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Clinical Factors Related to Histopathologic Grade in Meningioma

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Abstract

Background: Meningiomas are the most common intracranial tumor of central nervous system tumors. Although the prevalence is lower, the WHO grade II and III meningiomas are more aggressive, with higher mitosis rates, are more likely to recur after surgery, and have lower survival rates. The ability to differentiate between WHO I and WHO II/ III meningiomas before surgery can contribute to a significant clinical benefit in helping the neurosurgeon doing the best management planning.

Methods: This is a retrospective cross-sectional study of meningioma patients in Siloam Hospital Lippo Village between 2014 – 2018. The sample will be recruited using consecutive sampling. The relationship between analyzed variables and meningioma grades will be investigated using a chi-square test if the data was eligible; otherwise, the Fisher-exact test will be performed.

Result: Ninety eight (69%) patients diagnosed as low grade meningioma, and 44 (31%) as high grade meningioma. Tumor location, size, edema, necrosis, age, and gender had significant results with $p \leq 0.05$. Multivariate results also show that all six variables have a significant relationship with each other.

Conclusions: Tumor location, size, edema, necrosis, age, and gender have a significant relationship to histopathological meningioma grade in patients at Siloam Hospital Lippo Village in 2014-2018.

Introduction

Meningioma is the most common primary tumor in the Central Nervous System (CNS) around 25,5% of all CNS neoplasms.[1,2] Meningioma originates from arachnoid, especially from the outer layers of arachnoid and arachnoid villi, which are also referred to as arachnoid cap cells and the distribution is spread throughout the CNS.[3]

Based on histopathological characteristics, the World Health Organization (WHO) divides meningioma into three grades, namely, grade I, II, and III. Among these three grades, grade I meningioma has the most frequent occurrences, while grade II and III only occur in 21-27,8% of all meningioma cases.[1]

Despite their lower prevalence rates, grade II and III meningioma are considered high-grade meningioma. This high-grade meningioma has a higher mitosis rate so that it develops more progressively, has a higher risk of recurrence, and a lower survival rate. Histologically grade III meningiomas are malignant with atypical nuclei.[3]

A variety of modalities can be used to support the diagnosis of meningioma, including computed tomography (CT scan) imaging and magnetic resonance imaging (MRI).[4] The standard management of meningioma is operative resection. However, patients with small lesions can be managed with Gamma Knife Surgery (GKS) and no longer candidates for operative surgery. Radiologically findings, such as an invasion of the brain, bone and peritumoral edema around the brain area are also related to high-grade meningioma, and if managed

with GKS, subsequent management will be complicated.[5,6]

Therefore, the ability to differentiate the grade of meningioma before treatment can contribute to a significant clinical benefit in assisting surgeons to develop an operative plan so that it runs as well as possible. Providing information about the tumor's grade can be useful intra-operatively because the surgeon has to decide considering the risks and benefits of more aggressive resection of the tissue around the tumor.[6,7]

The aim of this study is to examine the relationship between clinical factors and grades of meningioma because of its essential role in the clinical course and management of the disease.

Material And Methods

Samples are obtained from patient medical records with a diagnosis of meningioma at Siloam Hospital Lippo Village, which includes demographic data such as gender and age, clinical factors such as tumor location, tumor size, edema, necrosis, and also tumor pathology based on WHO grade between 2014 to 2018. Tumor location, size, edema, and necrosis were assessed through radiologic findings. For patients who did not undergo a histopathological examination of tumor tissue and incomplete clinical information are excluded. Statistical analysis was performed using SPSS 22.

Result

Univariate analysis

A total sample that fulfilled the inclusion and exclusion criteria from 2014-2018 is 142 individuals. From all samples, 53 (37,3%) were male, and 89 (62,7%) were female. Age <65 was 112 (78,9%) and ≥65 was 30 (21,1%). In MRI can be seen that tumor size <3,2 cm and ≥3,2 cm were 73 (51,4%) and 69 (48,6%), respectively. Tumor with edema was 58 (40,8%) and 84 (59,2%) without edema. On the other hand, sample with necrosis was 25 (17,6%) and 117 (82,4%) without necrosis. The most common tumor locations were in the cranial base region with 89 patients. 98 (69%) people suffer from low-grade meningioma and 44 (31%) suffer from high-grade meningioma.

As an illustration, we confirmed the radiological features with microscopic images in patients with grade II and III meningioma. (Figure 1 and 2).

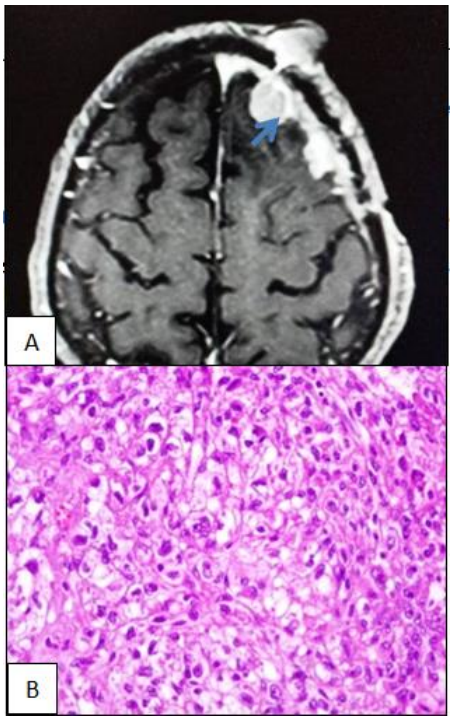
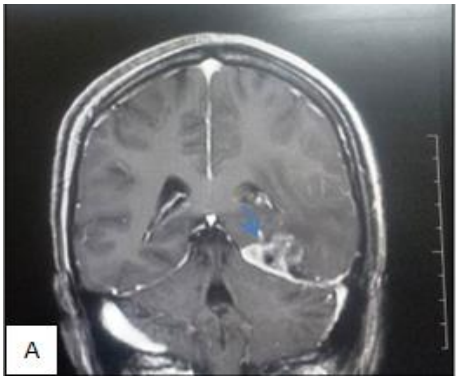


Figure1. A. MRI shows tumor mass in left frontal lobe with edema (arrow).
B. Histopathology appearance with atypical cells, confirmed as Meningioma WHO grade II.



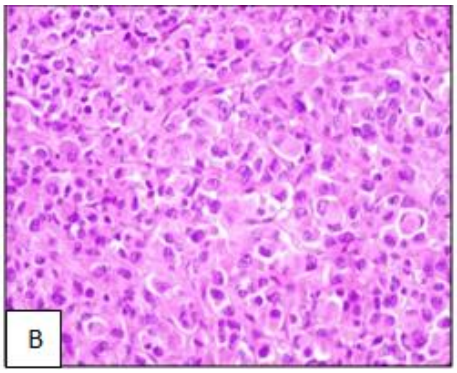


Figure2. A. MRI shows left occipital lobe tumor mass with central necrotic.
B. Histopathology appearance with anaplastic cells, confirmed as Meningioma WHO grade III.

Bivariate analysis

- **Relationship between Location and Grade of Meningioma**
  Most people who are diagnosed with high-grade meningioma were located in the parasagittal/falx/convection region, and low-grade meningioma was located in the cranial base region. This analysis was tested using Fisher-exact test and yielded a p-value <0.001.

- **Relationship of Size with Grade of Meningioma**
  Most people who are diagnosed with low-grade meningioma, are tumor size <3.2 cm. Thirty people with tumor size ≥3.2 cm are high-grade. These results were tested with Chi-square and produced a significant relationship with p=0.002.

- **Relationship of Edema with Grade Meningioma**
  Twenty-five (43,1%) tumor patients had edema with high-grade, and 19 (22.6%) people without edema were high-grade meningioma. This relationship was analyzed by Chi-square with a value of p = 0.009.

- **Relationship of Necrosis with Grade Meningioma**
  Patients with high-grade meningioma mostly had necrosis, which was 20 (80%), while 93 (79,5%) patients without necrosis had a low-grade meningioma. This relationship was analyzed by Chi-square with p<0,001.

- **Relationship of Age with Grade Meningioma**
  Most patients who were ≥65 years-old had high-grade meningioma while patients <65 years-old had a low-grade meningioma. This relationship was analyzed by Chi-square with p=0,011.

- **Relationship of Gender with Grade Meningioma**
  A total of 23 (43.4%) men suffer from high-grade meningioma, and 21 (23.6%) women suffer from high-grade meningioma. The relationship between the two variables was carried out using chi-square test with p=0.014, which means there is a significant relationship between the two variables.

Multivariate analysis

All six variables, tumor location, size, edema, necrosis, age, and gender were tested in multivariate analysis of tumor grade with linier regression. The analysis result is shown in Table 1.

Table 1. Data analysis of meningioma patient at Siloam Hospital Lippo Village.

Characteristic	Frequency	Percentage (%)	Sig.	Exp (B)
Gender				
Male	53	37,3	0,024	0,231
Female	89	62,7		
Age				
<65	112	78,9	0,006	0,135
≥65	30	21,1		
Size (cm)				
<3,2	73	51,4	0,006	0,135
≥3,2	69	48,6		
Edema				
Yes	58	40,8	0,019	0,237
No	84	59,2		
Necrosis				
Yes	25	17,6	<0,001	0,035
No	117	82,4		
Location				
Cranial base	89	62,7	0,001	<0,001
Parasagittal/ falx/ convection	41	28,9		
Others	12	8,4		
Grade				
Low	98	69		
High	44	31		

Discussion

Grade I (low-grade) meningioma has a relatively good prognosis. In contrast, grade II and III (high-grade) meningioma have a worse prognosis and often require adjuvant therapy.[7] The ability to predict the tumor's grade will help the clinician provide a more accurate direction for the management, without waiting for a histological diagnosis, which sometimes requires a longer time.[6,7]

Lots of research that focuses on molecular characteristics using genomic and proteomic technology. However, these approaches require invasive procedures to take tissue samples, and usually, only a small portion of the sample can be analyzed and cannot reflect the composition and heterogeneity of the tumor.[1] Conversely, imaging tests that do not have invasive properties have great potential in assisting tumor stratification and guiding management because imaging examinations provide a more comprehensive picture of the whole tumor and help monitor the ongoing therapeutic response, development, and recurrence process.[6,7]

Relationship between Location and Grade of Meningioma

This study found a significant relationship between location and grade of meningioma ($p < 0.05$). These results are similar to previous studies which state that anatomic location is a risk factor for atypical and malignant meningioma, where there is a more significant increase in risk at non-base of skull tumor (27% vs. 12%; $p < 0.001$).[8]

Previous studies have suggested that meningioma in non-skull locations have a more aggressive nature. Previous studies using genomic analysis have shown that meningioma located in the area around the cerebral hemisphere and cerebellum often have higher grades and have more frequent NF2 gene mutations and / or lose chromosome 22 with concurrent genomic instability.[9]

A study by Hashimoto et al. showed that meningioma on the skull base had a significantly higher percentage of chromosome loss of 1p (20.31%) compared to meningioma in the non-skull base. These results suggest that genetics play an essential role where tumors in the skull base region tend to be at a minimum of genetic defects and have less aggressive biological properties.[10]

Relationship of Size with Grade of Meningioma

In this study, as many as 46.6% meningioma with size ≥3.2 cm were high grade, while 14.5% meningioma with size <3.2 cm experienced high grade, with significant differences. A study by Palaniandy et al. also showed similar results and found that high-grade meningioma had a mean tumor volume three times greater than low-grade meningioma. This result was also statistically significant ($p=0.001$).[3,5]

Relationship of Edema with Grade Meningioma

This study compares the percentage of meningioma accompanied by edema and without edema with high-grade tumors that are twice different. Hale et al. examined the relationship between degrees of edema divided into 4 degrees with meningioma grade.[17] The study results showed a significant correlation between edema and meningioma grade with a value of $p = 0.022$.

