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Case Report

A Case of Metastatic Choriocarcinoma-Related Paraneoplastic Thyroid Storm

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Abstract

Thyroid storm due to gestational trophoblastic disease (GTD) with metastatic choriocarcinoma is a rare but potentially life-threatening endocrine emergency. We report on a woman with molar pregnancy and metastatic choriocarcinoma who presented with thyroid storm (Burch-Wartofsky point scale of 45) a few weeks after the evacuation of GTD. She was initially managed with intravenous hydrocortisone, oral propylthiouracil (PTU), and esmolol infusion. After stabilization in the intensive care unit, 10 cycles of chemotherapy with etoposide, methotrexate, leucovorin, dactinomycin, and cyclophosphamide (EMA-CO) were initiated for stage 4 choriocarcinoma with brain and lung metastases. She underwent a hysterectomy soon after completing chemotherapy and received an additional 3 cycles of chemotherapy after the hysterectomy. As human chorionic gonadotropin (hCG) levels normalized, thyroid function reverted to normal as well. At the last follow-up, the patient was asymptomatic, euthyroid (without antithyroid medication), had a normal hCG titer of 1.7 mIU/mL (normal nonpregnant reference is < 5 mIU/mL), and the lung and brain lesions had resolved entirely. Management of thyroid storm in the presence of untreated metastatic choriocarcinoma requires a high index of suspicion and a multidisciplinary team approach to prevent complications and improve survival.

Key Words: thyroid storm, metastatic choriocarcinoma

Abbreviations: BW, Burch-Wartofsky; D&C, dilatation and curettage; CT, computed tomography; EMA-CO, etoposide, methotrexate, leucovorin, dactinomycin, and cyclophosphamide; FT3, free triiodothyronine; FT4, free thyroxine; GTD, gestational trophoblastic disease; hCG, human chorionic gonadotropin; hCGi, intact human chorionic gonadotropin; PTU, propylthiouracil; T3, triiodothyronine; T4, thyroxine; TFT, thyroid function test; TSH, thyrotropin (thyroid stimulating hormone).

Introduction

Thyroid storm is a rare but potentially life-threatening endocrine emergency first described in 1926 by Frank Howard Lahey as "the crisis of exophthalmic goiter." It is more common in women, patients with Graves disease, and older adults with autonomous thyroid nodules. It is frequently precipitated by stressful conditions such as surgery, infection, trauma, metabolic acidosis, radioactive iodine therapy, nonadherence to antithyroid medications, and pregnancy and the postpartum state. Gestational trophoblastic disease (GTD) with metastatic choriocarcinoma is an uncommon cause of thyroid storm and diagnosis is usually delayed (1). We present the successful management of a woman with molar pregnancy and metastatic choriocarcinoma who presented in a thyroid storm a few weeks following the evacuation of GTD.

Case Presentation

A 38-year-old G3P1021 woman presented to an outside facility at approximately 6 weeks of gestation with vaginal bleeding, lower abdominal pain, fatigue, muscle cramping, nausea, and vomiting. Her hCG level was 663 200 mIU/mL (normal pregnancy reference range at 6 weeks 152 to 32 117 mIU/mL) with a positive urine pregnancy test. A transvaginal ultrasonography confirmed a uterine molar pregnancy. She underwent dilatation and curettage (D&C), and hCG levels were reduced to 550 500 mIU/mL after 2 days. Histopathology of the D&C specimen confirmed a malignant gestational trophoblastic neoplasm consistent with gestational choriocarcinoma. The patient did not have medical insurance, and when she was seen for follow-up in 2 weeks the plan was for her to be referred to a tertiary care gynecologic oncology service for further management of choriocarcinoma.

One month after discharge from the hospital, she presented to our emergency department with malaise, nausea, vomiting, cough, and shortness of breath. On examination, she was afebrile and oriented to time, place, and person but appeared anxious. Her vital signs were significant for sinus tachycardia (heart rate 150 beats/minute), blood pressure was normal at 136/82 mmHg, respiratory rate was 16 per minute, and oxygen saturation was 95% on room air. The thyroid gland was normal to palpation without a bruit. The rest of her physical examination was unremarkable.

