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Case Report

Placental site trophoblastic tumor: Immunohistochemistry algorithm key to diagnosis and review of literature ☆

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Introduction

Placental site trophoblastic tumors (PSTTs) are the rarest subtype of gestational trophoblastic neoplasm (GTN), characterized by intermediate cytotrophoblasts on histology (Hyman et al., 2013). They typically occur in reproductive-aged females, arising months to years after a term gestation, but can be seen after any pregnancy (Hassadia et al., 2005). While most GTNs are exquisitely susceptible to chemotherapy, PSTTs are relatively chemoresistance (Schmid et al., 2009). Because hysterectomy is necessary for appropriate treatment, it is imperative that PSTTs be diagnosed correctly. We present a case of a patient who was presumed post-menopausal with no reported pregnancies and non-classical histological presentation of PSTTs.

Case report

A 53-year old G0P0 presumed post-menopausal woman presented to her gynecologist with postmenopausal bleeding. She had been on oral contraceptives for birth control until approximately 12 months prior and had a six-month bleeding-free interval before the onset of intermittent spotting. Pelvic ultrasound noted thickened endometrium measuring 2.2 cm. FSH was elevated to 32.3 mIU/mL (post-menopausal = 23.0–116.3 mIU/mL), indicating of her post-menopausal status. She underwent a dilatation and curettage (D&C).

Initial pathology was reported as poorly differentiated cancer and the patient was referred to a gynecologic oncologist. On additional review, there was suggestion of gestational trophoblastic disease. The tumor cells formed at least three discernible patterns: (1) large, well-formed, irregularly outlined syncytial aggregates, (2) smaller clusters, often linear, more uniform cells resembling cytotrophoblasts, and (3) collections of large cells with markedly enlarged hyperchromatic nuclei resembling extravillous (intermediate) trophoblasts (Fig. 1A–B). Frequent strong expression of multiple trophoblastic markers within these tumor cells suggested a trophoblastic neoplasm.

Quantitative hCG was elevated to 1517.7 mIU/mL. She underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymphadenectomy and omentectomy. Intraoperatively, the tumor appeared deeply invasive and necrotic, without evidence of disease outside the uterus.

Gross examination revealed abundant friable and necrotic tumor involving 80% of the endometrial cavity, abutting the uterine serosa, and measuring 5 cm in largest dimension (Fig. 2A–B). Fallopian tubes, ovaries and lymph nodes were benign.

Microscopic examination revealed extensive tumor necrosis. The dominant pattern was cytologically bizarre, large, infiltrative single neoplastic cells (Fig. 2C–D). After extensive sampling, no syncytiotrophoblasts were identified. On immunohistochemical staining, human placental lactogen (hPL), a germ cell tumor marker often positive in PSTTs, was positive. Beta hCG, and placental alkaline phosphatase (PLAP) demonstrated scattered positivity. Tumor cells were positive for inhibin and negative for p63 and CK5/6. Ki-67 highlighted a few scattered positive cells. The immunohistochemical profile argued against choriocarcinoma or epithelioid trophoblastic tumor. However, extensive tumor necrosis and the dominant pattern of cytologically bizarre, large, infiltrative single neoplastic cells are atypical for PSTTs. Taken together, the neoplasm was best characterized as an unusual malignant trophoblastic tumor of intermediate cell type. The monophasic pattern of the tumor without syncytiotrophoblasts plus the immunoprofile was most consistent with PSTTs.

The patient underwent a CT scan that was negative for metastatic disease. Since the disease was confined to the uterus, the patient was

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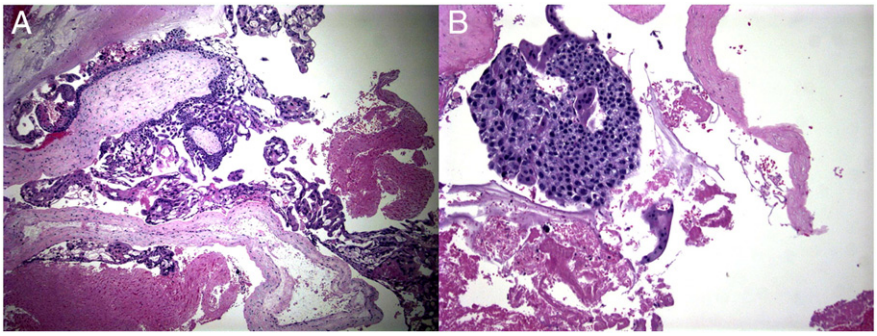

Fig. 1. Endometrial curettage. Histologically, the tumor cells form several discernible patterns. Some large, well-formed, irregularly outlined syncytial aggregates (A). Smaller clusters, often linear, tinier, and more uniform cells resembling cytotrophoblasts; and aggregates of large cells with markedly enlarged hyperchromatic nuclei resembling extravillous (intermediate) trophoblasts (B).

diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage I disease.

