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Correlation of Perceived Stress, Sleep Pattern, and Sleep Quality of Adult Residents of the Philippines during the Enhanced Community Quarantine for the COVID-19 Pandemic*

Frances Mary C. Agustin, MD

Keith Romeo A. Aguilera, MD

Abstract

Introduction: The COVID-19 pandemic and subsequent enforcement of enhanced community quarantine in the Philippines has forced residents to stay within the confines of their home, reducing social interaction, and causing changes in the usual routine. The appearance of a novel coronavirus has also brought about an unprecedented period of stress and uncertainty.

Objectives: The primary objective of this study was to determine the perceived stress, sleep patterns, and sleep quality of adult residents of the Philippines during the enhanced community quarantine.

Methods: This was a cross-sectional study which looked at the proportion of adult Filipinos with sleep difficulties during the period of the enhanced community quarantine, together with sleep quality and perceived stress. Three different questionnaires: the Perceived Stress Scale (PSS), the Insomnia Severity Index (ISI), and the Pittsburgh Sleep Quality Index (PSQI) were electronically administered to participants. Their demographic data were also recorded. Correlation between all scores recorded from the Perceived Stress Scale, Insomnia Severity Index, and Pittsburgh Sleep Quality Index were done. All collected data were statistically analyzed through descriptive statistics. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. Pearson's rho/Spearman's rank correlation coefficient were used in determining correlation between PSQI, ISI, and PSS scores.

Results: 301 participants were included. 64% had poor sleep quality on PSQI, and 73% were under moderate perceived stress. 45.5% were not tagged with clinically significant insomnia, while 36.5% were screened to have subclinical insomnia. Pairwise correlations among the PSQI, PSS, and ISI revealed a moderate positive relationship, where higher PSS, ISI, and PSQI scores correlated with higher scores across the three scoring systems. Conclusion: Stress levels were moderately high, and sleep quality was poor during the period of enhanced community quarantine. Majority of participants did not have clinically significant insomnia, but many were found to have subclinical insomnia. Based on our data, higher levels of perceived stress correlated to sleep difficulties and poor sleep quality. These findings suggest that aside from efforts in preventing and treating COVID-19, a premium must also be put on addressing and managing each individual's stress levels and sleep difficulties, and practicing sleep hygiene during the pandemic.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) first manifested in Wuhan, China as a pneumonia of unknown etiology, and was reported to the World Health Organization on December 31, 2019. Due to the subsequent outbreak, COVID-19 was declared a Public Health Emergency of International Concern on January 30, 2020. As of April 21, 2020, the World Health Organization has recorded a total 2,356,414 confirmed cases worldwide, spanning 213 countries, and resulting to 162,956 deaths.⁵

In the Philippines, the first case of COVID-19, a Chinese national, was reported on January 30, 2020.

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The first case of local transmission was recorded on March 7, 2020.⁶ A steady increase in the number of cases brought about the enforcement of enhanced community quarantine (ECQ) beginning March 16, 2020.⁷ As such, most Filipinos have been forced to stay at home, work from home, participate in online school activities or homeschool children, and reduce social interaction. According to the Department of Health, as of April 21, 2020, the country had a total of 6,599 confirmed cases, with a total of 437 deaths⁸

The sudden appearance of the novel coronavirus around the world brought about a period of stress and uncertainty. These emotions may negatively affect sleep quality², and vice-versa. In a study conducted by Pilcher et al., it was found that poor sleep quality correlated significantly with an increase in negative emotions such as tension, anxiety, depression, anger, fatigue, and confusion. This also correlated with a more negative affect, less satisfaction, and increased psychological and physical health complaints.⁹ In January 2020, a study performed on Chinese nationals under isolation for COVID-19 infection showed a correlation between anxiety levels and stress levels, which resulted to a reduction in the quality of sleep.¹ In addition to having effects on emotions, sleep quality also plays a role in immunity. According to Gamaldo et al., negative effects are seen in the immune response and function in individuals who were sleep deprived and had sleep disruptions.⁴

The enforcement of enhanced community quarantine has forced Filipinos all over the country to remain within the confines of their home, thereby reducing usual levels of physical activity. Most have adopted a work-from-home scheme. Students have been shifted to online modes of learning as well. This shift from the usual routines and levels of physical activity may affect an individual's circadian rhythm, and in turn, their sleep quality.

Currently, there are no published materials on the effect of home isolation during the COVID-19 pandemic on sleep in the Philippines. Considering the unprecedented events surrounding the world at this time, this study aimed to determine whether perceived stress, sleep patterns, and sleep quality of adults residing in the Philippines were affected during the period of enhanced community quarantine.

METHODS

This is a cross-sectional study involving adults who resided in the Philippines during the enhanced community quarantine between March 16, 2020 and May 15, 2020. Data collection began in July 2020 and ended in September 2020.

Inclusion criteria were the following: (1) Individuals aged 18 and older; (2) Individuals who were residing in the Philippines during the enhanced community quarantine between March 16, 2020 and May 15, 2020; and (3) Individuals who consented to take part in the study.

The following were the exclusion criteria: (1) Individuals diagnosed with sleep disorders (eg. Insomnia, Obstructive sleep apnea); (2) Individuals who were taking sleeping pills (eg. Zolpidem, Clonazepam, Alprazolam, Quetiapine); and (3) Individuals who were diagnosed with a neurologic disorder (eg. Stroke).

Subject Selection

All adult Filipinos who were residing in the Philippines during the period of the enhanced community quarantine were enjoined to participate in this study by means of information dissemination through social media outlets (Facebook, Instagram, Twitter).

Informed Consent Process

Information pertaining to the study were posted on social media outlets such as Facebook, Instagram and Twitter. Individuals who were interested in joining the study were asked to click on a link that was provided in the social media post. The link took the interested party to a Google Form containing information about the study, and the informed consent form. The investigator's name and contact details were provided for any questions or clarifications. The participant's willingness and intention to provide answers to the questionnaires were recognized as legitimate consent to participate in the study.

Consenting participants were subject to the inclusion and exclusion criteria. Participants were each be assigned a unique identifier code upon inclusion in the study.

Sampling Method and Randomization

Since this was an online survey, random sampling was impracticable. The inherent nature of online surveys is that of convenience sampling. To offset probable selection bias, we aimed to have a large sample for analysis, and disseminated to a wide variety of channels.

Screening for eligible participants were done online, using the information obtained from the Google Forms specific to the study. If the person fit the inclusion criteria, did not fit into any of the exclusion criteria, and was willing to participate, after obtaining informed consent, data collection began with a series of demographic questions, and questions about the conditions of the individual's living and sleeping environment. Because data collection ensued in varying environments, the questions tried to see if limitations or confounders could be identified, such as high scores being related to sleeping in a crowded and noisy room. Besides looking into test conditions, the Google Form confirmed the person's identity by requiring them to complete a captcha.

Data Gathering

Demographic data such as age, sex, marital status, and city or municipality of residence were recorded. Employment status was also noted. The nature of the participant's residence, whether a house, condominium, or apartment were noted. They were also asked regarding the number of persons they shared their residence with, and the number of persons who shared their bedroom. Three (3) questionnaires, in electronic form via Google Forms, were given to each participant in order to measure his/her level of stress, sleep pattern, and sleep quality. The scores from all questionnaires were recorded and interpreted accordingly. All respondents were also asked regarding bedtimes and rise times two (2) months prior to and during ECQ. They were also be asked to compare the quality of their sleep two (2) months prior to and during ECQ using a 3- point likert scale (better, same, worse).

Data Management, Archiving, and Confidentiality

Google Forms was used for the study. Age, sex, and city or municipality of residence were the only identifiers that were asked for in this study.

Procedures Done to Subjects

Information pertaining to the study were posted on social media outlets such as Facebook, Instagram and Twitter. Individuals who were interested in joining the study were then asked to click on a link that was provided in the social media post. The link took the interested party to a Google Form containing the informed consent form. Once the individual consented to participate in the study, he/she was directed to the data collection form, together with three short questionnaires via Google Forms: 1) the Perceived Stress Scale (PSS); 2) the Insomnia Severity Index (ISI); and 3) the Pittsburgh Sleep Quality Index (PSQI). Once the questionnaires were accomplished, the participant was asked to submit the Google Form. It is estimated that it took the participant 5-10 minutes to complete all questionnaires. The resulting scores from the questionnaires were reviewed by the investigator, and were analyzed accordingly.

Instruments Used for Measuring Outcome

This study utilized three questionnaires: the Perceived Stress Scale (PSS), the Insomnia Severity Index (ISI), and the Pittsburgh Sleep Quality Index (PSQI). These questionnaires assessed the participant's level of perceived stress, as well as his/her sleep pattern and sleep quality.

The Perceived Stress Scale (PSS) is the most widely used tool in measuring stress. The respondent was asked to rate the frequency of their thoughts or feelings in relation to events which occurred over the past month.¹⁶

The Insomnia Severity Index (ISI) is a seven-item tool which assesses the severity of an individual's difficulties with sleep initiation, sleep maintenance, satisfaction with the current sleep pattern, how the sleep problem interferes with daily function, any noticeable impairments brought about by the sleep problem, and the degree of distress brought about by the sleep problem. Each item is rated on a scale from 0 to 4, with a total score ranging from 0 to 28. Higher scores on the ISI indicate more severe insomnia.¹³

The Pittsburgh Sleep Quality Index (PSQI) is a questionnaire consisting of ten (10) questions to subjectively assess an individual's sleep quality.¹⁷

Follow-up Procedures

This study did not require any follow-up from the participants.

Adverse Events

No adverse events were expected, nor noted, in this study.

Sample Size

A minimum of 253 subjects were required for this study based on a level of significance of 5%, a prevalence of bad or very bad perceived sleep quality in a mandatory quarantine setting due to COVID-19 in Wuhan and surrounding cities in 20.7%¹⁸ with a desired width of confidence interval of 10%, as noted from the reference article by Liu, 2020.¹⁸

Legend:

n = minimum sample size

P = proportion of people with bad/very bad subjective sleep quality = 20.7%

d = absolute error/precision (± 0.05) = 0.10

$Z_{\alpha} = 1.96$

Sample size formula¹⁹:

$$n \geq \frac{Z^2_{\alpha} \times P \times (1-P)}{d^2}$$

$$n \geq \frac{1.96^2 \times 0.207 \times (1 - 0.207)}{0.10^2}$$

$$n \geq 252.24 \approx 253$$

Data Analysis

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. Pearson's rho/Spearman's rank correlation coefficient were used in determining correlation between PSQI, ISI, and PSS scores.

All valid data were included in the analysis. Missing variables were neither replaced nor estimated. STATA 15.0 was used for data analysis.

RESULTS

The 301 study participants who were included in the study had a median age of 33 years, were mostly female (67%), single (58%), and employed (61%). A little over three-fourths (76%) were based in NCR, while two-thirds (67%) lived in a house type of residence. Participants shared their residence and bedroom with a median of 5 (range 1–7) and 2 (range 1–8) other persons, respectively.

For 131 (43%) respondents, sleep quality during ECQ was neither better nor worse in comparison with that before onset of ECQ. Another 43% reported having a worse sleep quality, while 14% claimed to be sleeping better during the ECQ.

Table 1. Demographic profile of patients (n=301)

	Median (Range) Frequency (%)
Age, years	33 (19–75)
Sex	
Male	99 (32.89)
Female	202 (67.11)
Civil status	
Single	175 (58.14)
Married	126 (41.86)
Employment status	
Employed	184 (61.13)
Self-employed	76 (25.25)
Student	19 (6.31)
Unemployed	22 (7.31)
Region of residence	
NCR (Metro Manila)	229 (76.08)
Region IV-A (CALABARZON)	39 (12.96)
Region III (Central Luzon)	12 (3.99)
CAR (Cordillera Administrative Region)	9 (2.99)
Region V (Bicol)	3 (1.00)
Region VII (Central Visayas)	3 (1.00)
Region I (Ilocos)	2 (0.66)
Region VI (Western Visayas)	2 (0.66)
BARMM (Bangsamoro Autonomous Region in Muslim Mindanao)	1 (0.33)
Region XI (Davao)	1 (0.33)
Nature of residence	
House	202 (67.11)
Condominium	58 (19.27)
Apartment	33 (10.96)
Townhouse	4 (1.33)
Compound/Tenement	2 (0.66)
Workplace	2 (0.66)
Number of persons sharing the residence	5 (1–7)
Number of persons sharing the same bedroom with the participant	2 (1–8)
Sleep quality during ECQ compared to before ECQ	
Better	41 (13.62)
Same	131 (43.52)
Worse	129 (42.86)

On PSQI, majority (64%) of participants had poor sleep quality (Table 2). The 25th to 75th percentiles of subscale scores were interpreted as: fairly good to fairly bad (scores 1 to 2) subjective sleep quality; >7 to 6-7 hours (scores 0 to 1) sleep duration; and >85% to 75%-84% (scores 0 to 1) habitual sleep efficiency; and not using sleep medications during the past month (score of 0). For domains indirectly interpreted, the interquartile range of scores were interpreted as: fairly good to very bad (scores 1 to 3) states of sleep latency; fairly good to fairly bad (scores 1 to 2) levels of sleep disturbance; and very good to fairly good (scores 0 to 1) daytime functioning.

On ISI, majority of participants (45.5%) were not tagged with clinically significant insomnia, while 36.5%, 16%, and 2% were screened with subthreshold, moderate, and severe insomnia, respectively.

Based on PSS, slightly under three-fourths (73%) had moderate perceived stress, 15% had low stress levels, and 12% were under high stress.

Table 2. Sleep quality, insomnia severity, and perceived stress

	Median (Range, IQR); Frequency (%)
Pittsburgh Sleep Quality Index	7 (0–18, 4–9)
Good sleep quality (≤5)	109 (36.21)
Poor sleep quality (>5)	192 (63.79)
PSQI domain scores	
Subjective sleep quality	1 (0–3, 1–2)
Sleep latency*	2 (0–3, 1–3)
Sleep duration	1 (0–3, 0–1)
Habitual sleep efficiency	0 (0–3, 0–1)
Sleep disturbances*	1 (0–3, 1–2)
Use of sleep medication	0 (0–3, 0–0)
Daytime dysfunction*	1 (0–3, 0–1)
Insomnia Severity Index	8 (0–26, 5–13)
No clinically significant insomnia (0-7)	137 (45.51)
Subthreshold insomnia (8-14)	110 (36.54)
Moderate clinical insomnia (15-21)	49 (16.28)
Severe clinical insomnia (22-28)	5 (1.66)
Perceived Stress Scale	20 (0–39, 16–23)
Low stress (0-13)	44 (14.62)
Moderate stress (14-26)	220 (73.09)
High stress (27-40)	37 (12.29)

Possible scores range (higher scores indicate worse status): PSQI, 0-21; ISI, 0-28; PSS, 0-40.

All pairwise correlations amongst PSQI, ISI, and PSS global scores revealed moderate, positive relationships ($P < .001$) (Table 3). This means that higher PSS, ISI, and PSQI scores correlated with higher scores across the three scoring systems.

Table 3. Correlation between PSQI, ISI, and PSS scores

	Correlation coefficient	Relationship	P
PSS and ISI	0.563	Moderate, direct	<.001
PSS and PSQI	0.461	Moderate, direct	<.001
ISI and PSQI	0.699	Moderate, direct	<.001

Statistical test used: Spearman's rank correlation.

DISCUSSION

This study assessed whether perceived stress, sleep patterns, and sleep quality of adults residing in the Philippines were affected during the period of enhanced community quarantine. Sleep quality was measured through the Pittsburgh Sleep Quality Index (PSQI). The Insomnia Severity Index (ISI) was used to assess the severity of participants' difficulties with regards to sleep initiation, sleep maintenance, and their satisfaction with their sleep pattern. Stress levels were measured using the Perceived Stress Scale (PSS).

Overall, the majority of participants (64%) had poor sleep quality based on their PSQI scores. Majority (45.5%) of participants did not appear to have clinically significant insomnia, but 36.5% had subthreshold insomnia, and 16% had moderate insomnia. Majority of participants (73%) were under moderate perceived stress, while 12% were under high stress, and 15% were under low levels of stress.

There was a moderate positive relationship found between the scores on the PSS and PSQI, showing that higher perceived stress scores correlated with poorer sleep quality. Likewise, a higher perceived stress score also correlated with a higher score on the ISI, indicating the presence of difficulty initiating and/or maintaining sleep. A similar relationship was also found between the ISI and PSQI, where more severe sleep difficulties correlated with poorer sleep quality. The study found that a higher score on one scoring system correlated with higher scores across all three scoring systems. This shows that increased levels of perceived stress leads to changes in sleep patterns, resulting in sleep difficulties and poor sleep quality.

The presence of novel infectious diseases brings about elevated anxiety and stress levels among the general population. Infectious disease epidemics are also

known to have negative effects on the psychological health even of non-infected individuals.¹ The appearance of COVID-19 in the country and the rest of the world has brought about a period of uncertainty and unprecedented stress. The findings of this study showed that there were high perceived stress scores, and poor sleep quality in adults residing in the Philippines during the period of enhanced community quarantine. This indicates that a premium should be put on the psychological well-being of individuals in community quarantine, as it affects both sleep pattern and sleep quality. Similar findings were seen in a study by Xiao et al.¹, where high anxiety levels and high stress levels were correlated with poor sleep quality. Such stress may be due to limited social interactions brought about by self-isolation, and also due to fear of infection. It is known that negative emotions such as anxiety, stress, and anger are strongly associated with poor quality of sleep.² It is also important to note that sleep quality also influences the immune response in such a way that sleep deprivation and sleep disruptions contribute to negative effects on the immune system response.⁴

Aside from this, poor sleep has also been attributed to an increased risk for developing hypertension and dyslipidemia, as observed by Clark et al in 2016.²⁰

The master circadian clock, located in the suprachiasmatic nucleus, regulates the sleep-wake cycle, and is normally entrained by light-dark cycles, exercise, and feeding schedules, and social cues.¹⁰ Irregularities in circadian regulation usually present with longer sleep-onset latency, later bedtimes and later wake times, multiple daytime naps, less nocturnal sleep, and poor sleep quality.¹¹ In this study, majority of participants were not found to have clinically significant insomnia. However, 36.5% were found to have subclinical insomnia. It is posited that this subclinical insomnia may be due to alterations or irregularities in the timing of exposure to bright light, and a decrease in usual activity levels resulting from home confinement, leading to difficulty in initiating and/or maintaining sleep.³ Since higher stress is also associated with an increased risk of the persistence of insomnia²¹, it is

important that the stress levels of patients coming in with complaints of sleep difficulties be screened, and also managed accordingly. Sleep hygiene, which involves regular bedtimes and rise times, adequate exercise, properly-timed light exposure, and a consistent daily routine, must be discussed with patients in order to maintain a well-regulated sleep-wake cycle.

