Association of retroplacental blood with basal plate myofibers

ASSOCIATION OF RETROPLACENTAL BLOOD WITH BASAL PLATE MYOFIBERS

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Running Title: Retroplacental Blood and Basal Plate Myofibers

Abstract

Objectives: Diagnosed clinical abruption showing blood clot should be signed out in the pathology report as retroplacental hemorrhage with or without parenchymal indentation, and submitted clot separate from the placenta should be weighed. In our experience some cases sent as clinical abruptions have been cases of morbid adherence. This study was undertaken to evaluate the association of retroplacental blood with basal plate myofibers (BPMF).

Methods: 156 placentas reviewed by a board certified pediatric pathologist at a community hospital were evaluated for significant retroplacental blood. Basal plates were reviewed for deviations from normal.

Results: 33/156 placentas (21%) had significant retroplacental blood. 21/156 (13%) had a separate clot, of which 11/21 (52%) had basal plate myofibers (BPMF). 11 BPMF-associated separate clots ranged from 10.5-60 gms (average 23); while the clots of 10 cases with no demonstrated BPMF ranged from 19-440 gms (average 82), tending to be larger ($p<.03$). Basal plate damage prior to delivery was noted in both sets of placentas. BPMF placentas could have myometrial damage prior to delivery.

Conclusions: Since BPMF may confer a risk for accreta in a subsequent pregnancy, submission of a separate clot with the placenta should lead the pathologist to evaluate for basal plate myofibers on H&E, and consider if there is an evidence-based indication to do an actin stain; before presuming a diagnosis of abruption.

Key words: Placenta, basal plate myofibers, abruption, accreta

Introduction

This study was undertaken in the context of practice at a busy community hospital which also signs out placentas from 4 other community hospitals, after various hospital and laboratory mergers. Almost all placentas are signed out by general pathologists, who struggle to keep up with the placental workload, while giving priority to general surgical pathology in adults. Little or no clinical information is written on some placental pathology requisitions, especially in regard to abruptions; so it is unwise and inappropriate to regard the information on the pathology requisition as "the gold standard". This creates a common and somewhat problematic scenario that has been eloquently described by Dr. Frederick T. Kraus (1,2).

The recent Amsterdam placental workshop report (3) had a major impact in this practice setting. It was copied and distributed to all general pathologists, so that signouts would be guided by this 2016 expert consensus. This paper had a short section on retroplacental hemorrhage, stating that cases of clinical abruption where there is associated blood clot seen by the pathologist should be signed out as retroplacental hemorrhage; and that "Any clot that is separate from the placenta but submitted in the specimen container should be weighed." This provides pathologic confirmation of operative reports describing retroplacental blood detected during placental delivery; which may be important for medicolegal purposes (4). However, one can have abruption without the pathologist being able to detect significant retroplacental blood clot; and, retroplacental hematomas can be observed without clinical abruption (5).

No other cause for retroplacental hemorrhage was mentioned in the short section of the Amsterdam report, suggesting that a pathology diagnosis of retroplacental hemorrhage is equivalent to a clinical diagnosis of abruption. This interpretation was reinforced by a prior expert consensus (6), and by the frequent failure of such cases to have the word abruption written on the pathology requisition, implying that some clinicians felt that retroplacental blood "spoke for itself" (res ipse loquitur).

Nonetheless, we chose to study the association of retroplacental blood with basal plate myofibers because we have seen cases submitted as abruption that turned out to be cases of morbid adherence. It is well known that postpartum hemorrhage may be observed if there is morbid adherence of the placenta (7). Morbid adherence can result in retained placenta (7-10), and prolongs placental delivery; so we reasoned that retroplacental blood might appear behind part of the placenta while another part is still adherent. An indicator of morbid adherence is finding basal plate myofibers (BPMF), although only a fraction of BPMF placentas have clinical morbid adherence (7,9-17).

Recent studies have evaluated hemorrhage in morbidly adherent placentas vs. controls (15), and in recurrent morbid adherence, as compared to the first morbidly adherent placenta (17) However, the relative contributions of premature separation (abruption) vs. morbid adherence to retroplacental bleeding has not previously been studied.

