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Case report

Pulmonary metastasis as a primary manifestation of gestational choriocarcinoma in a third trimester pregnancy

Ahmad Arabi [a], Martins Ayoola-Adeola [a], Huy Q. Nguyen [b], Harpreet Brar [c], Christopher Walker [a,*]

[a] Wayne State University School of Medicine, Department of Obstetrics and Gynecology, 3980 John R, 7-Brush N, MB #165, Detroit, MI 48201, USA
[b] Wayne State University School of Medicine, Department of Pathology, Detroit, MI, USA
[c] Hutzel Women's Health Specialists, Detroit, MI, USA

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1. Introduction

Gestational trophoblastic disease (GTD) involves a spectrum of diseases originating from placental tissue characterized by abnormal trophoblastic proliferation (Berkowitz and Goldstein, 1996), characterized into neoplastic or non-neoplastic type. Non-neoplastic GTD includes partial and complete hydatidiform moles while neoplastic GTD includes invasive moles, choriocarcinoma, placental site trophoblastic tumors (PSTT), and epithelioid trophoblastic tumors (ETT).

A histologic diagnosis is not required for neoplastic GTD in patients with persistently elevated human chorionic gonadotropin (hCG) after a pregnancy. Where histological diagnosis was obtained, 75% were invasive moles and 25% choriocarcinomas (Carcangiu et al., 2014). Invasive moles strictly follow a molar pregnancy, and are locally invasive and lack the tendency to develop widespread metastases (Soper, 2006). Choriocarcinomas are more aggressive and can follow molar pregnancies, spontaneous abortions, ectopic pregnancies, or normal pregnancies (Yamamoto, 2009). They are more aggressive, invade into the vasculature, and frequently result in systemic metastases (Soper, 2006; Benirschke et al., 1998). Thus, the early diagnosis and treatment of choriocarcinomas is imperative.

Gestational choriocarcinomas diagnosed after a term pregnancy automatically receive a higher WHO prognostic score (Ngan et al., 2003). A pregnancy with coexistent choriocarcinoma is even more rare and difficult to approach (Steigrad et al., 1999). We present the case of a rare occurrence where choriocarcinoma presented during a term pregnancy in the form of pulmonary metastasis. The diagnosis of choriocarcinoma was not suspected and as such, certain diagnostic interventions and treatment were delayed.

2. Case report

The patient is a 22-year-old G2P0010 Bengali female who presented to the emergency room at a gestational age of 36 weeks with an eight-day history of isolated hemoptysis. She had no medical history outside of an uncomplicated first trimester spontaneous abortion 11 months prior to presentation. Her vitals were normal and she was afebrile. Bilateral crackles were noted on lung auscultation. BMI was 27 kg/m^2.

* Corresponding author at: Wayne State University School of Medicine, Department of Obstetrics and Gynecology, 3980 John R, 7-Brush N, MB #165, Detroit, MI 48201, USA.
E-mail addresses: aarabi@med.wayne.edu (A. Arabi), ck4145@wayne.edu (C. Walker).

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Evaluation in the emergency room revealed a troponin of 144 ng/L, and mild leukocytosis with a WBC of 11.7 K/mm^3. Chest radiograph showed diffuse bilateral patchy infiltrates.

The patient was admitted for empiric treatment of multifocal pneumonia. Shortly after admission to the hospital, she required supplemental oxygen due to persistent SpO_2 below 95%. Extensive infectious workup was negative. Computed tomography of the thorax was consistent with multifocal pneumonia, and negative for pulmonary embolism (Fig. 1). Echocardiogram was normal. Her troponin trended downward.

On day 7 of hospitalization, the patient continued to be hypoxic requiring supplemental oxygen. Following consultation with Maternal Fetal Medicine (MFM), decision was made to proceed with induction of labor due to concerns for patient's respiratory status and to pursue further invasive pulmonary workup.

Approximately 10 h into the induction, her respiratory status acutely worsened, requiring 10-liters/min of oxygen. Due to worsening maternal respiratory status, decision was made to proceed with cesarean delivery. The cesarean delivery was uncomplicated, resulting in the delivery of a healthy female infant. The ovaries appeared normal. The placenta appeared grossly normal, pathology initially negative, with no acute or chronic lesions.

On post-operative day 4, bronchoscopy was performed showing diffuse alveolar hemorrhage. Thoracoscopic wedge resection of the right upper and middle lobes was performed. The resections grossly showed soft dark red hemorrhagic lesions without distinct borders. Microscopically, the resections showed diffuse infiltration by markedly atypical, mononuclear cells in a background of extensive hemorrhage and necrosis. The tumor lacked intrinsic stromal and vascular elements. Lymphovascular invasion was present (Fig. 2). The histologic features and immunoprofile were characteristic of choriocarcinoma.

