

Exaggerated Placental Site, Consisting of Implantation Site Intermediate Trophoblasts, Causes Massive Postpartum Uterine Hemorrhage: Case Report and Literature Review

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Every year, 14 million cases of obstetric hemorrhage occur worldwide, causing 127,000 maternal deaths. About 75% of postpartum hemorrhage cases are due to atonic uterus, which is loss of uterine muscular tone or strength for contraction of the uterus after delivery. The prediction of atonic uterus is therefore important for the prevention of postpartum maternal death. However, prediction of occurrence of atonic uterus is difficult before delivery, because the precise pathophysiological mechanism to trigger this condition remains unclear. Here, we present a case of severe postpartum hemorrhage due to atonic uterus. A 35-year-old woman gave a birth by vaginal delivery to a healthy boy. However, due to intractable massive hemorrhage after the removal of the retained placenta, we performed supravaginal hysterectomy as the best option for survival. Pathological examination showed that implantation site intermediate trophoblasts (ISITs) formed unusually large clumps in the decidua, diagnosed as exaggerated placental site (EPS). EPS is thought to be a condition consisting of an excessive number of ISITs. ISITs are differentiated from a trophoblast lineage in the process of placenta formation. ISITs anchor the placenta to the maternal tissue and are considered to maintain pregnancy, but the postpartum role of these cells remains unclear. Excessive infiltration of ISITs, namely EPS, may cause postpartum atonic uterus. In this article, we also reviewed the literatures on EPS. The present case and other reported cases indicate that EPS causes mass formation in the uterus, continuous uterine bleeding, and massive hemorrhage, resulting in hysterectomy.

Keywords: atonic uterus; exaggerated placental site; intermediate trophoblast; postpartum hemorrhage; uterine bleeding

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Introduction

Every year 14 million cases of obstetric hemorrhage occur worldwide, resulting in 127,000 maternal deaths (World Health Organization 2007; Prata et al. 2013). Postpartum hemorrhage accounts for the majority of these hemorrhage deaths (AbouZahr 2003; Prata et al. 2013). Approximately 75% of the cases of postpartum hemorrhage are due to atonic uterus, which is loss of uterine muscular tone or strength to contract the uterus after delivery (Montufar-Rueda et al. 2013; Kramer et al. 2013). Prediction of atonic uterus is therefore important for the prevention of postpartum maternal death. However, prediction of the occurrence of atonic uterus is often difficult before delivery, because the precise pathophysiological

mechanism that triggers this condition remains unclear although a number of risk factors are recognized (Oyelese and Ananth 2010; Chelmos 2011; Hernandez et al. 2012; Kawamura et al. 2014). Recently, a case of exaggerated placental site (EPS) was reported to cause postpartum hemorrhage due to atonic uterus after cesarean section in a term pregnancy (Liu et al. 2013). EPS is thought to be a condition consisting of an excessive number of implantation site intermediate trophoblasts (ISITs). ISITs are differentiated from a trophoblast lineage in the process of placenta formation. ISITs anchor the placenta to the maternal tissue and are considered to maintain pregnancy, but the postpartum role of these cells remains unclear. Excessive infiltration of ISITs may cause postpartum atonic uterus. Here, we present a case of EPS with severe uterine hemorrhage due to

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atonic uterus. The present case indicates an association between atonic uterus and EPS.

