

Successful management of stage IV epithelioid trophoblastic tumor using multimodality treatment: A case report

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ABSTRACT

Epithelioid trophoblastic tumor (ETT) is a rare variant of gestational trophoblastic neoplasia (GTN) that develops from chorionic-type intermediate trophoblast, is more resistant to chemotherapy than choriocarcinoma, and presents with metastatic disease in 25–35% of cases.

We report a case of a 32-year-old who presented one week postpartum with severe abdominal pain and was found to have profound anemia and an elevated hCG level. CT scans and MRI revealed bleeding from hepatic masses, multiple hemorrhagic pulmonary nodules, a 7 cm uterine mass, and brain metastases. She underwent emergent hepatic embolization, was started on induction chemotherapy with weekly low-dose etoposide and cisplatin followed by a transition to etoposide, high-dose methotrexate, actinomycin D, etoposide, and cisplatin (HD EMA-EP), received stereotactic brain radiotherapy, and subsequently underwent minimally-invasive hysterectomy. She remains disease free over one year after the completion of treatment.

An aggressive multimodal treatment approach employing etoposide/cisplatin-based chemotherapy as well as surgical procedures to control hemorrhage or excise resistant disease, and radiotherapy for brain metastases can result in successful treatment of stage IV ETT.

1. Introduction

Gestational trophoblastic disease is a spectrum of disorders that arise from abnormal proliferations of the placenta. Both benign and malignant forms exist. Malignant forms, termed gestational trophoblastic neoplasia (GTN), include invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) (Lurain, 2011). ETT, the rarest form of GTN, arises from chorionic-type intermediate trophoblastic cells, and is often misdiagnosed as choriocarcinoma, PSTT, or squamous cell carcinoma. ETT confined to the uterus is often curable with surgical management; however, overall survival for metastatic disease is only 50–60%. Here we present a case of stage IV ETT successfully managed with multimodal treatment.

2. Case report

A 32-year-old gravida 2, para 2002, presented to the emergency department (ED) with severe abdominal pain seven days following a repeat cesarean section. Her obstetric history was significant for two uncomplicated full-term cesarean deliveries, in 2018 and 2020. Her initial evaluation in the ED revealed tachycardia, anemia (hemoglobin 6.3 mg/dL) and an elevated quantitative human chorionic gonadotropin (hCG, 5,038 mIU/mL). Computed tomography (CT) revealed hepatic masses associated with a subcapsular hematoma, multiple hemorrhagic pulmonary nodules, and a seven-centimeter uterine mass (Fig. 1a, 1b). The patient underwent emergent embolization of the hepatic hematoma by Interventional Radiology to control hemorrhage. After stabilization, brain magnetic resonance imaging (MRI) revealed hemorrhagic lesions involving the left middle frontal gyrus and left parieto-occipital junction (Fig. 1c). The patient was admitted for monitoring and further workup.

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Core needle liver biopsy initially returned consistent with metastatic gestational choriocarcinoma. Given large burden of disease and hemorrhage, low-dose induction etoposide-cisplatin (EP) chemotherapy was initiated.

The patient was referred to the John I. Brewer Trophoblastic Disease Center in Chicago, Illinois following the second cycle of induction chemotherapy. Hemoglobin levels remained stable and serum hCG had decreased to 1,513 mIU/mL. Internal pathology review of the liver biopsy demonstrated histologic and immunophenotypic findings consistent with metastatic ETT (Fig. 2). Multiagent chemotherapy with etoposide, methotrexate, actinomycin D, etoposide, and cisplatin (EMA-EP) was initiated. For management of the brain metastases, the methotrexate dose was increased from 300 mg/m² to 1000 mg/m² for cycles 1 and 2 to increase penetration of the blood–brain barrier, and Radiation Oncology performed concurrent gamma knife stereotactic radiosurgery to the two dominant brain metastases. The patient's hCG levels normalized to 0.7 mIU/mL following the second cycle of EMA-EP, after which 3 additional cycles of consolidation EMA-EP were given. Post-treatment CT demonstrated a resolving liver hematoma and heterogeneous uterus.

