CASE REPORT
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Impending thyroid storm caused by hydatidiform mole

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ABSTRACT

Introduction: Thyroid storm is a rare but life-threatening endocrine emergency. It is an acute exaggerated clinical manifestation of thyrotoxic state. We report an impending thyroid storm caused by a hydatidiform mole in a 14-year-old girl. This paper intends to describe hyperthyroidism secondary to molar pregnancy highlighting the rare but essential evaluation of hyperthyroidism.

Case: A 14-year-old girl was consulted by the obstetric division to evaluate and manage hydatidiform mole with suspected hyperthyroidism. She had frequent palpitations and tremors for 1 week ago. She also complained of nausea and vomiting 1 week before admission to the hospital. We found a Burch-Wartofsky score of 25, which was categorized as an impending thyroid storm. Laboratory results showed mild anemia, low thyroid stimulating hormone (TSH) levels, high free thyroxine (T4) levels, and markedly elevated beta-human chorionic gonadotropin (beta-hCG) levels, normal Thyroid-stimulating hormone receptor antibodies (TRAb). Other laboratory parameters are mediocre. The ECG results showed sinus tachycardia. A mole tissue biopsy of the uterus confirms the morphology of the hydatidiform mole. These findings established the diagnosis of Impending Thyroid Storm caused by a hydatidiform mole.

Conclusion: A hydatidiform mole can cause thyroid storm because the hormone hCG has similar structure to TSH. Doctors should always estimate the possibility of hyperthyroidism in a molar pregnancy.

Keywords: children, hydatidiform mole, thyroid storm.
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INTRODUCTION

Hyperthyroidism is defined as an inappropriately high synthesis and/or secretion of thyroid hormones from the thyroid gland. Thyrotoxicosis is the clinical condition where the effect of excess thyroid hormone on the tissues causes systemic clinical manifestations.[1] Hyperthyroidism may be referred to as "thyrotoxicosis" or toxic levels of thyroid hormone being produced. Similar to hypothyroidism, cases of hyperthyroidism may be broadly categorized as primary and secondary. Primary hyperthyroidism relates to the thyroid gland producing large amounts of hormone due to either uncontrolled growth of hormone-producing functional tissue or by way of an autoimmune process that interferes with normal feedback control. Primary hyperthyroidism also called "thyrotoxicosis" is caused by: thyroid nodules, thyroid adenoma, Graves' disease, thyroiditis. Graves' disease is the most common cause of hyperthyroidism in children. It is due to the effect of thyroid-stimulating hormone (TSH) receptor-stimulating antibodies which stimulate the thyroid to produce excess hormones.[2] The incidence of Graves' disease is believed to be between 0.1 and 3/100.000 children with a prevalence of 1 in 10.000 children in the United States.[2] In Indonesia, the case is found approximately in 1/100.000 children. Females are predominantly affected by this disease.[3] Secondary hyperthyroidism may be attributed to an overstimulation of the thyroid. This may be due to increased production of TSH from the pituitary gland or TSH-secreting tumor, or more rarely from overproduction of TRH from the hypothalamus or thyrotropin-releasing hormone (TRH)-secreting tumor. Secondary (or non-thyroidal) hyperthyroidism: Carcinoma, TSH-secreting tumors, TRH-secreting tumors.[3]

A thyroid storm is a rare but life-threatening endocrine emergency. This is an acute exaggerated clinical manifestation of a thyrotoxic state. According to the degree of systemic decompensation, it can be divided into 2 stages: the early stage (impending storm) and the actual crisis (thyroid storm).[4] Currently, there are no uniform diagnostic criteria for impending storms. In most cases, Burch and Wartofsky's Point Scale is used. It is generally believed that the impending storm is the intermediate stage of hyperthyroidism that finally develops into thyroid storm.[2] cases of hyperthyroidism may be broadly categorized as primary and secondary. Secondary hyperthyroidism may be attributed to an overstimulation of the thyroid. This may be due to increased production of TSH from the pituitary gland or TSH-secreting tumor, or more rarely from overproduction of TRH from the hypothalamus or thyrotropin-releasing hormone (TRH)-secreting tumor.[5]

One of the secondary causes of hyperthyroidism is hydatidiform mole,

which is a gestational trophoblastic disease.[4] Prompt and appropriate intervention starting with a proper diagnosis can provide good outcomes in patients with thyroid crisis. This case illustrates hyperthyroidism secondary to a molar pregnancy highlighting a rare but essential evaluation of hyperthyroidism.

