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Case Report

Just an Acute Pulmonary Edema? Paraneoplastic Thyroid Storm Due to Invasive Mole

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Keywords
Thyroid storm · Paraneoplastic syndrome · Acute pulmonary edema · Hydatidiform mole

Abstract
Hydatidiform mole is a malignant entity included in the gestational trophoblastic diseases. It usually produces pregnancy hormones such as beta-human chorionic gonadotropin (β-hCG), which in turn stimulates endogenous thyroid hormone production. We report the case of a high-risk complete invasive hydatidiform mole with pulmonary metastasis and associated paraneoplastic syndrome. The patient is a 30-year-old woman who presented symptoms of pregnancy and metrorrhagia. A uterine mass was detected. Urine β-hCG was found negative. In serum, 2,662,000 mIU/mL (normal range: <5) was found, together with parameters of severe hyperthyroidism. The patient underwent uterine curettage with diagnostic and therapeutic means. At that precise moment, her pregnancy-like symptoms worsened and she developed restlessness, tachycardia, diaphoresis, dyspnea at rest, and peripheral edema. A scan showed bilateral pulmonary nodules suggestive of metastasis, acute pulmonary edema, and bilateral pleural effusion without signs of pulmonary thromboembolism. At that time, she presented a free T4 of 2.34 ng/dL (normal range: 0.8–1.8 ng/dL), causing a thyroid storm with secondary cardiac dysfunction. The patient was treated with corticosteroid therapy to decrease peripheral conversion of thyroid hormone T4 to active T3. Her symptoms remitted within 8 h. After 48 h, T4 level was 1.2 ng/dL while serum β-hCG was 80,000 mIU/mL, with a positive urine result. The change in the urine analysis is due to the "hook effect" of the reactive test. An effective chemotherapy treatment was started according to the EMA-CO scheme, remaining free of disease at present. Knowing paraneoplastic syndromes is necessary to achieve the best clinical management and to start treatment early.

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Introduction

We present the clinical case of a high-risk disseminated hydatidiform mole with the development of acute pulmonary edema (APE) secondary to a thyroid storm (TS) as a result of the paraneoplastic effect of beta-human chorionic gonadotropin (β-hCG) on the thyroid gland. With this case, we highlight the existence of this rare tumor, its etiopathogenesis, the potential severity of a thyroid crisis, possible distractors in the diagnostic process, and its clinical management of curative intent where time is crucial to achieve the best results.

Case Report/Case Presentation

We present the case of a 30-year-old woman with no known drug allergies, toxic habits, or relevant family history. She experienced menarche at 12 years old. She took oral contraceptives for several years. Among her medical history, pathologic antecedents outstand a IIA diffuse large B-cell non-Hodgkin lymphoma at the age of 20, treated with poly-chemotherapy R-MegaCHOP and thoracic radiotherapy in complete remission, with no residual clinical toxicities including cardiological ones. She also presented a CIN III HPV16+ cervical lesion treated with simple trachelectomy when she was 27 years old. She lacked a personal history of thyroid disease.

The patient debuted with symptoms of hyperemesis, abdominal discomfort, and metrorrhagia. One month later, she consulted her general practitioner. A hard hypogastric mass of 19 × 20 × 18 cm without fetal heartbeat compatible with a hydatidiform mole was detected, with a uterus size similar to a 22-week pregnancy. She analytically presented negative β-hCG in urine (pregnancy test), with a β-hCG in serum of 2,662,000 mIU/mL and a hemoglobin of 11 ng/dL. A thyroid hormone profile was requested and analyzed according to the local iodine nutritional status and the manufacturer lab kit employed with undetectable TSH and a free T4 of 1.85 ng/dL (normal range: 0.8–1.8 ng/dL). After these findings, the patient was admitted for evolutionary control and diagnostic study. A radiography upon admission showed possible bilateral pulmonary nodules without other alterations.

On day +4 of admission, a uterine curettage was performed to obtain pathological characterization and reduce tumor volume. Two erythrocyte concentrates (totaling 700 mL) were transfused perioperatively due to anemia with a hemoglobin of 8 g/dL. No more replacement fluid was administered.