Diagnostic Assessment

Her Burch-Wartofsky (BW) score was 45, suggesting a thyroid storm (Table 1). The thyroid function tests (TFTs) were

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Table 1. Burch-Wartofsky score of the patient at presentation

Parameter	Patient's value	Scoring points
Heart rate (beats/min)	≥ 140 beats/min	25
Congestive heart failure	Absent	0
Atrial fibrillation	No	0
Precipitating event	No	10
Temperature (°Fahrenheit)	<99°F	0
Central nervous system effects	Absent	0
Gastrointestinal/hepatic dysfunction	Moderate (diarrhea, nausea, vomiting, abdominal pain)	10

notable for an undetectable thyroid stimulating hormone (TSH) (< 0.005 mIU/L; reference range 0.270-4.20 mIU/L), as well as an elevated free thyroxine (FT4) (4.88 ng/dL [62.8 pmol/L SI]; reference range 0.80-1.70 ng/dL [10.29-21.87 pmol/L SI]), and free triiodothyronine (FT3) (13.6 pg/mL [20.94 pmol/L SI]; reference range: 2.0-4.4 pg/mL [3.08-6.77 pmol/L SI]) (Table 2). The FT3/FT4 ratio was 2.79, and the hCG level was very high (932 993 mIU/mL), which was measured using electrochemiluminescence assay.

Treatment

The patient was admitted to the intensive care unit to manage the thyroid storm. She was initiated on intravenous steroids (hydrocortisone initially administered at 100 mg, then 50 mg every 12 hours) and an oral antithyroid medication, PTU (200 mg every 4 hours). An esmolol infusion was started and titrated to control tachycardia with a target heart rate of less than 110 beats/min). After stabilization of the patient, contrast-enhanced computed tomography (CT) of the chest and brain were performed, which demonstrated multifocal pulmonary and brain metastases, respectively (Fig. 1), confirming the diagnosis of stage 4 choriocarcinoma. Oncology was consulted, and chemotherapy with etoposide, methotrexate, leucovorin, dactinomycin, and cyclophosphamide (EMA-CO) was recommended. The esmolol infusion was ultimately replaced with oral propranolol (60 mg every 6 hours). PTU was substituted with oral methimazole (10 mg 3 times daily), and serial FT4 and FT3 were monitored to guide the titration of methimazole further (Fig. 2), which was decreased from 30 mg daily to 20 mg daily before discharge. To ensure patient adherence after discharge, propranolol was switched to atenolol 50 mg once daily.

Outcome and Follow-Up

Two weeks after hospital discharge, the patient was readmitted for inpatient chemotherapy. At admission, the patient was asymptomatic. The methimazole dose was further reduced to 10 mg daily based on a low FT4 level of 0.64 ng/dL (8.24 pmol/L SI); reference range 0.80-1.70 ng/dL (10.29-21.87 pmol/L SI)] and a normal FT3 level of 2.7 pg/mL (4.15 pmol/L SI); reference range: 2.0-4.4 pg/mL (3.08-6.77 pmol/L SI)]. During 10 cycles of EMA-CO chemotherapy over the next 5 months, hCG levels trended downwards and plateaued at 9.3 mIU/mL (normal nonpregnant reference is < 5 mIU/mL), indicative of low-grade chemotherapy resistance (Fig. 2). To treat the residual choriocarcinoma, a total hysterectomy was performed 10 days after the completion of chemotherapy on the recommendation of a multidisciplinary team. The excised hysterectomy specimen confirmed a 6.6-cm tumor limited to the uterine corpus that revealed atypical scatter cells with intermediate trophoblast appearance on histopathology (Fig. 3). The pathologic stage of choriocarcinoma was ypT1, FIGO (International Federation of Gynecology and Obstetrics) stage 1. Following the hysterectomy, the patient received an additional 3 cycles of EMA-CO chemotherapy. At 1-month follow-up, hCG titers were reduced to 1.7 mIU/mL. CT chest and magnetic resonance imaging (MRI) brain confirmed the resolution of metastatic lung and brain lesions, respectively (Fig. 1). The patient was asymptomatic at the last follow-up visit 3 months after the hysterectomy. Her subjective pain rating was 0/10, and her Eastern Cooperative Oncology Group (ECOG) performance status was 0. After normalization of TFTs, methimazole was discontinued at the 3-month follow-up visit, and the patient was continued on oral atenolol 25 mg once a day, which was ultimately discontinued 6 months after initial presentation in thyroid storm.

