Persistent trophoblastic neoplasia in the broad ligament, a case report

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Abstract

Gestational trophoblastic neoplasia (GTN), a malignancy arising from trophoblastic tissue of pregnancy, is an aggressive disease process with a high probability of metastasis if left untreated. This is a case report on metastatic invasive mole arising from a molar pregnancy. Four months after suction curettage, a mass was noted in the left broad ligament on exploratory laparotomy with intact uterine serosa. Clinical presentation, biochemical, and radiological parameters led to a diagnosis of persistent trophoblastic disease. Histopathological findings also confirmed the diagnosis. Prompt chemotherapy was given after removal of the left intraligamentary mass, and subsequent response to treatment was documented. We report a case demonstrating a different clinical presentation of invasive mole and its potential to metastasize to the broad ligament without uterine perforation or direct extension.

Key words: Gestational trophoblastic neoplasia, hydatidiform mole invasive, methotrexate chemotherapy, postmolar gestational trophoblastic disease

Gestational trophoblastic neoplasia (GTN), the malignant end of gestational trophoblastic diseases (GTD), may arise either from premalignant conditions such as complete and partial hydatidiform or from non-molar pregnancies. Development of GTN is mostly from postmolar gestations (50%) compared to history of abortion or ectopic gestation (25%) or history of normal deliveries (25%).[1] Complete molar pregnancy compared to partial hydatidiform has a higher incidence of malignant complications (post-molar GTN, local proliferation and metastasis)

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GTN encompasses four histopathologic disease types of which invasive mole is the most common localized GTN.[2] It is characterized as invasion beyond the normal placental site into the myometrium and often including the venous system. Its metastatic potential may lead to complications such as massive intraperitoneal hemorrhage or pulmonary symptoms. Invasive mole without myometrial invasion and a pulmonary component is rare.[3]

This case highlights the variable presentations of GTN, which might easily cause misdiagnosis and delayed treatment. Low risk GTN is chemosensitive and responds well to treatment. Therefore, early diagnosis and prompt initiation of management is essential for a successful course and preservation of fertility.

The Case

A 22-year-old, G1P0 (0010), came in because of intermittent vaginal spotting with hypogastric pain associated with nausea and vomiting of four days. With a positive a pregnancy test, she had an ultrasound prior

to consult showing a normal sized empty uterus with a thin endometrium (0.57 cm). A left adnexal mass measuring 1.94cm x 1.47cm x 1.65cm (Figure 1) was noted with a consideration of an ectopic pregnancy.

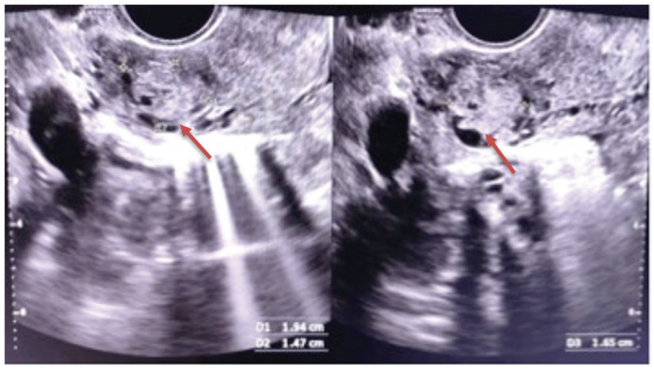

Figure 1. Initial transvaginal ultrasound, sagittal view showing a 1.94cm x 1.47cm x 1.65cm left adnexal mass (red arrow) probably ectopic pregnancy

Her previous pregnancy was a complete hydatidiform molar pregnancy where she underwent suction curettage four months prior to consult. Her baseline β-hCG was elevated at 816,276 mIU/mL. Pertinent diagnostics at that time revealed elevated liver enzymes and thyroid function tests. Imaging also showed a normal chest radiograph and hepatobiliary ultrasound showing no evidence of metastasis. She was discharged on the third postoperative day and was advised to monitor β-hCG, liver enzymes and thyroid function tests after one week. Despite counseling the patient was unable to comply with surveillance of β-hCG and contraceptive use. In the interim, the patient was allegedly asymptomatic but reported irregular vaginal bleeding episodes attributed to resumption of her menstrual cycle.

