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ORIGINAL ARTICLE

Diagnostic Patterns of Suspected Covid-19 Patients Using Scor Covid-19, PCR Test and Serological Test in Dr. Soetomo Hospital Surabaya, Indonesia

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ABSTRACT

Introduction: To find out the diagnostic pattern of COVID-19 using RT-PCR or a rapid antibody test in the suspected group patients.
Methods: The study was conducted in Dr. Soetomo General Hospital (referal hospital for covid-19, 1500 beds). The study used data on patients with suspected covid-19 who were hospitalized at the Dr. Soetomo General Hospital in Surabaya.
Results: There were 200 suspected COVID-19 patients enrolled in this study, the main complaints of cough, fever, dyspnoea, around 69.5%, 75%, and 76.5%, respectively. Although not a common symptom, it seems that anosmia (14%) is typical for COVID-19. Based on this scoring system, a total of 196 patients had a high risk of being infected with COVID-19, and 125 (64%) of them finally showed a positive PCR test. PCR test mostly positive (62.5%), while serological test (rapid imunoglobulin test) mostly non reactive, but there were nonsignificant different between PCR and Serological test (p=0.16 OR: 1.5(0.84-71). Furthermore, if we compare the various existing variables, namely the covid-19 score, immunoglobulin rapid test, and radiological examination, only the radiological examination results can be used as a strong predictor of positive PCR results (p=0.005, OR: 1.68 (0.17-16.43). In this study, we found that abnormal chest radiographs are a good parameter for diagnosing COVID-19, (OR: 2.92; 95% CI, 1.34 -6.34).
Conclusion: The initial radiological examination combined with the clinical symptoms of Covid-19 is the most important thing to predict the presence of this disease.

Keywords: Covid-19, Immunoglobulin rapid test, Anosmia, Indonesia

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INTRODUCTION

Corona virus disease -19 (COVID-19) was identified in January 2019 in the city of Wuhan, China. This disease is caused by SARS-CoV-2. This virus is very contagious, spreading in all over the world and become pandemic in 20 March 2020 (WHO-A, 2020).

This disease mainly affects the respiratory system, although it can affect other organ system, mostly around 80% symptoms resolve without treatment within five to seven days of symptom onset. However, about 20% of patients will develop serious disease most notably pneumonia, acute respiratory distress syndrome, sepsis or septic schock, thrombotic stroke and myocardial infarction (WHO-A, 2020; Salehi et al., 2020; Huang et al., 2020; Yang et al., 2020).

To establish a definite diagnosis using real-time PCR using nasal and throat swab. While using serology rapid test for diagnosis COVID-19, the accuracy is only 30% up to 70% after the second week.

Antibody rapid test especially is used for epidemiological purposes. Clinical sign or symptoms and serological examination or radiological examination can be used to make a presumptive diagnosis, in areas that do not have PCR facilities (WHO-B, 2020).

The morbidity and mortality rates in Indonesia are still quite high. Currently, there are more than 580 000 cases, with the death of more than 15000 patients. Therefore it is necessary to do further research to find out the diagnostic pattern of COVID-19 using RT-PCR or a rapid antibody test in the suspected group patients.

This study aims to determine the diagnostic pattern of COVID 19 at Dr. Soetomo Academic General Hospital Surabaya, the difference between the use of RT-PCR and rapid test in the suspected group, in Dr. Soetomo Hospital Surabaya. So that in the end the detection of COVID 19 cases can be mapped for use of RT-PCR or with an appropriate antibody rapid test or radiological examination.

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METHODS

Population and health care setting

The study was conducted in Dr. Soetomo General Hospital (referal hospital for covid-19, 1500 beds). The study used data on patients with suspected covid-19 who were hospitalized at the Dr. Soetomo General Hospital in Surabaya from April 2020 to June 2020 in accordance with the inclusion and exclusion criteria.

Study design and inclusion procedure.

Inclusion Criteria

Suspected Covid-19 patients who were hospitalized at the Dr. Soetomo General Hospital in Surabaya from April 2020 to June 2020.

Exclusion Criteria

Suspected Covid-19 patients with incomplete data, namely no date of admission to the hospital, and incomplete records, especially the diagnosis.

Prosedure of the research

The study was conducted by looking back at the medical records of Covid-19 patients who were hospitalized at the isolation room. Demographic data, subject characteristic, and underlying comorbidities, symptoms and signs at presentation, value of Covid-19 score, also complication and outcome were colected and evaluated.

Rreal time polymerase chain reaction (RT-PCR) testing was performed for confirmation of SARS-CoV-2, and laboratory test of SARS-CoV-2 IgM/IgG was also performed for all patients. A chest radiograph were obtained at baseline and as determined clinically by heatlh care practitioners on case by case basis.

RESULTS

Characteristics of research subjects

There were 200 suspected COVID-19 patients enrolled in this study in dr Soetomo General Hospital. All patients underwent rapid antibody test, RT-PCR, laboratory, and imaging examination during treatment. The patient is stratified using a scoring system to assess the risk of being infected with COVID-19. Based on this scoring system, a total of 196 patients had a high risk of being infected with COVID-19, and 125 (64%) of them finally showed a positive PCR test.

Most patients presented with complaints, the main complaints of cough, fever, dyspnoea, around 69.5%, 75%, and 76.5%, respectively. Although not a common symptom, it seems that anosmia (14%) is typical for COVID-19.

PCR test mostly positive (62.5%), while serological test (rapid immunoglobulin test) mostly non reactive, but there were nonsignificant different between PCR and Serological test (p=0.16 OR: 1.5(0.84-71).

Table 1 Characteristic Patients

Demographic Characteristic	Dr. Soetomo Hospital N(%) (200 patients)
Age, mean (SD), y	51.2 (14.1) years
Age > 60 y	55 (27.5)
Female	85 (42.5)
Cough	139 (69.5)
Nasal congestion	60 (30)
Dyspnea	150 (75)
Fever	153 (76.5)
Anosmia	29 (14)
Diarrhea	39 (19.5)
Nausea or vomiting	61 (30.5)
Abdominal pain	33 (16.5)
Comorbid conditions	Dr. Soetomo Hospital N(%)
Diabetes mellitus	82 (41.0)
Hypertension	74 (37.0
Chronic kidney disease	60 (30)
Obesitas	3 (1.5)
Malignancy	19 (9.5)
Autoimmun diseases	7 (3.5)
Heart disease	15 (7.5)
HIV	3(1.5)
Scoring at admission	Dr. Soetomo Hospital N(%)
5-8	4 (2)
9 >	196 (98)
Prior hospitalization symptoms	Dr. Soetomo Hospital N(%)
2- 3 days	37 (18.5)
4 – 7 days	131 (65.5)
8-14 days	32 (16)

Table 2 Diagnostic Laboratory

	Positive or reactive: N(%)	Negative or non reactive:N(%)
PCR	125 (62.5)	75 (37.5)
Rapid imunoglobulin test (IgM/IgG)	90 (45)	110 (55)

Furthermore, if we compare the various existing variables, namely the covid-19 score, immunoglobulin rapid test, and radiological examination, only the radiological examination results can be used as a strong predictor of positive PCR results (p=0.005, OR: 1.68 (0.17-16.43).

Table 3 Comparison between Serological, scor Covid-19, and Chest X-ray Result with PCR Test on Admission

	PCR (-)	PCR (+)	Chi-Square test
IgG/M: non reactive	46	64	p=0.106
IgG/M: reactive	29	61	OR: 1.5 (0.84-71)
Scor: 5-8	2	73	p=0.482
Scor: 9 >	2	123	OR: 1.68 (0.17-16.43)
Chest X rays: normal	19	56	p=0.005
Chest X rays: infiltrat +	13	112	OR: 2.92 (1.34 -6.34)

In this study, we found 65.5% of the final confirmatory diagnosis of Covid-19, this shows that there is still a possibility that non-Covid-19 (discharded) sufferers will

enter initial care as Covid-19.

Table 4 Final Diagnosis on Discharge

Final Diagnosis	Dr. Soetomo N(%)
Suspected Covid-19	46 (23)
Probable Covid-19	29 (14.5)
Confirmed Covid-19	125 (62.5)

DISCUSSION

To control the impact of its spread, early detection procedures are needed. WHO recommends RT-PCR examination as the gold standard for examining COVID-19, because as a developing country the fulfillment of these facilities cannot be achieved ideally. Therefore, a rapid antibody test that can be widely used is needed, does not require special facilities and is cheap to help detect COVID-19. A study reported that the antibody rapid test sensitivity and specificity were 64.8% and 98%, respectively (Ricco et al., 2020). Supports another study that divided the rapid test according to its working principle, which reported a combined sensitivity for LFIA of 66% (95% CI 49.3-79.3), and a combined specificity of 96.6% -99.7% (Bastos et al., 2020). In this study, the sensitivity obtained was only 55.28% and the specificity was much lower, namely 60.38%. These results are due to patients presenting for treatment varying in duration of symptoms from onset.

In this study, we found that abnormal chest radiographs are a good parameter for diagnosing COVID-19, (OR: 2.92; 95% CI, 1.34 -6.34). This finding is in line with previous studies that indicated chest radiographs were stated in COVID-19 patients often show bilateral lower zone consolidation, which peaks in 10-12 days from the onset of the disease (Wong et al., 2020). Another report showed that chest radiograph had a sensitivity of 89.0% (95% confidence interval (CI), 85.5% -91.8%), a specificity of 60.6% (95% CI, 51.6% -69.2 %), 87.9% positive predictive value (95% CI, 84.4% -90.9%), and a negative predictive value of 63.1% (95% CI, 53.9% -71.7%). These results indicate that the CXR examination together with RT-PCR for triage of suspected COVID-19 patients can provide a safe and efficient workflow (Salehi et al., 2020; Schiaffino et al., 2020; Shi et al., 2020).

A scoring system for COVID-19 triage is established in our hospital based on the latest reports on the risk factors, signs and symptoms of patients with COVID-19. This system is created to determine the need for isolation protocols. This study is the first study to evaluate the performance of our scoring system. The results showed that the scoring system was not correlated with the PCR test. A scoring system for COVID-19 triage is essential for alerting health workers and implementing the necessary protocols to prevent disease transmission. Several researchers developed an early warning system to identify highly suspicious COVID-19 patients during surgical planning. Based on literature search, the risk factors for COVID-19 are as follows: history of exposure, fever, cough, and radiographic infiltrates (Greenhalgh et al.,2020; Jacobi et al., 2020; Aljondi et al., 2020; Bhaskar et al., 2020). The components in this scoring system are relatively similar to our in-hospital scoring system, although the higher scores do not reflect a higher probability of COVID-19 confirmation. These results may be due to the limited sample size of our study, and we only included suspects or confirmed COVID-19 patients admitted to internal medicine isolation wards, so there would be patient selection bias.

CONCLUSION

Examining COVID-19, according to WHO standards, is still a challenge for developing countries such as Indonesia. The workload of the RT-PCR examination laboratory leads to a longer waiting period for examination results. On the other hand, the shortest possible diagnostic time is the key to controlling a pandemic. The initial radiological examination combined with the clinical symptoms of Covid-19 is the most important thing to predict the presence of this disease.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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ORIGINAL ARTICLE

Correlation Between HCV RNA Viral Load And HOMA-IR In Chronic Hepatitis C Patients

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ABSTRACT

Introduction: Insulin resistance (IR) is one of the extrahepatic complications of hepatitis C virus (HCV) infection that needs to be recognized early. HOMA-IR is an effective way to measure insulin resistancy. Core proteins, NS-3, and NS-5 are the main components of HCV RNA proteins which are involved in the incidence of IR. Seeing this, a hypothesis was developed that the level of HCV RNA viral load was related to the HOMA-IR. This study was designed to identify the correlation between HCV RNA viral load with HOMA-IR in chronic hepatitis C patients.
Methods: We conducted a cross-sectional approach from the medical record of chronic hepatitis C patients at the outpatient clinic dr. Soetomo Hospital, Surabaya. A total of 30 patients aged >19 years old with complete medical records were included. Clinical and laboratory (including HCV RNA viral load level and HOMA-IR) data were obtained from the availability of medical records.
Results: A total of 30 chronic hepatitis C patients, 17 (56.7%) were women and 13 (43.3%) were men, with mean age was 50.90 ± 7.17 years. The median of HCV RNA viral load level was 3,14 x106 IU/ml and the median of HOMA-IR was 4.50. The result of the Spearman correlation test showed a moderate positive association between HCV RNA viral load and HOMA-IR (r=0.537 ; p=0.002).
Conclusion: A positive moderate correlation was obtained between HCV RNA viral load with HOMA-IR in chronic hepatitis C patients.

Keywords: Chronic hepatitis C, HCV RNA viral load, HOMA-IR

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INTRODUCTION

Hepatitis C virus (HCV) infection is an important cause of liver disease in the world. Recent data estimates that 2.8% of the world's population - more than 184 million people - are infected with HCV. In 2016, WHO estimates that 399,000 people died from hepatitis C with various complications (Jafri & Gordon, 2018; Jefferies, 2018). Chronic hepatitis C is reported to be associated with a variety of diseases and complications, both intrahepatic and extrahepatic. Insulin resistance is one of the extrahepatic complications of HCV infection that needs to be recognized early because it can develop into other complications with serious consequences (Huang et al., 2011). HCV RNA protein is known to be involved in the development of insulin resistance in HCV infection (El-Zayadi & Anis, 2012).

Epidemiological studies show chronic hepatitis C triggers insulin resistance by 25% which will accelerate the progression of liver fibrosis, resistance to anti-viral treatment, and the development of hepatocellular carcinoma (Mohamed et al., 2011, Bernsmeiere & Heim, 2009; Mohamed HR et al., 2009; Bugianesi et al., 2005). Insulin resistance is a major pathogenetic factor of diabetes mellitus (DM) type 2 (Machado & Cortez-Pinto, 2009).

Several studies have reported that chronic hepatitis C patients have a threefold increased risk of developing insulin resistance and DM compared to healthy individuals or patients with hepatitis B virus infection (Huang et al., 2011). Liver cirrhosis is a diabetogenic disease. The risk of DM in cirrhosis associated with HCV is 3 to 5 times greater than in cirrhosis associated with other causes. The prevalence of DM in the population affected by HCV infection without liver cirrhosis is around 7.6 -21%, which is 2 to 4 times higher than in other chronic hepatitis (White, 2008). One of the effective and efficient ways to measure insulin resistancy is the Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) (Romero-Gomez, 2006).

The components of the HCV RNA protein that are mainly involved in the occurrence of insulin resistance are core protein, NS-3 protein, and NS-5A protein. HCV core protein induces TNF-α expression, decreases VLDL, increases lipogenesis, thereby inducing insulin resistance (El-Zayadi & Anis, 2012). NS-3 protein has been shown to induce oxidative stress and increase NOX-2 regulation, thereby accelerating the production of ROS which ultimately leads to liver fibrosis and insulin resistance (Bureau et al., 2001). NS-5A protein induces endoplasmic reticulum (ER) stress that

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leads to insulin resistance directly or indirectly by upregulation of the protein phosphatase 2A (PP2A) cellular gene (Christen et al., 2007). Looking at the involvement of HCV RNA protein components in the incidence of insulin resistance, a hypothesis was developed that the HCV RNA viral load was associated with an increased incidence of insulin resistance (Mohame et al., 2011).

The high prevalence of insulin resistance among patients with HCV infection has been consistently reported, and there is growing evidence to support this concept (Knobler et al., 2000; Mehta et al., 2000; Caronia et al., 1999; Mason et al., 1999). However, negative results regarding the association between HCV infection and insulin resistance have also been reported (Papatheodoridis et al., 2006; Mangia et al., 1998). The relationship between HCV RNA viral load and the incidence of insulin resistance remains controversial, while HCV RNA viral load examination is the initial routine check before starting therapy, so it is potential for screening insulin resistance in a large population of chronic hepatitis C. This study aims to analyze the correlation between HCV RNA viral load and HOMA-IR in patients with chronic hepatitis C thus it can predict the occurrence of complications of HCV infection, predict outcome of therapy, and assess prognosis of the disease from an early stage.