LIMITATIONS AND RECOMMENDATIONS

Majority of participants were located in the National Capital Region. Sampling was also limited to those who had access to the internet. It is recommended that future studies should have a broader scope, involving more participants in regions outside the nation's capital, and even those who do not have internet access. In this study, individuals previously diagnosed with sleep disorders such as insomnia were excluded. Future studies may focus on whether or not home confinement during the pandemic further affected these conditions.

CONCLUSION

The findings from this study showed that during the period of enhanced community quarantine, stress levels were moderately high, and sleep quality was poor. Although majority of participants did not have clinically significant insomnia, many were also found to have subclinical insomnia. In addition to this, study data suggest that higher perceived stress was correlated to having sleep difficulties and poor sleep quality. This demonstrates that in addition to focusing efforts on the prevention and treatment of COVID-19 infections, the psychological well-being, stress levels, and sleep difficulties encountered by the general population also need to be properly addressed during the pandemic. Sleep hygiene is of paramount importance. Practitioners must also be well-advised regarding the effects of stress on sleep in order to prevent and mitigate both short-term and long-term consequences on the patient's physical and psychological health.

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Appendix 1

Perceived Stress Scale

For each question choose from the following alternatives:

0 - never 1 - almost never 2 - sometimes 3 - fairly often 4 - very often

- _____ 1. In the last month, how often have you been upset because of something that happened unexpectedly?
- _____ 2. In the last month, how often have you felt that you were unable to control the important things in your life?
- _____ 3. In the last month, how often have you felt nervous and stressed?
- _____ 4. In the last month, how often have you felt confident about your ability to handle your personal problems?
- _____ 5. In the last month, how often have you felt that things were going your way?
- _____ 6. In the last month, how often have you found that you could not cope with all the things that you had to do?
- _____ 7. In the last month, how often have you been able to control irritations in your life?
- _____ 8. In the last month, how often have you felt that you were on top of things?
- _____ 9. In the last month, how often have you been angered because of things that happened that were outside of your control?
- _____ 10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

Appendix 2

Insomnia Severity Index

Insomnia Severity Index

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied Satisfied Moderately Satisfied Dissatisfied Very Dissatisfied
0 1 2 3 4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all A Little Somewhat Much Very Much Noticeable
0 1 2 3 4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all A Little Somewhat Much Very Much Worried
0 1 2 3 4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all A Little Somewhat Much Very Much Interfering
0 1 2 3 4

Guidelines for Scoring/Interpretation:

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 + 6 + 7) = _____ your total score

Total score categories:

0–7 = No clinically significant insomnia

8–14 = Subthreshold insomnia

15–21 = Clinical insomnia (moderate severity)

22–28 = Clinical insomnia (severe)

Appendix 3

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions. During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. When have you usually gotten up in the morning? _____
4. How many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed) _____

5. During the past month, how often have you had trouble sleeping because you...	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)
9. During the past month, how would you rate your sleep quality overall?				

Hitting the Target: An Uncommon Case of Obscure-Overt Gastrointestinal Bleeding Caused by a Jejunal Gastrointestinal Stromal Tumor

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Abstract

Significance

GIST are mesenchymal tumors of the GI tract, representing less than 1% of GI neoplasms. GIST arising from the jejunum is extremely rare and accounts for 0.1%-0.3% of all GI tumors. Symptoms are non-specific and relate to the tumor location and size. Large tumors have wide range of manifestations including nausea, vomiting, abdominal pain and bleeding. GI bleeding from GISTs are mostly obscure in origin and has always been a diagnostic and therapeutic challenge. We report an uncommon case of obscure-overt GI bleeding from a jejunal GIST. We aim to highlight the advantage of push enteroscopy and CT angiography (CTA) in the approach to patients presenting with obscure-overt GI bleeding.

Clinical Presentation

A 72-year-old female presented with sudden episode of massive hematochezia associated with lightheadedness and anemia.

Management

Esophagogastroduodenoscopy and colonoscopy was unremarkable. Push antegrade enteroscopy using a pediatric colonoscope showed an ulcer with a spurting blood vessel in the proximal jejunum. Endoscopic clips were deployed resulting to complete hemostasis. CTA showed a heterogeneously enhancing jejunal mass with prominent vessels. Embolization using polyvinyl alcohol embolic particles was performed. Post-embolization contrast showed complete revascularization of the tumor. She underwent exploratory laparotomy with segmental jejunal resection. Final histopathology diagnosis is CD117 positive, DOG1 positive, spindle cell-type GIST.

Recommendation

Jejunal GIST presenting as obscure-overt gastrointestinal bleeding is extremely rare. Normal findings from an upper and lower endoscopy in a patient presenting with GI bleeding should raise a suspicion of small intestinal bleed. When a vascular lesion is suspected, abdominal CTA should be performed. This case highlights the importance of a stepwise and multidisciplinary approach in such cases.

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are mesenchymal tumors of the gastrointestinal (GI) tract, representing less than 1% of GI neoplasms. The stomach is the most commonly involved site, followed by the small intestines, colon, rectum and esophagus. GIST arising from the jejunum is extremely rare and accounts for 0.1% to 0.3% of all GI tumors.^(1,2) Symptoms are non-specific and relate to the location and size of the tumor.⁽³⁾ Small GISTs that are less than 2 cm are usually asymptomatic. However, tumors larger than 4 cm have a wide range of manifestations including nausea, vomiting from intestinal obstruction, abdominal pain and bleeding from pressure necrosis and mucosal ulceration.^(2,4) GI bleeding from GISTs are mostly obscure in origin, which has always been a diagnostic and therapeutic challenge to gastroenterologists.⁽⁵⁾ We report an uncommon case of obscure-overt GI bleeding from a jejunal GIST, leading to anemia requiring blood transfusion. The objective of this case report is to highlight the advantage of push enteroscopy and CT angiography (CTA) in the approach to patients presenting with obscure-overt GI bleeding.

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CASE REPORT

A 72-year-old female with hypertension presented with sudden episode of hematochezia associated with lightheadedness. There was no melena, hematemesis, abdominal pain or anal pain. Further history revealed previous colonoscopy findings of colonic diverticulosis. She denied any family history of GI malignancy. On assessment, she had stable vital signs with unremarkable physical examination. Focused examination revealed a flabby, soft and non-tender abdomen with no palpable mass. Digital rectal exam showed maroon colored stools. Complete blood count (CBC) was within normal limits with an initial hemoglobin of 12.8 g/dL. After an episode of massive hematochezia, repeat hemoglobin was 10.7 g/dL, she was then advise to undergo endoscopy.

Colonoscopy revealed descending to sigmoid colon diverticulosis and grade 1 internal hemorrhoids; however, no sign of bleeding was identified. Esophagogastroduodenoscopy up to the distal portion of the duodenum was also unremarkable. Two episodes of hematochezia were reported few hours after endoscopy. Vital signs remained stable with no other associated symptom. Repeat CBC showed a 9.3 g/dL hemoglobin; hence, a unit of packed red blood cells was transfused. Repeat colonoscopy with terminal ileoscopy revealed black stools with maroon blood clots from the visualized terminal ileum to proximal transverse colon. Several diverticular openings were filled with black stools and clots but with no evidence of active bleeding. Two small, superficial clean-based ulcers without bleeding were seen in which endoscopic clips were applied. Push antegrade enteroscopy was performed using a pediatric colonoscope. An ulcer with an adherent clot was seen at the proximal jejunum (Fig. 1a). The clot was dislodged after continuous flushing which revealed a spurting and pulsating blood vessel (Fig. 1b). Seven endoscopic clips were deployed resulting to complete hemostasis (Fig. 1c). She was referred to interventional radiology service for abdominal CTA and possible embolization.

CTA with 3D reconstruction showed a heterogeneously enhancing mass measuring 4 x 3.9 x 4.4 cm with prominent vessels adjacent to the jejunum (Fig. 1d). Multiple linear densities medial to the mass representing endoscopic clips were noted. Superior

mesenteric arterio-portography showed intense neovascularity and tumor staining at this region supplied by the first jejunal branch of the superior mesenteric artery (Fig. 2a). Embolization using polyvinyl alcohol embolic particles (355-500 microns) was performed by superselective catheterization of the described jejunal artery. Post-embolization contrast showed complete devascularization of the tumor (Fig. 2b). She underwent exploratory laparotomy which revealed an 8 x 5 cm well-circumscribed, violaceous mass in the jejunum (Fig. 2c). Segmental jejunal resection and stapled anastomosis were performed. Histopathology (Fig. 2d-f) showed CD117 positive and DOG1 positive GIST of spindle cell type involving the jejunum, with a mitotic rate of 0-1/5 mm². She was discharged 3 days after surgery without recurrence of bleeding.

DISCUSSION

GISTs, despite considered the most common mesenchymal tumor of the GI tract, rarely occurs in the jejunum. It originates from the interstitial cells of Cajal which are the pacemaker cells of the gut, coordinating GI motility and peristalsis.⁽⁶⁾ Compared with large GISTs, small tumors (<2 cm) are commonly asymptomatic and incidentally found on endoscopy or imaging. When symptomatic, patients would present with abdominal pain/discomfort, vomiting, bloatedness or hemorrhage. GI bleeding, which is present in 50% of cases are obscure in origin due to its location, making it difficult to be identified by routine endoscopy. The main mechanisms leading to GI bleeding are ulceration of the overlying mucosa and pressure necrosis.⁽⁷⁾

The patient presented with episodes of hematochezia without hemodynamic compromise. Her initial endoscopy did not reveal any actively bleeding lesion hence, was inconclusive. It is estimated that 5% of patients with overt GI bleeding will have an initial non diagnostic endoscopy findings. Persistent visible evidence of bleeding anywhere from the GI tract after a negative diagnostic evaluation is defined as obscure-overt GI bleeding. As seen with this case, majority of patients with obscure-overt GI bleeding present with either melena or hematochezia.⁽⁸⁾ These patients are likely to possess a more serious lesion with a higher morbidity and mortality.⁽⁹⁾

Small bowel pathologies account for the majority of the etiologies of obscure-overt GI bleeding. The most common of which are vascular lesions. Other potential etiologies include small bowel tumors, inflammatory lesions and less commonly, extraluminal sources.^(10,11) Therefore, a high index of suspicion for these etiologies is warranted to prevent delays in the definitive diagnosis and management. In our case, push antegrade enteroscopy was able to reach the jejunum where the spurting blood vessel was noted.

According to Gralnek and colleagues, push enteroscopy may be performed directly in situations where in small bowel lesions are suspected. It would be beneficial since it permits direct visualization of the small intestines extensively into the jejunum and/or ileum. Simultaneously, tissue samples for histopathologic diagnosis can be obtained and more importantly, therapeutic endoscopic measures can be carried out. A dedicated videoenteroscope, pediatric or standard adult colonoscope can be used. Reported diagnostic yields in the evaluation of GI bleeding have ranged from 13% to 38% using a pediatric colonoscope, which increases with greater depth of scope insertion.⁽¹¹⁾ With the endoscopic findings suggestive of a vascular lesion, performing a CT angiography is the next best diagnostic imaging of choice to identify site of bleeding.⁽⁵⁾ Angiography can identify non-bleeding lesions with the demonstration of typical vascular features seen in vascular ectasias (i.e. slow-filling vein, vascular tuft in the arterial phase, and early-filling vein) and tumors. Simultaneously, interventional radiologists

are able to administer embolization therapy if an amenable lesion is detected.⁽¹¹⁾

In these rare occasions that GISTs present as obscure-overt GI bleeding, an early multidisciplinary management is of utmost importance. Collaborating with interventional radiology and surgery services will be the cornerstone in the approach to these patients, and should be considered in all cases of massive GI bleeding. A case report by Saad et al. described a 46-year-old male with jejunal GIST who presented with melena, dizziness, palpitations and anemia requiring multiple blood transfusions.⁽¹²⁾ Esophagogastroduodenoscopy was inconclusive, whereas colonoscopy showed fresh blood throughout the colon. CTA revealed a 5.2 x 4.2 cm heterogeneously mass in the proximal jejunum with persistent enhancement through the delayed phase. The patient underwent laparoscopic segmental small bowel resection, after failure of radiologic embolization.⁽⁷⁾

This case report underscores the importance of a systematic approach in managing patients with GI bleeding. Inconclusive findings from an upper and lower endoscopy in cases of overt GI bleeding should increase the suspicion of a small intestinal pathology. In the absence of a dedicated enteroscope, a pediatric or an adult colonoscope may be used for antegrade enteroscopy. In addition, this case highlights the utility and effectiveness of therapeutic endoscopy in the initial management of patients with massive small intestinal GI bleeding prior to definitive surgical resection.

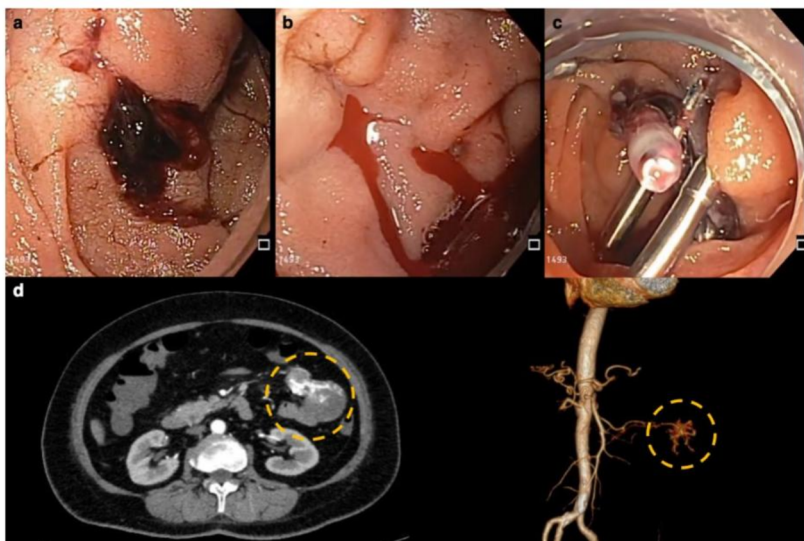


Figure 1. Push enteroscopy revealed an (a) ulcer with adherent clot at the proximal jejunum, (b) oozing visible vessel post-flushing and (c) partial hemostasis after application of endoscopic clips. (d) CT Angiogram with 3D reconstruction showed a heterogeneously enhancing mass with prominent vessels and multiple linear densities representing endoscopic clips.

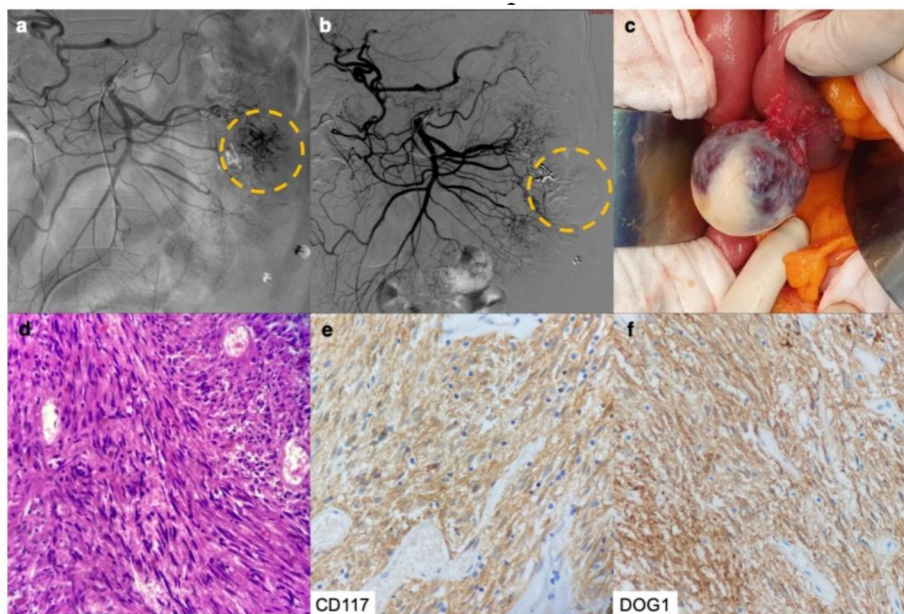


Figure 2 (a) Superior mesenteric arterio-portography showed intense neovascularity and tumor staining at the jejunal region supplied by the first jejunal branch of the superior mesenteric artery. (b) Complete devascularization of the tumor post-embolization. (c) Fungating mass in the antimesenteric side of the jejunum during exploratory laparotomy. (d) Histopathology showed cytologically bland spindle cells arranged in packets or whorls with normochromatic nuclei. Immunohistochemistry revealed (e) CD117 positive and (f) DOG-1 positive staining.

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Duodenal Papilla Morphology and ERCP Cannulation Difficulties, Failure and Complications in Manila Doctors Hospital, A Tertiary Private Hospital: A Cross-Sectional Study

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Abstract

BACKGROUND/OBJECTIVES: Different major duodenal papilla morphology pose various challenges of cannulation and development of ERCP complications. These morphologies may guide the endoscopist in his cannulation approach and complication prevention. The aim of this study is to determine the major duodenal papilla morphologies of ERCP patients in Manila Doctors Hospital and their associated cannulation difficulties, failure, and complications.

METHODS: This is a retrospective cross-sectional study of 246 ERCPs at the Manila Doctors Hospital from January 2017 to December 2018 with naïve duodenal papillae classified according to Watanabe (2019) as follows: oral protrusion (small, regular, large) and papilla pattern (annular, unstructured, longitudinal, isolated, gyrate). Association of papilla morphology with cannulation difficulties, failure, and complications were analyzed using logistic regression.

RESULTS: Among protrusions, small oral protrusions were more difficult to cannulate compared to regular (OR 0.493, $p=0.017$) and large protrusions (OR 0.702, $p=0.426$). Large protrusions had the highest risk for failed cannulation (OR 2.04, $p=0.445$). Among papilla patterns, unstructured papilla patterns had the highest risk for difficult (OR 3, $p=0.008$) and failed cannulation (OR 7.08, $p=0.020$). Complications developed in 7 in-patients with 3 (1.73%) post-ERCP pancreatitis, 1 (0.58%) post- sphincterotomy bleeding, and 1 (0.58%) cholangitis and 2 (1.16%) mortalities. One had myocardial infarction 2 days post-ERCP and another had septic shock after 2 days despite endoscopic biliary drainage and antibiotics.

CONCLUSION: Among protrusions, small oral protrusions had the highest risk for difficult cannulation while large protrusions had the highest risk for failed cannulation. Among papilla patterns, unstructured papilla patterns had the highest risk for difficult and failed cannulation.