Case Report

A 35-year-old woman (gravida 2 para 2) gave a birth by vaginal delivery to a healthy boy weighting 2,940 g at the gestational age of 38 weeks and 5 days. She was transferred to our institute for removal of a retained placenta. Upon arrival, the retained placenta in the uterine cavity was confirmed by ultrasonography. The uterine cervix was dilated smoothly under general anesthesia, allowing easy manual removal of the retained placenta. However, massive hemorrhage was observed along with atonic uterus after the removal of the retained placenta. Intravenous administration of oxytocin and methylergometrine maleate as well as direct injection of prostaglandin F 2α into the uterine myometrium improved uterine contraction and diminished the bleeding. However, about one hour later, recurrence of hemorrhage was noted, again together with atonic uterus. Further conservative treatment failed to restore uterine contraction. The Patient's hemoglobin and platelet count decreased to 6.1 g/dl and $8.4 \times 10^4/\mu\text{l}$, respectively, suggesting that the patient was developing disseminated intravascular coagulation (DIC). Supravaginal hysterectomy was performed as the best option for survival after obtaining the patient's consent. At operation, the uterus was found to be approximately the size of an adult's head and had a boggy consistency. There was no hemorrhagic infiltration of the uterine peritoneum. Total blood loss after admission to our hospital was more than 4,600 g, and blood transfusion was performed. The patient made satisfactory postoperative progress and was discharged 9 days after the operation. Macroscopic examination of the resected uterus showed no tumor formation, no laceration and no residual placenta on the placental site; that is, no macroscopic findings were detected as the cause of the massive hemorrhage.

Immunohistochemistry

Pathological examination showed intermediate trophoblasts forming unusually large clumps in the decidua, although no placental trophoblastic tissue was detected. There were numerous intermediated trophoblastic cells with abundant eosinophilic cytoplasm and hyperchromatic irregular nuclei (Fig. 1A, B). These cells infiltrating the endometrium and myometrium stained positive for human placental lactogen, which is the marker of extravillous trophoblast including intermediate trophoblasts. (Fig. 1C, D). Numerous intermediate trophoblasts with or without multi-nucleation surrounded the glands and arteries. Despite massive infiltration, the intermediate trophoblasts were exclusively confined in the decidua and myometrium, and destructive growth was not demonstrated. Furthermore cells stained with Ki67, which occurs in 8-20% of the cells of placental site trophoblastic tumor (PSTT), were seldom observed (Fig. 1E, F) (Shih and Kurman 2001). Based on

the histological features, it is evident that the diagnosis of this case was EPS (Shih and Kurman 2001; Nigam and Dass 2003).

Discussion

The cause of hemorrhage in the present case was considered to be atonic uterus, because the lack of myometrial contraction was noted simultaneously with the occurrence of severe hemorrhage from the uterus. Also, both macroscopic and microscopic examination of the resected specimen showed that there were no lacerations and no residual placenta in the uterus. Instead EPS was observed.

EPS is thought to be a condition consisting of an excessive number of ISITs in the decidua and uterine myometrium, and is the extreme end of a physiological process rather than a true lesion (Collins et al. 1990; Shih and Kurman 2001). The distinction between a normal placental site and EPS is somewhat arbitrary because there are no reliable data quantifying the amount and extent of trophoblastic infiltration at different stages of normal gestation (Shih and Kurman 2001). The pathological significance of EPS has not been clearly determined. Thus, EPS is a difficult condition for clinicians to diagnose, and EPS has not received much attention until now. In fact, only ten cases have been reported in English, based on PubMed from 1990 through 2013. The clinical courses of eleven cases, including the present case are shown in Table 1 (Kase et al. 1996; Menczer et al. 1999; Nigam and Dass 2003; Stolnicu et al. 2008; Hasegawa et al. 2008; Yeasmin et al. 2010; Harada et al. 2011; Akbayir et al. 2012; Chen et al. 2012; Liu et al. 2013). EPS has been detected in molar pregnancy, cervical pregnancy, abortion or induced abortion of early pregnancy, intrauterine fetal death of 24 weeks gestation and term pregnancy. It can develop from early to term pregnancy. In the case with the longest interval from the antecedent pregnancy, a lesion or clinical symptom appeared 15 years after delivery, and in the case with the shortest interval, EPS appeared during pregnancy. No bleeding was noted in a case with a small lesion in the uterine cavity, and in three cases with a relatively large lesion on the uterine wall. Continuous blood spotting or short term active bleeding appeared in five cases with a polypoid lesion, and severe uterine hemorrhage with atonic uterus occurred in two cases without macroscopic lesions. Nine of the cases were treated by hysterectomy in order to prevent progressive gestational trophoblastic disease or to control severe uterine hemorrhage. The lesions were resected in two cases during caesarian section. Based on clinical symptoms or features in these cases, most cases of EPS appear to develop lesion in the form of a mass, although EPS is defined as the extreme end of a physiological process rather than a true lesion.