METHODS

This analytical observational cross-sectional study was conducted in the gastrohepatology outpatient clinic Dr. Soetomo Teaching Hospital, Surabaya. All medical records of chronic hepatitis C patients from September 2016 to January 2017, aged >19 years old were analyzed.

All patients who has been diagnoses of chronic hepatitis C and examined HCV RNA viral load, fasting blood glucose, and fasting insulin were included. Data of demographic, clinical, and laboratory were obtained from the availability of medical records. The study was approved by the Local Ethics Committee. All data analyzed statistically using SPSS version 23. For the normality test using the Kolmogorov-Smirnov test and then the data examined using Spearman correlation test.

RESULTS

A total of 30 subjects,13 males (43.3%) and 17 females (56.7%), with chronic hepatitis C, aged >19 years old were analyzed as seen in table 1. Data that were normally distributed would be presented as mean ± SD, while data that were not normally distributed would be presented as median (minimum value-maximum value). The mean age of the study subjects was 50.90 ± 7.17 years, the youngest was 36 years old and the oldest was 59 years old.

From the characteristics of the laboratory results, the mean hemoglobin was 13.37 ± 1.53 g%, the mean leukocyte was 5.670 ± 1.725/uL, and the mean platelet count was 187 ±74.45 x 10^3/uL. The mean value of AST was 86.70 ± 52.49 U/L and the mean value of ALT was 78.63 ± 38.88 U/L. Bilirubin examination revealed a wide range data with an abnormal distribution. The direct bilirubin examination obtained the median value was 0.61 mg/dL with the lowest value was 0.11 mg/dL and the highest value was 2.03 mg/dL. While the median of total bilirubin was 0.99 mg/dL, with the lowest value was 0.27 mg/dL and the highest was 2.52 mg/dL. Blood albumin levels were still within normal limits with a mean of 3.95 ± 0.31 g/L.

Table 1 Characteristic of Study Subjects

Variabel	n = 30
	Mean ± SD or Median (min-max)
Age (years old)	50.90 ± 7.17
Haemoglobin (g%)	13.37 ± 1.53
Leukocyte (/uL)	5.670 ± 1.725
Platelet (x 10^3 /uL)	187 ± 74.45
AST (U/L)	86.70 ± 52.49
ALT (U/L)	78.63 ± 38.88
Albumin (g/L)	3.95 ± 0.32
Direct bilirubin (mg/dL)	0.61 (0.11 – 2.03)
Total bilirubin (mg/dL)	0.99 (0.27 – 2.52)
HCV RNA (IU/ml)	3.14 x10^6 (3.37 x10^5- 3.91 x10^7)

AST, aspartate aminotransferase; ALT, alanin aminotransferase; HCV RNA, hepatitis C virus ribonucleic acid

The metabolic characteristics of study subjects based on anthropometric data and laboratory (table 2). The median BMI of the study subjects was 23.76 (16.00 - 24.8) kg/m^2. The mean abdominal circumference of male subjects was 84.07 ± 5.93 cm and female subjects was 75.23 ± 5.46 cm. The mean blood cholesterol level was 154.77 ± 27.18 mg/dL. The mean fasting blood sugar level was 101.03 ± 18.80 mg/dL. Fasting insulin levels were measured after the study subjects fasted for 12 hours and obtained a median of 12.88 (3.54 – 46.38) mU/L.

In this study, data collected on HCV RNA viral load levels and HOMA IR calculations based on fasting blood sugar and fasting insulin laboratory data from the medical records of 30 patients who were concluded. The number of HCV RNA viral loads in the subjects of this study was obtained median of 3.14 x106 IU/mL, with the lowest level 3.37 x105 IU/mL and the highest level 3.91 x107 IU/mL. This study showed the value of HOMA IR subjects with a median of 4.50, with a minimum value range of 0.84 and a maximum value of 18.10.

Scatter plot of correlation between HCV RNA viral load level with HOMA IR value (Fig. 1) showed a positive linear relationship where the HOMA IR value tend to increase according to the increase in the number of HCV RNA viral load. Testing the significance level of the correlation between HCV RNA viral load and HOMA IR was carried out using the Spearman correlation test because the distribution of HCV RNA viral load data and HOMA IR value data were not normally distributed. Our study found that the result of Spearman correlation test showed a statistically significant positive correlation between HCV RNA viral load and HOMA IR (r= 0.537; p= 0.002).

Table 2 Metabolic Characteristic of Study Subjects

Variabel	n = 30
	Mean ± SD or Median (min-max)
BMI (kg/m^2)	23.76 (16.00 – 24.8)
Abdominal circumference (cm)	
Male	84.07 ± 5.93
Female	75.23 ± 5.46
Cholesterol (mg/dL)	154.77 ± 27.18
FPG (mg/dL)	101.03 ± 18.80
Fasting insulin (mU/L)	12.8 (3.54– 46.38)
HOMA-IR	4.50 (0.84 – 18.10)

BMI,body mass index; FPG,fasting plasma glucose; HOMA-IR, homeostasis model for insulin resistance

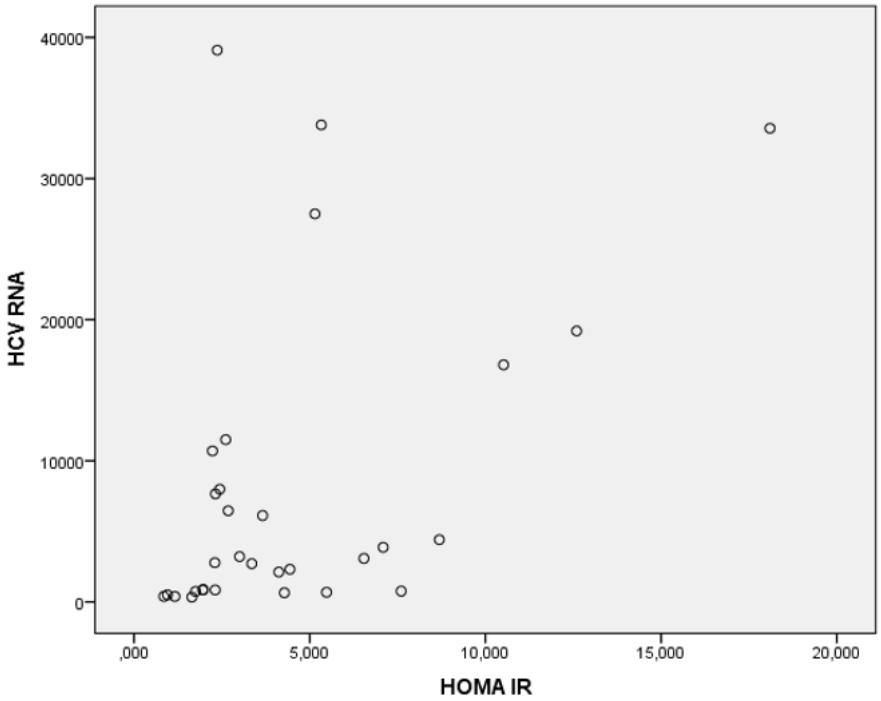

Figure 1. Scatter plot of correlation bet ween HCV RNA with HOMA-IR

DISCUSSION

In this study, we conducted 30 secondary data in the form of medical records of chronic hepatitis C patients who had met the inclusion and exclusion criteria with a percentage of 13 males (43.3%) and 17 females (56.7%), with more female subjects. This result consistent with previous studies (Umumararungu et al., 2017; Olmedo et al., 2017). The transmission route of HCV infection in this study was mostly through family relationships, followed by a history of surgery, blood transfusions, and having tattoos. Meanwhile, data from Direktorat Jenderal Pengendalian dan Penyehatan Lingkungan (Dirjen P2PL) Indonesia in 2007-2012 showed that the highest number of cases was found in men, with the ratio of men and women is 83% : 17% and the transmission route was mostly in intravenous drugs users, then in hemodialysis patients, family with hepatitis C infection, and patients with blood transfusion history (Dirjen P2PL, 2017). Differences in the results of this study can be caused by the difference of study methods, the inclusion and exclusion criteria used.

The acute manifestations of HCV infection range from asymptomatic (80%) to symptomatic (20%), both mild and severe. Patients who suffer from mild symptoms as well as those who are asymptomatic tend to ignore this disease and fall into a chronic condition. This causes the majority of chronic hepatitis C patients aged > 50 years (Dirjen P2PL, 2017). In this study, the mean age of subjects was 50.90 ± 7.17 years old. The results of this study are not much different from previous studies (Niu et al., 2016; Vagu et al., 2013; Barut et al., 2012). In our study, the result of the mean fasting blood glucose of study subjects consitent with the previous study (Li et al., 2019; Aksu et al., 2012). The mean was 101.03 ± 18.80 mg/dL. This result indicated that the

population in this study already had higher fasting blood glucose level than normal. Fasting blood sugar in HCV infection increased due to several reasons (Parvaiz et al., 2011). HCV RNA components, especially core protein, NS-3, and NS-5, the presence of excess iron, and the occurrence of liver fibrosis in HCV infection were some of the things that affect fasting blood sugar, so that affect HOMA IR value as well. Increasing fasting blood sugar can lead to insulin resistance.

HCV RNA viral load is the number of hepatitis C virus particles in every 1ml blood volume. Some of these virus particles are copies of the viral genetic material that circulates throughout the body. HCV RNA level of 800.000 IU/mL was considered as a high viral load level (Parvaiz et al., 2011). Some studies reported that high HCV RNA viral load level was consistently associated with high rates of infectivity and poor response to therapy. It was also associated with the development of hepatocellular carcinoma, liver problems related to hepatitis C infection, and a strong predictor of the occurrence of chronic kidney disease complications (Lai et al., 2017). The median of our study subjects' HCV RNA viral load was 3.14 x 10^6IU/mL, with the lowest level was 3.37 x 10^5IU/mL and the highest level was 3.91 x 10^7IU/mL. The median indicated that the study subjects had a high level of viral load.

HOMA IR was the most commonly used method of insulin sensitivity assessment in the hepatitis C population. HOMA IR was chosen by author because it has nearly the same sensitivity as the hyperinsulinaemic-euglycemic glucose clamp (HIEG) method, which is the gold standard for measuring insulin resistance. HOMA IR is easier to perform than HIEG, relatively inexpensive, and is widely available (Peres et al., 2013). In this study we used a cut-off value of ≥ 2.5 in accordance with the cut-off value used by a study conducted in Taiwan, taking into account the similarities in the demographic location with Indonesia, namely from Asia (Huang et al., 2014). Our study showed the median of HOMA IR was 4.50 (0.84 – 18.10). It means that there was an incidence of insulin resistance in our study subjects. This result was supported by previous studies that chronic hepatitis C patients attend to have high value of HOMA IR (Aksu et al., 2012; Andrade et al., 2018; Gualerzi et al., 2018).

HCV infection causes insulin resistance through several mechanisms. One of the mechanisms is due to β-pancreatic cell damage and the presence of HCV RNA protein in the pancreatic tissue which causes direct cytopathic effects (Laskus et al., 1998). The components of the HCV RNA protein that are mainly involved in insulin resistance are the core protein, NS-3, and NS-5. HCV core protein induces TNF-α expression, decreases VLDL formation, increases lipogenesis and thus induces insulin resistance. The core protein also inhibits IRS-1, thereby decreasing GLUT4 regulation and increasing the release of PKC, a gluconeogenic enzyme (El-Zayadi & Anis, 2012). NS-3 protein has been shown to induce oxidative stress and increase NOX-2 regulation thereby accelerating the production of ROS and the release of pro-inflammatory cytokines such as TNFα, TGFβ, IL-6, and IL-8, which ultimately lead to liver fibrosis and insulin resistance (Bureau et al., 2001). NS-5A protein induces endoplasmic reticulum (ER) stress that leads to insulin resistance directly or indirectly by upregulation of the protein phosphatase 2A (PP2A) cellular gene. PP2A itself decreases Akt regulation which results in inhibition of insulin signaling which leads to insulin resistance (Parvaiz et al., 2011).

The involvement of HCV RNA protein components in the incidence of insulin resistance was reflected in the relationship between HCV RNA viral load and HOMA IR. Our study showed a positive correlation with moderate strength between HCV RNA viral load and HOMA IR (r=0.537; p=0.002). Previous studies also found statistically significant correlation between the two. A high HCV RNA viral load level associated with high HOMA IR value indicated the incidence of insulin resistance in chronic hepatitis C patients, supported by others study (Hsu et al., 2007; Moucari et al., 2008).

This study has limitations because conducted with a cross-sectional design with one data collection chosen by author because it is relatively easy and the results are quickly obtained therefore unable to follow study subjects prospectively in analyzing the relationship between HCV RNA viral load and HOMA IR values in chronic hepatitis C patients. This study was conducted at the Gastrohepatology Outpatient Clinic Installation of Dr. Soetomo Teaching Hospital so that it did not describe the general public's situation.

CONCLUSION

The result of this study conclude that a positive moderate correlation was obtained between HCV RNA viral load and HOMA IR in chronic hepatitis C patients.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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CASE REPORT

Diagnostic and Management Problems of Chylous Effusion in A Patient with Newly-Diagnosed Tuberculosis

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ABSTRACT

Tuberculosis (TB) remains a major cause of morbidity and mortality globally. Although TB most commonly affects the lungs, any organ or tissue can be involved. Extra-pulmonary forms of TB are commonly unrecognized or late diagnosed. Chylous effusion, i.e. chylothorax and chylous ascites, which is characterized by the presence of chyle in the pleural and peritoneal cavities, is an uncommon manifestation of extra-pulmonary TB. A 22-year-old male, referred to Dr. Soetomo Hospital with complaints of dyspnea, fever, and abdominal distension. Chest X-ray showed pleural effusion. Analysis of fluid obtained from thoracentesis and paracentesis showed chylothorax and chylous ascites. M. tuberculosis had been found in sputum smear examination. ADA (adenosine deaminase) test was performed on ascites fluid and a positive result was obtained. Chylous effusion in this patient were concluded to be related to TB. Patient was then treated with anti-TB drugs and somatostatin. Chylothorax and chylous ascites improved after treatment with somatostatin for 1 week. Administration of anti-TB drugs was planned to be continued for 9 months. The most common causes of non-traumatic chylous effusion in developing countries are infection of TB and filariasis. Chylous effusion is caused by obstruction or disruption of the lymphatic system. ADA test is a new biomedical method that begins to expand its use in body fluids to diagnose extra-pulmonary TB. Fasting, together with total parenteral nutrition, can decrease the lymph flow and balance metabolic impairment. Somatostatin has been used in the treatment of chylous effusion as it diminishes peristalsis and intestinal absorption of fats as well as decreases portal pressure.

Keywords: Extra-pulmonary TB, Chylous effusion, Chylothorax, Chylous ascites, ADA test

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INTRODUCTION

Tuberculosis (TB) is one of the main causes of morbidity and mortality globally and it kills about two million people annually (Afrasiabian et al.,2013). In 2001, the World Health Organization (WHO) reported 2.4 million cases and approximately 2 billion people worldwide have latent TB infection. During 2008, an estimated 9.4 million new TB cases were diagnosed, with most cases living in Africa and Asia (Tseng et al., 2014).

TB is a granulomatous disease caused by Mycobacterium tuberculosis. TB primarily affects the lungs, but all organs may be affected. Extra-pulmonary forms of TB pose a big public health problem, because unlike pulmonary forms that lead patients quickly at health centers, they are commonly unrecognized or late diagnosed, which delay the treatment. This delay in diagnosis is not only due to the delay in the examination, but also due to the diagnostic difficulties related to extra-pulmonary TB (Tchaou et al., 2016).