Minimally-invasive hysterectomy and biopsy of liver hematoma were performed to rule out residual disease. Surgical pathology from the uterus and liver biopsy demonstrated treatment effect but were negative for active disease. No further therapy was recommended. Twelve months post-treatment, the patient remains disease-free and is being monitored with CT scan every 3 months in addition to monthly serum hCG.

3. Discussion

ETT is an extremely rare but distinct form of GTN. First described in 1998 by Shih and Kurman, existing literature is limited and largely based on data available from case reports, small series, and expert opinion (Shih and Kurman, 1998). This case presents a rare presentation of metastatic ETT and highlights the importance of implementing aggressive multimodality treatment in order to achieve cure.

3.1. Presentation

The most common clinical presentation of ETT is abnormal uterine

bleeding remote from a non-molar pregnancy. The majority of patients present with non-metastatic disease; however, in the 25–35% of cases diagnosed with metastatic disease at presentation, the most common site of metastatic disease is the lung (Sobecki-Rausch et al., 2018). Only 10% of patients present with stage IV disease and metastatic disease to the brain is exceedingly rare (Froeling et al., 2019). This case was highly unusual in that the patient presented seven days following term delivery with widely metastatic disease to the liver, lungs, and brain in addition to a uterine mass. Review of her obstetric ultrasounds did not report any uterine abnormalities to suggest disease was present during pregnancy or at time of delivery. Given initial presentation of aggressive, widely metastatic hemorrhagic disease in the setting of a recent pregnancy, the diagnosis of choriocarcinoma was presumed.

3.2. Histopathology

The clinical impression of choriocarcinoma initially resulted from interpretation of a biopsy specimen which showed an atypical trophoblast proliferation with immunohistochemical (IHC) staining focally positive hCG expression and p40 negativity. However, review of the histologic features and additional/complete IHC testing of the specimen at the John I. Brewer Trophoblastic Disease Center established the diagnosis of metastatic ETT. The diagnosis of ETT can often be challenging in differentiating from other forms of GTN, or even squamous cell carcinoma, especially in metastatic settings and small-tissue evaluations. ETT is a neoplastic proliferation of chorionic-type intermediate trophoblastic cells (ITs). Microscopic sections of ETT demonstrate a relatively uniform, monomorphic population of ITs growing in rounded nests, sheets, and occasionally cords (Hui, 2019). Characteristically, viable portions of ETT are seen surrounding vasculature within a background of hyalinization and abundant necrosis in a map-like distribution, termed “geographic necrosis” (Hui, 2019; Fadare et al., 2006). Choriocarcinoma comprises a dual trophoblastic cell population of cytotrophoblasts and syncytiotrophoblasts. Tumor cells of choriocarcinoma also show nuclear pleomorphism with varying chromasia beyond those of ITs in ETT. Frequently seen is abundant hemorrhage, termed “blood lakes,” differing from the background content of ETT. IHC evaluation of ETT is outlined in Table 1, and importantly it differs from choriocarcinoma in p63, hCG, hPL, SALL4 and Mel-CAM staining patterns.