KEYWORDS: ERCP, papilla morphology, cannulation success

INTRODUCTION and OBJECTIVES

Endoscopic retrograde cholangiopancreatography (ERCP) is a procedure requiring expertise with risks of life-threatening complications. Endoscopists who perform ERCP recognize the obvious differences in the macroscopic appearance of the major duodenal papilla or ampulla of Vater. This has led to a widespread conception among endoscopists that certain specified appearances of the papilla are more difficult to cannulate and therefore more prone to adverse events [1]. Difficult cannulation has previously been shown to correlate with increased complication rates, foremost being post-ERCP pancreatitis. Other complications include hemorrhage, cholangitis and perforation of the common bile duct or duodenum [2]. The quality indicators of ERCP practice include adequate indications and success rate of cannulation as well as low complication [3,4]. In 2019, Watanabe et, al. proposed a classification system of the duodenal papilla according to oral protrusion pattern and papillary patterns. They noted a significant difficulty in cannulating the protrusion-L type of papilla [5]. This study aims to investigate the morphologic differences of the major duodenal papilla of the ERCPs done in

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Manila Doctors Hospital from January 2017 to December 2018 and determine the cannulation success rates, and associated difficulties of cannulation and post-procedural complications encountered, hypogeusia, abdominal discomfort and gastrointestinal bleeding have as well been documented; these varies significantly among different study populations, presenting frequently with early and mild onset followed by the typical respiratory symptoms.⁴

METHODOLOGY

PATIENTS. This is a retrospective cross-sectional study of a total of 411 patients who underwent ERCP at the Manila Doctors Hospital, a tertiary hospital, between January 2017 to December 2018 by going through the report database (ImageArk Endosoft) and CD recordings in the endoscopy unit. Patients included were those who underwent ERCP for the first time either as outpatient or inpatient by experienced endoscopists (>300 career ERCPs). Patients excluded were those who have previous history of ERCP and sphincterotomy or stenting, surgically altered intestinal anatomy, and those with duodenal papilla appearing to be difficult to classify on video documentation (unclassifiable due to distortion from tumor invasion, hidden within diverticulum, incomplete/unclear/missing video documentation). Patient's demographic data, indication for ERCP, endoscopic diagnosis, procedural findings were likewise recorded. Inpatient records were reviewed to document complications arising post-procedure.

CLASSIFICATION OF DUODENAL PAPILLA. The classification used to identify the different papilla morphology was the proposed classification by Watanabe et. al. in 2019 [5]. They described the papilla according to the oral protrusion (OP) pattern or the ratio of length of oral protrusion to the transverse diameter of the papilla and the papilla pattern (PP) or the surface pattern of the orifice. The OP is classified into three types: small (S) for which the ratio of the length of the oral protrusion to the transverse diameter of the papilla was less than one-half; regular (R) for which the ratio was one-half or more but less than two; and large (L) for which the ratio is two or more (Figure 1A). The PP is classified into five types: annular (A) comprised of the typical papilla with an annular shape; unstructured (U), comprised those with no clear orifice; longitudinal (LO) comprised of longitudinal grooves continuous with the orifice with the length of the groove being longer than the transverse diameter of the biliary duct axis of the papilla; isolated (I) comprised of two separate isolated orifices of the biliary and pancreatic ducts; and gyrus (G) comprised of gyrate pattern of the papilla (Figure 1B) [5]. Other endoscopic finding that was noted and related to the papilla was the presence of a periampullary diverticulum. Two endoscopist classified the images of the papilla morphology independently, and a third endoscopist was consulted to decide the classification if there was disagreement.

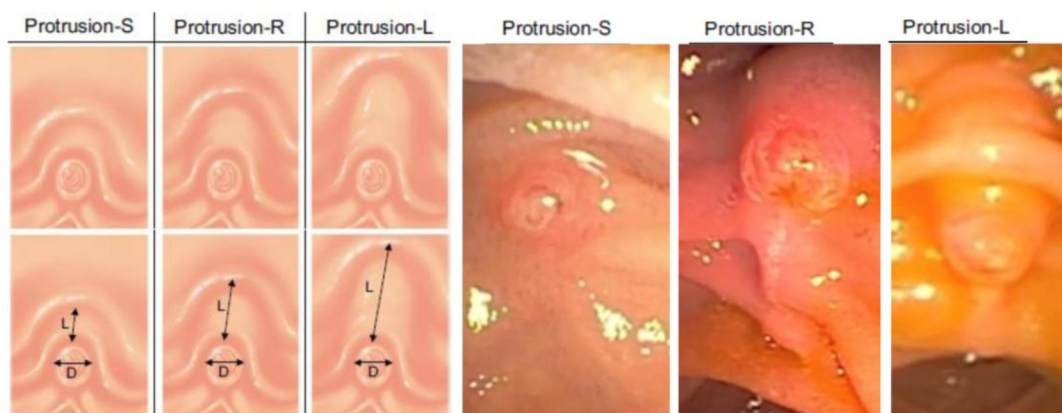


Figure 1A. Oral Protrusion Pattern Classification According to Watanabe 2019 with sample photos on the right from this study.

(Image from Watanabe M, Okuwaki K, Kida M, et al. Transpapillary Biliary Cannulation is Difficult in Cases with Large Oral Protrusion of the Duodenal Papilla. Dig Dis Sci. 2019;64(8):2291-2299. doi:10.1007/s10620-019-05510-z)

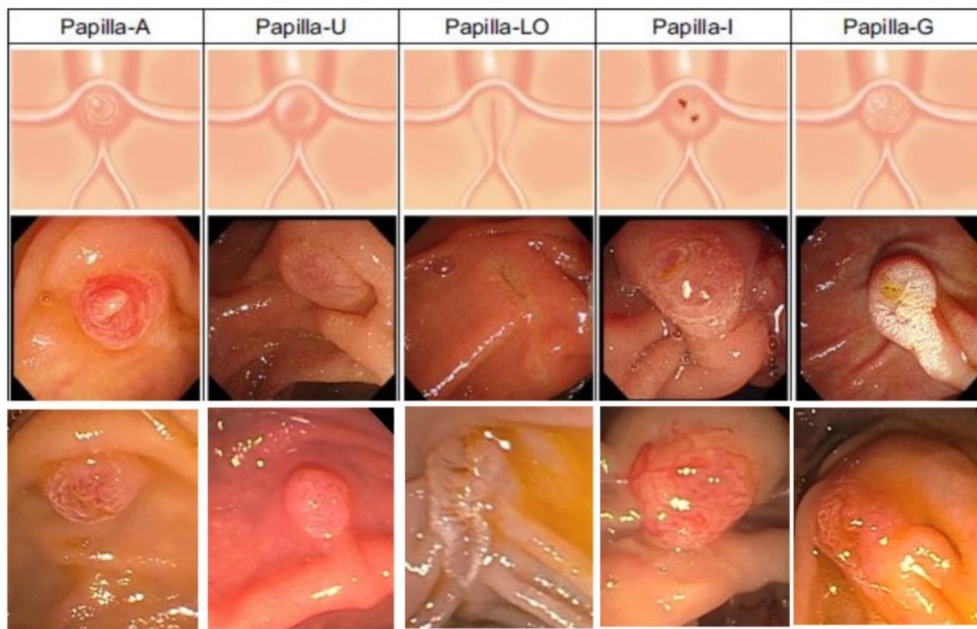


Figure 1B. Papilla Pattern Classification According to Watanabe 2019 and sample photos from this study.

(Image from Watanabe M, Okuwaki K, Kida M, et al. Transpapillary Biliary Cannulation is Difficult in Cases with Large Oral Protrusion of the Duodenal Papilla. Dig Dis Sci. 2019;64(8):2291-2299. doi:107/s10620-019-05510-z)

Difficulty of cannulation was defined by European Society for Gastrointestinal Endoscopy (ESGE) in 2016 by the presence of any of the following criteria: (1) more than five minutes, (2) five attempts at touching the orifice, or (3) two pancreatic guidewire passages [6].

Complications related to the ERCP procedure were reported for the inpatients only because outpatients do not have charts available for review. Complications included post-ERCP pancreatitis, bleeding, perforation, cholangitis, and death directly arising from the aforementioned events occurring within 30 days of ERCP. These were reported as percentage frequency

STATISTICAL ANALYSIS AND ETHICS

Quantitative variables are summarized as mean and standard deviation, while qualitative variables are tabulated as frequency and percentage. Inter-observer agreement with the oral protrusion and papilla pattern classifications were determined by using kappa statistics and interpreted as poor ($k \leq 0.2$), fair ($0.21 \leq k \leq 0.40$), moderate ($0.41 \leq k \leq 0.60$), good ($0.61 \leq k \leq 0.80$)

to very good ($0.81 \leq k \leq 1.00$) [7]. The association of papilla morphology and cannulation success and difficulty was analyzed using univariate analysis thru Epi Info Version 7, with p value <0.05 considered as significant. Minimum sample size of at least 144 patients was calculated based on the cannulation success rate of 97.6% on the study of Watanabe (2019) with margin of error of 2.5% and confidence level of 95%.

The study protocol was reviewed and approved by the Manila Doctors Hospital Institutional Review Board (Ref MDH IRB 2021-004 R).

RESULTS

A total of 411 ERCPs were reviewed. A total of 165 patients were excluded from the study due to the following reasons: 61 patients had previous ERCP, 14 had ampullary tumors precluding classification of the papilla, and 20 had unclear video images; 80 patients had missing video documentations (Figure 2). A total of 246 subjects were included in the study. Table 1 describes the demographics of our patient population.

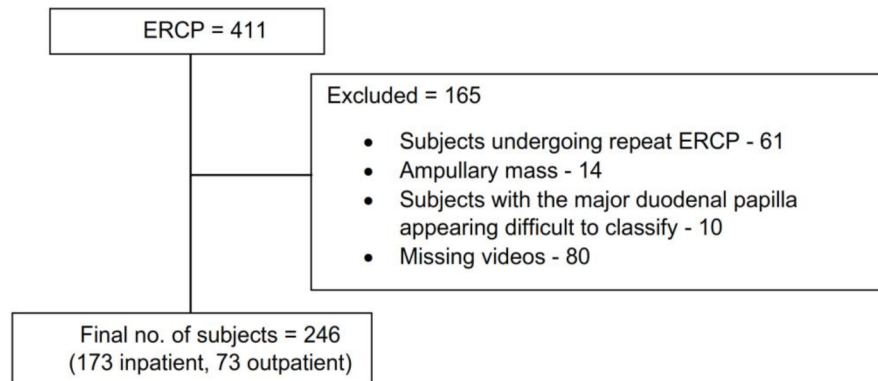


FIGURE 2. Flow diagram of patient enrolment and exclusion of ERCP naïve patients who underwent ERCP from 2017 to 2018 at MDH.

The most common indication was presence of choledocholithiasis (80.89%), followed by malignant obstruction (cholangiocarcinoma, pancreatic new growth) (8.94%), biliary stricture (4.87%), and cholangitis (3.66%). Other indications included evaluation and management of post-cholecystectomy biliary leak and consideration of sump syndrome (1.62%).

The most common endoscopic diagnosis post procedure was the presence of choledocholithiasis (59.35%) followed by recent passage of stone (37%), malignant obstruction (cholangiocarcinoma, pancreatic new growth) (7.32%), biliary stricture (6.91%) and normal pancreatic duct (3.25%). Other diagnosis included biliary ectasia, biliary leak post cholecystectomy, and sump syndrome (8.54%).

TABLE 1. Demographic data of patients who underwent ERCP for the first time in MDH Endoscopy Unit from 2017 to 2018

CHARACTERISTIC	N = 246	%
Age (years)	52 +/- 17	-
Female	148	60.16%
Male	98	39.84%
Inpatient	173	70.33%
Outpatient	73	29.67%
Indications		
• Choledocholithiasis	199	80.89%
• Malignancy	22	8.94%
• Stricture	12	4.87%
• Cholangitis	9	3.66%
• Others	4	1.62%
Diagnosis		
• Choledocholithiasis	146	59.35%
• Recent passage of stone	36	14.63%
• Malignancy	18	7.32%
• Stricture	17	6.91%
• Normal	8	3.25%
• Others	21	8.54%
Failed Cannulation	9	3.65%
Difficult cannulation*	80	32.5%
• > 5 min duration to cannulate	77	31.3%
• Pre-Cut sphincterotomy	25	10.16%
• Pancreatic duct cannulation	18	7.31%
Periampullary Diverticulum (PAD)	57	23.27%

The inter-observer agreement between the two endoscopists who classified the papillae according to oral protrusion and papilla patterns was calculated using kappa statistics with good and moderate agreement (OP k 0.619, CI 0.523 – 0.716; PP k 0.607, CI 0.459 – 0.754) for the oral protrusion and papillary pattern classifications, respectively (Table 2).

TABLE 2. Distribution and Kappa Inter-observer Agreement of the Different Classifications of Papilla Morphology

Papilla Morphology				
Papillary Morphology	n (%)	Kappa (k)	CI (95%)	Agreement
Oral protrusion pattern				
Small (Protrusion-S)	89 (36.18%)	0.619	0.523 – 0.716	Good
Regular (Protrusion-R)	127 (51.63%)			
Large (Protrusion-L)	30 (12.2%)			
Papilla pattern				
Annular (Papilla-A)	180 (73.17%)	0.607	0.459 – 0.754	Moderate
Unstructured (Papilla-U)	28 (11.38%)			
Longitudinal (Papilla-LO)	23 (9.35%)			
Isolated (Papilla-I)	2 (0.81%)			
Gyrus (Papilla-G)	13 (5.28%)			

Difficult cannulation was noted in 80 (32.5%) patients (Table 3). Among oral protrusion patterns, protrusion-S has the highest risk for difficult cannulation (Protrusion-R - OR 0.493, $p=0.017$; Protrusion-L -OR

0.702, $p=0.426$). Among the papilla patterns, papilla-U has the highest risk for difficult cannulation (OR 3, $p=0.008$).

TABLE 3. Logistic Regression Analysis of Papilla Morphology with Difficult Cannulation among ERCP-naïve patients who underwent ERCP at MDH from 2017 to 2018

Papillary Morphology	Difficult cannulation	Non-Difficult cannulation	OR	CI (95%)	P-value
Oral protrusion pattern					
Small (Protrusion-S) (n=89)	37	52	REF*	-	-
Regular (Protrusion-R) (n=127)	33	94	0.493	0.277 – 0.880	0.017
Large (Protrusion-L) (n=30)	10	20	0.702	0.294 – 1.674	0.426
TOTAL	80	166			
Papilla pattern					
Annular (Papilla-A) (n=180)	50	130	REF	-	-
Unstructured (Papilla-U) (n=28)	15	13	3	1.333 – 6.751	0.008
Longitudinal (Papilla-LO) (n=23)	8	15	1.387	0.554 – 3.472	0.485
Isolated (Papilla-I) (n=2)	1	1	2.6	0.160 – 42.37	0.502
Gyrus (Papilla-G).(n=13)	6	7	2.229	0.714 – 6.955	0.168
TOTAL	80	166			

*REF – Reference Category to which each other category is compared

Overall cannulation success rate was 96% (237/246) (Table 4). Nine patients had failed ERCP due to inability to cannulate the CBD. Of these 9 patients, 4 had protrusion-R (2 papilla_A, 1 papilla-U, and 1 papilla-LO), 3 protrusion-S (1 papilla-A, 2 papilla-U) and 2 had protrusion-L (1 papilla-LO, 1 papilla-G). Six of these patients also underwent pre-cut sphincterotomy

of the papilla, however, still failed at CBD cannulation. Among oral protrusion patterns, protrusion-L has the highest risk for failed cannulation, however, did not reach statistical significance (OR 2.04, $p=0.445$). Among papilla patterns, Papilla-U pattern has the highest risk for failed cannulation (OR 7.08, $p=0.020$).

TABLE 4. Logistic Regression Analysis of Papilla Morphology with Failure to cannulate among ERCP-naïve patients who underwent ERCP at MDH from 2017 to 2018

Papillary Morphology	Failed cannulation	Successful cannulation	OR	CI (95%)	P-value
Oral protrusion pattern					
Small (Protrusion-S) (n=89)	3	86	*REF	-	-
Regular (Protrusion-R) (n=127)	4	123	0.932	0.203 – 4.271	0.928
Large (Protrusion-L) (n=30)	2	28	2.04	0.325 – 12.884	0.445
TOTAL	9	237			
Papilla pattern					
Annular (Papilla-A) (n=180)	3	177	REF	-	-
Unstructured (Papilla-U) (n=28)	3	25	7.08	1.354 – 37.020	0.020
Longitudinal (Papilla-LO) (n=23)	2	21	5.619	0.887 – 35.575	0.067
Isolated (Papilla-I) (n=2)	0	2	-	-	-
Gyrus (Papilla-G).(n=13)	1	12	4.917	0.474 – 50.912	0.182
TOTAL	9	237			

*REF – Reference Category to which each other category is compared

ERCP-related complications occurred in 7 inpatients (4.05%) (Table 5). Three patients (2 patients with protrusion-R, papilla-A, and 1 patient with protrusion R, papilla-U) had post-ERCP pancreatitis (1.73%) resolved within 4-7 days hospital observation, one patient with protrusion-R, papilla-G had post-sphincterotomy site bleeding requiring endoscopic hemostasis (0.58%), and one patient protrusion R, papilla A had cholangitis developing after the procedure (0.58%) resolved with antibiotic therapy. There were 2 mortalities noted; one patient with protrusion R, papilla A was a 73

year-old female developing myocardial infarction 2 days post ERCP and another was a 43 year-old male with protrusion-R, papilla-U admitted for severe cholangitis prior to ERCP with sphincterotomy and balloon stone extraction with findings of purulent bile and three CBD stones, unfortunately, patient succumbed to the infection 2 days post procedure; both mortalities occurring within 30 days post procedure and was still considered an ERCP-related mortality. No perforation related to the endoscopic procedure was noted among the patients.

Table 5. Frequency of ERCP-related complications among patients undergoing ERCP at MDH from 2017 to 2018

Papillary Morphology	PEP	Bleeding	Perforation	Cholangitis	Mortality
Oral protrusion pattern					
Small (Protrusion-S) (n=89)	0	0	0	0	0
Regular (Protrusion-R) (n=127)	3	1	0	1	2
Large (Protrusion-L) (n=30)	0	0	0	0	0
TOTAL	3	1	0	1	2
Papilla Pattern					
Annular (Papilla-A) (n=180)	2	0	0	1	1
Unstructured (Papilla-U) (n=28)	1	0	0	0	1
Longitudinal (Papilla-LO) (n=23)	0	0	0	0	0
Isolated (Papilla-I) (n=2)	0	0	0	0	0
Gyrus (Papilla-G).(n=13)	0	1	0	0	0
TOTAL	3	1	0	1	2

There was noted significant occurrence of periampullary diverticulum among the studied subjects (57, 23.17%) and a Fishers exact test was conducted to determine if the presence of a

diverticulum posed a significant risk of difficulty in papilla cannulation. However, the test failed to show a significant association ($p=0.747$) (Table 6).

Table 6. Fishers exact test for association of periampullary diverticulum with difficulty cannulation.