During curettage, her pregnancy symptoms worsened and she developed restlessness, sinus tachycardia up to a maximum of 125 beats per minute, blood pressure of 110/70 mm Hg, 37.3°C, diaphoresis, dyspnea at rest with room air $SatO^2$ of 93%, dry cough, and peripheral edema. A radiography (see Fig. 1) and CT scan (see Fig. 2) were performed, showing bilateral reticular interstitial central bibasilar pulmonary infiltrates, bilateral de novo pleural effusion, and bilateral pulmonary nodules (3 in total), without signs of pulmonary thromboembolism. At that time, she presented an analytical peak of free T4 of 2.34 ng/dL. She was diagnosed with NYHA class IV heart failure with APE in the context of hyperthyroidism secondary to a β-hCG-producing mole.

A suspicion of a TS with cardiologic implications arose, supported by the Akamizu criteria for diagnosing TS corresponding to type 1 (thyrotoxicosis and cardiac heart failure) [1] and the Burch criteria with 65 points (accomplished items: 37.2°C, mild central nervous system effects, nausea, 125 beats/min, severe pulmonary edema, precipitant history present), considering a high probability of TS diagnosis with 45 points or more [2]. Corticosteroid therapy was started to reduce the T4-T3 conversion, together with oxygen therapy and diuretics. At 48 h, on day +6, β-hCG had decreased to 80,000 mIU/mL, TSH 1 mIU/L (normal

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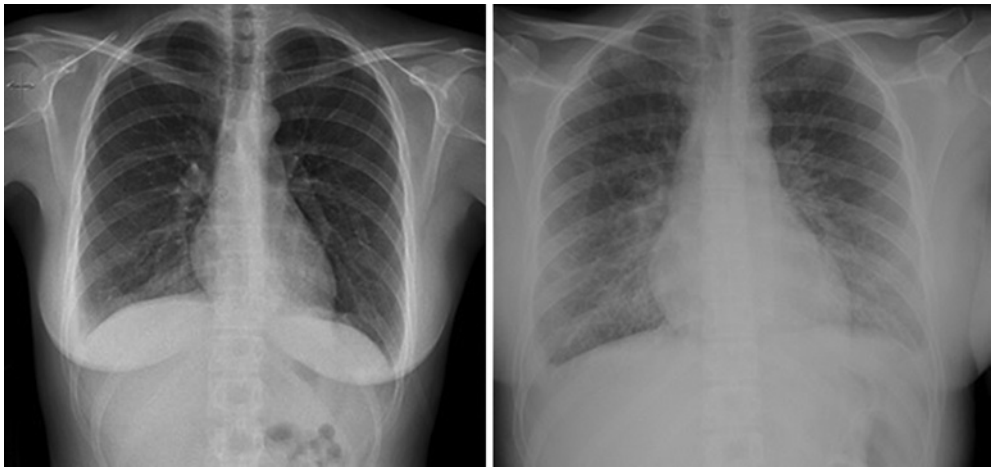

Fig. 1. Chest radiography at admission (left) and 4 days after admission, developing APE (right).

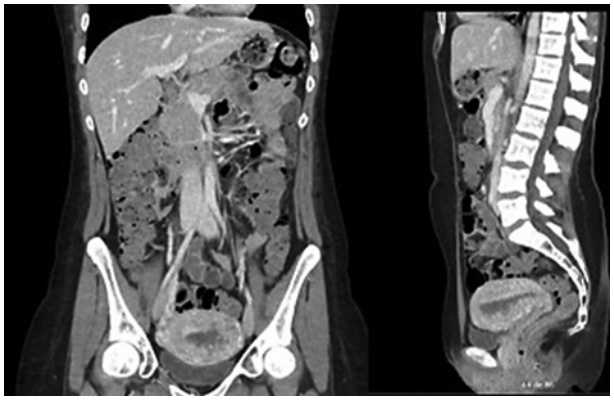

Fig. 2. Coronal (left) and sagittal (right) view in CT scan. A hydatidiform mole in uterus with a size of 22-week pregnancy can be seen.

range: 0.360–3,740), and free T4 had reversed to normal range (see Fig. 3). The β-hCG determination was repeated in urine and was positive. The endocrinology department was consulted requesting thyroid-stimulating antibodies, ruling out Graves' disease, and indicating secondary stimulation by β-hCG as the most plausible cause of hyperthyroidism.

