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Case series

Gestational trophoblastic neoplasia presenting as an interstitial ectopic pregnancy

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ABSTRACT

Gestational trophoblastic disease (GTD) is a group of benign and malignant tumors that develop from placental tissue and includes hydatidiform moles and gestational trophoblastic neoplasia (GTN). Invasive molar disease and choriocarcinoma are rare forms of GTN and can arise from any pregnancy event. An interstitial ectopic pregnancy occurs with implantation within the intramural portion of the fallopian tube covered by myometrium. We present two cases of an invasive mole with pathology consistent with choriocarcinoma in situ arising from an interstitial ectopic pregnancies. We review management strategies including a minimally invasive surgical approach. Additionally we present a review of the literature of gestational trophoblastic disease associated with interstitial ectopic pregnancies.

1. Introduction

Gestational trophoblastic disease (GTD) is a group of benign and malignant tumors that develop from placental tissue and includes hydatidiform moles and gestational trophoblastic neoplasia (GTN). Invasive molar disease and choriocarcinoma are rare forms of GTN and can arise from any pregnancy event, including term or and preterm pregnancies, spontaneous abortions, ectopic pregnancies or molar pregnancies Lurain, 2010.

Ectopic pregnancy describes all pregnancies that occur outside the uterine cavity, and are a frequently encountered diagnosis in the field of obstetrics and gynecology. An interstitial ectopic pregnancy occurs with implantation within the intramural portion of the fallopian tube covered by myometrium and is a rare event (Malinowski and Bates, 2006).

We present two cases of an invasive mole with pathology consistent with choriocarcinoma in situ arising from an interstitial ectopic pregnancies. We also present a review of the literature of gestational trophoblastic disease associated with interstitial ectopic pregnancies.

2. Case presentation

2.1. Case 1

The patient is a 31-year-old Asian G4P2012 female with an uncertain last menstrual period who presented to the Emergency Department with vaginal bleeding. She was otherwise healthy with no medical problems. Her obstetrical history was notable for two prior cesarean sections and a spontaneous abortion. On presentation, she was hemodynamically stable. Pelvic exam was notable for an 8-week-sized uterus with mild right adnexal fullness and associated mild tenderness as well as a small amount of vaginal bleeding. Laboratory evaluation revealed anemia with hemoglobin of 9.1 gm/dL, and a beta human chorionic gonadotropin (b-hCG) of 103,724 mIU/mL. Transvaginal ultrasound demonstrated a 31 × 43 × 31 mm mass arising from the right cornua containing echogenic internal debris and significant peripheral vascular flow, concerning for an ectopic pregnancy (Fig. 1).

The patient underwent laparoscopic right cornual wedge resection and right salpingectomy. Intraoperative findings were notable for a mildly enlarged uterus with a right cornual mass consistent with a right interstitial ectopic pregnancy (Fig. 2). Intraabdominal survey was otherwise unremarkable. Histologic examination demonstrated exuberant triphasic atypical trophoblast proliferation consistent with

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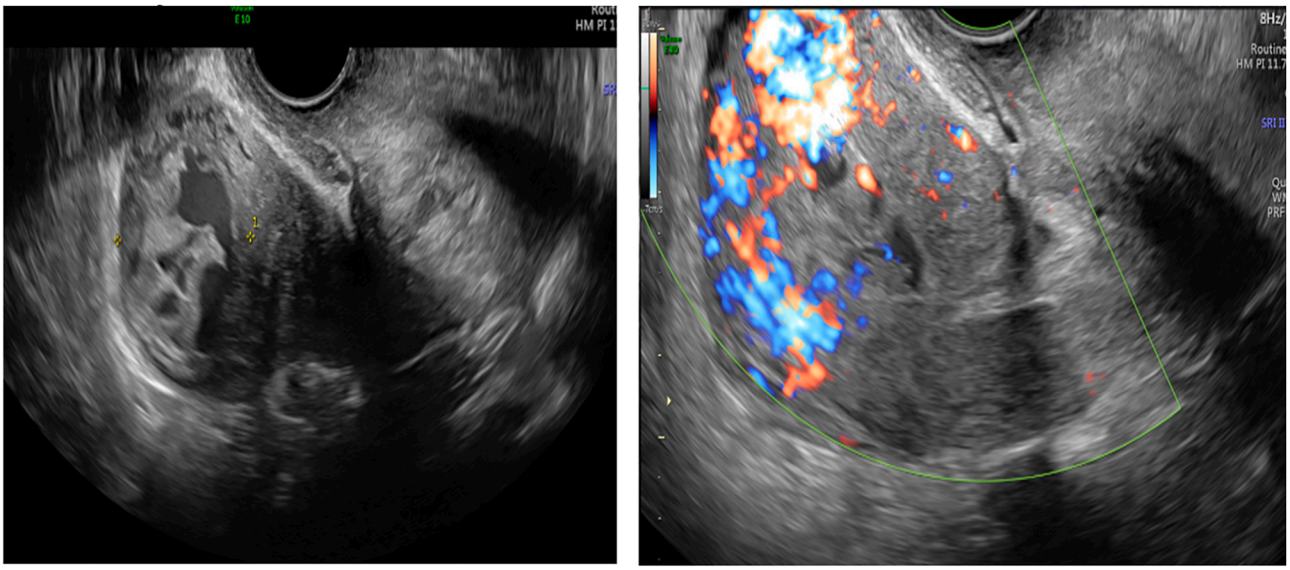