Discussion

Gestational transient thyrotoxicosis is common in normal pregnancy. GTD may lead to more extreme changes to thyroid function due to significantly higher hCG concentrations. Almost 25% to 64% of patients with hydatidiform mole have deranged TFTs, but only 5% have clinically overt hyperthyroidism (2). It has been proposed that sustained elevation of hCG levels greater than 200 000 mIU/mL over several weeks is required to induce clinical hyperthyroidism (3). Kaulfers et al noted that for every 10 000 mIU/mL increase in hCG, TSH decreases by 0.1 mIU/mL, and FT4 increases by 0.1 ng/dL (4). Our patient had a sustained elevation of hCG greater than 900 000 mIU/mL that probably precipitated a thyroid storm.

TSH, follicle-stimulating hormone, luteinizing hormone, and hCG belong to a family of heterodimeric glycoprotein hormones that share a common alpha subunit but have different functional beta subunits. Due to the common alpha subunit, there is a cross-reactivity of hCG with the TSH receptor. Further, hCG and TSH receptors exhibit 70% and 45% homology for transmembrane and extracellular domains, respectively (3). Despite significant homology between TSH and hCG receptors, only 5% of patients with choriocarcinoma develop hyperthyroidism. The likely reason is that the thyrotropic activity of the hCG molecule depends on the peptide linkage, number and structure of oligosaccharide side chains, and sialic acid content present in the hCG molecule. During normal pregnancy, intact hCG (hCGi) is the predominant form that has an additional 31–amino acid extension called a β-carboxy-terminal peptide (β-CTP). Both β-CTP and carbohydrate side chains reduce the affinity of the hCGi molecule by interfering with its binding to the TSH receptor and hence preventing hyperthyroidism despite the presence of a large amount of hCG during the first trimester of pregnancy. Metabolism of the hCGi molecule significantly alters its thyrotropic activity. Nicked (deglycosylated and desialylated) forms of hCG molecules, as seen in GTD, including choriocarcinoma, have 1.5- to 2-fold greater stimulation affinity for TSH receptors (5).

Table 2. Laboratory evaluation of the patient at admission and discharge

Laboratory parameter	At admission	At discharge	Reference range
Hemoglobin	**8.8 g/dL (88 g/L)**	**8.7 g/dL (87 g/L)**	12.0-16.0 g/dL (120-160 g/L)
Hematocrit	**28.6%**	**29.0%**	37.0-47.0%
RBC count	4.71 per mm^3 (4.71×10^6/L)	4.32 per mm^3 (4.32×10^6/L)	4.20-5.40 per mm^3 ($4.20\text{-}5.40 \times 10^6$/L)
Platelet count	**528×10^3 per mm^3 (528×10^9/L)**	430×10^3 per mm^3 (430×10^9/L)	$140\text{-}440 \times 10^3$ per mm^3 ($140\text{-}440 \times 10^9$/L)
WBC count	**13.94 per mm^3 (13.94×10^6/L)**	**3.68 per mm^3 (3.68×10^6/L)**	4.5-11 per mm^3 ($4.5\text{-}11 \times 10^6$/L)
Neutrophils	70%	45%	34-73%
Albumin	**3.1 g/dL (31 g/L)**	**3.3 g/dL (33 g/L)**	3.8-4.9 g/dL (38-49 g/L)
Aspartate aminotransferase (AST)	**159 IU/L**	21 IU/L	14-33 IU/L
Alanine aminotransferase (ALT)	**111 IU/L**	19 IU/L	10-42 IU/L
Alkaline phosphatase	**125 IU/L**	96 IU/L	35-104 IU/L
Estimated glomerular filtration rate (eGFR)	>59 ml/min/1.73 m^2	>59 ml/min/1.73 m^2	100 ml/min/1.73 m^2
Ferritin	**1057 ng/mL (1057 µg/L)**		15-150 ng/mL (15-150 µg/L)
Glucose	**121 mg/dL (6.71 mmol/L)**	82 mg/dL (4.55 mmol/L)	71-99 mg/dL (3.9-5.49 mmol/L)
Calcium	10 mg/dL (2.5 mmol/L)	9 mg/dL (2.25 mmol/L)	8.6-10 mg/dL (2.15-2.5 mmol/L)
Anion gap	14 mmol/L	12 mmol/L	4-16 mmol/L
Osmolality calculated	**267.1 mOsm/kg (267.1 mmol/kg)**	**271.3 mOsm/kg (271.3 mmol/kg)**	275-295 mOsm/kg (275-295 mmol/kg)
Cortisol	20 µg/dL (552 nmol/L)		0.4-62.9 µg/dL (11.04-1736.04 nmol/L)
Free T4	**4.88 ng/dL (62.8 pmol/L)**	1.66 ng/dL (21.36 pmol/L)	0.80-1.70 ng/dL (10.29-21.87 pmol/L)
Free T3	**13.6 pg/mL (20.94 pmol/L)**	2.6 pg/mL (4.0 pmol/L)	2.0-4.4 pg/mL (3.08-6.77 pmol/L)
Thyroid stimulating hormone (TSH), 3rd generation	**<0.005 mIU/L (<0.005 IU/L)**		0.270-4.2 mIU/L (0.270-4.2 IU/L)
β-human chorionic gonadotropin (β hCG)	**971 620 mIU/mL (971 620 IU/L)**	**588 mIU/mL (588 IU/L)**	0.0-5.0 mIU/mL (0-5 IU/L)
N-terminal pro b-type natriuretic peptide (NT-pro BNP)	43 pg/mL		0-125 pg/mL
High-sensitivity cardiac troponin T (hs-cTnT)	10 ng/L		<14 ng/L

