Clinical Oncology: Case Reports

Case Report

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Metastatic Choriocarcinoma after Full Term Pregnancy

Noor Sameh Darwich* and Michael Guy

Abstract

Gestational choriocarcinoma is a highly vascular fast-growing cancer arising from placental trophoblastic cells that can metastasize hematogenously to the lungs, liver, brain, spleen, kidney, and vagina. Choriocarcinoma is part of the Gestational Trophoblastic Neoplasia (GTN) which includes in its spectrum Invasive mole, choriocarcinoma, Placental Site Trophoblastic Tumor (PSTT), and Epithelioid Trophoblastic Tumor (ETT). Gestational choriocarcinoma is a rare occurrence after a full-term pregnancy with an incidence of 1 in every 160.000 to 500.000 pregnancies as the incidence of GTN varies widely depending on geographic location. 50% of all Gestational Choriocarcinoma occur after Molar pregnancies, 25% develop after spontaneous abortion (miscarriages), induced abortion and ectopic pregnancies, and 25% after normal pregnancies.

In this case, we describe a 22-year old women status post uncomplicated Spontaneous Vaginal Delivery (SVD) after full-term pregnancy who presented with pleuritic chest pain 4 weeks after delivery, found to have significantly elevated serum quantitative Beta -hCG and imaging including Chest x-ray, CT scan of chest/abdomen/pelvis showed bilateral pulmonary nodules and splenic lesion consistent with metastatic disease. The patient was diagnosed with metastatic choriocarcinoma FIGO stage IV, WHO risk score 11, and started on combination chemotherapy (EMA-CO).

Keywords

Gestational trophoblastic neoplasia (GTN); Choriocarcinoma; Pulmonary metastases

Introduction

Gestational trophoblastic neoplasia refers to malignant forms of Gestational Trophoblast Disease (GTD) which include invasive mole, choriocarcinoma, Placental Site Trophoblastic Tumor (PSTT), and Epithelioid Trophoblastic Tumor (ETT) [1]. Metastatic gestational choriocarcinoma is an aggressive form that develops in women with bearing age during or after all types of pregnancies from remaining placental trophoblastic cells attached to the uterus where trophoblast cells can continue to grow even after the placenta is removed then become transformed to become malignant cells which can spread locally and hematogenously to the lungs, liver, kidney, brain, spleen. Choriocarcinoma with its metastatic lesions are highly vascular and bleed easily. The lung is the most common site of metastases [2]. About 50% of all women with choriocarcinoma had a previous history of a hydatidiform mole or molar pregnancy, however, cases without previous history of the gestational trophoblastic disease are rare in occurrence after a normal full-term pregnancy. Post-full-term pregnancy gestational choriocarcinoma has a tendency for more extensive metastatic spread most likely due to delay in diagnosis. Most cases of choriocarcinoma after term pregnancy are usually diagnosed by histopathological microscopic examination of the placenta. However, postpartum histological examination of the placenta is not routinely performed. High clinical suspicion for gestational trophoblastic neoplasia is recommended for women during all kinds of pregnancies and after delivery, if they present with unexplained symptoms for prompt diagnosis and treatment [3]. Current chemotherapy and sometimes surgical and irradiation therapy have proven to be an excellent treatment for a patient with metastatic choriocarcinoma [4].

Case Report

A 22-year old female with significant past medical history of pre-eclampsia in prior pregnancy, and HSV2 (Herpes simples virus 2), Gravida 2, Para 2, who is 3 weeks status post uncomplicated Spontaneous Vaginal Delivery (SVD) of full-term uneventful pregnancy at 39 weeks, with the placenta delivered spontaneously and was normal by gross examination. The baby was a male, weight 2685 g, APGAR at 1 minute was 7 and at 5 minutes was 8, with fetal anemia, who was transferred to special care for blood transfusion and recovered. The patient tolerated delivery well and was discharged with a normal postpartum course. She was presented to the emergency department from home 3 weeks after delivery with a chief complaint of the left-sided shoulder and neck pain worse with movement. She reported having numbness in the right leg, shortness of breath, cough and wheezing, intermittent left-sided pleuritic chest pain, burning epigastric pain and generalized abdominal pain. She smokes cigarettes and occasionally smokes marijuana, however, denied IV drug abuse. Her vital signs are: Temp 98.1°F, Pulse 100 per minute, respiration 22 per minute, BP 145/64 mmHg, Oxygen sat 98% on room air. On exam: unremarkable findings with the exception of reproducible pain and tenderness on the left side of the chest wall in the axillary area and left upper back. Laboratory data: notable for sodium 133 mg/dl, creatinine 0.5 mg/dl (normal reference range 0.6-1.30 mg/dl), hemoglobin 11.7 g/dl, Hematocrit 35.6 percent, AST 27 U/L (normal reference range (15-37 U/L), ALT 25 U/L (normal reference range 12-78 U/L), TSH 0.012 Micro IU/ML (normal reference range 0.4-4.00 micro IU/ML) , Free T4 1.91 NG/DL (normal reference range 0.80-1.80 NG/DL). Chest x-ray showed multiple pulmonary nodules and masses throughout the lungs bilaterally (Figure 1) and CT chest showed no evidence of acute pulmonary embolism with numerous non cavitating pulmonary nodules and masses suggesting metastatic disease versus infectious etiology (Figure 2).

