Exaggerated placental site mimicking placental site trophoblastic tumor: case report and literature review

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Summary

Exaggerated placental site is defined as a non-neoplastic trophoblastic lesion featuring exuberant infiltration into the endometrium and myometrium by intermediate trophoblasts and syncytiotrophoblasts. Exaggerated placental site can occur following normal or ectopic pregnancy, abortion, or hydatidiform mole. We encountered a case of reactive exaggerated placental site seven months following normal pregnancy that clinically mimicked placental site trophoblastic tumor. Few reports have described the clinical course, histopathology and differential diagnosis of exaggerated placental site; we present our patient's case together with histopathological observations and review of related literature.

Key words: EPS, PSTT.

Introduction

Exaggerated placental site (EPS) is a non-neoplastic trophoblastic lesion featuring endometrial and myometrial invasion by intermediate trophoblasts and syncytiotrophoblasts. Morphology and biological behavior differ from those of other trophoblastic lesions [1]. Reports have noted development of EPS following a normal or ectopic pregnancy, abortion, or hydatidiform mole [2-6]. We report our experience with a 33-year-old woman whose normal delivery was followed seven months afterward by irregular vaginal bleeding and rising beta-hCG titer. Initial clinical diagnosis was placental site trophoblastic tumor (PSTT), for which chemotherapy regimens were tried. Finally, histopathology of the hysterectomy specimen confirmed exaggerated placental site. We reviewed other reported cases of EPS and their clinical course. The literature shows that EPS represents an extreme end of a physiological process and simple uterine curettage or endometrial ablation is curative [1, 7]. Reporting such cases can increase physician awareness and help prevent unnecessary hazards of surgery and chemotherapy, as well as unnecessary loss of fertility.

Case Report

A 33-year-old woman presented with irregular vaginal bleeding that began seven months after a normal vaginal delivery. On examination, the uterus was bulky. Transvaginal ultrasonography showed an echogenic lesion on the posterior wall of the uterus involving both the endometrium and myometrium. Serum beta hCG-CTP was 3.3 mlIU/ml (normal < 0.7 mlIU/ml). Endometrial cytology revealed trophoblastic cells but no chorionic villi. Immunohistochemistry revealed a weakly positive beta hCG, PLAP (placental alkaline phosphatase) and Ki-67 (7.6% of aspirated cells were positive for Ki-67). Whole-body computed tomography revealed no evidence of metastasis. Magnetic resonance imaging (MRI) identified an enlarged uterus with a slightly high-signal-intensity mass at the periphery of the posterior wall that showed mild gadolinium enhancement. There was also disruption of the integrity of the junctional zone (Figure 1). The findings suggested possible uterine trophoblastic disease. Relatively low levels of serum hCG and Ki-67 index and weak hCG expression by trophoblastic cells ruled out choriocarcinoma. Close monitoring of serum beta hCG showed continued elevation over the following three months. Finally, the diagnosis of placental site trophoblastic tumor (PSTT) was considered based on high beta hCG titer and the presence of trophoblastic cells with a relatively high Ki-67 index.

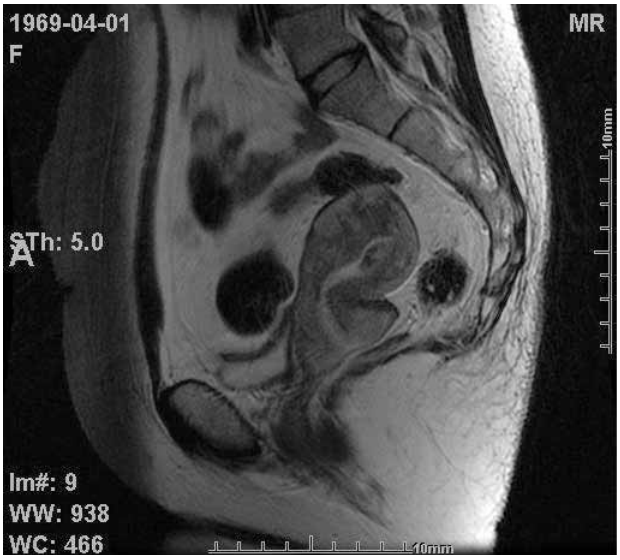

Figure 1. — MRI of abdomen and pelvis showing enlarged uterus with a slightly high-signal-intensity mass at the periphery of the posterior wall that showed mild gadolinium enhancement. There was also disruption of the integrity of the junctional zone.