Fig. 1. Transvaginal ultrasound images demonstrate 31 × 43 × 31 mm mass arising from the right uterine cornua containing echogenic internal debris and significant vascular flow.

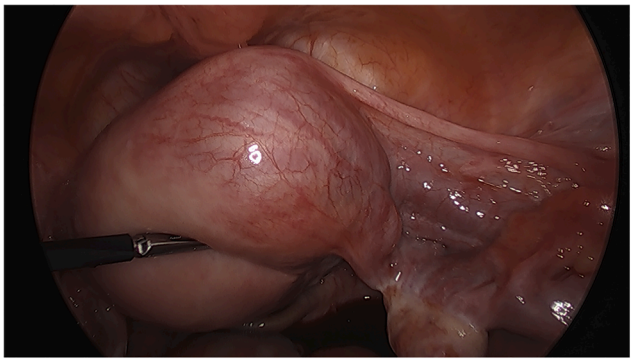

Fig. 2. Intraoperative findings demonstrate a 6 cm right uterine cornual mass consistent with a right interstitial ectopic pregnancy.

gestational trophoblastic neoplasia as well as occasional molar villi seen deep within the myometrium, concerning for an invasive mole (Fig. 3).

The patient was referred to Gynecologic Oncology for further management. Chest x-ray was negative for evidence of metastatic disease. Initially, the patient's b-hCG decreased to 2,489 mIU/mL, and the decision was made to continue observation. She was initiated on combined oral contraceptive pills for contraception. The patient's b-hCG nadired at 886 mIU/mL and subsequently exhibited a > 20% increase in three values over two weeks to 2,274 mIU/mL. Thus, the patient met criteria for stage I low risk GTN with a WHO score of 5. Methotrexate 0.4 mg/kg IM for five days every 14 days was initiated. The first cycle was complicated by severe mucositis for which day five was held and subsequent cycles were reduced to three days. B-hCG values normalized during cycle two, and she received three additional cycles of methotrexate without complication. At the time of most recent follow-up three months following therapy completion, the patient had no evidence of disease and a negative b-hCG.

2.2. Case2

This is a 27 year old Caucasian G2P2012 female who presented to the Emergency Department with acute onset lower abdominal pain, emesis and weakness. She was otherwise healthy with no medical problems, and past surgical history notable for laparoscopic right salpingoophorectomy for a tubovarian abscess. The patient was hemodynamically stable, and physical exam was notable for a tender and slightly distended abdomen. Laboratory evaluation revealed hemoglobin on 14.2 gm/dL,

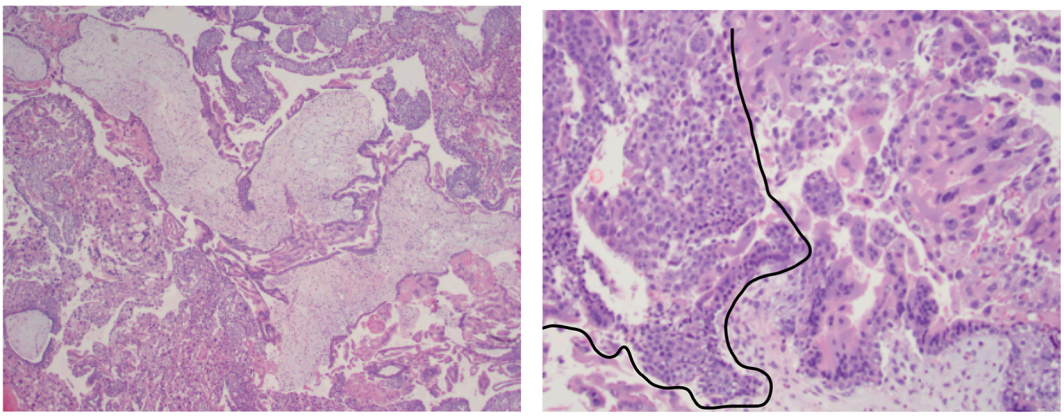

Fig. 3. Low power (3A) and high power (3B) histology demonstrate exuberant triphasic atypical trophoblast proliferation consistent with gestational trophoblastic neoplasia with abundant atypical intermediate trophoblast proliferation invading into myometrium concerning for early "intra-molar" choriocarcinoma versus invasive mole. In (3B) the intermediate trophoblasts have been outlined.

