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Gestational Trophoblastic Neoplasia with Hyperthyroidism

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ABSTRACT

Gestational Trophoblastic Neoplasia (GTN) is a malignant lesion arising from placental villous and extra-villous trophoblastand occurs in 1:40,000 pregnancies. Invasive mole and choriocarcinoma are the vast majority of GTN which produce substantial amounts of Human Chorionic Gonadotropin (hCG). Hyperthyroidism in GTN is due to the stimulation of the thyroid gland by hCG which has a similar structure with Thyroid-Stimulating Hormone (TSH). A 28-year-old female, suspected with choriocarcinoma and anemia, had a history of recurrent vaginal bleeding for eight months, accompanied with loss of appetite, weight loss, palpitation, and tremor. Physical examination such as pulse rate of 114x/minutes, the respiration rate of 26x/minutes, temperature 38^{0}C, conjunctival anemia, and dyspnea were reported. In addition, laboratory findings such as anemia, leukocytosis, hypoalbuminemia, hypokalemia, increase of LDH, increase of hCG >1,500,000 mIU/mL, T4 levels of 14.1 ug/dL (4.40-10.90 ug/dL), FT4 levels of 1.95 ng/dL (0.89-1.76 ng/dL), and decrease of TSH were also reported. Abdominal CT Scan suggested uterine mass suspected as malignancy infiltrating to the rectum with metastatic features in the liver, base of left lung, spleen and left kidney. Increased CA-125, and metastatic features of lung right paracardial and left suprahilar from Chest X-ray were found. Diagnostic criteria for gestational trophoblastic neoplasia are as follows: increased hCG 4 x tests; increased hCG three weekly tests; histology diagnosis of choriocarcinoma; increased hCG > 20,000 more than four weeks post evacuation and the presence of metastasis. Hyperthyroidism in GTN is potentially life-threatening because of heart failure and thyroid storm. Hyperthyroidism increases morbidity and mortality in GTN patient; therefore, periodic thyroid tests is essential to prevent further complication of hyperthyroidism.

Keywords: Gestational trophoblastic neoplasia, human chorionic gonadotropin, hyperthyroidism

INTRODUCTION

Gestational Trophoblastic Neoplasia (GTN) is a malignant disease arising from the placental and trophoblast villi, part of the group of Gestational Trophoblastic Disease (GTD) which requires chemotherapy. Gestational trophoblastic neoplasia occurs in 1:40,000 pregnancies, and is more common in Asia than Europe or North America. There are four types of GTN based on pathological features, namely, invasive mole, choriocarcinoma, Placental Site Trophoblastic Tumor (PSTT) and Epitheloid Trophoblastic Tumor (ETT). All of the types can cause uterine perforation, metastasis, and death if untreated. About 50% of GTN cases are the development of a molar pregnancy, 25% of abortion ortubal pregnancy, and 25% of preterm pregnancies. Invasive mole and choriocarcinoma are the most GTN, producing Human Chorionic Gonadotropin (hCG) and are very responsive to chemotherapy with a cure rate of more than 90%. The good cure rate is achieved because of tumor response to chemotherapy, the use of hCG as a marker for diagnosis, monitoring therapy and follow-up to the patient. The PSTT and ETT occur less frequently, produce less hCG and are relatively resistant to chemotherapy.[1,2]

Human chorionic gonadotropin is a glycoprotein produced by the placenta, with high levels in the first trimester of pregnancy. The similar structure between hCG and TSH, the same effect on the thyroid gland, and similarity of hCG receptors with TSH receptors can increase hCG levels that will affect thyroid hormone levels. Changes in thyroid hormone levels occur when hCG levels are around 50,000-70,000 mIU/L or more, and symptoms of hyperthyroidism will appear if hCG levels are very high.[3] The prevalence of hyperthyroidism in patients with hydatidiform mole and choriocarcinoma is 25-64%. One study reported that 30 of 52 patients with GTN had thyrotoxicosis. Other studies showed that the prevalence of thyrotoxicosis in GTN patients was around 50%, and it was potentiallyable to cause death. The development of an early detection test led to the decrease of the mortality rate.[3,4]

There was a case of an adult female with GTN with hyperthyroidism. This case was published to learn more about GTN with hyperthyroidism, to study the

importance of early detection of hyperthyroidism, and to prevent further complications.