Atypical and malignant meningiomas are reported to infiltrate more frequently around the tissue.[3] This also underlies the occurrence of edema around the tumor, while grade I meningioma are less likely to develop edema. There are various etiologies proposed for the mechanism of edema, namely compressive ischemia due to disruption of the blood-brain barrier, vascular shunting due to parasitism of the micro vial vessels, mechanical venous obstruction, increased elevated hydrostatic pressure in the tumor, and the phenomenon of secretory excretory tumor cells.[18,19]

Relationship of Necrosis with Grade Meningioma

The incidence of necrosis in this study was significantly different where 45.4% of tumors with necrosis were high-grade meningioma, while those without necrosis were only 54.6%. A study by Backer et al. reported that necrosis was found in 23% of cases of meningioma spread in 11.9% grade I meningioma, 45.8% grade II meningioma, and 100% grade III meningioma.[20]

Necrosis comes from nutritional insufficiency and hypoxia due to high metabolic demands, which suggest that this condition is associated with more aggressive development. Necrosis can be found in small and large tumor foci. Hypoxic tumor cells involving necrotic tissue can show areas that have experienced differentiation and transformation of malignant cells.[21]

Relationship between age and grade of meningioma

In this study, a significant relationship was found between age and the incidence of high-grade meningioma, where the age group ≥65 years had a higher percentage of high-grade meningioma (50%) compared to the age group <65 years (35.9%). However, the results of other studies are still controversial. Some studies state a relationship between age and grade of meningioma, where age ≥65 years shows a significantly higher percentage suffering from high-grade meningioma.[22] However, other studies report conflicting results.[5]

The relationship between age and grade of meningioma is still not known. Zhou et al. found that the pediatric group had a higher risk of developing meningioma with a higher grade. The reason that can explain this relationship may be due to embryogenic abnormalities, such as genetic mutations. But in this study, there were no samples with pediatric age.[1]

Relationship of Gender with Grade of Meningioma

In this study, men tend to experience higher meningioma grade ($p < 0.05$). Liang et al. conducted a study of 1,239 cases and reported that men had a higher risk of developing high-grade meningioma, whereas, in that study, the ratio of men to women with high-grade meningioma was 21.7% compared to 12.9% $p < 0.001$.[23]

The reason between the male gender and the occurrence of high-grade meningioma are still not clear. Various studies have suggested that hormone levels, hormone receptors, and chromosomal abnormalities can affect the tendency of high tumor grade.[23,24] Other studies have also shown an inverse relationship between levels of progesterone receptor expression and tumor histology grading.[24]

Conclusion

In this study, we concluded that clinical factors such as, tumor location, size, edema, necrosis, age and gender have a significant relationship to histopathological meningioma grade. Predicting clinical factors can be useful for surgeons to plan treatment strategies.

Conflicts of Interest

The authors affirm no conflict of interest in this study.

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Erna Kristiani

The Calamity Among Medical Students: Sleep Deprivation and Dry Eye Disease

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Abstract

Background: Medical students' burden upon academic and professional duties often blinded them from attending to themselves. Piling works and nightshifts interfere ferociously with their self-care behavior, including adequate sleep. The matter not only disrupts concentration and consciousness but also tolls the eye by reducing tear secretion. Hence, the present study urgently assesses sleep quality and dry eye disease (DED) among medical students.

Methods: The cross-sectional study observed 172 eyes among medical students in Indonesia. We assessed sleep quality and dry eye disease through Pittsburgh Sleep Quality Index and Schirmer test. Independent statistician analyzed the data with chi-square.

Result: From the eligible samples, there is a dominancy of females (55.8%) with poor sleep quality (55.2%). There is no significant difference in DED or sleep quality across gender though they lean toward females. Contrarily, poor sleepers significantly correspond to 2.96 times more risk of DED than an adequate sleeper.

Conclusions: Medical students' well-being is crucial. Aside from the academic burden, institutions and individuals shall strongly emphasize better sleep habits and eye care.

Introduction

Sleep is a transient unconscious state of the body where cells and tissues reparation happened. The National Sleep Foundation recommends seven to nine hours of daily sleep for the youth.[1] Medical student composed a lot of the sleep-deprived population niche due to the extensive academic, stress, and personal burdens.[2] A Brazilian study in 2017 also found that 39.5% of the respondents had poor or very bad sleep quality, while only 15.9% sleep more than seven hours.[3]

Abnormal sleeping duration and quality negatively affect an individual's mental and physical health. Morales et al. observed a significant increase in depression and anxiety as well as a decrease in happiness scores among medical residents who were sleep-deprived compared to those with normal sleep (Δ = 0.72, 1.74, -1.88 vs. 0.02, 0.45, and -0.99). The same study also emphasize that the case group did more medical errors (5.48) than the control (3.17) (p = .012).[4] Lack of sleep simultaneously contributes highly to the risk of cardiovascular, ophthalmological, and other diseases. A cohort study with 60,586 respondents conclude that daily sleep less than six hours have 1.10 times increase in coronary heart disease risk (0.96-1.26) even after controlling for demographic (e.g., age, gender, education, cigarette, alcohol

consumption, etc.) and medical factors (e.g., body mass index, cholesterol level, glucose, and blood pressure).[5]

Many sleep-deprived medical students nonetheless also complained about dryness or irritation in the eye. Dry eye disease (DED) is a condition where the eye orbit is too dry due to insufficient tear or unstable tear film.[6] DED prevalence needs to be monitored closely. There are 20-50% of DED prevalence globally, while 8.15% were diagnosed in Thailand university students.[7,8] However, six million adults in the United States of America are known to have undiagnosed DED.[9] If goes untreated, the dryness of the eye can induce irritation, infection, corneal ulcers, and eventually vision loss or blindness. Upon its natural course, DED also cost an individual from 687 to 1,267 USD every year for medications and other non-pharmacological treatments.[10]

Other studies had tried to examine the relationship between sleep quality to DED; however, they were using an older population (26-64 years old) and no isolation of other factors of DED (i.e., gadget exposure).[11,12] Per the authors' knowledge, this is one of the first studies to observe the sleep quality and DED in medical university students in Indonesia after excluding other influencing factors. The current study consequently investigated the sleep and DED relationship on the medical students with the exclusion of confounding factors as much as possible.

Material And Methods

Ethical Consideration & Study Design

The Ethics Committee of Pelita Harapan University had appraised and approved the cross-sectional study through 186/K-LKJ/ETIK/XI/2019 certification, following the Helsinki Declaration and Institutional Review Board (IRB) protocols. All participants of the current cross-sectional study had seen, understood, agreed, and signed the informed consent before taking part in the investigation.

Sample Size

The authors' calculated a 102 minimal sample size through the analytic independent categoric comparative equation of $\frac{(Z_\alpha\sqrt{2pq}+Z_\beta\sqrt{p_1q_1-p_2q_2})^2}{(p_1-p_2)^2}$ with 5% α and 20% β, which correspond to 1.64 Z_α and 0.84 Z_β. Cho et al. provide a proportion of students with DED and poor sleep amounting to 40.68%, while DED students with adequate sleep to 23.70%.[13] We also added a 10% addition to the minimal participant as a way to combat any loss to follow-up or incomplete filling of the questionnaire.

Subject Enrollment

The current study selected all medical students from the Pelita Harapan University, Tangerang to participate. Particularly, they were eligible if they are Indonesian medical students who were over 18 years old, have studied medicine for at least a month, and not in the exam period. However, they were excluded if: (1) wear contact lens, (2) consume daily medications (e.g., antihistamine, antimuscarinic, and oral contraception), (3) did abnormal duration of screen time, (4) had a history or were going to have an ophthalmology surgery, and (5) had systemic comorbidities which may manifest in the eye (e.g., diabetes, hypertension, Sjogren's syndrome, and thyroid disease).

Data Collection and Measurement

The authors' used a Schirmer primary exam and Pittsburgh Sleep Quality Index (PSQI) to evaluate the subjects' dry eye disease and sleep quality. Siloam Hospitals Lippo Village and Pelita Harapan University provided the materials and tools for the Schirmer test. The investigation was done in an ophthalmology outpatient department under the direct supervision of a practicing ophthalmologist. Individuals were considered having DED if they tested with under 15-millimeter wet Schirmer strip, and non-DED if

the contrary.

Meanwhile, we used PSQI to evaluate the subjects' sleep quality. The questionnaire containing seven major aspects with a total of ten questions described an adequate capability to investigate an individual's sleep quality with .74 Cronbach's alpha reliability and .33-.82 correlation validity.[14] However, the study did not use the original PSQI, but the Indonesian one. Translation to the local language decreased any language and cultural barriers that may arise while improving accuracy at the same time. The Indonesian version also had good capabilities with .79 Cronbach's alpha reliability, .89 content validity, and $p < .001$ group validity.[15] A score over five units indicates poor sleep and vice versa.

Statistical Analysis

Outsourced independent statistician tabulated the data using Microsoft Excel 365 (Microsoft, USA), while he used SPSS 26 (IBM, USA) to analyze it statistically. Relation on sleep quality and dry eye disease was computed by chi-square and presented with corresponding odds ratio and 95% confidence interval. P-value is considered significant if it is less than .05

Results

From the data collection period in November 2019 to January 2020, we observed a 100% participation rate on the randomly selected participants. Females were dominating among them by 55.8%, with DED and poor sleep happening on 41.3% and 55.23% of the respondents, respectively. Note that despite the gender disparity, it was not significant to both outcomes.

On the contrary, sleep quality had a relevant relationship to DED ($p = .001$), where an individual with poor sleep has a 2.96 increased risk of DED. **Table 1** showed a full description of the relationships.

Discussion

Amid the three-month observational study, there was a 41.3% of DED prevalence. The cases present with dominancy of females (52.1%). Matossian et al. in their work discovered that DED favors the female with a 1.7-2.6:1 gender ratio after reviewing six DED prevalence studies in the United States.[16] Women with higher estrogen levels were observed to have a higher DED severity score like those in the late follicular or luteal phase.[17] Estrogen and the ovarian hormone modulate the amount of tear secretion, drainage, and evaporation through their bond to the receptors on the cornea, lacrimal gland, and meibomian gland.[18] Liu et al. described that meta-analysis on seven randomized controlled trials yielded significant improvement on the dry eye disease after treatment with sex hormones (2.06 (0.74-4.46), $p = 0.006$).[19]

The female gender likewise possessed more poor sleep quality than males (53.7% vs. 46.3%). Australian medical students reported that females majorly experienced more tiredness and poorer sleep quality compared to males (63.1% vs. 53.2% and 65.6% vs. 34.4%).[20] Even after controlling for race, physical exercise, smoking, gadget use, medications, headache, and depression, the trend persists with the female having a 1.53 (1.23-1.90) times increased risk of poor sleep.[21] Hormonal differences have been insinuated as a culprit in sleep variance between males and females. Cusmano et al. observed that gonadectomy on mice eliminated their gender-specific sleep differences.[22] The fluctuating estrogen and progesterone levels in menstruation contributed to the variance of rapid eye movement (REM) and slow-wave sleep phases.[23] Further, progesterone also induces gamma-aminobutyric acid ($GABA_A$) receptors to heighten the sleep spindle activity.[24] Sleep distraction also happened a lot more in females aside from the hormonal disparity. A Chinese study estimated a 0.7% and 0.21 increase in females' insomnia prevalence and

PSQI score.[25]

Meanwhile, the study calculated a significant 2.96 risk increase of DED incidence in those with poor sleep quality (p = .001). Individuals with a lack of sleep experienced a decreased parasympathetic tone due to a reduced number of circulating hormones in the body (e.g., cortisol, epinephrine, and norepinephrine).[26] The impaired hormonal stimulant of tear secretion coupled with tear hyperosmolarity, unstable tear film, and lowered tear break-up time rapidly induce the DED development. Kawashima et al. from Japan also described that DED individuals had a higher PSQI score significantly (Δ = 0.8, p = .002) with 45.0% having poor sleep quality (p = .040).[11]

This study bridges the gap between sleep quality and dry eye disease in Indonesian medical students. There are however some notable limitations, such as the cross-sectional design, small sample size, and not being generalizable to the foreign or non-scholar population. Henceforth, further studies on the topic are needed with cohort or experimental design on a larger sample pool and various populations, including more assessment on the risk factors.

Conclusion

Numerous amounts of academic, financial, and personal burdens on medical students eloquently deprived their time to rationally think and take care of themselves. Institutions, caregivers, parents, and individuals shall put more concern on themselves especially upon the students' physical health and sleep awareness.

Disclaimer

The study also serves as a memorandum for the deceased first author, and accordingly, the research data is not available for any sharing or distribution. The authors declare no existing conflict of interest or external funding. We appreciate all of the respondents for their participation. All authors participated equally, from the conceiving of the research ideas to the execution and manuscript concoction.

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The Appropriate Acquisition Time Interval Following Injection of ^{99m}Tc-Sestam ibi with Water Protocol in Single Photon Emission Computed Tomography Myocardial Perfusion Imaging: First Experience in Indonesia

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Abstract

Introduction: According to EANM/ESC guideline, image acquisitions in stress test should be begun at 30-60 minutes after tracer administration. Our center is a referral hospital for nuclear medicine imaging with many patients but limited number of gamma camera. The shorter time between injection of radiopharmaceutical and imaging acquisition will add to the number of examinations that can be performed. The aim of this study was to evaluate the appropriate acquisition time interval with water protocol in ^{99m}Tc-Sestamibi SPECT myocardial perfusion imaging.

Methods: Patients who were referred to undergo stress MPI between October 2020 to December 2020 were included in this study. Cardiac stress procedure was performed using treadmill with modified Bruce Protocol. Subjects drank a total of 330 mL water following ^{99m}Tc-Sestamibi injection. Image acquisitions were performed 10 and 30 minutes afterwards. Quantitative assessment was done by calculating target background ratio (TBR). Statistical analysis was performed using student t-test with Microsoft Excel version 2019. *P*-value < 0.05 was considered to be statistically significant.

Result: Thirty out of 35 subjects were included in this study. Sixteen of them are male and 14 are female with a mean age of 48.7 years old (28 — 80). Mean target background uptake ratio (TBR) in 10- and 30-minutes images were 0.67 (0.44 – 1.11) and 0.76 (0.43 — 1.18) respectively (*p*-value = 0.15).

Conclusion: There was no significant difference of target to background ratio between 10- and 30-minutes acquisition time interval following injection of ^{99m}Tc-Sestamibi with water protocol in myocardial perfusion imaging.

