CASE REPORT

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Gestational trophoblastic disease in the late postpartum period

Enfermedad trofoblástica gestacional en el posparto tardío

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ABSTRACT

Gestational trophoblastic disease (GTD) is a term used for a group of pregnancy-related tumors arising from defective proliferation of trophoblastic tissue. Its incidence after term pregnancy is infrequent, being diagnosed in most cases incidentally, due to symptoms of metastasis. We present a case of GTD that occurred 9 weeks after a vaginal delivery at term. The serum beta-human chorionic gonadotropin (β-hCG) level was 38 084 mIU/mL and a chest CT scan showed multiple pulmonary nodules. The patient received actinomycin D for 3 cycles. The β-hCG normalized after the third cycle and the patient remained disease-free for 12 months after diagnosis. The clinical presentation and challenges in diagnosing GTD in the late postpartum period are described.

Key words: Postpartum hemorrhage, Trophoblastic neoplasms

RESUMEN

La enfermedad trofoblástica gestacional (ETG) es un término utilizado para un grupo de tumores relacionados con el embarazo que surgen de la proliferación defectuosa del tejido trofoblástico. Su incidencia después de un embarazo a término no es frecuente, siendo diagnosticada en la mayoría de los casos de forma incidental, por síntomas de metástasis. Presentamos un caso de ETG que ocurrió 9 semanas después de un parto vaginal a término. El nivel sérico de gonadotropina coriónica humana beta (hCG-β) fue de 38 084 mUI/mL y una tomografía de tórax mostró múltiples nódulos pulmonares. La paciente recibió actinomicina D durante 3 ciclos. La hCG-β se normalizó después del tercer ciclo y la paciente permaneció libre de enfermedad durante 12 meses después del diagnóstico. Se describe la presentación clínica y los desafíos en el diagnóstico de ETG en el período posparto tardío.

Palabras clave. Hemorragia posparto, Neoplasias trofoblásticas.

Introduction

Gestational trophoblastic diseases (GTD) encompass a group of pathologies that arise from abnormal trophoblast proliferation. This category includes non-neoplastic and neoplastic lesions. Non-neoplastic lesions are classified into placental site nodules and partial and complete hydatidiform moles. Neoplastic lesions or neoplastic trophoblastic disease (NTD) have the potential for local tumor invasion and may generate distant metastases and include invasive and metastatic hydatidiform moles, placental site trophoblastic tumor, epithelioid trophoblastic tumor and choriocarcinoma[(1)].

Hydatidiform mole is the most common form of GTD, representing 80% of cases. Hydatidiform moles are observed in 1 in 600 miscarriages and in 1 in 1,200 pregnancies.

Hydatidiform moles are divided into complete and partial hydatidiform moles. Fetal development, vessels or red blood cells are not observed in complete moles. Complete moles almost always have a chromosomal complement totally derived from the paternal genome. The 46 XX karyotype is the most common, representing reduplication of the haploid genome of the sperm and exclusion of the maternal chromosomal complement. It is estimated that 5-10% of complete moles have a Y chromosome consistent with dispermic fertilization causing 10-20% of complete moles[(2)].

Partial moles usually have a complete trisomy derived from two paternal and one maternal haploid sets of chromosomes. Most have a 69,XXX or 69,XXY karyotype derived from a haploid ovum with either reduplication of the paternal haploid set from a single sperm or from dispermic fertilization.

Progression to malignant hydatidiform mole is increased after a complete mole, but only slightly increased after a partial mole. The probabilities of this progression are 15%-20% and less than 5% for complete and partial hydatidiform moles respectively[2-3].

Choriocarcinoma is an extremely rare highly malignant epithelial tumor comprising neoplastic intermediate trophoblast, cytotrophoblast and syncytiotrophoblast elements without chorionic villi with central necrosis that can arise from any type of trophoblastic tissue (molar pregnancy, abortion, ectopic pregnancy, and preterm or term intrauterine pregnancy). The incidence of choriocarcinoma is around 1 in 50,000 deliveries and 1 in 160,000 after term pregnancies[3].

Intra-placental choriocarcinoma is not common, representing about 0.03% of GTD. It is generally found on examination of third-trimester placentas. Histologically, there is marked trophoblast proliferation around one or a cluster of villi, while the rest of the placenta is normal. Intra-placental choriocarcinoma is very important to recognize and report as there may be a metastatic disease in both mothers and infants[4].

