch biopsy showed caseating tuberculoid granulomas in the dermis consistent with cutaneous tuberculosis. Other work up for tuberculosis such as tissue culture, GeneXpert, PCR, tuberculin skin test and chest x-ray were all negative. Patient was started with a therapeutic trial of standard treatment regimen for tuberculosis.

As part of multidisciplinary care, the patient was referred to ophthalmology service due to complaints of blurring of vision which started one month after treatment initiation. She was managed as a case of TB Uveitis and was given Oral Prednisone with unrecalled dosage. She was likewise referred to plastic surgery and infectious disease for co-management of hypertrophic scars and tuberculosis.

Conclusion: Treatment of cutaneous tuberculosis is anti-Koh's (HRZE) medication and requires a multi-specialty approach. After 12 months of treatment, patient noted 80% improvement which greatly contributed to her increased self-esteem and patient satisfaction. The highlight of this case was to report a rare clinical manifestation of cutaneous tuberculosis arising on burn scar lesion which is the first case report in the Philippines.

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

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INTRODUCTION

Cutaneous tuberculosis or TB of the skin is a rare manifestation which presents with a wide array of clinical findings depending on the source of infection: Endogenous or Exogenous route of infection and the immune status of the patient.^[2] Tuberculosis is highly endemic especially in our country. It is estimated that 14% of TB patients present the extrapulmonary form of the disease and 1–2% of these have cutaneous presentation.^[1,2,8]

Lupus vulgaris, a subtype of cutaneous tuberculosis, is the most common form of cutaneous tuberculosis comprising of 64%.^[1,3] It is a chronic, progressive, endogenous paucibacillary form of cutaneous tuberculosis which presents primarily in a previously sensitized individual.^[1] Various types of lupus vulgaris include plaque, ulcerative, mutilating, vegetative, papular or nodular and hypertrophic forms. Of the different types, the most common of which is the plaque form which presents with irregular borders, surface with can either be smooth or covered with psoriasiform scales. Initial lesions would present as brownish to red, soft, solitary plaque, having a centrifugal growth which eventually coalesce to form plaques. The most common location of Lupus Vulgaris are the lower half of the body involving the legs, thigh and feet however, unusual locations like the extremities and face can also be affected.^[5,6] The epidemiology greatly affects female with a 2:3 ratio to males.^[1] The average prevalence of 0.37% among the general skin patients.^[7]

The diagnosis of this disease is a crucial factor since there are numerous published cases that were often misdiagnosed due to variations in clinical presentation. Most of the diagnostic methods for cutaneous tuberculosis confer lower sensitivity and specificities.^[3] There are numerous evidence supporting the role of therapeutic trial when diagnostic work up resulted to a negative result. If left untreated, this disease can cause extensive destruction and disfigurement which eventually can lead to development of squamous

cell carcinoma. The aim of this paper is to impart the importance of a good clinical correlation with a histological and diagnostic work up results in a multidisciplinary approach among inter-professional team members to optimize outcome results for our patients.

CASE REPORT

We are presented with a 24-year-old female, Filipino, housewife, from Bulacan city. Her chief complaint was the appearance of erythematous plaques arising on burn scar lesions that occurred twenty years ago. History started two years prior to consult when the patient noted appearance of few erythematous plaque on the left arm associated with pruritus. Patient self-medicated with topical application of BL cream (clobetasol + ketoconazole) applied once a day which provided temporary relief of pruritus with partial resolution of erythematous skin lesions on affected areas. In the interim, the patient noted gradual progression of similar lesions now with pustules and erosions specifically confined on areas of burn scar lesions on the right arm, trunk, left inner thigh, back and face associated pruritus and tenderness. Patient had no history of PTB nor exposure to close contacts with PTB. She denies weight loss, fever and night sweats. There was no history of non-resolving wound, and exposure to UV radiations. Numerous consults were done with different physicians wherein diagnosis was not disclosed and was prescribed with fourteen days of unrecalled dosage of oral antibiotics wherein the patient noted no resolution of skin lesions. This led the patient to sought consult in our institution for further evaluation and work up.

The review of systems was generally unremarkable. Patient had a history of a 3rd degree scald burn lesion at three years of age. The patient was hospitalized in a tertiary hospital with unrecalled management and disposition. Family history revealed a history of Pulmonary tuberculosis – completed six months of treatment on the maternal side, there was no exposure to

relatives who had PTB at the course of the disease. The patient is a non-smoker, non-alcoholic beverage drinker and denies illicit drug use. The patient claims to be compliant with sunscreen use and sun protective clothing prior sun exposure. There was no history of exposure to UV radiation.

Physical examination was generally unremarkable except for BMI of 28.1- overweight. No palpable lymph nodes were noted on the body. Cutaneous examination revealed multiple, well

defined, irregularly shaped, erythematous coalescing plaque topped with scaling, some with hemorrhagic crusts and excoriations on the bilateral side of the face, chest, abdomen, back, bilateral upper extremity and inner thigh. Dermoscopy examination showed Irregular dilated vessels, yellow to orange areas with follicular plugging, hemorrhagic crust and scales on the right and left side of the face, chest, abdomen, arms and back. Diascopy examination was negative for apple jelly sign.



Figure 1 A-C. Multiple, well defined, irregularly shaped, erythematous coalescing plaque topped with scaling on the face and shoulders



Figure 2 A-B. Multiple, well defined, irregularly shaped, erythematous coalescing plaque topped with scaling some with hemorrhagic crusts and excoriations on the chest, abdomen and back.



Figure 3 A-B.



Figure 4 A-B. Multiple, well defined, irregularly shaped, erythematous coalescing plaque topped with scaling on the bilateral upper extremity.

A 4mm skin punch biopsy was done which showed tuberculoid granulomas in the dermis with caseation necrosis, dermal lymphocytic infiltrates

and several Langhans type multinucleated giant cells. These findings were consistent with cutaneous tuberculosis.

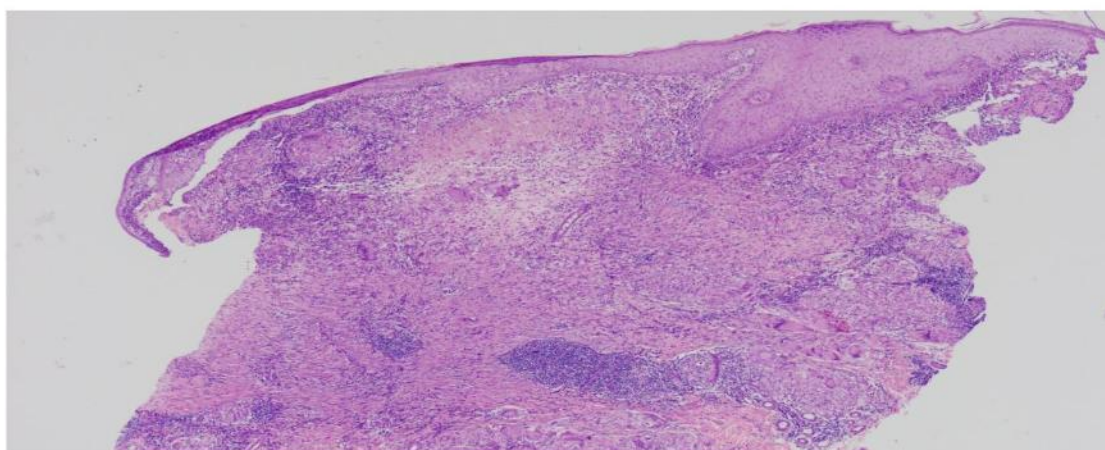


Figure 5. Histopathology (H & E stain) of the patient's skin showing tuberculoid granulomas in the dermis, lymphocytic infiltrates and Langhans type multinucleated giant cells in LPO.