PSTT is the most important differential diagnosis of EPS (Shih and Kurman 1998; Kim 2003; Yeasmin et al. 2010). PSTT usually forms a confluent mass of trophoblastic cells with unequivocal mitosis although mitosis, but sel-

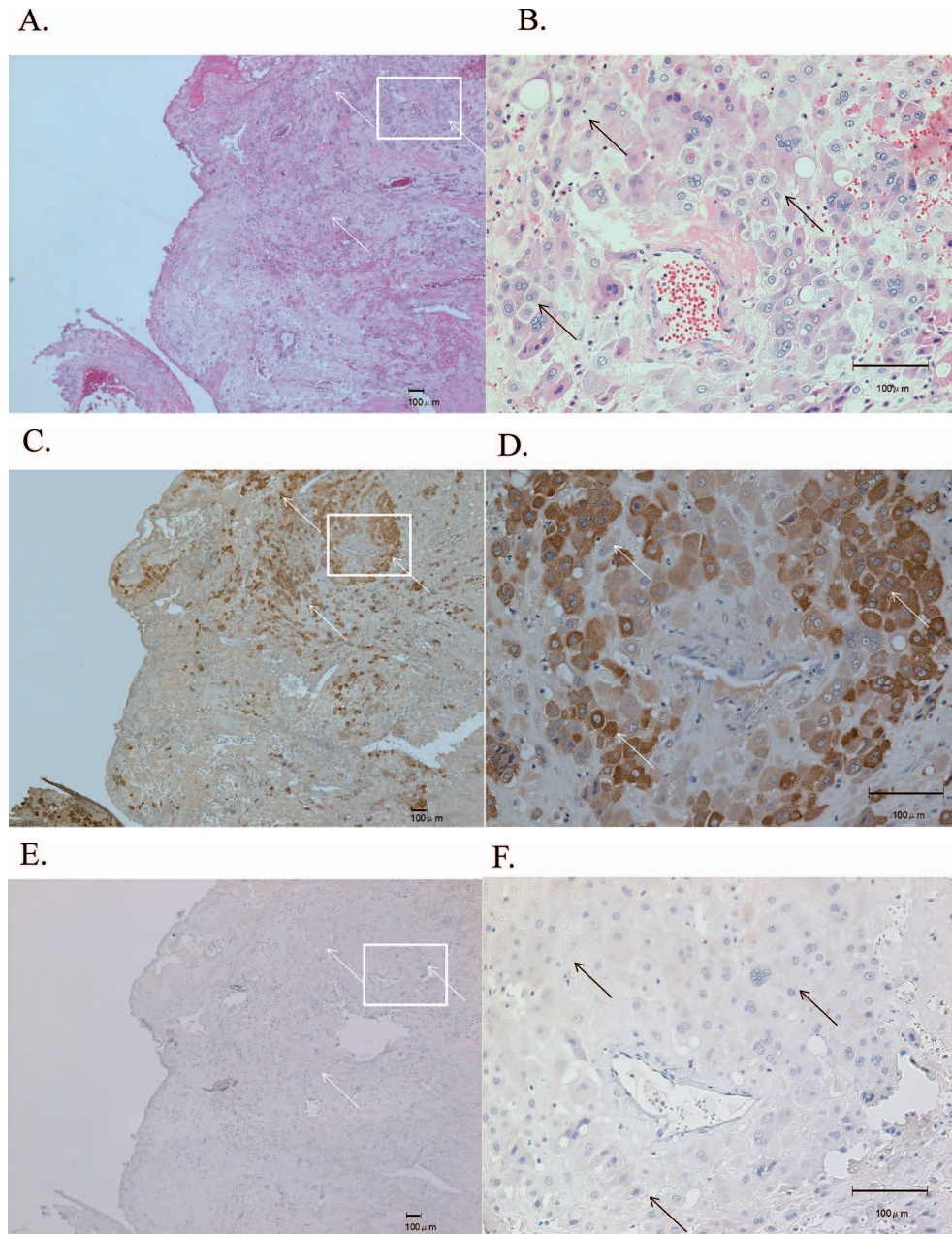


Fig. 1. Intermediate trophoblasts in the endometrium of the present case.

