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Case report

Conservative management of uterine rupture in gestational trophoblastic neoplasia

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1. Introduction

Gestational trophoblastic neoplasia (GTN) includes invasive mole, choriocarcinoma, and placental site trophoblastic tumors (Morgan, 2008). Approximately 50% of GTN are diagnosed after hydatidiform molar pregnancy, with diagnosis being made by the clinical and/or histopathologic criteria based on the following Federation of Gynecology and Obstetrics (FIGO) recommendations: (1) an hCG plateau for at least four values over 3 weeks; (2) an hCG increase of 10% or greater for at least three values over 2 weeks; (3) hCG persistence 6 months after molar pregnancy evacuation, (4) histopathologic diagnosis of choriocarcinoma; or (5) presence of metastatic disease (Morgan, 2008). Once GTN is diagnosed, patients are categorized by FIGO Stage and World Health Organization (WHO) risk score, and their stage and score dictate the initial treatment regimen to assure the best possible outcomes with the least morbidity (Lurain, 2003). Low risk disease defined as, patients with nonmetastatic (stage I) and low-risk metastatic GTN (stages II and III, score < 7), can be managed with single agent chemotherapy, and can be considered for a second dilation and evacuation with 40% chance of cure (Lurain, 2003; Osborne et al., 2016 Sep). High risk disease defined as, high-risk metastatic GTN (stage IV or score ≥ 7), requires multi-agent chemotherapy (Lurain, 2003). In the more unusual scenario of high risk GTN where there is large tumor burden and risk of respiratory distress or hemorrhage from rapid tumor destruction from full dose chemotherapy, a protocol of low dose induction cisplatin and etoposide can be initiated (Alifrangis et al., 2013). Here we report a case of a patient with low risk disease in the setting of life-threatening hemorrhage from uterine rupture.

2. Case

A 19-year-old G1P0010 was diagnosed with a complete hydatidiform molar pregnancy after dilation and evacuation was performed for nonviable intrauterine pregnancy. The patient was followed with serial hCG and her level initially started down trending from the time of evacuation value of 268,400. However, approximately 4 weeks post-evacuation, her level rose to 120,748, resulting in referral to gynecologic oncology for persistent GTN. Pertinent findings on a chest CT scan revealed multiple bilateral pulmonary nodules consistent with metastatic disease, and her abdomen/pelvis CT scan revealed a heterogeneous mass within the right uterine wall, extending slightly beyond the posterior uterine wall and measuring approximately $4.3 \times 3.5 \times 4.3$ cm (Image 1A). Pelvic ultrasound was also performed for better characterization of this mass (Image 1B). This constellation of

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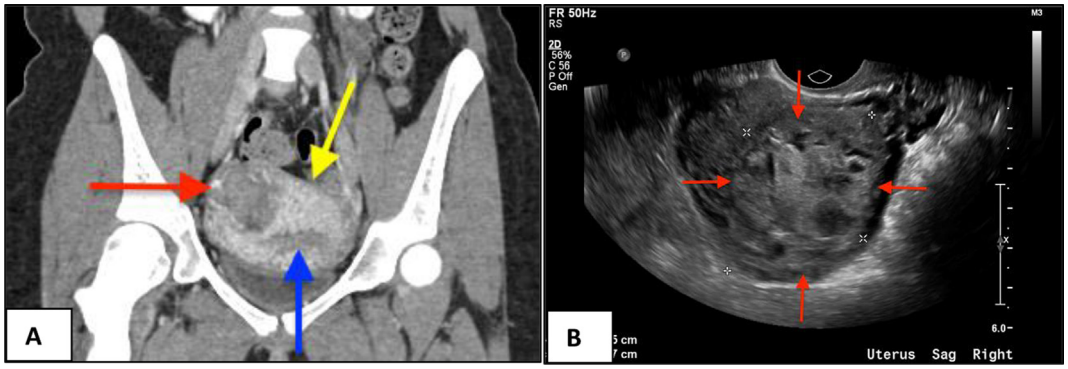

Image 1. (A) Coronal CT demonstrates the partially exophytic nature of the mass (red arrow) within the uterus (yellow arrow) and the relationship to the endometrium (blue arrow). (B) Endovaginal ultrasound demonstrates a 5.4 × 4 cm heterogeneous posterior uterine mass (red arrows) with hyperechoic and hypoechoic areas. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