CASE

A 28-year-old female was referred from Jombang hospital to the Emergency Department of Dr. Soetomo Hospital on June 3, 2017, with suspicion of choriocarcinoma and anemia. Patients had repeated vaginal bleeding since eight months ago. Six days before, the patient complained of abdominal pain accompanied with fever and chills, without nausea and vomiting. Patients had a history of abortion in November 2016 (due date: October 2016). The history of illness in patients can be seen in Table 1.

The patient also complained about a loss of appetite and weight, tightness, palpitations and trembling body since about one month ago. There were no complaints in urination and defecation. The patient said that she never had the same experience before. History of goiter, hypertension, heart disease, liver disease, kidney disease, and cancer were denied by the patients. History of the same disease in the family was also denied. The patient has married for 6 years and has one 4-year-old child who was born normally with vaginal delivery.

PHYSICAL EXAMINATION (June 3, 2017)

The general condition of the patient was weak, Glasgow Coma Scale (GCS) of 4-5-6, blood pressure of 110/70 mmHg, the pulse of 114x/minute, regular and strong, breathing of 26x/minute, axillary temperature 38°C. Head examination revealed anemic conjunctiva and dyspnea without jaundice and cyanosis. No enlarged lymph nodes in the neck, nodules or enlargement in the thyroid area. Thoracic examination showed an asymmetrical chest shape without chest wall retraction. Single S1 S2 heart sound without gallop or heart noise was reported. Vesicular breath sounds, without rhonchi and wheezing. Abdominal examination showed normal bowel sounds and no enlargement of the liver, spleen, and kidney. The acral extremity was warm and dry without edema. There was no enlargement of lymph nodes in the axilla and inguinal regions. Inspection of vulva vaginal showed slippery portions, ostium was open with one finger loose, with fluxus (+) and fluoralbus (-). Vaginal touch erexamination did not show painful portio, corpus uterine was difficult to evaluate, and there were no abnormalities found in adnexa, parametrium, and Douglas.

LABORATORY TESTS

A complete blood test showed anemia and leukocytosis. Clinical chemical parameters showed hypoalbuminemia, hypokalemia, and an increase of Lactate Dehydrogenase (LDH). Urinalysis showed positive nitrite results, proteinuria, increased urobilinogen, bilirubinuria, and eritrocyturia. The immunological test showed non-reactive HIV and

Table 1. History of illness

History of Illness	
Mid-November 2016	The patient had vaginal bleeding. Ultrasound examination of the abdomen in Jombang General Hospital was performed by intrauterine imaging of Gestational sacs. The patient was diagnosed with an imminent abortion and given strengthening drugs and vitamins.
December 2016	The patient came to Moejito Hospital Jombang with vaginal bleeding and diagnosed with incomplete abortion and had undergone curettage. Histopathological examination was not performed on the curettage tissue.
January-February 2017	The patient was still complaining of vaginal spots.
March 2017	The patient had unstoppable vaginal bleeding and clots. It was suspected as a malignancy. Curettage PA results reported remaining pregnancy tissue.
31 May 2017	Patients came to Jombang Hospital with abdominal pain, fever and chills since 3 days before, vaginal bleeding was still present. The patient was then referred to Dr. Soetomo Hospital

HBsAg, an increase of total quantitative hCG, T4, FT4, accompanied by normal T3, decreased TSH, and increased procalcitonin levels. Tumor markers test showed normal AFP and CEA with increase CA-125. ICT tests for dengue IgM and IgG, *S.Typhi* O and H, *S.Paratyphi* A and B were all negative. The examination of iron profiles showed a decrease in serum iron and TIBC. The coagulation test showed normal results. However, urine culture results were positive for *Stenotrophomonas malthophilia*, which was resistant to chloramphenicol. Blood culture was negative for bacterial growth.

Table 2. Results of hematology tests in Dr. Soetomo Hospital

Parameter	03/06/17	04/06/17	07/06/17	08/06/17	Reference Value
Hb (g/dL)	7.3	6.8	8.0	8.8	13-18
RBC (10^6/µL)	3.01	2.8	3.15	3.39	4.5-6.2
HCT (%)	24.2	22.4	25.4	27.3	40-54
MCV (fl)	80.4	80.0	80.6	80.5	81-99
MCH (pg)	24.3	24.3	25.4	26.0	27-31
MCHC (g/L)	30.2	30.4	31.5	32.2	33-37
RDW(%)	17.7	17.3	18.0	17.2	11.5-14.5
WBC (10^3/µL)	10.67	9.84	15.21	15.38	4-10
Plt (10^3/µL)	261	332	297	286	150-450
Parameter	**10/06/17**	**12/06/17**	**13/06/17**	**15/06/17**	**Reference Value**
Hb (g/dL)	8.7	7.3	8.1	9.5	13-18
RBC (10^6/µL)	3.28	2.72	2.97	3.52	4.5-6.2
HCT (%)	27.2	23.2	24.7	29.8	40-54
MCV (fl)	82.9	85.3	83.2	84.7	81-99
MCH (pg)	26.5	26.8	27.3	27.0	27-31
MCHC (g/L)	32.0	31.5	32.8	31.9	33-37
RDW (%)	16.3	16.0	15.3	15.0	11.5-14.5
WBC (10^3/µL)	14.79	10.55	15.09	14.85	4-10
Plt (10^3/µL)	337	300	197	130	150-450