Introduction

Coronary artery disease (CAD) remains the world's leading cause of death.[1] Single Photon Emission Computed Tomography (SPECT) Myocardial Perfusion Imaging (MPI) using ^{99m}Tc-Sestamibi can be used to diagnose and evaluate the prognosis of CAD. According to European Association of Nuclear Medicine/European Society of Cardiology (EANM/ESC) guideline, image acquisitions should be

begun at 30-60 minutes after tracer administration in stress test.[2]

In our center, patients should drink milk at time between injection and imaging to increase clearance of tracer from the liver and gallbladder as a standard protocol. However, some patients are lactose intolerant, and this may cause diarrhea and abdominal discomfort after consume milk and sometimes disturb/prolong the MPI procedure.

Our center is a referral center hospital for nuclear medicine imaging with many patients but a limited number of gamma camera and we often find patients with history of lactose intolerance. The aim of this study was to evaluate the appropriate acquisition time interval between injection of radiopharmaceutical and image acquisition using water protocol in SPECT myocardial perfusion imaging.

Material And Methods

Thirty-five patients who were referred to Department of Nuclear Medicine and Molecular Imaging Dr. Hasan Sadikin General Hospital for MPI procedure between October 2020 to December 2020 were included in this study. The exclusion criteria were as follow: patient with no history of essential fluid restriction, currently taking anti-motility or pro-motility drug, not pregnant or lactating at the time of MPI procedure, and had contraindications to perform exercise stress test using treadmill. Patients also should not consume caffeine containing products for at least 12 hours prior to MPI procedure, stop β-blocker treatment for 24 hours, and stop phosphodiesterase inhibitor for 24-48 hour before MPI procedure. All subjects were asked to fast for at least 4 hours prior to MPI procedure. Informed consent was obtained from all subjects.

Stress procedure was performed using treadmill with modified Bruce Protocol. ^{99m}Tc-Sestamibi was use as radiopharmaceutical. Subjects who reached minimal 85% of maximal heart rate were asked to drink a total of 330 mL water after radiopharmaceutical injection. Image acquisitions were performed at 10 and 30 minutes after radiopharmaceutical injection.

Region of interest (ROI) were drawn on heart and liver on 10- and 30-minutes images and then the target background ratio (TBR) was calculated, as shown in Figure 1. Statistical analysis was performed using student t-test with Microsoft Excel version 2019 to evaluate the quantitative assessment of heart to liver background ratio. *P*-value < 0.05 was considered as statistically significant.

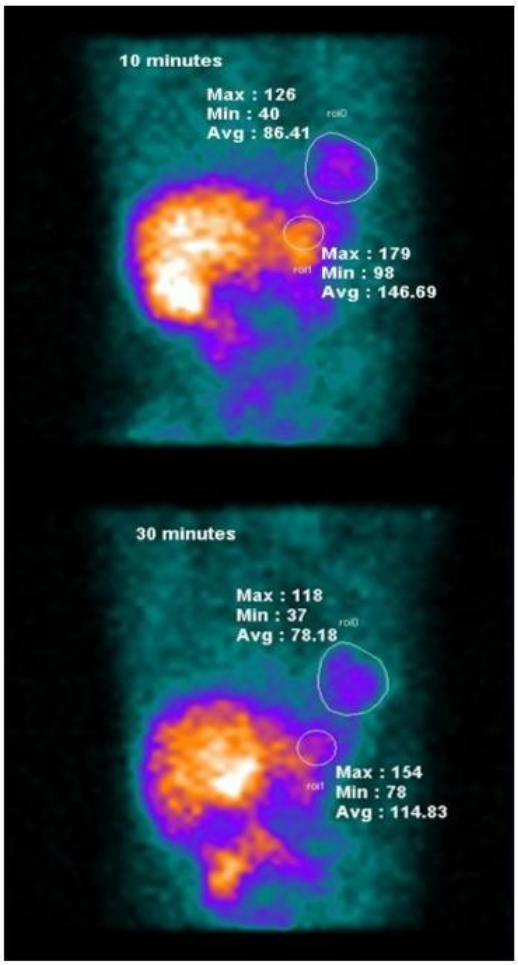

Figure 1. Comparison of ^{99m}Tc-MIBI uptake in the target (heart) and the background (liver) on 58 years old male with atypical chest pain

Result

A total of 30 out of 35 subjects (86%) were included in this study. Five of 35 subjects were excluded due to essential fluid restriction, had contraindications to perform exercise stress test using treadmill, and didn't reach optimal target maximal heart rate. Subjects consist of 16 males (53%) and 14 females (47%) with mean age of 48.7 (28 — 80 years-old). Mean target background ratio (TBR) in 10- and 30- minutes acquisition time interval following injection of radiopharmaceutical were 0.67 (0.44—1.11) and 0.76 (0.43—1.18) respectively (*p*-value = 0.15), as shown on Figure 2.

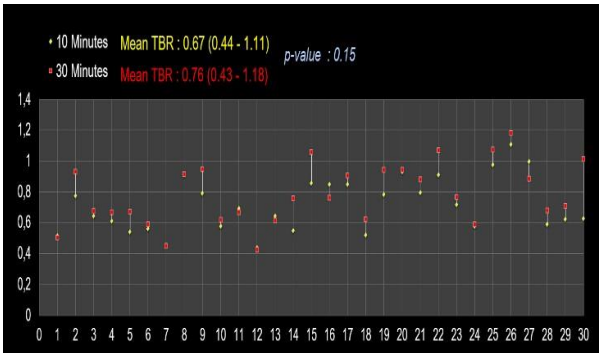

Figure 2. Mean target to background uptake ratio in 10- and 30-minutes post injection of radiopharmaceutical

Discussion

Coronary artery disease (CAD) remains the world's leading cause of death with 16% of the world's total death. According to World Health Organization, there were 2 to 8.9 million deaths in 2019.[1] Prevention and early non-invasive diagnosis or early detection with high sensitivity and high specificity must be the priority to slow down the increasing death caused by CAD. SPECT-MPI using radiopharmaceutical ^{99m}Tc-Sestamibi can be used to diagnose and evaluate the prognosis of CAD. It was found to be more cost effective than any other diagnostic modality, and more sensitive than exercise Electrocardiogram (ECG) in detecting myocardial ischemia. It has 85-95% sensitivity, and 75% specificity. The specificity can be increased up to 94% if combined with ECG gated data.[3-5] Stress images may help determine the degree of inducible ischemia or viable myocardium that are amenable to revascularization, evaluate myocardial viability before revascularization and following-up after revascularization such as coronary artery bypass graft or angioplasty.[3-6]

Physiological radioactivity uptake in the liver, bowel or stomach could interfere the interpretation of MPI. This phenomenon can be reduced by using iterative reconstruction and attenuation correction but a high tracer activity around the heart will still influence the evaluation of the myocardium.[7,8] Several methods to reduce the digestive activity have been described, such as filling the stomach with either solids or fluids[9-11], increasing the gastrointestinal activity by using metoclopramide drug[12], keeping the patient standing for several minutes after tracer injection[13], or even ingesting iodinated contrast medium to absorb the emitted gamma-rays[14]. Prolonging the delay imaging between injection and image acquisition can lead to a significant decrease in the hepatic activity but also by increasing the activity in the bowel loops adjacent to the inferior wall of the heart.[11,12,14]

Patients should take fatty meal at time between injection and imaging to increase clearance of tracer from the liver and gallbladder as a standard protocol of MPI in some centers.[2] Our department usually ask patients to drink milk to reduce physiological infra-cardiac organs uptake. However, some patients are lactose intolerant, and this may cause diarrhea and abdominal discomfort. Data on Indonesian population showed that the prevalence of lactose malabsorption and intolerance are quite high, between 21% to 73%.[15-17] Those patients will feel abdominal discomfort as well as diarrhea after MPI procedure, and sometimes disturb the MPI

procedure.[13] In this study we use water instead of milk, to minimize the infra-cardiac uptake that can interfere with the interpretation of SPECT MPI. Our previous study compared subjects in first group (drank 500 mL of milk) and second group (drank 330 mL of water) after doing physical stress MPI procedure with acquisition time 30 minutes after ^{99m}Tc-Sestamibi injection, and we found that water was as good as milk in reducing the infra-cardiac tissue tracer uptake. In this study, ^{99m}Tc-Sestamibi was used as radiopharmaceutical for MPI. Since this radiopharmaceutical is a lipophilic agent, patients were advice to take solid fatty meal for breakfast on the day of MPI procedure.[7, 8]

Preparation before MPI procedure is important to get a good quality of images. Subjects should not take any food for at least 4 hours to prevent stress-induced gastric distress and minimize splanchnic blood distribution.[18] Subjects must have no contraindications to perform exercise stress test using treadmill. Caffeine containing products must not be consumed for at least 12 hours prior MPI procedure, to avoid decreased vasodilatation respond from vasodilator stress agents, which will lead to reduced sensitivity in detecting myocardial ischemia. Subjects were also suggested to stop β-blocker treatment for 24 hour and phosphodiesterase inhibitor for 24-48 hour before MPI procedure.[19]

Out of 35 subjects, 5 subjects were excluded because they didn't reach minimal target heart rate (85% maximal heart rate) and had contraindications to undergo the exercise test. Based on EANM/ESC guideline, patients are said to achieve maximum exercise stress test when they are able to reach 85% of their age-predicted maximum heart rate (maximal age–predicted heart rate = 220 — age).[2]

In accordance to conventional guideline, image acquisitions should be performed 15 — 60 minutes after tracer administration.[19] Strauss, et al. said that image acquisitions with ^{99m}Tc based tracer should be performed after liver radioactivity has sufficiently cleared, this was usually between 15-30 minutes after tracer administration.[20] While according to EANM/ESC guideline, image acquisitions should be begun at 30-60 minutes after tracer administration.[2] In this study, MPI was done on 10 and 30 minutes following ^{99m}Tc-Sestamibi injection intravenously. Ten minutes acquisition time following injection of radiopharmaceutical based on the consideration that the time taken by patients between physical stress MPI, and imaging procedure was about 10 minutes. The 10 minutes image after radiopharmaceutical injection was considered as direct imaging, and 30 minutes image as control, based on EANM/ESC guideline, as an appropriate time for image acquisitions.[2]

All subjects were scanned in supine position with arms raised above the head and the knees supported with pillow under it. Shoulders and arms were comfortably positioned in order to reduce movement and pain, particularly in older subjects, to make them feel as comfortable as possible to minimize body motion as suggested by Dorbala, et al..[19] Female subjects were imaged without brassiere, and chest band was used to minimize breast attenuation and minimize motion. Chest band could also be used in male subjects to minimize body motion as suggested by Hesse B. et al.[2] From the quantitative assessment results, we found that there was no significant difference in TBR of heart to liver ratio between 10- and 30-minutes acquisition time interval after radiopharmaceutical injection as seen in Figure 2, with p-value = 0.15 ($p > 0.05$).

Conclusion

Our quantitative study showed that there was no significant difference in target to background ratio between 10- and 30-minutes acquisition time interval following injection of ^{99m}Tc-Sestamibi in water

protocol SPECT myocardial perfusion imaging procedure. The shorter acquisition time interval in stress exercise test using water protocol SPECT myocardial perfusion imaging (10-minutes following injection of ^{99m}Tc-Sestamibi) can be used in daily practice to increase the number of examinations that can be performed without reduce the image quality of MPI results.

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Author's Statement

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Nora A. Prasetyo

The Relationship Between High Emotional Intelligence and Stress in Medical Students of Medicine Pelita Harapan University During the Covid-19 Pandemic

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Abstract

Background: The World Health Organization (WHO) has declared Coronavirus Disease 2019 (COVID-19) a global pandemic. This also has an impact on student's lives. Most of the students have been in a stressful condition due to changes in the online teaching and learning process as an adaptation to COVID- 19. Although it has been reported that emotional intelligence can reduce stress, there are still a few studies that study about relationship between the two during COVID-19 pandemic, especially among medical students.

Methods: A cross sectional using comparative numerical analysis was conducted with 305 medical students. Data were collected by an online survey using Emotional Intelligence Appraisal (EIA) questionnaire, and Medical Student Stressor Questionnaire (MSSQ). Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 25.

Results: The EIA questionnaire showed that there were 1.3% low EI groups, 38.7% normal EI groups, and 60.0% high EI groups. The MSSQ questionnaire showed that there was 24% mild stress, 49% moderate stress, 26% severe stress, and 1% very severe stress. A normal data distribution was obtained through the Kolmogorov-Smirnov test, so that the T test could be used with a 95% confidence degree (p value <0.05). T-test analysis in the high EI group with an average stress (1.76±0.64) and the normal EI group with an average stress (1.40±0.75) showed a significant difference with p value = 0.008.

Conclusion: In accordance with the hypothesis in this study, during the COVID-19 pandemic, there is a significant relationship between high emotional intelligence and stress in UPH Medical Faculty students.