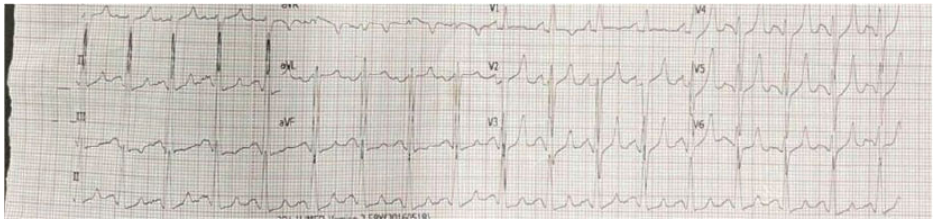

Figure 1. Sinus tachycardia on ECG.

CASE REPORT

A 14-year-old girl was consulted by the obstetric division to evaluate and manage hydatidiform mole with suspected hyperthyroidism. She had frequent palpitations and tremors for 1 week ago. Complaints became worse while being treated at the hospital. The patient complained of nausea and vomiting 1 week before admission to the hospital. She vomited 5 times per day with a volume of 50-100 ml each vomiting, containing the food consumed. There was no history of shortness of breath, frequent fatigue, or hair loss. There was no history of bulging eyes or problems in the thyroid glands. She lost 1 kg of her weight in the last 1-month, normal appetite was admitted. She has not menstruated for 2 months and the last menstruation was on 26th April 2023.

On the physical examination the patient was alert. Blood pressure was 100/70 mmHg, heart rate 115 times per minute, respiration rate 24 times per minute, oxygen saturation was 98% in room air. There was facial pallor and no anemic conjunctiva, there was no exophthalmos on both eyes. Lymph node enlargement was absent, no enlargement of the thyroid gland. There is no murmur on cardiac examination, vesicular breath sound on the lung, no rales and wheezing. On abdominal examination the liver and spleen were not palpable. Muscle's tone was normal with normal motor strength on both hands and feet. Physiologic reflexes were normal. The patient was moderate protein energy malnutrition on nutritional status (CDC 2000) with body weight 34.4 kg, body height 155 cm, weight for age (<P3), height for age (P10-P25), body mass index (BMI) 14.4 kg/m^2 (<P3).

From the physical examination, we found Burch-Wartofsky score of 25, categorized as impending thyroid storm. Laboratory examination showed mild anemia 10.30 g/dl (12.0-16.0). TSH result showed 0.01 uIU/mL (0.27-4.20 uIU/ml), free T4 3.93 ng/dL (0.70-1.48), and triiodothyronine (T3) total 2.14 ng/mL (0.35-1.93 ng/ml). Beta-HCG was markedly increased more than 225,000 mIU/mL (0-5 mIU/ml), and slight increase of aspartate aminotransferase (AST) 37.6 U/L (5-34 U/L), alanine transaminase (ALT) 50.8 (11.00 -34.00) and TRAb < 0.9 U/L (<1.75 U/L). Other laboratory parameters were unremarkable. Electrocardiography (ECG) results showed sinus tachycardia (Figure 1). A mole tissue biopsy of the uterus confirmed the morphology of the hydatidiform mole.

From the findings, we established a diagnosis of an impending thyroid storm caused by hydatidiform mole. The patient underwent dilatation and curettage for evacuation of the mole. Pharmacological therapy was given bolus hydrocortisone 2 mg/kg body weight then maintenance 36-45 mg, propylthiouracil (PTU) 100 mg every 8 hours for 1 month, and propranolol 10 mg every 12 hours for 1 month.

