

Case report

The role of pulmonary resection in the management of metastatic gestational trophoblastic neoplasia: Two cases of durable remission following surgery for chemo-resistant disease

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1. Introduction

Gestational trophoblastic neoplasia (GTN) is one of the most chemo-responsive and highly curative gynecologic malignancies. In selected patients with persistent or drug-resistant disease, surgical resection of metastatic foci can be critical. Here, we report two cases of durable remission following pulmonary wedge resection. These cases are unique due to their unusual initial presentations.

1.1. Case 1

Healthy 26 year-old G3P2012 (SAB at age 12, term SVD x2 with post-partum tubal ligation in 2013) presented with chest tightness and dyspnea in December 2016 (40 months from antecedent pregnancy). Chest X-ray (CXR) revealed a 3 cm ovoid mass at the periphery of the left upper lobe (LUL); chest computed tomography (CT) scan confirmed a 3.4 × 3.2 cm mass in the LUL, see Fig. 1. She was scheduled for outpatient Pulmonology follow-up; but re-presented to the ED weeks later with vaginal bleeding and nausea, last menstrual period (LMP) 3 months prior. CT abdomen/pelvis revealed only a cystic structure in the left adnexa. Her bHCG was 516 and no intra-uterine pregnancy was identified. She was given a dose of intramuscular methotrexate (IM MTX) by her gynecologist for presumed ectopic pregnancy (day#1, D1). Despite an additional dose on D9, her bHCG continued to rise and she was referred to Gynecology Oncology (GYO).

At the time of referral, bHCG was 724 (D28). Repeat chest CT (6 week interval from prior) noted the LUL mass, now 4.8 cm. Pelvic ultrasound revealed a hemorrhagic cyst in the left ovary, 4.1 cm. Given her unusual presentation, a CT-guided lung biopsy was performed, confirming metastatic choriocarcinoma; modified WHO score was 10.

She was treated with EMA-CO (etoposide, methotrexate, actinomycin-D, cyclophosphamide and vincristine) with growth factor support. Chemotherapy was delayed or held due to severe neutropenia (cycle 2), thrombocytopenia (cycle 2) and patient non-compliance. bHCG declined to 74 prior to cycle 3 but increased to 570 prior to cycle

4. She then underwent left video assisted thoracoscopy surgery (VATS) with wedge excision of the LUL nodule and a left lower lobe (LLL) nodule. The LUL pathology was metastatic choriocarcinoma. Post-operatively her bHCG decreased to 5. She was treated with 2 cycles of consolidation chemotherapy and has maintained remission (total surveillance 25 months).

1.2. Case 2

Healthy 31 year old G4P2022 with history of complete molar pregnancy in 2015. She had normal bHCGs for a year, then a term delivery August 2017. In February of 2018, a home pregnancy test was positive; this was followed by presumed clinical SAB. bHCG levels were followed and found to be persistently elevated between 55 and 74 with pelvic ultrasound notable for 4.7 cm ovarian cyst. CXR and brain MRI were negative. The patient was treated with MTX 50 mg/m² by her gynecologist with a diagnosis of ectopic pregnancy versus GTD. bHCG initially declined but rose to 97 on D18 and she was referred to GYO.

At presentation to GYO, bHCG was 369. Endometrial biopsy revealed secretory endometrium. Repeat imaging revealed a 0.9 cm LLL sub-pleural nodule, see Fig. 2. As she had not received appropriate MTX therapy, she was treated with weekly MTX 50 mg/m² for stage III GTD (WHO score 4), her treatment initiation bHCG was 853. However, her bHCG did not decline as expected and after 4 doses of the weekly regimen the decision was made to change to actinomycin-D 1250µg/m²; bHCG remission was achieved (total 6 cycles).

Four months later her bHCG rose to 12.8. Repeat imaging revealed persistent left LLL nodule. She underwent left VATS with wedge biopsies; pathology revealed metastatic choriocarcinoma. Her bHCG was undetectable a week after the procedure. She received 3 treatments of Act-D 1250µg/m² following surgery, and continues in remission (total surveillance 9 months).

