Placental Site Trophoblastic Tumor—A Challenging, Rare Entity

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Placental site trophoblastic tumor (PSTT) is a very rare and unique form of gestational trophoblastic disease (GTD). This tumor represents a neoplastic transformation of intermediate trophoblastic cells that normally play a critical role in implantation. PSTT can occur after a normal pregnancy, abortion, term delivery, ectopic pregnancy or molar pregnancy. Here we report a case of PSTT which was incidentally detected in the endometrial curetting of a 45-year-old woman and later confirmed on microscopic examination of the hysterectomy specimen.

A 45-year-old woman presented to the Department of Gynecology with the complaint of menorrhagia of 6 months' duration. Her past history included a spontaneous abortion 8 years before. Ultrasonography revealed multiple fibroids in the uterus. Speculum examination showed an endocervical cyst, which was excised; it was sent, along with specimen of endometrial curettings, for histopathological examination. Microscopy revealed multiple fragments of endometrium showing proliferative phase, as well as some fragments with invading tumor cells in nests and cords, separating myometrial muscle fibers, both individually and in groups (Figure 1). These tumor cells were large and polygonal with irregular vesicular nuclei and prominent nucleoli, and showed abundant dense eosinophilic to amphophilic cytoplasm with occasional vacuoles. Abundant extracellular fibrinoid material was seen around tumor nests (Figure 2). Tumor cells showed characteristic vascular invasions, replacing vessel walls (Figure 3). There were occasional mitotic figures (0–1/10 high power field). Possibility of PSTT was suggested. Serum beta human chorionic gonadotropin (β-hCG) level was within normal limits. The patient underwent hysterectomy and bilateral salphingo-oophorectomy.

On gross examination, hysterectomy specimen revealed a growth measuring 2 × 1.5 × 1 cm in the lower uterine segment, just above the endocervical canal

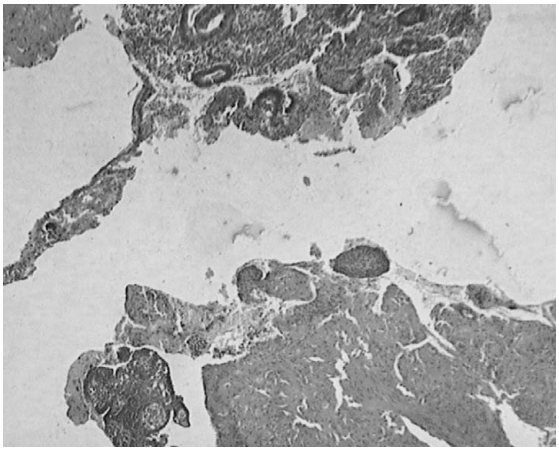

Figure 1. Fragments showing nests and cords of tumor cells infiltrating myometrium along with fragments of endometrium (hematoxylin and eosin stain, 100×).

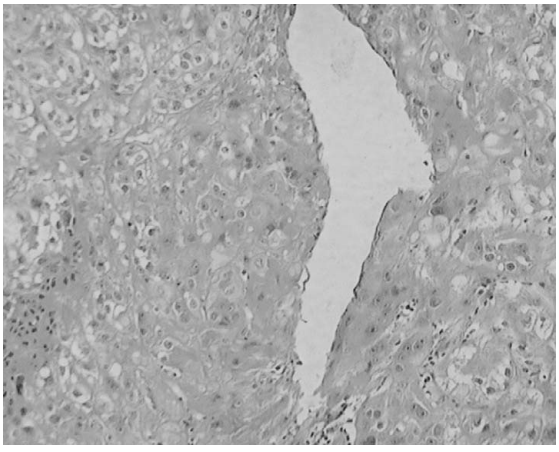

Figure 2. Higher magnification revealing sheets of intermediate trophoblasts replacing the wall of uterine blood vessel (hematoxylin and eosin stain, 200×).

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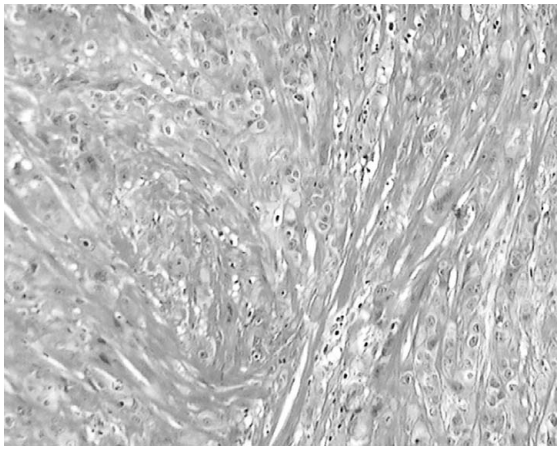

Figure 3. Large pleomorphic polyhedral cells with abundant eosinophilic cytoplasm, invading the myometrium (hematoxylin and eosin stain, 400×).

