**CASE REPORT**

**Novel histological findings in the uterus after interventional radiology: a case report of placenta accreta**

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Placenta accreta is one of the causes of postpartum hemorrhage (PPH). Recently, interventional radiology (IVR) techniques, such as arterial embolization and balloon occlusion, have become widely used to manage hemorrhage associated with placenta accreta. Although IVR techniques could prevent maternal death and even preserve the uterus in PPH, in pregnancies after IVR, there have been reports that the risk of placenta accreta is increased. In this case report, a 39-year-old primiparous patient underwent IVR for the treatment of a retained placenta after vaginal delivery. However, IVR failed to stop uterine bleeding. Hysterectomy was finally performed for the patient’s survival. Histological examination of the extirpated uterus after IVR showed changes in the expression of myosin heavy chain isoforms (SM1 and SMemb) in vascular smooth muscle cells due to inflammatory changes in the uterus following ischemic damage.

**Introduction**

Placenta accreta is one of the life-threatening conditions seen in pregnant women that can result in postpartum hemorrhage (PPH). PPH as well as stroke and obstetric pulmonary embolism have been reported as the leading overall causes of maternal death in developed countries, including Japan. Placenta accreta is the pathological state in which villous trophoblasts invade the myometrium through the endometrium due to decidua basalis lacks. The histological condition is classified according to the degree of invasion into the myometrium, and includes two types: placenta increta, with placental villi extending into the myometrium, and placenta percreta, with placental villi penetrating the uterine serosa.

Recently, interventional radiology (IVR) techniques, such as arterial embolization and balloon occlusion, have become widely used to manage hemorrhage associated with placenta accreta. Bakri reported the first case of successful pelvic arterial embolization for placenta percreta. IVR could prevent maternal death and even preserve the uterus in cases of PPH. Some studies have reported that pregnancy after IVR may be associated with an increased risk of placenta accreta, and that this process might involve local infectious responses as well as vascular remodeling due to ischemia in the region of the uterus treated by IVR. Another study reported that the composition of myosin heavy chain (MHC) isoforms in smooth muscle cells (SMCs) changes with the proliferation and de-differentiation of SMCs during angiogenesis.

Here we report a case in which IVR failed to stop uterine bleeding during the treatment of a retained placenta, leading to hysterectomy. To assess the reason underlying IVR failure, a histological study of the uterus was performed with a focus on changes in the expression of MHC isoforms in uterine arteries.

**Case**

The patient was a 39-year-old primiparous female with a history of 1 abortion at 9 weeks’ gestation and 1 induced abortion at 18 weeks’ gestation due to fetal hydrops. She was treated for infertility after 3 years of attempting...
pregnancy and became pregnant after blastocyst transfer. She delivered vaginally at 40 weeks’ gestation. However, the placenta could not be removed. Blood loss was approximately 2,000 ml. She was transferred to our hospital by ambulance for the management of PPH.

Upon arrival at our hospital, her face was pale, blood pressure was 105/62 mmHg, and pulse was 81 beats/min (shock index 0.77). Abdominal ultrasonography and MRI revealed a retained placenta and placenta accreta (Figure 1A1). According to guidelines for obstetric critical hemorrhage, her disseminated intravascular coagulation (DIC) score was 4 (pale face, blood loss 1,000-2,000 ml, elevated fibrin degradation products [FDPs], and decreased antithrombin). Uterine bleeding still remained even 8 hours after delivery. In order to preserve fertility, we chose to perform IVR rather than hysterectomy.

Angiography revealed pooling and leaking of contrast material in the area fed by the left uterine artery (Figure 1B1). Uterine artery embolization (UAE) with transfusion of 4 units of red blood cells (RBC) and 4 units of fresh frozen plasma (FFP) reduced uterine bleeding. On postpartum day (PPD) 2, we manually attempted removal of the remaining placenta under common iliac artery balloon occlusion (CIABO) due to continuing bleeding. Internal iliac artery embolization was added but did not interrupt blood flow in parts of the uterus with residual placenta fed possibly by the left ovarian artery (Figure 1B2). A Bakri balloon was placed in the uterine cavity and 4 units of RBCs were transfused.

MRI revealed the uterus to be smaller after two attempts at embolization. However, a high-intensity mass remained in the fundus (Figure 1A2) and a moderate amount of bleeding persisted. As treatment, we offered conservative treatment in the form of repeat UAE, repeat attempt at placenta extraction under hysteroscopy, and administration of methotrexate. However, the patient gave up on preserving the uterus because she preferred to avoid taking further time with treatment. Hysterectomy was performed on PPD 7, and her subsequent clinical course was uneventful.

The placenta in this patient had adhered to the uterine wall (Figure 2A and 3A). Histological examination led to a diagnosis of placenta accreta because chorionic villi were visualized in the uterine smooth muscle and were in contact with the myometrium by hematoxylin and eosin (HE) staining.

