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RECURRENCE OF BASAL PLATE MYOFIBERS

With Further Consideration of Pathogenesis

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ABSTRACT

Objectives: Basal plate myofibers (BPMF) may indicate morbid adherence. We assessed recurrence and clinical progression of BPMF.

Methods: In 5 years, 135 BPMF placentas were reported. Controls were the first 50 placentas in 2009, none of which had reported BPMF.

Results: 32% of BPMF patients had other placentas, with a recurrence rate of 100%. Actin stains were needed for diagnosis in 117/179 cases (65%). These cases had clinical features suggestive of morbid adherence in 69/117 (59%). 23/47 (49%) of BPMF recurrences progressed in severity, 5 to hysterectomy (11%). Thinning of the basal plate, perforating vessels, gaps in the basal plate, and villi under the basal plate were observed in BPMF placentas.

Conclusions: These findings appear to validate screening for BPMF. The 100% recurrence rate suggests evaluation for a heritable factor, i.e., protease inhibitor deficiency, which may explain pre-delivery basal plate damage.

INTRODUCTION

In 1997, the College of American Pathologists formulated guidelines for placental examination (1). Subsequent studies showed that some institutions followed those guidelines poorly, while others more recently followed them much better (2-4). However, there are still major obstacles to optimal use of placental pathology reports, including failure of clinicians to provide adequate history and failure of clinicians to understand pathology reports (2,5,6).

The fundamental purpose of placental pathology reports is to find something on the slides that has a significant impact on the future health of the patient, and is therefore meaningful to the clinician. Perhaps the best example of this is the relation of histologic chorioamnionitis to severity of illness in very low birthweight newborns (7). It has been shown that adequate sampling may be important in detecting histologic chorioamnionitis (8).

The placenta is the only tissue routinely submitted to pathology that had contributions from two separate human beings – the mother and her newborn; thus, placental pathology reports can also have implications for the future health of the mother (6). Placenta accreta can cause life-threatening postpartum hemorrhage, and its frequency has increased tenfold as the rate of Cesarean section has increased (9). This has caused increasing concern amongst clinicians, but it is not listed in the 1997 CAP guidelines for placental examination; at least partly because much of the important work in this area has been done after 1997. In 2001, Khong and Werger brought to the attention of general pathologists that basal plate myofibers (BPMF) can be found in the absence of clinical evidence of placenta accreta (10). Ernst and

co-workers have suggested that BPMF are a risk factor for future placenta accreta (11,12). Most recently, it was reported that half the cases with major hemorrhage (>1500 cc) in the following pregnancy were in cases where the only evidence of placenta accreta was histologic (13). Both submitting more blocks, and adjunctive immunostaining for muscle markers, can enhance detection of BPMF (6,10). In addition, it is only recently that the pathogenesis of pre-delivery basal plate damage in BPMF placentas has been seriously addressed (6,9,14).

The purposes of this study were 1) to assess recurrence and progression of BPMF placentas, and 2) to further evaluate pre-delivery basal plate damage in BPMF placentas.

METHODS

This is a “pathology only” study at a community hospital. The study was regarded by our Clinical Investigation Committee as a quality assurance study. Clinical information was limited to what was in the pathology report. This information was either written on the pathology requisition, or communicated to the pathologist at the time of placental diagnosis. All BPMF placentas 2009-2013 were reviewed. Pathology files were checked for a prior or a subsequent placenta.

Slides of these patients’ other placentas were reviewed for BPMF, with actin stains (MSA and/or SMA) as needed. Actin stains were done only for evidence-based indications (6), including either a history of a BPMF placenta, or a history of “prior Cesarean section, rule out accreta”. Other evidence-based indications included retained placenta, manual removal, fragmented placenta, ultrasound evidence of accreta, adherent placenta and/or fetal membranes (15) detected at

delivery, and torn cotyledons during placental removal (10). Diagnoses made on the BPMF placentas were reviewed. A few cases had curettages after placental delivery. Such specimens may have necrotic villi consistent with retained placenta, and/or retained fetal membranes (15,16). Curettages were classified as BPMF placentas only if myometrium was in placental tissue. All BPMF placentas were photographed, and evidence of pre-delivery basal plate damage (6,9,14) was further explored.