The emphasis was on identifying BPMF as a risk factor for morbid adherence in the next pregnancy, so that an antepartum ultrasound could be performed to try to anticipate significant postpartum hemorrhage (9,12-15,17). This makes detection of BPMF a screening test, and clinicians at the study institution accept that there may be false positives and false negatives. The approach was to use evidence-based indications for actin immunostains to enhance detection of BPMF. This may increase potential false positives (i.e., BPMF without clinical accreta) while reducing false negatives (clinical accreta without BPMF) (11,15,17).

Methods

This is a descriptive series, prospectively collected. Between June 2, 2016 and October 13, 2016. 156 routine placentas signed out by a board-certified pediatric pathologist (SFC) were evaluated for significant retroplacental blood. This constituted 11% of 1471 placenta cases in 2016,. None of the placentas were associated with perinatal autopsies, or urgent clinical scenarios. Routine gross examination had been done by experienced pathology assistants who had been trained by the pediatric pathologist to pay special attention to separate blood clots, and to subtle retroplacental blood of potential medicolegal significance (3,4).

The principal focus was on cases with separate blood clot submitted with the placenta. Cases with grossly identified retroplacental hematomas were included. In cases with "scant" retroplacental blood, noted on gross and/or microscopic exam, the subjacent placental tissue was scrutinized for microscopic indentation of the maternal surface and/or related findings (compressed villi, loss of intervillous space, marked villous congestion, intravillous hemorrhage), as in abruption (4); or

BPMF, consistent with morbid adherence (7,9-15,17). "Scant" was defined as areas of non-circumscribed retroplacental blood. These could measure up to 1-2 cm. thick on gross exam, or be purely microscopic. We also evaluated placental weight, gestational age, maternal age, other clinical history, and other pathology diagnoses.

The routine protocol was 1 block with cord and membranes, and 2 blocks of placenta, one central and one halfway to the margin; with extra sections for gross lesions. Separate blood clots were not examined microscopically, since none were admixed with tissue fragments. Gross retroplacental hematomas had representative sections to show the relation to underlying parenchyma, as did cases with "scant" retroplacental blood (4). On histologic review, deviations from the normal admixture of decidual and trophoblast cells were noted. All cases were photographed for documentation and analysis.

BPMF were considered hypertrophic if they had low nucleus/cytoplasm (N/C) ratios as in gestational hypertrophy of myocytes. Myofibers with higher N/C have been illustrated previously (7), and are described as shriveled. When it is difficult to be sure they are smooth muscle cells on H&E, they are described as spindle cells (Figure 3). When they lack nuclear staining, they are described as degenerated (Figure 2a).

At the time of this study, indications for doing actin stains were not standardized in either textbooks or previous literature (9-15). An evidence-based approach was used: 1) MSA actin immunostains were done if BPMF were suspected on routine H&E stains, but needed confirmation; 2) They were also done when BPMF were not suspected on routine H&E slides, if the history suggested possible

accreta (e.g., prior C-section, placenta previa, manual removal, retained placenta, grossly disrupted maternal surface, prior history of accreta, ultrasound suspicion of accreta) (9-14); 3) Based on previous work on morbidly adherent fetal membranes in association with morbidly adherent placentas (7), some cases had MSA stains after finding dilated endometrial gland remnants and infiltrative chorion in sections of fetal membranes. Such cases routinely have smooth muscle in the decidua of fetal membranes, and this finding also led to MSA stains for BPMF; 4) Based on the work of Stanek and Drummond (12), MSA actin stains were also done after finding decidual hemosiderosis, consistent with prior retroplacental bleeding. Cases lacking any indication did not get actin stains.

Statistical analysis was performed using independent t-tests to compare mean differences between placentas with and without demonstrated BPMF in regard to amount of separate blood clot, maternal age, gestational age, and placental weight. Chi square tests were also performed.