The following areas of the uterine wall were also examined: 1) the area with remaining villi and blood flow despite embolization (Figure 2A), 2) the area with remaining villi and reduced blood flow due to embolization (Figure 3A), and 3) the area without remaining villi and reduced blood flow due to embolization (Figure 4A). In the area with remaining high blood flow, HE staining revealed RBCs in arteries and few leukocytes in the myometrium (Figure 2B1 and 2). To examine phenotypic changes in SMCs of the uterine arteries, MHC isoforms were immunostained using monoclonal antibodies against

### Table 1. The blood examination

| Parameter       | Value       |
|-----------------|-------------|
| WBC             | 23.6 × 10^3/μl |
| RBC             | 2.3 × 10^6/μl  |
| Hb              | 6.7 g/dl    |
| Ht              | 21.00%     |
| MCV             | 91.3 fl     |
| MCH             | 29.1 pg     |
| MCHC            | 31.90%     |
| Plt             | 183 × 10^3/μl |
| PT (seconds)    | 14.6       |
| PT (%)          | 61         |
| PT (INR)        | 1.37       |
| PT ratio        | 1.2        |
| APTT (seconds)  | 27.4       |
| Fibrinogen      | 196 mg/dl  |
| Antithrombin III| 45%        |
| FDP             | 10.3 μg/ml  |

### Figure 1. MRI and angiography findings.

A. Serial MRI findings in the uterus, 1: on arrival at our institute, MRI revealed an enlarged uterus with fluid retention in the uterine cavity. A high-intensity mass (placenta) and unclear border between the placenta and smooth muscle in the fundus was observed, suggesting placenta accreta. 2: The uterus is smaller after two embolizations; however, there is a high-intensity mass (possibly placenta) remaining in the fundus.

B. Angiography findings. 1: Just before the first embolization, pooling and leaking (*) of contrast material is observed in the area fed by the left uterine artery. 2: Leaking and pooling (▲) is also observed in the area fed by the left ovarian artery.
Figure 2. Pathological examination of the uterine wall in the area with remaining villi and blood flow despite embolization.

Remaining villi (▲) are found in the uterine cavity. The histological specimen was obtained based on the section shown by line (A). There are few leukocytes in the myometrium by HE staining in the low-power field (B1). RBCs are observed in arteries in the high-power field (B2). Smooth muscle cells (SMCs) are stained by SM1 (C) and SMemb (D) in the high-power field.
Figure 3. Pathological examination of the uterine wall in the area of remaining villi and reduced blood flow due to embolization.

Remaining villi are observed in the uterine wall (arrow head). The histological specimen was obtained based on the section shown by line (A). Several leukocytes (*) are found in the myometrium by HE staining in the low-power field (B1) and few RBCs and embolic material are observed in arteries (arrow) in the high-power field (B2). SMCs were negative for SM1 (C) and SMemb (D) staining in the high-power field.
Figure 4. Pathological examination of the uterine wall in the area without villi and reduced blood flow due to embolization.

The histological specimen was obtained based on the section shown by line (A). Few leukocytes are observed in the low-power field (B1), and both RBCs and embolic material are observed in arteries (arrow) by HE staining in the high-power field (B2). SMCs were stained by SM1 (C), but not SMemb (D).
rabbit SM1, SM2, and SMemb (1:1,000, 1:400, and 1:1,000 dilutions, respectively, Yamasa Corp., Tokyo, Japan). In this area, SMCs stained positive for SM1 (Figure 2C), SM2 (data not shown), and SMemb in many arteries (Figure 2D). In the area of reduced blood flow by UAE, there was an increased number of leukocytes (Figure 3A). SMCs were negative for SM1 (Figure 3B) and SMemb (Figure 3C). In the area without remaining villi, there were few leukocytes (Figure 4A). SMCs in this area stained positive for SM1 (Figure 4B), but were negative for SMemb (Figure 4C).

Discussion

The present case was complicated by placenta accreta. IVR techniques, including UAE and CIABO, performed after vaginal delivery failed to stop bleeding, and hysterectomy was eventually performed.

IVR can prevent major hemorrhage and even preserve the uterus in patients complicated by placenta accreta. Thus, guidelines for critical obstetric hemorrhage in Japan propose the use of IVR in this patient population.7) Recently, it was reported that the risk for placenta accreta in the next pregnancy increases.3–5) IVR might be involved in the local infectious response in addition to vascular remodeling due to ischemia in the area of the uterus treated by IVR. SMCs in human arteries contain at least three MHC isoforms: SM1, SM2, and SMemb. The first two are specific to smooth muscle, but SMemb is a non-muscle type of MHC that is abundantly expressed in the embryonic aorta and down-regulated during vascular development.6,8) SMC proliferation and de-differentiation, coupled to the expression of SMemb, are involved in mechanisms underlying atherosclerosis.8) Furthermore, the composition of MHC isoforms changes with proliferation and de-differentiation of SMCs during angiogenesis.6)

In the area of the uterus that showed reduced arterial blood flow by angiography, histological examination revealed a lack of SM1 and SMemb staining in the arteries. We considered this area amenable to conservative management by embolization to interrupt blood flow. However, many leukocytes and extravillous trophoblasts were found in the myometrium, suggesting inflammation. In the area of reduced blood flow due to embolization without residual villi, SMCs stained positive for SM1, but not SMemb, and a few leukocytes were present.

Despite embolization of the internal iliac artery, angiography revealed blood flow in the area which was not available for IVR, likely because it received blood flow through a different route, possibly the ovarian artery. Furthermore, in this area, many arteries stained positive for SM1 and SMemb, suggesting that the arteries were intact and inflammatory changes did not occur in the area.

These results suggest that hemostasis caused by UAE damaged the arteries, and thus altered the expression of vascular MHC isoforms. Expression of the non-muscle type MHC, SMemb, depends on ischemia resulting from reduced blood flow. Furthermore, subsequent inflammatory reactions may cause tissue injury. In the area of residual placenta, strong inflammation was observed and the MHC isoform expression profile changed. Pregnancy after IVR has been reported to be associated with an increased risk of placenta accreta.3,5) Our results are consistent with these reports. As for placenta accreta, IVR may induce inflammatory changes in the uterus in addition to the ischemic damage caused by reduced blood flow. However, this was inconclusive in our case because the change of MHC phenotype happened too quickly. Further studies will be needed to clarify this aspect.

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Conflict of interest

None.

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