On examination, the patient was ambulatory and hemodynamically stable. Systemic findings were all within normal. Her abdomen was soft but with direct tenderness on the hypogastric area on deep palpation. On pelvic examination, the cervix was violaceous, smooth, with minimal clear non-foul-smelling discharge. Internal examination documented a closed cervix with cervical motion tenderness, a small uterus with left adnexal tenderness but no mass palpated. Rectovaginal exam revealed no further tenderness. Given the clinical presentation together with ultrasound finding of an adnexal mass, impression at this time was an ectopic pregnancy to rule out persistent trophoblastic disease (PTD). This was supported by an elevated β-HCG of 73,000 mIU/mL. Transvaginal ultrasonography showed an increased size of the previously identified left adnexal mass measuring 4.18cm x 3.82cm x 3.09cm posteromedial to the left ovary with minimal color flow (Figure 2). No fluid was detected in the abdomen and pelvis, however, a possible cornual ectopic pregnancy was also considered. Emergency exploratory laparotomy was contemplated.

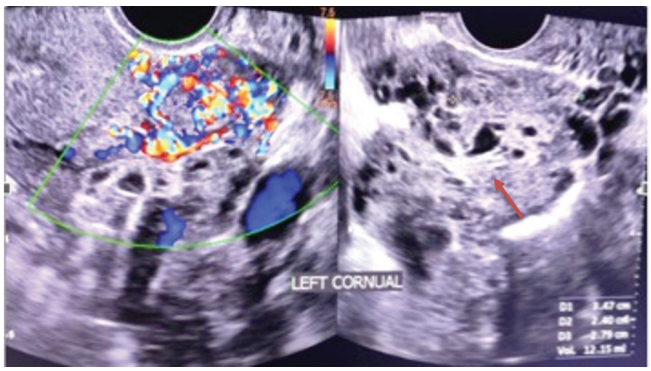

Figure 2. Follow up transvaginal ultrasound, sagittal showing a 4.18cm x 3.82cm x 3.09cm left adnexal mass posteromedial to the left ovary with minimal color flow.

The patient was placed in dorsal lithotomy position under regional anesthesia. The abdomen was entered through a vertical midline incision. Upon exploration, no hemoperitoneum appreciated. The uterus was grossly normal. A soft, irregularly shaped hyperemic mass measuring approximately 4cm x 4cm x 2cm was noted in the left broad ligament (Figure 3). The mass was isolated and had no distinct connection with the fallopian tube and uterus. The left fallopian tube was grossly normal and the absence of cornual pregnancy was confirmed. PTD was considered, thus an intraoperative referral to a gynecologic oncologist was done for further evaluation. Isolation and excision of mass was contemplated however active bleeding was noted while attempting to cut from the fimbriated end of the fallopian tube. In the background of a trophoblastic disease, excision of the mass and left salpingectomy was done to avoid profuse bleeding (Figure 4). The final histopathologic diagnosis was a complete hydatidiform mole with moderate trophoblastic proliferation, with paratubal chronic inflammation and fibrosis of the left fallopian tube (Figures 5A & 5B).

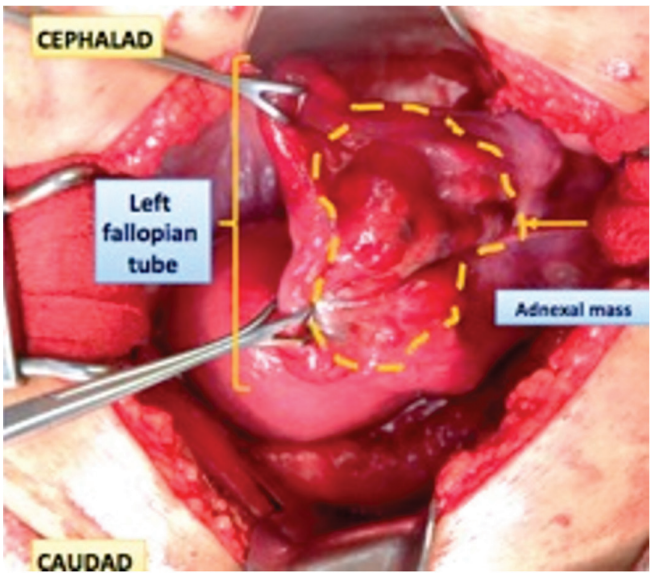

Figure 3. Intraligamentary 4cm x 4cm x 2cm soft, irregularly shaped, hyperemic mass in the left mesosalpinx of the broad ligament.