Pathological images of the uterus at low and high magnification (A, B). At the placental site of the present case, there are numerous intermediate trophoblasts with abundant eosinophilic cytoplasm and hyperchromatic irregular nuclei. Immunohistochemistry of human placental lactogen (hPL) at low and high magnification (C, D). Cells, stained positive for hPL that is specific to extravillous trophoblasts including intermediate trophoblasts, are seen to infiltrate the endometrium and myometrium. There are numerous multinucleated intermediated trophoblasts. Glands and spiral arteries are engulfed by intermediate trophoblasts (arrow). Immunohistochemistry of Ki67 in the intermediate trophoblasts at low and high magnification (E, F). Despite massive infiltration of intermediate trophoblasts, the structure of the decidua is not destroyed and proliferation of the intermediate trophoblasts is seldom seen. A bar shows 100 μm .

dom occurs in EPS. Depending on the rare occurrence of mitosis and the structure, all the reported cases of EPS, including the present case, were diagnosed as EPS. Considering mass formation found in nine of the reported cases, EPS may be a precursor lesion of PSTT (Liu et al. 2013). In the present case unusual large clumps of intermediate trophoblasts were detected although there was no

mass lesion found in the uterus, and hysterectomy was performed due to severe uterine hemorrhage. Liu et al. (2013) has also reported a case diagnosed as EPS in term pregnancy, resulted in severe postpartum hemorrhage. In these two cases no mass lesion could be found in the specimens, although the symptoms were severe. In mild or moderate case of atonic uterus the uterus is usually preserved by con-

Table 1. Clinical courses of EPS.

Published year	Authors	Age of patients	Type of (antecedent) pregnancy	Gestational age of (antecedent) pregnancy	When the lesion or clinical symptom was recognized	Clinical symptoms & features	Treatment
1996	Kase et al.	44	Cervical pregnancy	7 week	During pregnancy	Continuous uterine bleeding and abdominal pain, 40 mm of cystic mass in the uterine cervix	Hysterectomy
1999	Menczer et al.	48	Molar pregnancy	9 week	34 days after the second curettage	No symptom, reincrease of beta-hCG, 10 mm of nodule in the uterine cavity	Hysterectomy
2003	Nigam and Dass	40	Abortion	Not mentioned	Not mentioned	Markedly raise of hCG, bulky mass in the uterus, uterine bleeding with clots for a day	Hysterectomy
2008	Stolnicu et al.	55	Normal pregnancy	Term pregnancy	15 years after the delivery	Massive uterine hemorrhage, 20 mm of flat plaque like lesion	Hysterectomy
2008	Hasegawa et al.	39	Induced abortion	7 week	1 week after the D&C	No symptom, 36 mm of lesion on the arterial wall of the uterus	Hysterectomy
2010	Yeasmin et al.	33	Normal pregnancy	Term pregnancy	7 months after the delivery	Irregular uterine bleeding, 20 mm of lesion on the uterine muscle beneath the endometrium	Hysterectomy
2011	Harada et al.	43	Induced abortion	7 week	41 days after the D&C	Continuous genital bleeding, 45 mm of polyp attached to the protruding lesion of the uterus	Hysterectomy
2012	Akbayir et al.	24	Normal pregnancy	Term pregnancy	At caesarean section	No symptom, 30 mm of polypoid well-shaped smooth lesion on the uterine wall	Resection at the delivery
2012	Chen et al.	34	Fetal death, placenta previa	24 week	At fundal hysterotomy (Caesarean section)	No symptom, 30 mm of nodular mass at the uterine wall	Resection at the operation
2013	Liu et al.	30	Breech presentation	Term pregnancy	At caesarean section	Heavy uterine bleeding with atonic uterus, no mass lesion, diagnosed EPS based on pathology	Supravaginal hysterectomy
2014	Present case	35	Normal pregnancy, retained placenta	Term pregnancy	After the placental delivery	Severe uterine bleeding with atonic uterus, no mass lesion, diagnosed EPS based on pathology	Supravaginal hysterectomy