Blood Smear Evaluation (BSE) 03/06/17

- Erythrocyte: most of the population were hypochromic, remaining the population were normochromic, anisopoikilocytosis (microcyte (++), normocyte, spherocyte, teardrop cells, ovalocyte), polychromatophilic cells(-), normoblast (-)
- WBC: there was presumably increase of WBC count, dominated by segmented neutrophil, immature granulocyte (+) (metamyelocyte, stab), blast (-)
- Plt: platelet count were presumably normal, giant platelet(-)

Conclusion: anemia of hypochromic anisopoikilocytosis, left shift of leukocytosis

Table 3. Results of clinical chemistry tests in Dr. Soetomo Hospital

Parameter	03/06/17	06/06/17	08/06/17	12/06/17	15/06/17	Reference Value
BUN (mg/dL)	6.0	9.0	8.0	14	-	6-20
Creatinine (mg/dL)	0.44	0.5	0.29	0.65	-	0.67-1.5
Albumin (g/dL)	2.57	-	-	2.7	-	3.5-5.2
AST (U/L)	24	-	-	-	-	<41
ALT (U/L)	9	-	-	-	-	0-35
K (mmol/L)	3.1	3.9	-	3.9	5.7	3.5-5.1
Na (mmol/L)	136	132	-	128	130	136-145
Cl (mmol/L)	100	91	-	93	98	98-107
RBG (mg/dL)	104	-	96	-	382	<100: Normal ≥ 126: DM
LDH (U/L)	852	-	-	-	-	82-234

Table 4. Urinalysis result in Dr. Soetomo Hospital

Parameter	03/06/17	Reference Value
SG	1.025	1010-1015
PH	6.5	6-8
Leukocyte	Negative	Negative
Nitrit	Positive	Negative
Protein	2+	Negative
Glucose	Negative	Negative
Ketone	Negative	Negative
Urobilinogen (umol/L)	33	<17
Bilirubin	2+	Negative
Eritrocyte	2+	Negative - positive
Colour	Yellow	
Clarity	Clear	
Erythrocytes/HPF	2-5	0-2
Leukocyte/HPF	5-10	0-5
Epithelial/HPF	Many	Few
Crystal/thorax/others	Negative	Negative

Table 5. Results of immunology tests

Parameter	Other Lab	Laboratory of Dr. Soetomo Hospital			Reference Value
	31/05/17	03/06/17	04/06/17	12/06/17	
HIV		Negative	-	-	Negative
HbsAg		Negative	-	-	Negative
Total quantitative β hCG (mUI/mL)	> 300,000	>1,500,000	>1,500,000	-	Non-pregnant females, pre-menopause : < 4
Total T3 (ng/mL)	-	-	1.30	1.58	0.60-1.81
Total T4 (ug/dL)	-	-	14.1	-	4.50-10.90
TSH (uIU/mL)	-	-	0.007	0.005	0.55-4.78
FT4 (ng/dL)	-	-	1.95	1.76	0.89-1.76
Procalcitonin (ng/mL)	-	-	1.16	-	<0.05 : normal, ≥0.05 - < 0.5 : local infection ≥ 0.5-< 2.0 : systemic infection ≥ 2.0-< 10 : severe sepsis ≥10: septic shock
AFP (ng/mL)	-	<1.5	-	-	≤ 15
CEA(ng/mL)	-	1.18	-	-	≤ 5
CA-125 (U/mL)	-	128.3	-	-	≤ 35
IgM Dengue ICT	-	-	-	Negative	Negative
IgG Dengue ICT	-	-	-	Negative	Negative
S.Typhi O	-	-	-	Negative	Negative
S. Typhi H	-	-	-	Negative	Negative
S.Parathypi A	-	-	-	Negative	Negative
S.Parathypi B	-	-	-	Negative	Negative