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Fig. 2a

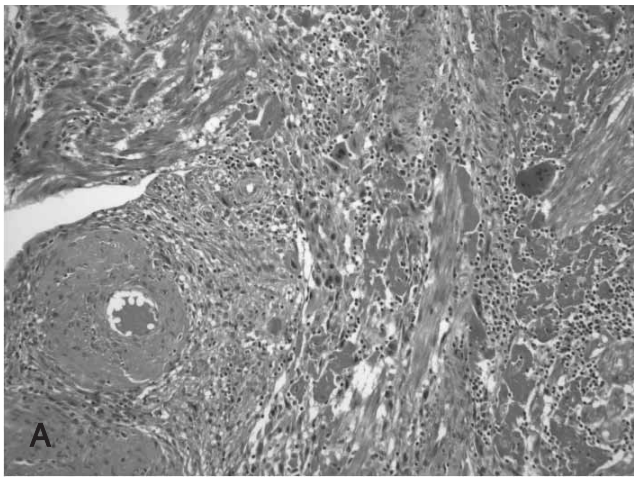

Fig. 2b

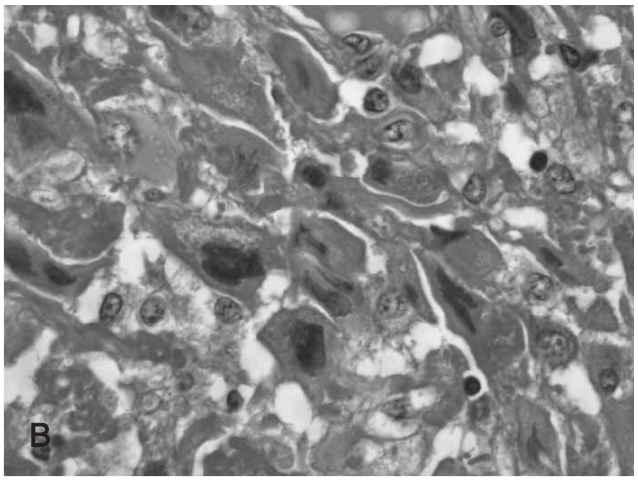

Fig. 3a

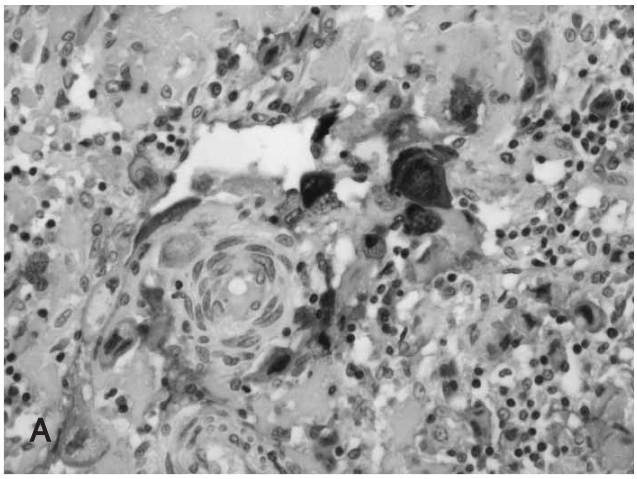

Fig. 3b

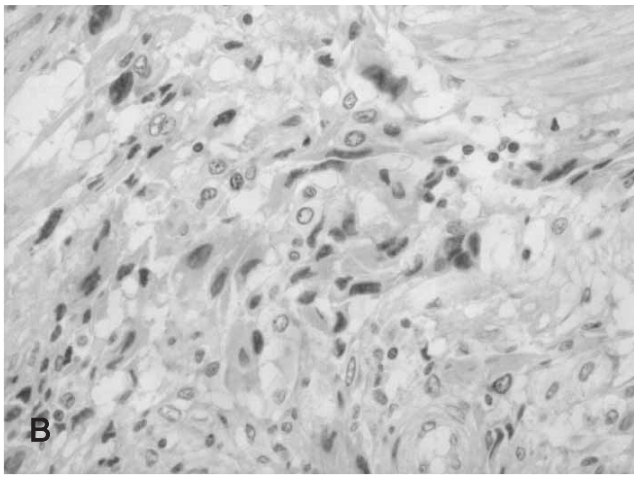

Figure 2. — (A) Low- and (B) high-magnification images of hematoxylin- and eosin-stained aspirate show mononuclear intermediate trophoblastic cells with intense eosinophilic cytoplasm that are infiltrating the myometrium.
Figure 3. — Immunostaining shows weak expression of (A) beta hCG and (B) Ki-67.