CT spine was negative and she denied any abnormal vaginal bleeding after delivery but only the expected minimal spotting. Her pregnancy screen urine test was positive, which was attributed to recent delivery. Ultrasound of the abdomen showed poorly distended gallbladder otherwise normal. Ultrasound venous Doppler of left lower extremity demonstrated no evidence of deep venous thrombosis. Her serum Beta-hCG was found to be elevated at 20, 215.0 mIU/ml (milli-

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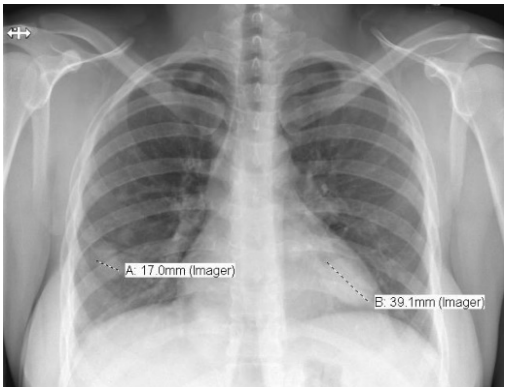

Figure 1: Chest x-ray showed multiple pulmonary nodules and masses throughout the lungs bilaterally.

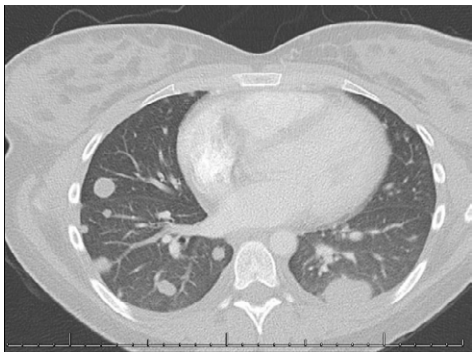

Figure 2: CT chest showed no evidence of acute pulmonary embolism with numerous non cavitating pulmonary nodules and masses suggesting metastatic disease versus infectious etiology.

international units/mL) initially and sequentially 94.786.7 mIU/ml and 274.785 mIU/ml a few days later during her hospitalization. Transvaginal ultrasound showed no evidence of intrauterine pregnancy or adnexal mass, minimal fluid in the endometrial canal and cervix. Pelvic ultrasound showed no obvious retained products of conception. Transthoracic echo and TEE showed normal cardiac valves with no evidence of endocarditis.

The patient underwent CT guided right lower lobe lung nodule biopsy which showed necrotic debris and alveolar parenchyma with reactive fibrosis and scattered acute and chronic inflammation (Figure 3).

The necrotic area which has scattered ghost cell nuclear outlines shows positive staining for immunostains AE 1/3, HCG and Inhibin. There was also staining of adjacent lung and fibrous tissue on the biopsy with HCG. GMS and AFB stains were negative for the fungal organism or acid-fast bacilli. Follow up CXR showed the development of moderate left pleural effusion, underwent Ultrasound-guided left thoracentesis with the removal of 400 cc of hemorrhagic fluid, with a cell count of white blood cells 7500/mm3, RBC 54250/mm3, Neutrophils 33%, Lymphocytes 61%, Eosinophils 2% and Monocytes 4%. Chemical analysis of pleural fluid showed Glucose 70mg/dl, LDH 782 U/L, Ph 7.40, protein 3.9 gm/dl and cytology examination of the fluid was negative for malignancy.

MRI cervical spine showed mild degenerative changes most notable at C4-C5 and MRI of the brain with and without Gadolinium showed punctate focus of acute lacunar infarction in the subcortical left posterior frontal lobe but no mass lesion or hemorrhage (Figure 4).