Introduction

COVID-19 is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which was first found in Wuhan, China at the end of December 2019.[1] In March 2020, 2 people were reported as the first case in Indonesia.[2,3] High number of cases in Indonesia has made the government published a policy to implement an online learning process during the pandemic through the Circular of the Minister of Education and Culture Number 4 of 20205. In the end, this also has an impact on increasing students stress.[4,5].

Stress itself is defined as a disturbance in homeostasis that triggers changes in physiological balance resulting from physical or psychological stimuli. A key component in the stress system is the hypothalamic-pituitary-adrenal (HPA) axis, which interacts with other vital centers in the central nervous system and peripheral tissues/organs to mobilize adaptive

responses to stressors.[6] Stress has an impact on the individual who experiencing it. Yet, the impact of perceived stress is determined by the individual's ability to cope with the situation.[7]

One way to reduce the impact of stress is to have emotional regulation or emotional intelligence.[8] Emotional intelligence consists of aspects of self-awareness, self-management, social awareness, and relationship management. Someone who has a good level of emotional intelligence can apply active and effective strategies in dealing with stress so that there is a high influence of emotional intelligence in reducing stress.[9]

In a previous study, conducted by Kauts Deepa (2016) in India, it was reported that students with high emotional intelligence had lower levels of academic stress.[10] In a study conducted by Muhnia and friends (2016) on 74 students of the Nursing Science Study Program, Faculty of Medicine, University of Hasanuddin showed that there was a negative relationship between emotional intelligence and stress levels of first-year students, with a *p* value = 0.036. [11]

Before the pandemic, there was a lot of research on the relationship between emotional intelligence and stress, but it still has a variety of results. In addition, there are still a few studies that study the relationship between intelligence and high emotional intelligence with average stress during the COVID-19 pandemic.

The purpose of this study was to determine the relationship between high emotional intelligence as measured by EIA and average stress as measured by MSSQ in students of the Faculty of Medicine, Pelita Harapan University during the COVID-19 pandemic.

Methods

This study used a comparative numerical analytical study to determine the relationship between high emotional intelligence as measured by EIA and average stress as measured by MSSQ in students of the Faculty of Medicine, Pelita Harapan University during the COVID-19 pandemic. Besides that, the General Health Questionnaire-12 (GHQ-12), Patient Health Questionnaire-9 (PHQ-9), Mood Disorder Questionnaire (MDQ) were also used to measure the mental health of the respondents. This research was conducted online from January 2021 to April 2021 using a Google form with a simple random sampling technique.

The inclusion criteria in this study were students of the Faculty of Medicine, Pelita Harapan University, both women and men with an age range of 17-24 years. Meanwhile, to reduce bias, students with minor depression and anxiety (measured by the GHQ-12 questionnaire with a score> 1), major depression (measured by the PHQ-9 with a score ≥10), and those with bipolar disorder (measured by the MDQ with a positive result) were excluded in this study.

Respondents who meet the inclusion criteria filled out the Emotional Intelligence Appraisal questionnaire (EIA) and the results were divided into 3 categories, namely low emotional intelligence, normal emotional intelligence and high emotional intelligence. Furthermore, respondents were given an MSSQ questionnaire to measure stress levels. The results were divided into mild stress, moderate stress, severe stress and very severe stress.

The sample in this study are 52 students that were randomly selected from 301 students who met the inclusion and exclusion criteria to fill out the MSSQ questionnaire.

The data that has been collected is summarized in Microsoft Excel. Statistical

tests were carried out with the SPSS 25 program and used comparative numerical analysis. Before the data was processed, the Kolmogorov-Smirnov normality test was carried out. After getting the results, the relationship between high emotional intelligence and average stress will be analyzed usingthe T-test.[12]

Result

Of the 450 students who have filled out the questionnaire, there are 305 students who met the inclusion and exclusion criteria. From 305 students who have filled out the Emotional Intelligence Appraisal questionnaire. The results of the interpretation of emotional intelligence can be seen in the table 1.

Table 1. Emotional intelligence level

Emotional Intelligence	**Frequency (n)**	***Percentage (%)***
Low (0-59)	4	*1.3%*
Normal (60-80)	118	*38.7%*
High (81-140)	183	*60.0%*
Total	**305**	***100%***

Through the EIA questionnaire, from 305 students there were 4 students (1.3%) with low emotional intelligence, 118 students (38.7%) had normal emotional intelligence and most of them had high emotional intelligence levels, as many as 183 students (60.0%).

In this study, we just wanted to know about the relationship between high emotional intelligence and stress, so that we didn't involve a low emotional intelligence group in the test. So that, from each group with normal and high emotional intelligence, 52 students were randomly selected to fill out the MSSQ questionnaire which was divided into 4 categories. These 52 students were related to sample calculations in comparative numerical analytical studies, The results of stress interpretation can be seen in the table 2.

Table 2. Stress levels in the group of Students with normal and high emotional intelligence

	Mild Stress (0-1.00)	***ModerateStress (1.01-2.00)***	***Severe Stress (2.01-3.00)***	***Very Severe Stress (3.01-4.00)***	***Mean ±SD***
Normal Emotional Intelligence(n=52)	7 (13%)	29 (56%)	15 (29%)	1 (2%)	**1.76± 0.64**
High Emotional Intelligence(n=52)	18 (35%)	22 (42%)	12 (23%)	0 (0%)	**1.40± 0.75**
Total	**24%**	**49%**	**26%**	**1%**	

In each group with normal and high emotional intelligence, the most stress was found at themoderate level by 51 students (49%) and the least at the very severe level by 1 student (1%).

To find out whether the data is normally distributed, the Kolmogorov-Smirnov normality test was carried out with a *p* value = 0.200. With this result of *p* value > 0.05, it can be concluded that the data is normally distributed. Since it was normally distributed data, the data was analyzed by the T test. The results of the T test on the two variables can be seen in the table 3.

Table 3. Differences between average stress and emotional intelligence on T test

	Variable	**N**	**Mean±SD**	**P Value**
Stress	Normal Emotional Intelligence	52	1.76±0.64	**0.008**
	High Emotional Intelligence	52	1.40±0.75	

The average stress that was compared between the two groups above showed significance with *p*value = 0.008.

Discussion

In this study, there were 305 students who met the inclusion criteria. The highest level of emotional intelligence is at a high

level (60.0%). This is in line with research by Sindy, et al (2020) who reported that 58% of the students of the Faculty of Medicine, Sebelas Maret University, had a high to very high level of emotional intelligence.[15] Hagelin, et al (2017) also report that, on average, students of the Faculty of Medicine at Udayana University have a high level of emotional intelligence[16]. This is possible because a high level of emotional intelligence is influenced by the existence of family support, university facilities and a good scope of lectures, which help them to manage their emotions well in preparation for dealing with problems and patients in the future.[9] During a pandemic, emotional intelligence, which consists of awareness and self-management components, is very important to have in dealing with critical and difficult situations [9,17].

In each group with normal and high emotional intelligence, the most stress was at a moderate level (49%) and the least at a very severe level (1%). This is in line with research conducted by Lorcan and colleagues (2021) that stress on medical students in Ireland during the pandemic was found to be moderate to severe stress levels (54.5%)[18]. In research that are conducted by Sania (2021) also reported that stress on medical students at the University of North Sumatra during the pandemic was at the most moderate level (49.1%)[19]. In the pre-pandemic period, it was reported by Riskia, et al (2019) that Andalas University medical students experienced the most moderate levels of stress (48.4%)[20]. Wahyudi, et al (2017) also reported that stress on medical students at the University of Riau was mostly at a moderate level (56.6%)[21]. The differences in the results of the research mentioned above are possible due to differences in the academic system of each university, the research sample environment and the type of stress measuring instrument used. The results of the study also showed that there was no difference in stress levels in medical students before and during the pandemic.[19,20] Allegedly, it is caused by a high level of emotional intelligence that will stimulate the limbic system and prefrontal cortex where the neurotransmitters serotonin and dopamine will be stimulated and cortisol will not be stimulated through the HPA axis, so that students with high emotional intelligence are not susceptible to stress during the pandemic. [9,22]

With the T-test, comparison of mean and standard deviation of stress in the normal and high emotional intelligence groups showed a significant difference (*p* value <0.05). This results in line with the theory that emotional intelligence is the ability to recognize and understand emotions in oneself and others, as well as the ability to use this awareness to manage individual behavior and relationships, making it an indispensable component during the COVID-19 pandemic.[9,22]

Conclusion

In conclusion, this study has proved that during the COVID-19 pandemic, high emotional intelligence showed a lower average stress among Faculty of Medicine, Pelita Harapan University students, with a very significant difference of *p* value = 0.008. For future research, it is hoped that there could be more varied samples being obtained from fellow medical faculty of other universities. In addition, it is also expected that in future research could be able to examine the factors that affect emotional intelligence and the factors that affect stress levels such as exams and study load during college.

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A Comparative Efficacy of Atezolizumab plus Bevacizumab Versus Sorafenib in Advanced Hepatocellular Carcinoma: A Review

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Abstract

Hepatocellular carcinoma (HCC) ranks sixth as the most common cancer and fourth as the most common cause of cancer-related death globally. The standard treatment for advanced HCC is by prescribing sorafenib, a tyrosine kinase inhibitor. Despite its moderate efficacy and concerning side effects, there is no better alternative to sorafenib to treat HCC. However, a new combination of atezolizumab (an inhibitor of PD-L1) and bevacizumab (an inhibitor of vascular endothelial growth factor), has shown a potential to surpass the efficacy of sorafenib. This review was written to provide an insight into pharmacodynamics of sorafenib and atezolizumab plus bevacizumab, effectiveness of sorafenib and the one of atezolizumab plus bevacizumab, utilization of atezolizumab plus bevacizumab in the clinical practice, as well as to argue that this combination can replace sorafenib as the standard palliative treatment for HCC.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy globally, in which its cases has been growing exponentially since 1980 and it is one of the leading cancer-related mortality.[1] HCC is often diagnosed in advanced stages because its signs and symptoms are usually unnoticeable until it already reached advanced stages. Advanced HCC are unresectable, however, since the cancerous cells are located near to a large blood vessel or might have invaded a vasculature. Thus, patients diagnosed with advanced HCC only receive palliative treatment. Currently, the standard palliative treatment of HCC is through the administration of sorafenib (SFB), an oral multi-kinase inhibitor.[2] However, SFB only prolongs life expectancy by 4.3 months, while it also induces moderate drug-related adverse events.[3] Thus, a more effective treatment is needed.

Over the years, cancer drugs that target tumor angiogenesis, such as anti-angiogenic drugs, have been developed. Moreover, cancer immunotherapy such as immune checkpoint inhibitors (ICI) has been available as well to treat various cancers. The combination of ICI with anti-angiogenic drugs could be useful to treat certain cancers. A particular example is the combination of atezolizumab (ATZ), the programmed death-ligand 1 (PD-L1) inhibitor, and bevacizumab (BVZ), the vascular endothelial growth factor (VEGF) inhibitor. This review was thus written to compare ATZ+BVZ with SFB in terms of its pharmacodynamics, general efficacy, and consideration in the real-world clinical practice to determine its likelihood of replacing SFB as the standard palliative care for advanced HCC.

Signaling Pathways as Target of HCC Drugs

The development of cancer-inhibiting drugs began when proto-oncogenes had been discovered in the 1980s.[4] Proto-oncogenes are genes that have the potential to cause cancer. Mutated versions of these genes are called oncogenes, which usually affect growth of mutated cells.

Growth factors in the liver are most active during the embryonic stage of life, when growth factors, such as the epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin-like growth factors (IGF), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF) and transforming growth factors -α and -β (TGF-a and TGF-β), are produced to support the liver development. In contrast, these growth factors are produced minimally or not at all in the liver of an adult.[5] In a case of liver injury or damage, however, hepatocytes could upregulate growth factors, such as EGF, VEGF, IGF and TGF-α. Those are the growth factors that oncogenes target as well. A dysregulation of growth factor production and growth factor receptor signaling pathways within adult's liver might lead to uncontrolled division and metastasis.

Critical growth factor signaling pathways in HCC include the Ras/Raf/MEK/ERK (MAPK/ERK), Phosphoinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) and the Wnt/catenin pathway.[6] The Ras/Raf/MEK/ERK (MAPK/ERK) pathway is especially critical for HCC initiation and progression. It transduces extracellular signals from tyrosine kinase receptors, such as EGF-receptor (EGFR), VEGF-receptor (VEGFR), IGF-receptor (IGFR) and the PDGF-receptor (PDGFR), into the nucleus.[6] This pathway is most frequently hyper-activated in HCC and occurs in about 50% of early-stage and most advanced cases.[7]

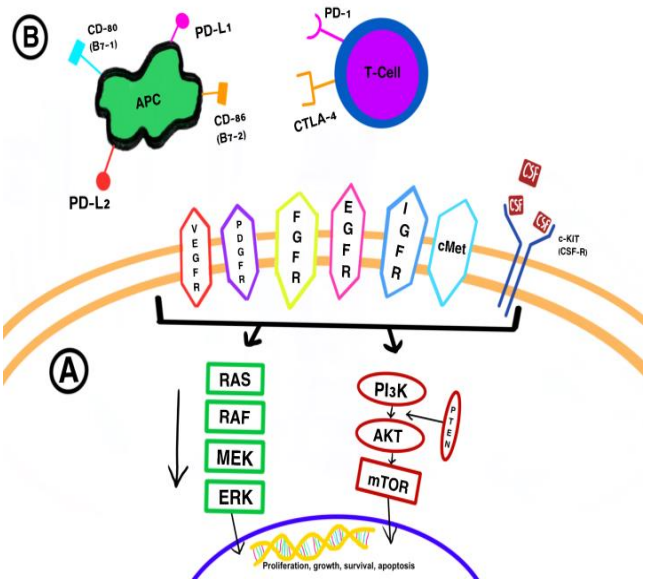

Figure 1. Major signaling pathways responsible for hepatocellular carcinoma and its progression. (*A*) The Ras/Raf/MEK/ERK (MAPK) and PI3K/Akt/mTOR pathways can be activated through receptors of VEGF, PDGF, FGF, EGF, or IGF as well as other receptor tyrosine kinases (including c-MET and c-Kit). The activation results in either proliferation, growth, survival or apoptosis. (*B*) The immune checkpoint inhibitor mechanism between antigen-presenting cells (APCs) and T cells.

