

A case of metastatic mixed trophoblastic tumor

E. Kertowidjojo¹, O. Taha², M. Pearl², R. Batiste¹, A. Kudelka³

¹Department of Pathology, Stony Brook Medicine, Stony Brook, NY

²Department of Obstetrics, Gynecology and Reproductive Medicine, Stony Brook Medicine, Stony Brook, NY

³Department of Medicine, Stony Brook Medicine, Stony Brook, NY (USA)

Summary

The authors present a case report of a patient with metastatic mixed trophoblastic tumor (MTT) comprised of choriocarcinoma (CC) and epithelioid trophoblastic tumor (ETT) with pulmonary metastases at presentation. The patient underwent surgical management followed by high-dose methotrexate EMA-EP (etoposide, methotrexate, and actinomycin-D - etoposide and cisplatin). Though the patient initially responded well to the therapy regimen, she eventually developed brain metastases, which were morphologically consistent with ETT. The authors conclude that while chemotherapy is likely effective against the CC component, the ETT component of the tumor remains relatively chemoresistant and continued to progress throughout her therapy. This case illustrates the difficulty in treating MTTs and a need for further studies and general guidelines.

Key words: Metastatic mixed trophoblastic tumor (MTT); Choriocarcinoma (CC); Epithelioid trophoblastic tumor (ETT).

Introduction

Accounting for less than 1% of all gynecologic malignancies, gestational trophoblastic neoplasms (GTNs) are classified into three clinicopathologic entities: choriocarcinoma (CC), placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). CC makes up the vast majority of GTNs, while PSTT and ETT are rare. Cases of mixed trophoblastic tumors (MTTs) have been reported, generally consisting of CC admixed with PSTT or ETT [1-3]. MTTs present a therapeutic predicament. While CC is known to be chemosensitive, PSTT and ETT are relatively chemoresistant. Furthermore, due to the rarity of MTT, there is currently no consensus on optimal treatment strategies. In this report, the authors present a case of MTT with components of ETT and CC throughout its disease course.

Case Report

The patient was a 39-year-old G2P1001 who had been on oral contraceptive pills from Portugal and had not had any menses for approximately six years. She presented to her gynecologist with vaginal spotting and a foul-smelling brownish discharge of one-month duration. A pregnancy test was persistently positive without evidence of an intrauterine pregnancy. She was referred to the present institution for further evaluation and management.

Upon initial presentation, she denied any complaints other than her discharge and spotting. Her past gynecologic, medical, and family histories were unremarkable, including a prior normal,

spontaneous vaginal delivery. She appeared well and her general examination was unremarkable. A speculum examination demonstrated yellowish, purulent-appearing, foul-smelling discharge coming through her cervical os. Her cervix was tender on palpation without motion tenderness, friable, dilated to approximately one centimeter, and nodular with a lesion near the os. Her uterus was approximately 16 weeks in size and non-tender.

Her white blood cell (WBC) count was 17.31 K/uL without a left shift, platelet count was 456 K/uL, and quantitative hCG was 15,400 mIU/mL. On ultrasound, no intrauterine pregnancy was identified. Her uterus appeared heterogeneous with foci of air and probable fluid suggestive of an infectious or inflammatory process within the uterus. On MRI, her uterus was markedly enlarged measuring 14.7×6.5×8.5 cm with virtual replacement by a poorly defined, heterogeneous, infiltrative, partially hemorrhagic mass with central necrosis, highly concerning for an invasive mole (Figure 1A). On computed tomography angiography (CTA) performed to evaluate dyspnea, there was no evidence of liver metastases but innumerable, bilateral pulmonary nodules measuring up to 5 cm were identified (Figure 3A). An MRI of her brain did not demonstrate any evidence of intracranial metastases.

As she was not interested in preserving fertility and her findings were worrisome for metastatic gestational trophoblastic neoplasia, immediate surgical intervention was performed. Exploratory laparotomy demonstrated a normal upper abdomen, including the undersurfaces of her diaphragm, liver, spleen, gallbladder, stomach, omentum, kidneys, bowel, and peritoneal surfaces. She did not have any palpable lymphadenopathy. Her uterus was markedly distended and extremely thin with tumor eroding through the serosa posteriorly, along the right lateral aspect, and anteriorly. A small segment of rectosigmoid colon was densely adherent to the anterior aspect of the uterus with apparent tumor extension, as