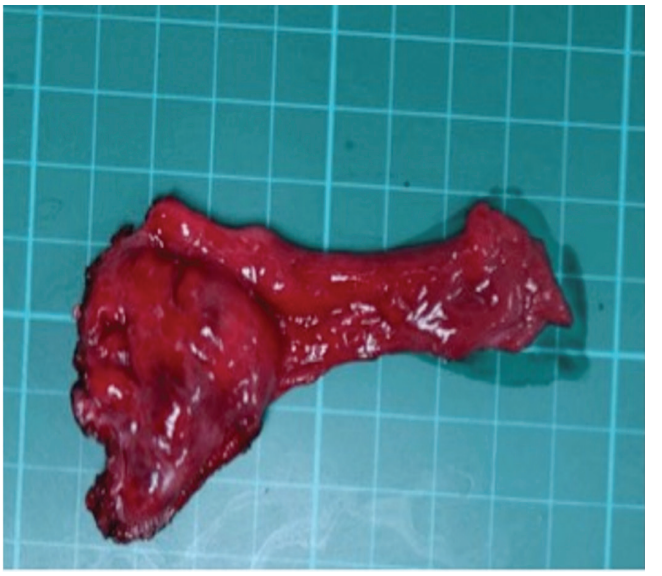

Figure 4. Left fallopian tube (5.5cm x 1.2cm x 1.0cm) with left adnexal mass.

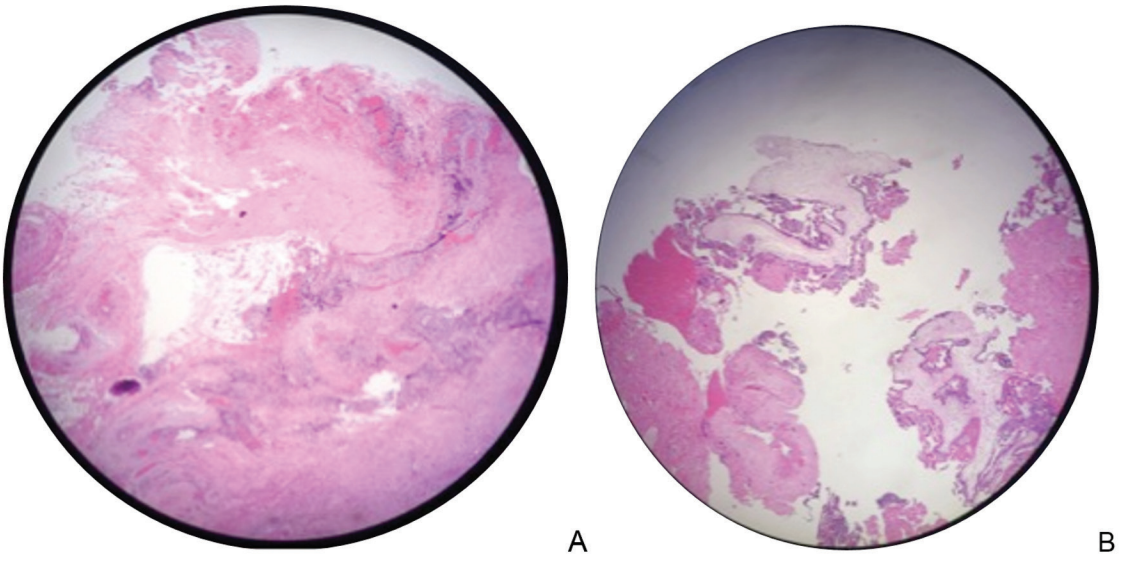

Figure 5. Microscopic examination of the (A) fallopian tube showing Intact luminal mucosal plicae with a surrounding intact fibromuscular layer and note of inflammatory infiltrates; (B) paratubal soft tissue showing hydropic chorionic villi with trophoblastic proliferation on the villous surface and the presence of inflammatory infiltrates (lymphocytes and plasma cells).

Combining the patient's symptoms, history of a complete molar pregnancy with previous suction curettage, and persistent elevated β-HCG, she was assessed as a case of GTN. Using the FIGO anatomical staging and WHO prognostic scoring system, the patient was classified as low-risk GTN and chemotherapy with methotrexate was started. Strict follow up with β-HCG monitoring and serial blood work up was done. Trends of β-HCG showed exponential decrease over the subsequent months with six cycles of chemotherapy as shown in Figure 6.