The diagnosis of choriocarcinoma is often delayed following a non-molar pregnancy resulting in poor outcomes. Choriocarcinoma is the most aggressive histologic type of GTN and is characterized by early vascular invasion and distant metastases. If choriocarcinomas are diagnosed and treated on time and properly, the cure rate reaches 87.5%[5].

Puerperium is the period following delivery during which pregnancy-induced maternal anatomical and physiological changes return to the nonpregnant state. Its duration is inexact but is believed to be between 4 and 6 weeks[6]. The postpartum period is distinct into three phases. The initial period involves the first 6-12 hours postpartum. The second phase is the subacute postpartum period which lasts 2-6 weeks. The third phase is the delayed postpartum period, which can last up to 6 months. Changes during this phase are extremely gradual and pathology is rare.

We present a case of choriocarcinoma with lung metastases after term pregnancy in a 31-year-old woman in the delayed postpartum period.

Case report

A 31-year-old G1 P1001 woman was evaluated in the office for moderate vaginal bleeding 9 weeks after a normal vaginal delivery. Pregnancy was complicated by gestational hypertension and chorioamnionitis. She was breastfeeding her infant and she denied pain, fever, nausea, or vomiting. On physical examination, vital signs were normal, the cardiovascular and respiratory exam was unremarkable and the abdomen was soft with no guarding or rigidity. By bimanual pelvic examination, the uterus was normal size, non-tender, and moderate vaginal bright red bleeding was noted during speculum exam. A transvaginal ultrasound (TUV) showed normal adnexa and a normal size anteverted uterus with a 6.5 mm endometrial lining without evidence of retained products of conception or mass.

A diagnosis of sub-involution of the placental site with retained blood clots was given and options of treatment, including expectant management, were discussed with the patient. The patient opted for methylergonovine 0.2 mg by mouth 3 times a day for 2 days

The patient was seen again in the office 8 days later for unrelieved vaginal bleeding and a second TVU showed a distinct 12 x 6 mm persistent echogenic area in the endometrium. The patient was scheduled for a dilation and curettage (D&C) based on her symptoms and ultrasound findings, but she presented to the emergency department (ED) four days later for evaluation of a new-onset abdominal pain and persistent vaginal bleeding.

Physical exam in the ED was remarkable for tenderness in the right upper quadrant with a positive Murphy's sign. A biliary tract ultrasound showed cholecystitis associated to cholelithiasis.

At admission, the patient showed β-hCG levels of 38,084 mIU/mL, hemoglobin of 12.2 g/dL, AST of 22 U/L, ALT of 43 U/L and serum glucose of

99 mg/dL. The patient underwent a laparoscopic cholecystectomy by the general surgery team. The gynecologic service was consulted on postoperative day one for evaluation of late postpartum vaginal bleeding and inappropriately elevated β-hCG.

Gynecological exam revealed a normal vulva, vagina, and a non-tender anteverted uterus of 8-10 cm in size. Cervix was closed with minimal bleeding. A TVU showed an unremarkable endometrial lining without evidence of adnexal masses or intrauterine pregnancy. A thyroid-stimulating hormone (TSH) and chest radiography were ordered due to suspected GTD and the patient consented to a D&C under ultrasound guidance.

TSH was suppressed to 0.28 uIU/mL and the chest radiography showed a 1 cm in diameter density in the left upper lobe. The patient was evaluated with a chest tomography that showed numerous bilateral pulmonary nodules (Figures 1 and 2). Brain magnetic resonance was unremarkable. The patient underwent a D&C without complications and the endometrial sampling revealed fragments of benign endometrial tissue with progesterone effect and Arias Stella reaction without evidence of chorionic villi, trophoblastic tissue, or malignancy.

β-hCG was 49,936 mIU/mL on postoperative day 3. Based on a persistently rising β-hCG and the presence of lung metastases, the disease was scored as per WHO 2000 criteria. Diagnosis of FIGO stage III low-risk GTN was made based on a score of 6 (antecedent of term pregnancy, pre-treatment serum β-hCG of 49,936 mIU/mL, and the number of metastases). The patient was transferred to the Gynecologic-Oncology service and counseled about her treatment options. She consented to single-agent chemotherapy with actinomycin D biweekly for 3 cycles until a negative β-hCG was reached and then to one additional cycle after that.

A levonorgestrel intrauterine device was inserted and she was advised to avoid pregnancy for 12 months. The third cycle of actinomycin D began 2 months after her admission to the emergency service, β-hCG remained negative for 12 months and a chest tomography showed no evidence of residual or recurrent disease (Figure 3).

Figure 1. There is a 7.6 mm rounded nodule peripherally in the anterior right apex without pleural contact.

