Hong Kong College of Physicians
Case Report for Interim Assessment
Specialty Board of Advanced Internal Medicine (AIM)

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Date(s) and place (hospital) of patient encounter: 5/10/2023, PYNEH
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Case report

Title: A rare cause of thyrotoxicosis

Case history:

A 53-year-old woman with good past health was admitted for 2-week history of non-productive cough, shortness of breath, and fever. She was treated as bronchitis before with a course of antibiotics and symptomatic medications by her general practitioner, but her symptoms were not improving. Her blood pressure was stable with heart rate 123 beats per minute. Body temperature was 37.7°C. She was on room air with respiratory rate 22 per minute. Auscultation of chest revealed bilateral crepitations without wheeze. Chest X-ray (CXR) showed nodular opacities over bilateral lung fields. Electrocardiogram (ECG) confirmed sinus tachycardia without ST-T changes or S1Q3T3. Empirical Augmentin (Amoxicillin-Clavulanate) was started.

Routine urine pregnancy test was performed after admission, and the results were weakly positive on two consecutive tests. She had irregular 1-2 monthly menstrual cycles all along. However, she reported prolonged spotting in recent 2 months. She had one previous uneventful spontaneous delivery. She was sexually inactive for five years, so she strongly denied any possibility of pregnancy.

Thyroid function was tested in view of tachycardia, showing overt thyrotoxicosis with suppressed thyroid-stimulating hormone (TSH) <0.01 mIU/L and elevated thyroxine (fT4) 69.6 pmol/L (reference: 7-21 pmol/L) as well as triiodothyronine (fT3) 9.5 pmol/L (reference: 3.2-6.1 pmol/L). Upon further history taking, she reported no hand tremor, heat intolerance, diarrhea, or weight changes. She reported no neck pain. There was no

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family history of thyroid disease. On physical examination, nodular goitre with retrosternal extension was noted. No thyroid bruit was detected. No sign of thoracic inlet obstruction was detected. There was no pretibial myxedema or signs of thyroid eye disease.

Other laboratory findings included leukocytosis with white cell count 11 $x10^9$/L and mildly elevated alkaline phosphatase (ALP) 136 IU/L (reference: 36-105 IU/L). The rest of liver and renal biochemical tests were unremarkable. Arterial blood gas showed type 1 respiratory failure. Procalcitonin was not elevated, and microbiological workups were negative. Serum beta-human chorionic gonadotrophin (hCG) was measured, and the level was strikingly high of 865,153 mIU/mL (reference for non-pregnant woman: <5 mIU/mL). CA125 was 75 U/mL (reference: <35 U/mL). Other tumor markers including alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), and CA19-9 were normal. Urgent computed tomography (CT) of pulmonary angiogram excluded pulmonary embolism, and multiple nodules were observed diffusely in both lungs which were worrisome of lung metastases. Multinodular goitre with retroclavicular extension was also identified in the CT.

The patient was assessed by endocrinologist. Hyperthyroidism was likely caused by excessive hCG from possible underlying germ cell tumor. Toxic multinodular goitre was a less likely differential diagnosis. Burch-Wartofsky score was 20, representing low likelihood of thyroid storm. Anti-thyroglobulin (anti-TG), anti-thyroid peroxidase (anti-TPO), and anti-TSH receptor antibodies were negative. Thyroid ultrasound and scintigraphy scan were arranged. Carbimazole and propranolol were started for treatment of thyrotoxicosis.

Gynecologist was consulted. Pelvic ultrasound revealed two uterine intramural fibroid-like masses. Right ovary was atrophic while left ovary was not well seen. Endometrial aspiration was performed, and histological exam showed malignant trophoblastic cells, suggestive of choriocarcinoma. Positron emission tomography (PET) scan was performed 1 week after admission, confirming a 5cm primary tumor over right-sided uterine wall. Metastasis to left-sided uterine wall, bilateral lungs, and right ilium of pelvis were also observed. She was referred to oncologist and was planned to start chemotherapy.