There is a series of phosphorylation events within the Ras/Raf/MEK/ERK (MAPK) pathway (**Figure 1**).[6] First, Ras will be activated and activate the serine-threonine kinase of the Raf family. Raf in turn phosphorylates the mitogen-activated kinase (MEK) 1/2 kinases, activating the extracellular regulated kinases (ERK) 1/2. ERK 1/2 kinase will migrate into the nucleus and subsequently regulates protein expression responsible for cell cycle progression, apoptosis resistance, cellular motility, angiogenesis and drug resistance. The oncogenic transformation of the Ras/Raf isoforms or gene upregulation will dysregulate this pathway, causing abnormal cell growth, proliferation and migration.[7]

In addition to Ras/Raf/MEK/ERK (MAPK) signaling pathway, a receptor called the VEGF receptor (VEGFR) is also important for angiogenesis. **Figure 2** depicts a role of VEGFR in HCC progression. Among three types of VEGF receptors (VEGFR-1, VEGFR-2 and VEGFR-3), VEGFR-2 mediates most of cellular responses for the angiogenesis.[6] Angiogenesis is critical for cancer cells since tumor growth in the liver induces hypoxia for cancer cells.[8,9] Therefore, new blood vessels are required to provide oxygen. Growth factors such as hypoxia-inducible factors 1 and 2 (HIF-1 and HIF-2) and insulin-like growth factor 2 (IGF-2) will be induced in hypoxic hepatocytes, stimulating VEGF expression.[6] High levels of VEGF in HCC patients result in tumor progression, poor prognosis after resection, disease recurrence, vascular invasion and portal vein embolism.[6] During the formation of new blood vessels, PDGFR is responsible for forming pericytes and smooth muscle cells around the new blood vessel.

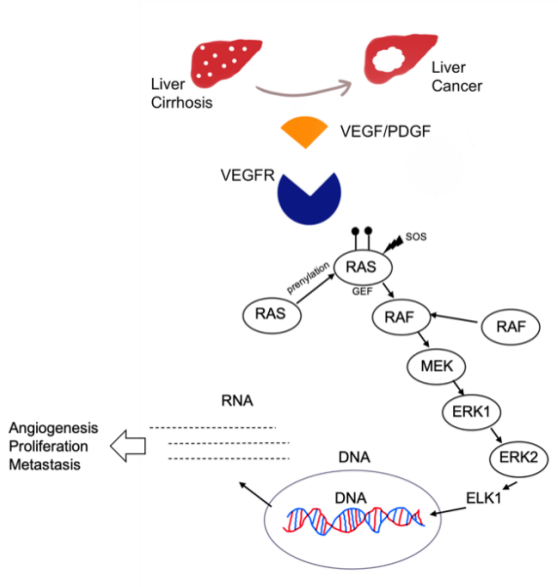

Figure 2. Role of VEGF/VEGFR in the hepatocellular carcinoma. During the progression of liver cirrhosis to liver cancer, an interaction of VEGF and VEGFR would activate the Ras/Raf/MEK/ERK signaling pathway. This would induce angiogenesis, proliferation and metastasis of hepatocellular carcinoma.

Aside from those growth factors, immune checkpoints, such as PD-1 and CTLA-4, could also be activated during HCC development (**Figure 1**).[6,8] In normal conditions, these checkpoints regulate the immune system by preventing the immune system from over-activation and from attacking normal cells. Thus, immune checkpoints may render immune cells, such as cytotoxic $CD8^+$ T cells, to be inactive. Malignant cells unfortunately could hijack these mechanisms to suppress the proper activation of immune system.[9]

It is obvious therefore that those mentioned growth factors and signaling pathways as well as the immune checkpoints are potential targets for treating HCC. Most cancer drugs target the VEGFR growth factor and/or the Ras/Raf/MEK/ERK (MAPK) pathway, in which a particular cancer drug could target a single pathway or multiple pathways at once. Such is the case for SFB and ATZ+BVZ drugs, which this paper will discuss further. For instance, SFB targets two pathways, i.e., the VEGFR and the Ras/Raf/MEK/ERK (MAPK) pathways, to mitigate the impact of dysregulated pathways. In contrast, certain drugs might target a single pathway, such as the ATZ (inhibiting PD-L1) and BVZ (inhibiting VEGF).

Parameters to Consider for Determining Drug Efficacy

To determine the efficacy of HCC drugs, various common parameters are used, including alpha-fetoprotein (AFP) level, Child-Pugh (C-P) score, albumin-bilirubin (ALBI) level, whether a patient is a molecular-targeted agent (MTA) naïve or experienced, as well as whether the cause of HCC is viral or non-viral.

Firstly, AFP serves as a diagnostic marker in AFP-positive HCC.[10] AFP is produced by neoplastic or regenerating hepatocytes. As AFP is made in the liver of infants, healthy adults should have very low levels of AFP, in which AFP levels exceeding 400 ng/mL could be a sign of malignancy. The significant decrease in AFP levels among clinical subjects suggests the good potency of the tested drug for HCC treatment.

Secondly, the C-P score acts to predict the mortality rate of HCC patients.[11] There are three categories: grade A indicates a good hepatic function; grade B indicates a moderately impaired hepatic function; and grade C indicates advanced hepatic dysfunction. The C-P score needs to be evaluated before treatment to analyze the suitability of the antineoplastic drug.

Thirdly, the albumin-bilirubin (ALBI) score uses objective parameters, i.e., albumin and total bilirubin levels, which supposedly provide a better evaluation than the C-P score.[12] There are three grades: grade 1 classifies 25% of patients with the lowest risk of death; grade 3 classifies 10% of patients with the highest risk of death; and grade 2 classifies patients in between.

Fourthly, the MTA-naive and experienced patients may present different responses toward drugs. Therefore, it is also critical to consider this as a parameter.[13] Finally, the HCC causes could be divided into viral, caused by hepatitis B (HBV) or hepatitis C (HCV) virus, and non-viral, due to excessive alcohol consumption, smoking, and obesity. This parameter is significant since, according to past studies, non-viral HCC presents a poorer prognosis.[14,15]

Sorafenib to Treat Advanced HCC

Sorafenib (SFB) is a multi-kinase inhibitor. Although it was initially identified as a Raf-1 kinase inhibitor, it is known now to target multiple tyrosine kinase receptors, including VEGF receptors 1-3, PDGFR-β, stem cell factor receptor (KIT), FMS-related tyrosine kinase 3 receptor (FLT3), FGFR1, RET proto-oncogene and downstream serine/threonine kinase, such as BRAF (mediating signals from RAS to MEK). SFB has been widely used since 2010 as the main palliative treatment option for advanced HCC. Upon ingestion, SFB will be metabolized mainly in the liver through two pathways, producing eight metabolites. Among those eight, M2 (N-oxidation), M4 (demethylation), and M5 (oxidative metabolite) are identified to inhibit VEGF, PDGFR, and members of the MAPK pathway.[16]

As mentioned (**Figure 3**), SFB inhibits tumor cell proliferation by blocking the B-RAF, RAF-1 and the kinase activity within the Ras/Raf/MEK/ERK signaling pathways.[17] It also prevents tumor-associated angiogenesis by targeting the PGFR-β, VEGFR-1,2,3, and c-KIT. Lastly, SFB could induce apoptosis of tumor cells by reducing eIF4E phosphorylation and downregulating Mcl-1 levels.[18]

The current problem of using SFB to treat advanced HCC is its modest efficacy, the growing numbers of resistance, and the side effects of SFB. Only 30% of patients are estimated to benefit from SFB, and usually, the drug resistance occurs within six months of treatment.[19] Furthermore, SFB might induce side effects, including diarrhea, fatigue, and hand-foot-mouth disease. In some patients, SFB even could cause an elevated blood pressure and abdominal pain. These adverse events may be caused by disruptions of multiple signaling pathways such as VEGF, PDGF, RAF1, B-RAF, KIT and FLT3 in normal organs.[17]

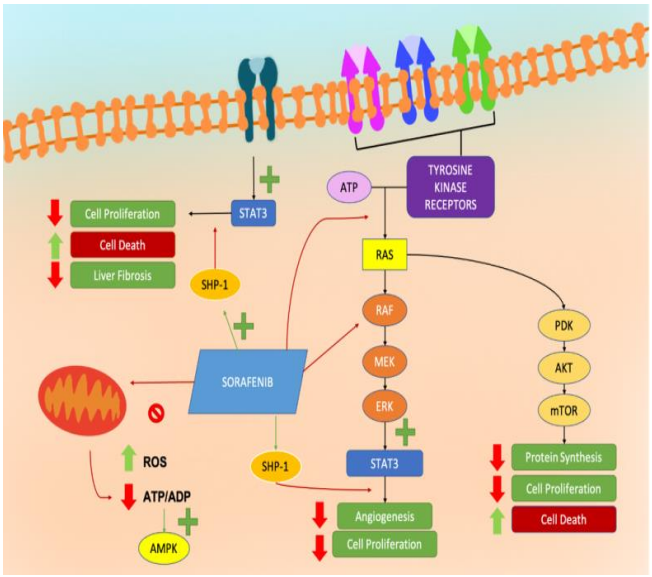

Figure 3. Responsible mechanisms of SFB-targeting signaling pathways for treating hepatocellular carcinoma[19]. SFB induces antitumoral effects by inhibiting tyrosine kinase receptors and TGF-b receptor, as well as altering mitochondrial function. SFB inhibits tyrosine kinase receptors (e.g., VEGFR, PDGFR, c-KIT) and downstream kinases (e.g., Raf), thus influencing key cellular pathways, such as Raf/MEK/ERK and PI3K/Akt/mTOR. The regulation of STAT3 activity leads to an increase in cell death and a decrease in proliferation, protein synthesis and angiogenesis within the tumor. SFB increases Tyr dephosphorylation activity of SHP-1, which in return decreases STAT3 activity. Furthermore, SFB-disrupted TGF-b pathway promotes cell death while suppressing liver fibrosis and cell proliferation. SFB alters AMPK activity by lowering the ATP/AMP ratio and/or eventually producing ROS, which inhibits the mTORC1 signaling pathway. Green arrow denotes an increase of cellular activity. Red arrow denotes a decrease of cellular activity. Stop sign denotes an inhibition of cellular activity. A plus sign denotes an upregulation of a particular molecule.

A combination of Atezolizumab and Bevacizumab to Treat HCC

Atezolizumab (ATZ) and bevacizumab (BVZ) are novel inhibitors utilized to target HCC (**Figure 4**). ATZ is an ICI for the programmed death-ligand 1 (PD-L1).[8] PD-L1 is expressed in tumor cells, while programmed death 1 (PD-1) is expressed on cytotoxic $CD8^+$ T cells. The interaction of PD-1 and PD-L1 suppresses the activation of cytotoxic $CD8^+$ T cells. Thus, ATZ will inhibit the PD-1 and PD-L1 interaction and subsequently prevent T-cell suppression.[3]

BVZ is a monoclonal antibody that targets VEGF (i.e., the anti-VEGF antibody).[9] Thus, this drug primarily induces anti-angiogenic effects since VEGF is most known for its angiogenic capability. However, VEGF could induce immunosuppressive activities within the tumor microenvironment (TME), including an inhibition of dendritic cell maturation, promotion of immune-suppressive cell infiltration and enhancement of the expression of immune checkpoint molecules.[23]

The immunosuppressive actvity of VEGF is possible through three main mechanism.[23] First, VEGF can inhibit dendritic cells maturation. VEGF inhibit dendritic cells since it secretes enzyme (2,3-dioxygenase), which inhibits immune response. Second, VEGF promotes regulatory T cell infiltration and myeloid-derived suppressor cell. Regulatory T cell suppresses immune response and myeloid- derived suppressor cell can inhibit antigen presentation and CD8+ cytotoxic T cell (CTL) activity. Third, VEGF increases immune checkpoint molecules expression on CTL, thereby, suppresses CTL activity.