The placenta was reviewed again after the diagnosis of metastatic choriocarcinoma. However, no abnormalities were identified. Microscopically, no tumor was visible with an additional twenty sections.

The patient was transferred to the oncology service for further management. Further imaging was consistent with metastatic lesions to the liver, spleen, and brain (Fig. 3). The patient was diagnosed with Stage IV choriocarcinoma, WHO Score 13.

She was started on low-dose therapy with Etoposide and Cisplatin chemotherapy shortly after diagnosis, followed by cycle #1 of EMA-EP regimen (etoposide, methotrexate, actinomycin, and cisplatin). Her hCG level decreased from 28,384 mIU/mL on diagnosis to 88 mIU/mL after her fourth cycle of chemotherapy. She has been tolerating treatment well.

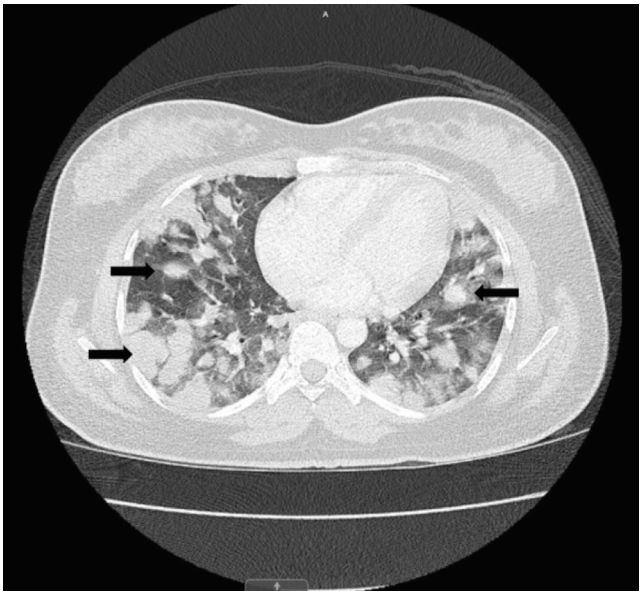

Fig. 1. CT scan of the thorax. Innumerable bilateral pulmonary masses (arrows). The masses are mostly spherical, are confluent, and have a random distribution. The masses do not demonstrate cavitation or calcification. No pleural effusion or pneumothorax.

3. Discussion

Although molar pregnancy still carries the most significant risk for gestational choriocarcinoma, approximately 50% of gestational choriocarcinomas are associated with normal genetic spontaneous abortions (25%) and term pregnancies (25%) (Carcangiu et al., 2014; Yamamoto, 2009). Thus, it is important for clinicians to maintain a heightened suspicion of choriocarcinoma and its presentation, even amidst non-molar pregnancies (Chung et al., 2008).

This case presented a significant diagnostic dilemma because it occurred simultaneously with a term non-molar pregnancy. This diagnosis is exceptionally rare and has a poor prognosis (Ghaemmaghami and Zarchi, 2008). Our patient presented with isolated hemoptysis and underwent extensive evaluation. It was only after delivery that the diagnosis of metastatic choriocarcinoma was made. This extremely rare diagnosis still remains elusive to many clinicians. In our patient, this diagnosis was not suspected after multiple discussions with Obstetricians, MFM specialists, and Pulmonologists at a large academic center.

The case also posed an etiological challenge. The placental pathology did not identify GTD, even after multiple examinations. In the setting of a simultaneous term pregnancy and history of spontaneous abortion 11 months prior, there are four potential etiologies for our patient's choriocarcinoma.

The first is the case of choriocarcinoma from her current pregnancy that was particularly aggressive and presented with metastatic symptoms prior to the completion of a term pregnancy. This has been previously noted in a 2017 case series report, in which three cases of gestational choriocarcinoma presented with hemoptysis as the primary manifestation, one of which presented in the third trimester (Zhang et al., 2017). She also had a delayed diagnosis, and was initially treated for severe pneumonia without improvement (Zhang et al., 2017). Although placental pathology was negative in our case, in the setting of metastatic choriocarcinoma as the presenting disease, the primary intraplacental tumor is not often detected (Jacques et al., 1998). The reason for this is because intra-placental choriocarcinomas sometimes present with more minute microscopic foci without overt macroscopic presentation (Brewer et al., 1978). Finding these lesions requires microscopic evaluation of the entire specimen (Brewer et al., 1978). Although further histopathological review of our patient's placenta after diagnosis did not reveal a tumor, similar cases in the literature have found the lesion after complete microscopic evaluation of the entire specimen (Brewer et al., 1978). It is not feasible, however, to histopathologically examine the entire placenta.