After discussion with the patient, the decision was made not to pursue adjuvant therapy. Monthly serum hCG and hPL have been negative for 10 months. She remains without evidence of disease.

Discussion

Placental site trophoblastic tumors were first described in 1981 by Scully and Young. They were considered to be a potentially malignant neoplasm arising from intermediate trophoblasts (Scully and Young, 1981). Since this initial description, approximately 300 cases have been reported in the literature.

PSTT typically presents in reproductive-aged females with irregular bleeding within two years of a normal term pregnancy. In a review of seven cases of PSTTs among 4998 cases of GTN, Gillespie described five of seven after normal female conception, one after multiple gestation and one with no recorded antecedent pregnancy (Gillespie et al., 2000). In a review of the literature, Baergen et al., found antecedent term pregnancy in 57% of cases, abortion in 17%, and with molar pregnancies accounting for 26% of cases (Baergen et al., 2006). Furthermore, while levels are often lower than in choriocarcinoma, they can be highly variable and may not correlate with either burden or outcome (Gillespie et al., 2000; Nigam et al., 2004).

While PSTT nearly two decades after the preceding pregnancy has been reported, this magnitude of interval is rare (Nigam et al., 2004). Post-menopausal PSTT is particularly rare. This diagnosis is difficult to ascertain, often presenting with amenorrhea, which can be overlooked in a perimenopausal setting (Nigam et al., 2004). Our patient was a G0 with long duration of OCP use, providing a low clinical suspicion for GTN.

PSTT derives from extravillous trophoblast. The term “intermediate” trophoblast is commonly used to represent all types of extravillous trophoblast (Baergen, 2011). PSTT shows high invasion and deep infiltration into the myometrium and can penetrate the uterine wall. PSTT typically lacks extensive hemorrhage though vascular involvement is common. Microscopic evaluation resembles trophoblastic infiltration but often appears as masses or sheets of cells with large, atypical nuclei (Shih, 2007). PSTT generally consists of round, polyhedral, or spindle cells with few multinucleated cells. The pathology of our patient's tumor showed the dominant pattern of cytologically bizarre, large, infiltrative single neoplastic cells, which could not discriminate between GTD and poorly-differentiated cancer. Notably, histologic morphology is frequently equivocal for PSTTs, with diagnosis depending upon immunohistochemical staining (Arato et al., 2000).

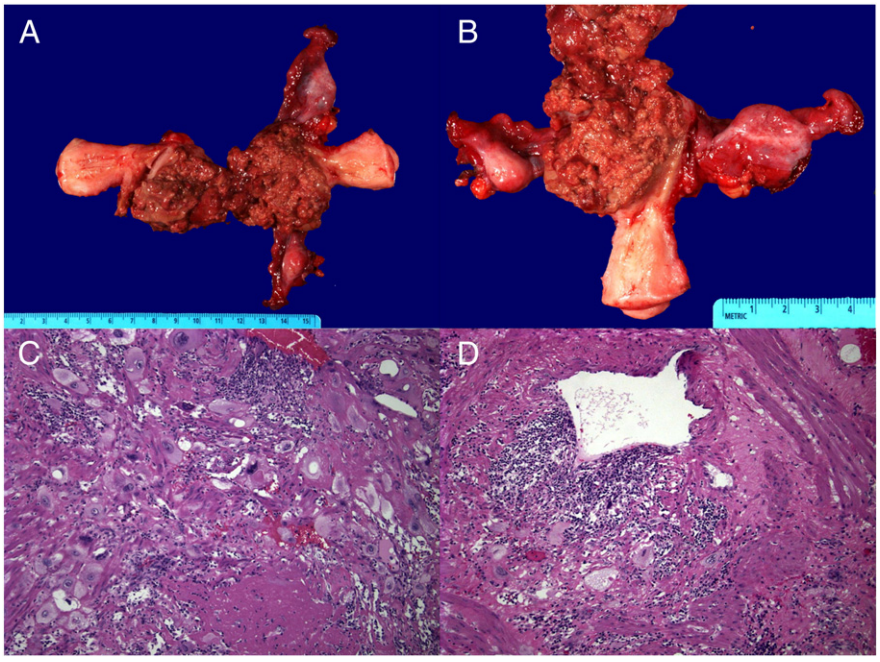

Fig. 2. Hysterectomy. Gross examination revealed abundant friable and necrotic tumor abutting the uterine serosa, and measuring 5 cm in largest dimension (A–B). The neoplasm demonstrates extensive tumor necrosis and the dominant pattern of cytologically bizarre, large, infiltrative single neoplastic cells (C–D).