However, her condition rapidly deteriorated 2 days after the PET scan. She developed respiratory failure requiring intubation and intensive care unit (ICU) management. She soon ran into repeated episodes of cardiac arrest despite resuscitation. Bedside echocardiogram revealed grossly dilated right ventricle. She was treated empirically as massive pulmonary embolism with alteplase, followed by heparin infusion. However, her condition continued to deteriorate and eventually succumbed on the same day.

Discussion and literature review:

The presence of sinus tachycardia provided clue to underlying thyrotoxicosis in our patient. Sinus tachycardia is commonly encountered in clinical practice. Considering our patient's concurrent respiratory symptoms, pulmonary embolism is another important differential diagnosis, which was excluded by CT pulmonary angiogram. Infection was another contributing factor of sinus tachycardia in our patient, given her low grade fever and leukocytosis. Other possible causes of sinus tachycardia include hypovolemia, severe heart failure, pheochromocytoma, sympathomimetic drug use, pain, and anxiety, which were all unlikely in our case in the absence of relevant history. Apart from sinus tachycardia, other cardiac manifestations of hyperthyroidism include hypertension, chest pain, atrial fibrillation, and high output heart failure. Thyroid storm represents the most severe spectrum of hyperthyroidism. Life threatening arrhythmia, heart failure, encephalopathy, and other complications can be seen which require urgent treatment.

Hyperthyroidism is most commonly caused by Graves' disease, toxic multinodular goitre, toxic thyroid adenoma, and thyroiditis. Several aspects of our patient were unusual for Graves' disease, including relatively old age, absence of pretibital myxedema, absence of Graves' ophthalmopathy, and negative family history. Neck pain is associated with thyroiditis but it was absent in our patient. The negative results of thyroid autoantibodies made these two diagnoses even less likely. Our patient's sky-high hCG level pointed towards hCG-mediated hyperthyroidism, which is a rare cause of hyperthyroidism. Physiological hCG elevation in pregnancy may cause mild hyperthyroidism, termed gestational transient thyrotoxicosis. In non-pregnant patients, data on hCG-mediated hyperthyroidism are sparse and mostly limited to case reports. There are various pathological causes of

hCG production such as germ cell tumor and gestational trophoblastic disease. Choriocarcinoma, a malignant tumor of trophoblastic cells, is a classic example of hCG-producing germ cell tumor. Gestational trophoblastic disease is a group of pregnancy-related disorders arising from abnormal placental trophoblast proliferation.[1] Overlap exists between these two entities as choriocarcinoma is one of the malignant forms of gestational trophoblastic disease. On the other hand, choriocarcinoma can be classified into gestational and non-gestational subtypes as well. In hCG-mediated hyperthyroidism, thyroid function test results are the same as other thyroid causes, showing TSH suppression and fT4 elevation. Next step of investigation involves source localization with gynecological assessment and imaging such as PET-CT to search for underlying tumor. Another reproductive system tumor which can lead to hyperthyroidism is struma ovari. It refers to ovarian teratoma predominantly composed of mature thyroid tissue.[2] As opposed to hCG-mediated hyperthyroidism, excessive thyroid hormone is secreted from the tumor in this disease. Toxic multinodular goitre and toxic thyroid adenoma were still possible causes of hyperthyroidism in our patient, and these would require thyroid ultrasound and scintigraphy results to exclude.

hCG is a hormone normally produced by placental syncytiotrophoblasts to maintain the corpus luteum during pregnancy. Excessive hCG level can result in hyperthyroidism because of its intrinsic thyroid-stimulating activity. This is due to structural homology between hCG and TSH. Both hormones consist of two subunits. Their alpha-subunits are identical, whereas their beta-subunits are also structurally similar. Beta-subunit of hCG can cross-react with TSH receptor and stimulate the thyroid gland to produce excessive thyroid hormone. Association between hCG level and incidence of hyperthyroidism was studied in patients with disseminated non-seminomatous germ cell tumors. For those with hCG above 50,000 IU/L, 50% of patients showed hyperthyroidism, whereas no patient showed hyperthyroidism if hCG level was below 50,000 IU/L.[3] Apart from quantity of hCG production, structural changes in hCG also influence its thyrotropic activity. Structural changes which have been found to enhance thyrotropic activity include excessive sialylation[4] and truncation of carboxyl-terminal tail of hCG[5]. These changes can be seen in paraneoplastic hCG production.