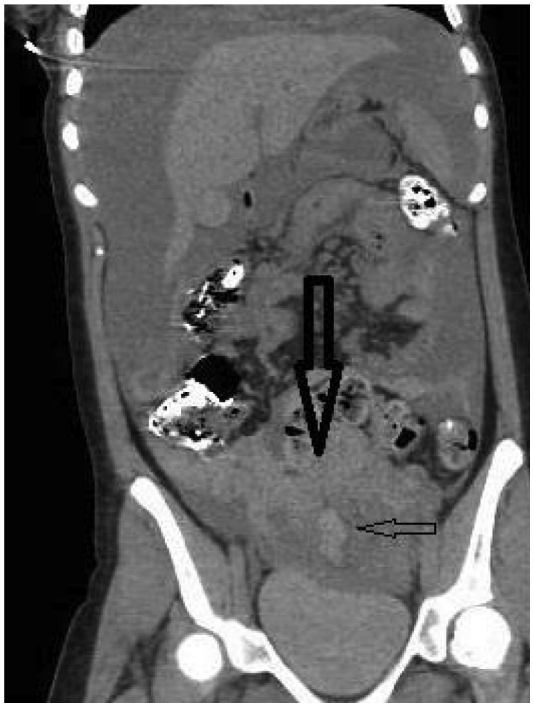

Image 2. Coronal CT demonstrating hemoperitoneum with uterine wall rupture (bold arrow) and blood within endometrial cavity (narrow arrow).

findings and a negative pre-treatment chest x-ray was consistent with invasive molar pregnancy and patient was diagnosed with low risk III:3 GTN. Single agent therapy with methotrexate was to be initiated however, 3 days prior to initiation of treatment, patient presented to a local emergency department with severe abdominal pain and near syncopal episodes. Physical exam was remarkable for abdominal distension and diffuse tenderness with rebound. Labs revealed severe anemia, Hgb 5.6, and CT scan imaging revealed large hemoperitoneum and uterine wall mass with uterine rupture (Image 2). After stabilizing the patient with transfusion of blood products, she was transferred to a tertiary care center and counseled on the management of uterine rupture in the setting of invasive molar pregnancy. The patient strongly maintained a desire to preserve her fertility; therefore a conservative management approach was employed. The interventional radiology team performed an angiogram which revealed a large hypervascular mass within the right pelvis with extravasation of contrast (Image 3A), and she subsequently underwent bilateral uterine artery embolization using Gelfoam slurry to temporize bleeding (Image 3B). Immediately after the embolization, the patient was taken to the operating room and underwent an exploratory laparotomy where 3 L of hemoperitoneum was evacuated, and a 5 cm bulging mass was noted on the right posterior fundal aspect of the uterus at the level of the serosa. Within the mass, a 1 cm serosal rupture was noted with extruding tumor and active bleeding. The site of bleeding was subsequently coated with thrombin spray and packed with Surgiflo and Gelfoam soaked in thrombin. Pressure was applied and inspection of the abdomen and pelvis was performed, revealing no other intraabdominal or pelvic masses. The site of bleeding was inspected again and excellent hemostasis was noted. At

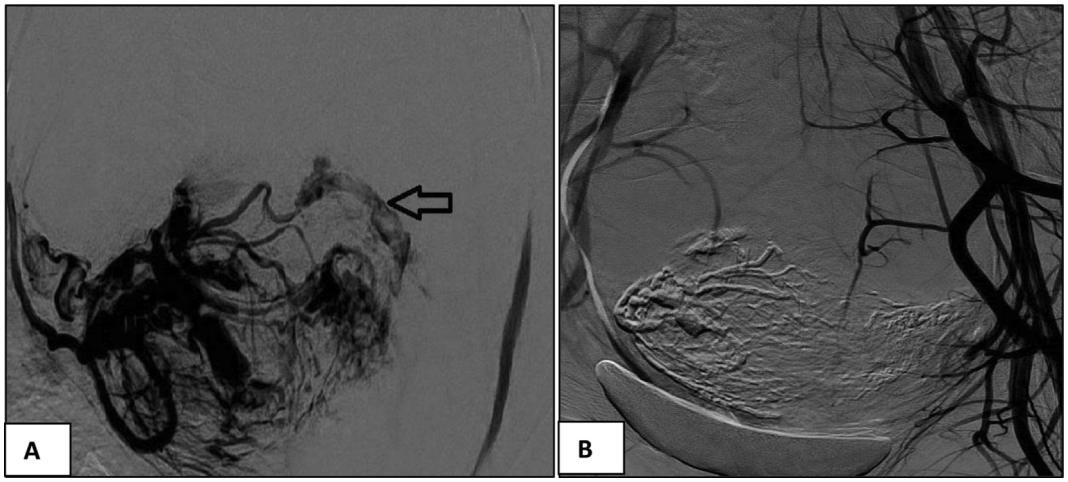

Image 3. (A) Angiogram showing extravasation (bold arrow). (B) Post-embolization angiogram.