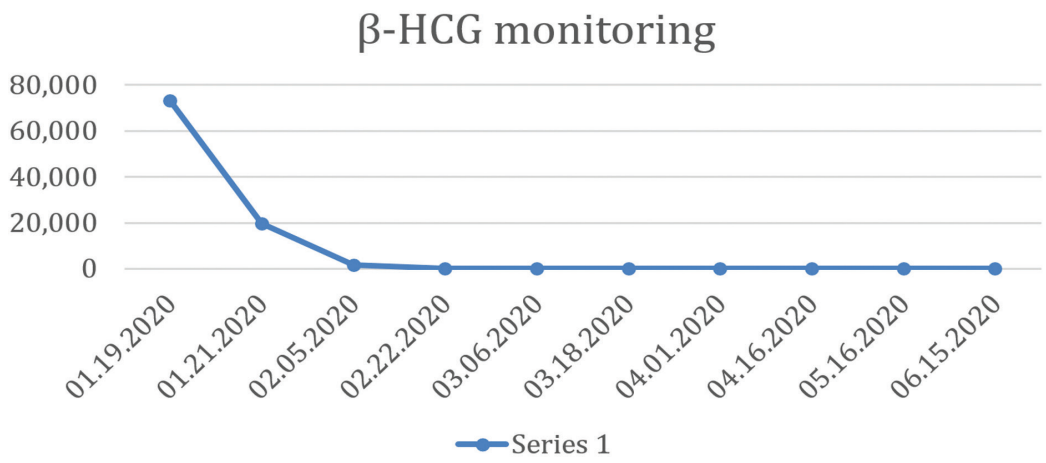

Figure 6. Serial monitoring of β–HCG showing a decrease in the levels.

Regular monthly monitoring and consultations were followed for the first six months since her procedure. On these consults, a thorough history and physical examination were done. On the patient's 6th postoperative month, the patient was hemodynamically and psychologically stable with normal systemic physical findings. Future pregnancies and family planning counseling, including strict compliance to contraceptive use for one year were discussed with the patient and her partner. In addition, early preconception consultation was emphasized. The long-term prognosis of disease as well as possible complications for future pregnancies (fetal abnormalities) were explained thoroughly.

Discussion

Gestational trophoblastic neoplasia (GTN), also referred to as postmolar trophoblastic neoplasia or persistent trophoblastic disease (PTD), is diagnosed based on FIGO 2000 criteria (β-hCG level remains elevated for 6 months or more).4 GTN results from a disruption of normal regulatory mechanisms controlling trophoblastic function such as myometrial implantation and production of β-hCG. It can aggressively proliferate and perforate the uterine wall, metastasize systemically and lead to maternal death if untreated.[1] Therefore, early detection of progression to GTN from a molar pregnancy (15-20% in complete H. mole and 0.5-5% in partial H. mole) is essential.[4] A history of previous molar pregnancy and extremes of reproductive age (< 15 and > 35 years) are two of the most important identifiable risk factors for GTN.[5] Although the patient is only 22 years old, GTD in general occurs within the reproductive age. This is evident in a study by Chhabra and Qureshi revealing a J-shaped age-specific incidence curve in GTN cases.[6] Other risk factors pertinent in this case for postmolar GTN include pretreatment hCG > 100,000 mIU/mL, enlarged uterus from date of gestation, uterus size > 16 weeks, and the presence of any medical complications associated with increased trophoblastic proliferation. The patient had a hydatidiform mole on the 14th week of her first pregnancy with uterine size of 18 weeks AOG. On her previous pregnancy, the patient was managed with molar-induced hyperthyroidism.

The clinical diagnosis of postmolar GTN relies on a complete and thorough medical history, clinical symptoms, and diagnostics (hormonal assay and imaging). Histopathology results although not necessary, aid in confirmation of disease.[2] The patient showed a typical course of disease and presentation of symptoms such as amenorrhea and vaginal bleeding. However, despite the patient's clinical background of previous molar pregnancy, a differential diagnosis of ectopic pregnancy was considered with an ultrasound finding of an adnexal mass and an empty uterus. At 6 1/7 weeks AOG by amenorrhea, she presented at the OPD with vaginal spotting and a positive pregnancy test, which is typical for both ectopic pregnancy and GTN. On physical examination, the patient had a small uterine size, which is not a typical presentation of a molar pregnancy. In contrast to GTD, the diagnosis of GTN is based on patient's clinical presentation.

More so, the pathological diagnosis of invasive mole is rarely reported due to conservative fertility sparing management. With only 2% of ectopic pregnancies located in the cornual area and a background of previous complete molar pregnancy in less than six months, with neither β-hCG, nor chemoprophylaxis, a persistent gestational trophoblastic disease cannot be totally ruled out.