BVZ can promote ATZ efficacy as the addition of BVZ could prevent the immunosuppression of immune cells. This therapy might also recruit cytotoxic $CD8^+$ T cells to the tumor microenvironment. Thus, BVZ can both act as an anti-angiogenic and immunomodulatory drug.[3]

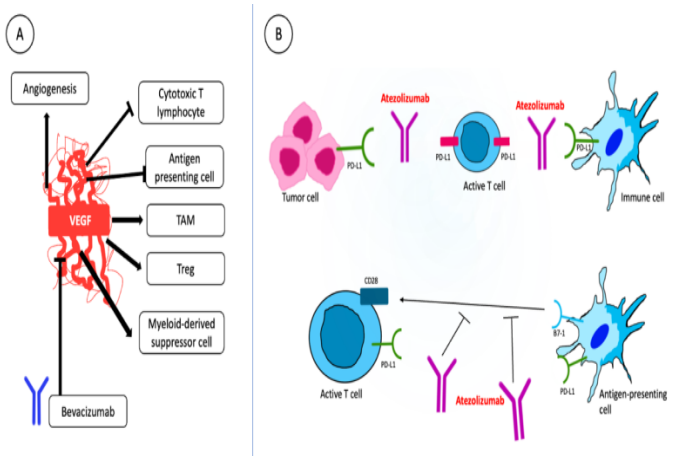

Figure 4. Mechanism of bevacizumab and atezolizumab.[20] (*A*) Bevacizumab inhibits VEGF and reverses the impact of VEGF signaling in HCC, i.e., suppressing angiogenesis, activating antigen-presenting cells and cytotoxic T lymphocytes, as well as inhibiting tumor-associated macrophages (TAM), regulatory T (T_{reg})cells and myeloid-derived suppressor cells. (*B*) Atezolizumab inhibits the interaction between PD-L1 and PD-1, preventing T-cell suppression.

A combination of ATZ and BVZ would provide a synergistic effect in treating HCC. Several studies indicate that a combination of anti-angiogenic and ICI could promote an immunity against cancerous cells.[24,25] It should be clear that immunotherapy efficacy is greatly affected by the immune effector cells within the TME. This claim is backed up by the data that shows 50-80% of patients who receives ICI are indicated to not benefit from the drug and many experiences adverse events (AE).[26] This occur because unsupportive TME such as low pH, hypoxia, and high interstitial fluid pressure, can reduce ICI efficacy.[25] Therefore, normalization of the TME with anti-angiogenic drug such as BVZ, which targets VEGF, might increase ICI efficacy and reduce serious AE from occurring.

Real-world Clinical Practice Considerations

Due to the recent usage of this combination, comparable real-world data between ATZ+BVZ and SFB are still limited. Clinical trial results for the ATZ+BVZ combination from the phase III IMbrave150 study demonstrated that ATZ+BVZ increased the survival time by 2.5 months as compared to SFB, reduced the risk of death by 42% as compared to SFB, and induced minor AE.[3] However, the enrolled patients were MTA-naïve and were C-P class A. A further study on ATZ-BVZ will need to be conducted to clarify whether this drug combination is safe for MTA-experienced patients and those with other C-P scores.

A study by Iwamoto et al.21 described an observational trial result of AT+-BVZ in patients with previous MTA history or other than ALBI grade 1. However, due to the small sample size of patients with C-P class B, a conclusion on the drug's safety for C-P class B patients could not be reached. The median progression-free survival of this study was 5.4 months. It was concluded that ATZ+BVZ could be safely administered to MTA-experienced and ALBI grade 1-3 patients.

Another study evaluated the safety and efficacy of using ATZ+BVZ in patients with viral/non-viral HCC and other C-P classes as well as other serious AE caused by ATZ+BVZ.13 The findings indicated that ATZ+BVZ performed better on HCC patients of viral origin than those with non-viral HCC. Also, ATZ+BVZ had a lower efficacy on patients with C-P class B and C. Aside from the well-known AE such as hypertension and proteinuria, variceal bleeding was a common AE of ATZ+BVZ.

An interesting study by Sho et al.22 reported the early response of ATZ+BVZ among patients who were ineligible for the IMbrave150 clinical trial. The results of this study reinforced the exemplary safety and effectiveness in the usage of ATZ+BVZ.

Based on the various studies above, it could be concluded that, in general, ATZ+BVZ is safe for use by patients with advanced HCC, and proves to presents a higher efficacy compared to SFB. However, its efficacy might decrease in patients with C-P class B and C, as well as with HCC of non-viral origin.21,13 However, due to the limited data, more studies are required to strengthen this hypothesis.

Safety and Clinical Guideline of Utilizing Atezolizumab and Bevacizumab

An updated data on the IMbrave150 study, 12 months after the clinical cut-off date of August 31, 2020, showed a consistent clinically successful treatment benefit and safety.[27] First, follow-up at a median of 8.6 months presents data that meets co-primary endpoints, overall survival (OS), and progression-free survival (PFS). Clinically meaningful improvements were also seen for OS (hazard ratio (HR), 0.58 [95% CI, 0.42, 0.79]; P<0.001) and independently-assessed PFS (PFS; per RECIST 1.1; HR, 0.59 [95% CI, 0.47, 0.76]; P<0.001). The second follow-up after 15.6 months was conducted on 156 patients (ATZ+BVZ, n=336; SFB, n=165). The OS for ATZ+BVZ patients was 19.2 months, while OS for SFB was only 13.4 months. Thus, the survival rate at 18 months for ATZ+BVZ 52%, and 40% for SFB (HR, 0.66 [95% CI, 0.52, 0.85]; P=0.0009).

Overall, ATZ+BVZ increases patients' quality of life, and AE.[3] Patients who receive ATZ+BVZ experience delayed deterioration of patient-reported quality of life (ATZ+ BVZ=median of 11.2 months; SFB=3.6 months). AE of any group in ATZ+BVZ patients were lower (98.2%, n=323) than in SFB patients (98.7%, n=154). The most frequent AE was hypertension, fatigue, and proteinuria. However, serious AE did occur more frequently in patients receiving ATZ+BVZ (38%, n=125) than SFB (30.8%, n=48). However, there was no specific incident that caused serious AE.

As of May 2020, ATZ+BVZ for patients who have not received systemic therapy has been approved by the Food and Drug Administration (FDA).[28] The recommended dose is 1,200 mg of ATZ and 15 mg/kg of BVZ, both intravenously. However, the dosing of each drug should be discussed further with the attending physician. Accordingly, ATZ+BVZ is better standard therapy than SFB, as seen from scores of OS, PFS, and AE of patients.

Conclusion

The combination of ATZ+BVZ presents a higher efficacy than SFB, according to the pharmacodynamics of ATZ+BVZ and the IMbrave150 study, as a palliative treatment for patients with advanced HCC. This notion is supported by real-world clinical findings from various studies. The pharmacodynamics of ATZ+BZ proves to be crucial to treat HCC as this combination targets both the PD-1/PD-L1 and VEGFR pathway. The incidence of adverse events were relatively low in most patients as well. However, parameters such as C-P score, ALBI score and type of HCC (viral/non-viral) would need to be considered in future studies, as data of patients with various HCC types are required. It is likely that this combination could replace sorafenib as the standard palliative care treatment of advanced HCC.

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A Case of Neuropsychiatric Systemic Lupus Erythematosus as A Sequela of Kikuchi's Disease

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Abstract

The aetiology of Kikuchi's Disease (KD), a benign condition associated with multiple lymph node enlargements, remains unknown but several reported cases associate it with systemic lupus erythematosus (SLE). A 34-year-old Indonesian woman presented with multiple painless lymph node enlargements around the neck with three weeks of fever, myalgia, arthralgia, night sweats, and weight loss. Laboratory examination showed pancytopenia and elevated ESR. HIV and tuberculin skin testing were negative. Lymph node biopsy confirmed the diagnosis of KD. One week later, despite improvement in lymphadenopathy, she developed fever. Her ANA, anti-Smith antibodies, and anti-Ribosomal-P protein antibodies were positive. She was diagnosed with SLE and managed as an inpatient with high dose methylprednisolone. One week later, the patient developed psychotic symptoms and fever. The results of Laboratory examinations with lumbar puncture were unremarkable. She was diagnosed with neuropsychiatric SLE (NPSLE) and managed with methylprednisolone, paracetamol, folic acid, alprazolam, and amitriptyline. One month later, the patient returned with three days of fever and dyspnea. Despite improvement in neuropsychiatric symptoms, pneumonia and tonsillopharyngitis were diagnosed based on physical examination and chest X- rays. Her condition deteriorated into septic shock. She suffered cardiac arrest and was pronounced dead, despite attempted resuscitation.While KD is a benign condition, diagnosis is challenging due to its rarity and similarity to other lymphadenopathy diseases. Its association with SLE and NPSLE carries poor prognosis with higher mortality rate from the disease progression and adverse medication effects. Thus, early intervention and prevention of complications are crucial in managing patientswith KD.

Introduction

Kikuchi's disease (KD), also known as necrotizing histiocytic lymphadenitis, is a benign and self-limiting condition with multiple lymph node enlargements along with a history of 2 – 3 weeks of fever. The disease's aetiology remains unknown; yet it is frequently associated with the onset of an autoimmunological process, such as systemic lupus erythematosus (SLE). Diagnosing KD clinically remains a huge challenge due to its similarities to other diseases, such as tuberculosis lymphadenopathy and malignant lymphoma. Hence, we present a case of neuropsychiatric systemic lupus erythematosus (NPSLE) in a 34-year - old woman which manifested one month after she had experienced the early manifestations of KD.

Case Illustration

A 34-year-old Indonesian woman came with multiple painless swellings around the neck, along with fever of 3 weeks duration. She also experienced myalgia, arthralgia, and night sweat, and had lost 5 kilograms from her body weight. There was no past history of previous chronic diseases or contact with tuberculosis. On physical examination, she appeared to be fully alert, oriented, and

febrile. She had multiple, enlarged, painless, mobile, bilateral, cervical lymph nodes of varying sizes, with the biggest lymph node palpated at the right posterior triangle of her neck and measuring around 1.5 cm x 1.5 cm x 1.5 cm. No lymph node enlargement was identified in other body regions. Routine hematological panel results were hemoglobin (Hb) 9.4 g/dL, white blood cells (WBC) 3,020 /µL, platelet count 92,000 /µL, and erythrocyte sedimentation rate (ESR) 68 mm/hour. Blood smear samples were taken and showed the appearance of microcytic hypochromic anemia with markers of viral infection. Tests for anti-HIV and tuberculosis showed negative results. She underwent an incisional biopsy procedure to her right cervical lymph node. Histopathological examination presented the appearance of a large area of necrosis filled with lymphoid cells, abundant karyorrhexis debris, and histiocytes, which suggested the diagnosis of Kikuchi's disease. (Figures 1, 2, 3, and 4)

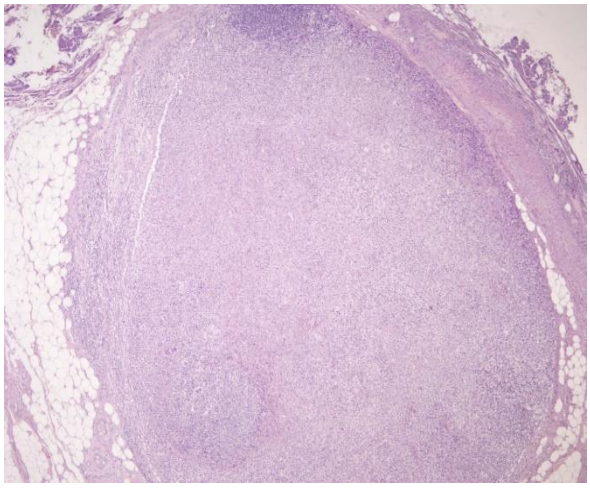

Figure 1. H&E 4x, cervical lymph node biopsy section showing a large necrotic area filled with abundant lymphoid cells.

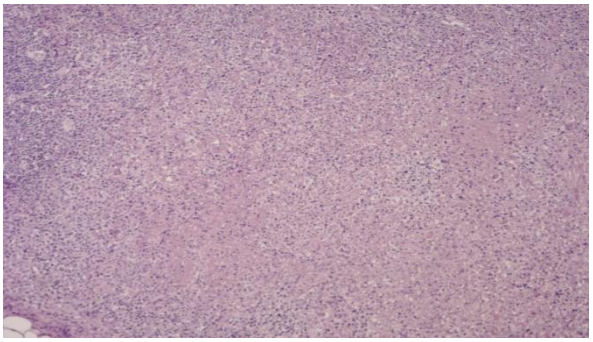

Figure 2. H&E 10x, cervical lymph node biopsy section showing debris without the appearance of any intact neutrophils around the necrotic area.

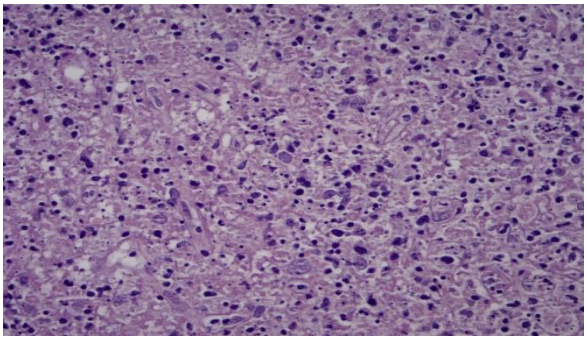

Figure 3. H&E 40x, cervical lymph node biopsy section showing abundant histiocytes with karryohexis debris. Some histiocytes appeared to have crescent-shaped nuclei.