Table 6. Results of iron profile tests in Dr. Soetomo Hospital

Parameter	03/06/17	Refference Value
Serum iron (mg/dL)	15	35-150
TIBC (mg/dL)	158	250-450

Table 7. Results of coagulation tests in Dr. Soetomo Hospital

Parameter	03/06/17	15/06/17	Reference Value
PPT (second)	10.8	10.3	9-12
APTT (second)	28.2	25.9	23-33

Table 8. Results of blood gas analysis in Dr. Soetomo Hospital

Parameter	12/06/17	Reference Value
pH	7.44	7.35-7.45
pCO2 (mmHg)	19	35-45
pO2 (mmHg)	97	80-100
TCO2 (mmol/L)	13.5	23-30
BEecf (mmol/L)	-11.3	-3.50-2.00
SO2c (%)	98	94-98
A-aDO2 (mmHg)	29	
%FiO2 (%)	21.0	
$HCO3^-$ (mmol/L)	12.9	22.0-26.0
Temp (°C)	37.0	

Tabel 9. Results of urine culture and antibiotic sensitivity test in Dr. Soetomo Hospital

10/06/2017		
Specimen: midstream urine		
Gram: Gram-negative Bacillus		
Colony count: = 10^5 CFU/mL		
Result: *Stenotrophomonas malthophilia*		
β- Lactam Cephalosporin	Ceftazidime	Sensitive
Sulfa-Trimethoprime	Cotrimoxazol	Sensitive
Chloramphenicol		Resistant
Quinolon	Levofloxacin	Sensitive

Abdominal CT scan results with and without contrast (May 31, 2017) showed a uterine mass or mass of uterine infiltrating adnexa, with size of 11.7x16.4x18.3 cm with the impression of suspicious malignancy infiltration into the rectum with multiple lymphadenopathies in paraaortic-paracaval, 1.4x0.8 cm was the largest size and an air-fluid level feature on the superior side was suspected as fistulation with the intestine. Also, there were multiple nodules with the central necrotic area in the liver, left lung basal, spleen, and left kidney suspected with the metastatic process accompanied with perihepatic ascites. There was no abnormality found in the gall bladder, pancreas, and right kidney.

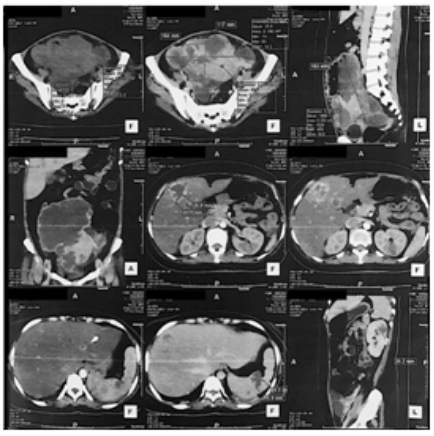

Figure 1. Abdominal CT scan result

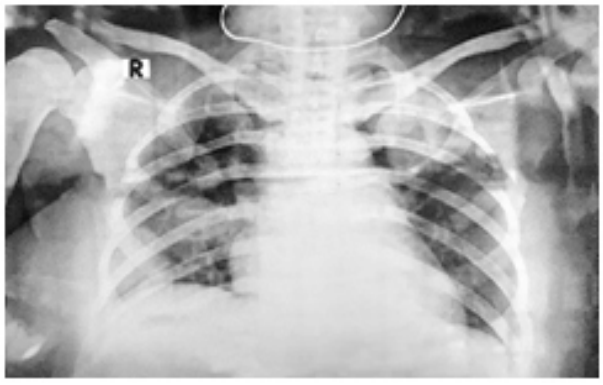

Figure 2. Chest X-ray result

Chest X-ray examination (June 3, 2017) showed multiple nodules with varying sizes projected in the right and left suprahilarparacardial which can be a metastatic process (cannonball type), no cardial and visualized bones abnormalities.

Results of the abdominal ultrasound examination (June 3, 2017) showed a malignant solid heteroechoic lesion with cystic components in the pelvic up to the abdominal cavity as high as infraumbilicus suspected from uterine, accompanied with hepatomegaly. No metastatic process in the liver and enlargement of paraaortic lymphoma were observed. No abnormalities were found in the gall bladder, pancreas, spleen, right and left kidney, and bladder.