Because the patient desired to preserve her fertility, three courses of systemic MAC chemotherapy were given (e.g., 15 mg methotrexate intramuscularly days 1-5, 10 µg/kg actinomycin D intravenously days 1-5, and 100 mg cyclophosphamide intravenously days 1-5 every two weeks). However, serum hCG remained high and bleeding persisted, leading to the conclusion the patient had chemoresistant PSTT. Hysterectomy was performed. Grossly, the uterus had normal appearance, weighing 66.8 g and measuring 9 cm x 7.3 cm x 2.5 cm. In the myometrium, microscopically there was extensive trophoblastic infiltration of the endometrium and myometrium by mononuclear intermediate trophoblastic cells with intense eosinophilic cytoplasm (Figure 2). There were aggregates of trophoblastic cells around blood vessels, but no vessel invasion or necrosis. Also, no chorionic villi could be detected. Immunohistochemistry of trophoblastic cells showed weakly positive staining for hCG, PLAP and Ki-67 (Figure 3). The final histopathologic diagnosis was EPS. Immediately after surgery, serum and urinary beta hCG became undetectable.

Discussion

Physiologically, intermediate trophoblast invades only the inner third of the myometrium in the first trimester of pregnancy and undergoes progressive regression thereafter. In the extremely rare condition called EPS, implantation site intermediate trophoblasts infiltrate the myometrium exuberantly, although there are no data to quantify amount and extent of pathological trophoblastic infiltration [1]. Histologically, there are more implantation site intermediate trophoblastic cells than normally present in the implantation site. The few reported cases have developed following normal or ectopic pregnancy, abortion, or hydatidiform mole [2-6] (Table 1). Although EPS is a non-neoplastic lesion, it can be confused with various neoplastic and non-neoplastic trophoblastic and non-trophoblastic lesions. Because of its rarity of occurrence, gynecologists and pathologists often miss the diagnosis, at least during initial workup. Appropriate diagnosis is important for specific therapeutic approaches and for avoidance of unnecessary hazards such as chemotherapy and surgery, as well as unnecessary loss of fertility.

The most important diagnosis in the differential is PSTT. Unlike EPS, PSTT usually forms infiltrating lesions that are associated with chorionic villi and are confined within a third of the myometrium. In EPS,

Table 1. — *Clinical courses of patients with EPS.*

Year	Authors/ ref number	Age of patient	Antecedent pregnancy	Interval before dignosis	Initial beta hCG	Initial diagnosis	Treatment	Prognosis
2008	Stolnicu *et al*. [2]	55	normal delivery	15 years	NM	NM	TAH	NED
2008	Hasegawa *et al*. [3]	39	abortion	following curettage	20 mIU/ml (serum)	Gestational trophoblastic disease	TAH	NED
1996	Kase *et al*. [4]	44	cervical pregnancy	Presentation cervical pregnancy	NM	Gestational trophoblastic disease	TAH TAH	NED NED
1999	Menczer *et al*. [5]	48	molar pregnancy	1 month following	1300 IU/ml (serum)	Postmolar trophoblastic disease	TAH	NED
2003	Nigam *et al*. [6]	40	abortion	NM	15855 IU/ml (urinary)	choriocarcinoma	TAH	NED
2009	present case	33	normal delivery	7 months	3.3m IU/ml (serum)	PSTT	TAH	NED

EPS, exaggerated placental site; NM, not mentioned; NED, no evidence of disease; TAH, total abdominal hysterectomy; PSTT, placental site trophoblastic tumor.