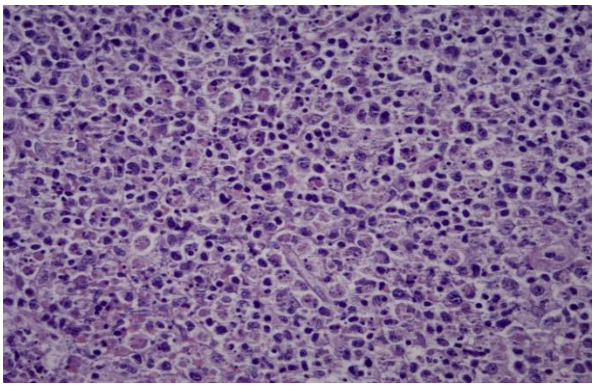

Figure 4. H&E 100x, cervical lymph node biopsy section showing the appearance of immunoblastic cells around the necrotic area.

A week after the patient underwent the incisional biopsy procedure, she presented with multiple discoid lesions around the nose, fever, arthralgia, headache, and bilateral palpebral edema. These symptoms started to show as her cervical lymph nodes regressed in size compared with her previous admission. On examination, she appeared to be alert, hypotensive, and febrile. Routine hematological panel results were Hb 8.20 g/dL, WBC 2,360 /µL, platelet count 45,000/µL and ESR 71 mm/hour. Another blood smear sample was taken and showed the appearance of microcytic hypochromic anemia along with fragmentocytes. Both liver and kidney function panels were within the normal range. Her ANA profile was positive for anti-nRNP/Smith and anti-Ribosomal-P protein antibodies. The patient was then diagnosed with systemic lupus erythematosus (SLE). She was admitted and given methylprednisolone injection 1 x 500 mg i.v for five days, and the dose was tapered off every two days. She went home with a maintenance dose of oral methylprednisolone 3 x 16 mg per day.

On a follow up examination one week later, the patient presented with anxiety and psychotic symptoms, including persecutory ideas and fluctuating disorientation, along with high fever of around 38-39^{o}C. The previously noted discoid lesions around her nose and bilateral palpebral edema had regressed after she received corticosteroid from her previous admission. Vital signs were within normal limits except for her fever. She was delirious and disoriented towards persons. Orientation towards time and place were intact. No neurological deficit was identified. Hematological panel only showed microcytic hypochromic anemia; WBC and platelet count were within the normal range. Head CT scan and lumbar puncture did not show any abnormalities. The patient was diagnosed with neuropsychiatric systemic lupus erythematosus (NPSLE) and admitted. She received methylprednisolone injection 1 x 125 mg i.v, paracetamol 3 x 1000 mg i.v, folic acid 1 x 400 µg p.o, alprazolam 2 x 1 mg p.o, and amitriptyline 2 x 10 mg p.o. After five days, she became fully alert and nonfebrile. Hence, she was discharged with a maintenance medication dose of oral methylprednisolone 3 x 16 mg, haloperidol 2 x 2.5 mg, and clobazam 2 x 10 mg.

One month later, the patient returned to the emergency department with a three day-onset of dyspnoea and fever. She appeared to be restless yet did not present any psychotic symptoms. She was hypotensive, tachycardic, tachypneic, febrile, and her oxygen saturation was 90%. Physical examination showed hyperemic pharynx and tonsils with the presence of pus, along with rhonchi and crackles heard all over both of her lungs. Chest X-ray showed nodular infiltrations on both of her lungs. Routine hematological panel showed Hb 10.10 g/dL, WBC 1,980/µL with neutrophilia, platelet count 71,000/µL, and ESR 67 mm/hour. Blood gas analysis panel showed respiratory acidosis. The patient was diagnosed with septic shock and respiratory failure caused by hospital-acquired pneumonia and suppurative tonsillopharyngitis. The patient received 15 lpm of oxygen through a non-rebreathing mask and a total of 1000 cc NaCl 0.9% fluid loading. She was given ceftazidime 3 x 2 grams i.v, levofloxacin 1 x 750 mg i.v, fluconazole 1x200mg p.o, dexamethasone 2x5mg i.v, and paracetamol 3 x 1,000 mg i.v. On the third day, she was found to be comatose ($E_1M_1V_1$) and her vital signs deteriorated. Two days later, she had cardiorespiratory arrest. Cardiopulmonary resuscitation was performed but unsuccessful. She was then pronounced dead.

Before her condition deteriorated, the patient had given consent to this case report for publication in a scientific journal without revealing her identity. The hospital's review board institution approved for publication this case report with undisclosed patient's identity for educational purposes.

Kikuchi's disease (KD), also known as necrotizing histiocytic lymphadenitis, is a rare, self-limiting, and benign condition of multiple lymphadenopathies that has a site of predilection at the cervical region. Most cases of KD are identified in a young population of about 20-30 years old, with a female to male ratio of 4:1. Higher

prevalence is found among Asian individuals.[1–4] Although exact aetiology and pathogenesis remain unclear, clinical findings in KD are similar to characteristics of viral infections, where it shows prodromal flu-like symptoms, unresponsiveness to antibiotics, and the same morphological features on lymph nodes, namely necrosis in the T-cell area, infiltrations of immunoblasts, and immunologic evidence of T-cell predominance (Figure 4). Numerous viruses, including Epstein-Barr virus, human herpes virus family, herpes simplex virus, parvovirus B19, HIV, HTLV-1 and dengue viruses have been proposed as implicated with the incidence of KD. Nonetheless, no studies have confirmed a causal relationship between viral infections and KD.[5–7]

Many KD cases have been reported to be associated with SLE. Hence, an underlying autoimmunity process in KD is postulated to have an association with other autoimmune diseases.[8–10] Due to similar aetiologies, signs and symptoms, and pathophysiology mechanisms, KD has also been described with association in Wegener granulomatosis, Sjogren syndrome, Graves' disease, and Still disease.[11] In SLE, the molecular pathogenesis is explained by aberrant innate immune responses that lead to tissue injury via release of pro-inflammatory cytokines, activation of T and B cells, and production of autoantibodies.[12] Changes in immune response are also associated with genetic and environmental factors, such as infections, that trigger the dysregulation of immune systems.[6,12] Even though the histopathology characteristic of KD simulates SLE, KD itself does not show seropositivity in markers like ANA, anti-dsDNA, etc.[6] A genetic factor that may play a role in KD that contributes to autoimmunity is the presence of particular human leukocyte antigens (HLA), particularly HLA-DPA1 and HLA-DPB1, which have been found in several autoimmune diseases including SLE. In addition to that, HLA-DPA1 has also been found in several immune-associated diseases, namely inflammatory bowel disease, post-streptococcal acute glomerulonephritis, ankylosing spondylitis, SLE, and other systemic vasculitis.[13] HLA-DP is also associated with SLE, even though the presence of HLA-DR in SLE with a higher immunostimulatory effect than HLA-DP.[14] These shared genetic predilections may explain the complexity of comorbidities between KD aSLE, and possibly other autoimmune diseases. Although several factors may link KD with the development of SLE, further studies are needed to confirm the exact mechanisms.

Sixty to ninety percent cases of KD show bilateral lymph node enlargements, with a 2-3 weeks history of fever in 30-50% cases.[7,11] Other symptoms such as weight loss, night sweats, myalgia, and arthralgia have also been reported.[15] Compared with SLE, most lymph node enlargements in KD have a predilected site at the cervical region, but lymph node involvement can happen in any body region.[16,17] 40% cases of KD show skin rashes, which can overlap with the manifestation of SLE. Rashes due to KD and SLE share the same histological findings.[18] Routine haematology profile in KD can show low haemoglobin, white blood cells, and platelet count, with a high ESR, even though there are also cases in which the haematological panels stay within normal limits. 30% cases show the appearance of atypical lymphocytes from the blood smear examination.[5] In this case, a blood smear sample was taken and showed the appearance of microcytic hypochromic anemia with markers of viral infection. This finding might relate to viral infection which started the development of KD. However, further serological examination was not performed to justify this theory.

The gold standard to diagnose KD is through histopathological examination, which shows the appearance of irregular paracortical necrotic areas that are surrounded with karyorrhexis debris and histiocytes with crescentic-shaped nuclei. Immunohistology samples show dominant presence of CD8+ T cells compared with CD4+ and minimum count of B cells, and express histiocytes antigens such as lysozyme, myeloperoxidase, and CD68.[6,19] Histopathological examination also excludes other causes of lymphadenopathies, especially to more

serious cases, such as lymphoma or malignancy.[2] KD has also been reported as an incomplete phase of lupus lymphadenopathy, which showed with a minimum count of cytotoxic T cells immunohistologically.[17]

KD is typically self-limited within 1 to 4 months. With the probability of an underlying autoimmunological process happening previously, a follow up examination is recommended for every patient diagnosed with KD. In this case, the patient showed discoid lesions as the presenting symptom of SLE one month apart from when she first experienced early manifestations of KD. According to LILACS reports in 2004, only 35 cases of KD correlate with the incidence of SLE.[19] This patient has fulfilled EULAR/ACR criteria for SLE with a total of 20 points: fever (2 points), low platelet count (4 points), discoid lesions (4 points), arthritis (6 points), and positive anti-Smith antibody (6 points).[20]

Early treatment for severe cases of SLE includes pulse therapy of high dose of intravenous methylprednisolone 1,000 mg for three days, followed by tapering off dosages, and cyclophosphamide once a month for the first six months. Hashimoto reported 535 cases of SLE had a better outcome after being treated with both steroid and immunosuppressive agents. However, there are also findings that report a similar outcome after being treated with steroid alone. In this case, the patient received 5 days of intravenous methylprednisolone without cyclophosphamide.[19] The steroid dosage was tapered off, and she went home with a maintenance oral dose of methylprednisolone 3 x 16 mg.

One week later, the patient developed flare from her SLE and showed neuropsychiatric symptoms. She fulfilled SLEDAI score of 9 points: psychosis (8 points) and fever (1 point).[21] Early assessments on SLE patients who develop neuropsychiatric manifestations should also consider risk factors for cardiovascular or cerebrovascular diseases. The diagnosis of neuropsychiatry systemic lupus erythematosus (NPSLE) is made per exclusion with the aid of CT scan, MRI, EEG, and lumbar puncture. A study in India shows 26.6% cases of SLE with positive anti-Ribosomal-P protein antibodies had psychotic manifestations.[22,23] The blood-brain barrier (BBB), antibodies, cytokines, such as tumour necrosis factor (TNF), interleukin-6 (IL-6), IL-1, and interferon alpha (IFN-α); and N-methyl-D-aspartate (NMDA) receptors are involved in the pathogenesis of NPSLE. It is disruption of BBB and binding of antibodies to their receptors responsible for the release of cytokines and toxic reactions that lead to damage to central nervous systems.[24]

Even though SLE itself is associated with a higher risk of infection that leads to a higher mortality rate, long-term use of corticosteroid can increase the burden in fighting the infections in patients with SLE.[25,26] The risk factors for infections are associated with anti-dsDNA titre, low complement levels, presence of nephritis, and long-term use of steroid and/or cyclophosphamide.[26] This patient with NPSLE was indicated for corticosteroid use and cyclophosphamide. Adjunctive treatment with short-term cyclophosphamide, in addition to steroid, carries more benefit in controlling seizures, peripheral and cranial neuropathy, and optic neuritis with no increased risk of infection compared to steroid alone.[27] 33% of SLE patients who received an equivalent dose of 7.5 mg prednisone daily suffer from E. coli, Staphylococcus pneumoniae and Streptococcus pneumoniae infections.[28] Another cohort study found an increased risk of nosocomial infection about 136 times in SLE patients who received steroid in the first three months compared with patients who did not receive steroid in their therapy regimen. A similar finding from a cohort study also reported a high prevalence of opportunistic infections caused by herpes zoster, Mycobacterium, Cytomegalovirus, and fungal infections.[29] With the high risk of infection, alternative immunomodulator agents with better side effect profiles, such as mycophenolate mofetil or IV immunoglobulin (IVIG), can be used for longer duration in patients with NPSLE.[27] In addition to that, a well-known therapy for SLE with hydroxychloroquine may be beneficial as a preventive approach in central nervous system (CNS) Lupus

associated with cerebrovascular disease; yet its role on NPSLE is still unknown.[22,30] SLE patients are also recommended to receive vaccination against influenza and Streptococcus pneumoniae, and prophylaxis therapy against possible opportunistic infection with anti-mycobacterials, antifungals, and antivirals.[31] Due to limitations in patient management in our country, patients with socioeconomic problems, such as in this case, may not eligible for optimal treatment. Therefore, in this case, an adjusted management with preventative and palliative approach is the last alternative option in addition to patient education about disease progression, complications, and associated worse prognosis. However, further studies are needed to determine the role in maximizing palliative treatment in patients with KD and NPSLE who are ineligible for other immunomodulators due to socioeconomic problems.