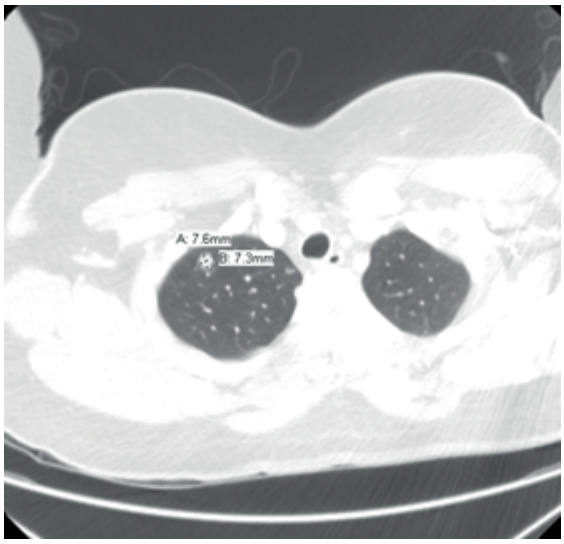


Figure 2. 1.3 x 1.8 cm wedge-shaped lesion in the right lower lobe extending to the posterior pleural surface

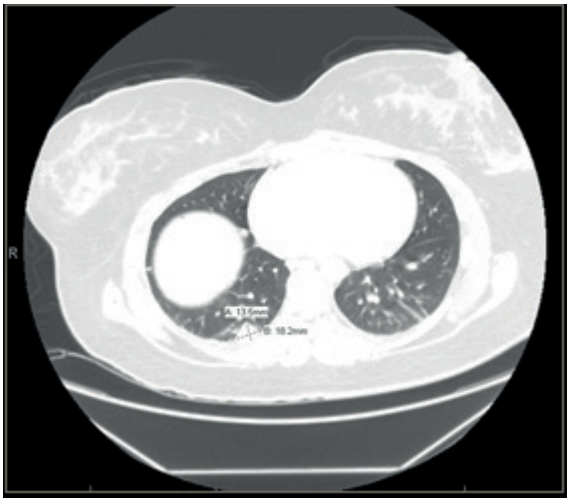
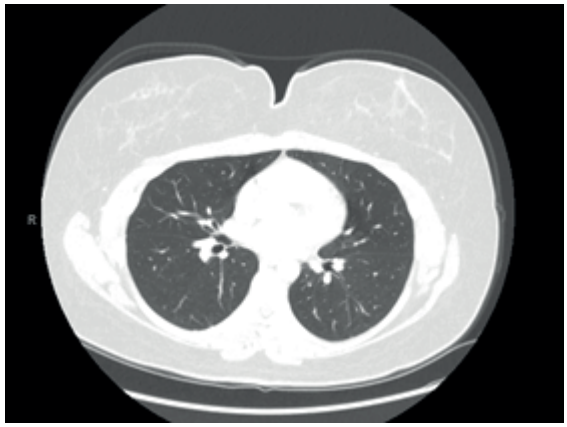


Figure 3. Absence of pulmonary lesions or nodules.



Discussion

Postpartum choriocarcinoma is usually diagnosed based on symptoms secondary to metastatic lesions, such as secondary or late postpartum bleeding; abdominal, pulmonary, or cerebral hemorrhage; hemoptysis, coughing, and neurologic deficits. Metastases often develop early in choriocarcinoma and are generally blood-borne and the most common sites are the lungs and vagina[7].

The main presenting complaint of the patient was late postpartum vaginal bleeding. She was prescribed methylergometrine and a pregnancy test was done almost 2 weeks after the initial clinical evaluation.

This malignant epithelial tumor in the late postpartum period is easy to misdiagnose and its symptoms frequently lead to mistaken late postpartum complications such as retained products of conception, sub-involution of the placental site, spontaneous abortion, and ectopic pregnancy[8].

One study reported 57 cases of postpartum choriocarcinoma. Of those, 52 cases (91.2%) were misdiagnosed and in 15 cases (28%) the patients died. 59.6% of patients were diagnosed between 3 and 6 months after delivery[9].

Vaginal bleeding is the most common symptom of choriocarcinoma diagnosed after a miscarriage or postpartum. Patients with central nervous system (CNS) metastases often exhibit signs and symptoms of increased intracranial pressure from intracerebral hemorrhage and patients who develop extensive pulmonary metastases may show signs of dyspnea, cough, or chest pain[10].