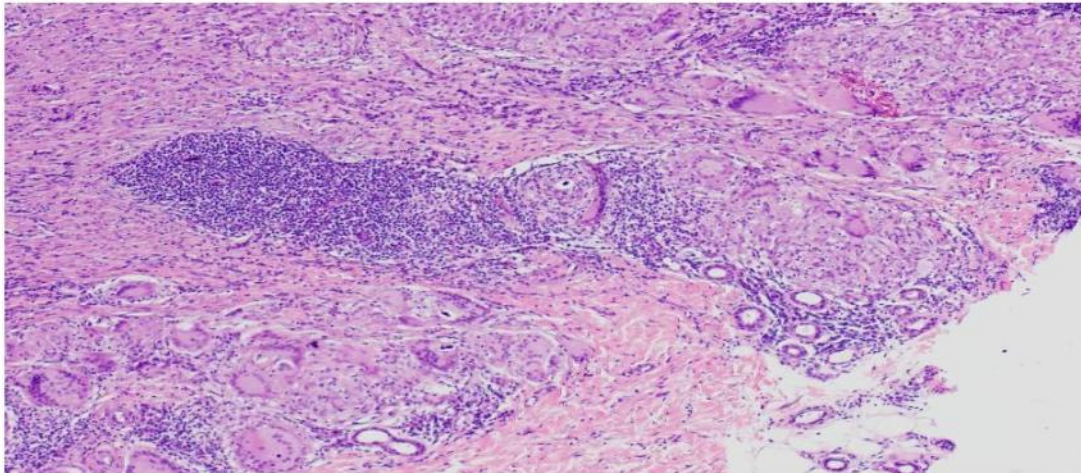


Figure 6. Histopathology (H & E stain) of the patient's skin showing tuberculoid granulomas in the dermis, lymphocytic infiltrates and Langhans type multinucleated giant cells in HPO

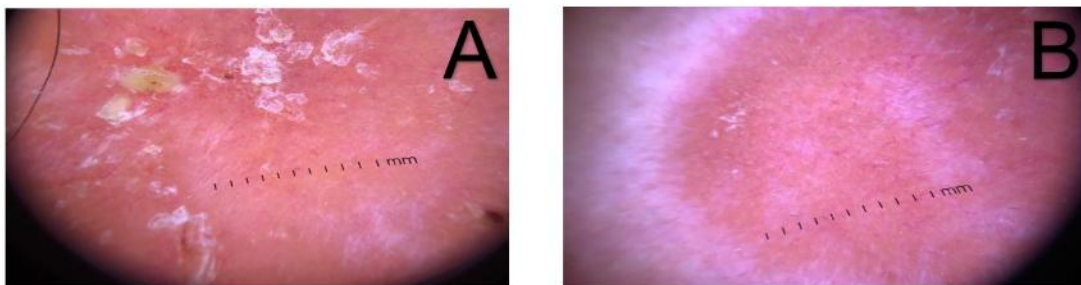


Figure 7 A-B. Dermoscopy examination of the Left (A) and Right(B) side of the face showing linear branching vessels, yellow to orange areas with white scales

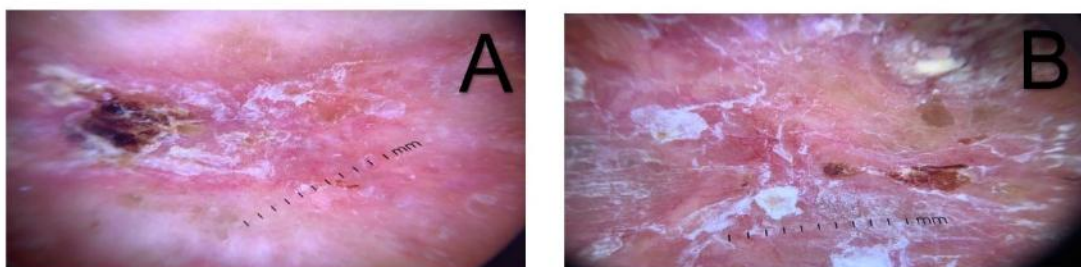


Figure 8 A-B. Dermoscopy examination of the chest showing linear branching vessels, yellow to orange areas with follicular plugging and hemorrhagic crust and white scales on the chest



Figure 9 A-B. Negative apple jelly sign as depicted by the diascopy examination of the abdomen (A) and left side of the face (B)

Other ancillary tests such as complete blood count showed monocytosis, eosinophilia and thrombocytosis, Blood chemistry showed a mildly elevated liver enzymes. Urinalysis and Chest Xray was generally unremarkable. Results of the slit skin smear showed no evidence of bacilli; fite faraco stain was negative. Fungal culture showed no fungus isolated after 4 weeks incubation. Gram staining of the wound tissue showed moderate pus cells, few epithelial cells with no organisms seen. Cutaneous tuberculosis work up such as tissue GeneXpert, sputum GeneXpert, tissue culture and PCR all yielded a negative result.

The patient was started with anti-tuberculosis medications: intensive phase consisting of Rifampicin 450mg/day, Isoniazid 300mg/day, Pyrazinamide 1500mg/day and Ethambutol 750mg/day and maintenance phase consisting of Rifampicin 600mg/day and Isoniazid 600mg/day. Patient was also given zinc + copper + sucralfate cream BID on affected lesions and mild soap for daily bathing. The patient was then referred to the service of ophthalmology, infectious disease and plastics surgery for co-management.

The patient noted an 80% improvement overall with noted decrease in the appearance of erythema and scaling all over the body. The plastic surgery service appraised the patient for possible excision and local advancement flap to address contractures on the sternal and back area. One month after initiation of treatment, patient developed blurring of vision and is being managed by Ophthalmology service as a case of Anterior Uveitis probably TB Uveitis; intermediate uveitis bilateral eye and is currently maintained on prednisone eye drops and on tapered oral prednisone.