The patient developed severe abdominal pain with peritoneal signs including diffuse tenderness and rebound tenderness on exam, with a significant drop of hemoglobin from 11.5 g/dl to 7.9 g/dl over 48 hours. Coagulation testing and Hypercoagulable panel were normal.

Ct abdomen showed 5.9 cm upper pole splenic mass consistent with metastatic lesion and mild splenomegaly with a moderate amount of fluid in the peritoneum with increased attenuation consistent with hemoperitoneum from the ruptured splenic metastatic lesion (Figure 5a and 5b).

A diagnosis of metastatic choriocarcinoma (International Federation of Gynecology and Obstetrics (FIGO) stage IV; World Health Organization (WHO) score 11): was made on the basis of clinical presentation, lab and imaging findings the patient underwent port placement for chemotherapy with EMA-CO with curative intent for her malignancy. She tolerated chemotherapy and was discharged

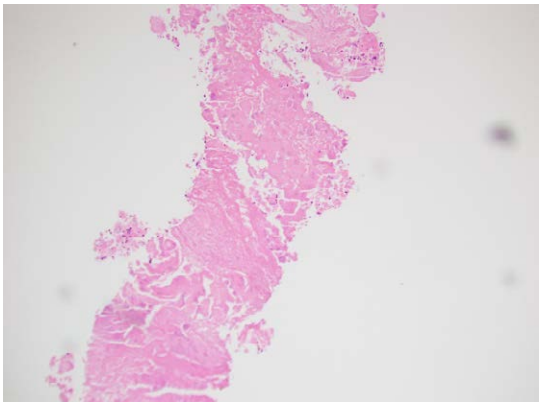

Figure 3: CT guided right lower lobe lung nodule biopsy which showed necrotic debris and alveolar parenchyma with reactive fibrosis and scattered acute and chronic inflammation.

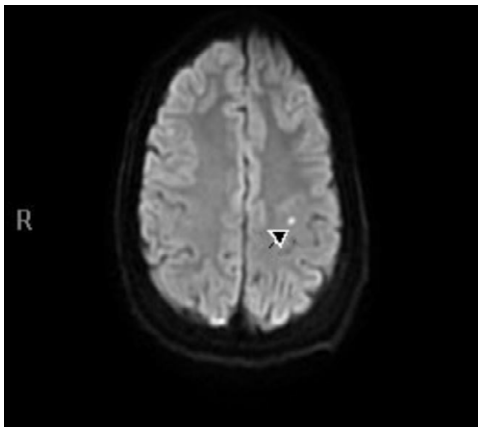

Figure 4: MRI of the brain with and without Gadolinium showed punctate focus of acute lacunar infarction in the subcortical left posterior frontal lobe but no mass lesion or hemorrhage.

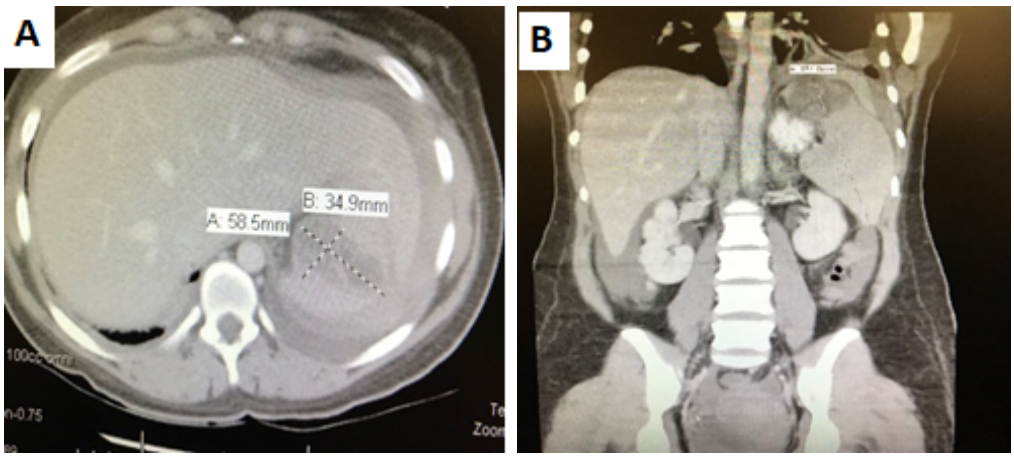

Figure 5: Ct abdomen showed 5.9 cm upper pole splenic mass consistent with metastatic lesion and mild splenomegaly with a moderate amount of fluid in the peritoneum with increased attenuation consistent with hemoperitoneum from the ruptured splenic metastatic lesion.