After curettage, the patient appeared pale and complained of palpitations. Laboratory results showed severe anemia: 5.5 g/dl (12.0 -16.0) and decrease from beta-HCG than before: >15.000 mIU/ml (0-5 mIU/ml). Blood transfusions stabilized the patient until the anemia was resolved.

DISCUSSION

Hyperthyroidism is a rare complication, occurring in 1 to 4/1000 pregnant women with 85% of these cases resulting from Graves' disease.[3] Untreated and inadequately controlled thyrotoxicosis is correlated with miscarriage, stillbirth, prematurity, pre-eclampsia, maternal congestive heart failure, low birth weight, and intrauterine growth restriction.[4,6]

Thyroid storms can be life-threatening, with a high mortality rate of 10% to 30% if not recognized immediately and aggressively treated.[7,8] According to the degree of systemic decompensation, it can be divided into 2 stages: the early stage (impending storm) and the actual crisis (thyroid storm).[9]

One of the triggers of hyperthyroidism is gestational trophoblastic disease, although gestational trophoblastic disease with thyrotoxicosis is a rare clinical scenario. Hydatidiform mole or better known as "wine pregnancy" is a gestational trophoblastic disease that is often found. This disease is one of the disorders of pregnancy which is characterized by abnormal embryonic development.[10] In hydatidiform mole, there is amenorrhea, vaginal bleeding and discharge of vesicles shaped like grapes, high levels of beta human chorionic gonadotropin in serum and urine. There may also be accompanied by hyperemesis gravidarum, tender uterus, inappropriate uterine size, bilateral theca lutein cysts, markers of thyrotoxicosis and pre-eclampsia in the first trimester of pregnancy.[11]

The glycoprotein hormone hCG is a specific tumor marker for trophoblastic diseases. The analogy in the structure between hCG and TSH can cause cross-reactivity with their receptors. It has been shown that the homology in the hCG and TSH molecules, as well as in their receptors, is likely to be responsible for the cross-reactivity of hCG with the TSH receptor.[12] Beta-HCG causes thyrotoxicosis through thyroid stimulation in patients with trophoblastic tumors.[13] Beta-HCG comprises two subunits. The alpha subunit is the same as TSH, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The beta subunit is similar to the beta subunit of TSH, but is larger. The thyroid-stimulating activity of beta-HCG has been shown in mice, rats and humans.[13-15] In trophoblastic diseases the spectrum of thyroid function changes varies from slight increases in free T4 (FT4) and free T3 (FT3) and low TSH

levels with no thyrotoxicosis symptoms, to moderate increases in FT4 and FT3 and up to increases large enough to cause clinical thyrotoxicosis or even thyroid storms.[16] In women with hydatidiform mole pregnancy and choriocarcinoma, pathologically high HCG levels cause clear hyperthyroidism. However, thyrotoxicosis is not observed in all trophoblastic patients. Although the majority of tropho-blastic tumors cause high fT4 and fT3 levels in women, some women have typical clinical findings with very few thyrotoxicosis symptoms.

Glinoer has estimated that "for every 10,000 mU/mL increase in serum hCG, FT4 increases by 0.1 ng/dL and TSH decreases by 0.1 mIU/mL".[13] Molecular variants of hCG found in molar pregnancies have increased thyrotropic potency.[17] When gestational trophoblastic disease causes a significant rise in hCG levels, it may induce hyperthyroidism that requires treatment. As expected, thyrotoxicosis resolves with treatment of GTD and normalization of hCG levels. The level of hCG largely influences the development of hyperthyroidism and usually resolves with treatment of GTD. The consideration of this cause of hyperthyroidism in pregnancy should be diagnosed early and managed efficaciously before imminent dilatation and curettage is required for definitive management of the hydatidiform mole.[18]