DISCUSSION

Lupus vulgaris, a subtype of cutaneous tuberculosis, is the most common form of cutaneous tuberculosis.^[1] It is an extremely chronic, progressive, endogenous paucibacillary form of cutaneous tuberculosis which occurs primarily in the previously sensitized individual especially that tuberculosis is highly endemic in our country. Lesions present as brownish to red, soft, solitary plaque, having a centrifugal growth which eventually coalesce into a plaque. The plaques grow peripherally with serpiginous borders accompanied by central discoloration and atrophy.^[3] Progression is characterized by elevation,

a deeper brownish and formation of a plaque. The most common location of Lupus Vulgaris are the lower half of the body involving the legs, thigh and feet, however, the extremities and the face can also be affected as seen in our patient. Spontaneous involution may occur, and new lesions may arise within old scars as depicted by the patient. Female are more likely to be affected 2 to 3 times as often as males.^[1] According to the Philippine Dermatological Society, there are a total of 260 cases of cutaneous tuberculosis, of the 260 cases diagnosed since 2011, 129 cases of which are lupus vulgaris type. Based from the data provided, there is a predominance of female genders presenting with the disease most commonly at second to third decade of life, however, it can occur at an early age. In our institution, we have a total of 9 cases of biopsy proven cutaneous tuberculosis since 2015. However, there are no other data supporting appearance of cutaneous tuberculosis on burn scar in our local setting, hence an enigmatic presentation.

The pathophysiology of CTB is attributed to Mycobacterium tuberculosis- occasionally M. bovis or BCG vaccination and can be contracted either primarily by direct inoculation of the bacilli or at the site of previous BCG vaccination individuals with moderate immunity or secondarily by hematogenous and lymphatic spread from an underlying distal focus.^[1,3] After infection, the macrophages in the infected tissues are first activated to eliminate the bacilli at the infected site. Monocytes, lymphocytes, neutrophils, and dendritic cells are then recruited by the chemokines and cytokines released by macrophages which eventually lead to granuloma formation.^[4] The host characteristics, the load and pathogenicity of the bacillus strain, and the method of infection determine the clinical outcome of CTB.^[4]

The diagnosis of cutaneous tuberculosis can either be bacteriologically confirmed or clinically diagnosed. For bacteriologically confirmed cases, patient with a smear/culture/rapid diagnostic test from a biological specimen in an extra pulmonary site positive for AFB or MTB complex and for clinically diagnosed cases, patient with histological and or clinical or radiologic evidence consistent with active extra pulmonary tuberculosis. The absolute criteria consist of finding of M. tuberculosis from tissue culture, inoculation on guinea pig, or positive result on PCR. The relative criteria are based on history taking and clinical manifestations which supported for the diagnosis of cutaneous TB, active TB found on other organs, finding of AFB on lesions, finding of tuberculous granuloma on histopathological examination, positive tuberculin test, and responsiveness toward anti-TB medications.^[8]

The differentials for Cutaneous tuberculosis includes the following:

Squamous cell carcinoma, the second most common skin cancer after basal cell carcinoma and the most common skin cancer in immunosuppressed organ transplant recipients worldwide. SCC was initially considered as a differential due to the typical clinical finding of skin-colored to erythematous plaques with marked hyperkeratosis on sun-exposed areas of the skin such as the face and the forearm which was present in the patient, however, was ruled out since lesions depicted by the patient are not seen on a background of pre-invasive tumors or in situ tumors such as actinic keratosis or Bowen's disease which are characteristic of SCC. Risk factors attributed to the growth of SCC involves increasing age, red hair, blue eye, white complexion, and increased sun/ UV exposure. All aforementioned risk factors and dermoscopy findings such as white

structureless area, looped vessels and central keratin were not presented in the patient, hence this disease is less likely.

Hansen's disease, a chronic granulomatous disease affecting mainly the skin and nerves caused by the obligate intracellular pathogen, mycobacterium leprae which infects mucous cutaneous tissues and peripheral nerves leading to loss of sensation of the skin. Hansen's disease was considered as a differential in this patient due to the presence of erythematous plaques on the body, however, was ruled out since Hansen's disease usually presents with loss of sensation in lesions associated with hypohidrosis, alopecia and nerve enlargement which is not present in the patient. The evolution of Hansen's disease which usually starts with hypopigmented macules or patches and dermoscopy finding yellow white areas, distorted pigment network, widened skin furrows/ chrysalis-like structures, slight diminution of appendageal structures and hairs were not depicted by the patient, hence this disease entity was ruled out.

Treatment options for Cutaneous tuberculosis following the standard regimen of WHO recommendation consists of Isoniazid, Rifampicin, Pyrazinamide and ethambutol are the first line treatment for all types of cutaneous tuberculosis. The minimum duration of treatment is 6 months- 2 months of intensive phase consisting of Rifampicin 450mg/day, Isoniazid 300mg/day, Pyrazinamide 1500mg/day and Ethambutol 750mg/day and 4-months of maintenance phase consisting of Rifampicin 600mg/day and Isoniazid 600mg/day. The patient was initially given a course of 6 months duration of anti- tuberculosis medications.

In 2018, Akinola et al reported a case of a 13 year old female who presented to Ear, Nose and Throat (ENT) clinic with a non-healing wound on the

tip of the nose extending on the bridge for 4-years duration. Despite a negative result for tuberculosis work up, the patient was given quadruple anti-tuberculosis medication for 7 months wherein resolution of lesions were noted. This was the basis for the treatment plan to our patient with marked improvement of skin lesions.^[1,10]

In 2019, Mann et al emphasized the importance of the histopathology (52.0%) as a diagnostic tool in Cutaneous Tuberculosis^[2], since in a significant portion of cases, the cultures are negative which is similar to our patient. Another study published 2018 by Khadka et al, claimed that a negative culture would be attributed to a decreased bacillary load and that a negative PCR/GeneXpert is linked to an unevenly microbial distribution in paucibacillary forms of cutaneous tuberculosis, specifically lupus vulgaris.^[3,5] The negative result from the tissue culture, the atypical localization of the lesion and its characteristic were factors which contributed to the diagnostic dilemma in our case similar to various journals published.

A case by Hagiwara et al presented with a similar clinical presentation to our patient. A 66-year old Japanese woman with squamous cell carcinoma arising from lupus vulgaris on an old burn scar on the left lower extremity was given a therapeutic trial of HRZE medications despite negative diagnostic work up. Resolution of lesions were noted after imitiation of medications.^[10]

Lupus Vulgaris is a long term disorder, and without appropriate therapy it can progress over many years often misdiagnosed. This disease entity can lead to extensive destruction and disfigurement which impairs functions of daily living and eventually if left untreated can develop carcinoma, most specifically squamous cell carcinoma and basal cell carcinoma.



Figure 10 A-F. Showed marked improvement in terms of erythema and scaling on the face and shoulders after twelve months of treatment.



Figure 11 A-B. Showed marked improvement in terms of erythema and scaling all over the body after twelve months of treatment.

CONCLUSION

Lupus Vulgaris arising on a burn scar lesion is an enigmatic presentation of cutaneous tuberculosis due to its diverse clinical manifestations and ambiguity in diagnosis. This case exhibits that a therapeutic trial of medications can be initiated in instances where diagnostic work up yielded negative results despite histological features consistent with cutaneous tuberculosis, specifically lupus vulgaris. The decision to extend treatment regimen would depend on correlation of clinical features and histopathologic findings. This study recommends the accessibility and availability of diagnostic work up for cutaneous tuberculosis in our country and lastly, impart the importance of treatment response as a means to clinically clinch the diagnosis despite a negative diagnostic work up due to the endemicity of tuberculosis in our country.