Patients received diet therapy for 2100 kcal/day, infusion of RL: Aminofluid 1:1, injection of Ceftriaxone 2x1 g/day, transfusion of the packed red cell (PRC) 2 bags/day until Hb≥ 10 g/dL, oral therapy of Thyrozol 2x10 mg and Propanolol 3x10 mg. Patients were planned for chemotherapy with Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, Vincristine (EMACO) if the Hb result ≥10 g/dL.

DISCUSSIONS

The diagnosis of GTN is based on an increase in hCG levels supported by histological and radiological evidence. Diagnostic criteria of gestationaltrophoblastic neoplasiadiagnosis criteria are as follows: increase of hCG for four measurements over a period 3-weeks; ten percent hCG increase on three consecutive weekly measurements over a period of 2-weeks; serum hCG increase > 20,000 more than four weeks after mola evacuation; histopathologic diagnosis of choriocarcinoma; and presence of metastasis.[1,5]

Clinical symptoms of GTN depend on the condition of the pregnancy that precedes, the spread of the disease and histopathological conditions. Post mole GTN (invasive mole and choriocarcinoma) most commonly show symptoms of irregular bleeding after evacuation of hydatidiform moles, with irregular uterine and bilateral ovaries enlargement. Vaginal metastatic lesions during evacuation are occasionally found which causes uncontrolled bleeding. Choriocarcinoma is associated with nonmolar GTN that has no typical symptoms and signs, associated with tumor invasion of the uterus or other metastatic sites. Uterine bleeding due to perforation or metastasis can cause abdominal pain, hemoptysis, and melena. Pressure from intracerebral hemorrhage causes headaches and seizures. Pulmonary symptoms, such as dyspnea, cough, and chest pain, are caused by extensive pulmonary metastases. Placental site trophoblastic tumor and ETT almost always cause irregular uterine bleeding and a mild increase of hCG hormone.[2]

The patient was referred from Jombang hospital suspected with choriocarcinoma and anemia, supported with the history of abortion eight months earlier and followed by recurrent bleeding. Additional laboratory tests such as complete blood tests showed anemia, ICT test showed hCG results > 300,000 mIU/mL, and abdominal ultrasound and chest radiographs showed the presence of metastasis. The results of an abdominal CT scan showed a uterine mass and adnexa mass suspected as malignancy with a metastasis. Diagnosis based on histopathology cannot be established because no further examination was carried out on the tissue of the initial curettage results; therefore, results of PA curettage only showed the remaining picture of pregnancy.

Uterine ultrasound examination in the first trimester can detect abnormalities in early pregnancy. The presence of hydatidiform mole is frequently detected from ultrasound, but a definite diagnosis is made based on the results of histological examination of the evacuated tissue material. In this study, evacuation was continued with hCG examination at least every two weeks. A diagnosis of GTN can be made that a high hCG can be obtained or an increase in hCG levels within a few weeks. Histological evidence of choriocarcinoma and

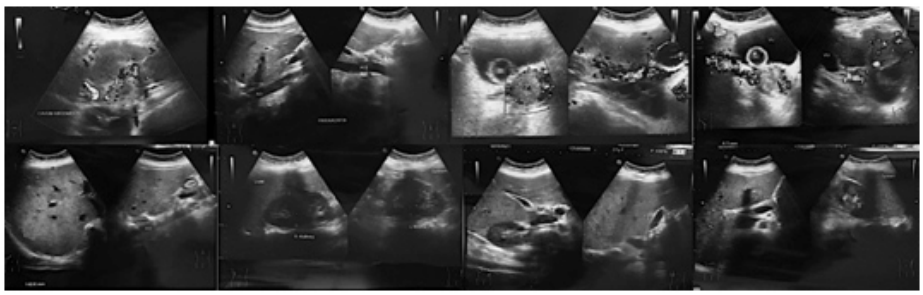

Figure 3. Abdominal USG result

evidence of metastasis with elevated serum hCG levels are indicator of chemotherapy.[6] In this patient it was not known whether the risk factors of GTN were from mola, because the imaging of mola was difficult to observe before eight weeks of pregnancy. In addition, histopathological examination was not performed on the results of the first curettage.