Subinvolution of the placental site refers to delayed or inadequate physiologic closure and sloughing of the superficial modified spiral arteries at the placental attachment site. Subinvolution can be identified by the histologic findings in postpartum endometrial curetting. The initial diagnosis of subinvolution of the placental site in this patient was based only on her symptoms and ultrasound findings, as a retained product of conception was not documented.

Although uterine curettage has a limited role in the evaluation of GTD, we recommended this procedure since this patient presented postpartum bleeding with an elevated β-hCG to determine whether the diagnosis was GTN, pregnancy of unknown location, or retained products of conception.

Staging for GTD defines prognostic groups to direct optimal therapy yielding to the highest possible cure rate by identifying patients likely to be resistant to single-agent chemotherapy. Patients are classified into different prognostic groups based on histologic characteristics, extent and duration of disease, hCG titer, nature of the antecedent pregnancy, and extent of prior treatment. Two systems are used to categorize patients with gestational trophoblastic neoplasia. The staging system of the International Federation of Gynecology and Obstetrics (FIGO 2000) is the standard classification, but patients are also assigned a modified World Health Organization prognostic index score.

The FIGO 2000 system is not universally predictive of individual patient outcomes. While nearly all patients with a score of 0-4 will be cured with single-agent chemotherapy, over 50% of patients who score 5-6 will fail single-agent treatment and require combination chemotherapy[11].

The principal treatment for gestational trophoblastic neoplasia (GTN) is chemotherapy, and patients diagnosed with GTN should undergo evaluation before treatment for an appropriate regimen determined via staging and grading. Most patients with low-risk GTN (stages I, II, and II and a risk score ≤ of 6) are treated with single-agent chemotherapy using either methotrexate (MTX-leucovorin) or actinomycin D. The Gynecologic Oncology Group Trial compared weekly intramuscular methotrexate 30 mg/m2 to bolus intravenous actinomycin D 1.25 mg / m2. Among 216 women treated in this trial, bolus actinomycin D demonstrated a superior primary remission rate compared with weekly methotrexate (70% vs 53%, p= .01). Primary remission rates with actinomycin regimens range from 69% to 94%.

The most recent Cochrane review (published in 2016) in low-risk gestational trophoblastic neoplasia concluded that actinomycin D regimens were more likely to produce primary remissions with higher risk of serious side effects. Moderate-certainty evidence indicates that actinomycin

D is probably more likely to lead to primary cure than methotrexate (RR 0.65, 95% confidence interval (CI) 0.57 to 0.75; six trials, 577 participants; I2=26%), and first-line methotrexate treatment is probably more likely to fail than actinomycin D treatment (RR 3.55, 95% CI 1.81 to 6.95; six trials, 577 participants; I2 = 61%; moderate-certainty evidence)[12].

A disease remission requires three consecutive weekly normal β-hCG values (less than 5 mIU/mL). Treatment should then be continued for three consecutive courses of the chemotherapy regimen to reduce the risk of relapse.

Persistent or progressive GTN is defined as an increase or a plateau in two consecutive β-hCG values over a two-week interval or detection of new metastases. After remission is achieved, β-hCG should be measured monthly until one year of normal β-hCG levels has been documented.

Multi-drug combined chemotherapy regimens are used to treat high-risk patients (stages II, III, and IV with a risk score >6). The most common regimen is etoposide, MTX-leucovorin, and actinomycin, followed a week later by cyclophosphamide and vincristine; the complete response rate is 85% and the 5-year overall survival rate is 75% to 90%. Unfortunately, the cumulative dose of etoposide has been associated with increase-risk for leukemia. Currently EMA-CO (etoposide, methotrexate and actinomycin D alternating with cyclophosphamide and vincristine) is used most frequently. Patients with FIGO risk scores of 13 or higher have a higher risk of mortality when treated initially with multi-agent therapy. These patients may develop an initial massive tumor response, with tumor lysis syndrome, catastrophic hemorrhage from metastatic sites, multiple organ failure, myelosuppression and sepsis[13].

Although the diagnosis of choriocarcinoma was made 3 weeks after the postpartum period, most likely that choriocarcinoma was established before. This case illustrates the importance of making an early and accurate diagnosis of postpartum choriocarcinoma. Having found a β-hCG value of 38,084 mIU/mL caught our attention as it must have been zero by 9 weeks postpartum.

Prudent and methodical examination in patients with late postpartum vaginal bleeding or early symptoms of choriocarcinoma including placental examination and blood β-hCG monitoring in high-risk patients can assist in the early diagnosis of postpartum choriocarcinoma and subsequent treatment and prognosis.

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