Table 1
Literature review of gestational trophoblastic disease associated with interstitial ectopic pregnancy.

Author	Patient Characteristics	b-hCG at presentation	Imaging	Histology	Treatment	Outcomes
Venturini et al. (2001)	31 yo with vaginal bleeding, abdominal pain History of abdominal myomectomy	13,380	US: no IUP, subserous 2 cm echogenic mass on left fundus HSG: intramural echogenic mass separate from uterine cavity	Choriocarcinoma	Dx lsc and D&C Two days later laparotomy and cornual wedge resection Single course methotrexate	NED at 2 years
Han and Kaye (2018)	38 yo G5P2212 with vaginal bleeding, abdominal pain History of ectopic s/p D&C, MTX × 1	79,465	US: no IUP, 5.6 cm left cornual mass with peripheral hypervascularity and subserosal hemorrhage extending to left lateral fundus	Cornual ectopic pregnancy Subsequent vaginal wall biopsy with metastatic choriocarcinoma	MTX × 1 Dx lsc, TAH/BS EMACO	n/a
Rotas et al. (2007)	35 yo G8P2052 with ectopic pregnancy s/p failed treatment History of prior ectopic × 2 s/p RS	1,900	US: no IUP, thin endometrium MRI diffusely heterogeneous mildly enlarged uterus with fibroids	Choriocarcinoma	MTX × 3 D&C Hysteroscopy, dx lsc, left cornual wedge resection Single agent MTX	NED at 4 months
Meddeb et al. (2014)	46 yo G4P3 with vaginal bleeding, abdominal pain	6,320	US: no IUP, 3 cm intramural echogenic mass at left fundus	Choriocarcinoma	Single dose MTX Dx lsc, left cornual wedge resection Represented with acute hemorrhage: underwent emergent hysterectomy	NED at 2 years
Khlifi et al. (2016)	40 yo G1 with abdominal pain	27,624	US: no IUP, 4 × 4 cm heterogenous vascular left uterine mass	Invasive mole	MTX × 3 cycles Dx lsc, mini-laparotomy, LS, left cornual wedge resection	NED at 48 weeks
Siegal, et al[3]	27 yo G6P2 with abdominal pain, nausea, vomiting	n/a	n/a	Hydatidiform mole	MTX × 8 cycles Laparotomy, supracervical hysterectomy	Post-op course complicated by rapidly enlarging pelvic mass, sepsis and internal hemorrhage; DOD
Chau et al. (2019)	25 yo History of invasive mole 5 years prior	2,989	US: 3.4x3.4x3.8 cm echogenic hypervascular mass in right fundus	Choriocarcinoma, recurrent	Mini-laparotomy with right corneal wedge resection, salpingectomy	NED at 2 years
Oskovi Kaplan et al. (2018)	24 yo with abdominal pain, vaginal bleeding	75,144	US: possible 3 mm gestational sac, 4.1x3.7 cm left adnexal mass	Invasive mole	EMACO × 4 cycles Laparoscopic resection of rudimentary horn	NED
Chen et al. (2017)	32 yo G2P0 with abdominal pain History of molar pregnancy s/p D&C 3 months prior	58,789	US, MRI: solitary left cornual heterogenous mass	Gestational trophoblastic neoplasia	Left cornuostomy MTX × 2	NED at 16 months
Hwang et al. (2010)	41 G0 with vaginal bleeding History of TAB s/p D&C 2 months prior	57,738	US: Hematometra, muticystic echogenic lateral uterine mass with Doppler flow	Partial mole	Left cornuostomy Adjuvant MTX	n/a
Chauhan et al. (2006)	41 yo P3 with AUB, abdominal pain	2,905 97,000	US: Hyperechoic mass in posterolateral uterine wall	Molar pregnancy Partial mole	TAH for suspected fibroid and AUB	NED at 3 weeks n/a

(*continued on next page*)

Table 1 (*continued*)

Author	Patient Characteristics	b-hCG at presentation	Imaging	Histology	Treatment	Outcomes
Zite et al. (2002)	Female with nausea, vomiting, abdominal pain		US: Intrauterine molar pregnancy near fundus		Dx lsc, laparotomy, cornual wedge resection, D&C	
Fang et al. (2014)	28 yo G2P1 with amenorrhea × 3 months	2,764	6 cm right adnexal mass	ETT	Dx lsc, laparotomy, right cornual wedge resection	n/a

Abbreviations: yo: year old; n/a: not available; s/p: status post; US: ultrasound; IUP: intrauterine pregnancy; dx lsc: diagnostic laparoscopy; TAH: total abdominal hysterectomy; RS/LS: right/left salpingectomy; NED: no evidence of disease; MTX: methotrexate; DOD: dead of disease; EMACO: etoposide, methotrexate, actinomycin-D, cyclophosphamide, vincristine; TAB: therapeutic abortion; AUB: abnormal uterine bleeding; ETT: epithelioid trophoblastic tumor.

and b-hCG of 23,397 mIU/mL. Transvaginal ultrasound demonstrated a large amount of free fluid in right adnexa and anterior and posterior cul-de-sacs extending to the abdomen without evidence of intrauterine pregnancy.