On day +8, the patient was asymptomatic. The pathological anatomy concluded that it was a complete hydatidiform mole. The radiological image was updated with a new scanner that showed resolution of pleural effusion and bilateral pulmonary infiltrates, with persistence of bilateral pulmonary nodules suspected of malignancy. The case study was completed with a brain MRI, thyroid ultrasound, and echocardiogram without pathological findings.

She was finally diagnosed with a complete invasive diploid hydatidiform mole, FIGO III stage, and a Modified WHO Prognostic Score of 7 points (4 points of $\geq 10^5$ pretreatment serum hCG mIU/mL, 2 points for ≥5 cm in the largest tumor size, and 1 point number for 3 metastases between 1 and 4) (high-risk disease) [3], and treatment was started with the EMA-CO regimen. She is currently disease-free after having completed 11 treatment cycles, with a negative β-hCG in urine and serum since the end of the 8th cycle and a quasi-complete radiological response of lung and uterine lesions. A hysterectomy was performed due to a residual image of tumor on MRI and PET-CT scan despite negative markers. The pathological review showed a millimetric and hyalinized persistent trophoblastic disease. Thyroid hormones were in the normal range, and the patient had no symptoms of heart failure until the current date.

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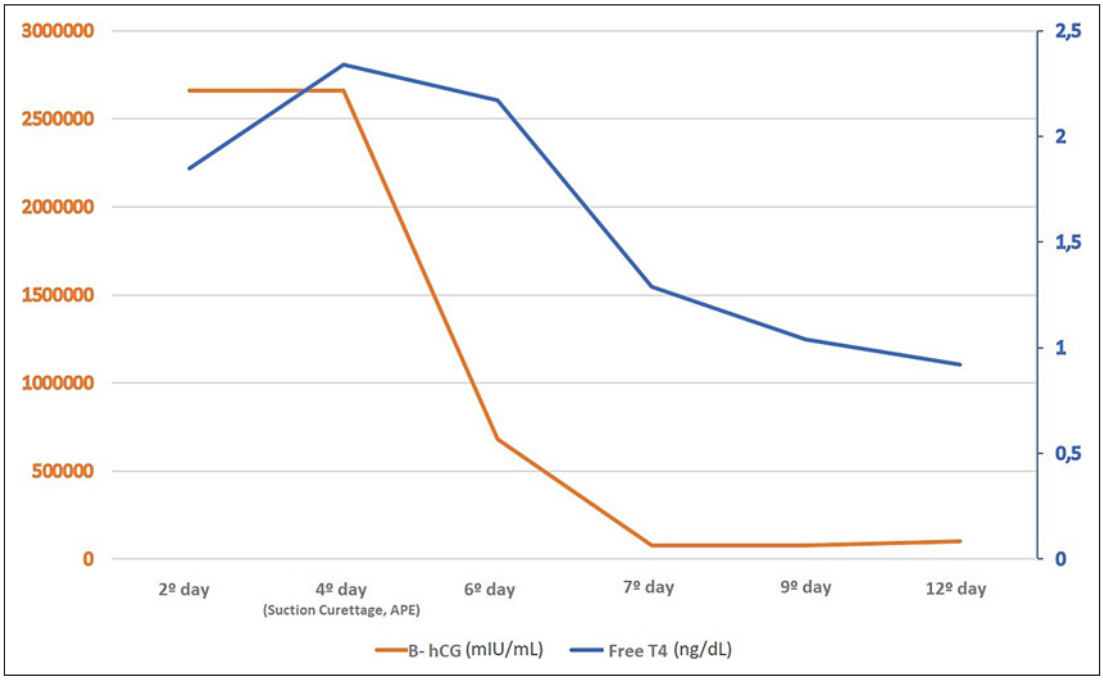

Fig. 3. Evolution of β-hCG and free T4 during hospitalization.