Values that depart from the reference range are shown in bold typeface.

Although thyroid storm affects only 1% to 2% of hyperthyroid patients, it is associated with a 10% to 30% risk of mortality. Any stress can precipitate a thyroid storm, and the patient usually presents with a fever with or without altered mental status. Tachycardia (heart rate > 140/min) usually has an abbreviated response to beta-blockers, calcium channel blockers, and intravenous fluids. Therefore, in patients with GTD-induced hyperthyroidism, the management of thyrotoxicosis should take precedence over the management of GTD. The BW and Akamizu scoring systems help detect and assess the clinical severity of thyroid storms. The BW score is commonly used globally, except in Japan, where the Akamizu scoring system is preferred (6). Criteria in the BW scoring system are precipitating events and the severity of symptoms due to multi-organ decompensation, such as body temperature, heart rate/atrial fibrillation, congestive heart failure, neurological dysfunction with alteration of consciousness, and gastro-hepatic dysfunction (7). Both scoring systems are designed for screening and diagnosis. Thus, they are sensitive but not very specific. Validating the diagnosis by good clinical judgment, preferably by an endocrinologist, is necessary.

In patients with GTD, the role of iodinated contrast in inducing thyroid storms has long been recognized. An iodine load can precipitate thyrotoxic symptoms through increased iodine uptake and production of circulating thyroid hormones (Jod-Basedow phenomenon) within 2 to 12 weeks after iodinated contrast exposure (8). Hence, imaging with contrast administration should be used judiciously in patients with suspected hCG-producing malignancies as it can precipitate or worsen thyrotoxicosis. In our patient, we performed CT of the chest and brain only after stabilizing and controlling the thyroid storm.

In patients with suspected GTD-induced thyrotoxicosis, if the hCG level is not concordantly elevated, reassessment of the hCG level by serial dilution should be considered to