The first 50 placentas received in 2009 served as a control group. Controls were submitted by Obstetricians as per guidelines of the College of American Pathologists (CAP) (1); although compliance with the guidelines was variable. As per CAP guidelines, a refrigerated placental storage unit was set up in Pathology, to store placentas not sent for Pathology examination, for a week. This permitted Neonatologists to request placental examination if the baby did not do well; which raised the frequency of placental reports available for review at monthly Perinatal Morbidity & Mortality Committee meetings from about 50% to nearly 100%. The controls did not get actin stains. Control placentas were mostly evaluated by general pathologists; whereas cases of suspected accreta and cases submitted by Neonatologists were often handled by a board certified pediatric pathologist.

Placentas submitted for indications unrelated to morbid adherence were called “routine placentas”. This included the controls, and also some BPMF placentas. Differences in clinical features suggestive of morbid adherence between BPMF patients with BPMF recurrence and BPMF patients with only 1 placenta were analyzed with a Pearson Chi-Square test.

RESULTS

135 BPMF placentas were reported at our institution from 2009-13 (Table 1). This constituted 3.4% of 4038 placentas signed out in 2009-13. One patient in 2009 was also on the list for 2011, and another for 2012. One patient on the list for 2011 was also on the list for 2013. Thus, the number of BPMF patients was 132.

None of the 50 control placentas had reported BPMF. Indications for placental examination included suspected infection (9), meconium (6), diabetes and/or macrosomia (8), pre-eclampsia or hypertension (6), possible abruption (2), cord lesions (3), twins (3), premature fetal death in utero (3), postdates (2), neonatal respiratory distress (1), and dysmorphic infant (1). 8 cases had no history given, and a few cases had more than one of the above indications.

32% (42) of the 132 patients with BPMF placentas had another placenta in the files, about half prior and half subsequent. The BPMF recurrence rate was 100%. 5 BPMF patients had 3 placentas each, and all 5 had 3 BPMF placentas. The total number of patients with recurrent BPMF was 42, and the total number of BPMF recurrences was 47. The total number of BPMF placentas reviewed was 179 (Table 1). There were other placentas in 28% of the control group, none reported as a BPMF placenta.

90 patients had only one BPMF placenta on file, and clinical features suggestive of morbid adherence are listed in Table 2. 24/90 (27%) had “retained placenta”; 21/90 (23%) had “manual removal”; and 17/90 (19%) had fragmented placentas (received in pieces). There were 3 hysterectomies for increta. Some cases

had more than one of these features, and/or other features of morbid adherence (see Methods). 21/90 cases (23%) were “routine” placentas.

The clinical information communicated to Pathology on the 89 placentas in 42 patients with BPMF recurrences are listed in Table 3. The only notable difference was that there were more routine placentas in this group - 32/89 (36%). This difference was analyzed with a Pearson Chi Square test, which gave a figure of 3.420, with DF =1, and $p=.0644$.

Among the “routine” placentas were 5 cases sent as abruptions, 8 with separate blood clots (ranging from 4-23 grams, with an outlier of 256 grams), and 31 with retroplacental blood clots seen on the slides. Two cases had membrane hematomas. 14 cases had evidence of low uteroplacental blood flow (5 with multiple infarcts, 9 with pre-eclampsia). Several cases had plasma cell deciduitis.

12 patients with >1 BPMF placenta 2009-13 had a history of retained placenta in the index placenta (Table 3). 4 patients with recurrent BPMF had a prior retained placenta, one of whom had 2 curettings for retained placenta after the original placenta was not sent. Two other patients with BPMF recurrence did not have the original placenta sent, but had a curettage for retained placenta, both of which turned out to have BPMF. The total was 19 histories of retained placentas among 89 placentas in patients with BPMF recurrence (21%), as compared to 24/90 (26%) in patients with only 1 BPMF placenta (not statistically significant). Two patients with recurrent BPMF placentas also had recurrent histories of retained placenta. 3 patients with recurrent BPMF placentas had histories of retained fetal membranes, one of which had a prior history of retained placenta.

