Exaggerated Placental Site: A Cause of Postpartum Collapse?

Nirmala Duhan Kadian, Sunita Singh, Nidhi Rajotia, Krishna Dahiya, Shweta Jain, Roopa Malik

ABSTRACT

Exaggerated placental site (EPS) is most often diagnosed retrospectively on histological examination of curettage specimens after first trimester miscarriage but may occasionally produce postpartum hemorrhage. We report the first case of EPS presenting as postpartum collapse consequent upon a small perforation in the placental bed and review the literature for this rare lesion.

Keywords: Exaggerated placental site, Hemoperitoneum, Postpartum collapse.

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INTRODUCTION

Exaggerated placental site (EPS), a miscellaneous trophoblastic nonmolar lesion known to occur in 1.6% of spontaneous and elective first trimester abortions, is characterized by extensive infiltration of the endometrium and myometrium by intermediate trophoblasts. It has been considered to represent an exaggeration of a normal physiologic process of pregnancy and is most often diagnosed on histological examination of curettage specimens of these early trimester miscarriages. We report EPS in a woman with postpartum collapse consequent upon a small perforation in the placental bed after vaginal birth and review the literature of this uncommon condition. To the best of our knowledge, this is the first case in English literature of such a presentation of EPS.

CASE REPORT

A 30-year-old gravida 3, para 2, presented with 36 weeks amenorrhea and severe anemia in the labor ward of this tertiary care center. At presentation, she had a fair general condition, a pulse rate of 100/min, blood pressure of 120/74 mm Hg with marked pallor and pedal edema but no cyanosis, icterus or raised jugular venous pressure. Abdominal examination revealed 32 weeks gravid relaxed uterus with a live fetus in cephalic presentation. She had a hemoglobin of 4% gm, a hypochromic microcytic peripheral blood film and serum proteins were 5.6% gm. Her urine examination and remaining blood biochemistry was normal. Ultrasound examination confirmed a single live unanomalous fetus of 33 ± 2 weeks maturity, an anteriorly placed placenta in the upper segment and optimum amniotic fluid. Two units of blood were transfused over the next 4 days following which the hemoglobin improved to 6% gm. The patient went into spontaneous labor after 96 hours of admission, had an uneventful intrapartum course and delivered a healthy baby girl weighing 2.6 kg after 8 hours of labor. However, the woman collapsed suddenly within 10 minutes of placental delivery on the delivery table, developing a feeble pulse of 136 bpm and a systolic blood pressure of 50 mm Hg. Cardiopulmonary resuscitation was carried out along with administration of uterotonics. This was followed by cervicovaginal exploration. Continuing moderate bleeding from the uterus and unresponsive vital signs inspite of resuscitative measures necessitated an immediate laparotomy. Although about 1.5 liters of blood filled the peritoneal cavity, there was no evidence of any gross uterine rupture or active bleeding from any other pelvic or abdominal organ. The spleen and liver were essentially normal in appearance. In view of intermittent atonicity of uterus in this parous woman, a quick subtotal hysterectomy was carried out and abdomen was closed over a pelvic drain after achieving satisfactory hemostasis. Postoperative period was uneventful. The body of uterus was sent for histopathological analysis which the pathologist reported as a thick walled grey white enlarged uterus with a shaggy and irregular endometrium on gross appearance (Fig. 1). A small defect (0.6 × 0.6 cm) in the myometrium of anterior wall of uterus, 3 cm below the fundus was detected. Microscopy revealed intermediate trophoblasts infiltrating into the muscles with areas of fibrinoid necrosis but without any mitotic activity (Fig. 2). These cells were also seen infiltrating into the blood vessels from outside to inside. On immunohistochemistry, the trophoblasts were negative for hCG, placental alkaline phosphatase (PLAP), Ki-67 proliferation activity but were...
positive for HPL and a diagnosis of EPS was made. At 3 months of follow-up, both mother and infant are healthy.