Chylous effusion, i.e. chylothorax and chylous ascites, which is characterized by the presence of chylous fluid in the pleural and peritoneal cavities, is an uncommon manifestation of extra-pulmonary TB (Kim et al., 2014). Diagnosis of extra-pulmonary TB often requires invasive procedures. There is need of precise and faster diagnosis for patient with extra-pulmonary TB. Accordingly, there develops tests based on biochemical response of body towards TB infection. Adenosine deaminase (ADA) test is one of biochemical test for TB (Stevanovic et al., 2011; Ninghot et al., 2017).

The management of chylous effusion is still a challenge. Therapeutic thoracentesis is the initial step in large chylothorax that cause respiratory distress. The cornerstone of therapy revolves around correcting the underlying disease and supportive strategies. Fasting, total parenteral nutrition, and somatostatin or octreotide are the supportive therapies for chylous effusion (Nair et al., 2007; Yang et al., 2013; Lizaola et al., 2017).

Here we reported a problematic case of young man consulted to our department with the complaints of dyspnea and abdominal discomfort due to chylothorax and chylous ascites. M. tuberculosis had been found in sputum smear examination, so that we concluded that chylothorax was related with pulmonary TB. Meanwhile, the cause of chylous ascites are investigated further by radiological and laboratory examination. The difficulty of diagnosing and managing chylous effusion as the extra-pulmonary TB makes this case interesting for further discussion.

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CASE REPORT

A 22-year-old man, Mr. K, unmarried, having his address at Mojokerto, East Java, referred by emergency room of Mojokerto Hospital with a diagnosis of fluidopneumothorax, coming to the emergency room of Dr. Soetomo Hospital, Surabaya, on January 9th, 2018, with chief complaint of dyspnea since the last month which worsened 2 days before admission. Shortness of breath improved with rest and lying down to the left. Patient also complained of coughing for 5 months, coughing with thick white sputum. Patient got his weight loss since the last 4 months. A history of coughing up blood was denied. Patient complained that his stomach was bloated since the last 4 months.

Physical examination of the patient showed the awareness was compos mentis, GCS of 456, and visual analog scale (VAS) of 2. Vital signs: blood pressure of 130/80 mmHg, pulse rate of 105 times/minute, respiratory rate of 24 times/minute, temperature 37.8°C, body weight of 50 kg, body height of 160 cm. On physical examination, it was found tachypnea. Breath sound was absent on right side, vocal fremitus and vocal resonance were absent on right side, and percussion was dull on right side. On the examination of abdomen, it was found with positive shifting dullness. On the examination of the extremities, it was obtained edema of both inferior extremities.

Automated blood count demonstrated leucocyte count of 11,640 cell/mm^3 with neutrophils of 81.1%, hemoglobin of 13.7 g/dL, platelet count of 378,000/mm^3, blood glucose of 100 mg/dL, BUN of 20 mg/dL, serum creatinine of 0.63 mg/dL, ALT of 34 U/L, AST of 23 U/L, albumin of 3.07 g/dL, direct bilirubin of 0.93 mg/dL, total bilirubin of 1.24 mg/dL, sodium of 133 mmol/L, potassium of 4.5 mmol/L, chloride of 102 mmol/L, LDH of 243 (normal: 85-227), PPT of 12.2 seconds (control: 10.3), APTT of 25.0 seconds (control: 27.1), non-reactive rapid test for HIV, and non-reactive HBsAg. Urinalysis showed negative glucose, bilirubin 1+, ketone 1+, protein 2+, negative nitrite, erythrocytes of 25-50 cells/mm^3, leukocytes of 5-10 cells/mm^3. Blood gas analysis showed pH of 7.48; pCO_2 of 33.1; pO_2 of 225; HCO_3 of 25.1; BE of 1.4; SO_2 of 99%. Radiological examination of thorax showed fluido-pneumothorax of right lung and pleuropneumonia of left lung.

In the emergency room, patient underwent pleural puncture, with the result of thick and milky white pleural fluid. Patient was admitted to Pulmonology ward, with the initial diagnoses of fluidopneumotorax of right lung, suspected new case of pulmonary TB, ascites, hypoalbuminemia, and edema of inferior extremities. Patient was consulted to Internal Medicine Department regarding the ascites, and a proof puncture of ascites was planned. Patient were also consulted to Cardiology Department regarding inferior extremity edema, however the echocardiographic examination was within normal limits. Patient was planned for chest tube insertion. Patient was administered oxygen via simple mask 6-8 liters/minute, infusion of branched-chain amino acid, intravenous injection of furosemide, spironolactone tablets, and albumin capsules.

On 2nd day of care (January 10th, 2018), patient still complained of dyspnea and abdominal discomfort. Patient underwent chest tube insertion and it was obtained milky white pleural fluid with a production of 400 mL/24 hours. Analysis of pleural fluid showed pH of 8 (normal: 3.4-5.0), glucose of 122 (normal: <100), LDH of 120 (normal: 100-190), leukocyte count of 187/mm^3, mononuclear cells of 64.2%, polymorphonuclear cells of 35.8%, total protein of 1.8 g/dL (normal 6.4-8.2), total cholesterol of 4 mg/dL (normal: 0-200), triglycerides of 378 mg/dL (normal: 30-150). Blood lab tests showed hemoglobin of 14.2 g/dL, leukocytes of 15,680/mm^3 with neutrophils of 90.9%, platelet count of 323,000/mm^3, albumin albumin of 2.7 g/dL, total cholesterol of 120 mg/dL, triglyceride of 82 mg/dL, non-reactive anti-HCV, AFP of 2.0 (normal: <15), BUN of 11 mg/dL, serum creatinine of 0.7 mg/dL, and CRP of 9.5 (normal: 0-1). Patient was performed a proof puncture of ascitic fluid, and a milky white liquid was obtained. Patient was diagnosed as chylothorax of right lung e.c. suspected new case of TB, ascites, hypoalbuminemia, and inferior limb edema. Patient was fasted, received oxygen mask therapy 6 liters/minute, infusion of 20% fat emulsion 500 mL/day, infusion of 10% dextrose 500 mL/day, furosemide 20 mg t.i.d. intravenously, ceftriaxone 1 gram b.i.d. intravenously, metronidazole 500 mg t.i.d. intravenously, and spironolactone tablets 100 mg once daily.

On 4th day of care (January 12th, 2018), CT scan of thorax showed pneumonia, bilateral pleural effusions, and chest tube via the right intercostal space III with a distal tip projected as high as vertebra thoracal-1. There was no picture of pneumothorax. CT scan of abdomen showed the presence of ascites, bilateral pleural effusion, and lymph node enlargement in the left and right inguinal paraaortas. The ascitic fluid analysis demonstrated pH of 8 (3.4-5.0), glucose of 115 mg/dL (normal: <100), LDH of 50 (normal: 100-190), leukocyte count of 226/mm^3, mononuclear cells of 86.3%, polymorphonuclear cells of 13.7%, total protein of 1.4 g/dL (normal 6.4-8.2), total cholesterol of 6 mg/dL (normal: 0-200), and triglyceride of 509 mg/dL (normal: 30-150). Cytology examination of ascitic fluid showed no malignant cells, bacteria, fungi, and smear, and negative results of Gram staining. Patient was diagnosed as chylothorax of right lung e.c. suspected new case of pulmonary TB, chylous ascites, hypoalbuminemia, leukocytosis, and inferior limb edema. Patient was fasted, administered infusion of 20% fat emulsion 500 mL/day, infusion of 10% dextrose 500 mL/day, and pump infusion of somatostatin 6 mg/24 hours.

On 7th day of care (January 15th, 2018), patient's complaint of dyspnea had diminished. Production of pleural fluid measured from chest tubes had decreased to less than 50 mL/day. Smear sputum examination showed 2+ result. GenXpert (nucleic acid amplification) examination showed positive for M. tuberculosis bacteria without rifampicin resistance.

Patient's complaints had diminished on the 9th day of care (January 17th, 2018). Abdominal discomfort had improved. The chest tube had been removed. Blood laboratory examination showed procalcitonin of 0.12 (local infection), C3 complement of 129 (normal: 50-120), C4 complement of 25.8 (normal: 20-50), ANA test of 25.91 (indeterminate), lipase of 25 IU/L (normal: 10-150), amylase of 50 IU/L (35-118), CEA of 2.5 ng/mL (normal: <3), and Ca-19.9 of 15 U/mL (normal: 0-37). ADA test for ascitic fluid was 50 IU/L (normal: <36 IU/L). Thoracic CT scan for evaluation showed no visible picture of pneumothorax, pneumonia, and pleural effusion. Finally, this patient was diagnosed as chylothorax related to new case of pulmonary TB, chylous ascites related to peritoneal TB, and hypoalbuminemia. Patient was begun receiving enteral diet, infusion of branched chain amino acid 500 mL/24 hours, drinking 700 mL/day, albumin capsules t.i.d. orally, and category I FDC anti-TB drugs of 3 tablets/day (total rifampicin of 450 mg, isoniazid of 225 mg, pyrazinamide of 1200 mg, ethambutol of 825 mg). Somatostatin was discontinued after 6 days of administration as the patient's clinical condition improved.

On 11th day of care (January 19th, 2018), complaints of dyspnea and abdominal discomfort had significantly improved. Patient was discharged. Category I anti-TB drugs and albumin capsules were continued. Patient was then followed-up in DOTS Outpatient Clinic to continue the anti-TB drugs for 9 months.

DISCUSSION

Chylous effusion, which consists of chylothorax and chylous ascites, is an uncommon clinical entities characterized by the accumulation of triglyceride-rich chylous fluid in the pleural and peritoneal spaces. The reported incidence of combined occurrence of chylothorax and chylous ascites has varied from 9% to 55% of chylous ascites. No differences in sex distribution have been cited. Chylous ascites is uncommon, with an occurrence of one in 20,000 hospital admission (Tchaou et al., 2016; Kim et al., 2014; Wolf, 2018).

Clinical features of chylotorax are typical of any pleural effusion. Dyspnea, cough, and chest discomfort are the main symptoms. Pleuritic chest pain and fever are uncommon because chylous fluid is not irritating to the pleural surface. The severity of symptoms depends on the size of chylothorax. The existence of symptoms such as weight loss, night sweating, hemoptysis, and a previous history of TB, should lead us to perform appropriate test for TB (Nair et al., 2007; Karapolat et al., 2008).

Progressive and painless abdominal distention (81%) and non-specific pain (14%) are the most common presenting symptoms in chylous ascites, occurring over a course of weeks to months depending on the underlying cause. Patients who have undergone abdominal or thoracic surgery may present with an acute onset of chylous ascites. Other features include weight loss, anorexia, malaise, steatorrhea, malnutrition, enlarged lymph nodes, fevers, and night sweating. From physical examination, chylous ascites can't be distinguished from ascites in general (Al-Busafi et al.,2014).

Etiology and Pathophysiology of Chylous Effusion

The causes of chylous effusion can be categorized as traumatic and non-traumatic. The most common traumatic cause is trauma after abdominal surgery. The traumatic causes of chylous effusion differ between developed and developing countries. In developed countries the most common causes are malignancy (hepatoma, lymphoma, angiosarcoma) and hepatic cirrhosis, while the most common causes in developing countries are infectious diseases (TB and filariasis). Other causes are spontaneous bacterial peritonitis, peritoneal dialysis, carcinoid syndrome, congenital disorders, Kaposi sarcoma, superior cava vein thrombosis, mediastinal fibrosis, hypothyroidism, nephrotic syndrome, pancreatitis, ischemic cardiomyopathy, constrictive pericarditis, systemic lupus erythematosus (SLE), and Henoch-Schonlein purpura (Tchaou et al., 2016; Kim et al., 2014; Wolf, 2018).

Infections with mycobacterial species, as M. avium and M. tuberculosis, tend to induce chylous effusion and contribute to 10% of all cases. Except for mycobacteria, no other bacterial or viral infection cause chylous ascites (Steinemann et al., 2011). TB needs to be suspected as the etiology in cases of chylous ascites, especially in developing countries like Indonesia, where the prevalence of TB is still high (Barman et al., 2015).

The combined occurrence of chylothorax and chylous ascites is usually caused by obstruction or disruption of the thoracic duct or of one of its main divisions, which is usually the result of malignancy, trauma, or inflammation. Chylous fluid can experience reflux from pleural to peritoneal cavities or vice versa through a diaphragm fistula (Kumae et al., 2013; Cueto-Aguilera et al., 2016). During mycobacterial infections, the activation of T cell receptors expressing CD4+ T cells is essential in the formation of granulomas. Granulomas are formed from a complex cascade of systems. Sensitized type I T-helper are attracted to the site of focally aggregated macrophages that contain ingested bacilli in the case of Mycobacterium infections, and the early granuloma organizes into its characteristic structure. The chylous effusion found in TB patient is likely a result of granulomatous infiltration of the lymphatic system, causing obstruction, in the setting of the abrupt restoration of the immune system (Dean et al., 2018).

Chylous effusion is the pathologic leakage of triglyceridesrich lymphatic fluid into pleural and peritoneal cavity. Because its volume is very large and rich in nutrients, it may lead to malnutrition, dehydration, electrolyte imbalance, and delayed wound healing. Moreover, as chylous effusion contains lymphatic fluid which is rich in lymphocytes and immunoglobulins, severe and long-term chylous leakage may cause hypoimmunity, therefore leading to severe infection or even death because of sepsis (Pan et al., 2016).

In this patient, there was no history of trauma, chest and abdominal CT scan showed no signs of malignancy, and cytological analysis of ascitic fluid did not show any malignant cell. Constrictive pericarditis, one of the causes of chylothorax and chylous ascites, was not obtained at echocardiography examination. In this patient, there was no other risk factors for chylothorax other than TB.

Diagnosis of Chylous Effusion

History taking can be very helpful in establishing the diagnosis. There is often a delay in diagnosis of TB, especially extra-pulmonary TB, because the symptoms are not specific.

Radiological Examination

Radiological examination plays an important role in the evaluation of chylous effusion. Chest X-ray with lateral views as well as decubitus views may be helpful in determining the size and location of the chylothorax, however it cannot differ chylothorax from simple pleural effusion (Nair et al., 2007). Lymphangiography is the gold standard diagnostic tool in cases of lymphatic obstruction. Lymphangiography and lymphoscintigraphy are useful in detecting abnormal retroperitoneal nodes, leakage, fistulization, and patency of the thoracic duct. These techniques are also effective for selecting patients for surgery and assessing the effects of treatment. CT scan and MRI are not specific to chylous ascites, however, they are useful in identifying intrathoracal and intraabdominal masses, fluid collections, or lymph nodes. The CT density of chylous ascites resembles that of water and is indistinguishable from simple pleural fluid, urine, bile, bowel secretions, or simple ascites (Lizaola et al., 2017).

In this patient, chest X-ray showed fluidopneumothorax and pleuropneumonia. CT scan abdomen showed ascites, bilateral pleural effusion, and lymph node enlargement in paraaorta as well as in right and left inguinal regions. However, these examination still could not determine the specific cause of fluidopneumothorax and ascites.

Mycobacterial Stain and Culture

A definitive diagnosis of TB can only be made by culturing M. tuberculosis organisms from a specimen obtained from the patient. However diagnosing extra-pulmonary TB remains challenging because clinical samples obtained from relatively inaccessible sites may be paucibacillary, decreasing the sensitivity of diagnostic tests. Since the conventional smear microscopy has a low sensitivity with a range of 0%–40%, negative results cannot exclude the presence of TB. The reported yields of mycobacterial culture vary from 30% up to 80%, but it usually takes 2 to 8 weeks to receive the results, which is too slow to help treatment decisions (Lee, 2015).