Patients with recurrent BPMF had other features suggestive of morbid adherence (Table 3). Most common were a history of manual removal (no further details supplied) in 13 placentas, and fragmented placenta noted either in the history or on gross description in 14 placentas. Other clinical histories included adherent placenta, hysterectomy for morbid adherence , trapped placenta, suspected accreta, grossly adherent myometrium, accreta on Ultrasound, uterine inversion, prolonged 3rd stage of labor, and accessory lobe sent separately.

Clinical and/or histologic progression was noted in 23/47 patients with recurrent BPMF placentas (49%), including 5 cases (11%) that required hysterectomy (Table 4). The most common histologic progression was from actin positive BPMF not seen on H&E to BPMF seen on H&E, in 12 cases. Progression to histologic increta was seen in 5 cases.

Clinical progression was seen in 19 patients, with both clinical and histologic progression in 12 patients. The most common clinical progression was from a clinically routine placenta to a placenta with clinical features suggestive of morbid adherence in 14 cases. One patient progressed from a BPMF placenta with features suggestive of morbid adherence to hysterectomy. Four patients progressed from a routine placenta to hysterectomy. Combined clinical and histologic progression included 11 patients, 2 of whom had 3 placentas: 5 patients who progressed to hysterectomy with increta, and 6 patients who progressed from a routine placenta to a placenta with clinical features suggestive of morbid adherence; with BPMF seen only on actin stain progressing to BPMF seen on H&E.

117/179 BPFM placentas needed actin stains for diagnosis of BPFM (65%). 69/117 (59%) of placentas needing actin stains had clinical features suggestive of morbid adherence (Table 5).

Basal plates were reviewed for pre-delivery basal plate damage, including previously described anuclear zones and spindle cells in the basal plate, as well as decidual hemosiderosis. Anuclear zones and spindle cells could each be focally transmural, with absence of decidual and trophoblastic cells. In addition, basal plates could be markedly thinned (Figure 1A), with actin-positive BPFM (Figure 1B).

Perforating vessels could be seen to traverse the basal plate from the intervillous space, almost to the maternal surface, with intravascular villi (Figure 1C), also associated with actin-positive BPFM. There could be gaps in the basal plate (Figure 2). CD31 endothelial marker was positive at the edges of these gaps, consistent with interpretation as perforating vessels. Actin-positive BPFM not seen on H&E could be seen adjacent to such gaps. Villi could be seen beneath the basal plate (Figure 3), with CD31 endothelial marker being positive just above these subjacent villi, and MSA-positive BPFM not seen on H&E were seen at these locations.

Fibrin exudate could be seen on the maternal surface (Figure 4), with MSA-positive BPFM above the fibrin. Shriveled BPFM, easily missed on H&E, were seen in these areas. Extravasated red blood cells (the precursor of decidual hemosiderosis (6,14)) could be seen inside the basal plate (Figure 5). In some cases, hypertrophic BPFM (6) could be seen nearby, with no actin stain required. In other cases, only spindle cells suggestive of shriveled BPFM were seen on H&E, but deeper levels with

actin stains showed hypertrophic BPMF (Figure 6). The maternal surface could appear disrupted (Figure 7), a microscopic analogue of torn cotyledons; whether or not there were torn cotyledons on gross exam. BPMF could be seen in the disrupted area, more obvious on MSA actin stains.

DISCUSSION

Given recent evidence that finding BPMF in a delivered placenta may increase the future risk of potentially life-threatening postpartum hemorrhage due to placenta accreta (11-13), we suggest that routinely screening placentas for BPMF may now be justified. This screening can be enhanced by submitting more blocks (10-12), but we feel it is more cost-effective to enhance BPMF detection by performing immunostains for actins (6,10), because human labor involved in processing more blocks is more expensive than automated immunostains. There can be both false positives (BPMF without clinical placenta accreta) and false negatives (clinical placenta accreta without BPMF) (6,10-13); but the only risk of a false positive is a noninvasive ultrasound (6).

We have previously suggested (6) that: “It is the pathologist’s job in routine practice to look for BPMF, based on 1) history 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 done postpartum (17), or in subsequent pregnancies, to try to anticipate and prevent postpartum hemorrhage.

