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CASE REPORT

Thyrotoxicosis in the Setting of Hydatidiform Mole with Subsequent Development of Takotsubo Cardiomyopathy Complicated by COVID-19

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Abstract

We present a rare case of hydatidiform molar pregnancy, which led to the development of thyroid storm, followed by a rare complication of takotsubo cardiomyopathy in the setting of a COVID-19 infection. A 21-year-old female of 22 weeks gestational age presented with heavy vaginal blood loss, brown emesis, tachycardia, and lethargy. Through clinical presentation and ultrasound confirmation, a molar pregnancy was diagnosed. Laboratory data and clinical presentation of thyrotoxicosis supported a diagnosis of thyroid storm. Test for COVID-19 was positive. The patient was treated with dilation and curettage, antithyroid medication, and blood transfusions, resulting in symptom resolution. Thereafter, echocardiography confirmed takotsubo cardiomyopathy. It is suspected that the homology in structure between the human chorionic gonadotropin (hCG) and thyroid stimulating hormone subunits resulted in thyroid storm secondary to receptor cross-reactivity. We speculate that subsequent cardiovascular stress of b-hCG-induced thyroid storm with superimposed COVID-19 infection facilitated the development of Takotsubo cardiomyopathy.

Keywords: Gestational trophoblastic disease, Thyrotoxicosis, Beta-hCG, Stress induced cardiomyopathy, COVID-19, Hyperthyroidism, Molar pregnancy

1. Introduction

The incidence of hydatidiform mole in the United States is about 1 in 1500 live births, and it most commonly presents as vaginal bleeding.[1] Clinical signs of hyperthyroidism manifest in 5% of these cases.[2] Biochemically, human chorionic gonadotropin (hCG) and thyroid stimulating hormone (TSH) share overlapping α- and β-subunit morphologies. It is thought that a life-threatening thyroid storm can develop secondary to b-hCG stimulation of TSH receptors in the setting of the highly elevated b-hCG of a hydatidiform mole.[3] Thyroid hormone, more specifically the biologically active triiodothyronine (T3), affects the cardiovascular system by increasing cardiac contractility, decreasing systemic vascular resistance, and increasing cardiac output, which results in a hypervolemic burden that can develop into heart failure. In this case we observe this cardiovascular strain precipitating stress-induced cardiomyopathy, also known as takotsubo cardiomyopathy. It is a reversible and non-ischemic form of cardiomyopathy resulting from stressful events.[4] Additionally, COVID-19 has been associated with myocarditis, pericarditis, thyroiditis, and heart failure in patients with no cardiac history.[5-7]

2. Case presentation

A 21-year-old pregnant female (gravida 2, primipara) presented to the emergency department

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with a complaint of abdominal pain, heavy vaginal blood loss, brown emesis, palpitations, and lethargy. Her past medical history was significant for a recent diagnosis of a molar pregnancy, untreated. Her last menstrual period was sixteen weeks prior to this presentation. The patient was taking no medications.

Her vital signs were notable for a blood pressure of 79/46 mmHg, a heart rate of 182 beats per minute, a respiratory rate of 22 breaths per minute, and a temperature of 97.9 °F. On physical exam, she appeared diaphoretic and in acute distress. She had a firm and distended abdomen that was diffusely tender to palpation, and blood emitted from the closed cervical canal. Her uterus was consistent in size with a 20-week gestational age. A pelvic ultrasound was performed and confirmed the presence of multiple anechoic cystic structures (Fig. 1). Her initial laboratory workup is presented in Tables 1 and 2.

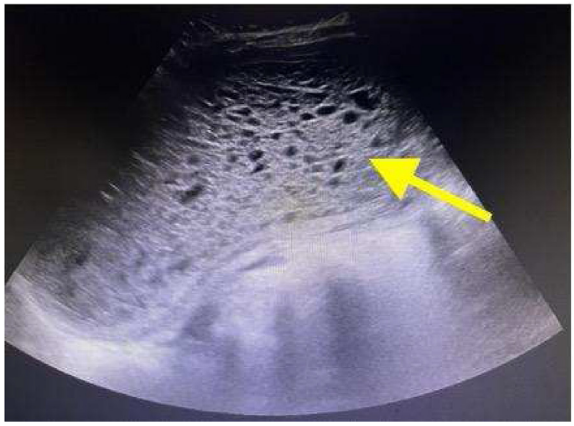

Fig. 1. Uterine ultrasound. Uterine ultrasound demonstrating multiple anechogenic cystic structures that represent hydropic swelling of trophoblastic tissue, creating the "snowstorm" appearance.

Table 1. Laboratory data at time of admission.