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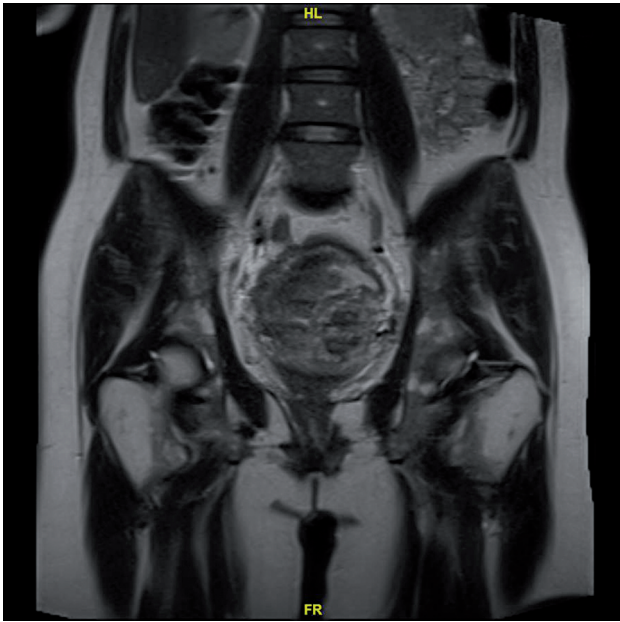


Figure 1. — Radiographic study at presentation. MRI scan of the abdomen and pelvis showing an enlarged uterus replaced by a heterogeneous hemorrhagic and infiltrative mass with central necrosis.

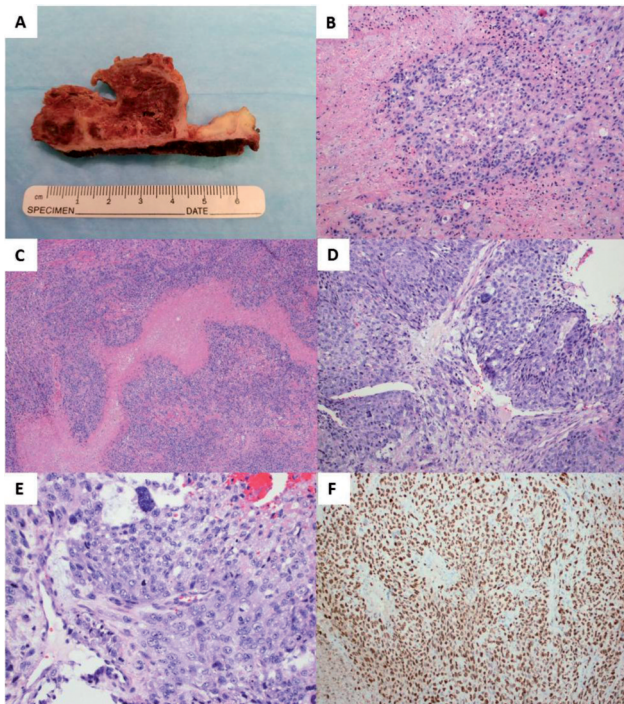


Figure 2. — Pathologic findings. Gross evaluation showed a transmural infiltration of the uterus by a hemorrhagic and necrotic tumor (A). Microscopic evaluation showed a nodular growth of uniform mononucleate tumor cells (B, $\times 100$) with geographic necrosis (C, $\times 40$) in the uterus and cervix, consistent with ETT. Foci of trimorphic population of syncytiotrophoblast, intermediate trophoblast, and cytotrophoblast are present in the vagina and cul-de-sac (C, $\times 100$ and D, $\times 200$). The proliferative index, Ki-67, is positive in approximately 90% of cells in these foci (F, $\times 100$).

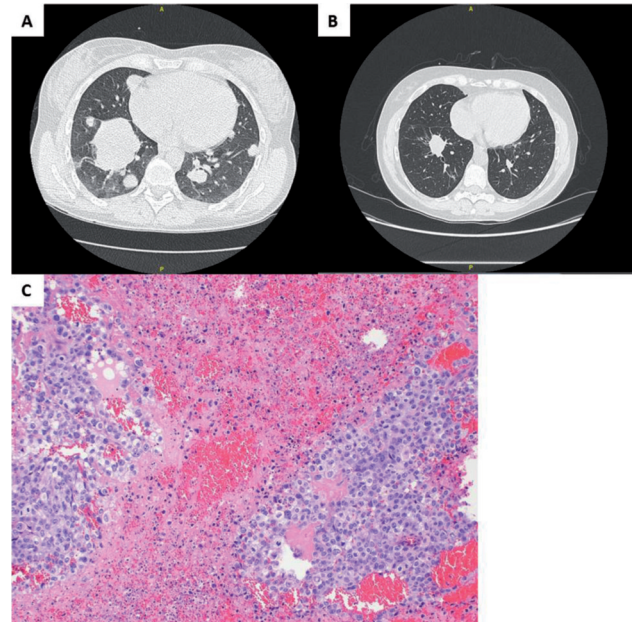


Figure 3. — Therapy effect. CT scans of the chest at the time of diagnosis (A) and after 11 cycles of chemotherapy (B), showing a significant decrease in sizes of the pulmonary nodules. Histologic evaluation of the brain metastases (C, $\times 100$) showing monomorphic cells consistent with ETT.

was a small segment of the right bladder dome. There was extensive tumor within the cul-de-sac and over the right pelvic sidewall, including encasing the right ureter.