Conclusion

Kikuchi's disease is a rare, benign enlargement of lymph nodes with unknown aetiology and can be misdiagnosed as tuberculosis lymphadenopathy or malignant lymphoma. KD may be a benign and self-limiting disorder, but the presence of SLE in this patient carried poor prognosis. A comprehensive, multidisciplinary approach in managing NPSLE with its complications is a must due to a higher risk of infections, putting the patient at a higher risk of mortality. Thus, a follow-up plan in KD cases is crucial to assess any potential autoimmune sequelae with an appropriate investigation, prevention of complications, and treatment plan.

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Authorship

Theo Audi Yanto evaluated and treated the patient. Nathania Raphaeli Mulia performed data collection from the patient and her medical files. Theo Audi Yanto, Nathania Raphaeli Mulia, and Abraham Fatah drafted the manuscript. Nathania Raphaeli Mulia and Abraham Fatah performed data analysis and interpretation. Theo Audi Yanto supervised and gave expert advice regarding the manuscript. Theo Audi Yanto, Nathania Raphaeli Mulia, and Abraham Fatah gave the final approval of the version to be published. All authors declared that all the images and figures in this manuscript is/are author's own work and/or has obtained necessary permission to re-use the content from the authors and publisher of respective materials.

Conflicts of interest

None

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Theo Audi Yanto

Case Report: Management Penetrating Brain Injury Across Middle Third of Superior Sagittal Sinus

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Abstract

Background: Penetrating cranial injuries are rarely reported on thick parietal bone. Goal of its management include removal of the foreign object while minimizing furher damage to the brain and associated neurovascular structures, also prevent further complications.

Case Description: We report a case of a 22-year-old male presented with machete stucked in his head following an accidentally fell down of the weapon from a coconut tree. The cranial location affected were midparietal. He was disoriented on admission, with neither neurological focal signs nor seizure. Computed tomography (CT) revealed that the object penetrate middle superior sagittal sinus. After emergency craniotomy to remove the objects, debridement, dural sinus repair were performed. Recovery was complete without sequelae.

Conclusion: Laceration of the middle thirds of the superior sagittal sinus require special handling and care during surgery. Operative approach and treatment strategies are among the most important considerations to achieve the best patient outcomes.

Introduction

Penetrating brain injury (PBI) are relatively uncommon, representing about 0.4% of head trauma.[1,2] It may caused by either low velocity sharp objects or high velocity projectiles.[3] Morbidity and mortality following PBI remains high due to severe brain and vascular injury, also the secondary lesions from edema and sepsis that may occur.[1] We report a case in which a foreign body invaded middle third of superior sagittal sinus (SSS) through the midparietal bone.

Case Description

A 22-year-old male, a pedestrian who received on the head long sharp iron machete in free fall from a 15 metres tall coconut tree. He was admitted after 2 hours of injury, complained with severe headache. History of convulsion, and signs of meningitis were absent. At the emergency room, he was clinically drowsy, Glasgow Coma Scale 14/15, stable vital signs without focal neurologic deficit presenting a parietal medial wound of 5 cm crossed by a sharp piece of 70 cm long weapon. (Figure 1)

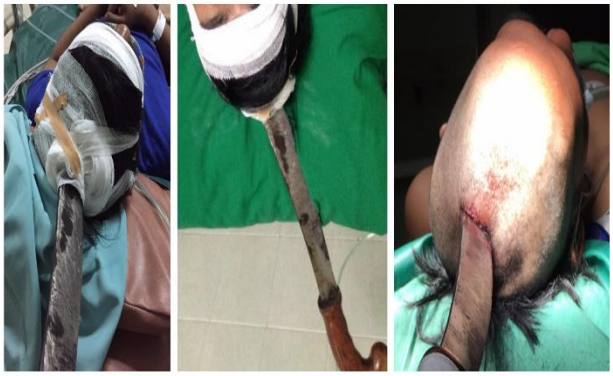

Figure 1. Macroscopic view of a penetrating craniocerebral injury caused by a machete, whose point of penetration is visible in the mid parietal region

Head computed tomography (CT) scan and 3D reconstruction was performed showing an open depressed skull fracture; with the weapon lodged in the mid parietal bone with a depth of approximately 6 to 7 cm. There was impression of both external and internal parietal bone tables and caused a slight subarachnoid hemorrhage. Because of the artifact, we could not determine the relationship between the objects and superior sagittal sinus (Figure 2).

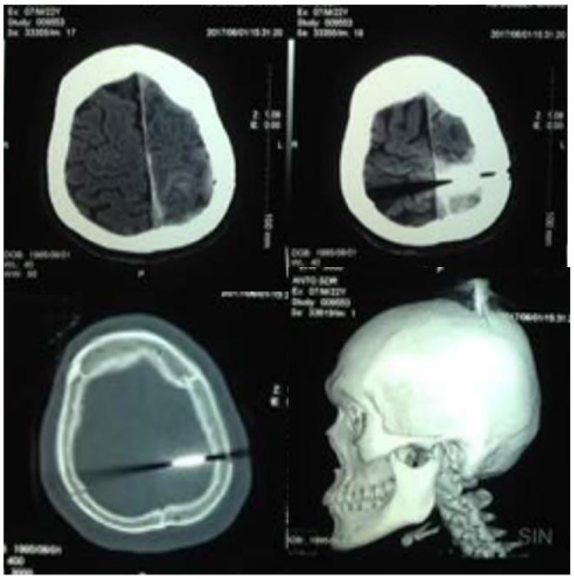

Figure 2. Computed tomography (CT) of the head and skull showed a hyperdense foreign body on the left side of the parietal region the associated presence of left cerebral contusion and subarachnoid hemorrhage

After blood transfusion preparation, antitetanus and prophylactic antibiotics, he underwent surgery under general anesthesia in supine position, slightly flexed neck. Surgical exploration was performed as follow: with a mid parietal horse shoe skin flap incision, the objects was removed along with a bone flap performed by 4 burr holes from each side of the superior sagittal sinus. A parasagittal craniectomy was done 3-4 cm around the objects, a fascia for dural graft was prepared. Dural cross opening with center at the site of the stab entry. Subsequently, we detected the penetrating point using a microscope

The objects was gently extracted keeping in line with its trajectory, removed by directly looking at its tip intracranially, followed by continuous irrigation to prevent air embolism. The dura was irregularly torn involving lateral wall of SSS with underlying 5 cm deep laceration of parietal cortex.The lateral sinus wall was gently pressured with cottonoid for few minutes and packed with absorbable hemostatic agent; Gelfoam (Pfizer, Brooklyn, New York, USA) and Surgicel fibrillar (Ethicon, Somerville, New Jersey, USA).

Subsequently, duraplasty using facial graft was performed to stop profuse bleeding. After careful hemostasis, the wound was inspected under direct vision for any bleeding, or cerebrospinal fluid flow. Bridging veins are preserved. The brain was thoroughly irrigated using normal saline and antibiotic. We excised bony fragments to prevent infection. The bone flap wasn't put back due to brain edema. Blood pressure, volume and viscosity were carefully monitored during and after surgery to assure sinus patency. Removed foreign body was cultured for aerobic, anaerobic, or fungal pathogens. All cultures were negative.

The patient improved post-operatively, he was awake, more coherent, ambulating without difficulty, no focal neurologic deficits, sign of infection and neither sign of raised intracranial pressure. He was managed with anti edema, analgesics, and anticonvulsants.

For antibiotics, we gave Ceftriaxone 4g/ day and Metronidazole 1500 g/ day. Patient was discharged on the 7th post-operative day without any sequele (Figure 3).

Figure 3. Post operative general condition

Discussion

PBI is defined as a lesion caused by an object that gets through the skull and the dura mater and remains inside, can result from a variety of objects, both low and high velocity objects which may cause significant damage to the brain resulting in severe neurological deficits. The traumatic dural venous sinus injury is one of the most dangerous complications of PBI, with its incidence to be raised to 4-12% of all brain trauma case, with a reported mortality rate of 41%. [4]

Usually, it occur on thin bones, especially the orbit and the squamous temporal bone. Parietal region is rarely traversed by a penetrating object as in our case.[5,6,7] Sharp objects causing PBI is also relatively uncommon, most of them are accidental injuries. Elkatatny et al, reveals most common cause traumatic dural venous sinus injuries was heavy object (45 %), road traffic accident (25%) followed by fall from height injury (20%), and sharp objects (10%).[8] Unusual PBI have been scattered reported to be caused by tree branches, sticks and fragments of wood, bamboo groove, nails, metal poles, ice picks, keys, pencils, chopsticks, and power drills.[9,10,11] Increased vascular complications and mortality were noted in penetrating retained objects compared to those which did not, because it tend to be deeply penetrating with a potential for more cerebral and vascular injury.[12,13]

According to its localization, most common site of dural sinuses injuries are superior sagittal sinus (75%), followed by transverse sinus (15%), sigmoid sinus (5%) and multiple sinus (5%). These injuries may be fatal due to the potential to cause prolonged disability or death, either due to profuse venous bleeding, venous hypertension, ischemia, hydrocephalus or increased intracranial pressure due to impaired cerebral venous drainage. Although rare, post traumatic dural sinus thrombosis may happen and lead to hemorrhagic infarction and fatal conditions.[8]

As preoperative study, it is necessary to evaluate not only head CT but also 3D reconstruction and angiography. Sinus injury should be suspected if preoperative CT shows hematoma overlying venous sinuses, or fractures which crossed the sinus. Due to lack facilities, we did not perform further angiographic evaluation prior to surgery.[14]

The surgical management depends on the extent of injury and structures involved. It is recommended to perform surgery within 12 hours after the injury to prevent infection.[15] Our treatment was immediate and identical to that reported by other authors, consists of wound exploration, craniotomy/ craniectomy, debridement of devitalized brain tissue, evacuation of hematoma, careful extraction foreign body and retained fragments if possible, bleeding control, vascular repair, lavage of the wound and water tight dural closure.[16,17] Continuous irrigation over the sinus during the elevation of the foreign body fragments are suggested to reduce the chance of embolism.

The use of broad spectrum antibiotics is recommended to prevent infectious complications. [8]

In our case, surgical removal of dthe foreign body from the bone may worsened SSS injury. In concordance with Fischer et al and Nussbaum et al, firstly, we tried to have a direct visualization through the puncture side. Skin flap and craniotomy should extend across the midline to permit visualisation of both sides of the sinus. Then parts of the bone were removed in order to remove the blade from the bone.[18,19] Direct visualization of foreign object should be achieved before its removal. Thorough debridement and irrigation along the exposed trajectory has a great significance to prevent postoperative infection and CSF leakage.[20,21]

Bleeding occurred due to sinus wall laceration during removal the tip of the machete. Various operative technique for sinus injury treatment including direct compression by gelfoam, stitching the dura up to adjacent bone, direct stitching of dural tear, and muscle duraplasty . During direct compression of the sinus, further complication should be considered. Sinus occlusion / thrombosis may occur following free muscle duroplasty or coagulation system activation due to damage endothelial lining of the sinus wall.[8] If there was total destruction of the sinus causing uncontrollable haemorrhage, however, ligation of the middle and posterior thirds might be considered, since it is not necessarily associated with a poor prognosis.[22]

Cerebral infections or meningitis are fatal complications.[20] Infection is the main complication of PBI with a reported overall rate of 64–70% and mortality rate of 14–57% In previous publications, prophylactic use of broad-spectrum antibiotic was suggested within 7–14 days after the injury, [22,23] while others indicated that antibiotic therapy should be administrated according to the findings of cerebrospinal fluid culture.[20] Intravenous antibiotics, laboratory examination and closed observation of any sign of infection are mandatory during post operative hospitalization.

Approximately 30%-% of patients with penetrating brain injury develop seizures. Between 4% and 10% have their first seizure within the first week of injury, and 80% of patients have a seizure during the first 2 years.[22,24] Antiepileptic medication has been shown to prevent the occurrence of early seizures. For this reason, prophylaxis is recommended for the first 7 days after injury.[23] Our patient had antiepileptic medication during hospitalization due to brain tissue damage and edema that had raised increased concern for risk of posttraumatic seizures.

During hospitalization, any sign of increased intracranial pressure should be taken into consideration. Post operative imaging follow up including non-contrast Head CT to assess hemorrhage, or venous infarction in the form of petechial hyperdensity and hypodense edema which may be seen in the cortical grey matter and sub cortical white matter due to sinus obstruction. Follow up MRV should be a good definitive diagnostic tool for those suspected cases. [8] Early detection and early management with anticoagulation of this potentially treatable condition will result in good outcome. In our case the patient was not showed any sign of raised ICP, we did not perform any post operative angiographic imaging studies, and the patient was not placed into anticoagulant therapy due to risk of postoperative bleeding

Conclusion

Penetrating brain injury with superior sagittal sinus tear is uncommon. It can pose unique difficulties and lifethreatening conditions. Therefore, it require rapid intensive resuscitation, comprehensive pre and post operative imaging study and careful individualized neurosurgical treatment. Further complication during recovery period should always be taken into consideration.

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