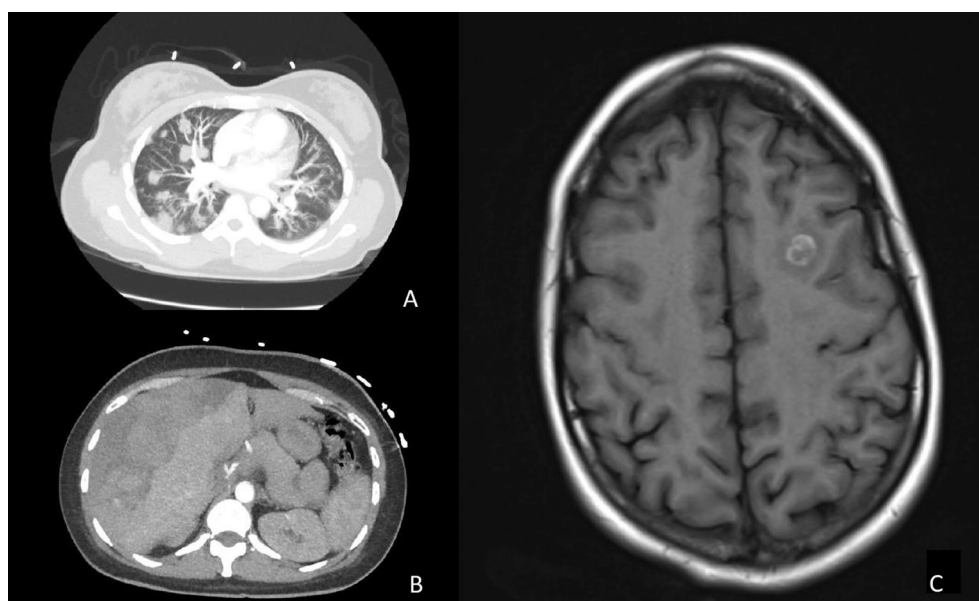


Fig. 1. Radiologic findings at presentation were significant for multiple pulmonary lesions (a), and hepatic lesions associated with subcapsular hematoma (b) on computed tomography scan. Axial T2 weighted magnetic resonance image of the brain demonstrated a left middle-frontal gyrus metastasis (c).

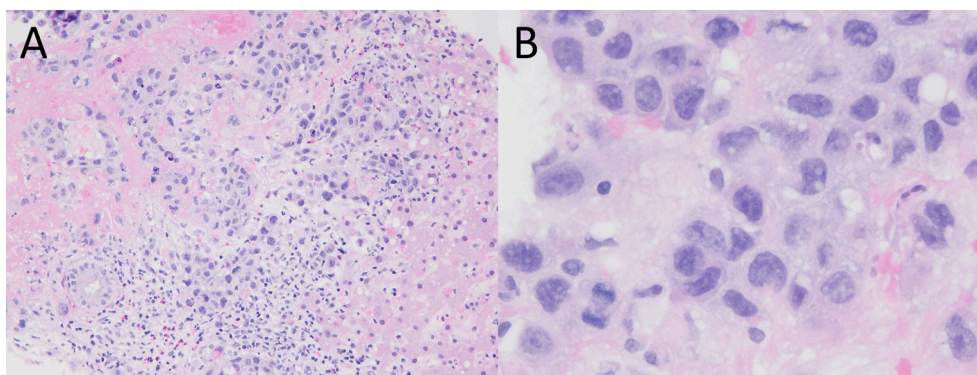


Fig. 2. Histomorphology of the liver metastasis. (a) Cords and nests of tumor cells associated with a hyaline-like matrix are seen infiltrating the liver parenchyma (H&E 100X). (b) The tumor cells demonstrate mitotic and apoptotic activity and are mononuclear with round to ovoid nuclei, fine chromatin, and pale eosinophilic to clear cytoplasm with fine granularity (H&E 400X).

Table 1
Immunoprofile for epithelioid trophoblastic tumor and differential diagnoses.

	ETT	PSTT	CC	APSN	SCC
AE1/AE3 (cytokeratin)	+	+	+	+	+
p63/p40	+	-	-	+	+
hCG	+	Scattered + cells	+	-	-
hPL	+	+	+	+	-
SALL4	-	-	+	-	-
Cyclin E	+	+	+	+/-	+
Mel-CAM	+	+	+	+	-
Inhibin- α	+	+	+	+	-
GATA-3	+	+	+	+	-
P16	-	-	-	-	+
					(diffuse) */-

ETT, epithelioid trophoblastic tumor; PSTT, placental site trophoblastic tumor; CC, choriocarcinoma; APSN, atypical placental site nodule; SCC, squamous cell carcinoma; hCG, human chorionic gonadotropin; hPL, human placental lactogen, *HPV-related SCC.