Results

33/156 cases (21%) had significant retroplacental blood. Table 1 has 12 cases with no BPMF on H&E, and no evidence-based indication to do an actin stain. Table 2 has cases that had either BPMF on H&E, or an evidence based indication to do an actin stain (all of which were positive). 21/156 cases (13%) had a separate blood clot submitted with the placenta, and the weight of these clots was measured.. Three gross retroplacental hematomas were identified, and purely microscopic clots with placental indentation were noted (Table 1, Table 2, Figure 1). Two cases had

decidual hemosiderosis,, and 4 cases had extravasated red blood cells inside the basal plate.

11/21 cases with separate blood clot (52%) turned out to have BPMF and are in Table 2. The amount of separate blood clot in these 11 cases ranged from 10.5 to 60 grams (average 23 grams) (Table 2). The 10 cases of separate blood clot in Table 1 (with no BPMF seen on H&E, and no evidence based indication to do an actin stain) ranged from 19 to 440 grams (average 82 grams) (Table 1). An outlier with 440 grams of separate clot (Table 1) was Winsorized by transformation to 2 standard deviations above the mean (i.e., 73.2), yielding a mean of 45 grams. The difference between placentas in Table 1 and Table 2 was then evaluated with an independent t-test and was shown to be significant ($t=2.72$, $df = 19$, $p<.03$).

An unexpected finding was that degenerated BPMF were directly associated in one case with subjacent intraplacental hemorrhage (i.e., intervillous thrombus) (Figure 2a). MSA stain was done for confirmation (Figure 2b), and separate blood clot had been submitted. A total of 7 cases had intervillous thrombi – 3 with BPMF.

Both placentas with and without demonstrated BPMF had histologic evidence of basal plate damage that has not been previously described, namely anuclear zones in the basal plate (Figure 1a) and spindle cells in the basal plate (Figure 3). 13/21 = 62% of BPMF placentas had anuclear zones, vs. 10/12 = 83% of cases without demonstrated BPMF. 3/12 cases without demonstrated BPMF (25%) had spindle cells in the basal plate, vs. 6/21 = 28% of placentas with BPMF. Chi-square analyses showed that these differences are not statistically significant. Less common basal plate abnormalities included acute deciduitis, chronic deciduitis with

plasma cells, gaps in the basal plate, villi under the basal plate, and extravasated blood inside the basal plate. Microscopic disruption of the maternal surface (defined as the microscopic counterpart of torn cotyledons on gross exam) was occasionally observed in placentas with and without demonstrated BPMF. This term was not used when there were torn cotyledons on gross exam (2 cases).

Clinical correlations (Table 1, Table 2) included 6 cases with diabetes or macrosomia (4 with BPMF); 7 cases with hypertension (6 with BPMF (not statistically significant)); 2 cases with pre-eclampsia (both with BPMF); 4 cases with prior C-section (all with BPMF); and one twin pregnancy, which had BPMF. There was 1 case of prematurity before 32 weeks (9), with 60 grams of separate clot, with no demonstrated BPMF.

BASAL PLATE MYOFIBERS

On H&E, BPMF were hypertrophic in 6/21 cases (30%); one of which had myofiber disarray (Figure 4). Hypertrophic BPMF could coexist with shriveled BPMF (5). Shriveled BPMF could resemble basal plate fibroblasts on H&E, with no discernible cytoplasm, or could be spindle shaped cells with scant cytoplasm. In addition to being hypertrophic, shriveled, or degenerated (Figure 2), BPMF could be frankly necrotic. Necrotic BPMF were sometimes seen inside the retroplacental blood. In our experience, tangential sections of basal plate vessels lead to small foci with a linear basal pattern on the maternal surface, easily distinguished from BPMF.

20/21 BPMF placentas had a finding on H&E that prompted either outright diagnosis of BPMF (6 cases), or an actin stain for further evaluation (14 cases) (Table 2). Besides seeing suspected degenerated, shriveled, or necrotic BPMF,

indications included smooth muscle or related findings in the fetal membranes, villi under the basal plate, spindle cells in the basal plate (Figure 3), and decidual hemosiderosis (10). In 1 case with separate blood clot, and microscopic clot with placental indentation, the MSA stain was done for a history of prior C-section.