Despite the sky-high hCG level, our patient's urine pregnancy test was only weakly positive. This phenomenon called hook effect can be seen in immunoassays when the concentration of the tested substance is very high. In urine pregnancy test, hCG will normally bind to fixed antibody and free antibody together, forming a complex to produce positive signal. When hCG concentration is in excess, both antibodies will bind to hCG molecules individually, so they are unable to form a complex, giving rise to a falsely low or negative result.[6] It is important to be vigilant about the hook effect in interpretating urine pregnancy test, especially in cases like our patient with unexpected weakly positive result. Another test should be repeated by measuring the serum hCG level in order to uncover the true hCG level. In some immunoassays, another solution is to repeat the test after dilution of the sample, but this is rarely required in urine pregnancy test.

Management of hCG-mediated hyperthyroidism is twofold. Hyperthyroidism should be controlled as in usual thyrotoxic patients. This includes use of thionamide, such as carbimazole or propylthiouracil, and beta blocker. Although most cases of hCG-mediated hyperthyroidism are mild, severe cases of thyroid storm have also been reported.[7] Burch-Wartofsky score is a useful clinical score to estimate the likelihood of thyroid storm (Table 1). In case of thyroid storm, patient should be closely monitored under ICU setting, and additional therapy would be required such as hydrocortisone and iodine solution. On the other hand, treatment of underlying hCG-producing condition is essential to achieve cure of the disease. Anti-thyroid drugs can be gradually tapered off once hCG production is controlled. Our patient suffered from choriocarcinoma which is an aggressive malignancy with early metastasis commonly seen. Chemotherapy is the mainstay of treatment, but prognosis is generally poor, especially in non-gestational cases.[8] After initiation of chemotherapy, there may be a transient surge in hCG level. Theoretical risk of worsening hyperthyroidism should be closely monitored.[3] Besides, patients with hCG-mediated hyperthyroidism frequently require imaging for their underlying malignancy. Iodine contrast is a rare but recognized precipitating factor of thyroid storm.[9] Although its use is not contraindicated in such setting, physicians should also be vigilant about the risk of deterioration after iodine contrast imaging.

Acute pulmonary embolism was the presumable cause of death in our

patient. Underlying malignancy is a well-known risk factor for venous thromboembolism. Apart from pulmonary embolism, choriocarcinoma syndrome is another notable differential diagnosis in choriocarcinoma patients presenting with acute respiratory symptoms. Choriocarcinoma syndrome refers to bleeding from metastatic sites of the highly vascular choriocarcinoma. As lung is the most common site of metastasis, this syndrome usually presents with pulmonary hemorrhage and respiratory failure.[10] Treatment is mainly supportive with high mortality. In our patient, pulmonary embolism was the more likely diagnosis in view of the echocardiogram finding, and choriocarcinoma syndrome usually occurs acutely after chemotherapy.[10]

Tables and figures:

Burch-Wartofsky score	Our patient
Temperature (˚C) 37.2-37.7 – 5 37.8-38.2 – 10 38.3-38.8 – 15 38.9-39.2 – 20	5

39.3-39.9 – 25 ≥40 – 30	
Heart rate (beats per minute) 100-109 – 5 110-119 – 10 120-129 – 15 130-139 – 20 ≥140 – 25	15
Atrial fibrillation Absent – 0 Present – 10	0
Gastrointestinal-hepatic dysfunction Absent – 0 Moderate (diarrhea, nausea/vomiting, abdominal pain) – 10 Severe (jaundice) – 20	0
Central nervous system disturbance Absent – 0 Mild (agitation) – 10 Moderate (delirium, psychosis, extreme lethargy) – 20 Severe (seizure, coma) – 30	0
Precipitating event Absent – 0 Present – 10	0
Total <25: unlikely of thyroid storm 25-44: suggestive of impending thyroid storm ≥45: highly suggestive of thyroid storm	= 20

Table 1. Burch-Wartofsky score of our patient

Reference:

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gonadotropin. Thyroid 1995;5(5):425-34.
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No of words in Case History and Discussion (excluding references): 1672

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

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(signature of Trainee)

Endorsed by Supervisor *

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(signature of Supervisor)

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