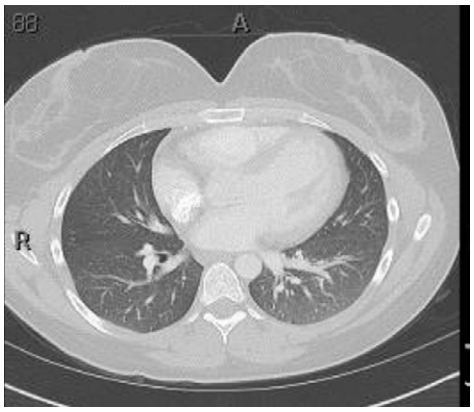

Figure 6: CT of the chest 9 months after chemotherapy showed a marked improvement with resolution of the bilateral pulmonary nodules and masses.

to complete her chemo treatment as an outpatient. She completed and tolerated a total of 6 cycles of EMA-CO. Follow up hCG level six months after the presentation was <1.0 mIU/ml. CT of the chest 9 months after chemotherapy showed a marked improvement with the resolution of the bilateral pulmonary nodules and masses (Figure 6).

Discussion

Gestational trophoblastic neoplasia is a spectrum of malignant diseases occurs in women of reproductive age during or after all forms of pregnancies [5]. It represents the abnormal proliferation of the trophoblastic tissue of a placenta. The incidence of GTN varies according to a different region of the world [6]. Risk factors for developing GTN include prior molar pregnancy, age of more than 40, and in Asian women. GTN includes invasive mole and choriocarcinoma, which both featured high Beta hCG serum levels. Other forms include Placental Site Trophoblastic Tumors (PSTT) and Epithelioid Trophoblastic (ETT) featured a low Beta hCG serum level.

Cases of Non-gestational choriocarcinoma with elevation of beta hCG can occur in men and women, in the absence of pregnancy, arise from germ cells of the gonads which includes hCG producing germ cell tumor of the ovary, ectopic cells producing hCG from non-trophoblastic tumors of stomach, liver, pancreas, breast, testicles, and pituitary gland.

Choriocarcinoma is a fast-growing vascular cancer that rapidly invades uterine wall blood vessels and metastasizes hematogenously to distant organs such as lungs, brain, liver, spleen, kidneys and has a tendency for severe hemorrhage either spontaneously or after biopsy [7].

Diagnosis is usually delayed after normal pregnancy especially if there were no gynecological symptoms such as vaginal bleeding/spotting after delivery which is usually looked at as a normal peripartum. Metastatic choriocarcinoma can mimic other conditions depending on the site of metastases [8].

Clinical Presentation can be variable including abnormal vaginal bleeding, anemia and other symptoms due to the location of metastatic diseases such as chest pain, cough, shortness of breath or hemoptysis in case of lung involvement, headache, dizziness, seizure, and altered mental status, local or generalized weakness from brain involvement, abdominal pain, nausea and vomiting from intra-abdominal metastases [9].

Patients with Choriocarcinoma can present with symptoms of hyperthyroidism with an abnormal thyroid function test due to hCG endocrine stimulation effects mostly at hCG level more than 100.000 milli-international units/ml.

The lung is the most common site of metastases and up to 80% of patients with choriocarcinoma develop pulmonary metastases [10]. Patients with pulmonary metastases can be asymptomatic for a prolonged period. Hemothorax has been reported as a presenting finding of pulmonary metastases of choriocarcinoma and Trophoblastic tumor emboli that may cause pulmonary artery occlusion leading to right-sided heart strain and pulmonary hypertension which can lead to a false diagnosis of pulmonary embolism or primary pulmonary hypertension if diagnosis of metastatic Choriocarcinoma is delayed after delivery and gynecological symptoms are minimal or absent [11].

Metastases to the gastrointestinal tract with upper or lower GI bleed has been reported. Patients with liver or spleen metastases are at high risk for intra-abdominal hemorrhage if tumor mass is ruptured. The hepatic lesion should not be biopsied because of the high risk of bleeding. Further, metastases to the bladder and kidney have been reported in choriocarcinoma with hematuria as a presenting symptom [12].

Central nervous system involvement occurs in 10%-20% of metastatic choriocarcinoma patients in the form of brain metastases with a mass lesion, intracerebral or subdural hemorrhage and rarely cerebral ischemic infarction due to tumor emboli [13].

Fetal complication due to choriocarcinoma includes FMH (Fetal Maternal Hemorrhage), intrauterine fetal death, hydrops fetalis and rarely metastatic disease in the infants, however, the most common presentation of FMH is anemia at birth.