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Spontaneous Remission of Classic Kaposi Sarcoma in an Elderly Filipino Female

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ABSTRACT

Background: Kaposi sarcoma (KS) is a lymphoangioproliferative condition linked to human herpesvirus-8. KS presents in four clinical variants: classic, iatrogenic, endemic, and AIDS-related. The classic type has a chronic course and primarily affects people of Eastern European Jewish or Mediterranean heritage, with a higher incidence in males.¹ Approximately 70% of patients respond partially or satisfactorily to treatment, 20% experience recurrence, and 10% show progression despite treatment.² Furthermore, there have been documented cases of self-regression in the classic type of KS.³

Observation: We report a case of a 74-year-old, Filipino, female, who has no known comorbidities, presented with a one-year history of multiple, non-pruritic, non-tender, violaceous, firm, nodules, widely disseminated ranging from 0.5 cm to 1 cm in its widest diameter which showed spontaneous regression. The histopathological analysis revealed spindle cells within collagen bundles and an associated vascular proliferation, which is indicative of Kaposi Sarcoma. Immunostaining with CD31 highlighted the presence of vascular channels within these collagen bundles. HIV test showed negative result. She was referred to an oncology clinic for further treatment but did not comply. Ten months after, patient followed up with clear lesions showing spontaneous resolution of KS.

Key message: This case presents a classic Kaposi Sarcoma in an elderly, Filipino, female who spontaneously regressed without any therapy.

INTRODUCTION

Kaposi sarcoma (KS) is a lymphoangioproliferative condition linked to human herpesvirus-8. KS presents in four clinical variants: classic, iatrogenic, endemic, and AIDS-related.¹ These variants share common histological characteristics, including the presence of proliferating malignant spindle cells and ill-defined vascular channels or slits. Classic KS, initially documented by Moritz Kaposi in 1872, predominantly affects older men from Eastern European and Mediterranean regions.⁴ These tumors follow an indolent course and usually start on the skin as unilateral or bilateral bluish-red macules resembling hematomas on the lower extremities. They progress slowly both horizontally and vertically, evolving into firm plaques and eventually nodules.⁵ Treatment options are mainly determined by the type and location of the lesions which include radiation therapy, chemotherapy, and surgical excision.⁶ Spontaneous regression of Kaposi's sarcoma is a rare occurrence, except in the iatrogenic immunosuppressive type. Nevertheless, there have been reported instances of classic Kaposi sarcoma exhibiting spontaneous regression.³

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

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CASE REPORT

A 74-year-old Filipino female presented with a one-year history of multiple non-pruritic erythematous macules that initially appeared on her lower extremities and gradually progressed into violaceous firm nodules not associated with weight loss, poor appetite, cough, colds, abdominal discomfort, or changes in bowel habits. Her past medical history did not include any blood-related conditions, diabetes, cancer, recent blood transfusions, or organ transplants. Additionally, her sexual history revealed monogamy and no documented cases of sexually transmitted diseases.

Physical examination revealed patient in a clinically stable condition, with no signs of mucosal lesions or enlarged lymph nodes. Dermatologic examination revealed multiple erythematous to violaceous firm, non-tender nodules on the face, trunk, upper, and lower extremities (Figure 1A).

Laboratory tests results, complete blood count, creatinine, blood urea nitrogen, SGPT, SGOT, TPAG, fasting blood sugar, lipid profile, urinalysis, stool analysis, RPR/VDRL, and HIV tests, were all within normal limits. Computed tomography scans of the neck, chest, and entire abdomen were unremarkable.

Histopathological analysis revealed the spindle cells in nodular aggregates, with some dissecting within collagen bundles. In certain areas, there was evidence of vascular proliferation, with small blood vessels protruding into a vascular space (Figure 3). Immunostaining with CD31 further emphasized the presence of vascular channels within the collagen bundles, a finding consistent with the diagnosis of Kaposi Sarcoma.

The patient was referred to oncology service for further treatment but was non-compliant. She followed up ten months later which showed resolution of previously noted KS lesions. Upon investigation, patient denied any treatment done for her condition signifying spontaneous resolution of KS (Figure 1B).





FIGURE 1. A. Skin lesions showing violaceous firm nodules on the back, and upper extremities, measuring between 0.5cm and 1 cm in their widest diameter. **B.** Patient skin showing spontaneous resolution of KS lesions.

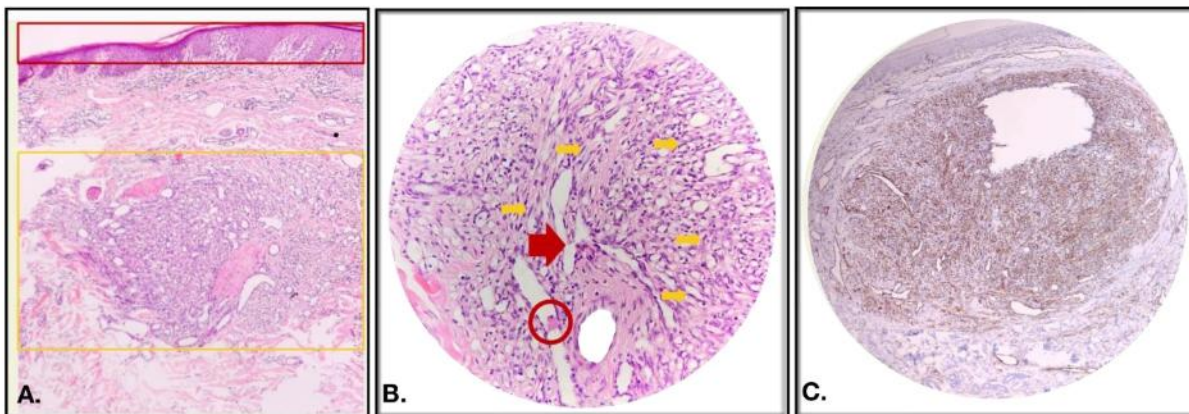


FIGURE 2.

A. H&E 10x magnification: Basketweave orthokeratosis (red box). Moderate superficial perivascular infiltrates composed of lymphocytes and few extravasated erythrocytes (yellow box).

B. H&E 40x magnification: Spindle cells in nodular aggregates, some dissecting within collagen bundles. (yellow arrow). Vascular proliferation with small-vessel protrusion into a vascular space, promontory sign (red arrow) containing few extravasated erythrocytes (red circle).