Discussion/Conclusion

The invasive hydatidiform mole, as reported in this case, is included in a group of diseases developed by an abnormal proliferation of the placental trophoblast after aberrant fertilization. Premalignant gestational trophoblastic diseases (GTDs) include partial or complete hydatidiform moles, as well as malignant ones such as the invasive mole, the choriocarcinoma, and other rare placental tumors. In Western countries, hydatidiform mole has an incidence of 1–3 in every 1,000 pregnancies, being slightly higher in Asia. This group of diseases usually occurs alone, but there are also cases of viable pregnancies coexisting with tumors of this type. Metastatic stages in these tumors are extremely rare. Risk factors are late menarche, low flow menstruations, and oral contraceptives, as well as mutations in NLPR7 (or NALP7) gene in chromosome 19q13 [4].

A mole is produced by the fertilization of a normal ovule by two spermatozoa (creating a partial mole, triploid 69 XXX, XXY, XYY) or an abnormal ovule empty of maternal genetic material by a spermatozoon, duplicating its genetic material (complete mole, diploid 46XX, no 46XY documented). This excess of paternal genome is postulated to be the pathogenic key to the consequent hyperplastic proliferation of the placenta and the absence of full embryonic development. As the days go by, the abnormal embryo will prepare the human body for a "false pregnancy" with a hypervascular gravid uterus and the release of multiple hormones such as β-hCG. Complete moles produce the highest cell proliferation and may develop invasiveness and metastasize, frequently to areas of the central nervous system, lungs, and liver, as well as producing high levels of β-hCG, sometimes over 100,000 mIU/mL [4, 5]. Imaging tests such as ultrasound, pathological analysis, and elevated β-hCG analysis are essential to confirm the diagnostic suspicion of hydatidiform mole. At present, other biomarkers such as microRNA molecules or circulating tumor cells in peripheral blood are being investigated [6, 7].

Elevation of β-hCG can produce paraneoplastic pregnancy signs and symptoms based on painful ovarian theca cysts, hyperemesis gravidarum, preeclampsia, and secondary

hyperthyroidism due to stimulation of β-hCG to the thyroid gland. The structure of the beta subunit of the hCG hormone is similar to the TSH and therefore has an agonist effect on the thyroid gland. It has been estimated that for every 10,000 mIU/mL increase in β-hCG units, TSH decreases 0.1 mIU/L and free T4 increases 0.1 ng/dL [8].

In a common pregnancy, a mild state of asymptomatic hyperthyroidism occurs, but with a placental tumor-producing β-hCG, severe hyperthyroidism can lead to a TS. TS is initiated by situations of discontinuation of anti-thyroid therapy or stress such as childbirth, infections, trauma, stroke, myocardial infarction, intense exercise, emotional stress, or the administration of iodinated contrast, among others. It includes symptoms of agitation or low state of consciousness, high temperature, tachycardia, heart failure, abdominal pain, diarrhea, hyperemesis, and/or jaundice. Thyrotoxicosis produced by GTDs is transient in time and does not usually share clinical signs of Graves' disease such as ophthalmopathy, clubbing, and pretibial myxedema [9]. In our patient, diagnosis could be confirmed according to two different sets of criteria. According to Akamizu et al. [1], it would correspond to a type 1 TS; according to Burch criteria, it would receive a total score of 65 points (considering a high probability of TS diagnosis with 45 points or more) [2].

In our patient, the mobilization of most of the tumor with curettage released a great amount of β-hCG into the bloodstream and stimulated the production of thyroid hormone, reaching maximum T4 values. A TS like the one that occurred in the patient could be fatal. Its management in the acute presentation is based on the use of glucocorticoids to reduce the T4 to T3 conversion. Adding thioamide derivatives (such as methimazole or carbimazole) is also possible, as to inhibit the production of new hormones. Iodinated scanner contrast or potassium iodide also inhibits thyroid precursor conversion [10].