MATERNAL AGE, GESTATIONAL AGE, AND PLACENTAL WEIGHT

For the BPMF placentas, maternal age ranged from 18 to 40 years (average 30.6). In the other placentas, it ranged from 20 to 39 (average 28.9). The BPMF placentas had gestational ages of 36 to 41 weeks (average 39), with no prematurity <32 weeks (7). The other placentas ranged from 22 to 40 weeks gestation (average 36), with 1 case < 32 weeks. The BPMF placentas (excluding the twin placenta) ranged from 315-724 grams (average 510 grams), while the other cases ranged from 211 to 793 grams (average 466 grams). Independent t-tests showed no statistically significant differences in maternal age, but gestational age was significantly higher for BPMF placentas ($p<01$). Placental weight was higher for BPMF placentas, as expected due to higher gestational age, but this was not statistically significant due to small sample size.

Discussion

The incidence of placenta accreta has increased 10-fold as the rate of Cesarean section has increased (1,13,15). As a result, a major concern in obstetric practice is whether there is a risk of accreta in a subsequent pregnancy. At Rochester General Hospital, this has led to a focused effort to detect BPMF, so that an ultrasound before the next delivery may help prevent postpartum hemorrhage from a morbidly adherent placenta (10-15,17,18). Decidual deficiency is not

required to report a BPMF placenta because 1) decidual deficiency is usually focal, 2) decidual deficiency may not explain all morbid adherence, and 3) clinical morbid adherence can yield a BPMF placenta with no decidual deficiency (7,15,16,19). Outright diagnosis of placenta accreta is not made in placental pathology reports at Rochester General Hospital. Instead, reports of BPMF placentas may have comments about accreta, such as "consistent with", "suspicious for", or "cannot be excluded".

Some clinicians at this community hospital may feel that separate blood clots imply abruption (res ipse loquitur), since the pathology requisitions said abruption in only 2/21 cases with separately submitted blood clots. Indeed, a 440 gram separate clot with an 8 cm retroplacental hematoma did not have abruption written on the pathology requisition (Table 1). Alternatively, this may simply reflect poor communication, as eloquently described by Kraus (1,2). On the other hand, one BPMF placenta was submitted as "consistent with abruption", one as "marginal blood clot" (with no gross hematoma and no separate clot), and one as "anemia" (with a 4.5 cm gross retroplacental hematoma) (Table 2). Ironically, no BPMF placentas in this study had clinical evidence of morbid adherence noted on the requisition.

We now feel that cases with separate blood clots, with evidence-based indications to assess for BPMF, should have actin stains, if necessary. In this small study, 11/21 (52%) of cases with separate blood clots had BPMF placentas. However, we feel this should be confirmed by others before recommending actin stains on all cases with retroplacental hemorrhage. Further study is needed.

At first glance, premature separation (abruption) and failure of separation (morbid adherence) would seem to be mutually exclusive mechanisms for retroplacental hemorrhage. However, it was recently suggested that low uteroplacental blood flow may co-exist with morbid adherence (15). On further consideration, ischemic injury to retroplacental blood vessels leading to abruption before delivery does not seem inconsistent with morbid adherence during delivery.

Although Ernst et al reported multiple infarcts as evidence of low uteroplacental blood flow in 5/101 cases of morbid adherence (15), we had no multiple infarct cases. Table 2 suggests that 2/21 BPMF placentas in this study, with histories of pre-eclampsia, may have had both low uteroplacental blood flow and morbid adherence. Numbers in both studies are small, so more study is needed.

The BPMF placentas in the present study are different from the 101 placentas clinically classified as morbid adherence by Ernst et al (15). Using a classification system ranging from stage 1 (intact decidua) to stage 3 (absent decidua), they reported that 10% of morbidly adherent placentas were stage 1, 13% stage 2, 34% stage 3, and 50% qualified as placenta increta or percreta. Their control placentas from cancer patients could have histories of simple manual removal, and although 60% had no BPMF, 32% were stage 1, with 8% stage 2. Our BPMF placentas included Ernst stages 1 to 3, and none had clinical histories of manual removal, retained placenta, or clinical suspicion of accreta; although paradoxically – 11/21 had separate blood clots and 1 had a gross retroplacental hematoma (Table 2).

