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PLACENTA INCRETA PRESENTING AS RETAINED PLACENTA

A report of 3 cases

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Abstract

Objectives: Morbid adherence is a risk factor for retained placenta(RP). We encountered 3 cases of placenta increta presenting clinically as delayed postpartum hemorrhage.

Methods: This was a retrospective study of 3 cases of placenta increta presenting as RP.

Results: One “routine” term placenta had heavy bleeding 2 weeks later; one missed abortion at 16 weeks with fetal and placental tissue submitted, had heavy bleeding 6 weeks later; and one elective abortion (no tissue submitted), had delayed postpartum bleeding leading to a curettage with blood only, then 6 weeks later a hysterectomy for menorrhagia. All 3 pathology specimens showed necrotic villi. However, all three also showed myometrium with keratin-positive interstitial trophoblasts in a zone of damaged myometrium, consistent with increta. All 3 cases had basal plate myofibers (BPMF) in the placenta, with BPMF recurrence in the 2 cases with another pregnancy.

Conclusion: RP may be a presenting clinical manifestation of placenta increta.

INTRODUCTION

Retained placenta is defined as failure of placental delivery 30 minutes after childbirth, although some authorities favor a time limit of 60 minutes (1). Manual removal is advised; but in some rural, impoverished, and/or underdeveloped areas this procedure is not generally available, and the case fatality rate due to immediate hemorrhage can approach 10% (1,2). Retained placenta is also accepted as a leading cause of delayed postpartum hemorrhage, defined as bleeding with onset more than 24 hours after delivery (3). Retained placenta is more common in developed countries, possibly due to more common interventions such as therapeutic abortion or labor induction, but mortality approaches zero (1,2,4-6). Various clinical factors increase the risk, foremost of which is a prior retained placenta (1,7). Ultrasound studies suggest that failure of contraction of retroplacental myometrium may be a major factor, so that oxytocin treatment can reduce the need for manual removal (2,4). Retained placental fragments may resorb spontaneously, so conservative or hormonal management may be effective (8,9). As compared to curettage, hysteroscopic resection may improve both completeness of removal, and reduction in subsequent development of intrauterine adhesions (Asherman's Syndrome) (9).

Placenta increta usually presents with immediate postpartum hemorrhage, requiring hysterectomy (10). It can present with uterine inversion (11). It can also simulate abruption, with retroplacental bleeding during delivery, and submission of separate clot along with the placenta (12,13). Mild cases can require manual placental removal, sometimes in pieces (8,13). Although it is well known that

placenta increta can lead to retained placenta (8,13); it is not widely appreciated that the mundane finding of necrotic villi consistent with retained placenta can also be the presenting manifestation of placenta increta. We present 3 cases of placenta increta with necrotic villi, presenting as delayed postpartum hemorrhage, thought by the clinician to be cases of retained placenta.

Case Reports

Case 1

A 37 year old woman had an elective abortion at 6 weeks + 4 days, from which no tissue was submitted. She subsequently presented with delayed postpartum hemorrhage and a mild elevation of beta-HCG (38 units). Curettage was performed to rule out hydatidiform mole, but the specimen was blood only, with no villi identified. Although beta-HCG subsequently fell to zero, she continued to bleed. Six weeks later, she underwent a hysterectomy for menorrhagia and pelvic pain.

The hysterectomy specimen was not described as having any grossly obvious placental tissue, but the endometrium appeared to be scarred and retracted, and a blood clot was noted on the endometrial surface near the right cornu. A section at this location had necrotic and sclerotic villi, as usually seen in retained placentas, underneath the surface clot (Figure 1a). Sclerotic villi appeared to be in direct apposition to myometrium in the middle third of the wall (Figure 1b), suggesting placenta increta (11,14,15).

Keratin stains (AE1/AE3) showed that interstitial nonvillous trophoblasts went much deeper than the villi (Figure 1c). Deeper location of interstitial nonvillous trophoblasts was easily identified in other areas on the H&E stain (Figure

1d). However, it was not clear on H&E that myometrium was being destroyed, which we believe is the sine qua non for a diagnosis of placenta increta (11,14,15). Actin stain (MSA) showed myometrial destruction in the retroplacental zone of deep interstitial trophoblasts (Figure 1e).

The previous placenta from 9 years previously was reviewed. It was postdates (41 weeks), large (770 grams), and had torn cotyledons on gross exam, with basal plate myofibers (BPMF) on routine microscopy. Six weeks later, there had been a curettage for retained placenta.