the time of abdominal wall closure, a JP drain was placed in the pelvis to monitor any post-operative bleeding. Post-operatively, the patient's GTN work up was completed with confirmed negative brain MRI, and repeat hCG which was persistently elevated at 60,826. In light of the massive hemorrhage from uterine rupture as a result of invasive molar pregnancy, and the conservative management of this rupture with retained viable tumor tissue, chemotherapy with induction low dose cisplatin and etoposide was initiated on post-operative day 1. Patient was subsequently transferred to her home institution where she received cycle 2 of induction low dose cisplatin and etoposide, and eventually completed 5 cycles of Etoposide 90 mg/m^2/Methotrexate 300 mg/m^2/Dactinomycin 450mcg (EMA) on a q14 day schedule. Her hCG normalized after cycle 3 of EMA, and she received 2 additional cycles for consolidation. At her 12 month follow up visit, patient was without evidence of disease, and at her 20 month follow up visit she had a confirmed viable intrauterine pregnancy with suspected placenta accreta.

3. Discussion

Uterine rupture in the setting of high-risk GTN is a rare and potentially catastrophic event (Aminimoghaddam and Maghsoudnia, 2017). The incorporation of uterine artery embolization (UAE) in the management of complicated GTN has been described (Lurain et al., 2006). However, it is not common, and this case report is one of few reported cases where pre-treatment UAE was performed and uterus was retained for fertility preservation (Wang et al., 2017). There is data that supports fertility-preservation in select cases with recurrence rate of 3.85%, a rate comparable to all GTN treated with definitive management (Wang et al., 2017). With the implementation of multi-drug regimens, survival among patients with high-risk GTN has improved, however, GTN-related death still exists (Alifrangis et al., 2013; Neubauer et al., 2015). As many as 20% of metastatic high-risk choriocarcinoma patients will succumb to their disease and risk factors related to fatal GTN include choriocarincoma histology, high initial hCG levels, long duration of disease, multiple and increasing number of metastatic sites, antecedent nonmolar pregnancy, and extent of prior treatment (Neubauer et al., 2015). The main cause of death was sequela of heavy disease burden related to chemotherapy-induced rapid tumor destruction (Alifrangis et al., 2013). This observation led to a new treatment approach, including low-dose chemotherapy induction for patients at high-risk for hemorrhage, resulting in gradual reduction in tumor volume (Alifrangis et al., 2013). This protocol consisted of etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 on days 1 and 2. Treatment was repeated weekly for 1 or 2 cycles before initiating EMA-CO (etoposide, methotrexate and dactinomycin, alternating every week with cyclophosphamide and vincristine). After the development of this treatment protocol, investigators noted a significant reduction in early death among high-risk GTN patients treated at their institution, a decrease from 7.8% to 0.7% in their cohort (Alifrangis et al., 2013). Our case highlights the use of this low dose induction chemotherapy regimen in a patient who experienced life threatening hemorrhage, with retained high tumor burden within a ruptured uterus, a very high risk clinical scenario.

An alternative multi-drug regimen to consider is EP-EMA (etoposide and cisplatin with etoposide, methotrexate and dactinomycin), which is well known as an effective treatment strategy for patients resistant to EMA-CO, the standard therapy for high-risk GTN (Han et al., 2012). The efficacy of this alternative regimen prompted investigators to evaluate it in the primary treatment setting for patients considered to have high-risk and very-high-risk GTN (Han et al., 2012; Ghaemmaghami et al., 2004). A commonly reported toxicity of treatment was leukopenia, with one study reporting out of 100 courses of treatment given, 71% tolerated full dosage and the most common cause of dose reduction was leukopenia (Ghaemmaghami et al., 2004). Han et al described a remission rate with this regimen of 89% whereby no patient recurred over a median of 19 months (Han et al., 2012).

In summary this is a rare case of high-risk GTN complicated by uterine rupture. In addition, the patient strongly desired future fertility and every effort was made to respect her wishes and goals. UAE and a conservative surgical approach were utilized to control hemorrhage, while low-dose induction chemotherapy was administered to prevent potential complications including a higher risk of death that can occur from rapid tumor destruction associated high-dose therapy. Furthermore the patient completed her treatment regimen following EP with a short course of EMA, comprising a multi-drug regimen with reported benefit in the front line treatment setting. Her treatment was well-tolerated and she remains free of disease at this time.

CRediT authorship contribution statement

Gizelka David-West: Conceptualization, Writing - original draft, Writing - review & editing, Supervision. **Sumithra Jeganathan:** Data curation, Writing - original draft. **Natalie Cohen:** Data curation, Writing - original draft. **Shekher Maddineni:** Data curation, Resources. **Barak Friedman:** Data curation, Resources. **Samantha Cohen:** Conceptualization, Writing - original draft, Supervision.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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