C. Immunohistochemical staining: CD31 highlighted vascular channels between collagen bundles.

DISCUSSION

Kaposi's sarcoma (KS) is a rare and malignant vascular condition that arises from lymphatic endothelial cells. It primarily affects the skin and mucous membranes but can also involve the lymphatic system and internal organs like the gastrointestinal tract, lungs, or liver. This condition

was initially documented in 1872 by Moritz Kaposi.⁷ Prevalence of KS remains unknown and still considered rare in the Philippines despite recognition as one the common malignancies associated with HIV infection. However, it is expected to increase due to the rising number of Filipinos being diagnosed with HIV infection each day.⁸

There are four primary types, classic (occurring sporadically), African (endemic), transplant or immunosuppression-related (iatrogenic), and acquired immune deficiency syndrome (AIDS)-related (epidemic) KS.¹ Classic KS predominantly affects men, with a male-to-female ratio ranging from 2:1 to 17:1, and is commonly observed in people of Eastern European and Mediterranean descent. This subtype typically appears after the age of 60. The primary risk factors linked to the development of classic KS are prior HHV-8 infection and increasing age. Endemic KS, which is not associated with HIV infection, is also prevalent in equatorial Africa, particularly among children and adolescent males. It accounts for 9% of all cancers in Central Africa, particularly in sub-Saharan Africa. Iatrogenic KS may develop in individuals who are subjected to extended periods of immunosuppressive therapy. The chances of developing KS are notably increased, ranging from 50 to 500 times higher, in organ transplant recipients when compared to the general population. Epidemic HIV-associated KS is the most common AIDS-defining neoplasm, and since the start of the HIV pandemic, has become the most common form of KS. The advancement of this condition can exhibit considerable variation, extending from isolated, stable lesions that persist for years to fast and fatal courses. Approximately 95% of all KS are attributed to human herpes virus 8 (HHV-8).⁷

HHV8 is a herpesvirus that has an affinity for lymphatic and blood vessel cells. Its genetic makeup contains numerous proteins responsible for promoting cell growth, preventing cell death, and inducing inflammation. In KS, many of the spindle cells primarily express dormant HHV8 genes, but some also express lytic genes. These lytic genes might play a role in the formation of new blood vessels and in signaling between cells, contributing to the development of KS. While various laboratory and animal models have been

created to study this virus, a comprehensive system that accurately represents the full process of KS development is still lacking.⁹

The primary mode of HHV8 transmission is through horizontal means, primarily via saliva. However, it necessitates prolonged and frequent contact for transmission to occur, as seen in cases such as mother-to-child transmission or sexual interactions.¹⁰ Although KSHV transmission through blood transfusions is rare, isolated instances of transmission through organ transplants have been reported. Conversely, vertical transmission routes seem to have a minimal role in the virus's spread.⁹

Diagnosing KS begins with a thorough history and physical examination, but the key step is histopathological testing, that including H&E and immunohistochemical staining.^{7,11} These examinations often show the presence of spindle cell growth within intricate blood vessels in the dermis, along with the "promontory sign" denoting branching vessels around larger ectatic pre-existing vessels and skin adnexa. Findings may also include extravasated red blood cells, macrophages filled with hemosiderin, occasional hyaline globules, and the presence of lymphocytes and plasma cells. As KS progresses, these features become more prominent, and the slit-like openings in the vessels become more noticeable. Immunohistochemistry is crucial for identifying endothelial cells in KS and aiding diagnosis. CD34 and CD31 staining indicates differences from normal endothelial cells. Spindle cells in KS lesions test positive for CD31 and CD34.¹¹ Additionally, while qualitative or quantitative assessments of HHV-8 PCR and HHV-8 antibody tests can be conducted due to HHV8's association with KS, these tests are not routinely necessary in clinical practice. HIV serology should be also carried out to exclude AIDS-related KS.⁷

Goals of treatment of KS is to induce regression of the lesions, control the disease's progression, and alleviate symptoms. Currently, there is no a universally accepted "standard therapy regimen" for KS treatment. The choice of treatment should depend on prognostic factors, the patient's overall health, and their preferences. Local treatment options include surgery, local immunotherapy, cryotherapy, local chemotherapy, and electrochemotherapy. These approaches have been investigated in clinical trials, especially for classic KS. For treating deeper or mucosal lesions radiotherapy can be effective. However, if with lymph node involvement, or with internal organ complications, it is important to promptly consider systemic treatment, regardless of the specific type of KS.⁷ Spontaneous regression of KS is rare, except in the case of iatrogenic immunosuppressive type, but there have been reported instances of classic Kaposi sarcoma demonstrating spontaneous regression.³

CONCLUSION

We present a rare case of spontaneously resolved, immuno and histopathologically confirmed case of Classic Kaposi Sarcoma in an elderly Filipino female.

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Pregnancy in a Case of Chronic Myeloid Leukemia: A Case Report*

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ABSTRACT

Chronic Myeloid Leukemia, a chronic hematopoietic stem cell disorder, is uncommon among younger age group such as pregnant patients. Due to the rarity of this condition in pregnancy, there are no randomized controlled trials to address the optimal management of this condition. We are presented with a 26 year old patient, who had an unplanned pregnancy in the advanced phase of the disease. Due to the risk to the mother in delaying treatment, she was continued on Imatinib, a tyrosine kinase inhibitor, which is a known fetal teratogen. Her pregnancy was carried to term. The patient delivered via spontaneous vaginal delivery to a live, neonate, with findings of hydrocele and syndactyly on the 4th and 5th digit of the right foot. Due to the maternal disease progression, she presented with postpartum hemorrhage, in contrast to an augmented procoagulant state among normal pregnancies. Obstetric adjunctive measures, such as intrauterine balloon tamponade and uterine artery ligation, were done. The patient was discharged stable.

Keywords: chronic myeloid leukemia, imatinib, postpartum hemorrhage, pregnancy

INTRODUCTION

Chronic Myeloid Leukemia (CML) is associated with the fusion of two genes: BCR (on chromosome 22) and ABL1 (on chromosome 9) resulting in the BCR-ABL1 fusion gene. This condition signals uncontrolled production of granulocytes, resulting in decrease of healthy blood cells in the bone marrow. Hence, symptoms are usually associated with anemia & leukocytosis. The diagnosis of leukemia in pregnancy is more complicated than in a non-pregnant state due to its non-specific symptoms, which are also attributed to pregnancy.

For patients presenting in the advanced phases, the risk to the mother in delaying treatment is higher. In the first trimester, consideration must be given to terminating the pregnancy, and immediate treatment is warranted. In the second or third trimester, it may be possible to deliver the baby earlier. The first line therapy is Imatinib, a tyrosine kinase inhibitor, which is a known teratogen. It does not only target BCR-ABL tyrosine kinase, but also several other proteins that are known to have functions that may be important in gonadal development, implantation, and fetal development.

In advanced phases of CML, occurrence of bleeding is not uncommon, and may be due to abnormal quantity or quality of thrombocyte.

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

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OBJECTIVES

Main Objective:

To present a case of an unplanned pregnancy in a patient in the advanced phase of Chronic Myeloid Leukemia

Specific Objectives:

- To report a rare case of Chronic Myeloid Leukemia in pregnancy
- To report the clinical presentation of a patient in advanced phases of Chronic Myeloid Leukemia
- To present the approach to management of a patient with Chronic Myeloid Leukemia in pregnancy
- To present a suggested algorithm for the management of patients who are planning an elective pregnancy
- To present the possible pregnancy outcomes of patients in advanced phases of Chronic Myeloid Leukemia

CASE REPORT

This is the case of a 26-year old patient, Gravida 3 Para 2 (2002), admitted at 36 weeks 5 days Age of Gestation (AOG).