About 10%–50% of extra-pulmonary TB patients have concomitant pulmonary involvement. Therefore, all suspected cases of extra-pulmonary TB should be assessed for concomitant pulmonary TB to determine whether the case is infectious and to assist with diagnosis. Some extra-pulmonary TB patients have positive sputum culture results despite normal chest radiography findings (Lee, 2015).

A Ziehl-Neelsen stain can reveal AFB only if the sample contains greater than 10,000 bacilli per mL. Different culture methods, such as Lowenstein-Jensen medium, radiometric (Bactec 12B liquid medium), and non-radiometric (Bactec MGIT 960 system), can be used for confirming diagnosis in the paucibacillary state (Tseng et al., 2014).

In this patient, M. tuberculosis had been found in sputum smear examination. Mycobacterial cultures of sputum, pleural and ascites fluid were not performed due to it took too long time to receive the result, which was too slow to help treatment decisions. Based on the positive result of sputum smear examination, chylothorax in this patient was very likely related to pulmonary TB.

Chylous Effusion Fluid Analysis

Pleural puncture and abdominal paracentesis are the most important diagnostic tools in evaluating and managing patients with chylous effusion. In contrast to the yellow and transparent appearance of pleural effusion and ascites due to cirrhosis and portal hypertension, chylous fluid typically has a cloudy and turbid appearance. This should be distinguished from pseudochylous effusion, in which the turbid appearance is due to cellular degeneration from infection or malignancy without actually containing high levels of triglycerides. The serum to ascites albumin gradient (SAAG) should be calculated to determine if the ascites is related to portal hypertension or other causes (Al-Busafi et al., 2014).

The diagnosis of chylothorax and chylous ascites is made by analyzing the fluid obtained through pleural puncture and abdominal paracentesis. Among others, usual findings that point towards the identification of this condition are milky white fluid with triglyceride levels greater than 200 mg/dL, although some authors use a cutoff value of 110 mg/dL, and high leukocyte count of mononuclear cell predominance (Al-Busafi et al., 2014; Shaik et al., 2014).

In recent years, there has been a great demand for finding new biomedical diagnostic method to diagnose TB quickly

and accurately. Measuring adenosine deaminase (ADA) activity is a biological method, especially to diagnose extra-pulmonary TB through body fluid. ADA is an enzyme in the purine salvage pathway that catalyzes the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine with the release of ammonia. ADA is essential for proliferation and differentiation of lymphoid cells, especially T cells, and helps in the maturation of monocytes to macrophages. Activity of this enzyme increases in TB patients. In some studies, the level of ADA in sputum and serum was used for diagnosis of TB, and it was monitored during TB treatment (Afrasiabian et al.,2013; Stevanovic et al., 2011).

A TB smear and culture as well as ADA test should be performed in selected cases when TB is suspected. ADA has high sensitivity and specificity in the diagnosis of TB peritonitis (Al-Busafi et al., 2014). The sensitivity and specificity for diagnosing TB have been reported to be 100% and 97% respectively, using cut-off values from 36 to 40 IU/L, with the optimal cutoff point of 39 IU/L (Lee, 2015). Other causes of increase in ADA activity include bacterial infections, rheumatic disease, and lymphoproliferative disorders. ADA test is still an effective method to distinguished TB from non-TB through pleural, ascitic, synovial fluid, and cerebrospinal fluid (Stevanovic et al., 2011).

Table 1. Characteristics of Pleural and Ascitic Fluid in Patient

	Normal Range[12]	Findings in Patient	
		Pleural Fluid	Ascitic Fluid
Total cholesterol	0-200 mg/dL	4	6
Triglycerides	30-150 mg/dL	378	509
pH	3.4-5.0	8.0	8.0
Glucose	<100	122	115
LDH	100-190	120	50
Leukocyte		187	226
Mononuclear cell		64.2%	86.3%
Polymorphonuclear cell		35.8%	13.7%
Total protein	6.4-8.2 g/dL	1.8	1.4
ADA test	<40	Not performed	50

Pleural and ascitic fluid analyses of the patient showed chylothorax and chylous ascites. Chylothorax could be related to pulmonary TB that had been diagnosed through sputum smear examination. Meanwhile, the patient's chylous ascites was concluded to be related to extrapulmonary TB in the presence of a positive ADA examination.

Other Diagnostic Examinations

Other diagnostic examinations for TB are tissue biopsy, nucleic acid amplification by polymerase chain reaction (PCR) method, and immunological test such as Interferon Gamma Releasing Assay (IGRA) (Al-Busafi et al., 2014; Lee, 2015; Arend et al., 2007).

PCR can use a variety of specimens including effusion fluid and shows high specificity and sensitivity, fast, and non-invasive. However, PCR test for TB diagnosis is expensive and it requires skilled personnel and lot of equipments (Afrasiabian et al., 2013; Tseng et al., 2014). PCR tests also cannot differentiate living bacilli from dead bacilli. Thus, these tests continue to give positive results even after successful treatment. The PCR tests are positive in 95% to 100% of culture positive cases and in 50% to 60% of culture negative cases (Kim et al., 2011).

IGRA, a T-cell assay relies on the stimulation of host blood cells with M. tuberculosis-specific antigens and measure the production of interferon gamma. The T-cell assays have proven to be more specific than the TST but are currently unable to distinguish between active disease and latent tuberculosis infection. Therefore, interpretation of the results remains dependent on the clinical context. The costs and technical demands of IGRA will most likely limit their wider use in resource-poor setting, where better tests are the most needed (Arend et al., 2007).

Tissue biopsy to diagnose peritoneal TB was not performed to this patient because it was an invasive examination. Nucleic acid amplification test of the sputum showed positive M. tuberculosis without rifampicin resistancy. IGRA was not performed because sputum smear examination and ADA test of ascitic fluid had already found to be positive for TB. Finally, we conclude that chylothorax and chylous ascites in this patient were related to TB infection.

Management of Chylous Ascites

Ideal treatments for patients with combined occurrence of chylotorax and chylous ascites are still challenging. Therapy for the underlying causes of chylous effusion is the most important thing. Therapeutic thoracentesis is the initial step in large chylothoraces that cause respiratory distress. Intercostal tube drainage is the preferred method of thoracentesis in most centers (Nair et al., 2007). In patients with symptomatic ascites, a therapeutic paracentesis should be performed to relieve symptoms and could be repeated as needed. Unless the patient has cirrhosis, the replacement of albumin to prevent post-paracentesis circulatory dysfunction is not recommended (Al-Busafi et al., 2014).

Fasting, together with total parenteral nutrition, can decrease the lymph flow in thoracic duct dramatically from 220 mL/(kg.hour) to 1 mL/(kg.hour). Furthermore, total parenteral nutrition restores nutritional deficits and balances metabolic impairments imposed by chylous ascites and repeat sessions of paracentesis (Yang et al., 2013). As long-chain triglyceride (LCT) intake through the gastrointestinal tract will cause an increase in chylous leakage, nutrition support should consist of a low-fat diet supplemented with medium-chain triglyceride (MCT), an enteral nutrition plan with MCT, or total parenteral nutrition plan. Indeed, since MCT and total parenteral nutrition, as two nutrition support methods, can effectively prevent LCT from being absorbed by the gastrointestinal tract, they have been used to reduce chylous leakage early (Pan et al., 2016). MCTs are the diet of choice since they are absorbed directly into the intestinal

cells and transported as fatty acids and glycerol to the liver via the portal system, while the LCTs need to be converted to monoglycerides and free fatty acids in order to be transported as chylomicrons by the lymph ducts. Monitoring of serum electrolytes, serum albumin, total proteins, and body weight is recommended (Cueto-Aguilera et al., 2016).

Somatostatin and its analog, octreotide, have been used in conservative therapy of chylothorax and chylous ascites. Event though the exact mechanism of somatosatin in the treatment of chylous effusion is not well known, somatostatin reduces the amount of lymph circulation in the major lymphatic vessels, suppresses lymph excretion via somatostatin receptors in the wall of the intestine, and may contribute to a reduction in the production of lymph fluid. Somatostatin and octreotide inhibit the secretion of some pituitary and gastrointestinal hormones, increase splanchnic arteriolar resistance, and consequently reduce gastrointestinal flow and the lymph flow. The use of somatostatin is recommended in the early stages before any invasive treatment starts because it has effects on fistula closure. Somatostatin must be administered intravenously due to its short half-life of 1-3 minutes. Octreotide has a longer half-life of 2 hours and the advantage of subcutaneous administration. Somatostatin is given by continuous infusion pump at a dose of 6 mg a day. Octreotide is given by subcutaneous injection at a dose of 0.1 mg three times a day (Lizaola et al., 2017; Pan et al., 2016; Lee et al., 2014).

Hypoalbuminemia is commonly caused by malnutrition, liver and kidney diseases. Hypoalbuminemia might have resulted from nutritional deficiency or from sepsis. The mechanisms of hypoalbuminemia in patients with sepsis are reduced liver synthesis, accelerated catabolism and increased leakage into the interstitium due to enhanced vascular permeability (Lee et al., 2014).

Surgical management should be adopted if medical management fails. The clinical parameters that prompt surgical intervention are the daily chylous fluid leak exceed 1.5 L/day in an adult or more than 1 L/day for a period more than 5 days. Lymphangiography will help to deliniate the anatomy of the lymphatic channel and thoracic duct as well as the site of leak. If the cylous fluid leak can be identified, direct ligation with non-absorbable suture should be performed on either side of the leak (Nair et al., 2007).

This patient was performed thoracocentesis and chest tube insertion to reduce the complaints of dyspnea due to fluidopneumothorax which was later obtained as chylothorax. After chylous ascites was established through proof puncture of ascites, patient was fasted and administered somatostatin pump infusion for 6 days. Anti-TB drugs were adminstered after the diagnosis of TB had been established through sputum smear examination and ADA test of fluid chylous ascites.

During treatment for 11 days, the production of chylothorax gradually decreased and stomach complaints had improved, so it was decided that surgical management was not needed.

Prognosis

In the past, the mortality due to chylothorax was in excess of 50%. Currently, the morbidity and mortality have improved due to the more aggressive management strategies adopted (Nair et al., 2007). Patients of chylous effusion due to TB infection usually have a very good response to the administration of anti-TB drugs and supportive treatment (Barman et al., 2015).

CONCLUSION

It had been reported a 22-year-old male patient with complaints of dyspnea, fever, and abdominal distension. Chest X-ray showed fluidopneumothorax and pleuropneumonia. Chylothorax was obtained from the thoracentesis, and chylous ascites was obtained from paracentesis. M. tuberculosis was found on sputum smear examination. Abdominal CT scan showed ascites, bilateral pleural effusion, and lymph node enlargement in the left and right inguinal paraaortas. ADA test was performed on ascitic fluid and positive result was obtained. Chylothorax and chylous ascites in this patient were concluded to be associated with TB infection. Patient was then treated with somatostatin pump infusion and anti-TB drugs. Chylothorax and chylous ascites improved after treatment with somatostatin for 1 week. Anti-TB drugs were planned to be continued up to 9 months.

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CASE REPORT

Hepatic Hydrothorax in A Patient with Liver Cirrhosis

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ABSTRACT

Hepatic hydrothorax is a transudative pleural effusion which presents in 5-10% patients with liver cirrhosis. Although fairly uncommon, it is associated with higher morbidity and lower survival rate. The mechanism is yet to be understood fully, but the most widely accepted pathogenesis involves the presence of portal hypertension, diaphragmatic defects, and negative intrathoracal pressure, all of which lead to the formation of unidirectional passage of ascitic fluid from peritoneal cavity into pleural space. Due to its origin, the pleural effusion has similar characteristics to ascitic fluid. We herein report the case of a 60-year-old woman with advanced liver cirrhosis and right-sided moderate hepatic hydrothorax. Treatment given to the patient includes diuretics, sodium restriction, and repeated thoracentesis. Subsequent evaluation of the patient revealed improvement both clinically and radiologically.

Keywords: Hepatic hydrothorax, Liver cirrhosis, Transudate, Pleural effusion

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INTRODUCTION

Hepatic hydrothorax is an infrequent complication of liver cirrhosis, which presents as transudative pleural effusion not secondary to cardiopulmonary disease or other causes. Although the earlier cases of pleural effusion in liver cirrhosis was described by Laennec, but not until 1958 the terminology of hepatic hydrothorax was first introduced, stressing the role of liver cirrhosis as the cause of transudative pleural effusion (Morrow et al., 1958). The prevalence of hepatic hydrothorax is estimated to be 5-10% in liver cirrhosis (Lv et al., 2018). Although quite uncommon, the presence of hepatic hydrothorax is associated with morbidity and mortality. Patients with hepatic hydrothorax have poorer prognosis, with median survival time 8-12 months (Hou et al., 2016).

The exact mechanism of hepatic hydrothorax has not been well understood, but it is thought to occur due to direct passage of ascitic fluid from peritoneal to pleural space via diaphragmatic defects (Silva Cruz et al., 2019). These defects are usually small (<1 cm) and mostly occur on the right side. Histologically, right diaphragm is more tendinous while left diaphragm is more muscular. Diaphragmatic defects are known to develop on these tendinous part; this might explain the right-side predominance of hepatic hydrothorax (Lv et al., 2018). Other factors contributing to the development of hepatic hydrothorax are negative intrathoracal pressure, positive intraabdominal pressure, and malnutrition (which causes thinning of diaphragm), creating a unidirectional passage of ascitic fluid and accumulation in pleural space (Lv et al., 2018; Chaaban et al., 2019). It must be noted that while in the majority of cases it is associated with the presence of ascites, it may also occur without the evidence of ascites (Chaaban et al., 2019).

We report a case of a 60-year-old patient with advanced liver cirrhosis who was admitted due to variceal bleeding but was found to have right-sided hepatic hydrothorax on following workup. The patient was successfully treated with multiple thoracentesis, diuretics, and low sodium diet and was subsequently discharged from hospital.

CASE REPORT

A 60-year-old woman was admitted due to fresh blood vomiting several hours before hospital admission. She had been hospitalized 4 times in the last year due to recurrent episodes of haematemesis and melena. She had previously been diagnosed as having chronic hepatitis B and liver cirrhosis for 2 years and had undergone upper gastrointestinal endoscopy twice, with the last procedure taken on 3 months before admission and was diagnosed with grade 2 esophageal varices. Medication regularly taken including propranolol, furosemide, and spironolactone. On history taking, she also complaint of having persistent dyspnea for 2 months especially on recumbent position and therefore she had to use 2 pillows to be able to sleep. The shortness of breath was sometimes accompanied by intermittent cough. No chest pain or palpitation were noted. There was no history of diabetes mellitus, hypertension, asthma, nor any heart, lung, or kidney disease.

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On admission the patient was alert. Her vital signs were stable, with blood pressure of 100/60 mmHg, heart rate of 76 beats per minute, repiratory rate of 22 breaths per minute, and axillary temperature of 36.6^{O}C. Her thorax examination revealed decreased breath sounds and dull percussion on right side. No rhonchi or wheezing was found. There was no distention of jugular veins. Her abdomen was moderately distended with evidence of ascites. Bilateral pitting edema on lower extremities were noted. No active bleeding was observed on admission. Chest radiography showed moderate right-sided pleural effusion without any infiltrates or visible mass. Her laboratory results were as follows: hemoglobin 7.1 g/dL, WBC 9,680/µL, platelet 145,000/µL, AST 43 U/L, ALT 18 U/L, total bilirubin 2.65 mg/dL, random blood glucose 98 mg/dL, serum albumin 2.05 g/dL, BUN 16 mg/dL, serum creatinine 0.70 mg/dL, and normal urinalysis. Sputum smear and culture results were negative. Abdominal ultrasound on previous admissions showed shrunken liver with increased coarse echogenicity, blunted edge, and irregular border, with free extraluminal fluid, suggesting liver cirrhosis and ascites. Transient elastography was also done on previous admission with score of 39.7 kPa (F4), interpreted as severe fibrosis (cirrhosis). Both electrocardiography and echocardiography findings were normal.