We do not believe it is the pathologist’s job in routine practice to do a complete review of the patient’s medical records before issuing a report of a BPMF

placenta. Not only is this highly impractical, it is also unreliable – since this study demonstrated that many BPMF placentas (55/179 = 31%) were found in the absence of clinical suspicion of accreta (6,9,10). Indeed, some cases submitted as clinical abruptions turn out to have BPMF placentas (6).

We advocate using evidence-based indications for actin immunostains (6), when BPMF cannot be diagnosed with certainty on H&E stains. We have shown that BPMF can be shriveled (higher N/C ratio), degenerated (no intact nuclei), frankly necrotic, or may appear as nondescript spindle cells on routine H&E stains (6). More study is needed to determine if some nondescript spindle cells may actually be myofibroblasts reacting to basal plate damage (6). We take the view that if one believes that it is useful to screen for BPMF as a guide to future management, 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 (6).

It is well known that placenta accreta tends to recur (9,11-13); but to the best of our knowledge, there is no previous formal study of the rate of recurrence of BPMF placentas, most of which do not have a clinical diagnosis of placenta accreta (6,10). Somewhat to our surprise, this 5 year review of BPMF placentas at a university-affiliated community hospital suggested that the BPMF recurrence rate may be 100%. However, this study has significant limitations (see below), so further study of the subject is needed.

Although it is well established that local tissue factors predispose to morbid adherence (e.g., prior C-section, placenta previa); it is well known that only a fraction of C-sections lead to morbidly adherent placentas (9). The present findings

suggest that the possibility of a heritable factor merits consideration. Specifically, given the role of proteases and anti-proteases in the biology of nonvillous trophoblast; we hypothesize that a heritable protease inhibitor deficiency may be involved in the pathogenesis of BPMF placentas (17-20). This possibility is made more likely by the new evidence presented herein regarding pre-delivery basal plate damage in BPMF placentas.

The first evidence of pre-delivery basal plate damage in BPMF placentas lacking a clinical diagnosis of placenta accreta was the observation of decidual hemosiderosis by Stanek and Drummond (14). In confirming this observation, we previously suggested that perhaps damage occurred during Braxton-Hicks contractions, with hemosiderosis evolving from pre-existing red blood cell extravasation in the basal plate (Figure 5). Ernst and co-workers later demonstrated association of clinical placenta accreta with other placental and basal plate pathology, including plasma cell deciduitis and evidence of low uteroplacental blood flow (multiple infarcts) (9). The present study supports those previous observations (9).

Our previous report demonstrated anuclear zones and spindle cells zones as evidence of predelivery basal plate damage in BPMF placentas that presented with retroplacental bleeding, simulating abruption (6). Both of these pathologic features might theoretically be due to excess protease activity causing damage or destruction of BPMF. Excessive protease activity due to protease inhibitor deficiency might also mediate loss of decidual and trophoblastic cells, leading to focal thinning of the basal plate (Figure 1).

It is a basic principle of pathobiology that tissue damage tends to induce angiogenesis, so it seems logical to suggest that basal plate damage may induce the formation of perforating vessels (Figure 1c), leading to gaps in the basal plate (Figure 2), and villi under the basal plate (Figure 3). Damage to these vessels may in turn explain fibrin exudate on the maternal surface of the basal plate (Figure 4) and extravasated red blood cells in the basal plate (Figure 5). Rupture of perforating vessels may also explain association of BPMF with retroplacental bleeding during delivery, simulating abruption (6).

The best known protease inhibitor deficiency disease is alpha-1-anti-trypsin deficiency, which varies greatly in severity (20). This type of phenotypic/genotypic variation may explain why some BPMF placentas present with no clinical evidence of morbid adherence, while others present with or progress to increta requiring hysterectomy. This fits well with the recent observation that accreta patients with no significant clinical morbidity may have recurrent accretas with no significant morbidity; while those which first present with significant morbidity can progress to major hemorrhage (13). It also fits with the observation that greater amounts of BPMF may be seen in patients who progress to clinical placenta accreta (11). Table 4 shows that most “routine” placentas in this study found incidentally to have BPMF had clinical features suggestive of morbid adherence in the recurrence.

Protease inhibitor deficiency diseases generally have co-factors (20), which fits with: 1) a role for local tissue factors in morbid adherence, e.g. placenta previa (9); and 2) association of morbid adherence with smoking, which promotes activity of macrophage proteases (17,20-22).