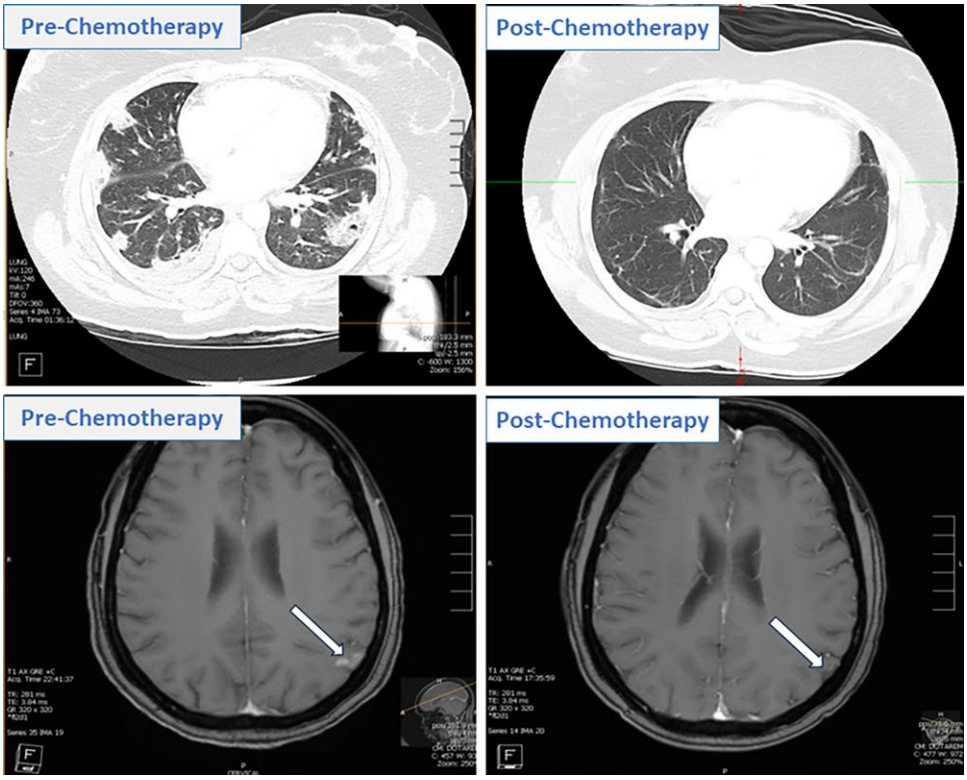

Figure 1. CT chest showing lung metastasis and MRI brain showing brain metastasis pre-chemotherapy and resolution post-chemotherapy.

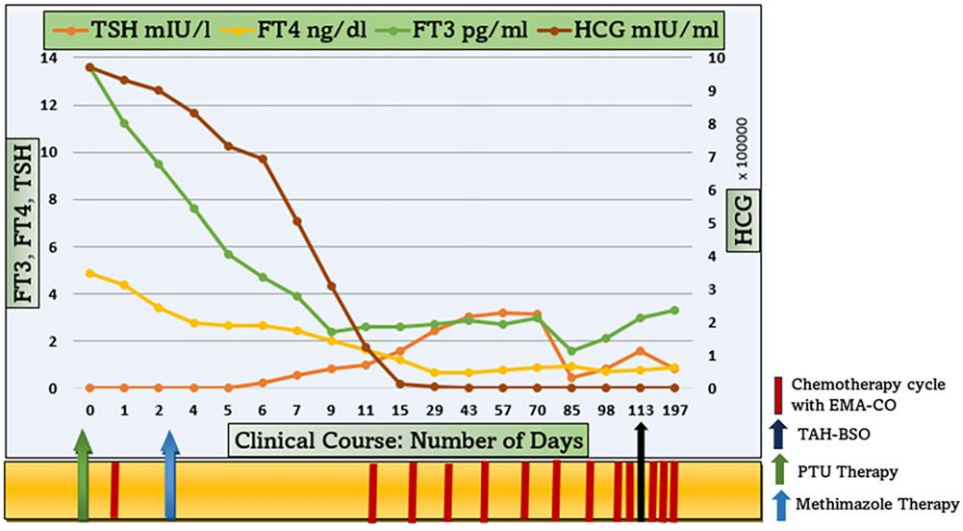

Figure 2. Trend of thyroid function tests, including free T3, free T4, TSH, and β-hCG during the clinical course over 200 days.

minimize the chances of falsely low hCG levels due to the "hook effect" (9).

Thyroid storm has a high mortality risk due to multi-organ failure, sepsis, as well as cardiac and respiratory failure (1). Hence, emergent management of thyroid storm is imperative, which includes adequate volume resuscitation, decreasing the synthesis and release of thyroid hormone, blocking its peripheral actions, alleviating systemic decompensation, and removing the precipitating event. Both PTU and methimazole block thyroid hormone synthesis by inhibiting thyroid peroxidase enzyme and blocking iodine organification. Iodine also helps to acutely lower thyroid hormone concentration by decreasing the release of hormones from the thyroid gland and inhibiting its organification (Wolff-Chaikoff effect). Iodine is usually used with thionamide for a short course of 10 days. PTU should be given at least an hour before the iodine therapy to avoid reflex thyroid hormone release. PTU, beta-blockers, and glucocorticoids also decrease the peripheral conversion of T4 to T3. Beta-blockers further help reduce the peripheral effects of thyroid hormone (2).