Diagnosis of liver cirrhosis CTP C (hepatitis B related) with complications of variceal bleeding, right-sided pleural effusion, anemia, and hypoalbuminemia were made. Treatment administered including 1 bag packed red cell transfusion aiming for a hemoglobin level of 8 g/dL, 40 g albumin infusion, octreotide 25 mcg/hour for 5 days, omeprazole 40 mg 12-hourly, cefotaxime 1 g 8-hourly, lamivudine 100 mg/day, lactulose syrup 10 g 8-hourly, and low sodium diet. After 5 days, octreotide infusion was stopped and switched to propranolol 20 mg 8-hourly.

Pleural fluid analysis revealed transudates with clear pale yellow color, pH 8, WBC 119 cells/mL, PMN 37 cells/mL, MN 82 cells/mL, albumin 0.7 g/dL, protein 0.8 g/dL, LDH 68 U/L, glucose 118 mg/dL, with serum albumin 2.6 g/dL, serum protein 5.6 g/dL, and serum LDH 171 U/L which were taken at the same time as the pleural fluid sampling. Ascites fluid analysis also showed transudates with similar characteristics, with pH 8, WBC 62 cells/mL, PMN 22 cells/mL, MN 40 cells/mL, albumin 0.5 g/dL, protein 0.7 g/dL, LDH 51 IU/mL, glucose 125 mg/dL. Serum-pleural albumin gradient obtained from the calculations was 1.9 g/dL.

Based on the above results and after excluding other causes of transudative effusion, the patient was assessed as having hepatic hydrothorax. Furosemide 40 mg/day and spironolactone 100 mg/day were added to treatment. Thoracentesis were done 3 times with interval of 2-3 days, with a total of 1.5 L fluid being evacuated. The patient responded well to treatment and remain stable. After twelve days of hospital care, there were both clinical and radiological improvements and the patient was subsequently discharged.

DISCUSSION

Hepatic hydrothorax is defined as the accumulation of transudative pleural effusion (typically more than 500 mL) in liver cirrhosis with portal hypertension which is not caused by cardiac, pulmonary, renal, or any other etiologies (Chaaban et al., 2019). It develops mostly in decompensated cirrhosis, with more than 90% occurs in CTP class B and C (Chaaban et al., 2019). As in our case, the patient presented with recurrent variceal bleeding and was diagnosed with decompensated cirrhosis with CTP score of 12 (CTP class C). While pleural effusion due to cardiac origin is usually bilateral, hepatic hydrothorax occurs mainly (80-85%) on the right side, although it may also occur on the left side in 13-17% and bilateral in 2-3% of cases (Krok & Cárdenas, 2012; Lv et al., 2018). This characteristic may help to differentiate between hepatic hydrothorax and pleural effusion due to cardiac disease. In our patient, pleural effusion was found to be solely on the right side. Common clinical manifestations include dyspnea and hypoxia related to the volume of pleural effusion. Most patients present with progressive dyspnea and may be accompanied by cough or pleuritic chest pain, while some may remain asymptomatic (Chaaban et al., 2019). Our patient also presented with progressive dyspnea and intermittent cough which developed within 2 months.

Diagnosis of hepatic hydrothorax can be made based on the presence of liver cirrhosis with portal hypertension and exclusion of pulmonary, cardiac, or any other diseases which may cause pleural effusion. Pleural fluid analysis should be performed to help with diagnosis and exclude other possible causes (e.g., infection, malignancy). In hepatic hydrothorax, pleural fluid has transudative quality with characteristics similar to that of ascitic fluid. Light criteria is widely used to differentiate between transudates and exudates. According to this criteria, an effusion is considered to be exudate if one or more of the following conditions are met: pleural fluid/serum protein ratio >0.5; pleural fluid/serum LDH ratio >0.6; or pleural fluid LDH level is greater than two-thirds of the serum LDH upper normal limit (Light, 2011). Calculating serum to pleural fluid albumin gradient is also a useful method; due to its origin, hepatic hydrothorax usually has albumin gradient ≥1.1, similar to serum-ascitic fluid albumin gradient in ascites secondary to portal hypertension (Runyon et al., 1992). In our patient, both pleural and ascitic fluid did not fulfill any of the Light criteria. Calculated serum-pleural fluid and serum-ascitic fluid albumin gradient were 1.9 g/dL and 2.1 g/dL, respectively. These findings suggested transudative quality, with similar fluid components between pleural and ascitic fluid. Negative sputum stain and culture, no other abnormalities on chest radiography, normal electro-

cardiography and echocardiography, normal renal function and urinalysis, combined with data from physical signs and symptoms excluded other possible causes of transudative pleural effusion. Thoracoscopy, scintigraphy, or other imaging methods can be considered to confirm the presence of diaphragmatic defects and/or the passage of ascitic fluid into pleural space when the diagnosis is uncertain (Lv et al., 2018). We did not perform thoracoscopy in our patient due to its invasive nature and weak general condition. Scintigraphic study was also not done due to resources limitations.

Currently there is no specific guideline for the management of hepatic hydrothorax. Initial therapy involves diuretics and sodium restriction (2-4 g/day). Diuretics most commonly used are spironolactone (100 mg/day initially, can be titrated up to 400 mg/day) which can be combined with furosemide (40 mg/day initially, up to 160 mg/day) (Cárdenas et al., 2020). Repeated thoracentesis might be necessary to relieve respiratory symptoms in patients with large volume of effusion. Large volume paracentesis with albumin infusion is recommended in patients with hepatic hydrothorax with tense ascites (Garbuzenko and Arefyev, 2017). In our patient, we gave medical treatments (diuretics and low sodium diet) combined with repeated thoracentesis. For diuretics we used combination between spironolactone 100 mg/day and furosemide 40 mg/day which were both maintained until the patient was discharged. We considered repeated thoracentesis needed to be done in our patient due to moderate volume of pleural effusion and the presence of respiratory symptoms. We did not perform large volume paracentesis because the ascites was not large and tense.

Chest tube insertion to drain effusion in hepatic hydrothorax can lead to volume depletion and electrolyte imbalance and therefore should be avoided (Silva Cruz et al., 2019). Other interventions which could be considered particularly in refractory cases include indwelling pleural catheter, pleurodesis, transjugular intrahepatic portosystemic shunt (TIPS), peritoneovenous and pleurovenous shunting, and thoracoscopy to repair diaphragmatic defects (Garbuzenko and Arefyev, 2017; Lv et al., 2018). These procedures are invasive and may not be suitable for every case. In our case, the patient's condition improved after treatment with diuretics and repeated thoracentesis, therefore we deemed these procedures unnecessary. Moreover, our patient was admitted due to recurrent variceal bleeding and weak general condition, which we considered to be high risk to undergo such invasive procedures. Until now, liver transplantation is the only definitive treatment for hepatic hydrothorax, since most patients have advanced stage of liver cirrhosis (Lv et al., 2018). However, liver transplantation is still rarely done in our country due to resources limitations.

CONCLUSION

In conclusion, we report a case of hepatic hydrothorax in a patient with advanced liver cirrhosis which was successfully managed using combination of medical management and repeated thoracentesis. Hepatic hydrothorax is relatively uncommon but may posed serious complications and higher morbidity in patients with liver cirrhosis, which underlines its importance to diagnose carefully and exclude other possible causes. Pleural fluid analysis should be routinely performed in every patient. The main treatment consists of diuretics, sodium restriction, and repeated thoracentesis if necessary. Chest tube placement should be avoided while other invasive procedures might be considered on a case-by-case basis.

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CASE REPORT

Management of Gestational Diabetes Mellitus in A Beta Major Thalassemia Patient

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ABSTRACT

Gestational diabetes mellitus (GDM) is a hyperglycemic condition that is first discovered during pregnancy. GDM is a high-risk condition during pregnancy, for both mother and fetus. GDM affects about 1–14% of pregnancies. In the last 20 years, the incidence of gestational diabetes has been increasing. High iron load and disorders of iron metabolism have been associated with glucose metabolism. The beta thalassemias are a group of hereditary hemoglobinopathies. Treatment for beta thalassemias patients is transfusion, but intensive transfusion can aggravate iron overload in patients. In this study, a case of GDM in a pregnant woman with beta-thalassemia was reported.

Keywords: Gestational diabetes mellitus, Management, Thalassemia

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a hyperglycemic condition that is first discovered during pregnancy. GDM is a high-risk condition during pregnancy, for both mother and fetus. The risk of miscarriage, pre-eclampsia, and preterm labor are higher in women with diabetes (Zhang et al., 2018; NICE, 2019).

GDM affects about 1–14% of pregnancies. In the last 20 years, the incidence of gestational diabetes has been increasing. There are a lot of risk factors for GDM, such as high body mass index (BMI), older age, family history of diabetes, and disorders of iron metabolism. High iron load and disorders of iron metabolism have been associated with glucose metabolism (Helin et al., 2012; Zhang et al., 2018).

The beta thalassemias are a group of hereditary hemoglobinopathies. Treatment for beta thalassemias patients is transfusion, but intensive transfusion can aggravate iron overload in patients. Pregnancy causes metabolic changes that promote adipose tissue in early gestation and insulin resistance in late pregnancy. It causes GDM can be easier occurred (Petrakos et al., 2016; Zhang et al., 2018).

Studies of total iron intake and the risk of GDM are rare. Some studies have reported the correlation of iron intake only from food or drug and diabetes so they failed to report the effect of total iron intake (Helin et al., 2012). In this study, a case of GDM in a pregnant woman with beta-thalassemia was reported.

CASE REPORT

Lady ER, age 28 y.o. from Surabaya. She was consulted by obgyn colleagues with a request for gestational diabetes screening. The patient was pregnant with gestational age 27/28 weeks with the first day of menstruation at last April 24th, 2017. She did not feel any complaints. There are no increase of appetite, excessive thirst and hunger, frequent urination, nor weight loss. She was diagnosed beta-thalassemia major since the age of 11 y.o and received Packed Cell Leucoreduction transfusions every 2 months with consumption of deferasirox. Patients also had a history of splenectomy in 2004. During pregnancy, haematology and oncology division planned to give her transfusion of Packed Cell Leucoreduction every month to maintain Hb above 10 g/dl. There was no personal history of diabetes, hypertension and other diseases, also no history of contraception before. There weren't other family members suffering from diabetes.

On physical examination, she was alert with Glasgow Coma Scale (GCS) E4V5M6. Blood pressure (BP) was 100/60 mmHg, pulse 84 beats/minute, regular, respiratory rate (RR) 20 times/minute and axillary temperature 36.8°C. The patient was 150 cm in height with a body weight 51 kg (BMI: 22.67 kg/m^2), her body weight before pregnant was 37 kg (BMI: 16.45 kg/m^2). Head and neck examination showed conjungtival pallor. There was no abnormality detected in lung and heart examination. From abdominal examination, fundal uterine height 24 cm, head position, fetal heart rate 12-12-13 (normal), no uterine contraction detected.

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Extremities perfusion were warm and dry, no edema and cappilary refill time < 2 seconds. From laboratory examination, Hemoglobin 8.8 g/dl, hematocrit 28.1%, leukocytes 12750/µL, neutrofil 60.3%, platelets 771000 /µL, 1-hour 50-gram glucose load test 144 mg/dl, ferritin 12696.12 mcg/l.

Based on examination, the patient'sinitial assesment was Gravida 1 P0000 27-28 week intrauterine with major beta thalassemia and suspect gestational diabetes mellitus. The patient was given 3x1 mg of folic acid, calsium 2x500 mg, and transfusion of Packed Cell Leucoreduction every month to maintain Hb above 10 g/dl. Complete blood tests are planned every month. An oral glucose tolerance test 3 hours with 100 gram glucose as well as HOMA IR and HOMA β examination are planned.

Clinical Progression

On 1 week after, the patient had no complaints. From laboratory tests, Hb 8.4 g/dl, hematocrit 27.8%, leukocytes 16380 /µL, platelets 757000 /µL. An oral glucose tolerance test was performed with 100 gram glucose load and obtained fasting blood sugar results 99 mg/dl, 1 hour 224 mg/dl, 2 hours 183 mg/dl and 3 hours 116 mg/dl, fasting insulin 18.8 uIU/ml, HOMA IR 4.6, HOMA β 67%. Patient was diagnosed with Gravida 1 P0000 28-29 weeks, single intrauterine with beta major thalassemia and gestational diabetes mellitus. We treated the patient with lifestyle modification (diet B1 T3 1800 calories/day) and other therapies were continued. We planned to performed complete blood count (CBC) test, fasting glucose and 2 hour post prandial test 1 week after lifestyle and diet modification.

On 1 week after diet management, the patient came again with laboratory tests showed fasting blood sugar 89 mg/dl, blood sugar 2 hours after meals 108 mg/dl. Patient was diagnosed with Gravida 1 P000 29-30 weeks, intrauterine with beta major thalassemia and controlled gestational diabetes mellitus. Therapies were continued and patient was planned to take complete blood tests, fasting glucose and 2 hour post prandial monthly.

The patient came every month for check up. Her condition was within normal limit. Her fasting blood glucose, 2 hours post prandial and other laboratory tests were within normal limit. Therapies were continued.

The patient gave birth a baby girl at 37/38 weeks of gestation with a birth weight 2400gr, a length 48 cm by caesarean sectio for indications of the secondary arrest of dilation. One week after giving birth, patient had no complaints. Laboratory examination showed Hb 9.8 g/dl, hematrocrit 31.7%, leukocytes 14170 /µL, platelets 770000 / µL, fasting blood sugar 79 mg/dl, blood sugar two hours post prandial 95 mg/dl. Planning: diet B1 1500 calories with oral chelating agent, OGTT 1 month after.

The patient returned two months after giving birth. Patient had no complaints. The patient was 150 cm in height with a body weight 50 kg (BMI: 22.22 kg/m^2). From laboratory tests Hb 7.7 g/dl, hematrocrit 24.8%, leukocytes 13320 /µL, platelets 715000 /µL, fasting blood sugar 87 mg/dl, blood sugar one hour post 75 gram glucose load 155 mg/dl, two hours 131 mg/dl. Planning diet B1 1500 calorieswith oral chelating agent and control monthly for monitoring.

DISCUSSION

Hyperglycemia during pregnancy can be caused by diabetes (patient with history of diabetes) or gestational diabetes mellitus. Gestational diabetes mellitus (GDM) is a hyperglycemic condition that's first discovered during pregnancy. GDM is a high-risk condition for both mother and fetus (Adam et al., 2014; NICE, 2019).

Women in South East Asians countries have high prevalence of type II diabetes mellitus and genetic predisposition so universal screening for GDM is needed. Screening for GDM shoud be performed at 24-28 weeks of gestation because insulin resistance increases during the second trimester and glucose levels rise in women who had glucose metabolism disturbances. One of condition related with an increased risk of disturbances in glucose metabolism is high iron load and disorders of iron metabolism. The patient had been diagnosed with beta thalassemia and had been on routine blood transfusion with ferritin 12696.12 mcg/l. She was also from South East Asian countries (Indonesia), so she needed to be screened for GDM (Helin et al., 2012; Rani et al., 2016; ADA, 2018; Zhang et al., 2018).

There are two criteria diagnosis of GDM, from World Health Organization (WHO) and American Diabetes Association (ADA). From American Diabetes Association 2018, there are two strategies one-step and two-step strategy. We used two-step strategy from ADA. The protocol for two step strategies:

First, perform a 50-g GLT (nonfasting), then check plasma glucose at 1 hour, at 24-28 weeks of gestation in women not previously diagnosed with overt diabetes. If the plasma glucose level is ≥130 mg/dL (7.2 mmol/L), proceed to step 2.