A limitation of this study is the lack of systematic chart reviews, although this may not have been fruitful. This limits clinicopathologic correlation, particularly in regard to which of these cases might qualify for a clinical diagnosis of placenta accreta (morbidly adherent placenta). However, in routine practice at this community hospital, clinicians generally do not diagnose placenta accreta unless there is a hysterectomy. This conforms with the CAP analysis in 1997, which noted that accreta is usually diagnosed accurately only when there is a hysterectomy (1). Stanek and Drummond gave criteria for diagnosing clinically occult placenta accreta in a delivered placenta in 2007 (14), and this practice appears to have been adopted by some experts in placental pathology (9,11-13); but at this community hospital, we have taken the position that such cases should be sent out for expert consultation, whenever this may be requested by our clinicians. Such requests occur roughly once a year or less.

Our view is that it may be more important to note presence of BPMF on the slides, and to note clinical features suggestive (but perhaps not diagnostic) of morbid adherence; than to be concerned about whether the clinician felt they could make an outright diagnosis of placenta accreta in the absence of hysterectomy.

This study suggested that there were more “routine” placentas in patients with recurrent BPMF (32/89) (36%), as compared to 23/90 (23%) in the patients with only 1 BPMF placenta. This difference was analyzed with a Pearson Chi Square test, which gave a figure of 3.420, with DF =1, and $p=.0644$. It is conceivable that some clinicians may discourage future pregnancies when a patient with a BPMF placenta has clinical features suggestive of morbid adherence; (e.g., manual

removal) but may be more likely to encourage future pregnancy when a patient with a BPMF placenta had no clinical features suggestive of morbid adherence. This seems to fit with the experience of Roeca et al (13).

Another limitation of this study is that the pathologists were not blinded - quite to the contrary. Although the 50 controls were mostly diagnosed by general pathologists at this community hospital; while cases with features suggestive of morbid adherence (manual removal, retained placenta, etc) were more intensively scrutinized by a board certified pediatric pathologist; the pediatric pathologist actually reviewed more than 50 "routine" placentas in which BPMF were found (the number was 55). Nonetheless, due to less intensive scrutiny of controls by general pathologists, the difference between the BPMF placentas and the controls may have been exaggerated.

This does not – in our view – detract from the 100% recurrence rate of BPMF placentas. However, it does suggest that some control placentas might have been found to have BPMF if studied more intensively. Table 4 demonstrates that many of the BPMF placentas in this study were clinically "routine", as suggested in other studies (9,11-13); although we note that "simple manual removal" was permitted in the controls of some other studies (9), but would not be considered "routine" placentas by us.

Another possible difference concerns the frequency of having other placentas. One academic center reported that only 11.5% of patients had a followup placenta at their hospital after a first placenta was diagnosed as placenta accreta (13). Another academic center reported that only 13% of patients had a prior

placenta at their hospital, before getting a subsequent diagnosis of placenta accreta (11). This study looked both forward and back, and found other placentas in about 30% of both BPF patients and controls.

The rate of progression to hysterectomy in this study (5/47 =11%, including 4 progressions from routine placenta to increta) might have been lower if more BPF in control placentas were identified. This needs further study in the future. Nonetheless, we note that in the study of Roeca et al (13), half of all major hemorrhages (>1500 cc) in followup placentas were in cases where the diagnosis of placenta accreta in the first placenta was made only by the pathologist. We suggest that careful assessment and management of patients may be warranted even when the only evidence suggesting morbid adherence is histologic (13).

In contrast to the consideration that we may have missed some BPF placentas due to insufficient scrutiny of control placentas, is the possible concern that we may have “overdiagnosed” BPF placentas by performing so many actin stains. Some might suggest that all placentas should get actin stains in order to properly compare controls to BPF placentas; but such an enterprise would be fraught with obstacles, as discussed previously (6). First of all, many “routine placentas” may have limited sampling of the basal plate. Secondly, many “routine placentas” may have basal plate damage not currently described in textbooks; such as anuclear zones and spindle cells (6); as well as thinning of the basal plate, perforating vessels, gaps in the basal plate, villi under the basal plate, retroplacental fibrin exudate, and extravasated red blood cells in the basal plate. Thirdly, many “routine placentas” may have degenerated, shrunken, or necrotic BPF (6).