The patient was diagnosed with Chronic Myeloid Leukemia (CML) four years prior to admission, initially presenting with generalized body weakness and undocumented fever. At that time, she presented with pallor. Other physical examination findings were normal. Upon diagnostic work-up, complete blood count (CBC) revealed anemia, leukocytosis, and thrombocytopenia, with left shifted differential count. Ultrasound of the whole abdomen revealed splenomegaly. Hence, she was worked up for probable hematologic disorder, such as Flow Cytometry, Bone Marrow Biopsy, and Fluorescence in situ hybridization (FISH). The results were compatible with a myeloproliferative neoplasm, and indicated Chronic Myeloid Leukemia, in Chronic Phase. The patient was started on Hydroxyurea 500

mg/capsule, 1 capsule once daily, and Nilotinib 150 mg/tablet, 2 tablets twice daily. She was compliant with her medications for a year. However due to financial constraints, she eventually discontinued her medications. She was asymptomatic and no follow-up consultation was done. She had her first and second pregnancies two and four years after being diagnosed, respectively. She had irregular prenatal consultations at a lying-in clinic for both pregnancies, and did not disclose her history of CML. Both pregnancies were carried to term, and delivered via spontaneous vaginal delivery at a lying-in clinic. She had an unremarkable labor and delivery, and was discharged 2 days postpartum.

Two years prior to admission, the patient experienced abdominal fullness, which prompted her to seek consultation with a hematologist. Upon diagnostic work-up, there was noted progression of disease to Accelerated Phase diagnosed by complete blood count, and peripheral blood smear. Her medication was revised to Imatinib 400 mg/tablet, 1 tab once daily, which she took regularly until her unplanned third pregnancy.

One year prior to admission, the patient became pregnant, but did not immediately seek prenatal consultation. At 8 weeks 3 days AOG, she sought follow up consultation with her hematologist. Due to the risk to the mother in delaying CML treatment in the advanced phase of the disease. All possible fetal & maternal complications were discussed to the patient, as well as treatment options and plan. The patient decided to continue with her pregnancy. The patient was continued on Imatinib. At 21 weeks AOG, she had her first prenatal consultation with a private obstetrician in Rizal. CBC revealed anemia (Hemoglobin: 99 g/L, Hematocrit: 0.31), leukocytosis (WBC: $79.26 \times 10^9/L$) and thrombocytosis (Platelet count: $1123 \times 10^9/L$). The rest of the diagnostics requested were normal. She had irregular prenatal consultations. Due to high risk pregnancy, she was

advised consultation with a perinatologist, which she did at 35 weeks 2 days AOG. She was advised labor and delivery at a tertiary hospital. Third trimester ultrasound done revealed an incidental finding of hydrocoele on the left fetal scrotum. No other anomalies were noted at this time. She had 2 prenatal consultations prior to admission.

Few hours prior to admission, the patient had irregular uterine contractions. Physical examination revealed normal vital signs, but with an enlarged spleen measuring 18 x 12 cm. On internal examination, cervix was dilated to 6 cm, 50% effaced, intact bag of water, cephalic, station - 2. The patient was admitted for trial of labor. CBC upon admission revealed anemia (Hemoglobin: 96 g/L, Hematocrit: 0.29), leukocytosis (WBC: 179.4 x 10⁹/L) and thrombocytosis (Platelet count: 1222 x 10⁹/L). She had an unremarkable labor course, and delivered via spontaneous vaginal delivery, to a live, term, singleton, male, birth weight 2860g, APGAR score 9,9, Maturity Index 37 weeks, appropriate for gestational age. There was minimal blood loss intrapartum. The uterus was maintained well-contracted. The patient then underwent postpartum bilateral salpingectomy. Upon re-examination post-operatively, blood clots were evacuated from the vagina, amounting to approximately 800 mL. Due to the blood loss, the patient was transfused with 1 unit of packed red blood cells (PRBC). Post-operative medications were Oxytocin drip, Methylergometrine Maleate, Tranexamic Acid, Cefuroxime, and Ketorolac.

On the second hospital day, there was moderate vaginal bleeding consuming 4 diapers per day. On examination, vital signs revealed tachycardia and fever. She had pale palpebral conjunctivae, and pale lips. There were clear breath sounds on chest auscultation. The uterus was well contracted. Serial pelvic examination, and reinspection of the vaginal canal, and cervix were done. There is accumulation of blood clots in the

vaginal canal. On re-examination, retained placental fragments was ruled out. CBC revealed anemia (Hemoglobin: 85 g/L, Hematocrit: 0.24), leukocytosis (WBC: 204.5 x 10⁹/L) and thrombocytosis (Platelet count: 1196 x 10⁹/L). Urinalysis revealed 4-8 pus cells/hpf, and negative esterase. Chest radiograph revealed no significant cardiopulmonary findings. Hematology service ordered to hold blood transfusion. Hydroxyurea was increased to 500 mg/capsule, 2 capsules twice daily.

On the third hospital day, there was persistence of heavy vaginal bleeding, consuming 7 fully-soaked diapers per day. On examination, there was persistence of tachycardia and fever. She had pale palpebral conjunctivae, and pale lips. There were clear breath sounds on chest auscultation. The uterus was well contracted. CBC revealed anemia (Hemoglobin: 63 g/L, Hematocrit: 0.20), leukocytosis (WBC: 191 x 10⁹/L) and thrombocytosis (Platelet count: 1272 x 10⁹/L). Coagulation tests, such as prothrombin time (PT), activated partial thromboplastin time (aPTT), were normal. Hematology service ordered blood transfusion of 2 units PRBC. Transvaginal ultrasound (Appendix 1) done revealed a *slightly enlarged, well contracted uterus (measuring 10.6 x 7.7 x 11.2 cm); thickened endometrium (measuring 2.0 cm, described as hyperechoic, endometrial midline not defined, with regular endometrial-myometrial junction, and no cystic areas; minimal color on Doppler flow)*, compatible with postpartum findings.

As adjunctive procedures to help arrest postpartum hemorrhage, intrauterine balloon tamponade and uterine artery ligation were done. A sterile glove was used as an improvised balloon, and instilled approximately 300 mL of plain normal saline solution (PNSS). The balloon was inflated in the uterus, until the uterus became firm. Transvaginal uterine artery ligation was done.

On the fourth hospital day, vaginal bleeding stopped with the balloon tamponade in place. On examination, there was persistence of tachycardia and fever. There was decrease in pallor noted. There were clear breath sounds on chest auscultation. The uterus was well contracted. CBC still revealed anemia (Hemoglobin: 70 g/L, Hematocrit: 0.22), leukocytosis (WBC: $148.6 \times 10^9/L$) and thrombocytosis (Platelet count: $1127 \times 10^9/L$). The intrauterine balloon tamponade was subsequently removed. The patient was closely monitored.

On the fifth hospital day, there was vaginal spotting, with no increase in amount after removal of balloon tamponade. On examination, there was resolution of fever. The patient had pink palpebral conjunctivae, and pink lips. The uterus was well contracted. CBC revealed anemia (Hemoglobin: 89 g/L, Hematocrit: 0.29), leukocytosis (WBC: $142.1 \times 10^9/L$) and thrombocytosis (Platelet count: $1040 \times 10^9/L$). The patient was closely monitored. The rest of the hospital stay was unremarkable, and the patient was discharged on the seventh hospital day.

