A Case of Refractory Gestational Trophoblastic Neoplasia requiring Hysterectomy after Methotrexate

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INTRODUCTION

Gestational trophoblastic neoplasia (GTN) refers to a group of malignant conditions that develop due to abnormal fertilization causing abnormal proliferation of tissue. GTN is primarily treated with surgical evacuation of the underlying proliferative tissue. Approximately half of cases of GTN arise from molar pregnancy[1]. GTN include invasive moles, choriocarcinomas, placental-site trophoblastic tumors and epithelioid trophoblastic tumors. The most common risk factors associated with GTN are prior molar pregnancy, advanced maternal age (>40 years of age), and Asian and Native American ancestry[2-4]. Following evaluation of a molar pregnancy, a post-molar GTN is diagnosed based on the International Federation of Gynecology and Obstetrics (FIGO) criteria, which includes elevated human chorionic gonadotropin (hCG) levels, hCG levels increasing >10% across three values recorded over a two-week duration, weekly hCG level plateauing (remaining within +/- 10% of the previous week's results) over a three-week period, and persistence of detectable serum hCG for more than six months after molar evacuation[5]. A pathologic diagnosis of prior molar pregnancy by curettage with increased hCG levels also would be acceptable for diagnosis. According to the World Health Organization scoring system of GTN, factors including age, antecedent pregnancy, interval months from index pregnancy, pretreatment HCG, largest tumor size, site and number of metastases and previous failed chemotherapy help stratify the risk of patients and determine the type of treatment (**table 1**).

CASE REPORT

A 30 year-old female with a history of hypertension and chronic sinus tachycardia was found to have a complete molar pregnancy at the time of her 8-week ultrasound. A subsequent D&C was performed, and D&C pathologic findings demonstrated an invasive mole. She was found to have a hCG level of 7,000. One week later, her hCG was 15,387. The following week, her hCG was found to be 23,883. A pelvic ultrasound demonstrated findings consistent with thickened, heterogeneous and hypervascular endometrium with cystic areas, consistent with possible residual or recurrent molar pregnancy; however, a mass was never seen on imaging. Given her pathologic findings and serum values, she was classified as a low-risk GTN. Between July 2018 to August 2019, she was treated for her low-risk GTN with a regimen including methotrexate (MTX) 80 mg SQ three days a week alternating with leucovorin. She completed 19 cycles of methotrexate and achieved normalization of hCG levels with 3 normal values recorded (**table 2**).

However, increasing hCG levels two months after cessation of methotrexate led to concern for residual disease. As such, she was referred to our center for a second opinion. She was classified as FIGO stage I with a WHO score of 6 points, due to: time frame of 12 months since index pregnancy, baseline hCG and previous utilization of single drug (**table 1**). Her serum hCG increased to 110, leading to the resumption of MTX. She initially responded well to retreatment with MTX, demonstrating undetectable HCG levels for almost three months. After three months, her hCG again began to increase while on treatment (**table 2**). Possible treatment options at that point included actinomycin-D, EMA/CO, avelumab and radical hysterectomy. The patient had completed child bearing and elected to undergo a radical abdominal hysterectomy- bilateral salpingectomy. Post-surgical pathology ultimately demonstrated a gestational trophoblastic tumor, most consistent with choriocarcinoma invading into the myometrium. Her post-operative HCG was undetectable.

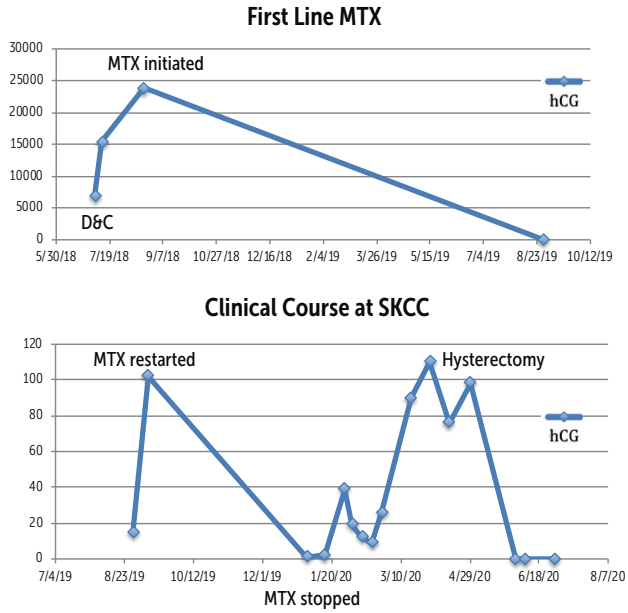
Table 1: Staging & Prognostication

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

Modified WHO Prognostic Scoring System as Adapted by FIGO[b]

Scores	0	1	2	4
Age	<40	≥40	–	–
Antecedent pregnancy	mole	abortion	term	–
Interval months from index pregnancy	<4	4–6	7–12	>12
Pretreatment serum hCG (iu/l)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Largest tumor size (including uterus)	<3	3–4 cm	≥5 cm	–
Site of metastases	lung	spleen, kidney	gastrointestinal	liver, brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	single drug	≥2 drugs

Table 2: Clinical Course



DISCUSSION

Complete hydatidiform mole and choriocarcinoma are rare, distinct disease processes with characteristic histologic and clinical features. In North America, there is a 0.1% incidence of molar pregnancy in all pregnancies. Although rare, low-risk GTN due to molar pregnancy is almost always curable with single-agent chemotherapy. A 2016 Cochrane database meta-analysis compared chemotherapy regimens for low-risk GTN and concluded that although pulsed actinomycin-D may achieve high primary cure with less chance of treatment failure in women with low-risk GTN, worsening serious adverse events were seen with this regimen than with a methotrexate regimen[6]. Actinomycin-D (Act D) may be used for patients who cannot tolerate methotrexate due to side effects of hyperemesis, alopecia and tissue extravasation. In a clinical trial in low-risk GTN, patients with a hCG value >4000 IU/L were found to respond poorly to Act D[7]. Alternatively, a study examining 1072 low-risk GTN patients with WHO score <6 demonstrated that hysterectomy as a first-line treatment is effective without salvage chemotherapy in approximately 82% of these patients. However, it was also concluded that young patients, such as the case mentioned above, should be considered for single-agent chemotherapy instead of surgery-only, as chemotherapy has been almost always curative while maintaining fertility[8,9].

In high-risk or refractory GTN, consideration can be given to combination chemotherapy with cyclophosphamide and vincristine (EMA/CO). The cumulative 5 year survival rate for these patients is greater than 85%, and patients who developed resistance to this regimen generally were salvaged by further cisplatin-based chemotherapy and surgery. For low risk GTN patients who are resistant to single-agent MTX or Act D, preliminary data from a phase II multicenter, cohort trial investigating the anti-PDL-L1 antibody avelumab has shown promise, with 8 out of 15 patients demonstrating 8 months of complete response[10]. Due to this promising data, many ongoing clinical trials in the low-risk GTN population include immunotherapy as a single agent or in addition to MTX (NCT03135769, NCT04303884).

CONCLUSION

Although complete molar pregnancy related GTN is a generally rare condition, low and high-risk tumors have a high cure rate with chemotherapy. In the above case, our patient had low-risk GTN, however, given she had an increase in hCG upon cessation of single-agent methotrexate she had evidence of persistent disease or possible relapse. Treatment options for this included hysterectomy, which the patient elected to undergo. Hysterectomy led to undetectable post-operative HCG levels, and surgical pathology proved that her underlying etiology was choriocarcinoma.

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