Addressing these issues may require a large scale systematic study, as suggested previously (6).

A related consideration is the question of whether a BPMF placenta diagnosed only using actin stains is of any clinical significance (6,13). In this study, 69/117 (59%) BPMF placentas requiring actin stains for diagnosis had clinical features suggestive of morbid adherence noted on the pathology requisition (e.g., manual removal, retained placenta, etc.)(Table 5), while 41% were clinically “routine”. This may in part reflect that performing actin stains can compensate for submission of fewer routine blocks than in some academic studies (10-12). Indeed Figure 6 shows that performing an actin stain when one suspects shriveled BPMF constitutes cutting deeper in the block, so that hypertrophic BPMF missed on the original H&E stain can be clearly observed. Evidence-based indications for performing actin stains also facilitated demonstration of the association of BPMF with perforating vessels, gaps in the basal plate, and villi under the basal plate as part of the pathogenesis of predelivery basal plate damage in BPMF placentas.

Evidence of low uteroplacental blood flow was seen in a small fraction of cases both by Ernst et al and Wyand et al (6,9). The present study had evidence of low uteroplacental blood flow in 14/179 BPMF placentas (8%). Wyand et al reported that retroplacental blood during delivery - simulating abruption - was often associated with BPMF (6). In the present study over half of the 55 BPMF placentas with no other clinical features suggestive of morbid adherence (“routine” placentas) had retroplacental blood noted in the pathology report.

Many actin-positive spindle cells in the basal plate of BPMF placentas may be shriveled BPMF (Figure 6); but others may be myofibroblasts reacting to tissue damage by placental proteases (6,17-19,23). This needs further study. We have previously associated pre-delivery basal plate damage in BPMF placentas with myometrial damage prior to delivery (6). Not only may myometrial damage result in myofiber disarray, it may also explain softening of the myometrium that can lead to uterine perforation during curettage for termination of pregnancy (6,21,23).

CONCLUSIONS

It appears that the rate of recurrence in BPMF placentas may be 100%. This may reflect a heritable protease inhibitor deficiency disease. The resulting enhancement of placental protease activity may explain the wide spectrum of pre-delivery basal plate damage in BPMF placentas. Other placental/decidual diseases such as low uteroplacental blood flow and plasma cell deciduitis may contribute to pathogenesis (9), and promote progression to clinical placenta accreta. The rate of progression to hysterectomy in this study (11%) may overestimate the risk posed by a “routine” placenta with BPMF, since the controls were studied less intensively. On the other hand, about 60% of BPMF placentas that needed actin stains for diagnosis had clinical features suggestive of morbid adherence. Furthermore, most “routine” placentas with BPMF recurrence showed progression to clinical features of morbid adherence in the recurrence. We suggest that careful assessment and management of BPMF patients may be warranted even when the only evidence suggesting morbid adherence is histologic.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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LEGENDS FOR ILLUSTRATIONS

Figure 1 – A) Thinned basal plate on right has loss of decidual and trophoblastic cells; B) actin-positive BPMF in thinned basal plate; C) thinned basal plate under perforating vessel,,which has intravascular villi.

Figure 2 – Gap in basal plate, consistent with perforating vessel (see text).

Figure 3 - Villi under the basal plate.. CD31 endothelial marker shows linear staining above these subjacent villi..

Figure 4 – Fibrin exudate on maternal surface of basal plate.

Figure 5 – Extravasated red blood cells in basal plate, the presumed precursor of decidual hemosiderosis.

Figure 6 – MSA actin stain shows hypertrophic BPMF underneath shriveled BPMF. H&E showed only shriveled BPMF, and cutting deeper was necessary to see hypertrophic BPMF.

Figure 7 – Microscopically disrupted basal plate,. In the lower center of the basal plate is a zone that is largely anuclear, as described previously (6). The maternal surface of the basal place is far from smooth and regular, with ragged fibrinous and bloody tissue on the right and left. Actin-positive BPMF were seen in this area, even though they are not clearly apparent on the H&E stain. This appears to be a microscopic tear in the basal plate, analogous to torn cotyledons on gross exam.