Table 2. — *Histopathological findings of patients with EPS.*

Authors/ ref number	Site of EPS	Chorionic villi	Ki-67 index	Staining for neta hCG	hPL
Stolnicu *et al*. [2]	cervix	not found	1%	only focally positive	positive
Hasegawa *et al*. [3]	uterus	present	2%	negative	NM
Kase *et al*. [4]	uterus	present	NM	weakly positive	strongly positive
Menczer *et al*. [5]	uterus	not found	insignificant	NM	NM
Nigam *et al*. [6]	uterus	present	insignificant	NM	NM
present case	uterus	not found	7.6%	weakly positive	NM

EPS, exaggerated placental site ; NM, not mentioned.

mitosis is frequently absent and the Ki-67 labeling index is usually 0-1%; in contrast, the labeling index is higher, 14% ± 6.9%, in cases of PSTT [1]. Our patient was initially misdiagnosed with PSTT on the basis of a relatively high labeling index and the presence of a few mitotic figures.

Although a diagnosis of PSTT is recommended if the Ki-67 index in implantation site intermediate trophoblastic cells exceeds 5%, certain features are important in estimating the labeling index. Implantation site intermediate trophoblastic cells can closely resemble natural killer cells and activated T lymphocytes, both of which can be found in the placental site and are highly positive for Ki-67. Some pathologists believe a double staining technique using MIB-1 antibody to determine Ki-67 proliferative index and Mel-CAM (CD146) to identify implantation site intermediate trophoblastic cells can be very useful. EPS cells are diffusely positive for Mel-CAM (CD146) [1, 7]. In addition, the proximal portions of trophoblastic columns contain proliferating trophoblastic cells that normally have a high Ki -67 labeling index. Thus, all of these cells should be taken into consideration while estimating Ki-67 labeling index. A tangential sectioning of trophoblastic columns has been suggested to avoid a high false-positive Ki-67 index [1]. Keeping these points of distinction in mind can minimize the possibility of a diagnostic dilemma. Another point of confusion with our patient was the absence of chorionic villi on cytologic aspiration. Some published cases of EPS reported an absence of coexisting chorionic villi [8], so an absence of chorionic villi in a histopathological sample does not rule out the diagnosis of EPS.

In EPS, infiltrating intermediate trophoblasts in the myometrium are a bit different from normal placental site trophoblasts. If we consider different immunologic markers, hCG is usually focally positive whereas human placental lactogen (hPL) and cytokeratin are diffusely positive in intermediate trophoblasts associated with normal pregnancy. However in EPS, intermediate trophoblasts show a lower level of production of hPL. On the other hand, hPL is expressed in most intermediate trophoblastic cells in PSTT, and thus hPL can be used as a diagnostic and monitoring marker [9]. In Table 2 the different histopathologic findings for reported cases of EPS are shown.

Approximately 10-15% of PSTTs are clinically malignant, and the mortality rate for patients with PSTT is about 15-20% [1]. Surgery is the cornerstone of treatment. In contrast, EPS is a benign condition that can be cured by simple curettage or endometrial ablation. However, there are times where a differential diagnosis of EPS versus PSTT is quite difficult and a definitive diagnosis is made only after hysterectomy. For example, one patient reported in the literature was diagnosed with EPS and treated conservatively. Later, she was diagnosed correctly with PSTT [10]. As a consequence, one group has concluded that patients diagnosed with EPS, especially those patients who want to preserve fertility, should have serial monitoring of beta hCG [5]. Another point of clinical importance is the possible coexistence of EPS and PSTT, a situation in which PSTT remains potentially dangerous. Although EPS can be treated successfully by curettage, the hypervascular variety of PSTT can cause profound post-procedure bleeding. Pre-procedure imaging is helpful in determining lesion vascularity.

Although over-diagnosis may cause an unnecessary therapeutic hazard, under-estimating the risk of PSTT can complicate the clinical picture through severe hemorrhage after conservative treatment or by spreading malignant cells.

In reviewing published cases, we found that a long interval from previous pregnancy does not rule out the possibility of EPS (Table 1). Our patient developed bleeding seven months after a normal vaginal delivery. A similar case was described by Stolnicu *et a*l. [2], in which diagnosis was made 15 years after the last pregnancy. These cases indicate that EPS can remain asymptomatic for a long time, with symptoms presenting weeks to years after the preceding pregnancy.

Due to advances in cytologic diagnosis with different immunohistological markers, it has become easier to diagnose different placental lesions. Continued reporting of cases of EPS should be encouraged because analysis of a larger number of cases may provide important information to help establish standard diagnostic criteria and treatment regimens.

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