The second potential source is her previous pregnancy, noted to be a complete abortion eleven months prior to her presentation to the hospital. On review of prior records, four days after her complete abortion, her hCG had decreased from 20,496 to 10,589 mIU/mL. During her one week follow-up visit, she reported that her symptoms had mostly resolved, outside of some intermittent spotting. She did not return for a repeat blood draw and there were no documented negative pregnancy tests in the interpregnancy interval. The average time of antecedent pregnancy to diagnosis of choriocarcinoma is about 10.5 months (Diver et al., 2013). Whether the prior pregnancy was a complete abortion or molar pregnancy, it could have been the source. A study which performed DNA analysis on gestational trophoblastic tumors reported a case in which the choriocarcinoma did not have the DNA complement of the current pregnancy but the preceding molar pregnancy (Fisher et al., 1992). Choriocarcinomas from a normal term gestation would contain biparental chromosomes identical to those of the fetus (Gompel and Silverberg, 1994).

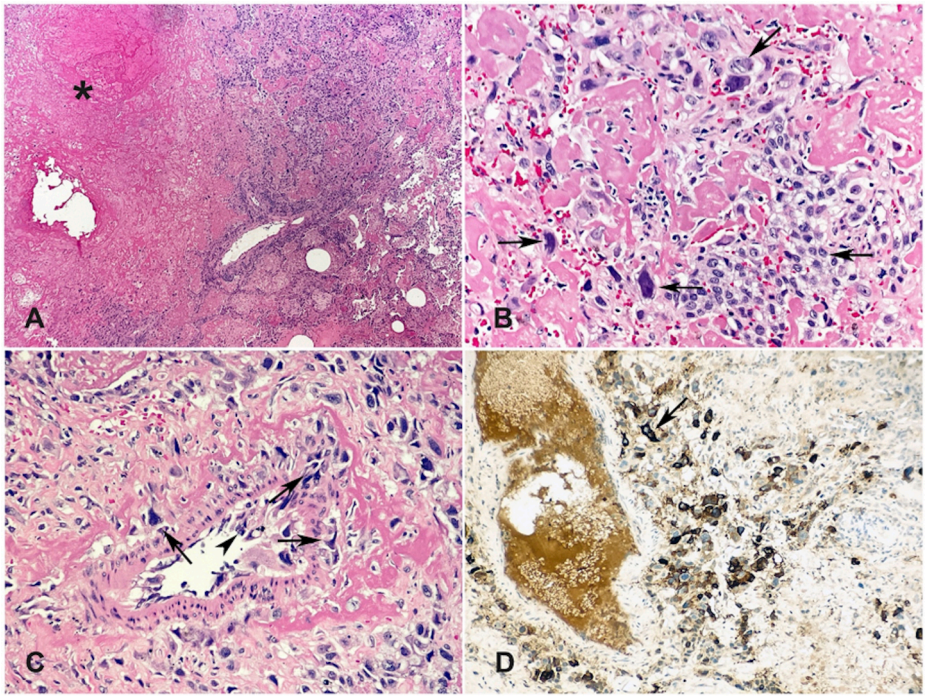

Fig. 2. Histopathology showing lymphovascular invasion by the tumor cells. (A) Areas of hemorrhage and necrosis (asterisk) surrounding by malignant cells (40X). (B) The tumor cells show marked nuclear pleomorphism, hyperchromasia and atypia (arrows) (200X). (C) The tumor cells surround (arrows) and invade (arrow head) the blood vessels (200X). (D) Tumor cells are strongly positive for hCG immunohistochemical stain (arrow).