Second, the 100-g OGTT should be performed when the patient is fasting. If minimum two of the subsequent four criterias are met or exceeded, the diagnosis of GDM can be made: Fasting 95 mg/dL (5.3 mmol/L), 1 h 180 mg/dL (10 mmol/L), 2 h 155 mg/dL (8.6 mmol/L), 3 h 140 mg/dL (7.8 mmol/L) (ADA, 2018).

The patient test results was 144 mg/dl for 1-hour 50-gram glucose load test with fasting blood glucose results of 99 mg/dl, 1 hour 224 mg/dl, 2 hours 183 mg/dl and 3 hours 116 mg/dl for 100 gram OGTT. So we diagnosed with GDM.

GDM is commonly the result of cell dysfunction on a background of chronic insulin resistance during pregnancy. In most cases, these impairments exist before pregnancy and can be progressive representing an increased risk of T2DM post-pregnancy. Insulin resistance occurs because an increase in pregnancy hormones (human placental lactogen, progesterone, cortisol and prolactin) which peak at the third trimester of pregnancy (Barbour et al., 2007; Adam et al., 2014; Plows et al., 2018).

One of the causes of glucose impairment before pregnancy is iron overload. Iron overload can be caused by intensive transfusion. Transfusion is a treatment for beta thalassemias. Intensive transfusion treatment for beta thalassemias patients can provoke iron overload, increasing oxidative stress and promoting organ failure. The precise mechanism of iron-induced diabetes is uncertain. There are three hypotheses key mechanisms of iron induced diabetes i.e insulin deficiency, insulin resistance, and hepatic dysfunction. In a study of thalassemic patients, most patients were found to be insulin resistance (Swaminathan et al., 2007; Petrakos et al., 2016; Origa, 2018; Zhang et al., 2018).

The presence of insulin resistance can be determine by HOMA IR (normal value < 4). The function of pancreatic beta cells is measured by HOMA B (normal value of 70-150%). We found the patient was in iron overload with ferritin 12696,12 mcg/l. There was also insulin resistance and β cell dysfunction with fasting insulin 18.8 uIU/ml, HOMA IR 4.6, HOMA β 67% (Wallace et al., 2004; Swaminathan et al., 2007; Adam et al., 2014).

After diagnosis, treatment starts with medical nutrition therapy, physical activity, and weight management and glucose monitoring aiming for the targets: Fasting < 95 mg/dL (5.3 mmol/L), One-hour postprandial < 140 mg/dL (7.8 mmol/L) or two-hour postprandial < 120 mg/dL (6.7 mmol/L). Studies show that 70–85% of women diagnosed with GDM can be treated with lifestyle modification alone. The food plan should be based on a nutrition assessment with guidance from the Dietary Reference Intakes (DRI). The DRI for all pregnant women recommends a minimum of 175 g of carbohydrate, 71 g of protein, and 28 g of fiber. Nutritional therapy at Dr. Soetome Hospital using diet B. For GDM, the diet B1 is given by calculating the number of calories as [Height (in cm) -100] x 30. For first trimester plus 100 calories, plus 200 calories for second trimester, 300 calories for third trimester and for breastfeeding mothers plus 400 calories. The composition of diet B1 is 60% carbohydrate, 20% protein and 20% fat (Askandar et al., 2015; ADA, 2018).

Women with greater initial degrees of hyperglycemia or uncontrolled with lifestyle modification require pharmacologic therapy. Insulin is the first-line agent recommended for treatment of GDM.

The other pharmacology treatment for GDM are metformin and glyburide. Glyburide was associated with a higher rate of neonatal hypoglycemia and macrosomia. Metformin was associated with a lower risk of neonatal hypoglycemia and less maternal weight gain, however, metformin may slightly increase the risk of prematurity. We gave lifestyle modification with diet B1 T3 1800 calories, consisting of 270 gram of carbohydrate, 90 gram of protein, 40 gram of fat and 25-35 gram of fiber without glucose-lowering medication (ADA, 2018).

Women with a history of GDM have a greatly increased risk of conversion to type 2 diabetes. The OGTT is recommended at the time of the 4-12 week postpartum. If the result is normal, they should also be tested every 1–3 years thereafter with frequency of testing depending on other risk factors including family history, pre-pregnancy BMI, and need for glucose-lowering medication during pregnancy. Our patient returned two months after giving birth (8 weeks postpartum) with normal value of OGTT. Because our patient didn't breastfeed with a body weight 50 kg (BMI: 22.22 kg / m2), we gave her diet B1 1500 calories and oral chelating agent (ADA, 2018).

CONCLUSION

We have reported a case of pregnant woman 28 y.o with gestational diabetes mellitus and beta major thalassemia. GDM was controlled with lifestyle modification. The patient gave birth to a normal baby girl. GDM was caused by insulin resistance and beta cell dysfunction. Other risk factor in our patient was iron overload. The mechanism of iron-induced diabetes is likely to be mediated by insulin deficiency, insulin resistance, and hepatic dysfunction.

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CASE REPORT

Management of Residual Pituitary Adenoma Patient with Manifestation of Acromegaly and Hyperprolactinemia

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ABSTRACT

Pituitary adenoma is one of intracranial tumors that grows and develops in the pituitary gland which plays a role in regulating the hormonal balance in the body. Most pituitary adenomas are benign and do not spread to other organs. Pituitary adenoma can be classified based on radiological features, tumor size and the type of hormone produced. There are several ways to establish of diagnosis of pituitary adenoma, in addition to recognizing the symptoms and clinical signs are hormonal function tests and imaging. The surgery is the first medical actions. The postoperative recovery rate reached 90% in relatively benign cases and tumor recurrence rate is 5-10% depending on the size of the tumor, the stage of the tumor during surgery, experience of neurosurgical. A woman, 46 years old referred to Dr Soetomo General Academic Hospital from Soebandi Jember Hospital for treatment the recurrent adenoma pituitary with complains of headache, double-vision and changing shape of his face, his enlarged lips and nose. Patient was diagnosed based on head CT scan and already had surgery on January, 2015. The head MRI evaluated post surgery was still a residual mass from the previous tumor. Three months after surgery no complains any more. The complains reappear at the end of 2017. The head CT scan on January, 8, 2017, size tumor: 1.2 cm x 1.8 cm. The head MRI results on December, 20, 2017 size tumor : size 1.6cm x 2.1cm and abnormal hormonal result, high prolactine, low cortisol and high IGF1. In Dr Soetomo General Academic Hospital was diagnosed as pituitary macroadenoma with acromegaly and hyperprolactinemia and received bromocriptine 3x5 mg evaluated for 2 weeks then lowered to 3x 2.5 mg after obtaining a decrease in prolactin levels and methyl prednisolone 3x1/day until cortisol level was normal. Patients will also plan for surgery of EETH (Endoscopic Endonasal Transphenoidal).

Keywords: Pituitary adenoma, Hyperprolactinemia, Acromegaly, Endoscopic endonasal transphenoidal

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INTRODUCTION

Pituitary adenoma is a benign tumor that develops in the pituitary gland, the part of the brain responsible for regulating the hormonal balance in the body, plays a role in regulating growth hormone and some other important hormones that regulate the function of the thyroid gland, adrenal glands, gonadal glands and lactation control. This pituitary adenoma causes a change in hormone production in the pituitary gland, causing too much or too little of the hormone to affect body function. This adenoma grows confined to the pituitary gland or surrounding tissue and does not spread to other parts of the body (Lake et al., 2013).

About 10% -15% of all intracranial tumors are pituitary tumors, making it the third most brain tumor after glioma and meningioma. Epidemiological data in the United States shows that the incidence of this case has a range of 0.4 to 18.7/100.000 population. The width of this incidence range is due to the nature of this tumor which is generally asymptomatic.

This pituitary adenoma is primarily about the age of 20-50 years, with a balanced incidence in males and females (Philips, 2013). Most pituitary tumors are found in adults of about 10% to 25% of intracranial neoplasms but can also be found at the age of children and adolescents (Chanson and Salenave, 2004).

The surgery is the first line of medical action. The postoperative recovery rate reached 90% in relatively benign cases. The tumor recurrence rate is 5-10% depending on the size of the tumor, the stage of the tumor during surgery, experience of neurosurgical (Laws et al., 2014). The surgical technique currently employed in Indonesia is transfenoid per endoscopy. This procedure is performed using an endoscope that is inserted through the nose and sinus to reach the bottom of the brain without an external incision and leaving no visible scars. The technique has an advantage in field surgery visualization as well as lower morbidity rate per microscopic technique (Dallapiazza et al., 2015).

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This paper will discuss the management of residual pituitary adenoma with hyperprolactinemia and acromegaly manifestations. In the case of the residif indicates some problems related to the selection of therapy. The most important thing to note is a strict follow-up to the possibility of recurrence of recurrence of the tumor.

CASE REPORT

A woman, Mrs. Mf, 46th, housewife, Javanese, and resident in Jember, came to Dr Soetomo General Academic Hospital referral from neurosurgeon of Soebandi Jember Hospital. The patient was referred to Dr Soetomo General Academi Hospital of neurosurgery for treatment of recurrent pituitary adenoma. The patient was diagnosed as pituitary adenoma in January 2015.

Her chief's complain was often headache and double vision since early January 2015. Her complaints are not accompanied by a sense of fever, nausea, vomiting or spinning head. Patients have no history of using minus or plus glasses. In addition, patients also complain of changes in the hands, feet and face shape. Patients feel the size of hands and feet larger than the original, so that the rings and shoes are commonly worn no longer fit. The patient also complained about the changing shape of his face, his enlarged lips and nose. Menstruation is also felt irregularly, but patients are not using contraception. A few months later, headache and double vision got worse, even the patient had fainted because of headache. So the patient decided to seek medical eye doctor. A number of checks have been done by an ophthalmologist, and the results show that the patient had severe field disturbance. So the patient is given a referral to examine the CT scan of the head with contrast. The results was a pituitary tumor (adenoma) in the patient (CT scan of the head on 8 January 2018). Then by an ophthalmologist, the patient was referred to a neurosurgeon at Soebandi Hospital in Jember. Based on the results of an examination by a neurosurgeon at Soebandi Hospital in Jember, the patient was adjudged for an operational action plan (January, 22, 2015). After surgery, the patient re-evaluated her adenoma condition via head-up MRI (January 30, 2015), and the result was still a residual mass from the previous tumor. After the surgery, patient still control to a neurosurgery doctor until 3 first month because there is still a complaint headache. After 3 months post operation, the patient has no more complaints so the patient does not come control to the doctor. But headache is felt again by the patient at the end of 2017, then the patient performed MRI repeated with the results of the remaining tumor relatively larger size and from laboratory examination there is high prolactin hormone results, so patient referred to the neurosurgery of Dr Soetomo General Academic Hospital. Patient no history of Diabetes, hypertention or heart disease.

Physical examination on January 3, 2018, She was alert, compos mentis, general condition enough, blood pressure 120/70 mmhg, pulse 82 times/minute, temperature 36.8 celcius and breathing 18 times/minute. Head examination is not found anemis, jaundice, cyanosis or tightness. On neck examination did not get enlarged neck gland. On examination of the chest region there was symmetrical breathing, no respiratory muscle retraction, no murmurs, and no gallops. In both lung fields there was a vesicular breath sound, neither ronki, nor wheezing. On abdominal examination obtained normal bowel sounds, liver and lien in normal limits. On examination of the extremity obtained akral warm, dry, the bones of hands and feet enlarged.

Laboratory examination on December 9, 2017: GH 18.5, TSHs 1.27, FT3 2.22, Ft4 0.730, prolactin 33.96, cortisol 4.23. Hemoglobine 11.3 mm/dl, leucocyte 5.67/mm3, thrombocyte 417.000/mm3. The head CT scan on Januri, 8, 2017 before surgery showed a mass of itrasella that began to extend into the cavernosus sinus, sphenoid sinuses and ethmoid measuring 1.2 cm x 1.8 cm. The head MRI results on December 20, 2017 showed lobulated-shaped mass of firm borders, the irregular edge of intracellar urgent posterior left sphenoid wall (size 1.6cm x 2.1cm). Thorax photo examination in normal limit.

Patients was diagnosed as pituitary macroadenoma with abnormalities of acromegaly hyperprolactinemia and hypocortisol. Patients was planned Endoscopic Endonasal Transphenoidal (EETH) by Soetomo's neurosurgeon and received bromocriptine 3x5 mg/day and methyl prednisolone 3x1/day.

Disease Progression

Second visit Endocrine poly, the patients with complaints headache and view felt sandy. Vital sign examination are good, blood pressure 120/80 mmhg, pulse 84 times/min, respiratory rate 20 times/min, laboratory testosterone 24.85, cortisol 9.63, Hb 12.7, leukocytes 5830/ul, plt 323.000, GDP 105, Gd 2jpp 115, SGOT 20U/L, SGPT 27 U/L, BUN 10, SK 0.5, Na 142, K 4.5, Clorida 111, calcium 9.2. T SH 0.948, FSH 1.67, LH 0.49 ACTH 12.6, cortisol 9.63. Patients received bromocropine 3x 5mg/day.

The third visit of Endocrine Poly, the patients with slight headache and sandy outlook showed that the vital sign was good, blood pressure 110/80, pulse 80 times/min, respiratory rate 18 times/min, the results of laboratory test prolactin was 13.38, cortisol 9.42, TSH 0.713, FT4 0, 76, LH 0.6, FSH 0.86. Patients will be planned to examine insulin-like Growth Factor 1 (IGF-1) and Thyroid Ultrasonography. Patients received bromocriptine therapy 3 x 2.5mg/hr.

The fourth visit of Endocrine Poly, the patients with headache were not found and the view was still sandy , vital sign examination was good, blood pressure 120/80 mmhg, pulse 80 times/min, respiratory rate 20 times/min, laboratory test result Hemoglobine 12, Leukocytes 6.48, neutrofil 49. 2%, platelet 344,000, K 4.3, Na 141, Cl 107, Ca 9.1,

prolactin 3.36, GH 17.1, cortisol 9.90. IGF-1 695 ng/ml (N: 74-196), GDP 110, Gd2jpp 101, Bun 9, creatinine serum 0.7, total cholesterol 267, Triglyceride 232, HDL 29, LDL 175. Patients received bromocriptine 1x 2.5 mg/day, atorvastatin 20mg.

The fifth visit of Endocrine Poly, the patients with sandy outlook complaints with vital sign examination are good, blood presure 110/80 mmhg, pulse 82x/m, respiratory rates 18 times/min with laboratory test results of GDP 105, Gd2jPP 155, TSH 0,557, FT4 0.66, prolactin 15,33, cortisol 5.8, Thyroid ultrasound bilateral thyroid cyst, colloid thyroid nodule left. Patients received bromocriptine therapy 1x 2.5mg/day. The patient is waiting for a call for EETH surgery.

DISCUSSION

Pituitary Tumor is a tumor that grows and develops in the pituitary gland. The pituitary gland lies in sella tursica, at the base of the skull. It called the master gland, which plays a role in regulating growth hormone and some other important hormones that regulate the function of the thyroid gland, adrenal glands, gonadal glands and lactation control. This pituitary gland consists of two lobes, the anterior lobe (adenohipofisa) and the posterior lobe (neurohipofisis). The anterior lobe produces five peptide hormones: prolactin hormone, growth hormone (Growth Hormone), glycoprotein hormone; Luteinezing Hormone (LH) and Stimulating Hormone Follicle (FSH), Thyroid stimulating hormone (TSH) hormone and Adrenocorticotropic hormone (ACTH), while the posterior lobe produces two hormones: oxytosis and vasopressin (Arafah and Nasrallah, 2011).