Pathologic features of complete H-mole with direct invasion into the myometrium and beyond the placentation site defines invasive mole, a locally invasive trophoblastic neoplasia. Its aggressive trophoblastic growth characteristics lead to destruction, penetration, and invasion of myometrial wall and eventually parametrium and uterine vasculature. It is usually confined within the uterus and extra uterine involvement occurs in 5% of complete hydatidiform mole, and rarely in partial hydatidiform mole.[1] Its potential for metastasis to distant sites such as the lungs, liver, and brain can occur from hematogenous or lymphatic spread. However nearby metastasis to the vagina or adjacent pelvic area are mostly through direct extension.[7]

In a study by Shen, a metastatic invasive mole was diagnosed secondary to an iatrogenic uterine perforation despite having no myometrial invasion histologically. Molar lesions found at the pelvic peritoneum, posterior uterine serosa, and omentum metastasized by direct spread through the perforated site.[8] This patient had an atypical invasive mole with metastasis to the broad ligament with no evidence of myometrial invasion more and no uterine rupture. Due to the lack of reports of metastasis to the broad ligament, the exact pathophysiology for this atypical disease presentation remains unclear. Possible explanations were considered to rationalize and clarify etiology of disease.

In a study by Moser, trophoblast invasion happens in all luminal structures in the placental bed such as arteries, veins, lymphatics and glands. Prior to endoarterial invasion, trophoblasts were observed to have invaded large caliber veins and lymphatics as early as five weeks of pregnancy. Endovenous and endolymphatic trophoblastic invasion function to connect vessels to the intervillous space for removal of waste products and fluid balance.[9]

Wong hypothesized that distant metastasis occurred by intravasation to blood vessels or lymphatic routes. The trophoblastic cells may prefer the lymphatic route due to its permeability from lack of tight interendothelial junctions and reduced shear fluid flow. In his study, morphological differences and accessibility of a vascular pathway contribute to this route of metastatic spread.[10] In support of the former theory, Kleppe studied lymphatic drainage pathways of the ovaries and Hironori also confirmed lymphatic routes in the broad ligament.[11,12] The broad ligament contains lymph vessels accompanied by the uterine ovarian anastomosis alongside the whole corpus. Presumably there is an element of stasis in this region as it is a site of predilection for secondary deposits from the uterus region. This theory of the pathophysiology of an independent invasive mole without uterine rupture has not been verified by any studies. This anatomical relationship most likely explains the spread of metastasis and is compatible with patient's case presentation and disease pattern.

GTN is typically sensitive to chemotherapy as well as continued β-HCG monitoring. Treatment success is about 80-90%. The cure rate may increase to 100% with appropriate initial classification and proper treatment. The patient belongs to the low-risk group based on FIGO prognostic score; hence methotrexate alone was given. Chemotherapy was continued until response to treatment was noted via documentation of three consecutive normal serum β-HCG levels (< 5 mIU/mL).[2] Thorough surveillance for evidence of drug resistance (plateau or increase in β-HCG) was done since 30-50% of patients develop resistance to first line-chemotherapy agents and 5-15% may require multi-agent chemotherapy and/or other modalities. The patient has been on close follow up since surgery and has shown good response evidenced by an exponential decline in β-HCG. After six cycles of single agent methotrexate, the patient had three consecutive normal β-HCG levels.

Patient was reassured of a high overall survival rate for GTN which is attributed its high sensitivity to chemotherapy and effective surveillance of β-HCG. With this, the patient was started on oral contraceptives and was informed of possible complications (spontaneous miscarriage, stillbirths, repeat molar pregnancy) if pregnancy occurs within one year. The patient and her partner are both desirous of pregnancy. Garcia reviewed 18 articles and reported that chemotherapy did not show a decrease in fertility, however, those who conceived within six months of treatment had increased abortion rates.[13]

Family counseling and psychosocial counseling was done. It was emphasized that first trimester ultrasound and serum β-HCG testing are indicated for the first pregnancy after treatment of GTN to establish a normal intrauterine pregnancy. Moreover, a repeat quantitative β-HCG should also be requested postpartum to assure that there is no recurrence of GTN.

Summary

This case highlights the different clinical presentations of GTN. Possible etiologies were examined and correlated with the clinical presentation. The high invasive ability of trophoblastic disease should always be considered and help broaden the perspective of the disease process. GTN accounts for less than 1% of cancers among women and is highly treatable with cure rates of 80 to 90% with intensive therapy.

Invasive mole with metastasis is a rare occurrence. Its early detection is important because it is responsive to chemotherapy with high remission rates. A complete and thorough history and physical examination cannot be overemphasized. A history of a prior molar pregnancy and other risk factors should immediately prompt a high index of suspicion for a possible GTN. Determination of serum β-HCG levels, with subsequent monitoring is recommended. Management of such patients is individualized with consideration of fertility preservation. The patient should be counseled postoperatively regarding future pregnancies.

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