BPMF placentas are found in routine practice at this community hospital at a similar rate to some previous reports. In 2009-13 at Rochester General Hospital, 137/4038 placentas (3.4 %) were reported to have BPMF. This figure is similar to that at another institution that submitted 2 routine blocks per case (12). It also resembles the data at a hospital that submitted 4 blocks per case, but did less immunostains (10). BPMF were found more frequently in some academic studies that submitted more blocks (11,13-15).

To aid screening for BPMF without the added time and expense of submitting more blocks, it is helpful to have clues for when to do actin immunostains. One clue is a history of placenta previa (15), but there were no previas in this study. Another is prior C-section, and all cases in this study with prior C-section had BPMF. Manual removal, retained placenta, prior accreta, grossly disrupted maternal surface, and ultrasound evidence of accreta are all rational reasons to do actin stains, if needed.

Some clues are microscopic. Infiltrative chorion and dilated endometrial gland remnants in the decidua of fetal membranes may be seen in morbidly adherent fetal membranes; associated with placenta increta (7). In our experience, such cases have smooth muscle in the decidua of fetal membranes, and also tend to have BPMF. Six BPMF placentas in this study had clues in sections of fetal membranes. Four had subchorionic fibrous nodules in the decidua of fetal membranes, a lesion first observed at the placental margin in a case submitted as placenta percreta. Two cases were scrutinized for BPMF after finding decidual hemosiderosis (12). This constitutes an evidence-based approach.

The frequent use of actin stains may make the BPMF cases in this study different from those in other studies. An early study reported no immunostains (9). Khong and Werger did immunostains in 11/27 BPMF cases, 4 of which were not helpful (11). Four other papers illustrated immunostains, but did not give data on how often they were helpful (10,12-14). We found actin stains to be helpful in 15/21 (70%) BPMF placentas. Actin stains can be positive when BPMF are shriveled (7), degenerated (Figure 2b), necrotic, or not seen at all on H&E stains (perhaps due to sampling variation).

Hypertrophic BPMF may correspond to most BPMF placentas reported previously, including some with grossly visible myometrium (9-14); but comprised only 30% of our BPMF placentas. This report documents that hypertrophic BPMF may have myofiber disarray – as seen in C-section scars and postablation scars; suggesting prior myometrial damage before being cleaved from the uterus by shear stress during placental delivery (7,16,19,20). Our experience suggests that actin-positive BPMF not seen on H&E may be markers for hypertrophic BPMF that can be found on H&E if more blocks are submitted and/or sections are cut deeper.

Nonetheless, the question may legitimately be raised whether BPMF requiring immunostains for diagnosis are clinically significant (17). There is as yet no published data to answer this question definitively, but we have had many cases with histories of manual removal, retained placenta, clinically suspected accreta, torn cotyledons, and even placentas received in pieces, where BPMF were demonstrable only with actin immunostains (but not in this study). If one believes that it is useful to screen for BPMF as a guide to management of future pregnancies,

we do not believe that utility is compromised just because the disease process damages the BPMF to the point where actin stains may be needed for confirmation.

In addition to decidual hemosiderosis (12), we found other evidence of basal plate damage prior to delivery – namely anuclear zones (Figure 1a) and spindle cells in the basal plate (Figure 3). Both BPMF placentas and cases of retroplacental blood without demonstrated BPMF could have these features. Anuclear zones seem to be an early stage, with spindle cells being a later stage. In our experience, both findings can be focally transmural across the basal plate, with no residual decidual or trophoblast cells. Usually, however, they are quite patchy. These findings of basal plate damage prior to retroplacental bleeding provide further insight into the pathogenesis of morbid adherence (15).

We note that "spindle cells" is a descriptive H&E term, while "shriveled myofibers" can be a descriptive actin stain term in cases with no BPMF seen on H&E. Some cases have a one to one correlation of spindle cells on H&E with shriveled myofibers on the actin stain. When a one to one correlation is lacking, this may be due to sampling variation. The possibility that some spindle cells may be actin-positive myofibroblasts in reaction to basal plate damage cannot be excluded. More study is needed on this question.