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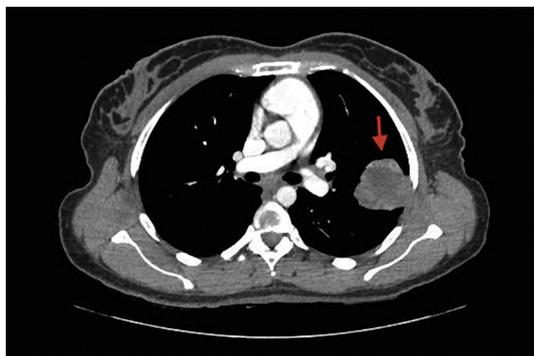


Fig. 1. Left upper lobe mass measuring 4.8 cm \times 4.3 cm demonstrating enhancement at the periphery with a necrotic center.

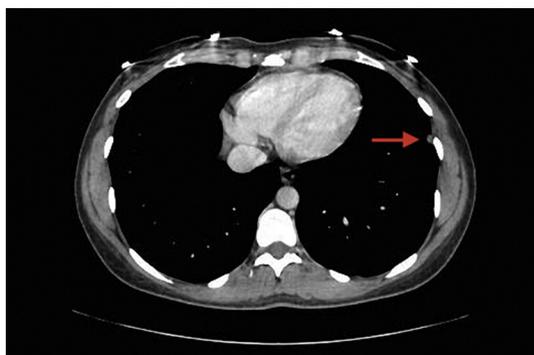


Fig. 2. Left lower lobe pulmonary nodule between the lateral basal and anteromedial basal segments abutting the pleura measuring 0.9 cm \times 0.6 cm.

2. Discussion

The majority of women with metastatic GTN can be cured with chemotherapy alone. Pulmonary metastasis with no other evidence of metastatic disease outside of the lungs, pelvis, or vagina is consistent with International Federation of Gynecology and Obstetrics (FIGO) stage III disease. The modified World Health Organization (WHO) prognostic scoring system as adopted by FIGO designates that even in the setting of metastatic disease, a score of ≤ 6 suggests a low risk of resistance to single-agent chemotherapy. Low-risk metastatic GTN has an excellent prognosis with single-agent chemotherapy treatment, with cure rates close to 100% (Soper et al., 1994). Even high-risk disease (≥ 7) has a cure rate of about 75% with chemotherapy (Soper et al., 1994), albeit combination chemotherapy, typically with EMA-CO as utilized for patient #1. However, surgical intervention may be beneficial in as many as two-third of patients with high-risk GTN (Lehman et al., 1994). Indications for surgical intervention include control of hemorrhage from metastases, excision of chemo-resistant disease (most common), or treatment of other complications in order to stabilize high-risk individuals during therapy (Lehman et al., 1994). Hysterectomy is the most frequent procedure performed and can be considered in patients with non-metastatic or low-risk metastatic GTN who are resistant to chemotherapy (Hanna and Soper, 2010).

Approximately 30% of patients with GTN have metastases at the time of diagnosis, most commonly to the lungs (80%) (Soper et al., 1994). As such, thoracotomy with pulmonary wedge resection is the most frequent surgical procedure performed for excision of extra-uterine metastases (Hanna and Soper, 2010). Resection of lung disease is typically not necessary but may be considered in highly selected patients. Thomford et al. established four principles indicating operative treatment for pulmonary metastasis of any malignant primary in 1965 (Thomford et al., 1965). Criteria for selection included 1) technical respectability, 2) tolerable general and functional surgical risk, 3)

control of the primary tumor process and 4) exclusion of any further, extra-thoracic metastasis. Thus, relatively extensive preoperative imaging is required to rule out other sites of disease.