Common symptoms in thyrotoxicosis are restlessness and anxiety, excessive sweating, warm skin, can't stand the heat, pounding, excessive defecation, easily tired, decreased weight but increased appetite (Von Muller's paradox) and menstrual disorders. On physical examination will often find enlargement of the thyroid gland, hyperactivity, tachycardia or atrial fibrillation, systolic hypertension, easy sweating and feels warm on the skin, tremor, muscle weakness, ocular abnormalities such as Mobius sign, von Graefe's sign, Joffroy's sign, Stellwag's sign, lid lag, exophthalmos.[19] The symptoms of hyperthyroidism are often worsened by the precipitating events, ultimately leading to thyroid storm.[17,18] Patients with hyperthyroidism during pregnancy are 10 times more likely to develop a thyroid storm than in the non-gestation period.[20] Various stress conditions, such as surgery, childbirth, infection, pre-eclampsia, induced labor, diabetic ketoacidosis, etc, can induce maternal thyroid storm. Therefore, the choice of anesthetic technique and drugs for cesarean section are particularly important in pregnant women with hyperthyroidism.

Criteria	Score	Criteria	Score
Thermoregulatory dysfunction		**Gastrointestinal-hepatic dysfunction**	
Temperature (°C)	5	Manifestation	0
37.8 – 38.2	10	Absent	10
38.3 – 38.8	15	Moderate (diarrhea, abdominal	
38.9 – 39.3	20	pain	20
39.4 – 39.9	25	nausea/vomiting)	
≥ 40	30	Severe (jaundice)	
Cardiovascular		**Central nervous system disturbance**	
Tachycardia (beats/minute)		Manifestation	0
100 – 109	5	Absent	10
110 – 119	10	Mild (agitation)	20
120 – 129	15	Moderate (delirium, psychosis,	
130 – 139	20	extreme lethargy)	30
≥ 140	25	Severe (seizure, coma)	
Atrial fibrillation			
Absent	0		
Present	10		
Congestive heart failure			
Absent	0		
Mild	5		
Moderate	10		
Severe	20		
Precipitating event		**Total score**	
Status	0	> 45	Thyroid crisis
Positive	10	25-44	Impending storm
Negative		< 25	Storm unlikely

Figure 2. Burch and Wartofsky score.[20]

In 1993, precise criteria for thyroid storm were defined by Burch and Wartofsky based on the patient's clinical symptoms, including thermoregulatory and cardiovascular dysfunction, gastrointestinal–hepatic dysfunction, and central nervous system disturbance.[20] In This Case The Burch and Wartofsky score of the patient was 25 implying that she was still in the stage of impending thyroid storm. But if not recognized in time and treated properly, it might have developed into a thyroid storm. As thyroid storms occur abruptly and with a high mortality rate, people who are highly suspected of impending storms should be treated as thyroid storms. Figure 2 shows a Burch-Wartofsky score.

Based on clinical symptoms, the biochemical evaluation of TSH and thyroid hormone is the most important as an initial diagnostic test in individuals with suspected hyperthyroidism or thyrotoxicosis crisis. Measurement of serum TSH has the highest sensitivity and specificity, in hyperthyroidism, serum TSH <0.01 mU/L or even undetectable. To increase the accuracy of the diagnosis, serum thyroid hormone examination is also carried out, it will be found to increase thyroid hormone levels in patients with hyperthyroidism. Other tests that can be done are radioactive iodine uptake (RAIU) and thyroid scanning to determine the cause of thyrotoxicosis if no manifestations of Grave disease are found, in patients with contraindications to RAIU, a TRAb examination can be performed. Ultrasound can distinguish a mass whether a nodule or a cyst, and estimate thyroid size, vascular flow, and guide fine needle aspiration biopsy (FNAB).[16]