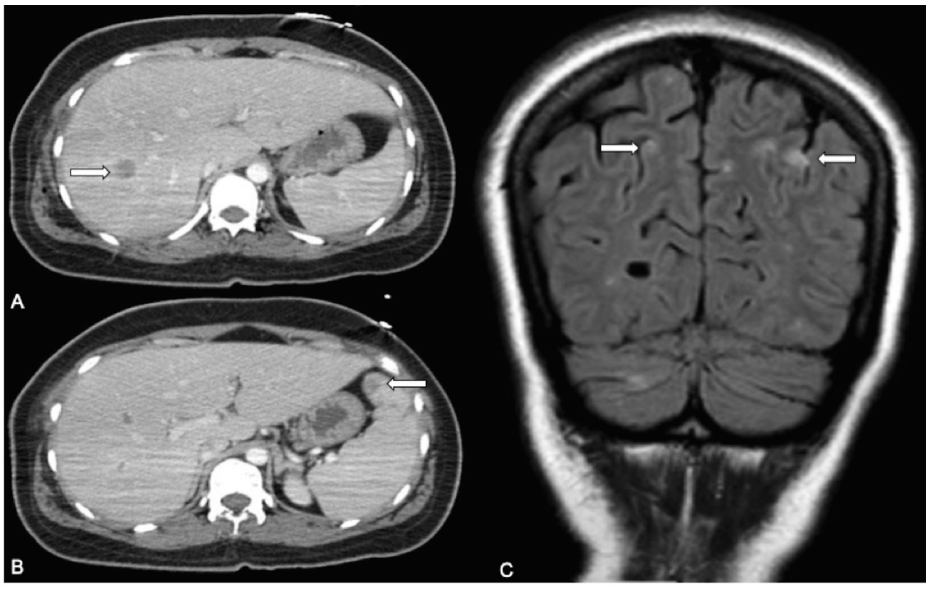

Fig. 3. Choriocarcinoma with metastases to the liver, spleen and brain. (A) CT of the abdomen showing hypoattenuating lesion in the right lobe of the liver (arrow). (B) CT of the abdomen showing hypoattenuating lesion in the most anterior aspect of the spleen (arrow). (C) MRI of the Brain showing hyperintensities in the bilateral parieto-occipital cortex demonstrated by T2-weighted images.

The third potential etiology is a primary "non-gestational" choriocarcinoma, an ovarian germ cell tumor with an identical histological appearance to that of a gestational choriocarcinoma. Park et al. reported a case in which a 55-year-old female who presented with pulmonary symptoms was diagnosed with choriocarcinoma (Park et al., 2009). The patient was 5 years post-menopausal and had no sexual contact since her husband's death 10 years prior, so her case was thought to be non-gestational in origin. However, this is difficult to confirm clinically (Park et al., 2009). In the study exploring the DNA complement of GTD, a tumor originally diagnosed as a germ cell choriocarcinoma was reclassified as a gestational choriocarcinoma. Conversely, a diagnosis of gestational choriocarcinoma was subsequently found to be non-gestational in origin (Fisher et al., 1992). The gestational tumors contain genetic polymorphisms confirming the presence of paternal DNA. This etiology is far less likely as the incidence of non-gestational choriocarcinoma is less than 1 in 300,000,000 while the incidence of gestational choriocarcinoma is about 1 in 50,000 pregnancies (de Mello et al., 2017). Her aggressive response to chemotherapy also points to

gestational choriocarcinoma as the more likely diagnosis, as non-gestational choriocarcinoma is less responsive to chemotherapy (Soni et al., 2017).

A fourth and extremely rare potential etiology of this patient's tumor is a primary pulmonary choriocarcinoma. There are only a few of these tumors reported in the literature and their origin is controversial. Proposed theories include the differentiation of pulmonary epithelium into trophoblastic structures, or metastatic emboli from gestational trophoblastic tissue that spontaneously regresses (Aparicio et al., 1996). In a reported case of hemoptysis, the patient was found to have a tumor in the right lower lung removed and diagnosed histopathologically as choriocarcinoma. This patient was not found to have gestational tissue on endometrial curettage or with laparoscopy. Thus she was diagnosed with primary pulmonary choriocarcinoma (Seol et al., 2009).

Although the origin of this patient's tumor remains a mystery, it will not affect her management plan. EMA-EP regimen is a multiple agent chemotherapy for high-risk GTD but also used for chemo-resistant non-gestational choriocarcinoma (Soni et al., 2017). She is responding to chemotherapy and her clinical status is improving. Different hCG producing tumors have been shown to have different chemosensitivities, however (Crawford et al., 1986). If this patient's response to chemotherapy changes, she may benefit from genotyping to assess the origin of the tumor.

It is universally accepted that prognosis of choriocarcinoma relies heavily on the time of diagnosis and treatment (Carcangiu et al., 2014). Suspicion for choriocarcinoma, even in the setting of a current, uncomplicated term pregnancy, should be maintained by all obstetricians when patients present with atypical symptoms not generally associated with pregnancy.

Informed consent:

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review upon request.

CRediT authorship contribution statement

Ahmad Arabi: Investigation, Writing - original draft, Writing - review & editing, Visualization. **Martins Ayoola-Adeola:** Writing - review & editing, Visualization. **Huy Q. Nguyen:** Writing - review & editing. **Harpreet Brar:** Supervision, Resources, Writing - review & editing. **Christopher Walker:** Supervision, Resources, Investigation, Writing - review & editing, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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