	Non-difficult Cannulation (n=166)	Difficult cannulation (n=80)	P= value
Without Diverticulum	126 (75.9)	63 (78.75)	0.747
With Diverticulum	40 (24.10)	17 (21.25)	

DISCUSSION

Several studies have acknowledged that the morphology of the major duodenal papilla posed a challenge to cannulating the CBD [8]. In 2017, Harraldson et. al. proposed a classification scheme of the duodenal papilla which predicted cannulation difficulty. The 4 types of papilla (regular, small, protruding/pendulous, ridged) provided a reliable classification and in 2018, a follow-up study provided correlation with regards to cannulation difficulty with the small type being the most difficult to cannulate and highest risk for post-ERCP pancreatitis [9,10]. In 2019, Watanabe et. al. proposed a new classification scheme incorporating elements of Harraldson's, with their classification of Protrusion S corresponding to Type 2 small papilla, Protrusion R to Type 1 regular papilla and Protrusion L to Type 3 protruding papilla. They found protrusion L to be more difficult with higher risk of cannulation failure probably due to misalignment between the ERCP catheter and the biliary duct axis during cannulation leading to difficult cannulation and failure [5]. Our study showed that both small and large oral protrusions were more difficult to cannulate than regular protrusions, however, only large protrusion pattern was noted to have a greater risk for failed cannulation, though, not statistically significant probably due to sample size limitation and small event rate for failed cannulation. After we started our study, Balan et al published another classification in 2020. Their classification appears to be an expanded Harraldson classification of the major papilla morphology [11]. Balan regular type corresponds to the Harraldson's Type 1 Regular papilla, Balan Types 1

and 2 corresponds to Harraldson's Type 2 Small papilla, and Balan Types 3 and 4 corresponds to Harraldson's Type 3 Protruding papilla. Similarly, their study found that their Balan Type 1 papillae (small and/or retracted papilla, without a recessus and infundibulum) were significantly linked to difficult cannulation and the Balan type 4 papillae (large papilla with multiple overlying folds over the orifice (commonly referred to as a hooded papilla or a Shar-Pei dog papilla) were noted to be independent risk factors for post-ERCP pancreatitis [11].

Haraldsson's classification included only 1 papilla pattern – the ridge pattern. Watanabe's classification included 5 patterns with the longitudinal pattern corresponding to the ridge pattern of Haraldsson's. In Watanabe's study, papilla pattern A and G proved more difficult to cannulate requiring more attempts. In contrast, our study found that papilla pattern A to have the lowest risk for difficult and failed cannulation. In our study, the unstructured papilla (papilla-U) was the most difficult and at risk for failed cannulation. This might be due to difficulty in directing the catheter tip in a papilla without a discernible orifice. Balan's classification did not include papilla patterns.

Several studies have investigated the influence of periampullary diverticulum (PAD) in the success and difficulty of duodenal papilla cannulation. Failures in cannulation may be partially attributable to difficulties in detecting the papilla, especially in cases where the papilla is found deep within, often at the very bottom of, the diverticulum. But in some other studies,

the presence of PAD had no influence on cannulation of CBD [12]. Our study noted the presence of PAD in 23.17% of the cases and analysis thru Fisher's exact test did not find a significant difference towards difficulty cannulating the duodenal papilla among subjects with clearly visible and classifiable papilla with PAD.

In the literature, complications directly attributed to ERCP are as high as 6.8%. Mortality rates are about 0.3%. The incidence of post-ERCP pancreatitis (PEP) is 3.5%, making it the most frequent complication following the procedure. In 90% of cases, pancreatitis is mild-to-moderate in severity. Gastrointestinal bleeding happens 1.3% of the time. Infections, as cholangitis and cholecystitis, occur at a rate of 1.4% [4]. Haraldsson's study showed that small papillae were found to be associated with higher frequency of PEP, which increased in parallel with the frequency of difficult cannulation, probably due to the biliary or papillary manipulation, but they were not able to support this statistically. Watanabe's study was not able to analyze the association of the different papilla morphology with the incidence of PEP because their population included patients who had undergone preventive procedures and those who have not, rendering evaluation impossible [5]. On the other hand, Balan's recent study have found out that their type 4 papilla have proven to be an independent risk factor for post-ERCP pancreatitis (OR = 12.176, 95%CI, $p = 0.005$), attributed indirectly to difficult cannulation and contributive factors of increased frequency of rescue needle-knife papillotomy and prophylactic pancreatic stenting for patients with type 4 papillae [11]. Our study results showed complication rates with the same figures seen in literature. However, due to the small occurrence of the specific post-ERCP complications, we were not able to statistically correlate the papilla morphology with the risk of their development. In our study, post ERCP pancreatitis occurred in 3 patients with regular oral protrusion pattern and unstructured papilla probably because of prolonged and multiple attempts at cannulating the papilla predisposing to edema and inflammation as these cases have not reported any incident of pancreatic duct cannulation or contrast injection. The other complications noted in the study were a case of post-sphincterotomy bleeding (case of cholangitis, with no coagulation derangement with a 1.5 cm sphincterotomy done at 11 -12 o'clock position) and two cases of severe cholangitis and a

case of myocardial infarction post-procedure were probably isolated cases that cannot be associated with difficult cannulation of the duodenal papilla. There were no noted complications on the patients who had failed cannulation.

LIMITATION

Being a retrospective study, data gathering relied on the accuracy of data recorded in the endoscopy reports, ERCP video documentations, and inpatient charts. Pancreatic duct cannulation, particularly, was considered only on review of the endoscopic reports which some may have not reported the inadvertent pancreatic duct cannulation therefore, underestimating the number of patients with difficult cannulation. The influence of a fellow-in-training doing the cannulation process may also affect classifying the procedure as difficult cannulation if the process takes more than 5 minutes and more than 5 attempts to successfully cannulate the papilla. This influence is not documented in the reports, though most of the procedures are fully performed by the expert endoscopists in our institution.

CONCLUSION

Among oral protrusion pattern, a small oral protrusion pattern has the highest risk for difficult cannulation while a large protrusion pattern has the highest risk for failed cannulation; among papilla pattern, an unstructured papilla pattern was a risk factor for cannulation failure. Though the rate of complication is found to be small in our institution, these morphologic differences of the papilla and risk for difficult cannulation and post-ERCP complications should be considered.

RECOMMENDATIONS

We recommend prospective multicenter studies to include more patients to observe cannulation difficulties performed by experienced endoscopists related to the differences in papilla protrusion and orifice pattern and observe for post-ERCP complications. This can also be used to develop cannulation techniques for each specific papilla morphology minimizing risk for complications.

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A Rare Case of Functional Pancreatic Neuroendocrine Tumor with Multi-organ Involvement in a 25-year Old Female*

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Abstract

Significance: Pancreatic neuroendocrine tumors (pNET) account for 1-10% of tumors arising in the pancreas, with functional pNETs reported less commonly than their non-functional counterpart. Glucagonoma is an even rarer form of functional pNET which has a reported annual incidence of 0.01-0.1 per 100,000.

Clinical Presentation: This is a case of a 25-year old female presenting with a two-year history of palpable epigastric mass, abdominal pain and weight loss. She came in at our institution with worsened signs and symptoms in which she already had chronic diarrhea, anemia, glossitis, and dermatitis eventually leading to development of early onset diabetes, stroke and cardiomyopathy.

Management: Initial contrast-enhanced CT scan revealed a pancreatic mass and was confirmed by endoscopic sonography as a large solid encapsulated mass at the head to the body of the pancreas measuring 7.7x5.5cm. Histopathologic and immunohistochemical tests to tissue specimen obtained by fine needle aspiration biopsy of the mass revealed a well-differentiated pancreatic neuroendocrine tumor confirmed as glucagonoma by a remarkably elevated plasma glucagon level. The mass was deemed non-resectable at the time of diagnosis, hence the patient was started on octreotide LAR depot injection. Multi-systemic complications caused by the functional tumor were also managed through multidisciplinary approach. Medical management resulted to marked improvement of the signs and symptoms and lead to a better quality of life.

Recommendation: In rare cases such as this, diagnosis is often a dilemma and causes delay in treatment. Prompt diagnosis will lead to early intervention preventing life-altering complications, disease progression, and mortality.

INTRODUCTION

Pancreatic neuroendocrine tumors (pNET) account for 1-10% of tumors arising in the pancreas, with functional pNETs reported less commonly than their non-functional counterpart (1, 2). Glucagonoma is an even rarer form of functional pNET which has a reported annual incidence of 0.01-0.1 per 100,000⁽³⁾.

Glucagonoma secretes excessive amounts of glucagon and the syndrome, characterized by dermatitis, glossitis, cheilitis, glucose intolerance, anemia, venous thrombosis, diarrhea, abdominal pain, and neuropsychiatric disturbance, has an estimated incidence of 1 in 20 million (4). Early recognition allows prompt diagnosis of the tumor and subsequent intervention. All patients with localized tumor should be planned for resection (5) but initial medical treatment is directed at symptomatic management, improvement of nutritional status, and control of hyperglycemia, since patients generally are poor operative candidates markedly affected by their nutritional status and greater risk of venous thrombosis⁽⁶⁾.

CASE PRESENTATION

We present a case of a 25-year old female with a 2-year history of palpable epigastric mass associated with progressive unintentional weight loss. No consult was done until further progression in the size of the

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mass after a year, which prompted consult with a surgeon. Initial complete blood count showed anemia and whole abdominal ultrasound revealed a pancreatic mass. She was then advised further workup. In the interim, there was onset of generalized weakness, poor appetite, glossitis, nausea, bilious vomiting and watery diarrhea, 6-12 bouts per day, hence consult to our institution. She was initially seen by Surgery service and requested for a Dynamic CT scan of the pancreas revealing a large lobulated heterogeneously enhancing mass with mixed cystic and predominantly soft tissue components at the region of the pancreatic head-body measuring 7.7 x 8.4 x 12.0 cm, with intralesional vascularity, dilated

biopsy of the mass revealed a well-differentiated, pancreatic neuroendocrine tumor, grade 3 (Chromogranin A and synaptophysin positive, CA19-9 negative, mitotic rate 22 per 10 hpf, Ki-67 index 33.6%).

Patient was then referred to Endocrine and Medical Oncology services with orders for further testing to confirm the type of pNET and rule out MEN-1 syndrome. Initial tests available were all within the reference range (Gastrin, prolactin, iPTH, ACTH, Vitamin D). Plasma glucagon and VIP were not available and were sent out to Mayo Clinic Laboratory for testing. Multidisciplinary supportive management were provided while waiting for the confirmatory results.

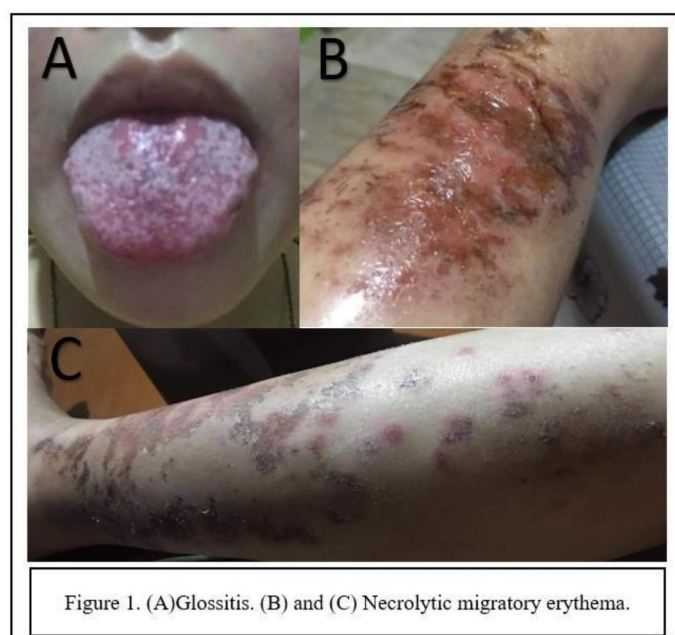


Figure 1. (A)Glossitis. (B) and (C) Necrolytic migratory erythema.

(2 cm) pancreatic duct, splenomegaly, encasement of the superior mesenteric vein, inferior portion of the portal vein, left gastric artery and non-delineation of the splenic vein. Also seen is a 2.7 x 3.6 cm hypoenhancing nodule with a central fluid density in the segment IVB of the liver. Patient was then referred to our service, underwent endoscopic ultrasound revealing mixed echogenic and anechoic areas at the head to the body of the pancreas measuring 7.7 x 5.5 cm abutting the bifurcation of the celiac trunk going to the common hepatic artery. There were no lymphadenopathies noted. Histopathologic and immunohistochemical tests to tissue specimen obtained by fine needle aspiration

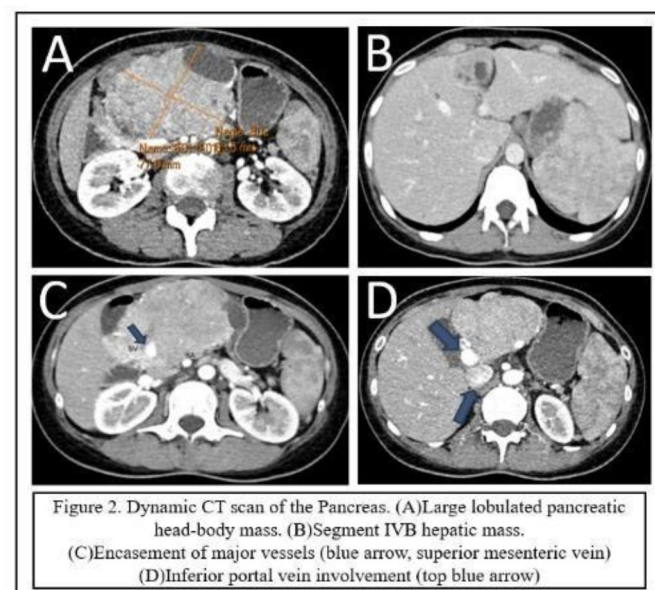
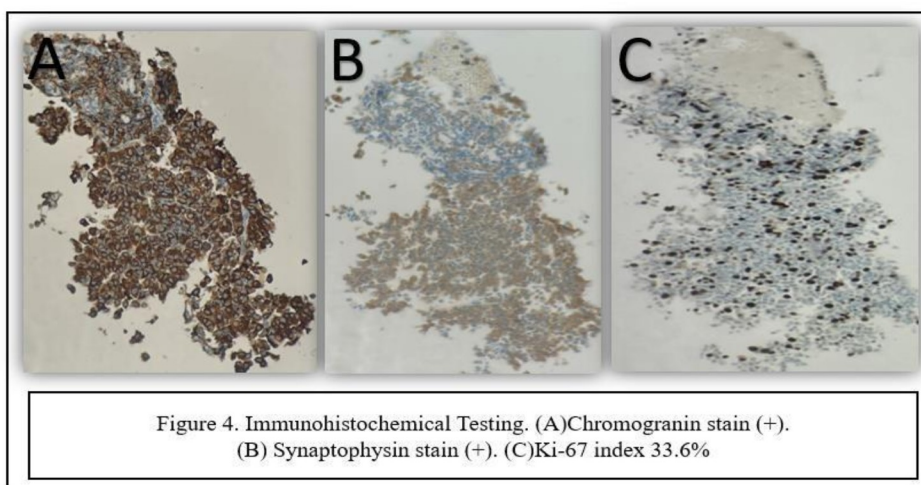
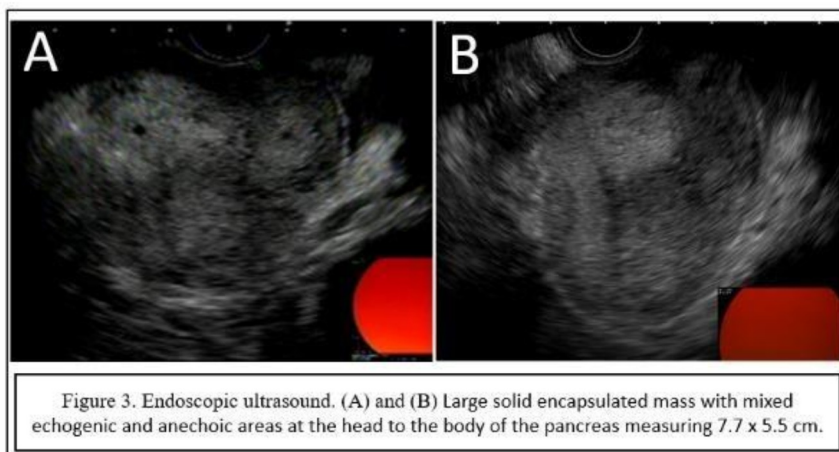


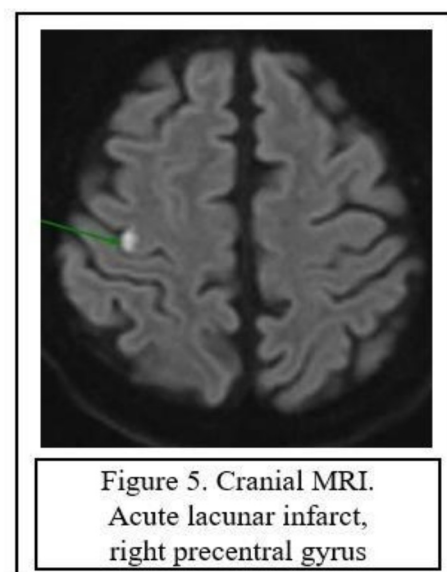
Figure 2. Dynamic CT scan of the Pancreas. (A) Large lobulated pancreatic head-body mass. (B) Segment IVB hepatic mass. (C) Encasement of major vessels (blue arrow, superior mesenteric vein) (D) Inferior portal vein involvement (top blue arrow)

During her course, patient eventually had sudden onset of right sided body weakness, slurring of speech and dysphagia confirmed by cranial MRI as Acute lacunar infarct of the right precentral gyrus. She also developed heart failure symptoms (NYHA class III-IV) confirmed by echocardiogram as dilated left ventricle, global hypokinesia, and an ejection fraction of 20.9%. Patient's functional status declined (ECOG 4), enteral feeding was started.



Referral to Neurology, Cardiology, Clinical Nutrition and Rehabilitation services for optimal management was done.

After confirmation of Glucagonoma (plasma glucagon >25,000 pg/mL, ref.<80 pg/mL, VIP within normal range), treatment with Octreotide LAR depot injection every 28 days ensued, with subsequent significant improvement of all parameters including control of abdominal pain, resolution of watery diarrhea, improvement of skin rash and glossitis, improvement in the functional status (ECOG 4→2, MRS 4-5→2) and functional class (NYHA class III-IV→II). Although tumor was assessed to be advanced and non-resectable, optimal medical management resulted to marked improvement of the signs and symptoms and lead to a better quality of life.