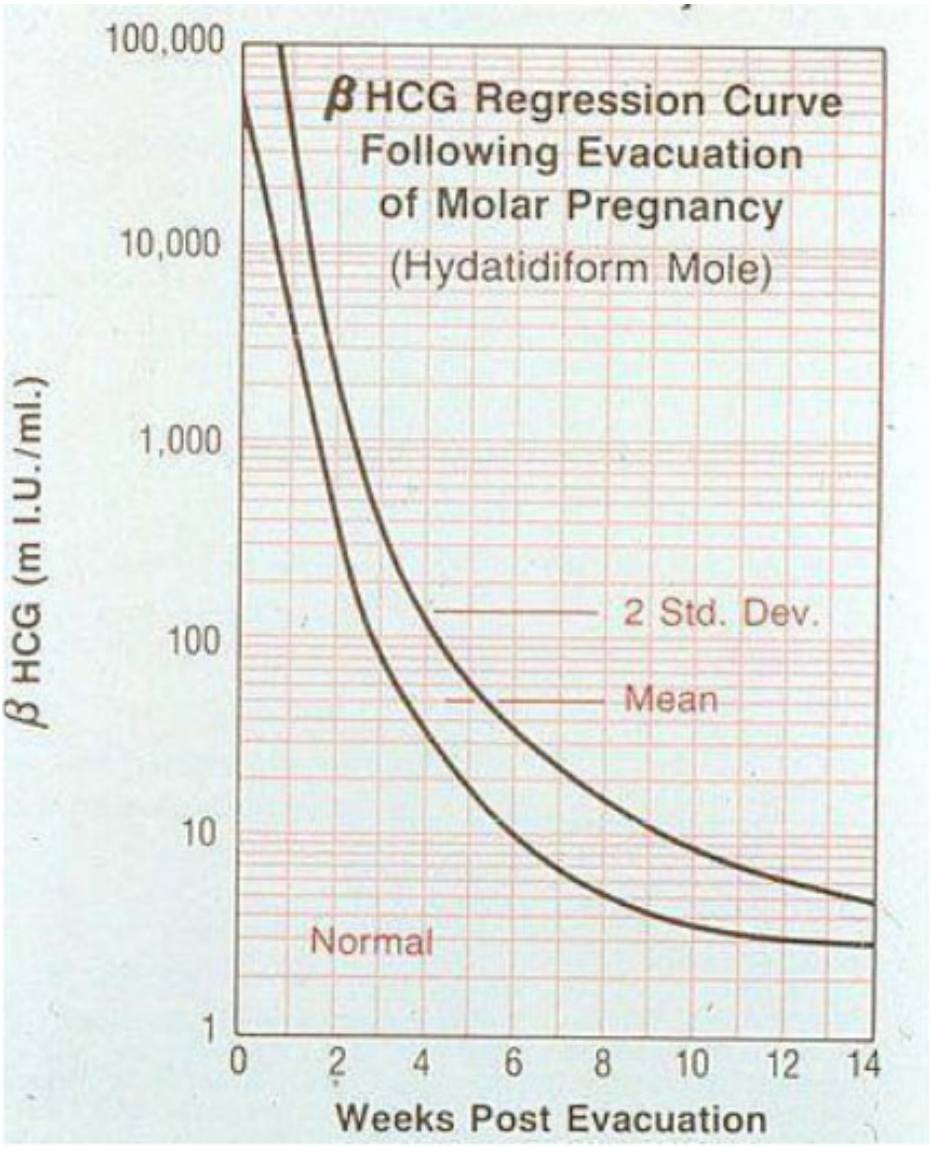

Figure 3. Regression curve beta-hCG normal and abnormal after mole evacuation.

In a molar pregnancy, the increase in hCG levels occurs not only in the early trimester, but also continues to increase to levels above 100.000 mIU/ml. The increased hCG will then stimulate the thyroid gland through the TSH receptor to produce and release T3 and T4 on a large scale. When thyroid hormone is released into the bloodstream, it still harms Thyroid Releasing Hormone (TRH) and TSH, this explains why patients with thyrotoxicosis in hydatidiform mole patients have very low TSH levels.[21] In This Case Laboratory result TSH showed 0,01 uIU/ml, free T4 3.93 ng/dl, and T3 total 2.14 ng/ml, beta HCG was increased (more than 225.000 mIU/ml).