Test	Value	Reference range
Complete blood count		
Hemoglobin	4.9 g/dL	Pregnant female: >11 g/dL
Hematocrit	16.7%	36%–44%
Platelets	321,000 × 109/L	150–450 × 109/L
Red blood cells	1.59 × 1012/L	3.80–5.80 × 1012/L
Comprehensive metabolic panel		
Sodium	131 mEq/L	135-145 mEq/L
Potassium	5.0 mEq/L	3.7–5.2 mEq/L
Carbon dioxide	<10.0 mEq/L	23-29 mEq/L
Alkaline phosphatase	179 IU/L	44–147 IU/L
Alanine transaminase	14 IU/L	7–56 IU/L
Aspartate aminotransferase	42 IU/L	8–33 IU/L
Creatinine	1.90 mg/dL	0.7–1.3 mg/dL
Estimated glomerular filtration rate	37 mL/min	>60 mL/min
Lactic acid	2.4 mmol/L	0.5–2.2 mmol/L

An electrocardiogram on admission revealed sinus tachycardia (Fig. 2).

2.1. Hospital course

The patient underwent emergent dilation and curettage with successful removal of the hydatidiform mole. Pathology revealed multiple fragments of hemorrhagic and hydropic tissue that contained variably sized semi-transparent vesicles with a grape-like appearance. It measured 18.2 × 14.5 × 7.1 cm. In the operating room, she required multiple blood transfusions. She was intubated secondary to respiratory failure and pulmonary edema and was admitted to the intensive care unit. Due to hospital protocol, the patient was tested for COVID-19 upon admission to the ICU and she was found to be positive.

Due to her presenting symptoms of fever, lethargy, vomiting, tachycardia, and eventually, pulmonary edema, there was high clinical suspicion for thyroid storm. Hormonal laboratory data revealed elevated free triiodothyronine and free thyroxine with suppressed TSH and a drastically elevated b-hCG (Table 2). Her Burch and Wartofsky score was 80, highly suggestive of thyroid storm (Supplementary Table 1).[8] She was treated with propylthiouracil 200 mg twice daily, intravenous hydrocortisone 50 mg every 6 h, and an esmolol drip. Serial free thyroxine and b-hCG were followed with adequate reduction noted daily. The patient was later extubated. Her steroids were tapered, antithyroid medications were titrated, and she was transferred to the medical floor.

On the third hospitalization day, electrocardiogram changes were significant for diffuse T-wave changes that were not present previously (Fig. 3). The typical ECG changes for takotsubo cardiomyopathy include ST-segment elevation and T-wave inversion, primarily in the precordial leads. It is not uncommon for it to present solely with T-wave inversion.[9] A transthoracic echocardiogram was ordered, and she was found to have stress-induced (takotsubo) cardiomyopathy. Specifically, these echocardiogram findings included: anterior wall apical akinesis, diastolic dysfunction, and heart failure with an ejection fraction of 20–25%. B-type natriuretic peptide levels were elevated. She received intravenous furosemide 20 mg every 12 h, which was continued until discharge due to her left ventricular dysfunction.

A comprehensive endocrine workup was completed to investigate other causes of this patient's thyroid storm, which was inconclusive (Table 3). Unfortunately, a radioactive iodine uptake study

Table 2. Thyroid hormones throughout hospital course.

Hormone	Day 1	Day 2 (Treatment initiated)	Day 3	Day 5	Day 8 (Discharge)	Reference Range
Thyroid stimulating hormone	0.372	0.018	<0.008	<0.008	–	0.3–4.2 mIU/mL
Free thyroxine	2.220	2.010	1.240	0.740	0.35	0.8–2.0 ng/dL
Free triiodothyronine	5.17	–	1.13	0.58	0.69	2.3–4.1 pg/mL
Beta-human chorionic gonadotropin	>200,000	>200,000	>200,000	153,525	45,638	<5 mIU/mL

Laboratory values were trended throughout the patient's hospitalization. Prior to treatment, the elevated free triiodothyronine and free thyroxine combined with a suppressed thyroid stimulating hormone and vastly elevated beta-human chorionic gonadotropin increased clinical suspicion for the diagnosis of thyroid storm.