Compared with the 4 published cases of TS with APE secondary to hydatidiform mole, this case presents the highest β-hCG value achieved with more advanced tumor staging [11–13]. The first reference shows two similar cases in 1971 with severe APE, one of them with supraventricular tachycardia treated with diuretics, experimental plasmapheresis, carbimazole, and hysterectomy, with resolution of the condition. The second reference shows 1 case of severe APE treated with suction curettage, chemotherapy, and potassium iodide, dating from 1981. Finally, a 2015 case is presented, with spontaneous abortion of a mole with subsequent hypertensive crisis, severe APE, and severe acute renal failure requiring hemodialysis, with resolution of the condition by improving renal function and clearing β-hCG. In our case, the use of diuretics, corticosteroids, and the effect of iodinated contrast was sufficient for symptom improvement, without requiring other measures.

The conversion from negative to positive β-hCG-based urine pregnancy test is due to a detector saturation phenomenon, also known as the "hook" effect. High levels of β-hCG >500,000 mIU/mL can give negative results in some pregnancy urine tests. Therefore, when the hormonal value decreases, the result in urine converts to positive [14]. This is especially important since a negative pregnancy test in a case of mole can delay the diagnosis. If there is sufficient diagnostic suspicion, β-hCG in serum should be requested or urine diluted and the determination repeated.

Regarding antineoplastic treatment, while a low-risk invasive mole can be treated with monochemotherapy in a short period of time with low-dose methotrexate, a high-risk invasive mole requires aggressive poly-chemotherapy to be started as soon as possible, as to reduce the relapse rate. However, there are no randomized clinical trials, the EMA-CO regimen, dating from 1988 the highest remission rate of all series, reaching 91% being more effective and less toxic than other regimens such as EMA-EP and CHAMOCA. EMA-CO treatment (day 1: etoposide 100 mg/m^2, dactinomycin 0.5 mg, methotrexate 300 mg/m^2; day 2: etoposide 100 mg/m^2, dactinomycin 0.5 mg; day 8: cyclophosphamide 600 mg/m^2, vincristine 0.8 mg/m^2; repeated every 14 days) requires weekly determinations of β-hCG in serum and urine until 3 consecutive negative

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determinations are achieved, at which time 3–4 more cycles of consolidation are continued [4]. GTD is a pathology characteristic of young patients, in which curative intention treatments should be aimed for. It is also important to highlight aspects such as meticulous dosing to reduce the appearance of second neoplasms and unwanted residual toxicities. At the end of treatment, it is proposed to make serum and urine controls. Close surveillance must be maintained in the first year after treatment since the risk of global relapse of a hydatidiform mole reaches 3% in this time space. After chemotherapy, hysterectomy (including resection of metastases) should be considered based on persistence of β-hCG and/or birth desire at that time [15].

We can draw several conclusions from this case. A placental tumor should be suspected in all women with symptoms of pregnancy, metrorrhagia, a uterus larger than expected, and very high levels of β-hCG. Knowledge of paraneoplastic syndromes is essential when we approach an oncological scenario. TS is a very rare condition, but without its detection and correct management, it can be life-threatening and delay the start of oncological treatment with curative intent. Finally, if there is a clear suspicion of GTD and we have a negative pregnancy test, we must request a serum hormone test to rule out a possible false negative in urine.

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Statement of Ethics

The procedures performed and described in this article were carried out in accordance with international guidelines and with the ethical standards of the Institutional Research Committee and the 1964 Declaration of Helsinki and its later amendment. Ethical approval was not required for this study in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

All authors have no conflicts of interest to declare.

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Author Contributions

Pablo Jiménez-Labaig and Joan Manuel Mañe were the responsible physicians for the case hereby reported and wrote the original draft for this article. Lara Lombardero and Maria Pilar Rivero provided assistance in the discussion for the case. Aintzane Sancho provided the

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figures included in the case. Guillermo López-Vivanco provided senior supervision. Pablo Jiménez-Labaig, Joan Manuel Mañe, María Pilar Rivero, Lara Lombardero, Aintzane Sancho, and Guillermo López-Vivanco have read, revised, and approved the final manuscript.

Data Availability Statement

All data generated during this study are included in this article. Further inquiries can be directed to the corresponding author.

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