



Case report

Heterotopic atypical trophoblasts mimicking ectopic choriocarcinoma coexistent with a viable intrauterine pregnancy: A diagnostic dilemma

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1. Introduction

Choriocarcinoma can arise following any gestational event including term pregnancy, abortion, molar pregnancy, and ectopic pregnancy. It may also occur as part of a mixed germ cell neoplasm arising in the ovary or testes. Most commonly, choriocarcinoma occurs following a molar pregnancy. Ectopic gestational trophoblastic disease (GTD) is an extremely rare occurrence. In one study of 6708 patients referred to a GTD center, 42 had possible ectopic GTD and/or choriocarcinoma and only 12 of these were confirmed after histologic review (Hassadia et al., 2012). Of these, 4 patients had ectopic choriocarcinoma, 5 had partial moles, and 3 had complete moles. Fallopian tube ectopic choriocarcinoma coexisting with a concurrent intrauterine pregnancy is rarer, with only 5 cases reported in the literature (Cianci et al., 2014; Crisp, 1956; Lee et al., 2005; Zanetta et al., 1997). Histologic diagnosis of choriocarcinoma in setting of an early pregnancy is difficult, as atypical and proliferative trophoblasts are normal in an early conceptus. Here we present a case of a possible tubal choriocarcinoma coexisting with a viable intrauterine pregnancy and discuss diagnostic and management considerations.

2. Case report

The patient is a 33yo G6P4014 who presented to the emergency department at 4 + 6/7 weeks gestation age (WGA) by last menstrual period with acute right-sided abdominal pain. Her past medical history was notable for a postpartum bilateral tubal ligation in 2009, followed by subsequent tubal re-anastomosis performed abroad in 2016. Pelvic ultrasound demonstrated an intrauterine gestational sac without yolk sac or fetal pole, and free fluid in the pelvis. A β -hCG was 12,643 and she underwent a laparoscopic right salpingectomy for a suspected ruptured ectopic pregnancy.

One week post-operatively, her β -hCG rose to 20,775. Pelvic ultrasound revealed an intrauterine pregnancy measuring at 5 + 6/7 WGA, concordant with the LMP, with an appropriate fetal heart rate. An outside institution pathology review of the right fallopian tube reported

concern for choriocarcinoma arising in the fallopian tube with intramural and mucosal atypical trophoblastic proliferation focally involving the fimbriated end of the fallopian tube. Sections of the tube had multinucleate (syncytial) and mononucleate trophoblasts within the wall and lumen (Figs. 1 and 2). No chorionic villi or fetal tissue were identified. Given these findings, the patient was referred to Gynecologic Oncology clinic. She presented to clinic at 7 + 6/7 WGA. Physical exam was unremarkable and β -hCG showed an appropriate rise to 89,000. Chest X-ray and MRI of the abdomen and pelvis were negative for any evidence of metastatic choriocarcinoma, ongoing ectopic pregnancy, or any other acute findings.

Our institution's gynecologic pathology service reviewed the case and immunohistochemistry (IHC) and molecular genotyping was positive for p57, inhibin, and pancytokeratin, while negative for p63 (Fig. 3). Additionally, molecular genotyping utilizing microsatellite analysis was consistent with a biparental conception. Given these findings, along with a normal IUP on US, and an appropriate rise in β -hCG, her case was reviewed in our tumor board and we favored the diagnosis of a non-neoplastic trophoblast of a very early conception. This was a highly desired pregnancy and she was counseled for continuation of the pregnancy over termination and aggressive chemotherapy. However, the possibility of the earliest form of an intraplacental biparental choriocarcinoma could not be excluded therefore she was followed closely with serial β -hCGs which rose appropriately then plateaued. The remainder of her pregnancy was unremarkable. She delivered a viable male infant at term via normal vaginal delivery. The placenta was not sent for pathological examination. Her postpartum course was without complications, and she plans no further pregnancies.

3. Discussion

The histologic hallmark of choriocarcinoma is nests and sheets of atypical trophoblasts and syncytiotrophoblasts, usually without chorionic villi – although villi may be seen in the rare case of intraplacental choriocarcinoma (Jiao et al., 2016). The finding of a biphasic pattern of

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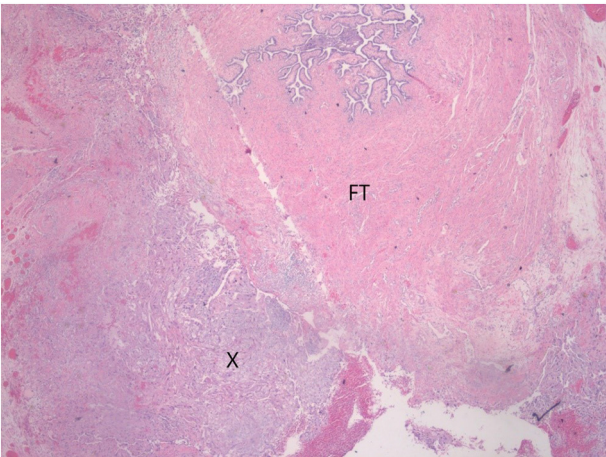


Fig. 1. Hematoxylin and eosin (H&E) showing fallopian tube (FT) adjacent to atypical trophoblastic proliferation (X).