The patient was advised not to breastfeed. Although in some literatures, imatinib is demonstrated not to reach therapeutic concentrations in an infant's blood during breastfeeding¹, there is still lack of clinical evidence in infants, and the excellent alternative of bottle feeding supports this recommendation. The patient was likewise advised to continue regular consultations with her hematologist.

CASE DISCUSSION

Chronic Myeloid Leukemia (CML) is a chronic hematopoietic stem cell disorder driven by the BCR-ABL1 chimeric gene product – a constitutively active tyrosine kinase resulting from a reciprocal balanced translocation. It is associated with the fusion of two genes: BCR (on

chromosome 22) and ABL1 (on chromosome 9) resulting in the BCR-ABL1 fusion gene. It signals the bone marrow to produce too many white blood cells (WBC).² Uncontrolled production of mature and maturing granulocytes, predominantly neutrophils, but also basophils and eosinophils. As a result, the number of healthy blood cells in the bone marrow is usually lower than normal.³

CML has no identified risk factors or cause. It is probably a genetic abnormality, and is not an inherited disease. Exposure to high-dose ionizing radiation increases the incidence, with a mode of increased incidence that ranges from 4-11 years in different exposed populations.² The patient has no personal history of exposure to radiation, nor a family history of hematologic disorders.

CML accounts for approximately 15% of all cases of leukemia. Its annual incidence is 1.5 cases per 100,000 individuals. It presents as approximately 10% cases of pregnancy-associated leukemia. Leukemia in pregnancy is rare, and is estimated to occur in only 1 in 75,000 to 100,000 pregnancies, although its incidence is poorly documented. The median age at diagnosis is 55-65 years.³ Hence, it is uncommon in children, and younger age group, such as pregnant patients.

Approximately 30% of patients are asymptomatic at the time of diagnosis. The disease is discovered coincidentally when an elevated WBC is noted upon prenatal evaluation.⁴

Symptoms are gradual in onset, and may include easy fatigability, abdominal discomfort, early satiety, and many other symptoms associated with anemia & leukocytosis. Unfortunately, women with cancer have non-specific symptoms which also are attributed to pregnancy. Hence, the diagnosis of a disease such as leukemia in pregnancy is more complicated

than in non-pregnant women, since anemia, leukocytosis and thrombocytopenia are common in pregnant women.

The diagnostic criteria for leukemia in pregnant women are the same as for the normal population. Apart from the history and physical examination, diagnostic work-up may include: complete blood count (CBC), peripheral blood smear (PBS), flow cytometry, bone marrow aspiration, and fluorescence in situ hybridization (FISH).²

There is no staging system in CML. However, it has three (3) phases, the Chronic, Accelerated and Blast Phases.² Phases are based mainly on the number of immature WBC (blasts) in the blood or bone marrow. The natural history of the disease is to evolve into an Accelerated Phase, in which cytopenias develop and response to Chronic Phase therapy is lost. In general, Chronic Phase has a higher probability of survival. Whereas, advanced phases such as Accelerated and Blast Phases, have more symptoms, and has higher resistance to therapy. Pregnancy, however, does not alter the normal course of CML.⁵

Since pregnancy is rare in CML, there are no randomized controlled trials to address the optimal management of this condition.^{6,7} At the present time, there is no consensus on how to manage different pregnancy situations in CML. But there is a suggested algorithm for the management of pregnancy in patients with CML who are on treatment with Imatinib (Appendix 2).¹

For patients presenting in the advanced phases, such as the patient, the risk to the mother in delaying treatment is higher. In the Accelerated Phase, during the first trimester, consideration must be given to terminating the pregnancy, and immediate treatment is warranted.⁶

Imatinib or second-generation tyrosine kinase inhibitor (TKI) can be used after pregnancy termination. For patients diagnosed in the second or third trimester, it may be possible to deliver the baby earlier. In these cases, sensitive and compassionate counseling of the parents, and careful examination of all possibilities, is mandatory. Treatment options and plan were discussed to the patient. The patient decided to continue with her pregnancy, and the patient was continued on Imatinib.^{1,7}

In the Blast Phase, chemotherapy is recommended. In Chronic Phase, prepubertal patients may be started immediately on TKI. Whereas, for post pubertal patients, they are counseled about the risks and benefits of TKI on fertility & pregnancy, such as impaired functions in gonadal development, implantation, and fetal development.¹ They may be offered sperm or oocyte cryopreservation.⁸ Then, TKI may be started.^{1,7}

For post pubertal patients in Chronic Phase already under TKI therapy, and with unplanned pregnancy or diagnosis of CML in pregnancy, they are counseled about the risks and benefits of TKIs on pregnancy. They are also advised to stop TKI. During the first trimester, leukapheresis is a treatment option, since persistence of abnormally high blood counts increases the chance of obstetric complications including thrombosis, bleeding, placental insufficiency, and intrauterine growth restriction. Leukapheresis as a cytoreductive measure is a temporizing procedure, however, with no curative potential or lasting effect, and availability of this procedure is limited.⁶ In the second and third trimester, leukapheresis & interferon alpha (IFN α) are considered. IFN α is considered safe for the fetus,⁵ however, has a slower and less certain ability compared with TKI to induce control of abnormal blood counts, and therefore, may not be a

sufficient treatment for high leukemic burden at CML onset.^{1,7}

For patients in the Chronic Phase planning an elective pregnancy, TKI may be discontinued if patient is in complete or major molecular response (CMR / MMR) for ≥ 2 years.

Management is the same for that of an unplanned pregnancy, if there is loss of complete or major molecular response, such as no cells containing the Philadelphia chromosome by cytogenetic analysis, BCR-ABL1/ABL1 ratio is $< 0.1\%$, or a 3-log reduction in quantitative PCR from pre-treatment baseline.⁴

All patients with CML need treatment. The patient is on Imatinib, which is the first line therapy for CML. This blocks the tyrosine kinase receptor, which somehow prevents the production of myeloblasts. Due to the advent of Imatinib, treatment has been dramatically improved in the last 15 years, reducing the annual mortality from 10–20% to about 2%. However, Imatinib is a known teratogen. It does not only target BCR-ABL tyrosine kinase, but also several other proteins that are known to have functions that may be important in gonadal development, implantation, and fetal development. There are a number of case reports of the fetal outcome of patients on Imatinib during pregnancy. It may cause miscarriage, low birth weight, and is associated with a number of congenital abnormalities. Congenital anomalies recorded were omphalocele, craniosynostosis, clinodactyly, polydactyly, hypospadias, renal & vertebral anomalies, etc.^{1,6,7} For the patient, her baby has hydrocele, noted with a positive transillumination test, and syndactyly on the 4th and 5th digit of the right foot (Appendix 3).