Case 2

This 31 year old had a missed abortion at 16 weeks, with fetal death in utero due to excess coils and stricture of the umbilical cord. The placenta weighed 60 grams and had a rough maternal surface with a retroplacental blood clot. The basal plate had MSA+ BPMF not seen on H&E (Figure 2a).

Six weeks later, a specimen of retained placenta was submitted after the patient had vaginal bleeding. As usual, there were necrotic villi. Pieces of myometrium were present, with interstitial trophoblasts. The myometrium had a lymphoid infiltrate with no plasma cells (Figure 2b). Myometrium was degenerated with loss of nuclei in some areas (Figure 2c). MSA actin stain confirmed striking muscle damage (Figure 2d). CAM5.2 keratin stain showed interstitial trophoblasts at the site of muscle damage (Figure 2e). Keratin-positive endovascular trophoblasts were seen in an abnormally dilated vessel (11,14).

Two years later, this patient had recurrence of BPMF in a large for gestational age term placenta.

Case 3

A routine placenta from a 36 year old woman at term was submitted with no clinical history, and was signed out by a general pathologist as having meconium effect, laminar necrosis, intervillous thrombus, increased syncytial knots, and chorionic microcysts. Two weeks later, she presented with heavy postpartum bleeding, which led to a curettage for retained placenta. The initial placenta was then reviewed by a perinatal pathologist, and note was made of grossly torn cotyledons. Although no BPMF were seen on H&E, MSA actin stain showed BPMF near the site of torn cotyledons (Figure 3a).

The curettage 2 weeks later showed acutely inflamed necrotic villi, consistent with retained placenta. Myometrium was present in the curettage, and MSA actin stain showed shriveled myofibers amidst a lymphoid infiltrate with no plasma cells (Figure 3b). Keratin-positive interstitial trophoblasts were seen amidst the damaged myometrium, consistent with increta (Figure 3c) (11,14). On followup, this case had no other placentas.

DISCUSSION

Placenta Increta Presenting with Delayed Hemorrhage and Retained Villi

Standard teaching is that incretas invade myometrium, while “true” accreta adheres to myometrium (10). However, recent studies suggest that morbid adherence may be a disease of nonvillous trophoblast, best appreciated with immunostains for actin and keratin (11,14). Cases previously called “true” accretas may actually be “early” incretas (10,11); with keratin-positive interstitial trophoblasts causing myometrial damage due to decreased inhibition of placental

proteases (11,14,16,17). Subclinical accreta may present as a BPMF placenta, with bleeding during delivery; simulating abruption (12,18).

Our 3 incretas presented with delayed bleeding (2-6 weeks later); 1 after placental delivery and 2 after abortions. In all 3, the clinician suspected retained placenta; and slides showed necrotic villi, consistent with retained placenta. However, all 3 had immunohistochemical features of increta (11,14). One case had a clinically occult intramural mass of necrotic/sclerotic villi; which was not a placental polyp, because the mass was not intracavitary (19-21). Two curettages after miscarriage were scrutinized for myometrium with interstitial trophoblasts, and actin stains showed myometrial damage not seen on H&E (14).

Morbid adherence with both delayed postpartum hemorrhage and retained villi was observed by Ober and Grady (22). In their 100 cases with subinvolution of the placental site (SOPS) (22), scrutiny showed 53 with retained villi, a few apposed to myometrium - indicating accreta. Retained villi apposed to myometrium were also seen in a series of 32 uteri with placental site involution, either Cesarean hysterectomies or postpartum hysterectomies for sterilization (23). Anderson and Davis saw retained villi in a few cases, some apposed to myometrium (accreta) (23), and some with retained membranes, consistent with morbid adherence (18,23).

Polypoid masses of intracavitary villi - placental polyps - can bleed months to years after pregnancy; and may actually be accretas, but actin and keratin stains were not done to exclude "early incretas" (11,14,19-21).

A prospective study compared 49 retained placentas with focal adherence, requiring manual removal, with 47 controls delivered in <30 minutes, with no

adherence or manual removal (24). Cases with placenta trapped behind the cervix were excluded. Retained placentas were smaller, with histologic features of low uteroplacental blood flow; although no patients had pre-eclampsia. Focal accreta - diagnosed on the basis of decidual deficiency (25) - was seen in 12% of retained placentas, vs 4% of controls (not statistically significant). BPMF placentas were significantly more common (22%) than in controls (3%). All 3 of our cases had BPMF placentas, and the 2 with another pregnancy had BPMF recurrence (13).