The patient initially underwent diagnostic laparoscopy which noted hemoperitoneum and a deeply embedded right interstitial pregnancy. The decision was made to proceed with laparotomy and open cornual wedge resection. Histologic examination revealed villous trophoblasts with large, pleomorphic nuclei and consistent with choriocarcinoma.

Initially, the patient's b-hCG values decreased but subsequently demonstrated a $>$ 20% increase in three values over two weeks. She was referred to Gynecologic Oncology. Computed tomography of the chest, abdomen and pelvis revealed pulmonary nodules consistent with metastases but no evidence of intraabdominal disease. Brain MRI was performed for persistent headaches and did not reveal evidence of metastasis. Patient met criteria for stage III GTN with WHO score of 4. Methotrexate 0.4 mg/kg IM for five days every 14 days was initiated, and b-hCG normalized after cycle two. The patient received a total of five cycles, and she had no evidence of disease with a negative b-hCG at the time of most recent follow-up18 months after therapy completion.

3. Discussion

GTD is a group of benign and malignant tumors that develop from placental tissue and includes hydatidiform moles and GTN. GTN is a rare diagnosis, carries metastatic potential, and includes invasive moles, choriocarcinoma, placental site trophoblastic tumors (PSTT), and epithelioid trophoblastic tumors (ETT). GTD can arise from any pregnancy event, including term or preterm pregnancy, spontaneous abortion, or ectopic pregnancy. Ectopic pregnancies are pregnancies with implantation that occurs outside the uterine cavity, accounting for only two percent of all reported pregnancy events. An interstitial ectopic pregnancy occurs when implantation occurs within the intramural portion of the tube covered by myometrium. Often, interstitial ectopic pregnancies are incorrectly termed cornual ectopic pregnancies; however cornual ectopic pregnancies are implantations that occur in the horn of uteri with Mullerian abnormalities Malinowski and Bates, 2006. Individually, the incidence of interstitial ectopic pregnancies and molar pregnancies is very low, and cases of GTD arising from interstitial pregnancies are extremely rare Lurain, 2010. Herein we present two cases from our institution where this unique clinical scenario occurred.

We performed a literature review of reported cases of GTD arising from interstitial ectopic pregnancies. A MEDLINE search using the keywords "interstitial ectopic," "molar ectopic," and "ectopic choriocarcinoma" was performed. Given the often used but incorrect terminology of interstitial and cornual ectopic pregnancies, "cornual ectopic" was also included in the search. Case reports up until June 2020 were included. Case report language was restricted to English, and the reference lists of all articles were reviewed for additional eligible reports. The search yielded 13 cases for review (see Table 1).

Of the 13 cases, six were molar pregnancies (two partial moles, two invasive moles, and two unspecified), five were choriocarcinoma, one was ETT, and one was unspecified GTN. Presentation varied widely with some cases presenting months to years after initial treatment for a prior intrauterine molar pregnancy. Laboratory values revealed b-hCG values ranging from 1,900–97,000 on initial presentation. Imaging was primarily was with ultrasound, although MRI was also used as an adjuvant imaging modality. Management widely varied from cornuostomy with adjuvant methotrexate to hysterectomy. Cornual wedge resection is the most common surgical management, with a majority completed minimally invasively through laparoscopic approaches with or without minilaparotomy. Most patients had favorable outcomes, though one case was notable for a rapidly enlarging pelvic mass that resulted in internal hemorrhage and death shortly after the patient's initial surgical treatment Siegal and Rudolph, 1949.

In summary, we present two cases of an GTN arising from an interstitial ectopic pregnancy. Our first case represents unique pathology, demonstrating invasive mole with elements of early choriocarcinoma. Both cases support existing evidence that GTN arising from interstital pregnancies often have favorable prognoses with appropriate therapy.

Author contribution

Dr. Coralee Toal is the corresponding author of the research letter, and the contributing authors are Dr. Alison Garrett, Dr. Kostadinov and Dr. Michelle Boisen. All authors have made a significant contribution to this report, and all authors have read and approved the final version submitted.

Informed consent

Informed consent was obtained from all individual participants for who identifying information is included in this article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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