Total abdominal hysterectomy, bilateral salpingectomy, excision of the cul-de-sac mass, and placement of a right subclavian infusa-port was performed. An intraoperative frozen section was consistent with choriocarcinoma. At the completion of her procedure, the residual tumor consisted of a small portion in the cul-de-sac and overlying the right pelvic sidewall.

Gross pathologic evaluation showed an $11 \times 6 \times 4$ cm hemorrhagic and necrotic tumor in the uterine corpus and cervix transmurally infiltrating the myometrial wall with multiple foci of serosal erosion (Figure 2A). Histologic evaluation showed a nodular and nested growth of relatively uniform mononucleate intermediate trophoblastic cells with “geographic” necrosis in the uterus and cervix, consistent with ETT (Figures 2B and 2C). On the other hand, the cul-de-sac and posterior vagina had multiple foci of trimorphic population of syncytiotrophoblast, intermediate trophoblast, and cytotrophoblast, consistent with CC (Figures 2D and 2E).

The proliferation index, Ki-67, was positive in 90% of tumor cells in the cul-de-sac and posterior vagina (Figure 2F). On the other hand, only 25% of tumor cells in the uterus and cervix showed Ki-67 positivity. The final diagnosis was of an MTT with components of ETT and CC, pathologic stage pT2 for extension into the vagina and a FIGO Stage of III for lung metastases.

The patient tolerated the surgery well, and her hCG decreased to 3,464 mIU/mL. Based on the FIGO/WHO Prognostic Scoring System for GTN, the patient was considered at very high risk for monotherapy resistance at the time of presentation (score 14 for term antecedent pregnancy, greater than 12 months interval from antecedent gestation, pretreatment hCG between 10^4 - 10^5 mIU/mL,

tumor size greater than 5 cm, and innumerable lung metastases) [4]. Consequently, a regimen of multiple-agent chemotherapy was initiated, consisting of high dose methotrexate EMA-EP (etoposide, methotrexate, and actinomycin-D - etoposide and cisplatin). The patient completed 11 cycles without any significant adverse reaction. Imaging showed a gradual decrease in the size of her pulmonary nodules (Figures 3A and 3B) and a serum hCG of 6 mIU/mL at its nadir. However, eight months after her initial diagnosis, the patient experienced seizures and was found to have multiple foci of metastases in her right frontal lobe, right parieto-occipital lobe, and left cerebellum. Resection of the tumor foci revealed morphology consistent with ETT (Figure 3C). The patient underwent multiple craniotomies for tumor removal, and radiation therapy was initiated. Two months following the diagnosis of her brain metastases, the patient developed a pulmonary embolism, complicated by worsening cerebral edema secondary to her hemorrhagic metastases. The patient opted for comfort care and subsequently succumbed to her disease.

Discussion

Developing an optimal treatment strategy for MTTs is a difficult undertaking for multiple reasons. First, these tumors are exceedingly rare. Thus, knowledge of their behavior and therapeutic responsiveness is limited. Furthermore, the components of MTTs are known to respond differently to therapy. Specifically, while CC is greatly responsive to chemotherapy, ETTs and PSTTs are relatively chemoresistant. Therefore, while combined chemotherapy may be effective in targeting the CC component, the ETT or PSTT component may be refractory. Currently, there is no universally accepted guideline for the treatment of ETT and PSTT, though surgery remains to be the primary mode of treatment. On the other hand, chemotherapy, particularly EMA-EP, has found increasing usage in cases of ETT and PSTT with a large tumor burden or metastases [5, 6].

In 2015, Imamura *et al.* reported a case of metastatic MTT comprised of CC and ETT in which the patient was successfully treated with surgical resection and MEA (methotrexate, etoposide, and actinomycin D) with no disease recurrence after 26 months [1]. Another report of mixed CC and ETT from Luk and Friedlander, also showed successful treatment with adjuvant EMA-EP [3]. Unfortu-

nately, the present patient's metastatic disease ultimately progressed after an initial response despite combined chemotherapy. Though the pulmonary nodules were never biopsied, the morphology of the brain metastases was consistent with ETT. Thus, it is likely that, while chemotherapy was effective against the CC component, the ETT component of the tumor continued to progress. Ultimately, this case illustrates the difficulty of treating MTTs and the necessity for further case analysis in order to determine the behavior of this tumor and to elucidate an optimal therapeutic approach.

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Corresponding Author:
E. KERTOWIDJOJO, M.D.
Stony Brook University Hospital
Department of Pathology
101 Nicolls Rd, Level 2
Stony Brook, NY 11794 (USA)
e-mail: liz.kertowidjojo@gmail.com