Pathogenesis of Delayed Hemorrhage Associated with Necrotic Villi

Delayed bleeding in these 3 incretas with necrotic villi may have the same pathogenesis as retained placenta with necrotic villi. Empirically, necrotic villi explain delayed bleeding, because curettage usually stops the bleeding (71%) (9). Some feel that rare villi don't explain bleeding (26), but that reservation may apply to all cases with necrotic villi; since structures with no blood flow cannot bleed. Retained placenta is part of the placental site; so the source of bleeding must be vascular. More study is needed to determine if delayed bleeding comes from arteries or veins; and to determine if the vessels are involuted or subinvolutated (3,22,23).

Sampling variation may explain why some slides show only necrotic villi, while others show involuted or subinvolutated vessels (3). Random sections rarely sample spiral arteries (27); and if the literature is any guide, veins are appreciated even more rarely (26,28,29). When the placental site is not grossly obvious, serial sections are needed to show these vessels (23,30).

The observations of Khong and Khong in cases of delayed postpartum hemorrhage (3) may support this idea. They confirmed the association of retained

villi and SOPS with delayed bleeding (3,22) – 45/169 cases had retained placenta, and 30 had SOPS. Retained villi were concurrent with SOPS in 23/30 cases (77%), a higher rate than observed by Ober and Grady (53%) (3,22).

Furthermore, 31 cases had involution of the placental site (obliterated spiral arteries), only 3 of which (10%) had retained villi (3). Obliterated spiral arteries do not cause bleeding, so the observation of obliterated spiral arteries in 31/169 cases - as compared to 30/169 cases with SOPS - probably reflects sampling variation. Any one case of delayed postpartum bleeding may have multiple components of the placental site – retained villi, involuted vessels, and/or SOPS; with sampling variation explaining why some components are seen on the slides, while others are not. Thorough sampling and serial sections may be needed to evaluate this idea.

Arterial vs. Venous Delayed Bleeding in Cases with Necrotic Villi

PLACENTAL SITE ARTERIES

Prior observations do not support arterial bleeding in cases with necrotic villi. During placental site involution after placental delivery, myometrial contraction to stop bleeding leads to luminal obliteration, then intimal and medial fibrosis of spiral arteries (23,31,32). Involuting (obliterated) spiral arteries do not thrombose (23,32). No one has ever explained how an obliterated spiral artery on day 1 after delivery can turn into a dilated, thrombosed, bleeding subinvoluting artery weeks to months later. Neither has anyone explained how a dilated thrombosed subinvoluting artery that causes bleeding was prevented from bleeding for weeks to months.. Thus, interpretation of subinvoluting vessels as arteries contradicts the presentation as abrupt onset of bleeding weeks to months later.

Acute spiral artery thrombosis may be associated with coagulopathies, low uteroplacental blood flow, infarcts, and ischemic changes; but not with hemorrhage (27). Reactions to chronic, organizing thrombi distort the vessel wall, so that it is hard to tell arteries from veins (22,23,27), favoring the diagnosis of “maternal decidual vasculopathy” (15). However, these thrombosed vessels - recognized as arteries by clustering (23,27,29) - do not cause bleeding.

PLACENTAL SITE VEINS

Brosens did serial sections to study placental site veins in Cesarean hysterectomies and placental bed biopsies before placental site involution, although his primary interest was spiral arteries in pre-eclampsia (30). He noted that veins run parallel to the basal plate, have nonvillous trophoblasts around them and in fibrinoid in the wall, with tips of villi in the lumen; and with intimal cushions of fibrous tissue and smooth muscle (30). Rutherford and Hertig noted that immediate control of bleeding by myometrial contraction after placental delivery results in thrombosis of placental site veins (31). In retrospect, it is clear that increased intramural pressure (33) must obstruct venous drainage before it can obstruct flow in physiologically transformed spiral arteries. Increased pressure probably causes endothelial injury (34); and hypoxia probably promotes coagulation (33); completing Virchow’s Triad (33), and resulting in venous thrombosis (23,31,32). Hemorrhagic necrosis due to placental site venous thrombosis - i.e., venous infarction - best explains sloughing of bloody necrotic tissue after delivery.

Ober and Grady noted that thrombosed vessels in SOPS were so altered that it was difficult to tell if they were arteries or veins (22). Nonetheless, they were

interpreted as arteries because they were thick-walled and hyalinized (22,31). Despite failure of elastic stains to confirm that they were arteries; later authors eventually ceased to consider that they might be veins (26,28). However, studies of failed saphenous vein grafts in coronary artery surgery have shown that thrombosis can lead to intimal hyperplasia, thickened walls, and frank atherosclerosis (34).

When Rutherford and Hertig first described SOPS, they did not address the need to replace obliterated spiral arteries in order to restore placental site endometrium to "the nongravid state readied for reimpregnation" (31). Placental site tissue damage after delivery probably stimulates angiogenesis (13). Indeed, Doppler ultrasound now shows that cases of retained placenta develop a zone of myometrial hypervascularity (35). Thus, when bleeding is delayed for weeks to months, histology probably reflects reactions to tissue damage after delivery.