DISCUSSION

Pancreatic neuroendocrine tumors produce multiple GI hormones, which can be localized by immunohistochemical methods. Functional pNET syndrome should be diagnosed only if the appropriate clinical symptoms are present, and not only based on immunohistochemistry alone. Poorly differentiated neuroendocrine carcinomas are highly aggressive with high proliferative activity and virtually all poorly differentiated tumors are high grade.

Glucagonoma can be confirmed by demonstrating an increase in fasting plasma glucagon concentration with marked elevation in plasma glucagon level seen at presentation in most patients (7). The high level of glucagon secreted by the tumor promotes glycogenolysis and gluconeogenesis which causes hyperglycemia. Weight loss is secondary to the catabolic effect of glucagon (8). Prolonged elevation of glucagon levels causes the typical rash and the presence of hypoaminoacidemia may also cause the dermatitis. Decreased erythropoiesis due to hyperglucagonemia is said to contribute to anemia. The role of glucagon in causing venous thromboembolism and neuropsychiatric problems is still unclear (9).

Somatic mutations of MEN-1 were observed in 44% of cases in a whole-exome study of 68 sporadic pNETs by Jiao et al. and glucagonoma could be part of the MEN-1 syndrome (10). Testing is prudent to allow adequate intervention.

While tumor confirmation and localization studies are ongoing, initial medical management of glucagonomas is directed at symptomatic treatment, improving nutritional status, and controlling hyperglycemia.

Surgical resection is the recommended treatment for localized tumors. For advanced, metastatic, non-resectable tumors, somatostatin analogs have been useful in controlling symptoms. A small randomized, controlled trial demonstrated an improvement in time to tumor progression with octreotide LAR injection compared with placebo for

metastatic midgut tumors with extrapolation of data occasionally considered for pNET tumor stabilization ⁽¹¹⁾.

CONCLUSION / RECOMMENDATION

A multidisciplinary, collaborative, and proficient team augments the management of patients with pNETs. Different options may be significant and of considerable importance at different times in the disease process.

In rare cases such as this, diagnosis is often a dilemma and causes delay in treatment. Lack of accessible tests also cause this delay. Prompt diagnosis will lead to early intervention preventing life-altering complications, disease progression, and mortality.

Author's Statement

The manuscript is original material and is not being considered for publication or has not been published or accepted for publication elsewhere, in full or in part, in print or in electronic media.

The manuscript has been read and approved by all the authors and all four criteria for authorship have been met by each author.

Conflict of Interest

The authors declare no conflict of interest.

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Unmasking Tumors: A Case of a CD30-Negative MycosisFungoides Masquerading as Erythema NodosumLeprosumin a Filipino Male

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Abstract

Mycosis Fungoides is the most common type of primary cutaneous lymphoma. Early in its course, it usually presents as erythematous patches and plaques similar to a lot of cutaneous conditions. A 68-year-old male presented with a 13-year history of multiple erythematous patches and plaques on the arms and trunk. The lesions were pruritic and chronically relapsing over the years, temporarily relieved by topical corticosteroids. Thereafter, there was onset of multiple nodules on the trunk, extremities and face. Initial biopsy was done by a different dermatologist, revealed Hansen's Disease, Borderline Borderline spectrum. Fitefaraco stain was positive but no bacillary index was given. The patient was subsequently started on rifampicin 600mg/capsule once a day, Ofloxacin 400mg/tablet once a day, and Minocycline 100mg/capsule once a day. The lesions were noted to worsen, eventually developing ulcerations over the trunk and extremities prompting referral to our institution. The biopsy results were as follows: Cutaneous T-Cell Lymphoma, diffuse cluster of differentiation (CD) 3 staining, focal CD20 staining, and negative FiteFaraco stain. The histopathologic findings combined with the clinical presentation led to the diagnosis of Mycosis Fungoides. He was then referred to medical oncology for proper staging and definitive management. The prognosis of Mycosis Fungoides is generally dependent on the stage as determined by the extent of skin involvement as well as presence of lymph node invasion and/or metastasis.

Keywords: *Mycosis Fungoides, Lymphoma, T-Cell, Cutaneous*

ACKNOWLEDGEMENTS

We would like to acknowledge Dr. Vilma C. Ramilo, FPDS, chairman of the Department of Dermatology of Dr. Jose N. Rodriguez Memorial Hospital and Sanitarium for her support and guidance throughout the duration of this case report. We would also like to acknowledge the department's research consultants, Dr. Wilsie Salas-Walinsundin, FPDS, and Dr. Jamaine Cruz-Regalado, FPDS, for their valuable suggestions leading to the improvement of this paper. Lastly, we would like to acknowledge all the consultants and residents of the Department of the Dermatology for inspiring us to provide the best possible care to our patients.

INTRODUCTION

Mycosis Fungoides is a type of primary cutaneous T-cell lymphoma that begins as erythematous patches and plaques before progressing to the tumor stage. It can be similar in presentation to a multitude of other cutaneous conditions making it difficult to diagnose early in the course. Multiple biopsies are often needed before a definite diagnosis can be reached. This case report intends to discuss a cutaneous disorder that is difficult to diagnose and is usually diagnosed later in its course.

CASE REPORT

We present a 68-year-old male with a 13-year history of multiple erythematous, pruritic, and chronically relapsing patches and plaques, which started on the arms then spread to the trunk. The patient applied clobetasol propionate cream intermittently over

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the years which gave temporary relief. One year prior to admission, he developed erythematous nodules on the trunk that progressed to the upper and lower extremities. No consult was done during this time and no medications were applied or taken. Seven months prior, the nodules increased in number now involving the face. The tumors were noted on the trunk and extremities. He sought consult with a private dermatologist where a biopsy was done which revealed Hansen's disease, Borderline Borderline spectrum. Fite stain was positive but no bacillary index given. He was subsequently started on rifampicin 600mg/cap once a day, Ofloxacin 400mg/tab once a day, and Minocycline 100mg/cap once a day. No improvement was noted during the interim.

Two months prior to admission, ulcerations started to develop on existing plaques and nodules on the trunk and extremities. He followed up with his dermatologist and daily wound care with plain normal

saline solution compress, mupirocin cream, and dry gauze. All his oral medications were continued. Despite compliance to medications and wound care, new ulcerations appeared on the trunk and extremities while old ulcers enlarged, with some forming crusts. Impression during this time was Erythema Nodosum Leprosum. The patient was referred to our institution for further evaluation and management. The referral team had a different clinical suspicion hence a skin punch biopsy was done and the patient was subsequently admitted. Upon admission, physical examination showed multiple well-defined erythematous to violaceous plaques and nodules on the face; multiple well-defined erythematous to hyperpigmented plaques, nodules and tumors some topped with ulcerations over the trunk and extremities; and multiple well-defined erythematous to hyperpigmented plaques and nodules some with hemorrhagic crusting over the trunk and extremities (Figure 1).



Figure 1. Multiple well-defined erythematous plaques, nodules, and tumors some with erosions and ulcerations on the face (A), trunk (B) and extremities (C)

Histopathological findings revealed Cutaneous T-Cell Lymphoma (Figures 2 and 3). Fite- Faraco was negative.

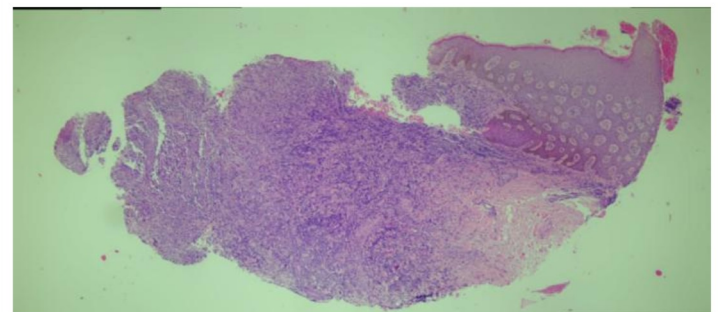


Figure 2. Skin biopsy specimen from abdomen shows an acanthotic epidermis with mild spongiosis and Pautrier's microabscess. (Hematoxylin-eosin stain; original magnification: X4.)

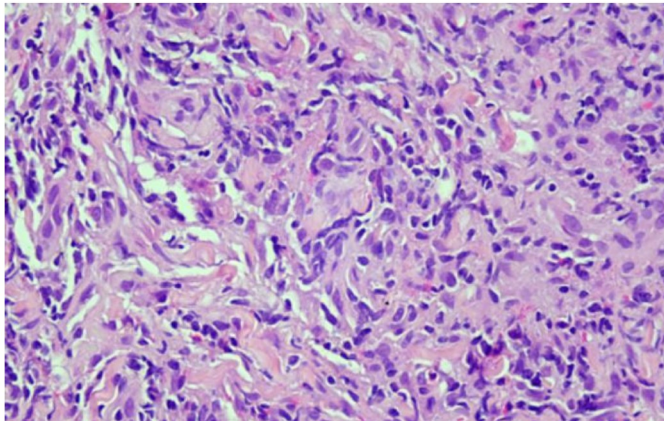


Figure 3. In the dermis are numerous atypical lymphocytes in between the collagen bundles. (Hematoxylin-eosin stain; original magnification: X40.)

Immunohistochemistry was also done for confirmation of diagnosis: CD3 strong and diffuse (Figure 4), CD20 and CD30 negative (Figures 5 & 6).

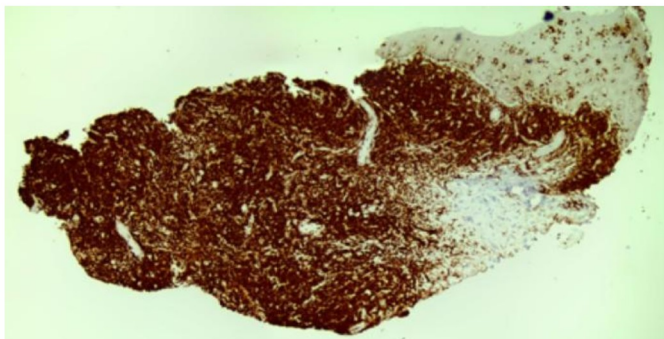


Figure 4. CD3+ atypical lymphocytes in both the epidermis and dermis. (Original magnification: X4.)

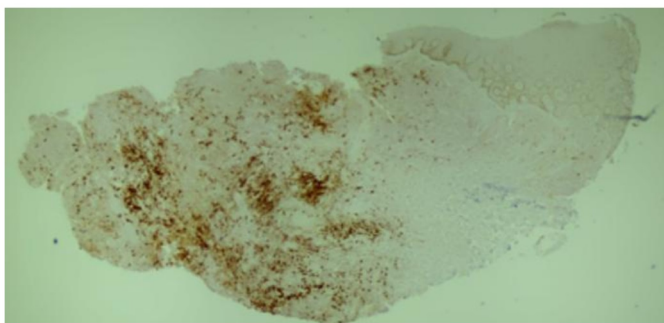


Figure 5. CD20 negative. B lymphocytes are less than 30% of the section. (Original magnification: X4.)

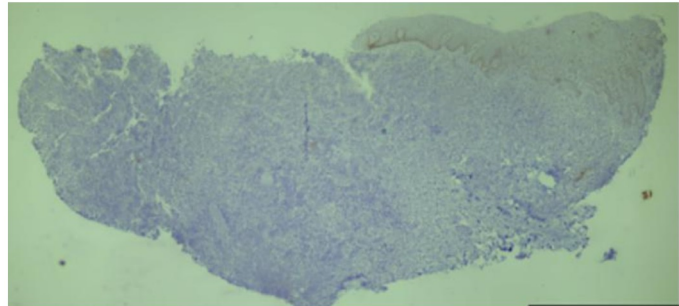


Figure 6. CD30 negative. No evidence of large cell transformation. (Original magnification: X4.)

DISCUSSION

The diagnosis of Mycosis Fungoides is challenging. Its early presentation consists primarily of erythematous patches and plaques that resemble more common cutaneous conditions such as eczematous dermatitis or psoriasis. More often than not, there is a delay in diagnosis. The median time from onset of symptoms to diagnosis usually takes 3-4 years but in some instances, may exceed four decades.ⁱ Histopathologic findings of acanthosis and mild spongiosis are non-specific and can be seen in numerous dermatologic conditions such as drug reaction, spongiotic dermatitis, scabies, arthropod bite, and mycosis fungoides.ⁱⁱ Dermal lymphocytic infiltration is manifested in many inflammatory and infectious dermatoses, including Hansen's Disease.

Skin punch biopsy with immunohistochemistry are warranted to arrive at a definitive diagnosis. When there is a high index of suspicion for Cutaneous T-Cell Lymphoma, CD3 and CD20 stains must be requested. A CD3 positive stain will confirm that the lymphoma is of T-cell origin while a CD20 positive stain is indicative of B-cell origin.ⁱⁱⁱ Different thresholds have been set for determining the positivity of CD3. Certain studies have deemed a stain of 30% T-lymphocytes as CD3 positive while other studies have set 60% as their threshold.^{iv} T-cell lymphomas have been shown to be positive for CD3 in 85-100% of cases with the exception of anaplastic large cell lymphoma (ALCL) for which CD30 is the preferred marker.^v CD30 will help determine whether or not this is a case of Mycosis Fungoides transforming into Anaplastic Large Cell Lymphoma, a CD30 positive variant of Cutaneous T-Cell Lymphoma with a more aggressive course.^{vi} In terms of clinical presentation, it is

common in Anaplastic Large Cell Lymphoma to have ulcerative nodules and tumors easily mimicking Erythema Nodosum Leprosum. Thus, it is important to rule out Erythema Nodosum Leprosum through slit-skin smear and Fite-Faraco.

There are many treatment options for Mycosis Fungoides. For early stages, particularly the patch and plaque stages, the approach to treatment is skin-directed therapy. This includes topical corticosteroids, imidazoquinolines, mechlorethamine hydrochloride, carmustine, topical retinoids and phototherapy.^{vii} In addition, methotrexate may also be given for patch and plaque stages as it not only causes remission, but may also prevent progression to later stages.^{viii} Mycosis Fungoides is highly radiosensitive and thus, radiotherapy is administered on all stages of the disease. For the early stages, radiotherapy can be curative and for the later stages, it serves as part of palliative care.^{ix} On the other hand, late stages of mycosis fungoides are commonly treated with biologic response-modifying agents.^x Several of these have already been approved by the Food and Drug Administration for the treatment of cutaneous T-cell lymphoma, namely: vorinostat, denileukindifitox, romidepsin, brentuximab and mogamulizumab; all of which may be used after at least one failed systemic therapy.^{xi} Lastly, chemotherapy may be considered depending on the patient's tolerance of adverse effects and risk of infection.

For prognosis, the serum lactate dehydrogenase may be requested as there is a significant correlation between a high LDH level with advanced stages of mycosis fungoides. In a retrospective study conducted by the department of dermatology at King Saud University, 100% of their patients with advanced stage had high LDH.^{xii} Thus, it is recommended to request this marker as an independent prognostic factor.

Histopathology of Cutaneous T-Cell Lymphoma may appear non-specific on routine H&E staining. Immunohistochemistry remains the gold standard for diagnosing this condition. The histopathologic and immunohistochemistry findings combined with the clinical presentation of the patient will confirm the diagnosis of Mycosis Fungoides.

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A Rare Case of Disseminated Histoplasmosis Mimicking Varicella in A 28-Year-Old Immunocompetent Female

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Abstract

Histoplasmosis is well-characterized as a fungal disease that more commonly occurs in North America, mostly endemic in Ohio and Mississippi river valleys.¹ The clinical spectrum of histoplasmosis ranges from asymptomatic infection to a fatal disease. Progressive disseminated histoplasmosis is typically seen in immunocompromised individuals and presents with non-specific systemic symptoms associated with cutaneous manifestations of papules and nodules.² We report a case of a 28-year old Filipino female with a history of exposure to soil activities months before consult. The patient presented with a 3-week history of erythematous macules, vesicles, and pustules over the face, arms, and trunk, which evolve into papules and plaques with hemorrhagic crusting. Patient was initially diagnosed and treated as a case of varicella but had no improvement with initial management. Histopathologic findings were consistent with histoplasmosis. The patient was started with oral itraconazole, but unexpectedly expired before any improvement in cutaneous symptoms were noted.

Key Words: *Disseminated histoplasmosis, Itraconazole, Nonendemic area*

INTRODUCTION

Histoplasma capsulatum is a dimorphic fungal organism found most in fertile soil contaminated by bird or bat droppings. It is most endemic in certain parts of North, Central and South America, particularly in Mississippi and Ohio River Valleys when more than 80% acquire the infection asymptotically.² Transmission occurs via inhalation of spores from the soil,

and infections may range from asymptomatic to the disseminated fatal type. In immunocompromised individuals, disseminated histoplasmosis occurs when cellular immunity is impaired and the organism continues to reproduce intracellularly and disseminate via lymphatic and hematogenous circulation. Patients usually present with weight loss, fever, respiratory symptoms and cutaneous lesions with different morphologies such as papules, nodules or ulcers. Untreated disseminated histoplasmosis is fatal within a few weeks of inappropriate treatment. Therefore, a prompt diagnosis and initiation of therapy is very important.³

Here, we present the case of a young patient with no evidence of existing immunosuppression from a nonendemic area infected by *H. capsulatum*, initially treated as a case of varicella due to its clinical presentation at the time of referral. One of the few cases of disseminated histoplasmosis in the Philippines.

CASE REPORT

A 28-year old female was admitted under the service of Internal Medicine service due to community acquired pneumonia and was referred to the service of Dermatology due to the presence of papules and plaques with hemorrhagic crusting over the face, trunk, upper and lower extremities. The patient's history started 3 weeks prior to referral when the patient had erythematous macules, vesicles, and pustules over the arms, spreading to the face and trunk which were non-pruritic and non-tender, associated with undocumented fever but no consult for the skin lesions were done. Patient claims to have exposure to a farm they visited months prior to the appearance of the lesions. During the interim, the patient noted spontaneous crusting of

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the lesions, no topical medications were applied and still no consult was done. Three days prior to referral, the patient was admitted under the service of Internal Medicine with an assessment of community acquired pneumonia, moderate risk and to consider pulmonary tuberculosis. Upon review of systems, patient had easy fatigability, generalized body weakness, unintentional weight loss, productive cough, shortness of breath, hemoptysis and low back pain. Past medical history revealed that the patient has been treated with unrecalled antibiotics as a case of Community Acquired Pneumonia, moderate risk three months prior to admission and was treated for two months with Anti-Koch's therapy for clinically diagnosed pulmonary tuberculosis. Laboratories upon admission revealed normocytic and normochromic anemia with hazy opacities in the right upper lobe on the chest xray. The patient was initially assessed by the service of Dermatology as a case of varicella based on the clinical history of vesicles and pustules over an erythematous base which spontaneously evolved into crusted papules, and was given Acyclovir 800 mg five times a day for one week with noted no progression of the lesions. Hence, team then signed out from the case. However, one month interval history showed no evolution of some the lesions to crusted nodules and plaques, hence, patient was referred back to Dermatology.