The clinical courses of eleven EPS cases including the present case are shown. EPS is variously detected in molar pregnancy, cervical pregnancy, abortion or induced abortion of early pregnancy, intrauterine fetal death of 24 weeks gestation and term pregnancy. It can develop from early to term pregnancy. In the case with the longest interval from the antecedent pregnancy, a lesion or clinical symptom appeared 15 years after delivery, and in the case with the shortest interval, EPS appeared during pregnancy. No bleeding was noted in a case with a small lesion in the uterine cavity, and in three cases with a relatively large lesion on the uterine wall. Continuous blood spotting or short term active bleeding appeared in five cases with a polypoid lesion, and severe uterine hemorrhage with atonic uterus occurred in two cases without macroscopic lesions. Nine of the cases were treated by hysterectomy in order to prevent progressive gestational trophoblastic disease or to control severe uterine hemorrhage. The lesions were resected in two cases during caesarian section.

servative treatment and pathological diagnosis cannot be obtained. Therefore, we speculate that an excessive infiltration of intermediate trophoblast, or a type of milder EPS often occurs in cases of atonic uterus.

After an embryo attaches to the uterine endometrium, chorionic villi, consisting mainly of syncytiotrophoblasts and cytotrophoblasts, start invading the uterine endometrium called decidua. Cytotrophoblasts differentiate to two different lineages. They fuse together to form an overlying multinucleated syncytiotrophoblast layer that directly con-

tacts with the intervillous blood space, or remain as interstitial cytotrophoblast cells in the villi. Later, differentiation from cytotrophoblasts to villous intermediate trophoblasts takes place at the columns of the villi, also called anchoring villi. At the base of these trophoblastic columns where the villous intermediate trophoblasts makes contact with the decidua, the villous intermediate trophoblast loses their ability to proliferate and transforms into ISITs (Kaufmann and Castellucci 1997; Handwerger 2010; Wallace et al. 2012; Knöfler and Pollheimer 2013). Then, the ISITs infil-

trate the decidua and myometrium, and a portion of them replaces the walls of the arteries of the implantation site to establish the maternal fetal circulation (Kaufmann and Castellucci 1997; Wallace et al. 2012; Knöfler and Pollheimer 2013). ISITs are considered to maintain pregnancy, but the postpartum role of the cells remains unclear. In the present case, we speculated that an excessive number of intermediate trophoblasts caused the occurrence of postpartum atonic uterus. It is likely that an excessive number of ISITs promoted vasodilatation in the decidua and myometrium after placental expulsion as such cells do during pregnancy, causing continuous hemorrhage into the uterine cavity and leading to poor perfusion of the myometrium. Alternatively the ISITs invading the deeper decidua may have secreted some substances that blocked contraction of the myometrium, resulting in atonic uterus. Multiple gestation and heavy for weight are thought to be risk factors for atonic uterus as these are thought to make uterine muscle more extended. However, a reminder should be given that a greater number of ISITs should be present in the decidua and myometrium in cases of multiple gestations and heavy for weight.

As stated, the clinical significance of an excessive number of ISITs as a cause of atonic uterus has not been investigated sufficiently. This condition appears to be a disease or a condition causing postpartum hemorrhage. Pathological examination should be performed to evaluate the status of ISITs infiltration when the uterus is resected in the postpartum period. If the association between atonic uterus and infiltration of an excessive number of ISITs, or EPS is proved, it will contribute to the development of a diagnostic method to foresee atonic uterus. Further investigation is needed to support this hypothesis.

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Conflict of Interest

The authors declare no conflict of interest.

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