Meticulous comparison of veins to arteries during placental site involution in uteri from postpartum maternal deaths, Cesarean hysterectomies, and postpartum hysterectomies for sterilization (23,32) showed that venous thrombosis can involve deep myometrial veins, and that placental site veins can be hyalinized. Ober and Grady showed that thick-walled vessels in SOPS were increasingly hyalinized from about 2 weeks after delivery to about 4 weeks after delivery (22). This further suggests that the histology weeks to months later is a reaction after delivery. We have observed hyalinized thick-walled veins in the evolution of hemorrhagic venous infarcts induced by venous thrombosis in benign endometrial polyps (33). We suggest that the vessels of SOPS may be thrombosed veins. Venous origin of SOPS

may explain why uterine artery embolization is an ineffective treatment for postpartum bleeding due to SOPS (36).

Anderson and Davis suggested in 1968 that trophoblasts might be found in and around placental site veins, verified by Brosens in 1988; while Andrew et al saw keratin-positive cells in and around the vessels of SOPS (23,28,29). This further supports a venous origin of bleeding in SOPS, but it must be acknowledged that placental site veins have never been scrutinized with the keratin stains that are now considered essential for optimal identification of trophoblasts (11,14,28). When hysterectomies are not available, future studies should consider hysteroscopic resection, rather than curettage; since hysteroscopic sampling is more often complete (99% vs 71%), and results in fewer intrauterine adhesions (Asherman's Syndrome) (13% vs 30%) (9).

In closing, we note that studies of uterine vasculature show that uterine veins run next to arteries (37); so that observation of the large dilated thrombosed vessels in SOPS next to involuted arteries with normal elastica on EVG stains also suggests that subinvoluted vessels are veins (22,26). In conclusion, we suggest that thrombosed veins at the placental site - and in deeper myometrium - at the time of placental site involution; may become thick-walled and hyalinized, with endothelial proliferation and intimal fibrosis over a period of weeks to months; and that revascularization of the placental site may cause hemorrhagic venous infarction as the most likely cause of delayed bleeding in cases with necrotic villi.

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Legends for Illustrations

Figure 1a – Blood clot in cornu was above a grossly occult intramural mass composed of necrotic and sclerotic villi, consistent with retained placenta.

Figure 1b – Despite the delayed postpartum hemorrhage and sclerotic villi, consistent with retained placenta; there appeared to be direct contact of villi with deep (middle third) myometrium, suggesting placenta increta.

Figure 1c – Keratin stain (AE1/AE3) at this location showed predominance of nonvillous trophoblasts, going much deeper (right side of photograph) than villi.

Figure 1d – H&E stain of another area shows interstitial trophoblasts going deeper than sclerotic villi, as seen in placenta increta. Outer surface of uterus was located about 1 cm. from bottom of this field. On H&E, myometrium appears intact.

Figure 1e– MSA actin stain showed myometrial damage in the zone where keratin stain demonstrated deep interstitial trophoblasts. Deep myometrium (on right) is relatively intact. Nuclei of nonvillous trophoblasts are evident in zone of muscle destruction.

Figure 2a - MSA+ myofibers not seen on H&E are high in the basal plate in the spontaneous abortion specimen. Blood is present above basal plate.

Figure 2b – Myometrium had a lymphoid infiltrate, but no plasma cells were seen. Note pale grey-pink matrix in that area.

Figure 2c – Pieces of myometrium had conspicuous interstitial trophoblasts, with degenerated myometrium in lower left corner.

Figure 2d – Shriveled myofibers are amidst lymphoid infiltrate. More normal myometrium is at bottom.

Figure 2e – Top left has keratin-positive interstitial trophoblasts without dendrites. Center has keratin-positive endovascular trophoblasts in a dilated vessel. Bottom right has keratin-positive interstitial trophoblasts with dendrites, which was in the zone of degenerated myometrium. Dendrites may connote active invasion.

Figure 3a – MSA actin-positive BPMF were seen at a site next to where the maternal surface had grossly torn cotyledons.

Figure 3b – The curettage 2 weeks later had pieces of damaged myometrium with a lymphoid infiltrate (but no plasma cells) (top), best demonstrated with the MSA actin stain. More normal myometrium is at bottom.

Figure 3c – CAM5.2 keratin stain shows darkly stained trophoblasts in the zone of damaged myometrium. Myofibers stain weakly in the background on the keratin stain, which is not uncommon.