Table 1
Outcomes for reported stage I cases treated with surgery alone.

	# of cases	Stage	Treatment	Disease status	Follow-up (years)
Hyman et al. (2013)	1	I	TAH/BSOw	1 NED	1.2
Hassadia et al. (2005)	6	I	TAH	6 NED	.25–11
Schmid et al. (2009)	17	I	TAH ± BSO ± LND	16 NED 1 Recurrence	2.3–10.0[a]
Gillespie et al. (2000)	3	I	TAH ± BSO	3 NED	3–10
Baergen et al. (2006)	33	I	TAH ± BSO	31 NED 1 AWD 1 DOD	1–13

TAH: total abdominal hysterectomy, BSO: bilateral salpingo-oophorectomy, LND: lymph node dissection, NED: no evidence of disease, AWD: alive with disease, and DOD: dead of disease.
[a] Follow-up time for all stages.

Shih provides a two-step model for differentiating confirmed trophoblastic lesions using p63, hPL, and Ki-67 stains (Shih, 2007). p63, a p53-like tumor suppressor, is used in differentiating PSTTs and exaggerated placental site (EPS) from other trophoblastic lesions, with positive staining associated with chorionic-type trophoblastic disease. Human placental lactogen (hPL), normally expressed by syncytiotrophoblast, is highly expressed in the trophoblasts of placental site trophoblastic tumors and EPS but minimally expressed in epithelioid trophoblastic tumors (ETT) and placental site nodules (PSN). Together, p63 and hPL can be used to differentiate implantation site trophoblastic disease from chorionic disease and choriocarcinoma. Ki67 is a marker of proliferation. In separating implantation site trophoblastic diseases, Ki-67 can be used to differentiate EPS from PSTTs. In PSTTs and ETT, 8–20% of cells will stain positive for Ki-67, whereas in EPS, the intermediate trophoblasts stain negatively for Ki-67. Lastly, B-hCG is used to identify choriocarcinoma. In this case, the tumor stained negative for p63 and positive for hPL with rare B-hCG positivity. These results are consistent with the trophogram results of implantation site lesions. Ki-67 staining was scattered positive, which is more consistent with PSTTs than EPS.

Clear diagnosis of PSTTs drastically alters the predicted clinical course and recommended treatment. While GTNs are generally exquisitely sensitive to chemotherapy, treatment of PSTTs is primarily surgical, particularly if the disease is confined to the uterus. In a review by Gillespie et al., patients with disease confined to the uterus were treated surgically without chemotherapy and remained disease free with follow-ups ranging from 3 to 9 years (Gillespie et al., 2000). Similarly, Hassadia et al., found no recurrences in stage I disease, with six of eight treated with surgery alone, with 3 months to 10 years of follow-up (Hassadia et al., 2005). Additionally, Schmid et al. provided evidence for less recurrence for local disease treated with surgery when compared to treatment with chemotherapy (Schmid et al., 2009). If the disease is widespread, prognosis is much poorer and chemotherapy may play a larger role. In the review by Gillespie, the two patients who died had metastatic disease at diagnosis (Gillespie et al., 2000). Hassadia's data exhibited a similar pattern: while disease confined to the uterus was treated surgically with good success, four of nine patients with metastatic disease died and one continued to have active disease at follow-up (Hassadia et al., 2005). In a review of 17 patients with PSTTs, Hyman et al. described nine patients with advanced disease all receiving cisplatinum-containing therapy. The three surviving patients had all received EP/EMA. Of the five stage IV mortalities, an average of four lines of therapy was used and median survival was 12.6 months (Table 1).

Prognostic factors for PSTTs include: mitotic index, time since antecedent pregnancy, serum beta hCG, necrosis, and depth of myometrial invasion (Baergen et al., 2006). In 2009, FIGO adopted a staging system that reflects extent of the disease coupled with a prognostic score modified from the World Health Organization criteria. Both interval time since antecedent pregnancy alone and FIGO stage have been shown to be strong prognostic factors. Our patient has stage I disease with a suspected antecedent pregnancy within the last year. Her tumor also lacked many of the concerning histologic features: vascular invasion, deep myometrial invasion, serosal involvement or a high-mitotic index (Schmid et al., 2009). Overall, this patient has a good prognosis for remaining disease-free after surgical treatment.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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