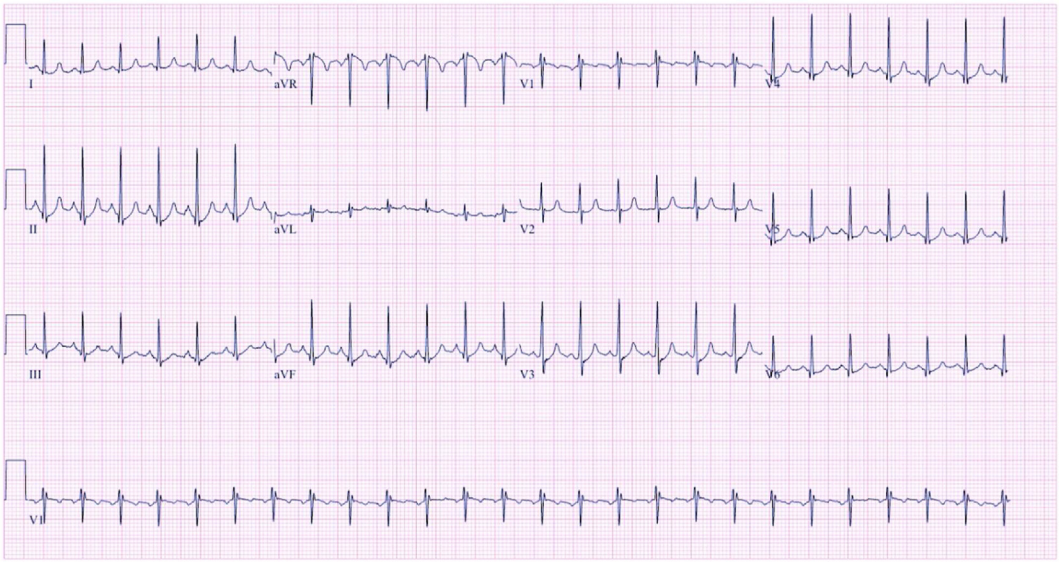

Fig. 2. Electrocardiogram at the time of admission. ECG on admission showing sinus tachycardia.

was unable to be completed due to a lack of follow-up from this patient. At discharge, the patient's T3 and T4 were low, and her b-hCG was trending downwards (Table 2). Up to this publication, there has been no follow-up or resolution.

3. Discussion

In this case report, we had a complex case of a 21-year-old pregnant female with a molar pregnancy who subsequently developed a thyroid storm with secondary takotsubo cardiomyopathy. Her case was complicated by COVID-19 infection and hemorrhagic shock. It is unclear why this patient developed takotsubo cardiomyopathy. However, we speculate that the cardiovascular stress of b-hCG-induced thyroid storm with superimposed COVID-19 infection may have facilitated the development of takotsubo cardiomyopathy.

It was initially considered that the patient may have had undiagnosed hypothyroidism at baseline, such as Hashimoto's disease. These circumstances could, theoretically, lead to TSH receptor up-regulation and super sensitivity, increasing susceptibility to b-hCG-provoked thyroid storm. However, the patient's anti-thyroglobulin antibody was within normal limits at 19.5 IU/mL. Hashimoto's disease is specifically less likely due to the patient's normal anti-thyroid peroxidase antibody of 18 IU/mL, which has a sensitivity of 90–95% for the diagnosis of Hashimoto's disease.[10] Other causes of thyroid storm were also considered, including postpartum thyroiditis, Graves' disease, thyroid adenoma or carcinoma, among others. Suspicion for these differentials was reduced by normal: thyroglobulin, thyroid-stimulating immunoglobulin, and ultrasound findings, respectively.

There are cases whereby familial alteration in the binding region of the TSH receptor was postulated to increase responsiveness to physiologic levels of b-hCG, causing recurrent gestational hyperthyroidism.[2] When applied here, this theory could underlie augmented susceptibility to thyroid storm in the setting of the supraphysiological b-hCG levels of a complete molar pregnancy. However, this is unlikely given the reportedly normal progression of the patient's first pregnancy.

The gradient of influence active COVID-19 infection had on this case cannot be determined with certainty. The novel coronavirus has been