The question may also be raised as to actin stains on "normal controls", a subject not previously addressed (10-14). We believe this is a challenging question to address because 1) many cases that might be considered "normal controls" have inadequate sampling of the basal plate, as observed in placentas from hysterectomies for placenta accreta (21); and 2) many cases signed out as having

normal basal plates may have evidence of basal plate damage before delivery. In addition, shrunken, degenerated or necrotic BPMF may have been overlooked in "normal controls". A large scale systematic study may be needed to correlate actin stains of "normal controls" with basal plate sampling and diverse abnormalities of the basal plate.

Some prior studies of BPMF placentas have noted differences in maternal age, gestational age, and/or placental weight; but none of these studies is strictly comparable to ours or to each other (9-14). One focused on association of BPMF with prematurity<32 weeks; another focused on gross disruption of the maternal surface; and others chose to study pre-selected cases with clinical accreta on follow-up, as compared to control placentas from cases of maternal malignancy. Most recently, some BPMF placentas were classified as morbid adherence based on operative reports, while others were classified as controls even if there was a history of simple manual removal (15).

CONCLUSIONS

These observations support the idea that retroplacental blood may accumulate when part of the placenta is delivered, while another part is still adherent to the wall. Bleeding may come from the disrupted basal plate and/or the subjacent myometrium, both of which may have tissue damage prior to delivery. We sometimes observed actin-positive BPMF predominantly adjacent to placental indentation (Figure 1b); suggesting that indentation may occur during placental delivery. This may be an early step in BPMF-associated retroplacental bleeding. As more blood accumulates, presumably with more force (likely iatrogenic); blood may

be seen subjacent to BPMF; degenerated or necrotic myofibers may be seen projecting from the maternal surface and/or in the clot itself; or BPMF may be seen in association with submission of separate blood clot. As in abruptions, BPMF placentas may be associated with fetomaternal hemorrhage (intervillous thrombi (Figures 2a,b)) (15). We have also seen intravillous hemorrhage (4) in BPMF placentas. When BPMF placentas have decidual hemosiderosis (12), we speculate that subclinical bleeding occurred during Braxton-Hicks contractions; permitting hemosiderosis to evolve from extravasated blood in the basal plate.

Although clinical variables (9-15,17) may increase the risk of morbid adherence; such information is usually not on the pathology requisition. We suggest that it is the pathologist's job in routine practice to look for BPMF, based on 1) history received on the requisition, 2) data in the pathology files, 3) gross findings, and 4) microscopic examination. Conversely, it is the clinician's job to make the judgment – taking all known clinical data into account - whether an ultrasound should be performed in subsequent pregnancies to try to anticipate and prevent postpartum hemorrhage (18). Evaluation for BPMF may be perceived as a screening test; but a false positive in the absence of significant morbidity (17) may only lead to a non-invasive ultrasound. More work is needed regarding the recurrence rate and clinical significance of BPMF placentas, in the absence of clinical accreta (7,9-15,17).

Lastly, we note that although some may regard most BPMF placentas as being of questionable significance, it was recently reported that half the cases with major hemorrhage (>1500 cc) in the following pregnancy were in patients where the initial placenta accreta was recognized only by the pathologist (17). We agree

with those authors that careful assessment and management of future pregnancies merits consideration when the only evidence of accreta is histologic (17).

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LEGENDS FOR ILLUSTRATIONS

Figure 1a – Retroplacental blood with indentation of maternal surface at 37 weeks. Basal plate above clot in center appears hypocellular, almost anuclear.

Figure 1b - MSA actin stain shows BPMF adjacent to and partly above placental indentation by microscopic retroplacental clot (lower left).

Figure 2a – Degenerated basal plate myofibers have loss of nuclear staining (arrow), subjacent to fetomaternal hemorrhage (intervillous thrombus).

Figure 2b – MSA actin stain confirmed BPMF under the intervillous thrombus.

Figure 3 – Spindle cells in basal plate. MSA actin stain was positive in these spindle cells.

Figure 4 – Hypertrophic basal plate myofibers with myofiber disarray at 40 weeks. Scant retroplacental blood was nearby.