Most pituitary adenomas are benign and do not spread to other organs. Prevalence between women and men is no different, but most pituitary tumors are found in adults of about 10% to 25% of intracranial neoplasms but can also be found at the age of children and adolescents (Chanson and Salenave, 2004).

The pathogenesis of pituitary adenoma isn't certain known, but until the last decade there are two theories applicable to the origin of the tumor. The most commonly accepted theory is that this tumor is an intrinsic abnormality in the pituitary gland itself. Other theories are caused by the hypothalamus. According to the second hypothesis that pituitary tumors are the result of continued stimulation by hormones or hypothalamic factors. Some other opinions mentioned that the emergence of pituitary tumors is caused by the genetic defect of the presence of genes that trigger the occurrence of neoplasia that is multiple endocrine neoplasia type 1 (MEN I) which is a dominant autosomal disorder that shows the incidence obtained from malignant neoplasm and benign ones involving the pituitary gland, the parathyroid gland and the ancreas (Freda and Wardlaw, 2010).

Pituitary tumors can be classified based on radiological features, tumor size and the type of hormone produced. Based on the radiological features it consists of Grade 0: adenoma is not seen radiologically, 2. Grade I and II: limited adenoma in sella turcica 3. Grade III and IV: adenoma that invade into surrounding tissue. Based on the size of the adenoma is divided as: A. Microadenoma : size less than 1 cm, the location is always still in sella turcica and have not invaded surrounding structures such as sphenoid and sinus cavernosus, often when diagnosis is made of, tumor size 50% <5mm B. Makroadenoma: Size more than 1 cm, usually extends from sella turcica and already invaded surrounding structures, was found because of the compression efect of the tumor, such as bitemporal hemianoption, in addition to endocrine disorders, may be hyper or hyposecretion. Based on hormones produced pituitary adenomas consists of 1. Non-functional pituitary adenoma (not producing hormones) 25% of pituitary adenoma 2. Functional pituitary adenoma (hormone production) of 70% of pituitary adenoma consisting of: a. prolactin-secreted adenomas (52%) b. adenoma secreted growth hormone (GH) 27%, c. adrenocorticotropic hormone (ACTH) 20% and d. adenoma secreted TSH 0.3% (Chanson et al., 2015; Olsson, 2014).

In these patients based on the classification of the tumor, it can be categorized as adenoma 0f grade 3-4, functional pituitary macroadenoma with hyperprolactinemia and acromegaly manifestations. This patient had a tumor size greater than 1 cm accompanied by an increase in prolactin hormone production and an increase in insulin-like growth factor 1 (IGF 1).

There are several ways to establish of diagnosis of pituitary adenoma, in addition to recognizing the symptoms and clinical signs are 1. Hormonal function tests to measure hormone levels. This test is required for each patient with a pituitary tumor. Hormone tests can detect or confirm functional adenomas, as well as determine if there is evidence of pituitary insufficiency. Some functional tumors, especially prolactinomas, can be effectively treated without surgery and therefore, it is imperative that a comprehensive hormone test be performed before consideration of surgical removal of the tumor. 2. Imaging, one of the imaging methods used to detect pituitary adenomas is magnetic resonance imaging (MRI) scans. MRI is believed to detect adenomas larger than four millimeters. MRI is preferred for detecting pituitary adenomas, in addition computed tomography (CT) scans can also be used (Bergsneider, 2011; Laws et al., 2013).

In these patients there are frequent complaints of headache and double vision which is felt since early January 2015, the patient also felt a change in the size of his hands and feet are larger than the original. The patient also complained about the changing shape of his face, his enlarged lips and nose.

In this patient have performed several examinations that support the direction of pituitary tumor is the examination of growth hormone (GH), thyroid hormone (TSH), hormone levels prolactin and cortisol levels. Obtained some results of disruption in hormone production of prolactin hormone increased 33.96 and decreased levels of cortisol 4.23. A CT scan of 8 Januri 2017 before surgery showed a mass of diitrasella that began to expand into the cavernosus sinus, shenonoid sinuses and ethmoid measuring 1.2 cm x 1.8 cm. Head MRI results dated December 20, 2017 post operative mass visible lobulated shape of firm borders, irregular edges on intrasella that push the left posterior right sphenoid wall (size 1.6cm x 2.1 cm).

Patients with pituitary adenoma showed a variety of clinical signs and symptoms that can be categorized as follows: 1. Signs and symptoms associated with excessive or defisiency hormone production, such as hyperprolactinemia in patients secreting the hormone prolactin, therefore an endocrine evaluation is required to confirm the presence or or at least endocrinopathy in patients 2. Signs and symptoms associated with mechanical effects of tumor expansion such as headache symptoms, visual disturbances and cranial nerve palsies (Katznelson et al., 2014).

Prolaktinoma is a prolactin hormone producing pituitary adenoma. Prolactinoma is the most common type of hyperprolactinemia-related pituitary adenoma. Hyper-prolactinemia is a state of elevated serum prolactin level exceeding 25 ng/ml in basal conditions. The normal value of serum prolactin is 5-25 ng/ml; lower in men and children. Prolactin levels in nonpregnant women were less than 20 ng/ml and prolactin levels in men were less than 15 ng/ml. Prolactin had daily variation increased at night, maximum at 01.00-06.00 in the morning. Increased levels of prolactin often cause various reproductive system disorders. Menstrual disorders arise due to hyperprolactinemia block the hypothalamus-pituitary ovarial axis in hypotalamus, resulting in decreased secretion of FSH and LH. Decreased secretion of FSH and LH interfere with the process of folikulogenesis, so that estrogen secretion decreases. A low estrogen causes LH surge does not occur, so ovulation does not occur. Hyperprolactinemia can also be found in certain conditions, eg pregnancy, stress, hypoglycemia, renal failure, hypothyroidism and drugs: sedatives: trifluoperazine, haloperidol, and metoclopramide. Symptoms of hyperprolactinemia in women may be amenorrhea, oligomenore, galactorrhea, infertility, osteoporosis, headache, visual disturbances, and signs of elevated androgen levels in women. In men, it is usually asymptomatic but may lead to symptoms of gyneconomic impotence, decreased libido and sexual potency in men (Ajmal et al., 2014).

In these patients were found frequent complaints of headache, double vision and menstrual disorders experienced since early 2015 and prolactin levels obtained 33.96.

Another manifestation of pituitary adenoma is growth hormone hypersecretion (growth hormone), which, if it occurs in children whose epipheseal has not closed, is called to gigantism and if it occurs in adulthood is called acromegaly. Acromegaly is a disorder that arises from excess growth hormone resulting in excessive growth in various tissues of the body, muscles, and bones, especially in the legs and hands. The incidence of acromegaly in both men and women occurs equally, usually in the fifth decade (Katznelson et al., 2014; Iuliano and Laws, 2013).

Symptoms arise gradually because of the influence of elevated levels of GH in chronic. Most new sufferers find themselves stricken with Akromegaly after years. Early symptoms include shoe size and enlarged shirt, then visceromegaly, Skin tags, changes in the cuticle and subcutaneous tissue slow fibrous hyperplasia found primarily in the fingers, lips, ears and tongue (Katznelson et al., 2014; Chanson et al., 2009).

Growth hormone is produced and secreted from somatotropic cells in the anterior pituitary lobe. The presence of GH in the circulation triggers the liver in producing insulin like growth factor I (IGF-1). Insulin-like growth factor (IGF), formerly called somatomedin, is one of several peptide hormones that work primarily to stimulate growth but also has the ability to lower blood glucose levels. IGFs were discovered when researchers began studying the effects of biological substances on cells and tissues outside the body. IGF 1 has effects like insulin in some tissues, although they are much less powerful than insulin in reducing blood glucose concentration. IGF-1 is a major mediator of the growth hormone (GH) effect that stimulates systemic body growth, and has an increased growth effect on almost every cell in the body, especially skeletal muscle, cartilage, bone, liver, kidneys, nerves, skin, hematopoietic cells , and lungs. In addition to effects such as insulin, IGF-1 can also regulate cell growth and development, especially in nerve cells, as well as cellular DNA synthesis (Melmed, 2009).

There are two IGF: IGF-1 and IGF-2. Both of these factors, regardless of their similarity in name, can be distinguished in terms of specific actions on the network because they bind and activate different receptors. The main action of IGFs is on cell growth. Indeed, most of the pituitary growth hormone measures are mediated by IGFs, especially IGF-1. Growth hormone stimulates many tissues, especially the liver, to synthesize and secrete IGF-1, which in turn stimulates hypertrophy (increased cell size) and hyperplasia (increased cell count) of most tissues, including bone. Serum concentrations of IGF-1 increased during childhood and peak at puberty, and they declined subsequently (as was the secretion of growth hormone). Children and adults with growth hormone deficiency had low serum IGF-1 concentrations compared with (eg, acromegaly) has increased

serum IGF-1 concentrations. IGF-2 production is less dependent on growth hormone secretion than IGF-1 production, and IGF-2 is much less important in stimulating linear growth (Mesfro et al., 2004).

Clinical manifestations of IGF 1 disorders, including 1. Dwarfism; is a rare disease characterized by an inability to make or respond to IGF-1 and produce a specific type of growth failure. One such disorder, called Larwar dwarfism, does not respond entirely to the treatment of growth hormone because of the lack of GH receptors, 2. Acromegaly. Acromegaly is a syndrome that occurs when the anterior pituitary gland produces excess growth hormone (GH). A number of disorders may increase the pituitary GH output, although most often involving a tumor called pituitary adenoma, originating from different cell types (somatotrophs). This leads to changes in anatomy and metabolic dysfunction caused by increased GH and insulin growth rate 1 (IGF-1) (Akin and Yerlikaya, 2011; Molitch et al., 2006).

Measurement of GH levels can not be trusted because of the secretion of this hormone in the form of spark, although in the state of adenoma. Normal basal levels of GH <1 ng/ml, in patients with measurements of somatemedin C levels are more reliable, since their levels are constant and increase in acromegaly. Normal levels of 0.67 U/ml, Acromegaly may increase to 6.8 U/ml Acromegaly may increase to> 5 ng/ml, although in patients it is usually normal (Melmed, 2009).

In these patients there is a complaint of changes in the hands and feet are enlarged, it is known from the rings and shoes that are usually worn no longer fit. In addition, the patient also complained of enlarged lips and nose, and the jaw bone prominence. Laboratory examination was obtained by the increase of Insulin Like Growth Factor (IGF 1) 1695 ng/ml (N: 74-196).

Management of pituitary adenoma should be done comprehensively and individually, with objectives 1. Overseeing clinical and biochemical signs of excessive hormone secretion, 2 Maintenance of normal function of the pituitary wherever possible, 3. Managing weakness of pituitary function, 4. Monitoring tumor growth and mechanical effect on structure surrounding. There are three modalities of therapy that can be performed in cases of pituitary adenoma, surgery, medical and radiotherapy (Katznelson et al., 2014).

Surgical action is expected to lift the entire mass of the tumor so that control of growth hormone secretion can be achieved. This action becomes an option in patients with complaints arising from tumor compression. . Size of tumor before surgery affects the success rate of therapy. In patients with microadenoma the normalization rate of IGF I reaches 75-95%, while in macroadenoma the hormonal normalization rate is lower at 40-68%. In addition to the size of the tumor, other factors that determine the success of the surgery are the surgeon's experience and hormone levels before surgery (Laws et al., 2014).

The surgical technique currently employed in Indonesia is transfenoid per endoscopy. Transsphenoidal Surgery is a procedure for removal of a pituitary tumor located at the base of the brain that is difficult to reach. This procedure is performed using an endoscope that is inserted through the nose and sinus to reach the bottom of the brain without an external incision and leaving no visible scars. The technique has an advantage in field surgery visualization as well as lower morbidity rate per microscopic technique (Dallapiazza et al., 2015).

Medical therapy in acromegaly consists of three classes, namely dopamine agonists, somatostatin analogues, and growth hormone receptor antagonists. Dopamine agonists consist of bromocriptine and cabergoline. Monotherapy with cabergoline has a efficacy of between 10-35% in normalizing IGFI levels. In the 64 series of patients with acromegaly treated with cabergoline for 3 to 40 months at a dose of 1.0-1.75 mg/week reduced GH and IGF I levels in 40% of patients. Bromocriptine can be used to treat hyperprolactinaemia and also acromegaly. For hyperprolactinemia the initial dose of bromocriptine can be given 1.25 mg or 2.5 mg orally daily with a maintenance dose: 2.5 mg to 15 mg orally daily. For initial doses Acromegaly starts at 2.5mg with maintenance doses reaching 20-30mg (Arafah and Nasrallah, 2011).

Somatostatin analogues work to resemble somatostatin hormone, it is used to block hormone release in endocrine tumors, incuding inhibiting growth hormone secretion. Native somatostatin reduces symptoms in patients with carcinoid syndrome. However, its use is limited by its short half-life (∼2 minutes). With the availability of synthetic somatostatin analogues, octreotide (half-life, 90 minutes) and lanreotide. This group of drugs has an effectiveness of about 70% in normalizing levels of IGFI and growth hormone. Its high effectiveness makes the somatostatin analog group drug as the first choice in medical therapy. Studies assessing the effectiveness of this class of drugs show that IGFI normalization is achieved in 51% of subjects after long-acting somatostatin analogue for 36 months. In addition to normalizing levels of IGFI, somatostatin analog therapy can also shrink tumor size (80%), improvement of heart function, blood pressure, and lipid profile. The main problem faced to date is the high cost to be incurred. There are two effective long-acting somatostatin analogue preparations: intramuscular ocreotide long acting release (LAR), and deep sc lanreotide depot/autogel given monthly. The approved initial dose of ocreotide LAR is 20 mg/month with a dose titration every 3-6 months down to 10 mg or up to 40 mg/month. Lanreotide autogel/initially approved dose depot

90 mg/month dose is titrated down to 60 mg/month or up to 120 mg/month (Calao et al., 2009).

The growth hormone receptor antagonist is a new class in acromegaly medicament therapy. Pegvisomant is an analogous recombinant human growth hormone that acts as a selective GH receptor antagonist. This class of drugs is recommended in cases of acromegaly that can not be controlled with surgical therapy, administration of dopamine agonists, or somatostatin analogues. Pegvisomant was administered subcutaneously at a dose of 10, 15 or 20 mg/day. normalization of IGFI is dose dependent and can be achieved in patients receiving doses up to 40 mg day (Neggers et al., 2011).

Radiotherapy is generally not used as first-line therapy in acromegaly cases but is used as adjuvant therapy for pituitary tumors because of the length of time the effective therapy has been reached since it was first started. The purpose of radiation therapy for pituitary tumors is to reduce or control tumor size. Two types of radiation therapy are used to treat pituitary tumors: 1. Conventional External Beam Radiation 2. Radiosurgery stereotactic. Conventional External Beam Radiation uses fractionation, where treatment is delivered in daily fractions for several weeks. Whereas in stereotactic radiosurgery, the tumor tissue is irradiated with the appropriate dose and conformal volume so that healthy tissue is spared from the effects of radiation (Bergsneider et al., 2016).

In these patients received 3x5mg of bromocriptine therapy evaluated for 2 weeks then lowered to 3x 2.5 mg after obtaining a decrease in prolactin levels from 33.97 to 13.38. Patients will also plan for surgery of EETH (Endoscopic Endonasal Transphenoidal).