The patient came to the emergency department of Dr. Soetomo Hospital with complaints of vaginal bleeding accompanied with pallor, fever, tightness, chest palpitations, and trembling. Anemia and leukocytosis from complete blood examination, features of hypochromic anemia anisopoikilocytosis with left shift of leukocytosis from peripheral blood smears were reported. Decreased SI and TIBC can be caused by iron deficiency anemia due to chronic bleeding in patients with a differential diagnosis of anemia due to chronic disease. The presence of left shift of leukocytosis can be caused by inflammatory conditions or infection in the patient. Clinical chemistry test found hypoalbuminemia which can be caused by chronic inflammation in patients and lack of patient intake, hypokalemia suspected to occur due to poor patient intake, and increased LDH due to high levels of cell damage due to tumors. In urinalysis, positive nitrite was found, accompanied with the growth of *Stenotrophomonas malthophilia* which was suspected as a urinary tract infection. There was an increase in hCG> 1,500,000 MIU/mL at two times examination, with an increase in T4 and FT4, and a decrease in TSH. Increased procalcitonin can be caused by systemic infection and an increase in CA-125 which may be caused by the presence of a primary tumor or metastasis in the ovary. Chest radiology and abdomen ultrasound showed malignancy in the uterus with suspicion of surrounding organ and lung metastasis. Based on the history, physical examination, and other investigations, patients were diagnosed with high risk gestational trophoblastic neoplasia with hyperthyroidism, hypochromic anemia anisopoikilocytosis, hypoalbuminemia, hypokalemia, suspicion of urinary tract infections and sepsis. Patients were classified as high-risk GTN based on the criteria of stage I, II and III FIGO with WHO score 7 or FIGO stage IV.

The hCG glycoprotein hormone is a tumor marker that is specific to trophoblast disease and correlates with the severity of the disease. For diagnosis and follow-up, the patient used all forms of hCG molecules and subunits.[7] This hormone is synthesized mainly in syncytiotrophoblastand composed of subunits and specific hormones. The subunits have similar structures with pituitary hormones, Thyroid-Stimulating Hormone (TSH), Luteinizing Hormone (LH), and Follicle-Stimulating Hormone (FSH). The hCG subunit has a target of one or more G-protein coupled seven transmembrane receptors and has homologous degrees in the transmembrane domain. The LH or hCG receptor has a 45% similarity in structure with TSH receptors.[8] The similarity in structure between hCG and TSH can cause cross-reactivity with each receptor. Glinoer estimated that any increase of 10,000 mU/mL of serum hCG will be followed by an increase in FT4 of 0.1 ng/dL and a reduction in TSH of 0.1 mIU/mL; however, GTD patients with high hCG concentrations do not always show symptoms of hyperthyroidism.[7,9] The thyroid stimulation activity of hCG has been proven by many studies. Azukizawa *et al*. found that hCG inhibits binding of TSH labeled with plasma membrane receptors found in follicular cells of the thyroid gland and activates adenylcyclase in mouse thyroid glands and cells that have been given human TSH receptors. The presence of hCG will increase iodide uptake by increasing the expression of sodium/iodide transporter in thyroid cells.[7]

The changes of thyroid function in GTD may vary from mild increases in FT4 and FT3 concentrations accompanied with decreased TSH, moderate increases in FT4 and FT3 without symptoms of hyperthyroidism, to a marked increase in symptoms of severe hyperthyroidism and even thyroid storm. Lack of symptoms of hyperthyroidism in patients with high levels of FT4 and FT3 may be due to a short duration of increased thyroid function, which does not cause clinical symptoms of hyperthyroidism.[7] Hyperthyroidism which can be observed in less than 10% of cases is a rare complication in GTN, and has the potential to cause death. Hyperthyroidism status can vary from increasing asymptomatic thyroid hormone to thyroid storm. The two most common causes of maternal complications if hyperthyroidism is not treated are heart failure and thyroid storm. Secondary heart failure due to hyperthyroidism occurs due to the effect of thyroxine on the heart muscle. Hemodynamic problems such as tachycardia, hypertension, increased blood volume, decreased vascular resistance, and increased cardiac output will cause cardiac decompensation and arrhythmias. Symptoms of heart failure include shortness of breath, tachypnea, increased jugular venous pressure, pleural effusion, peripheral edema, and peripheral vasodilation. Thyroid storm can cause heart failure, with symptoms of fever, dehydration, tachycardia, tachypnea, sweating, diarrhea, atrial fibrillation, anxiety that affecting consciousness and hemodynamic instability due to failure of cardiovascular function.[3,10]

CONCLUSIONS

A 28-year-old female has been reported with hyperthyroidism caused by GTN based on history, disease history, patient symptoms and clinical signs, and results of laboratory tests. This case was interesting to be taken care of because it is rare and the condition of hyperthyroidism will increase morbidity and mortality in GTN patients. Therefore, thyroid function tests are very important to prevent further complications of hyperthyroidism.

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