Initial radiographic work-up for GTN should include pelvic ultrasound and CXR. Pelvic ultrasound is the imaging modality used to evaluate the uterus and adnexa and should be completed in all individuals. Given the relatively high frequency of pulmonary metastasis in high-risk patients, a CXR should also be performed. It is important to note that up to 40% of patients with negative findings for lung metastases on a CXR will have metastases diagnosed on a chest CT (Soper, 2006), as was the case in Patient #2. There are four principal radiographic patterns seen in individuals with GTN and metastatic pulmonary disease; including 1) discrete rounded densities; 2) an alveolar or “snowstorm” pattern; 3) pleural effusion; or 4) embolic pattern caused by pulmonary arterial occlusion (Bagshawe and Garnett, 1963). If there is metastatic disease on initial evaluation, further imaging should include CT of the abdomen and pelvis, MRI or CT of the brain, and potentially a PET scan to help differentiate sites of active disease. This is especially important before consideration of surgery.

Tomoda et al. reported on 122 patients with choriocarcinoma, including 82 with pulmonary metastasis, treated from 1965 to 1977 (Tomoda et al., 1980). Individuals with low pre-operative urinary hCG levels and unilateral disease saw the greatest benefit from surgery. As a modification of Thomford's principles, Tomoda proposed the following criteria for successful pulmonary resection: 1) Surgically fit patient, 2) Primary malignancy must be controlled (the uterus must have already been resected or no radiographic evidence of tumor in the uterine cavity), 3) No evidence of widely disseminated metastatic disease, 4) Unilateral lung involvement, and 5) Urinary hCG ≤ 1000 mIU/ml. Other predictors of favorable outcome include a serum level of hCG < 1500 mIU/mL, a solitary lung lesion, individuals who had a good response to pre-operative chemotherapy, and normalization of hCG within two weeks after resection of a pulmonary metastasis (Hanna and Soper, 2010; Xu et al., 1985).

When evaluating patients for thoracotomy, it is important to remember that non-viable fibrotic nodules may persist indefinitely after tumor regression and can mimic areas of active disease (Mapelli et al., 2013). For this reason, PET/CT may be useful in identification of viable tumor before surgery (Lybol et al., 2012). Additionally, undetectable bHCG is sufficient in ruling out persistent disease due to its profound sensitivity. Histological confirmation of metastatic disease is not required and biopsy, in some instances, can be dangerous due to increased risk of hemorrhage. Choriocarcinoma in particular, is a highly vascular neoplasm and avoiding biopsy is preferred when feasible. However, when a safe biopsy is possible, it can provide histological confirmation of the diagnosis and material for genetic analysis, especially when the diagnosis is uncertain (as in case #1).

Since most resistant pulmonary nodules contain tumor, patients may require further chemotherapy to treat occult disease following surgery. There are no clear guidelines surrounding use of adjuvant chemotherapy, however consolidation therapy among individuals with chemo-sensitive disease generally consists of two to three cycles following normalization of HCG levels (Lybol et al., 2012). Thus, it is reasonable to extrapolate that an additional two to three adjuvant cycles post-surgery is appropriate. Radiation has a limited role in the management of patients with pulmonary metastasis, and is more frequently used to treat patients with brain or liver metastases, primarily in an effort to minimize hemorrhagic complications at these sites (Hanna and Soper, 2010).

In both cases, the patients had isolated pulmonary disease and GTD was not the antecedent pregnancy. Furthermore, both were initially treated as ectopic pregnancies due to initial mis-diagnosis. These cases highlight the need for vigilance when treating a presumed ectopic. Furthermore, while it is classic teaching to avoid biopsy, when the diagnosis is uncertain and a safe biopsy is possible in a controlled environment, it should be considered. Last, acknowledgement of chemo-

resistance is crucial and rather than continuing administration of futile therapies, early consideration of surgery among select individuals is key.

3. Conclusion

Surgical resection of pulmonary metastases of GTN is effective and should be considered in carefully selected individuals. After failing various chemotherapy regimens, both of our patients achieved durable remission with pulmonary wedge resection.

Author contribution

JS was a major contributor in reviewing the literature and organizing and writing the Discussion portion of the text. SP was a major contributor in chart review of the cases and organization of the Case portion of the text. LD was a major contributor in synthesizing and editing the manuscript. All authors reviewed and approved the final manuscript.

Declaration of Competing Interest

The authors have no relevant conflicts of interest to disclose

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