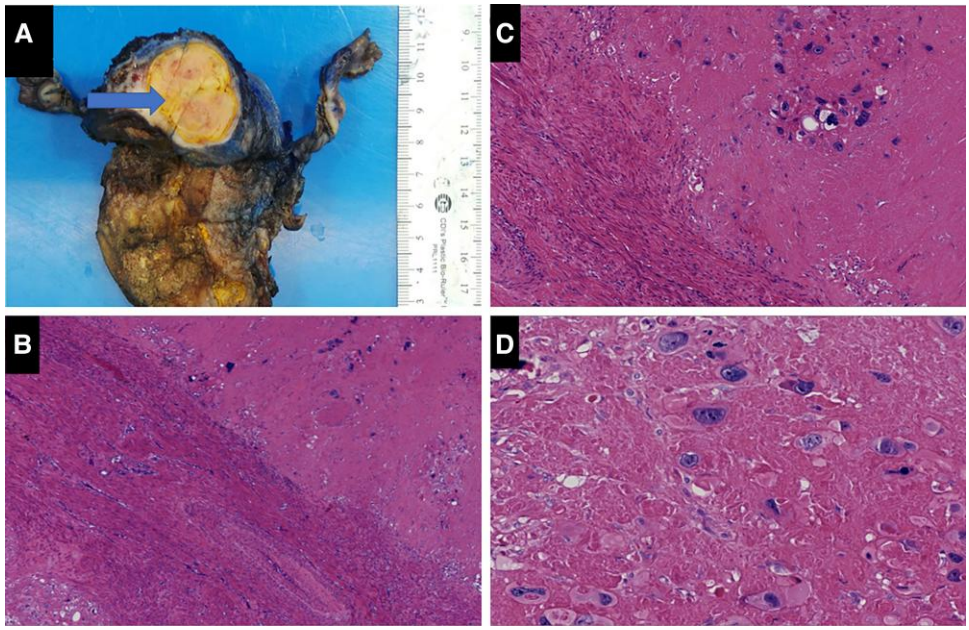

Figure 3. The gross image of the specimen showing tumor (a) histopathology of the uterus showing hyalinization (b) with scattered atypical cells with intermediate trophoblast appearance (c, d) limited to the residual tumor in the uterine corpus.

Following the management of thyroid storm and stabilization of the patient, care needs to be directed toward definitive management of GTD under the care of a multidisciplinary team, including oncology, gynecology, and endocrinology. D&C is usually the preferred method of evacuation of GTD limited to the uterus; extrauterine GTD may need more invasive and extensive surgical treatment if medical management fails. Hysterectomy is generally reserved for patients with residual disease after chemotherapy, as in our patient, or for patients who do not desire further pregnancy—the evacuation of mole results in a rapid reduction in thyroid hormone levels. Postevacuation follow-up with serial quantitative β-hCG measurements is crucial to rule out persistent molar tissue or development of choriocarcinoma since 15% to 20% and 1% to 5% of patients with complete and partial mole, respectively, may develop choriocarcinoma. Multi-agent chemotherapy is the preferred treatment for choriocarcinoma since 91% to 93% of patients achieve complete disease resolution with excellent long-term survival. Stage IV metastatic choriocarcinoma and resistance to chemotherapy, however, are risk factors for increased mortality (10). Despite stage IV disease and partial resistance to chemotherapy, surgical removal of residual tumor with hysterectomy helped improve the outcome in our patient. In patients with metastatic choriocarcinoma, methimazole should be initiated before chemotherapy as there is a risk of a surge in hCG levels and potential worsening of thyrotoxicosis after initiating chemotherapy (8, 11).

Learning Points

- A thyroid storm in the presence of untreated metastatic choriocarcinoma is a life-threatening endocrine emergency that requires a high index of suspicion, early diagnosis, careful treatment planning, and a multidisciplinary team to prevent complications and improve survival.
- Antithyroid drugs are the initial mainstay of treatment until response to oncological-directed therapy is achieved.
- Thyroid function tests should be closely monitored as patients can experience rapid symptomatic improvement.
- Persistent biochemical normalization of hCG during follow-up confirms the abolition of any residual disease.

Contributors

All authors made individual contributions to authorship. L.G. and G.Y.G. were involved in the diagnosis and management of this patient and edited the manuscript. N.G. was involved in the literature review, preparation, and manuscript submission. M.C. was involved in the histopathology section and preparation of histopathology images. G.Y.G. provided overall supervision and approval of the work. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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