DISCUSSION

An intermediate trophoblast is a distinctive trophoblastic cell population from which four trophoblastic lesions are thought to arise: EPS, placental site nodule (PSN), placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT). While EPS and PSTT relate to differentiation of the intermediate trophoblast in the implantation site, the PSN and ETTs arise from the intermediate trophoblast of the chorionic leave. Exaggerated placental site and PSNs are non neoplastic lesions, whereas PSTTs and ETTs have a potential for local invasion and metastasis.2

Exaggerated placental site is defined as an increased number of implantation site intermediate trophoblastic cells exceeding those normally present in the implantation site.

The condition was earlier called ‘syncitial endometritis’ but more recently, WHO has introduced the term EPS as the lesion is neither inflammatory nor confined to the endometrium and most of the constituent cells are not syncitial.1 It may represent an exaggeration of a normal physiologic process. The condition can occur in a normal pregnancy or first trimester miscarriage (1.6% of spontaneous and elective first trimester abortions), although EPS with a cervical pregnancy too has been reported.1

Although PSTT has a unique sex chromosomal requirement in its genome that requires a paternal X chromosome (i.e. a female antecedent gestation), Dotto and Hui analyzed 20 cases of EPS and demonstrated unique paternal alleles to that of the paired maternal tissue in all cases, thus confirming the trophoblastic origin of EPS. The identification of XY genome (male) in 11 cases (55%) and an XX genome (female) in the remaining cases (45%) of the study did not support a neoplastic association between PSTT and EPS.3

Most often, EPS is a histological diagnosis made after examination of uterine curettage specimens obtained after first trimester spontaneous or induced abortions. Rarely, it may present as hemorrhage in first trimester. Postpartum hemorrhage was the primary clinical presentation of EPS in a series of 13 cases reported by Chen et al who concluded that EPS is a preneoplastic lesion of PSTT and the diagnosis should be considered in women with PPH.4 Histologically, an EPS is characterized by extensive infiltration of the endometrium and myometrium by intermediate trophoblastic cells, many of which are multinucleated.5 Despite the massive infiltration by trophoblastic cells, the overall placental site architecture remains undisturbed. The endometrial glands and spiral arteries may be completely engulfed by the trophoblastic cells, but without any necrosis.5 Similarly, the myometrial smooth muscles are separated by cords, nests and individual trophoblastic cells that diffusely infiltrate the myometrium without producing necrosis.

Cytologically, the trophoblastic cells in an EPS are identical to the implantation site intermediate trophoblasts in the normal placental site. They contain abundant eosinophilic cytoplasm with hyperchromatic and irregular nuclei. In many cases, there are profuse numbers of multinucleated implantation site intermediate trophoblastic cells. However, mitotic activity is absent and the associated placentae are morphologically unremarkable.5 The trophoblastic cells in the exaggerated placental site display an immunophenotypic profile identical to that of the implantation site intermediate trophoblastic cells found in the normal placental site. These cells are strongly positive for Mel-Cam (CD 146), propyl 4-hydroxylase, oncofetal fibronectin and HPL, moderately positive for

Fig. 1: Gross appearance of enlarged uterus revealing thickened wall, shaggy endometrial cavity and a perforation
Fig. 2: Photomicrograph showing intermediate trophoblasts infiltrating into myometrial cells (H&E: 100×)
EGFR and E-cadherin, and negative for Ber-EP4, EMA, HNK-1 and NCAM. These findings indicate that the differentiation of implantation site intermediate trophoblastic cells is unaltered in an exaggerated placental site and suggest that an exaggerated placental site is a normal variation of an implantation site. Despite the profuse infiltration of implantation site intermediate trophoblasts in an EPS, the Ki-67 indices of implantation site intermediate trophoblast are near zero. Complete hydatidiform moles are always accompanied by exaggerated placental sites in which the implantation site intermediate trophoblastic cells are often more atypical and the Ki-67 labeling index is higher (5%) than those in the EPSs that are not associated with complete moles. The most important differential diagnosis of an exaggerated implantation site is placental site trophoblastic tumor (PSTT). Occasionally, implantation site intermediate trophoblastic cells that infiltrate the myometrium may resemble the atypical smooth muscle cells found in symplastic leiomyomas. The presence of chorionic villi, the infiltrative growth pattern of the trophoblastic cells and positive cytokeratin and HPL stains support the diagnosis of an exaggerated implantation site.