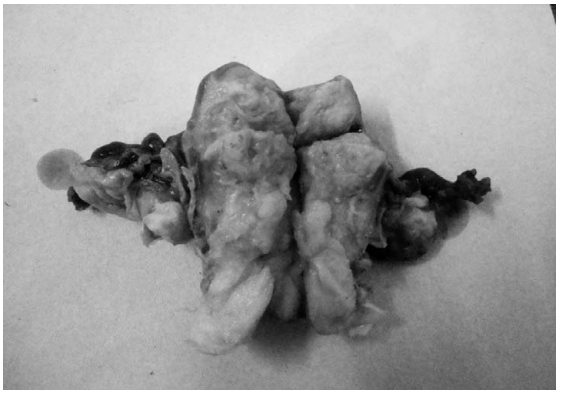

Figure 4. Hysterectomy specimen revealing a shaggy gray-white growth protruding from the lower uterine segment.

(Figure 4). The growth was gray-white in cut section and invaded the myometrium. In addition, there were multiple intramural and subserosal fibroids. Microscopic examination of the growth revealed similar features as the endometrial curettings, with invasion of more than half of the myometrium, confirming the initial diagnosis of PSTT.

PSTT is a rare form of GTD that originates from the implantation site of an intermediate trophoblast. It accounts for about 1% of all GTDs, with an estimated incidence of 1 per 100,000 pregnancies [1]. This clinical and pathological entity was first described in 1976 by Kurman et al [2], when the term "trophoblastic pseudotumor" was used to describe a disease following a benign clinical course. It soon became apparent that those cases in the original report were not wholly representative of the disease spectrum and that this tumor did indeed have a malignant potential [3], leading to the current nomenclature [4].

PSTT is a rare neoplastic proliferation of extravillous intermediate trophoblasts at the implantation site. It belongs to an extraordinary group of neoplasms that are fetal in origin and associated with infiltration of the maternal endometrium and myometrium. It is seen in patients 19–62 years, with an average age of 30 years, and can present with either amenorrhea or abnormal bleeding, often accompanied by uterine enlargement [5]. It can occur after a normal pregnancy, spontaneous abortion, termination of pregnancy, ectopic pregnancy or molar pregnancy [6].

β-hCG is a tumor marker used in evaluating treatment and follow-up of patients with choriocarcinoma and molar pregnancies, in which the β-hCG level correlates with tumor bulk and persistence of disease. This is not true of PSTT; rather, a low β-hCG estimation in patients with a relatively large tumor burden should elicit clinical suspicion of a PSTT. The low levels of β-hCG produced by PSTT reflects the cellular origin of this tumor type: intermediate trophoblast cells produce little β-hCG and larger quantities of human placental lactogen (hPL) [7]. The serum levels of β-hCG are usually in the range of 1,000–2,000 mIU/mL. The usual immunohistochemical staining pattern for PSTT shows a high proportion of cells positive for hPL and CD146, and rarely positive for β-hCG or placental alkaline phosphatase [8]; it is also immunoreactive for cytokeratins, epithelial membrane antigen and inhibin-α.

Data regarding genetic analysis of PSTT are quite limited. Hui et al [9] have analyzed four archived cases of PSTT by comparative genomic hybridization (CGH). One case showed chromosomal gains in the regions of 19p13.2, 21q11–21 and 22q12. The second case demonstrated a single regional chromosomal gain involving 21q21. No chromosomal loss was observed. The remaining two cases showed a balanced CGH profile without detectable chromosomal gain or loss. In a recent study conducted by the same authors, it was suggested that the development of this tumor might require a paternally derived X chromosome and the absence of a Y chromosome as they observed. The presence of an X chromosome and the absence of a Y chromosome were observed in all the 20 cases they studied [9].

The differential diagnosis of PSTT includes exaggerated placental site, choriocarcinoma, epithelioid trophoblastic tumor (ETT), and epithelioid smooth muscle tumor. The most difficult differential diagnosis is that of an exaggerated placental site. Both lesions are characterized by an exuberant infiltration of intermediate trophoblastic cells in the implantation site. The immunophenotype of both lesions is similar. Histologic features associated with PSTT include confluent masses of trophoblastic cells, unequivocal mitotic figures, and the absence of chorionic villi. In addition, exaggerated placental sites contain larger numbers of multinucleated

trophoblastic cells compared with PSTT. In contrast to the biphasic pattern of choriocarcinoma, PSTT is composed of a monomorphic population of intermediate trophoblast. The distinctive pattern of vascular invasion and deposition of fibrinoid material are key diagnostic features which help in distinguishing PSTT from ETT. Poorly differentiated carcinoma and metastatic melanoma can sometimes be confused with PSTT; the above-described characteristics help in the diagnosis, as do immunohistochemical stains for hPL, inhibin-α and HMB-45.

More than half of patients present with disease limited to the uterus; the remainder present with disease extension beyond the uterus. The overall mortality rate is 25%. The most important adverse prognostic factor is disease extension beyond the uterus. Other adverse prognostic factors are interval from antecedent pregnancy > 2 years, mitotic count > 5 mitotic figures/10 high-power fields, and age > 40 years. Since PSTT is less sensitive to chemotherapy than GTDs originating from cytotrophoblasts and syncytiotrophoblasts (hydatidiform mole, invasive mole, and choriocarcinoma), hysterectomy is the mainstay of treatment [10]. The most common metastatic sites are lungs, liver and vagina [11]. Systemic multi-agent chemotherapy is administered in the presence of disease extension beyond the uterus and is considered in the presence of other adverse prognostic factors. The EP/EMA (chemotherapy with etoposide, methotrexate, actinomycin, and cisplatinum) regimen seems to be the most effective chemotherapy available to date for PSTT [10].

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