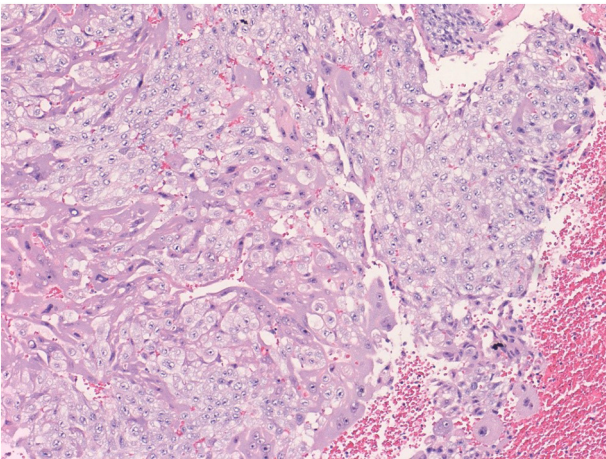


Fig. 2. Higher power view H&E staining of atypical trophoblastic proliferation.

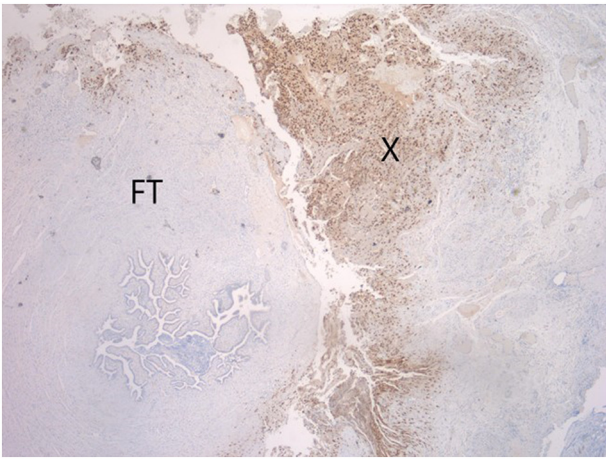


Fig. 3. Immunohistochemistry (IHC) staining for p57 showing strong positive staining (X).

highly atypical mononuclear trophoblastic cells in close association with multinuclear cells (syncytiotrophoblasts) is essentially pathognomonic of choriocarcinoma. However, the histologic diagnosis of choriocarcinoma in setting of an early pregnancy can be problematic (Table 1). Immature gestational tissue without villi and with trophoblasts showing atypical features may be encountered in curettage

Table 1
Histology and diagnostic features in the differential diagnosis of ectopic choriocarcinoma.

Histologic features	Nonmolar pregnancy		Hydatidiform mole		Choriocarcinoma	
	Endometrium and implantation site without villi may be encountered		Complete		Partial	
	Ki-67, PCNA, p53 negative		- Absent fetus/embryo - Diffuse swelling of villi - Diffuse trophoblastic hyperplasia		- Abnormal fetus/embryo - Focal swelling of villi - Focal trophoblastic hyperplasia	
Immunohistochemical markers	Ki-67, PCNA, p53 negative		p57 negative		p57 positive	
Parental origin	Biparental		Paternal (androgenetic)		Biparental Triploid	
	Intraplacental Cytokeratin diffusely positive in tumor cells		Post-normal gestation Strong staining for hCG, inhibin, and cytokeratin. Ki 67 diffusely expressed in half of the cells		Postmolar p57 positive	
	Most commonly paternal (androgenetic)		Biparental: identical to fetus Rarely, DNA complement of preceding pregnancy		Biparental	

performed for early pregnancy loss.

Based on morphologic features alone, the differential diagnosis included early non-molar conceptus, choriocarcinoma, and very early hydatidiform mole. IHC analysis for p57 excluded the possibility of a complete molar pregnancy; p57 is a paternally imprinted, maternally expressed gene whose expression indicates the presence of maternal DNA. Negative staining indicates a complete mole, lacking any maternal DNA, while positive staining argues for the presence of either a partial mole or a hydropic abortus (Duffy et al., 2015). In this case, positivity for p57 argued against a complete mole (Fig. 2). Additionally, molecular genotyping by analysis of DNA microsatellites was performed to assess for the presence of maternal versus nonmaternal DNA. Microsatellite analysis demonstrated a DNA pattern most consistent with a biparental conception. This argued against the presence of gestational choriocarcinoma, as gestational choriocarcinoma is purely androgenic (genetically paternal), except in the rare case of intraplacental choriocarcinoma (Savage et al., 2017). Intraplacental choriocarcinoma was considered highly unlikely given the early gestational age at time of presentation. Therefore, based on p57 staining and DNA microsatellite analysis supporting the presence of maternal DNA/biparental conception, the most likely diagnosis was a non-neoplastic abortus – although the very earliest form of an intraplacental choriocarcinoma could not be definitively ruled out.

Ectopic GTD is an exceptionally rare entity; risk factors are similar to risk factors for conventional ectopic pregnancy, including a history of pelvic inflammatory disease and previous pelvic surgery, as is seen in this patient's case (Hassadia et al., 2012). Prognosis for ectopic GTD is excellent, with most cases resolving with surgical management alone; close observation with monitoring of β -hCGs is needed (Hassadia et al., 2012). When chemotherapy is required, conventional chemotherapy is effective (Lee et al., 2005).

This case highlights the challenging diagnostic dilemma when there are histologic findings concerning for choriocarcinoma in setting of an early pregnancy. After extensive counseling with the patient and multidisciplinary discussion of her case, she elected to continue her pregnancy, which was ultimately uncomplicated, and she continues to be in excellent health at postpartum follow up.

Consent

Informed consent was obtained from the patient for publication of this case report.

Conflict of interest

The authors have no personal or financial affiliations to disclose.

Author contributions

Varvara Mazina wrote the manuscript with support from Christopher Morse, Rouba Hadi and Heidi Gray. Rouba Hadi obtained the Pathology images. All authors provided critical feedback, contributed to and approved the final version of the manuscript. Heidi Gray supervised the project.

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