Balancing the potential teratogenic risk to the fetus from Imatinib, against the risk to the mother if she discontinues treatment, is difficult. In

this case, the principle of double effect was applied. The patient was informed of the possible fetal, as well as maternal complications, such as possible thrombotic or vaso-occlusive events (due to hypercoagulable state of pregnancy on top of her leukocytosis & thrombocytosis), possibility of hemorrhage during delivery, or even maternal death from all the possible complications. With all these explained, the patient decided to continue with her pregnancy, where principle of autonomy was applied.

After spontaneous vaginal delivery, the patient had postpartum hemorrhage. Possible causes such as Tone, Tissue, Trauma, and Thrombin were assessed.⁹ Uterine atony (Tone), which is failure of the uterus to contract adequately after delivery, was ruled out by intermittent physical examination. The uterus was maintained well contracted. The patient was continued on oxytocin drip, and was given methylergometrine maleate to ensure uterine contractility. Retained placental tissues (Tissue) was ruled out with attempted manual evacuation, where no placental fragments were obtained. Transvaginal ultrasound was done to assess the endometrial cavity. Genital tract trauma (Trauma) was also ruled out on cervical and vaginal inspection since no hematoma was noted. Hence, coagulopathy (Thrombin) was highly considered, even if coagulation parameters were normal.

During normal pregnancy, both coagulation and fibrinolysis are augmented but remain balanced to maintain hemostasis. Extensive changes develop to create a procoagulant state. Some of these include appreciable increases in the plasma concentration of coagulation factors. In CML, occurrence of bleeding usually suggests disease progression such as in this patient in Advanced or Accelerated Phase, which is caused by abnormal quantity or quality of thrombocyte. Unlike in Chronic Phase

CML, bleeding is unusual due to the generally preserved function of platelets. There are some reported cases which presented with bleeding, but show almost normal results of clotting screening tests.¹⁰ As a matter of fact, there are few rare defects which cannot be recognized by prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count in a hemorrhagic patient.

SUMMARY

Chronic Myeloid Leukemia in pregnancy is rare. All patients with CML need treatment, especially in the advanced phases of the disease. Balancing the potential teratogenic risk to the fetus from Imatinib, against the risk to the mother if she discontinues treatment, is difficult. In these cases, sensitive and compassionate counseling of the parents, and careful examination of all possibilities, is mandatory. Different pregnancy situations in CML may be managed, given the advances in treatment. Intrapartum and postpartum hemorrhage must always be anticipated, even with coagulation parameters, due to abnormal quantity or quality of thrombocyte, and a few rare defects in coagulation factors.

CONCLUSION

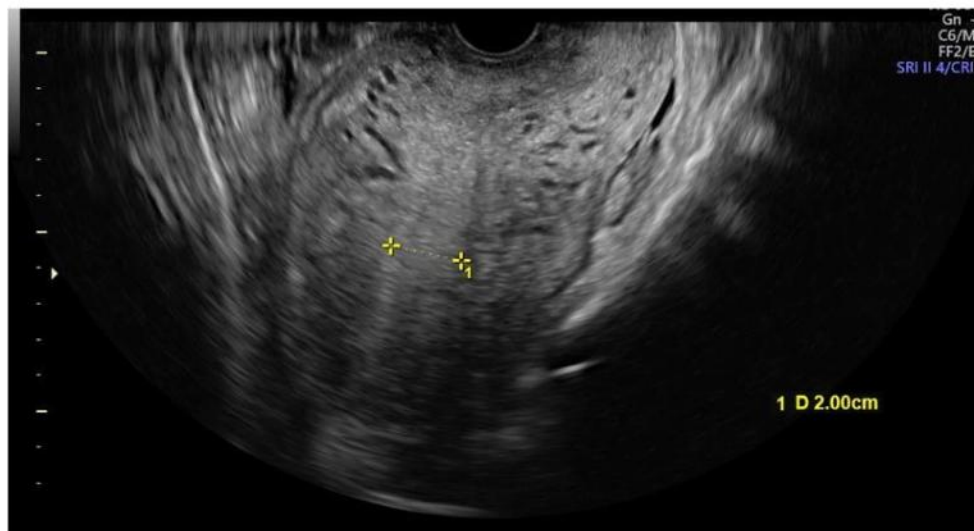
The patients with Chronic Myeloid Leukemia should be encouraged to pursue a normal life including planning a family, given advances in treatment. In CML in pregnancy, three factors must always be considered: the mother, the baby, the illness; all equally important and related.

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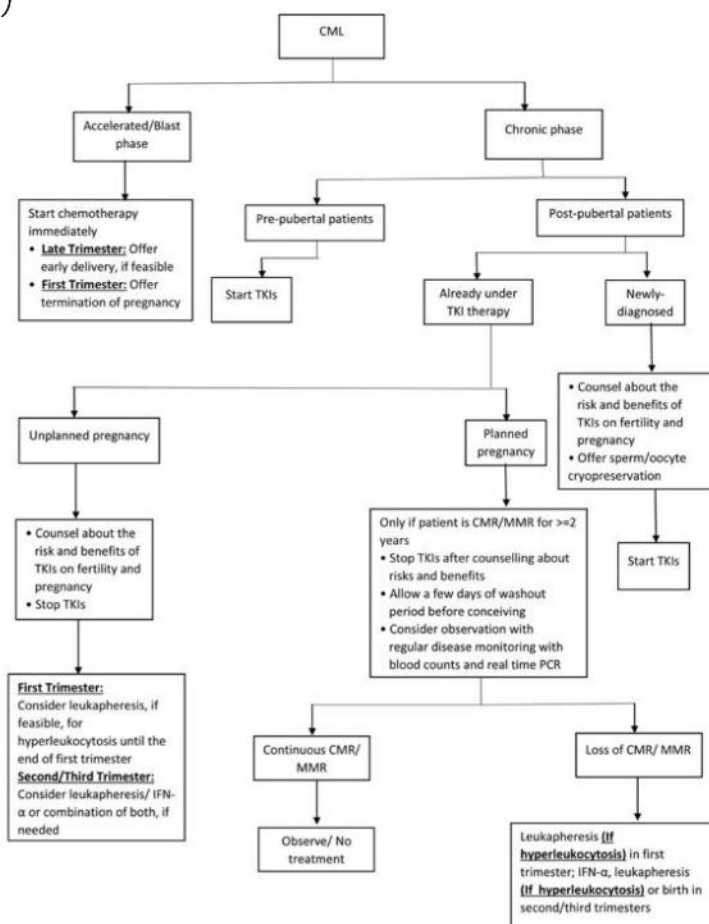
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Appendices

Appendix 1: Transvaginal Ultrasound showing a thickened endometrium, measuring 2.0 cm, described as hyperechoic, endometrial midline not defined, with regular endometrial- myometrial junction, and no cystic areas; minimal color on Doppler flow



Appendix 2: Suggested Algorithm for Management of Patients with Chronic Myeloid Leukemia (source: Bhandari A, Rolan K, Shah B. Management of Chronic Myelogenous Leukemia in Pregnancy. Anti-Cancer Research, 2015.)



Appendix 2: Suggested Algorithm for Management of Patients with Chronic Myeloid Leukemia
(source: Bhandari A, Rolan K, Shah B. Management of Chronic Myelogenous Leukemia in Pregnancy. Anti-Cancer Research, 2015.)