The initial cutaneous examination revealed multiple, well-defined, erythematous papules with hemorrhagic crusting over the face and trunk. (Figure 1) associated with slightly pale palpebral conjunctiva. The rest of the physical examination was unremarkable. The patient had symmetric chest expansion with clear breath sounds, as well as a normal neurologic examination. Upon the 2nd referral, patient now had multiple, discrete, crusted papules, nodules and plaques scattered all over the body, predominantly the face, some with erythematous borders (Figure 2)

During admission, complete blood count revealed normocytic normochromic anemia and thrombocytopenia. The chest xray revealed hazy opacities in the right upper lobe, suggesting pneumonia, but could not rule out presence of tuberculosis. Sputum Gram stain, culture and sensitivity revealed gram (+) pairs and tetrads, isolating *Streptococcus* sp. while the acid fast bacilli sputum test turned out negative. HIV

screening also tested negative. The rest of the laboratories were unremarkable.

Initially, during the course of admission, the patient was noted to be stable without subjective complaints. However, despite treatment with Meropenem, anti-Koch's therapy, blood transfusion and ferrous sulfate, she became febrile again with associated tachycardia, crackles over the right lung field and grade I bipedal edema. On further workup, she still had normocytic, normochromic anemia with the peripheral blood smear revealing mildly hypochromic and slightly anisopoikilocytic erythrocytes with decrease platelets. In addition, fecal occult blood test turned positive, she had increased total and direct bilirubin, and her chest xray suggested progression of the pneumonia bilaterally with consolidation to the right.

Skin punch biopsy was done over the face and abdomen revealing diffuse granulomatous infiltrates composed of multinucleated giant cells, lymphocytes, plasma cells, and neutrophils. Interspersed within these infiltrates are small, round spherules with an artefactual halo. The dermatopathology report was signed out as diffuse granulomatous infiltrate suggestive of systemic mycosis, specifically histoplasmosis (Figure 3). Other stains were requested to confirm the diagnosis. Periodic acid-Schiff stain turned out to be negative for visualizing the fungal cell wall (Figure 4) while Giemsa and Gomori's Methenamine Silver stains turned out to be positive for intracellular clusters of budding yeast and fungal capsule, respectively. (Figure 5 and 6)



Figure 1. First Referral (February 26, 2020) Patient presenting with multiple, well-defined, erythematous papules with hemorrhagic crusting over the face and trunk



Figure 2. Second Referral (March 21, 2020) Patient with multiple, discrete, erythematous to violaceous papules, nodules and plaques with hemorrhagic crusting, scattered all over the body, predominantly the face, some with erythematous borders

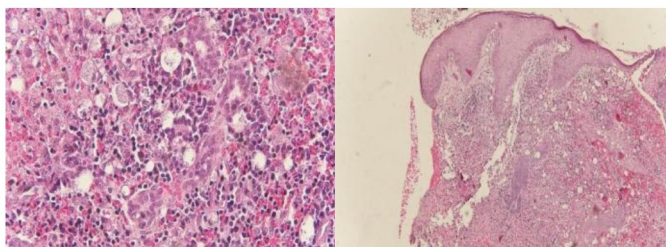


Figure 3. H&E Staining

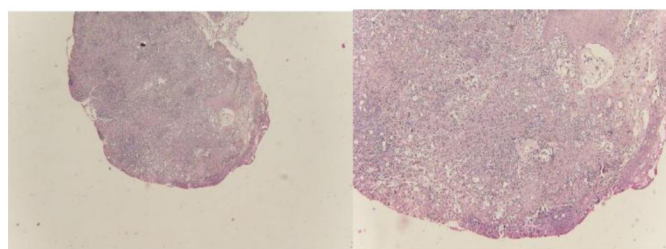


Figure 4. PAS Staining

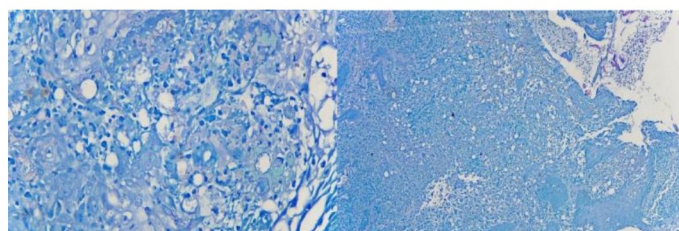


Figure 5. Giemsa Staining

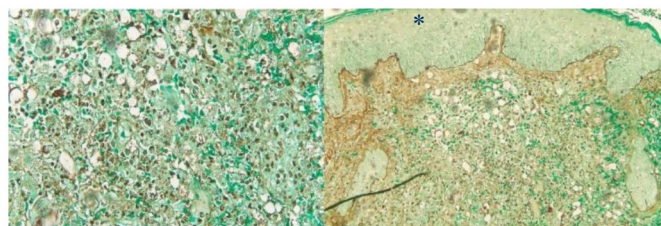


Figure 6. GMS Stain

Overall, based on the history, physical examination, diagnostics, and histopathologic examination, all led to the diagnosis of disseminated histoplasmosis.

The plan was to initiate Itraconazole 200 mg per capsule three times a day and shift to Itraconazole twice a day indefinitely. However, patient expired a day before initiating therapy due to respiratory failure secondary to aspiration pneumonia.

DISCUSSION

Histoplasma capsulatum is a soil saprophytic fungi that usually produces a subclinical infection that may present as asymptomatic, but some may occur as an acute or progressive disorder, disseminated, or chronic disease.⁴ Histoplasmosis is globally distributed, although thought to occur more commonly in North America, mostly endemic in Ohio and Mississippi river valleys. In the Philippines, at least nine cases of Histoplasmosis have been reported and presented mainly as papulonodular lesions with umbilication or as ulcerated plaques.¹

None of the cases reported mentioned a papulovesicular eruption mimicking the lesions of varicella. A study by Bulmer, et al, revealed that atleast 26% of test subjects tested positive for histoplasmin hypersensitivity, revealing that *Histoplasma capsulatum* is sufficiently present in the Philippines to come in contact with one-fourth of the test population.⁵ Histoplasma is a dimorphic fungus that is widespread and is able to grow between 15 and 20 °C, and when nitrogen content is high. Human infection usually follows

inhalation of fungal aleurioconidia which changes into a pathogen yeast. This causes an asymptomatic or acute, self-limiting respiratory infection. On the other hand, immunocompromised patients infected with *H. capsulatum* may spread through the blood stream involving the reticulo-endothelial system causing a systemic disease. The main risk factors of acquiring histoplasmosis are exposure to sites likely to acquire high levels of *H. capsulatum* mold such as chicken coops, bird roots, and bat droppings, and a concurrent state of immunosuppression such as having HIV/AIDS with a CD4 count of <150cells/uL. For this patient, a history of visit to a farm in Antipolo may be associated with inhalation of the fungi.

The clinical features of disseminated histoplasmosis are usually non-specific, presenting as fever, weight loss, hepatosplenomegaly, lymphadenopathy, cough with pulmonary infiltrates, pancytopenia and hypergammaglobulinemia, and is usually misdiagnosed as visceral leishmaniasis, military tuberculosis, or lymphoproliferative malignancies. Cutaneous involvement usually presents in about 20% of cases.² The most frequent disease-related cutaneous manifestations seen in HIV-seronegative patients include exfoliative erythroderma, petechiae, purpura and ecchymoses mostly occurring over the face, arms and trunk.⁶ One case of an immunocompetent male with a history of motorcycle accident presented with a solitary nodule that evolved into a nonhealing ulcer revealed to be a case of cutaneous histoplasmosis.¹⁵ Another case report of an immunocompetent male with exposure to bird droppings presented with multiple skin-colored to erythematous papules of varying sizes over the body.¹⁶ There was also one rare case of disseminated histoplasmosis in an HIV positive patient where the patient simulates a case of varicella as papulovesicular lesions.¹⁷ The diverse morphology of histoplasmosis should prompt biopsy in immunocompromised patients presenting with these lesions.⁷

The pathogenesis of disseminated histoplasmosis starts from inhalation of the microconidia. The changes in temperature towards the alveoli facilitates the mycelial-to-yeast phase which is the pathogenic form of *H. capsulatum*, causing the acute disease, or it becomes latent, being able to

reemerge once the patient is in a state of immunosuppression. The phagocytised yeasts replicate within macrophages within which they can disseminate hematogenously, utilizing the macrophage's phagosome as a vehicle to translocate to hilar or mediastinal lymph nodes. T cells produce interferon gamma to assist macrophages in killing the organism, while IL-12 and TNF- α play an essential role in cellular immunity. In immunocompetent hosts, granulomas are formed to contain the organism, which eventually fibrose and calcify. While in immunocompromised individuals, the infection is not contained and can disseminate.¹¹

Although excellent laboratory methods are widely available, diagnosing histoplasmosis in nonendemic areas in an immunocompetent individual remains a challenge. A proven diagnosis of histoplasmosis is done by confirmation either through histopathology or culture while a probable diagnosis is based on the presence of an appropriate clinical presentation, a predisposing condition and mycological evidence such as presence of antigen in urine. The identification of *H. capsulatum* through culture is the gold standard in the diagnosis of histoplasmosis, however, may take up to 2 weeks to 8 weeks. Histopathology supports the diagnosis and may reveal ovoid yeast cells that have thin, non-refractile cell walls with characteristic narrow base budding, with yeast predominantly found phagocytized within macrophages and histiocytes. The use of histochemical stains facilitates the differentiation of pathogens, with the Gomori methenamine silver (GMS) and periodic acid-Schiff (PAS) stains being used to visualize the cell wall. Antigen testing and serology are also available, with the former proven to be more sensitive and easier to interpret. One of the emerging non-invasive diagnostics is testing the presence of antigen in urine which appears to have a similar specificity and sensitivity with culture.¹³ Finally, molecular methods such as PCR may be proving to be more sensitive than fungal culture but is limited by its availability in the laboratories.⁹

The first line agent for patients who have mild or moderately severe symptoms of disseminated histoplasmosis is oral itraconazole 200 mg three times a day for 3 days then twice a day for around 6 to 18 months of treatment in total.¹⁰ In our case, itraconazole 200 mg three times a day was ordered since the patient was

relatively stable without the need for mechanical ventilation at the time of referral.

Generally, acute histoplasmosis has a good prognosis. However, risk factors such as immunosuppression, age >54 years old, or infancy were associated with fatal or disseminated histoplasmosis. One rare case reported of a 13 year old female with no history of immunosuppression was admitted for 16 days and was being worked up for lymphoma died without initiating treatment.¹⁸ Untreated disseminated histoplasmosis has a 90% fatality rate.¹²

CONCLUSION

In summary, we report a case of a 28-year old Filipino female who presented with a 3-week history of vesicles and pustules surrounded by an erythematous base which spontaneously ruptured and dried with crusting over the face, arms and trunk, mimicking a resolving case of varicella, which later evolved into papules, nodules and plaques with crusting. Histopathologic findings revealed findings consistent with histoplasmosis. Unfortunately, the patient expired when the appropriate management was just started. Due to the rarity of the disease and fatality once unable to be managed promptly, it is important to have a high index of suspicion for these kinds of lesions. A complete work-up for identifying any possible underlying systemic disease/s, monitoring disease activity, and most importantly preventing delay in diagnosis such as performing a skin punch biopsy, culture and antigen testing.

RECOMMENDATION

First, histoplasmosis can mimic a common benign disease such as varicella so performing a biopsy should always be considered in patients not showing improvement in the initial mode of treatment.

Second, to address the difficulty in obtaining fungal cultures, which is the gold standard in diagnosing histoplasmosis, urine antigen testing may be done in suspected cases to avoid delay in diagnosis which is proving to be similar in sensitivity and specificity with faster results.

Third, this could be an area of research where further researchers may dwell into performing newer diagnostic modalities available in order to promptly diagnose a patient with histoplasmosis and to prevent delay in the management.

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A Case Report on Hepatocellular Carcinoma with Inferior Vena Cava and Right Atrium Tumor Thrombus in a Patient with COVID-19 Infection *

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Abstract

Background

Hepatocellular carcinoma (HCC) is the fourth most common cancer in the Philippines and is the second leading cause of cancer-related death due to advanced stage at diagnosis in many patients. Advanced HCC commonly has macrovascular invasion such as portal and hepatic veins however, cases that describe tumor extension into the inferior vena cava (IVC) and right atrium (RA) are rare.

Case Summary

We present a case of a 50-year old female with liver cirrhosis from Chronic Hepatitis B infection who presented with shortness of breath. She was diagnosed with HCC based on dynamic enhancement pattern on CT scan with IV contrast and highly elevated alpha-fetoprotein. CT imaging demonstrated hepatic vein invasion with large tumor thrombus extending to the inferior vena cava and right atrium. Patient also had a mild COVID infection. We treated her with modulated radiotherapy targeting the tumor thrombus along with lenvatinib, tenofovir, and apixaban. The COVID infection did not significantly affect the patient's over-all clinical status.

Conclusion

Vascular invasion of HCC into the IVC and RA portends poor prognosis. While there is no consensus on the intervention on these patients, our case may suggest the use of radiotherapy and oral anticoagulation along with lenvatinib to prolong survival and preserve quality of life.

INTRODUCTION

Hepatocellular Carcinoma (HCC) is one of the leading causes of cancer and cancer-related deaths worldwide. In the year 2020 in the Philippines, HCC was the fourth most common site of new cancer diagnosis but ranked second in terms of cancer-related death in the country ⁽¹⁾. This is partly due in fact because there is a high prevalence of hepatitis B (approximately 17%) in the Philippines ⁽²⁾. Hepatocellular carcinoma is often diagnosed late and may invade major hepatic vessels, the most common of which will be the portal vein (3)(4). However, tumor extension into the inferior vena cava (IVC) and right atrium (RA) may also occur but are relatively rare with an incidence rate of 4% or less (3,4). Once HCC has spread to hepatic vasculature especially the IVC and RA, prognosis tends to be poor and in some studies, median survival is less than two months as patients may succumb to pulmonary embolism, heart failure or sudden cardiac death (4)(5). Once patients present with IVC and RA thrombus, treatment options will be limited and commonly they will be managed with best supportive care ⁽⁴⁾. However, recent studies have shown that transarterial embolization, external-beam radiation therapy, systemic chemotherapy, surgery or combination therapy may show promise in prolonging survival and increasing time to tumor progression ^(4,6,7).

Our case describes a patient with IVC and RA thrombus from HCC secondary to chronic hepatitis B who was also infected with COVID-19.

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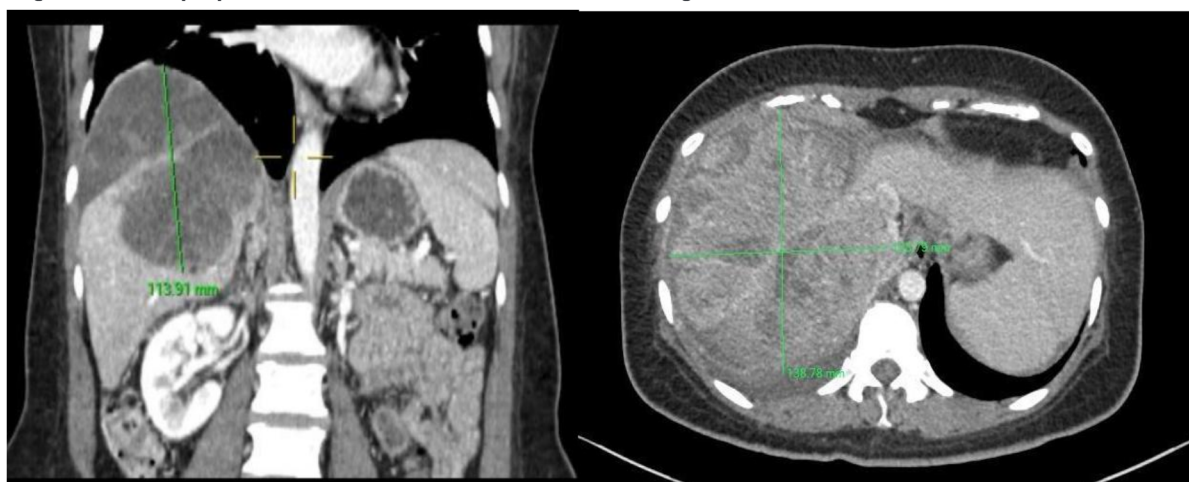
CASE REPORT

Presentation

We describe the case of a 50 year-old female who presented with a two-month history of bloatedness and progressive exertional dyspnea without abdominal pain or jaundice. She has not had significant weight loss, tea-colored urine, acholic stools, or edema. She was initially worked up in another institution where ultrasound incidentally showed right hepatic lobe mass. Follow-up CT scan of the abdomen with IV contrast in our hospital showed cirrhotic liver with nodular margins with a large heterogeneously enhancing mass (arterial

enhancement and venous washout) predominantly involving segments 8, 7 and 6 approximately 138 x 123 x 130 mm with features of tumoral hemorrhage (Figure 1). Tumor thrombus was also present in the suprahepatic inferior vena cava and right atrium. The right and middle hepatic veins were not clearly delineated and the portal veins were patent. Tumoral extension was noted in both external iliac veins. There was some minimal pelvic fluid and note of few prominent lymph nodes in the porta hepatis and perigastric region. Spleen was normal in size and the rest of the abdominal organs were unremarkable. There was minimal ascites on initial CT scan of the abdomen.

Figure 1. Quadruple-phase contrast CT scan of the abdomen showing the liver mass

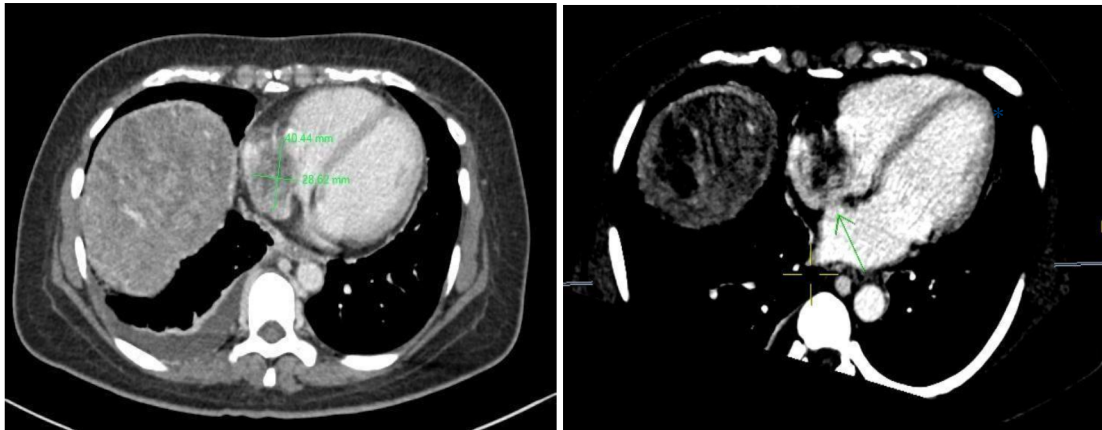


Patient's Alpha-feto protein was 82,965 ng/mL and CEA and CA 19-9 were both normal. She was positive for Chronic HBV (reactive HbsAg and Anti-HBS) with a viral load of 26,392,277 IU/mL.