Monitoring of the biochemical response of the therapy was performed by examining growth hormone levels and IGFI. Generally the examination is performed 3-6 months after surgery. Biochemical control is defined as a growth hormone level <1.0 ng/ml and normal IGFI levels. Postoperative MRI examinations are generally performed 3-4 months later. In patients undergoing medical therapy MRI examination is performed every 3-4 months after starting therapy (Vincent et al., 2007). Acromegaly is associated with an increased risk of mortality of 2-2.5 times, and normalization of GH or IGFI or both has shown to reduce the risk of mortality. Control of GH and IGFI should be an important focus of therapy for acromegaly, in particular to reduce the risk of mortality (Sherlock et al., 2010).

CONCLUSION

A case of a female, Mrs. Mf, 46th references to Soebandi Jember Hospital with a diagnosis of residual pituitary macroadenoma with hyperprolactinemia and acromegaly manifestations. The patient was diagnosed as a pituitary macroadenoma based on a CT scan of January 8, 2015 with a headache complaint, a double glance and changes in the hands, legs, facial shape and enlarged jawbone. The patient had undergone tumor surgery on January, 22 2015 and declared residif based on MRI in December 2017 with a headache and sandy-like outlook so the patient was referred to Soetomo Hospital. There have been several hormonal checks related to this patient's disease. High levels of prolactin and IGF 1 were obtained. Patients received bromocriptine 3x 5 mg therapy with evaluation of prolactin hormone levels and planned EETH surgical removal by neurosurgeon. The success rate of surgical therapy depends on the size of the tumor, the stage of the tumor during surgery, the hormone level and the surgeon's experience. Good control of GH and IGF 1 may decrease mortality.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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CASE REPORT

Challenges in The Management of Toxic Multi Nodular Thyroid in Pregnancy who had Crisis Thyroid

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ABSTRACT

Managing crisis thyroid in toxic multi nodular thyroid in pregnancy is challenging. The challenges are controlling thyroid hormone in mother without affecting development of fetus. This case objective is to highlight comprehensive treatment going to avoid maternal & infant mortality. Actually, crisis thyroid in pregnancy is a preventable death. An upgrading resources team in peripheral public health service is necessary. A woman, 43 years old in 13th week of her third pregnancy, admitted in emergency room with palpitating and vomiting as her chief complaints. Her complaints had started since she stopped taking propylthiouracyl. She used to take it since diagnosed hyperthyroid. She was diagnosed crisis hyperthyroid in pregnancy. The first main goal was to stabilize the patient, curing the precipitate factors, and assist her to have a healthy baby. She was discharged from hospital day 7th. She was routinely checked FT4 for evaluation and switch on Thyrozol during 25-26th weeks and continued it until postpartum. Her baby was delivered vaginally with normal APGAR score and growing well. Based on her experience, she agreed to have IUD to prevent unplanned pregnancy.

Keywords: Crisis thyroid, Hyperthyroid in pregnancy, Toxic multinodular thyroid, Maternal mortality, Infant mortality, Preventable death, Public health

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INTRODUCTION

Toxic Multinodular Thyroid is one causal of crisis thyroid. In Pregnancy, it can be overlapping with hyperemesis gravidarum and Grave's disease. Toxic multi nodular goiter (MNG) becomes second causal of thyrotoxicosis. It is unremitting and develops slowly, with more subtle than Grave's. It induces a hyperthyroid since the functional capacity of the thyroid cells then become independent of regulation by thyroid-stimulating hormone (TSH) focal and/or diffuse hyperplasia of thyroid follicular cells occurs, a long phase of subclinical hyperthyroidism can precede the appearance of overt symptoms (Fulara and Fulara, 2017). MNG are characterized by systemic symptom such as agitation to psychosis, warm skin, tachycardia as sign of increasing cardiac output, 60% hyperthyroid patient has atrial fibrillation, dyspnea, hyper defecation, malabsorption, abnormality bone composition, and polyuria (Ross, 2018).

CASE REPORT

In July 2017, a woman, 43 years old in 13th week of her third pregnancy, admitted in emergency room with palpitating and vomiting as her chief complaints. She had nausea and vomiting for a month. Nausea and vomiting didn't come with headache. She drooled more than usual then it was followed with nausea and vomiting. She also had fever, palpitation, and shortness of breath, stomachache, and dizziness. Her complaints had started since she stopped taking propylthiouracyl (PTU) which she used to take it regularly since diagnosed hyperthyroid 2 years ago. She had stopped taking PTU since her nausea was getting worse. This complaints appeared at the same time with absent of menstrual period and her breast became tender this last 3 months. Now, she urinates more often these recent days.

In 2015, Pts was diagnosed with hyperthyroid then given PTU and Propanolol. She visited a Midwife then stopped her Depo Medroxy Progesterone Acetate (DMPA) as her contraception at that time without replacing with other contraception. She had twice previous premature birth, her first son is 25 years old and the younger is 23 years old now. Her last menstruation was in April 2017 and had positive result for pregnancy test. In June 2017, she had hyperemesis then stopped taking PTU.

The patient was in weak condition, agitated, with blood pressure of 160/100 mmHg, heart rate was 130 beat per minute (bpm) regular, respiration rate 27 times per minute (tpm), body temperature 37.6 degree celcius. From head and neck examination we found enlargement of thyroid glands

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and no exophthalmos with increase of jugular venous pressure. On heart examination we found strong heart pulsation of ictus cordis in mid clavicular line. Single S1 and S2, with gallop, but without murmur nor extra systole. From the extremities we found no myxedema, but with wet and cold palm. Total of Burch – Wartofsky (BW) score was 55. Body weight was 51 kg, body height was 155 cm, BMI was 21 (normal).

We performed several examination to establish diagnosis and to find out her future management strategies. The admission of thyroid function test were Thyroid Stimulating Hormone (TSH) is 0.001 (0.55-4.78 IU/ml), Free Thyroid-4 (FT4) is 19.51 (0.89-1.76 mg/dL). From obstetric ultrasonography, the gestational age was equal to 14/15 weeks, singleton, with fundal placenta, normal amount of amniotic fluid with normal fetal movement and was concluded that there are no suspicion of major congenital anomaly. She was advised to have ultrasonography examination repeated next month. ECG showed sinus tachycardia 130 beat per minute.

Both physical and laboratory examination results indicate that the patient is inflicted with Toxic Multinodular Thyroid in pregnancy, a particularly high risk case and demanding a well management to safe patient and her baby's life.

The first main goal was to stabilize the patient, curing the precipitate factors in order to treat the thyroid crisis. We managed patient using guideline crisis thyroid in pregnancy of Association Thyroid of America (ATA). Patient should be in Intensive Care setting. First of all we gave oxygenation to the patient with reservoir mask 8 to 10 liter per minute (lpm), with normal saline infusion 500 cc in 6 hours. We gave high calorie and high protein diet of 1800 kcal. Hyperthyroid medication started with therapy for thyroid crisis. Patient should take PTU tablet every 4 hours, it was started by 400 mg of loading dose, then followed by maintaining dose PTU 100 mg every 4 hours, orally. She was also given Iodine drops, methylprednisolone, symptomatic therapy in order to relieve her condition. Her baby was regularly evaluated by obstetric team. Vital sign monitoring and complaints must be taken as priority. On second day, her condition was well improved with BW score 40 without vomiting. On seventh day, the result of TSH was 0,008 (0.55-4.78 IU/ml), and FT4 was 1,75 (0.89-1.76 mg/dL). So, we diagnosed her with subclinical hyperthyroid. She was planned to continue PTU 100 mg, Propranolol 10 mg, and ASA 80 mg, all once daily and also MP 16 mg three times a day orally. The PTU had must be taken until 1st semester, Propranolol had must be taken 3 days after discharge only, regarding its effect on pregnancy.

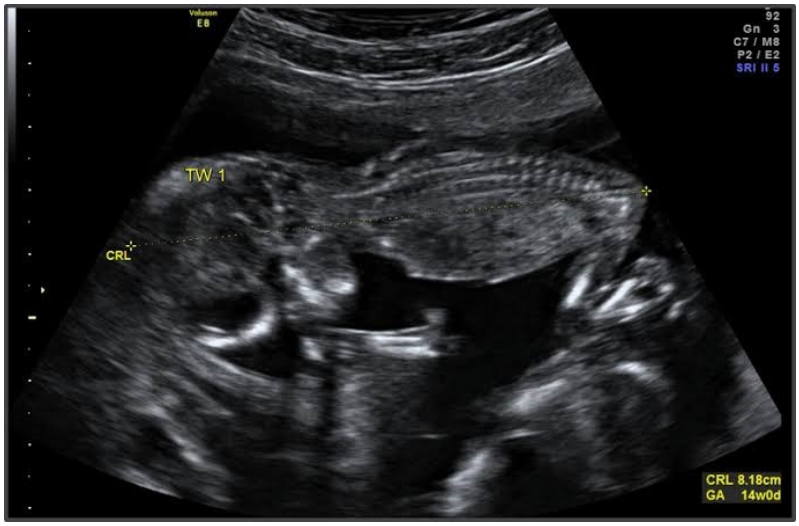

Figure 1. Obstetric USG of patient on 14-15 weeks old

Figure 2. A 6 month old baby boy

DISCUSSION

Overt hyperthyroidism (low thyroid-stimulating hormone (TSH), elevated free thyroxine (T4) and/or triiodothyronine (T3) is relatively uncommon during pregnancy, occurring in 0.1 to 0.4 percent of all pregnancies (Krassas et al., 2016). About 1-2% of hyperthyroidism has thyroid crisis during pregnancy (Ma et al., 2018). The most frequent causal of hyperthyroidism are Grave's disease, toxic adenoma, and toxic multinodular goiter (Ross, 2018). Genetically, Asian women are more likely to have gestational thyrotoxicosis and hyperemesis gravidarum due to raising in production and metabolism of human-chorionic gonadotropin (hCG) (Purnamasari et al., 2013).

Toxic multi nodular goiter (MNG) becomes second causal of thyrotoxicosis. It is unremitting and develops slowly, with more subtle than Grave's (Fulara and Fulara, 2017). Its characterized by systemic symptom such as agitation to psychosis, warm skin, tachycardia as sign of increasing cardiac output, 60% hyperthyroid patient has atrial fibrillation, dyspnea, hyper defecation, malabsorption, abnormality bone composition, and polyuria (Ross, 2018). Toxic or hot nodules secrete THs independent of the pituitary because this tissue contains mutated TSHRs. Thyroxine levels typically are elevated in these patients sometimes only T3 levels are increased. Consequently if T4 concentrations are normal in such patients T3 levels should be determined to rule out T3 toxicosis. In toxic multinodular goiter, the thyroid gland normally enlarges in reaction to an increased demand for THs that occurs in pregnancy, iodine deficiency and immunologic, genetic disorders. Autonomous follicles may produce excessive TH unregulated by TSH, resulting in thyrotoxicosis symptoms similar to GD without infiltrative ocular manifestations or myxedema (Alemu et al., 2016).

In laboratory findings, measurement of TSH level is the only initial test necessary in a patient with a possible diagnosis of hyperthyroidism without evidence of pituitary disease. If the TSH level is low, then FT4 should be measured to evaluate for thyrotoxicosis. Measurement of FT3 is helpful in the clinical diagnosis of thyrotoxicosis when the FT4 values are unexpectedly normal (Alemu et al., 2016). Women with FT3, FT4 above the reference range along with TSH value <0.1 mIU/L were classified as having overt hyperthyroidism while those having FT3, FT4 in normal range with TSH <0.1 mIU/L were diagnosed as having sub-clinical hyperthyroidism. Normal range for TPO antibody was <35 IU/mL and value greater than or equal to indicate elevated Anti-TPO in serum (Rajput et al., 2015).

In patient with hyperthyroid and stop menstruation period we have to think about differential diagnoses such as gestational trophoblastic disease and gestational hyperthyroid. In the past, approximately 55 to 60 percent of women with trophoblastic disease had clinically evident hyperthyroidism at the time of diagnosis, which could be severe. However, in a review of 196 patients from the United Kingdom treated for gestational trophoblastic disease between 2005 and 2010, biochemical hyperthyroidism was present in 7 percent and clinical hyperthyroidism in only 2 percent (Walkington et al., 2011).

Pregnancy poses to maternal thyroid gland as hormone requirements are increased during gestation. Beta HCG are homolog of TSH, so it seats on TSH receptors to stimulate thyroid hormones. In the other hand, there is also an estrogen mediated increased in circulating of thyroid – binding globulin (TBG) 2-3 times in serum during pregnancy and increase TBG production in liver. Enhance, TBG is one of numerous protein that transport thyroid hormone in the blood with high affinity for thyroxin (T4) in serum a few weeks after conception and ranges a plateau during mid-gestational period. Both mechanism between estrogen mediated and hepatic synthesis of TBG lead to increases the half-life from 15 minutes to 3 days to fully sialylated TBG. Elevated levels of TBG lead to lowered free T4 concentrations which results in increased TSH secretion by pituitary and automatically enhanced production and thyroid hormone secretion (Alemu et al., 2016).

Treatment for thyroid storm or heart failure is similar and should be carried out in an intensive care area that may include special-care units within labor and delivery. An hour or two after initial thionamide administration, iodide is given to inhibit thyroidal release of T3 and T4. It can be given intravenously as sodium iodide or orally as either saturated solution of potassium iodide (SSKI) or Lugol solution. With a history of iodine-induced anaphylaxis, lithium carbonate, 300 mg every 6 hours, is given instead. Most authorities recommend dexamethasone 2 mg intravenously every 6 hours for four doses, to further block peripheral conversion of T4 to T3. If a β-blocker drug is given to control tachycardia, its effect on heart failure must be considered. Propranolol, labetalol, and esmolol have all been used successfully. Coexisting severe preeclampsia, infection, or anemia should be aggressively managed before delivery is considered (Cunningham, 2014). Thyrotoxicosis during pregnancy can nearly always be controlled by thionamide drugs. Propylthiouracil (PTU) has been historically preferred because it partially inhibits the conversion of T4 to T3 and crosses the placentaless readily than methimazole. The initial thionamide dose is empirical. For non-pregnant patients, the American Thyroid Association recommends that methimazole be used at an initial higher daily dose of 10 to 20 mg orally followed by a lower maintenance dose of 5 to 10 mg. If PTU is selected, a dose of 50 to 150 mg orally three times daily may be initiated depending on clinical severity. At Parkland Hospital, it is initially given for 300 or 450 mg daily in three divided doses for pregnant women.

Occasionally, daily doses of 600 mg are necessary. As discussed, they do not transition women to methimazole during the second trimester. The goal is treatment with the lowest possible thionamide dose to maintain thyroid hormone levels slightly above or in the high normal range while TSH levels remains suppressed (Fulara and Fulara, 2017). Serum free T4 concentrations are measured every 4 to 6 weeks (Cunningham, 2014).

All pregnant women should consume approximately 250 μg iodine daily. In order to achieve a total of 250 μg iodine ingestion daily, strategies may need to be varied based on country of origin (Alemu et al., 2016).

Given PTU hepatotoxicity concerns, experts currently recommend using low-to-moderate MMI doses as a first-line therapy in lactating mothers. PTU should be reserved only as a second-line agent for cases of severe hyperthyroidism especially thyroid storm and allergic reactions to previous MMI treatment. ATD should be administered in divided doses immediately following each feeding. Evaluation of thyroid function tests is advisable at least 3-4 weeks after the initiation of breastfeeding (Hudzik and Zubelexicz-Szkodzinska, 2016).

CONCLUSION

A 43 year old woman whom diagnosed thyroid crisis with comorbid gravida, had been treated with PTU, lugol, and metilprednisolon. Since her pregnancy during first trimester, therapy of methimazole was not the first choice. She was discharge with sub clinical hyperthyroid then routinely had her thyroid condition and pregnancy checked up in local area. The therapy target was to keep her in subclinical hyperthyroid. She was routinely checked FT4 for regular evaluation and also under supervision of obstetrician. Combination of well pregnancy program and obvious care treatment in hyperthyroid will safe mother and child.

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