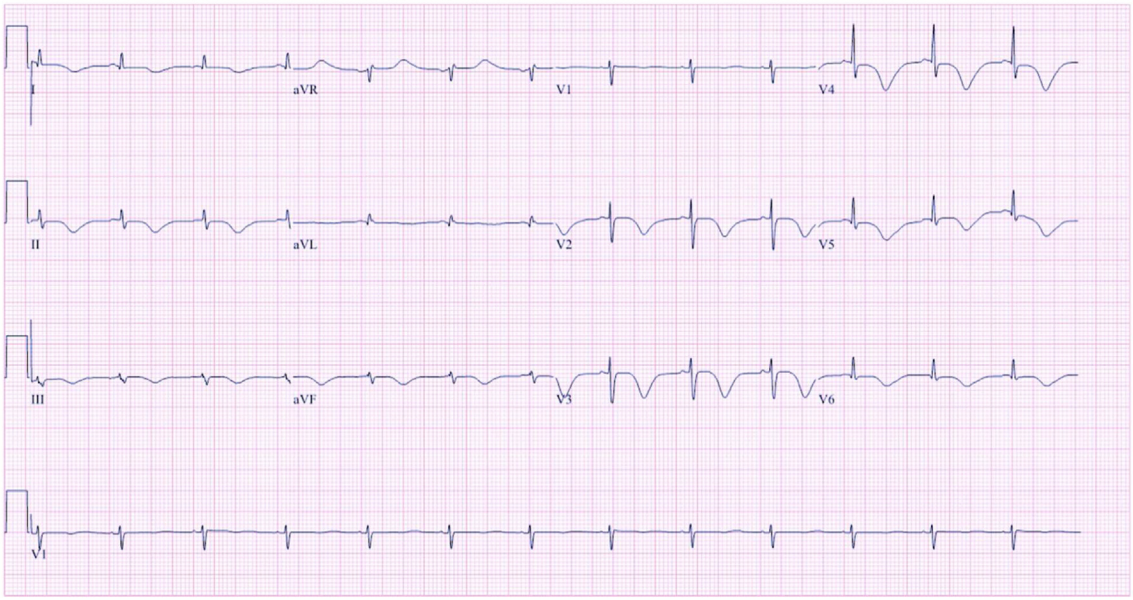

Fig. 3. Electrocardiogram changes on day 3 of hospitalization. ECG changes notable for sinus rhythm with diffuse T-wave depressions present in leads I-III, aVF, and V2–V6 with a prolonged QT interval.

associated with myocarditis, pericarditis, thyroiditis, and heart failure in patients with no cardiac history.[5-7] It is suspected that active COVID-19 infection contributed an additive stress response via pro-inflammatory cytokines and a prothrombotic state, resulting in characteristic stress cardiomyopathy on echocardiography.[11,12] However, COVID-19 infection may have predisposed to this unique cardiomyopathy by mechanisms not yet elucidated. One possible mechanism of cardiac involvement is direct myocyte injury via ACE2 receptors on cardiac myocytes.[5,12] The relatively mild magnitude of this patient's troponin elevation supports a stress-induced etiology. In sum, this case highlights that stress cardiomyopathy should be a differential diagnosis in patients with a suspected hydatidiform mole who present with symptoms of heart failure, in addition to valve defects, peripartum cardiomyopathy, among others. It also reflects an optimistic prognosis for return of cardiac function upon removal of the physiologic instigator.

Table 3. Endocrinology tests.

Test	Value	Reference range
Thyroid peroxidase antibody	18 IU/mL	<35 IU/mL
Thyroglobulin	8.3 ng/mL	3–40 ng/mL
Thyroid stimulating antibody	<0.10 IU/L	<1.75 IU/L
Anti-thyroglobulin antibody	19.5 IU/mL	<20 ng/mL
Thyroid ultrasound	Normal sized thyroid gland without discrete nodularity	

4. Conclusion

Molar pregnancy causes a vast excess of b-hCG production. The homology in structure between hCG and TSH subunits results in the cross-reactivity of their receptors. The b-hCG concentration is proportional to the degree of thyroid stimulation and, in this case, induced a severe episode of thyrotoxicosis.[13] Due to the severe systemic effects of increased T3 on the cardiovascular system, our patient developed takotsubo cardiomyopathy.

Disclaimer

This case report was previously presented in poster format at Manatee Memorial Hospital Research Day on April 27, 2022, in Bradenton, Florida.

Sources of support

None.

Conflict of interest

M.Z.- EMD Serono (consulting). Other authors have no financial relationships relevant to this article to disclose.

Notes on patient consent

Informed consent has been obtained from the patient.

APPENDIX

Supplementary table 1. Burch-Wartofsky score calculation. The Burch and Wartofsky is a clinical scoring method to assess the risk for present/impending thyroid storm. It is based off the patient's symptomatic presentation to allow for prompt treatment intervention, if necessary.[8] *The patient's vital and status are highlighted in yellow, yielding to a total score of 80, which is consistent with thyroid storm.*

Criteria	Points
Thermoregulatory Dysfunction Temperature (°C)	
37.2-37.7	5
37.8-38.3	10
38.4-38.8	15
38.9-39.4	20
39.4-39.9	25
>40	30
Cardiovascular Tachycardia (beats per minute)	
100-109	5
110-119	10
120-129	15
130-139	20
≥140	25
Atrial Fibrillation	
Absent	0
Present	10
Congestive Heart Failure	
Absent	0
Mild	5
Moderate	10
Severe	20
Gastrointestinal-hepatic dysfunction Manifestation	
Absent	0
Moderate(diarrhea, abdominal pain, nausea/vomiting)	10
Severe (jaundice)	15
Central nervous system disturbance Manifestation	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure, coma)	30
Precipitating event Status	
Absent	0
Present	10
Total score	**80**
Thyroid storm	>45
Impending storm	25-45
Storm unlikely	<25

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