Initial ALT was 60 U/L (normal range: 5-55) AST was 312.8 U/L (normal range: 5-34). Total Bilirubin was 1.2 mg/dL (normal 0.2-1.2), Direct 0.71 mg/dL (normal 0-0.5), and Indirect bilirubin was 0.5 mg/dL (normal 0.2-0.7). Albumin was 2.69 g/dL (normal 3.5-5) and INR ranged from 1.2 to 1.4. Sodium was 128 meq/L and Creatinine was 0.76 mg/dL. Hemoglobin 11.6mg/dL, Hematocrit 35.5 WBC 4.4 platelet 130 x 10⁹/L. Child-Pugh Turcotte score on admission was B8 with MELD score of 9.

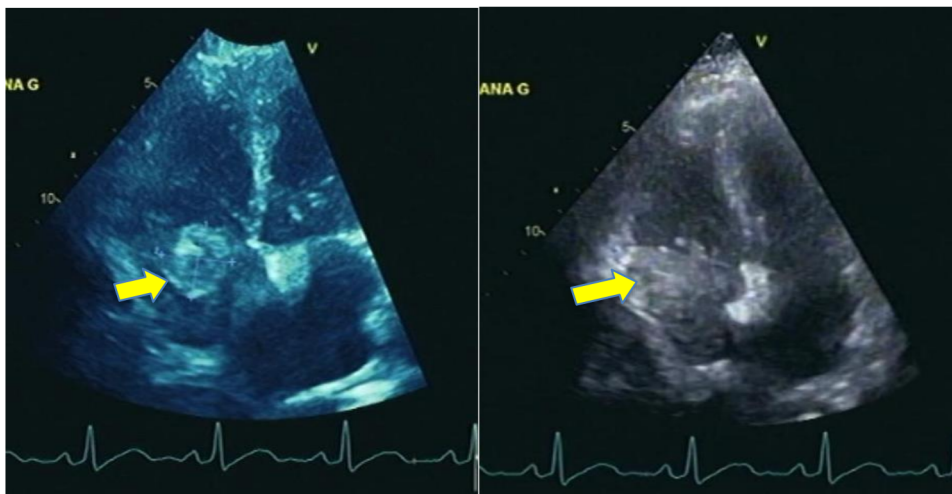
CT scan of the chest with IV contrast showed an irregular filling defect in the right atrium and inferior vena cava which appeared contiguous with the hepatic mass, likely representing tumor thrombus (Figure 2). Filling defects were noted in the left lower lobar pulmonary artery, medial segmental artery and distal lobar artery of the right middle lobe and segmental artery of the superior segment of the right lower lobe, which could represent pulmonary embolism. There were ground-glass densities in both lobes, possibly infectious pneumonia and non-calcified pulmonary nodules in both upper and left lower lobes (largest 6x6mm), thought to be pulmonary metastases. There was also note of minimal pleural effusion in the right. Heart was normal in size without pericardial effusion.

Figure 2. Contrast CT of Chest showing the thrombus in the right atrium and IVC (green arrow).



Transthoracic echocardiography revealed a 4.2 x 2.6cm echogenic density occupying almost the whole right atrium. Right atrium and ventricle size as well as pulmonary artery and left atriums and ventricular dimensions were normal. Pulmonary artery pressure and ejection fraction were normal as well.

Figure 3. Transthoracic echocardiogram showing the right atrium thrombus (yellow arrow)



COVID RT-PCR done on initial consult was positive for SARS COV-2. However, the patient was only mildly symptomatic with cough but no desaturations. Her AST and ALT were transiently elevated 2-3x upper limit of normal and inflammatory markers such as CRP, LDH and Ferritin were elevated as well. CT scan of the chest revealed some ground glass opacities but this resolved on follow-up imaging done 3 months later. Patient was given vitamin C and zinc supplementation and was quarantined for 14 days without any any deterioration in clinical status. Repeat PCR done after 14 days was negative.

The patient however, developed right-sided pleural effusion during her final days of admission. Pleural fluid tested positive for atypical cells (likely malignant pleural effusion), and was negative for bacteria or tuberculosis culture and GeneXpert. A chest pigtail was then placed for drainage of malignant fluid.

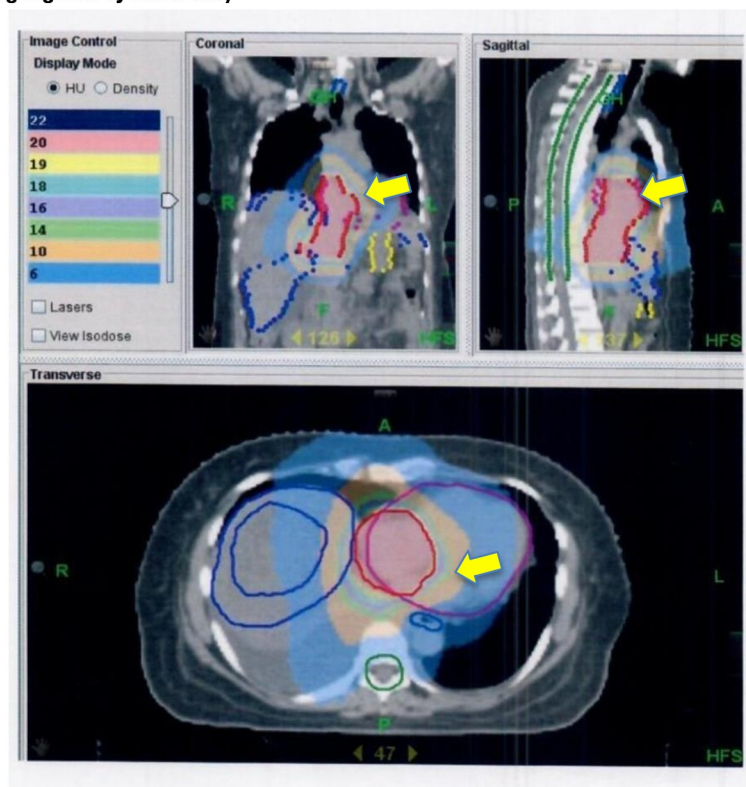
Management

A multidisciplinary discussion with a team composed of medical oncology, radiation oncology, interventional oncology, cardiovascular and pulmonary medicine was convened. Systemic

chemotherapy was contemplated but the risk of bleeding in light of the patient's cirrhosis was deemed too risky. The patient was thus given TomoHelical

Intensity modulated Radiotherapy with 5 fractions of 400 cGy (total 2000 cGy), targeting the venous thrombus in the right atrium.

Figure 4. Radiation dose distribution into tumor thrombus in the inferior vena cava and right atrium (highlighted by red areas)



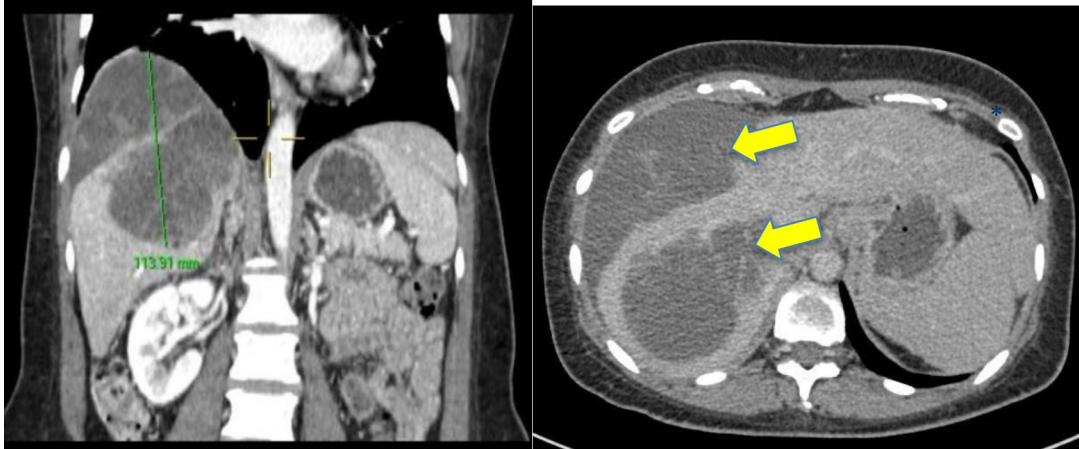
Along with this, Lenvatinib was given at a dose of 8mg/day. Tenofovir 300mg/day was given for her Chronic hepatitis B. During admission, she was also put on lycyrrhizic acid (Minopahgen-C) drip and ursodeoxycholic acid at 1000mg/day. To help stabilize the thrombus, patient was given subcutaneous injections of enoxaparin and later, oral apixaban on discharge. Carvedilol and Ivabradine were also given. Treatment for HCC was not withheld despite the patient's COVID infection.

Follow-up

On follow-up 7 weeks after radiation therapy, patient's liver function was relatively stable. She no longer felt short breath, was able to ambulate and had better over-all well-being with an ECOG performance status of 1-2 from 3. Repeat IV contrast CT of the upper abdomen (Figure 5) showed

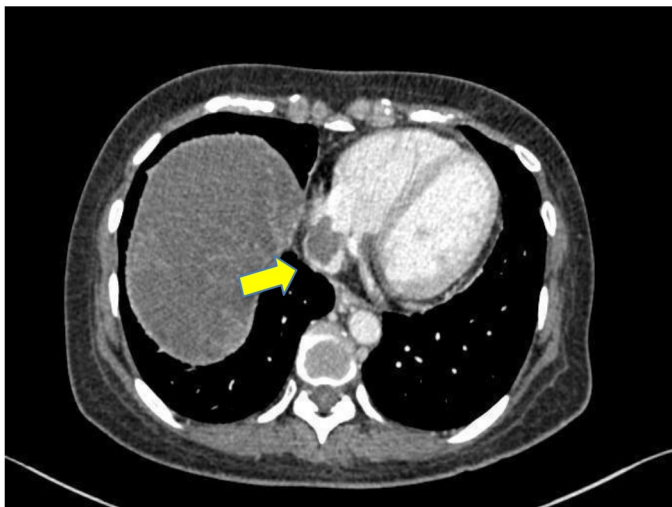
decrease in the size of the mass occupying hepatic segments 7/8 and 6 slightly measuring 136 x 113 x 114 mm (APxWxCC) (previously 138 x 123 x 130 mm). There was note of some cystic degeneration. Extension to the suprahepatic inferior vena cava and right atrium were still noted along with non-enhancement of the left and middle hepatic veins. The portal veins remained patent. Spleen was normal in size and there was minimal ascites. Intra-abdominal lymph nodes remained to be subcentimeter in size as well.

Figure 5. Follow-up upper abdominal CT scan with IV contrast showing the size of the liver tumor after 7 weeks of lenvatinib.



Patient's Chest CT scan with IV contrast done three months after RT showed stable thrombus size in the right atrium and inferior vena cava (Figure 6). However, there were filling defects noted in the right superior segmental artery and pars basalis with extension to the proximal portion of the superior lingular artery, worrisome for pulmonary embolism. Clinically however, patient remained well and able to ambulate. Oral apixaban was continued without any incidents of bleeding episodes.

Figure 6. Chest CT scan IV contrast after 3 months with stable size tumor thrombus in IVC, RA (yellow arrow)



DISCUSSION

Hepatocellular carcinoma with tumor invasion into the inferior vena cava and right atrium are said to occur with a prevalence of 0.6% to 4⁽⁸⁾. In literature, it was found that having significantly elevated AFP >1,000 ng/mL and tumor size >5cm both independently predict tumor vascular invasion in HCC⁽⁹⁾. These two factors were present in our patient.

Studies have shown that treatment for IVC/RA thrombus may be approached through several methods, ranging from surgical, locoregional, systemic chemotherapy or a combination of the above. A study by Chun et. al showed that only active treatment beyond best supportive care may provide prolonged survival for patients⁽⁴⁾.

For this particular case with a Child Pugh score of B9 and Barcelona Clinic Liver Cancer (BCLC) stage C, we used a combination of targeted external beam palliative radiotherapy and oral lenvatinib. Response was favorable as there was slight decrease in size of the liver-dominant mass, stable tumor thrombus in the IVC and RA, preserved liver function and most of all, good performance status more than three months after diagnosis and initiation of treatment. Our patient's clinical course is consistent with some studies which show that radiotherapy can prolong survival in patients with IVC and RA tumor invasion. A study done by Li et. al revealed that time to tumor progression was

significantly longer among patients who were given external beam radiotherapy (EBRT) compared to those who had surgery ⁽⁶⁾. However, this same study also showed that there was no significant difference in over-all survival between the EBRT group and surgery group ⁽⁶⁾. Meanwhile a small retrospective cohort study done by Lou et. al. on patients with either IVC thrombus or IVC and RA thrombus showed a high efficacy among patients who were given hypofractionated radiotherapy with nearly all patients having either partial or complete response and stable disease ⁽⁵⁾.

Lenvatinib, a multi-kinase inhibitor which is an antagonist to endothelial growth factor, has been approved for first-line treatment of advanced HCC since 2018 (9). It has been shown to be more significant in producing longer progression-free survival and non-inferior to sorafenib in over-all survival ⁽¹⁰⁾.

Finally, COVID 19 infection can present with a wide spectrum from asymptomatic to severe disease. Patients with pre-existing liver conditions, especially hepatocellular carcinoma, are known to be at higher risk for both acquiring infection and progression to severe disease ⁽¹¹⁾. Hepatic injury may occur in patients with COVID-19 through either of the following mechanisms: direct cytopathic effect on hepatocytes, immune-mediated inflammation, and/or hypoxia from pneumonia ⁽¹¹⁾. Fortunately, our patient presented with minimal symptoms for the duration of her infection and liver enzymes were only transiently elevated.

CONCLUSION

Our case demonstrates that for advanced HCC with extensive vascular invasion and tumor thrombus to the IVC and RA, offering a combination of treatment modalities may offer patients the best chance for longer over-all survival, even if management is palliative. In the era of COVID-19, HCC patients must be continually followed up and treatment tailored to their needs. Overall, the value of a multidisciplinary approach to management cannot be overemphasized in order to achieve the most appropriate plan for patients.

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A Case of a 62-Year Old Male with Actinomycetoma Successfully Treated using Combined Medical and Surgical Therapy

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Ma. Luisa Abad-Venida, MD, FPDS³**

Abstract

Introduction: Actinomycetoma is a neglected infectious disease that presents with a triad of subcutaneous mass, with sinus formation and seropurulent discharge containing grains. This causes severe functional disability to patients if not treated early and properly.

Case Report: We report a case of a 62-year-old adult Filipino farmer diagnosed with actinomycetoma of the left foot. For 8 years, the patient medicated with several antibiotic therapies affording minimal improvement of symptoms. Hence, surgical intervention with combination antimicrobial therapy was done which provided resolution of symptoms, improving the quality of life of the patient.

Conclusion: Treatment of actinomycetoma must be individualized among patients. Although oral antibiotics became the standard of treatment, combining surgical treatment with oral medications may be considered to ensure effective management of the disease.

Key Words: actinomycetoma, cotrimoxazole, dapsone, surgery, case report

INTRODUCTION

Actinomycetoma is an infectious disease caused by the bacteria, *Nocardia* sp., *Streptomyces* sp., or *Actinomyces* sp. It commonly affects agricultural workers in developing countries in tropical and subtropical zones including the Philippines. It is characterized by chronic inflammation with discharge and sinus formation. Actinomycetoma continues to pose huge public health threat in many countries since its course can be quite devastating ^[1].

There is no proposed algorithm in the management and treatment of Actinomycetoma. Currently, the disease is treated with prolonged course of antibiotics. However, in some instances, medical cure even with prolonged combination of antibiotics is difficult to achieve. Extension of the disease may lead to chronic progressive lesions and sometimes gruesome deformity of the limbs. This causes significant life-long disabilities and pain. It may also provide physical and socio-economic burden on the patient and the family members ^[2].

CASE REPORT

A 62-year-old Filipino male who worked as a farmer in Pangasinan, Philippines presented with an 8-year history of swelling on the dorsum of the left foot associated with multiple nodules, seromucoid discharge and whitish grains after a penetrating injury by a thorn from a tree trunk. Several consultations were done, and he was given numerous unrecalled oral medications, which did not provide resolution of the lesions. Excision biopsy revealed Mycetoma (Maduromycosis) of the left foot leading to referral to a specialty center where he was treated as a case of Actinomycetoma. The patient was immediately given Trimethoprim-Sulfamethoxazole (TMP-SMX) 800mg+160mg tablet three times a day continuously for 4 years with good compliance to medications. However, the patient opted to use a generic brand due to financial difficulty, which caused the reactivation of the disease. He was advised to return to TMP-SMX with free Dapsone 50mg/tablet to be taken once daily for one year.

Cutaneous examination revealed multiple, well-defined, firm, fixed, hyperpigmented nodules, with thick central scaling and sinus tracts on the dorsal aspect of

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the left foot. There was no discharge or grains noted (Figure 1). Baseline laboratory tests such as complete blood count, urinalysis, blood chemistry and chest x-ray were all within normal limits. An x-ray of the left foot was done which revealed cortical irregularities and increased opacification with associated interspersed cystic lucencies of the 4th metatarsal bone, as well as cortical thickening of the 3rd and 5th metatarsal bones, suggestive of osteomyelitis (Figure 2).



Figure 1. Cutaneous examination of the left foot



Figure 2. AP and Oblique views of the left foot

Due to the prolonged intake of oral medications, a wide excision biopsy was done. An irregularly shaped tissue with superficial white plaques measuring 8.0 x 5.0 x 0.4 cm was obtained (Figure 3). Intraoperatively, sinus tracts with whitish to yellowish discharge were observed. Hematoxylin and eosin (H&E) staining of the tissue revealed a normal epidermis with pigmented basal layer, areas with pseudoepitheliomatous hyperplasia with densely packed collagen and infiltrates of histiocytes suggestive of a scar tissue. Gram stain and culture of the discharge revealed no growth after 5 days of incubation.