Treatment of thyroid storm consists of supportive measures like intravenous (IV) fluids, oxygen, cooling blankets, acetaminophen, as well as specific measures to treat hyperthyroidism. If any precipitating factors, for example, infection, are present, they need to be taken care of. Patients with thyroid storm must be admitted to the intensive care unit with close cardiac monitoring and ventilatory support if needed.[22]

After initial supportive measures, a beta-blocker should be started for any case of suspected thyroid storm. Typically, propranolol 40 mg to 80 mg is given every 4 to 6 hours. Then, either a loading dose of PTU 500 mg to 1000 mg followed by 250 mg every 4 hours or Methimazole (MMI) 20 mg every 4 to 6 hours should be given. Propylthiouracil is favored because it has a small but additional effect of blocking the peripheral conversion of T4 to T3. An hour after the administration of propylthiouracil or Methimazole, give five drops of SSKI (supersaturated potassium iodide) by mouth every 6 hours. Always administer thionamide before starting iodine solution (SSKI) therapy.[23] This prevents the imminent increase in thyroid hormone synthesis due to increased iodine load from super saturated potassium iodide. Hydrocortisone 100 mg IV every eight hours (or Dexamethasone 2 mg every 6 hours) should also be started. If available, oral cholestyramine 4 grams four times daily can be started for severe cases. One should look for precipitating factors and treat them accordingly.[18] The use of aspirin should be avoided due to its potential risk of increasing free thyroid hormone levels by interfering with thyroid-binding protein. In this case patient has been treated by hydrocortisone 2 mg/kg body weight continued with maintenance 36-45 mg, PTU 100 mg Every 8 hours, and propanolol 10 mg every 12 hours.[19]

In the first 24 hours of treatment, propylthiouracil decreases T3 level by 45%, but Methimazole drops T3 level by only 10 % to 15%. Methimazole, whereas, causes more rapid normalization of serum T3 level after a few weeks of treatment and it has less hepatotoxicity compared to propylthiouracil.[20] Therefore, after initial stabilization, we should treat with Methimazole (if propylthiouracil was started at the beginning, it should be changed to Methimazole). For patients who cannot take oral antithyroid medicine, liquid preparation (pharmacist may have to compound) can be given as enemas. Sometimes, pharmacists can prepare an IV form of antithyroid medicine by dissolving the tablet.[24,25] In this case patient treatment by PTU, T3 level has significantly decreased 33% after treatment PTU.

The prognosis of hyperthyroidism in hydatidiform mole pregnancy depends on the molar tissue's post-evacuation state. The state of secondary hyperthyroidism generally will quickly improve after the evacuation of the mole tissue. Approximately 15-20% of patients with post-evacuation moles can undergo malignant transformation into gestational

trophoblastic tumors.[26-28] If this happens then the prognosis will be poor. One year of follow-up is necessary, but it can also be up to two years. Patients are asked to come for control every two weeks in the first three months after evacuation. Then in the next three months every one month. Then in the last six months every two months. After the mole tissue is evacuated, beta-hCG levels will decrease slowly, until they are no longer detectable.[29-31] In This case after patient discharged from the hospital, the patient is advised to control polyclinic pediatrics but the patient didn't come and we can't see the last condition of the patient, the prognosis will be poor.

The median time required to reach normal levels (<5 mIU/ml) is 12 weeks. There are several types of regression curves, including those created by Mochizuki. According to Mochizuki, beta-hCG levels will fall under normal conditions following the regression curve (Figure 3). There is a distortion of the normal regression curve, meaning malignancy occurs. Therefore, an early diagnosis of GTT can be established by observing this regression curve, on the condition that the patient must adhere to follow-up.[32]

CONCLUSION

A hydatidiform mole can cause thyroid storm because the hCG hormone has similar structure to TSH. Doctors should always estimate the possibility of hyperthyroidism in a molar pregnancy.

CONFLICT OF INTEREST

All authors declare there is no conflict of interest regarding publication of this report.

FUNDING

None.

ETHICAL CONSIDERATION

Patient/legal guardian had received signed written informed consent regarding publication of current case report in scientific medical journal with confidentiality aspect to personal information.

AUTHOR CONTRIBUTION

All authors had contributed to manuscript writing and agreed to the final version of manuscript for publication.

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