3.3. Treatment

ETT is more chemoresistant than choriocarcinoma, thus treatment focuses on surgical excision of disease and aggressive use of multiagent chemotherapy. Unlike choriocarcinoma, where surgery is usually reserved for management of hemorrhage or resection of sites of chemoresistant disease, surgery is the mainstay for treatment of ETT. The current standard of care for ETT is total hysterectomy for early stage disease and resection of metastatic or residual disease sites following chemotherapy in metastatic disease (Froeling et al., 2019). For patients with stage I disease diagnosed ≥ 48 months from prior pregnancy or with metastatic disease, platinum-based systemic chemotherapy with either EMA-EP or TP/TE (paclitaxel-cisplatin/paclitaxel-etoposide) is recommended (Taylor and Hancock, 2015). Radiotherapy is reserved for treatment of unresectable oligometastatic diseases or palliation of symptoms. Froeling et al. recently demonstrated that intensified therapies improved survival in patients identified with PSTT or ETT (Froeling et al., 2019). This case demonstrates that timely implementation of aggressive multimodality treatment can lead to successful management of stage IV widely metastatic ETT.

3.4. Management of hemorrhage and use of induction chemotherapy

A hallmark of metastatic GTN is the propensity for hemorrhage due to increased vascularity within the tumor. A main cause of early death

(defined as less than 4 weeks from diagnosis) is hemorrhage secondary to a large disease burden or rapid tumor destruction following administration of full-dose chemotherapy (Alifrangis et al., 2013). This patient presented with symptoms related to active hemorrhage, requiring emergent embolization of liver metastasis. Once stabilized, given the large tumor burden and risk of ongoing hemorrhage, low-dose induction EP chemotherapy was initiated. Induction chemotherapy with low dose EP (etoposide 100 mg/m² IV and cisplatin 20 mg/m² IV on days 1 and 2) every 7 days for 1–3 cycles has shown to decrease the early death rate from 7.2% to 0.7% (Alifrangis et al., 2013). This is the first case report to our knowledge to utilize induction EP chemotherapy for the management of metastatic ETT.

3.5. Brain metastases

Brain metastases from GTN are rare events, occurring in approximately 10% of patients diagnosed with metastatic disease. Despite being regarded as a poor prognostic indicator, the use of multimodality treatment, including a combination of multiagent chemotherapy, surgery and/or brain radiotherapy, offers excellent local control of brain disease and survival is good, especially if brain lesions are identified before they are symptomatic (Neubauer et al., 2012). In this patient, asymptomatic brain metastases were identified at diagnosis by brain MRI and subsequently managed with a combination of systemic multiagent chemotherapy and stereotactic brain radiation. Although asymptomatic, brain radiation was added given data demonstrating that a multimodal approach increases response rate from 62% with multiagent chemotherapy alone to 100% with multimodal therapy (Newlands et al., 2002). This case highlights the importance of thorough staging, including central nervous system (CNS) evaluation, in cases of suspected metastatic GTN, and early initiation of aggressive multimodality treatment in management of CNS involvement.

3.6. Conclusions

Aggressive implementation of multimodal treatment is successful in the management of patients presenting with metastatic ETT. While treatment for ETT generally parallels the recommendations for PSTT, this case report highlights that ETT can behave in a biologically aggressive manner similar to choriocarcinoma, and treatment principles, such as embolization and induction chemotherapy for early control of disease, as well as application of multimodal chemotherapy and brain radiation therapy for control of CNS metastases, can be applied successfully to the management of metastatic ETT.

Statement of consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the

written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Brad Nakamura: Writing - original draft. **Matthew Cowan:** Conceptualization, Writing - review & editing, Visualization. **Brannan B. Griffin:** Writing - original draft, Resources, Visualization. **Jean Victoria Fischer:** Writing - original draft, Resources, Visualization. **John R. Lurain:** Writing - review & editing. **Anna E. Strohl:** Conceptualization, Writing - review & editing, Supervision.

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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