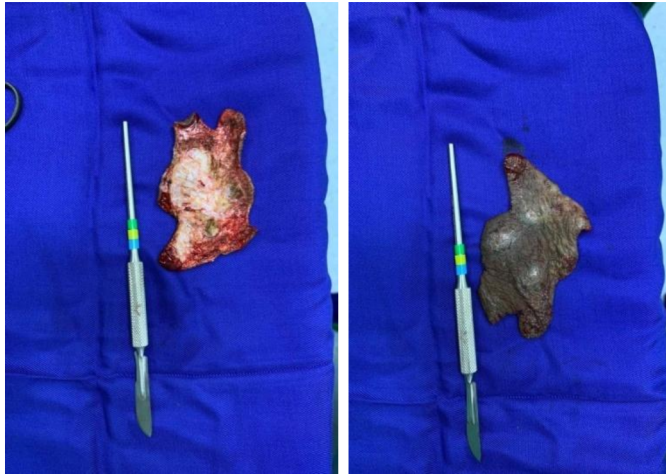


Figure 3. Intraoperative findings during wide excision biopsy

After surgery, TMP-SMX was continued for another 3 months. At 3 months of follow up, there were no new lesions observed. No new growths of nodules with sinuses were noted (Figure 4). The patient had ease of pain on ambulation with no difficulty in executing normal activities of daily living.



Figure 4. Clinical improvement after surgical and medical management

DISCUSSION

Actinomycetoma has been included in the top 17 list of neglected tropical disease by the World Health Organization in 2013 [3]. As of 2015, there were only 97 reported cases seen in the Philippines. Although the incidence of actinomycetoma is rare in the country, this

disease causes disfiguring lesions in affected individuals, limiting their mobility and affecting their quality of life [4].

The triad of subcutaneous mass, multiple sinuses and discharge with whitish grains were suggestive of actinomycetoma [5]. Risk factors such as traumatic injury, walking barefoot on land and the low socioeconomic status of the patient increases the likelihood of the disease.

Diagnostic procedures such as direct examination of the grains from the sinuses, special stains and biopsy may be done to confirm the diagnosis. However, H&E staining of the mass on the left foot shows fibrosis and scar tissue even though the clinical picture was suggestive of actinomycetoma. Gram stain and culture of the discharge from the sinuses were also negative. According to Tahiri, et al, in long standing disease of actinomycetoma, inadequate amount of grains and granules may be apparent if the patient had multiple prior treatments such as in the case of our patient wherein he was taking antibiotics for 4 years [6]. This is supported by the case report of Koley, et al which suggested that late presentation of the disease may show mainly fibrosis and scarring on histopathology. The extent of the fibrosis can make the discharge from the sinuses inapparent [7]. These factors may reveal non-specific findings on histopathology. Therefore, in such cases, it is important for the histopathological report to be correlated clinically.

A review of related literature states that there is no proposed algorithm for its treatment, and therapy is individualized with antibiotic treatment as first line [8]. The latest systematic review done by Scolding, et al. shows that TMP-SMX is the first line drug with minimum expected duration of treatment for 12 months [9]. The disappearance of the swelling, complete healing and closure of sinuses, absence of evidence of mycetoma on histology and/or culture, and absence of disabilities secondary to pain or deformity are the criteria for clinical cure [9].

Our patient has been taking these medications for 4 years but has not reached the clinical criteria for cure. Thus, wide excision biopsy was done to debulk the

lesion, debride all damaged tissues and remove all possible sinuses. Studies have shown that antibiotics combined with surgical procedures have the best therapeutic response [10]. Surgical procedures such as debridement, excision and amputation are useful in extensive infections and those with failed medical therapy. Surgery is done to reduce the bacterial load, provide a better response to therapy and prevent recurrence of the disease. The systematic review conducted by Salim, et al recommended antimicrobials in conjunction with surgery in successfully managing actinomycetoma patients [8].

CONCLUSION

Actinomycetoma is a unique forsaken disease that has a profound and negative impact on the physical, emotional and socio-economic aspects of the lives of the patients, their families and their communities. Most often, it is seen amongst the poorest of people who have less access to healthcare. In a third world country like the Philippines where the chronic and progressive nature of the disease requires a prolonged and consistent intake of medications, sustainability of treatment is a challenge that we need to overcome in order to ensure treatment success. Thus, treatment must be individualized among patients. Although oral antibiotics became the standard of treatment for actinomycetoma, combining surgical treatment with oral medications may be considered to ensure effective management of the disease.

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Vasculitis Associated with COVID-19 Reinfection in a Fully Vaccinated 66-Year-Old Filipino Male: A Case Report

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Abstract

COVID-19-associated vasculitis is a term used to describe a genuine vasculitis associated with SARS-CoV-2 infection when all other possible causes of vasculitis have been ruled-out. We report a case of a 66-year-old-male, reinfected by COVID-19 after 5 months, who presented with a 2-week history of multiple petechiae on bilateral anterior legs that gradually evolved into targetoid purpura with central blisters, spreading to the proximal medial thighs and the trunk, associated with pruritus and a warm sensation over the affected areas. The patient also presented with marked periorbital swelling, abdominal and joint pains, and decreased kidney function. Histopathology of the skin biopsy showed leukocytoclastic vasculitis while direct immunofluorescence study came out positive result for fibrinogen but negative for IgA, IgG, IgM and C3. Skin lesions resolved and kidney function improved prior to discharge after treatment with IV antibiotics (azithromycin 500 mg and ceftazidime 1 g) and IV steroids (hydrocortisone 50 mg). Recurrence of the vasculitic skin lesions occurred 2 weeks after being tagged as COVID-recovered but improved after 14 days of treatment with oral prednisone. We highlight the importance of recognizing cutaneous vasculitis as a possible marker of a severe COVID-19 disease which could be in the form of single-organ damage particularly acute kidney injury.

Keywords: COVID-19-associated vasculitis, SARS-CoV-2-associated vasculitis, case report

INTRODUCTION

Since the start of the COVID-19 pandemic, 232,703,120 cases have been documented globally, including 4,746,620 deaths, as reported by the World Health Organization (As of September 28, 2021)[1]. In the Philippines, cases continue to rise, now totaling to 2,490,858 cases, with over 37,000 deaths [1]. This situation has brought a lot of challenges to the healthcare system of the country as well as to its economy, as the medical, scientific and lay communities continue to battle the disease.[2] Several literatures were already published documenting the vast clinical manifestations of COVID. Commonly, it involves the respiratory system ranging from mild symptoms such as fever and cough, to severe manifestations such as dyspnea secondary to severe COVID pneumonia, some leading to acute respiratory distress, and ultimately, death [3]. Aside from the respiratory system, it has been proven that the virus can affect any organ, including the skin, with cutaneous manifestations frequently being underreported [2].

There are varying theories regarding the dermatologic findings in COVID-19. Most of the published literature describes a myriad of cutaneous manifestations ranging from morbilliform lesions to vasculitis-like skin eruptions [4]. Depending on the skin manifestation, literatures were able to relate it with disease severity [4] and presented theories about their pathophysiology. Some case reports even noted the timing of onset of the dermatologic findings [5], which could be useful in predicting the prognosis of the COVID-19 infection, identify complications that require treatment or may even aid in identifying asymptomatic carriers [6]. One of the most important

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skin manifestation that has been linked to poor prognosis and mortality is the presence of cutaneous vasculitis [6]. Some of the skin lesions with features of vasculitis that have been described in the literature range from asymptomatic to fulminant disease, which include rounded, well circumscribed erythematous to violaceous plaques or nodules, necrotic purpura, diffuse digital erythema, and chilblain-like lesions [7]. To date, COVID-19-associated vasculitis is a possible complication that needs further research, especially now that the COVID-19 pandemic is yet to end. As knowledge about the virus continues to grow, it is also of great importance that all doctors, not just dermatologists, be able to identify the disease when faced with patients presenting with cutaneous manifestations such as vasculitis, in the absence of other possible causes.

As such, we report a case of vasculitis associated with COVID-19 reinfection in a fully vaccinated adult male and to our knowledge, this is the first case to be reported in the Philippines.

CASE REPORT

A 66-year-old, Filipino male, previously admitted due to severe COVID five months prior, presented with a 2-week history of multiple petechiae on bilateral anterior legs that gradually evolved into targetoid purpura with central blisters, spreading to the proximal medial thighs, associated with pruritus and a warm sensation over the lesions. In the interim, he complained of intermittent, undocumented fever, abdominal pain, and joint pains. One day prior to admission, he developed periorbital edema which prompted consult at the emergency room. Other pertinent medical history includes uncontrolled hypertension and diabetes, a 46-pack-year history of smoking and completion of 2 doses of COVID-19 vaccine (Sputnik).

At the time of admission, the patient's vital signs were stable and cutaneous examination revealed multiple, well defined, targetoid purpuric lesions some with central hemorrhagic bulla on the extremities, trunk, and pelvic area, predominantly on the anterior legs and the proximal medial thighs, with noted bilateral

periorbital swelling (Figures 1, 2,3). Dermoscopic findings showed irregularly shaped, red to violaceous patches with clusters of petechial hemorrhages or ill-defined globular structures with blurred borders (Figure 4). A SARS-COV-2 RT-PCR test via oropharyngeal and nasopharyngeal swab came out positive for COVID-19 infection. Laboratories showed elevated BUN and creatinine, with an eGFR of 26 mL/min/1.73m² as well as elevated CRP(155.7mg/L) and D-dimers (8,262). Chest radiograph showed suspicious bilateral opacities consistent with COVID-19 pneumonia.

A 4 mm skin punch biopsy on 2 sites was done at the ER for H & E stain and direct immunofluorescence studies. Histopathology showed superficial and deep infiltrates composed of neutrophils and eosinophils, with fibrinoid degeneration of blood vessels, extravasated erythrocytes and swollen blood vessels consistent with a histopathological diagnosis of leukocytoclastic vasculitis (Fig.5). Direct immunofluorescence study came out positive for fibrinogen but negative for IgA, IgG, IgM and C3. Serum IgA done at day 6 of admission showed normal values (3.550 g/L). Upon admission, the patient was immediately started with intravenous antibiotics (ceftazidime 1 g, azithromycin 500 mg), intravenous steroids (Hydrocortisone 50 mg IV) and cetirizine. Lesions on the trunk were noted to progress to erythematous, annular and edematous plaques and targetoid lesions on the lower extremities were noted to develop multiple vesicles and blisters at the periphery (Fig.6).

During the course of the admission, creatinine was persistently elevated leading to the diagnosis of an acute kidney injury. On the 8th day of admission, creatinine levels started to decrease and skin lesions also started to resolve (Figure 7). Upon completion of his antibiotics and with decreasing trend of creatinine levels, the patient was then cleared for discharge, with strict home quarantine for 2 weeks.

The patient was monitored closely via teledermatology and 2 weeks after discharge, the patient again presented with multiple petechiae on the lower extremities that gradually enlarged into purpura,

but with no noted bullae or blister formation, associated with periorbital swelling. Patient also complained of pruritus and minimal abdominal pain (Figure 8). Repeat laboratories were requested which showed normal results for kidney function tests (BUN, Creatinine) but RBC was noted on urinalysis. Patient was given Prednisone (0.5mg/kg/day) and Cetirizine 10 mg/tab for 14 days, with noted improvement of the lesions (Figure 9 and 10).

DISCUSSION

The SARS-CoV-2 infection, or more commonly known as COVID-19, has been known to affect several organ systems in the body, causing mild to severe manifestations, depending on the host immunity [7]. In a report done by Gottlieb & Long in 2020 about common dermatologic manifestations and complications of COVID-19, they stated that the dermatologic manifestations in the setting of COVID-19 infection could be due to the presence of angiotensin-converting enzyme 2 (ACE2) receptors that can also be found in the skin [6].

COVID-19-associated vasculitis is defined as a genuine vasculitis associated with COVID-19 infection, including cutaneous vasculitis, when all other possible causes of vasculitis have been ruled-out [2]. Features of vasculitis range from asymptomatic to fulminant disease[9], which include rounded, well-circumscribed erythematous to violaceous plaques or nodules, diffuse digital erythema, chilblain-like lesions [10,11], retiform purpura, livedo racemosa, erythema-multiforme like eruption, true acral ischemia [4] and urticarial vasculitis[12]. What is note-worthy about this case is that the patient presented with a mixture of different forms of vasculitis such as retiform purpura, livedo racemosa, erythema-multiforme like eruptions and urticarial vasculitis.

A report by Nasiri, et.al. in 2020 described a case presenting with prominent periorbital edema with annular purpuric rash and urticarial lesions, with associated warm sensation on the lesions after recovering from COVID-19 infection [12]. The authors characterized it as urticarial vasculitis, defined as persistent urticarial lesions, resolving with purpura and

hyperpigmentation, with evidence of a leukocytoclastic vasculitis. Clinically, the cutaneous manifestations of this type of vasculitis is the closest when compared to our case, although other forms of vasculitis-like skin eruptions were also found in the patient.

There is conflicting evidence regarding the time of onset of vasculitis-like lesions in COVID-19 infected patients. In one systematic review, they concluded that for vascular patterns, there are differences among its subtypes [5]. Livedoid lesions occurred mainly in the first 2 weeks while purpuric/petechial lesions were equally distributed during the first 4 weeks [5]. In contrast, a review about the rheumatologic complications of COVID reported that cutaneous vasculitis associated with severe respiratory failure and ARDS, manifesting as lower limb purpura, bullous hemorrhagic rash, necrotic lesions and cutaneous vasculitic lesions with gangrene, are late manifestations of COVID-19 infection [14]. However, there are also vascular patterns that do not fall under the subtypes which include erythema multiforme and Kawasaki-like disease [5]. In the case of our patient, he was reinfected with COVID-19 after 5 months when the lesions occurred. This may be a rare case because the patient presented with a myriad of vasculitis-like skin eruptions, hence, we cannot entirely conclude that the lesions are complications of the first COVID-19 infection, an acute manifestation of the more recent infection, or both.

Guidelines are not yet available on the laboratory work-up to diagnose COVID-associated vasculitis, however, it is important to rule out other possible differential diagnoses. In a review done by Criado et. Al in 2020, they reported about the characteristics of severe COVID-19 which include an upregulated innate immune response, hypercoagulopathy state, pulmonary tissue damage, neurological and/or gastrointestinal tract involvement, and macrophage activation syndrome which could lead to fatal outcomes due to cytokine storm [13]. Dermatological manifestations can occur with these systemic conditions and abnormalities such as hyperferritinemia, increased levels of D-dimer, lactic dehydrogenase, reactive C-protein and serum A amyloid [13] may aid in the diagnosis.

For the treatment, one systematic review was able to tabulate treatment options per dermatologic manifestation. For purpuric “vasculitic” pattern, the authors suggested topical corticosteroids for mild cases and systemic corticosteroids for severe cases [15].

The importance of knowing the different cutaneous vascular manifestations of COVID-19 lies in its possible use as a predictor of the severity of the disease. [4,7]. In a systematic review done by Conforti et.al in 2020, different patterns of vascular lesions were reported which include chilblain-like, non-necrotic purpura, necrotic purpura, retiform purpura, livedo reticularis, livedo racemosa, petechial rash, eruptive cherry angiomas, porcelain-like macules, and dry gangrene. Chilblain-like non-necrotic purpura are more common in the young, while vasculitis like, with necrotic, retiform purpura are more common in the elderly [4]. Majority of the lesions appeared after onset of COVID symptoms, occurring within 2-112 days [4]. In the review, they were able to conclude that chilblain-like lesions appeared in patients with relatively mild COVID-19 disease courses which suggest that the underlying mechanism might be protective, making pernio (chilblain) a marker of a robust, effective host anti-viral response, limiting COVID-19 complications. In contrast, older patients, may have an inadequate or delayed IFN-I response leading to an exacerbated hypercytokinemia which can manifest as purpura. These lesions were associated with subsequent increased morbidity and mortality [4]. However, not all purpura leads to a severe outcome. In the same journal, they mentioned that livedoid/necrotic lesions in older patients are associated with severe disease (10% mortality) whereas fixed livedo racemosa, retiform purpura, and true acral ischemia are related to critical or poor prognosis. Livedo racemosa and retiform purpura are hallmark manifestations of cutaneous thrombosis, appearing due to partial and complete occlusion of cutaneous blood vessels, respectively [4].

In the patient’s case, although he presented with mild respiratory symptoms possibly due to the history of previous COVID-19 infection and completed doses of COVID-19 vaccine, the occurrence of

decreased kidney function due to acute kidney injury may still be a manifestation of severe disease.

Lastly, one case report also presented a patient who developed a leucocytoclastic vasculitis for COVID-19 with positive SARS-CoV-2 PCR in skin biopsy. It is believed that SARS-CoV-2 antigens may promote the development of antibodies, forming antigen-antibody complexes that target the vascular endothelium of the skin and provoking the appearance of the leucocytoclastic vasculitis. This finding supports a relationship between leucocytoclastic vasculitis and coronavirus instead of relating it with other infections or medications.

This finding is important because it reiterated that further work-ups are needed to clarify if particles detected by PCR in skin tissue, specifically in endothelial cells of small dermal vessels, are viable virions or, more probably, just immune complex with non-viable viral particles. Further studies should also be done if ulcerated skin lesions could be infective.

CONCLUSION

The end of the COVID-19 pandemic remains to be out of sight as cases still continue to rise. Understanding the different pathologic mechanisms of the virus may help in the early diagnosis and treatment of COVID-19 infection. Vascular dysfunction could be one of the indicators of a severe illness and may manifest as cutaneous vasculitis. By recognizing these skin lesions, clinicians may be able to predict the course of the COVID-19 infection. As a recommendation, a PCR test on the skin biopsy sample could be done to show the presence of SARS-CoV-2 in the skin lesions in order to establish causation.

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APPENDICES

Figure 1. Targetoid purpuric lesions on anterior legs and proximal medial thighs



Figure 2. Periorbital swelling and multiple petechiae on the trunk

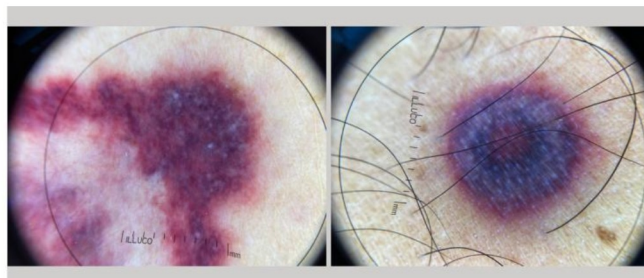


Figure 3. Dermoscopic findings of the lesions

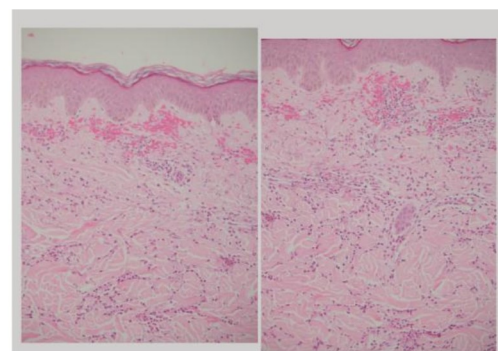


Figure 4. Histopathological findings of leukocytoclastic vasculitis



Figure 5. Evolution of the lesions on Day 2 Admission



Figure 6. Resolution of the lesions on Day 8 of admission