Choriocarcinoma lesions seen in the placenta in term pregnancies can be easily missed by the gross examination of the placenta and post-partum microscopic histological examination of the placenta is not routinely performed.

Choriocarcinoma is a clinical diagnosis made on the bases of clinical presentation, elevated serum quantitative Beta hCG combined with imaging suggesting metastatic lesions, after excluding normal viable pregnancy. Tissue diagnosis with histopathologic confirmation by performing a biopsy is not necessary unless there is doubt about the diagnosis because the tumor with its metastatic lesions is highly vascular and tends to bleed easily.

Due to the presence of a large area of tumor necrosis, the yield of biopsy from the metastatic disease of choriocarcinoma for histological examination is usually low. Choriocarcinoma is one of the exceptional malignancies that histological verification (tissue diagnosis) is not required to establish the diagnosis and start chemotherapy [14]. However, FIGO accepts the supporting evidence of GTN by a histological diagnosis of choriocarcinoma when available by surgical resection specimen or biopsy [15]. Staging of GTN is typically done by using a combination of FIGO, The International Federation of Gynecology and Obstetrics staging system and the WHO world health organization prognostic scoring system (Tables 1 and 2) [16,17].

Table 1: FIGO staging of gestational trophoblastic neoplasia.

Stage I	Disease confined to the uterus
Stage II	Disease extends outside of the uterus, but is limited to genital structures (adnexa, vagina)
Stage III	Disease extends to the lungs, with or without genital tract involvement
Stage IV	All other metastatic sites

High-risk GTN are cases with stage IV or WHO score 7 or greater, while low-risk disease includes patients with FIGO stage I or score 0 to 6. The low-risk and high-risk score by WHO predicts both resistance to single-agent chemotherapy and clinical outcome [18].

The goal of treatment is to induce remission. The selection of treatment is based on the stage of disease and risk score. Most patients classified as non-metastatic disease (stage I) and low-risk disease metastatic disease (stage II and III, score <7) can be treated initially with single-agent methotrexate or actinomycin-D chemotherapy while patients with high-risk metastatic disease (stage IV, and stage II and III with score >6) should be treated initially with combination chemotherapy such as EMA-CO. With recent chemotherapeutic agents, a 5 years survival rate in patients with high-risk treated with EMA-CO varies from 75% to 90%.

EMA-CO includes Actinomycin -D, methotrexate, vincristine, Etoposide, cyclophosphamide, is highly effective for a high-risk patient with GTN with remission rate up to 90%. In the past, GTN was considered a fatal disease, however, with recently advanced chemotherapy, it became a curable disease in most cases.

The role of surgery in choriocarcinoma is limited, however, local resection may be needed to control bleeding complications such as intracerebral bleed needing craniotomy to remove the metastatic lesion and control bleeding, or in case of hepatic or splenic bleed from metastatic lesions rupture. Whole-brain irradiation for brain metastases has been used [19,20].

The risk of relapse after chemo is 3%-9% mostly occurs during the first year follow up. Serial monitoring of serum hCG level during chemotherapy treatment done weekly until undetectable for three consecutive weeks then monthly for at least 2 years after completing treatment and achieving remission is essential and some even advocate monitoring for life as late recurrence may occur in less than 1%. Pregnancy should be avoided during the first year.

Conclusion

Choriocarcinoma must be considered in the differential diagnosis of women in child bearing age during all type of pregnancy and after delivery particularly in a patient with prior history of molar pregnancy, who present with hemorrhagic event, such as upper or lower GI bleed, Hemoptysis, hemothorax, hematuria or metastatic lesions on imaging studies With or without uterine/vaginal bleed. Diagnosis of GTN after term pregnancy is difficult and can be delayed causing poor outcomes. GTN is very responsive to the current recommended chemotherapeutic agents and cure rate up to 90% has been reported. Our challenging case was diagnosed literally after 4 weeks of delivery.

Table 2: Modified who prognostic scoring system adapted by FIGO.

FIGO Score	0	1	2	4
Age (years)	<40	>40	-	-
Prior pregnancy	Molar	Abortion	Term pregnancy	-
Months from prior pregnancy	<4	4 to 6	7 to 12	>12
Pretreatment Serum hCG (mIU/mL)	$<10^3$	10^3-10^4	$>10^4$-10^5	$>10^5$
Largest tumor including uterus	<3 cm	3-4 cm	≥ 5 cm	-
Site of metastases	Lung	Spleen, kidney	GI tract	Brain, liver
Number of metastases	0	1-4	5-8	>8
Prior failed chemotherapy	-	-	Single drug	≥ 2 drugs

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