Microscopically, intermediate trophoblastic lesions can be confused with a variety of trophoblastic and non-trophoblastic tumors, but an appreciation of its morphologic features and immunophenotype helps in arriving at the correct diagnosis which is important as all these lesions require different therapeutic approaches. Inspite of these differences, at times, it may indeed be difficult to distinguish EPS from PSTT, specially in curettage samples, because the diagnostic criteria for EPS are imprecise. There are no reliable data quantifying different stages of normal gestation. Collins et al detected a PSTT with histologic features between those of an EPS and a PSTT that persisted after 5 months of initial uterine evacuation. They suggested that the possibility of a PSTT should be considered if there is a suggestion of excessive intermediate trophoblastic activity in the products of gestation, irrespective of the presence of chorionic villi. Besides the overlap in the morphologic features of EPS and PSTT, the trophoblastic cells in early gestation have a primitive appearance and invade the uterine wall and spiral arteries extensively, thus invalidating the conventional histologic features used to distinguish a benign from a malignant process.

Studies show that the Ki-67 nuclear labeling index using a Ki-67 specific (MIB-I) antibody is superior to the mitotic index as a diagnostic aid in the differential diagnosis of EPS vs PSTT. Specifically, the Ki-67 index of the trophoblastic cells in an EPS is near 0, in contrast to 14 ± 6.9% in a PSTT. As Ki-67 labeling may occur in the lymphoid cells normally by present at the placental site, it is important to be certain that Ki-67 labeling is assessed only in an intermediate trophoblast using strict cytologic criteria. In case of difficulty, double immunostaining using an antibody against melanoma cell adhesion molecule (Mel-CAM) or HLA-G that specifically defines implant site intermediate trophoblastic cells can aid in this distinction.

An EPS behaves as a benign trophoblastic lesion that involutes after curettage. It does not include the EPS like implantation site associated with moles and is not associated with any increased risk of persistent gestational trophoblastic disease. No specific treatment or follow-up is necessary. Menczer J et al while reporting a case of a 48 years old woman who underwent hysterectomy for a clinical diagnosis of nonmetastatic trophoblastic disease which finally turned out to be an EPS, suggested operative hysteroscopy to be useful in the diagnosis and management of EPS. When an EPS cannot be confidently distinguished from PSTT by morphology and immunohistochemistry, close follow-up and serial hCG titers is advisable.

Can EPS cause perforation? The invasion of trophoblast into the myometrium may result in thinning of the wall of uterus at site of placental bed. However, there is no previous report of such an etiological association. The present case is unusual by virtue of its presentation as postpartum collapse consequent upon a perforation in the placental bed which was tiny enough to be missed on gross examination at laparotomy. The perforation in the placental bed may have occurred in the late first or second stage of labor and may have continued to ooze blood from the site into the peritoneal cavity. The administration of uterotonic after delivery of baby in this case could have contributed to further narrowing of the opening and sealing of the blood loss from the site. However, the hemoperitoneum that had occurred in this woman with pre-existing severe anemia resulted in collapse soon after the birth of the baby.

Moreover, the dessicative effect of formalin used for histopathological preparation of the specimen resulting in tissue shrinkage could also contribute to the prominence of the uterine wall defect in vitro.

CONCLUSION

Exaggerated placental site is a histological diagnosis wherein the intermediate trophoblast of the implantation site proliferates exuberantly and extensively into the myometrium and may represent an exaggeration of the normal physiology of gestation. It is usually asymptomatic but occasionally may result in bleeding in early pregnancy, postpartum hemorrhage or even perforation.
at the affected site. The diagnosis is retrospective but the possibility should be considered in above-mentioned presentations. As the most important differential diagnosis of EPS is PSTT, a careful follow-up with serum β-hCG is advocated in all women with this condition.

REFERENCES