Massive perivillous fibrin deposition and chronic intervillositis: frequently missed diagnoses with a high recurrence risk.

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Introduction

Massive perivillous fibrin deposition (MFD) and its related entity maternal floor infarction (MFI) are rare placental lesions.[1-5] Their cause and pathogenesis are unknown,[6] and the histological criteria for diagnosis are poorly defined. Chronic intervillositis (CI), too, is an infrequently diagnosed placental disorder,[7 8] and in most cases the aetiology is unknown. Both MFD/MFI and CI are associated with poor fetal outcome, and both conditions can recur.[2 3 5 7-10]

We report a case of MFD and CI occurring in the same placenta. Although increased fibrin deposition is described in CI,[7 8 10 11] to our knowledge, this is the first time that the co-occurrence of both MFD and CI is reported in the English literature. This article gives a concise overview of the relevant issues pertaining to these unusual but important disease entities, including possible aetiologies, diagnostic challenges, risks of recurrence, and possible implications not only for pathologists but also for obstetrical and neonatal care.

Methods

We performed a comprehensive literature search through Medline using the terms "maternal floor infarction", "massive perivillous fibrin deposition", "massive intervillous fibrin deposition", "chronic intervillositis", "intrauterine growth restriction", and "intrauterine fetal death."

Case report

The patient is a 22-year old mother, gravida 5, para 1, with one previous apparently uncomplicated pregnancy resulting in a live birth at term. Three previous pregnancies

had been terminated at her request. Her latest pregnancy had been complicated by intrauterine growth restriction (IUGR), resulting in intrauterine fetal death at 37 weeks gestation.

A consented post mortem examination revealed a severely growth restricted infant, weighing 1450g. Foot length (6.3cm) averaged for around 33 weeks gestation. There were no dysmorphic features or congenital abnormalities. Histological examination showed marked autolysis of the fetal tissues but was otherwise non-contributory. Consent was withheld for examination of the brain.

The placenta weighed 520g (untrimmed) and showed a centrally inserted, three-vessel umbilical cord. The cut surfaces of the placental disc had a mottled pale grey and red appearance. These grey deposits were present throughout the entire placenta, occupying more than 50% of the total placental volume and extending from the maternal to the fetal surface (Figure 1). Histological examination revealed massive perivillous fibrin deposition (Figures 2 and 3) characterised by extensive perivillous deposits of eosinophilic fibrinoid material, this fibrinoid material corresponding to the pale grey deposits observed macroscopically. In addition, there was a chronic intervillositis characterised by an infiltrate of CD68-positive (PGM1, 1:200, Dako) macrophages and monocytes in the maternal intervillous space (Figure 4). No evidence of infarction was seen. There was delayed villous maturation, and numerous nucleated fetal red blood cells were seen. A chorioamnionitis, but no funisitis, was also noted.

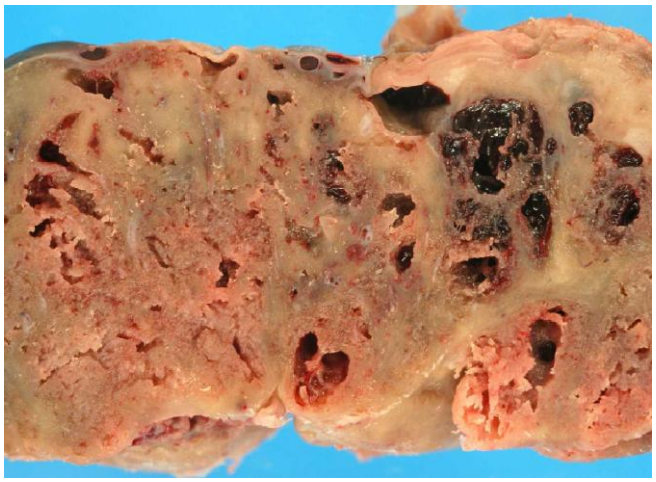
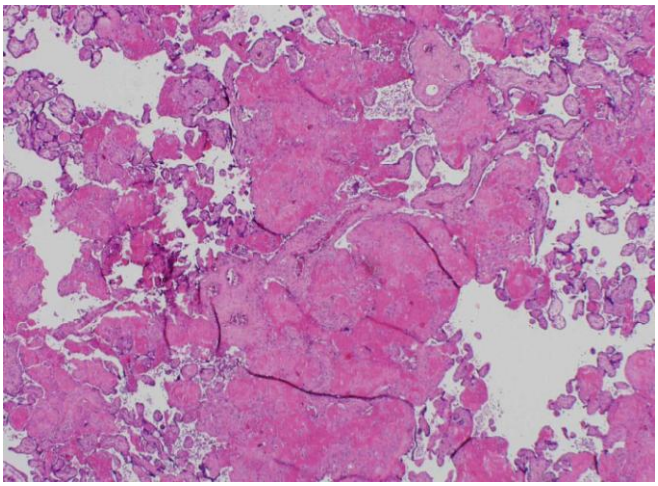


Figure 1



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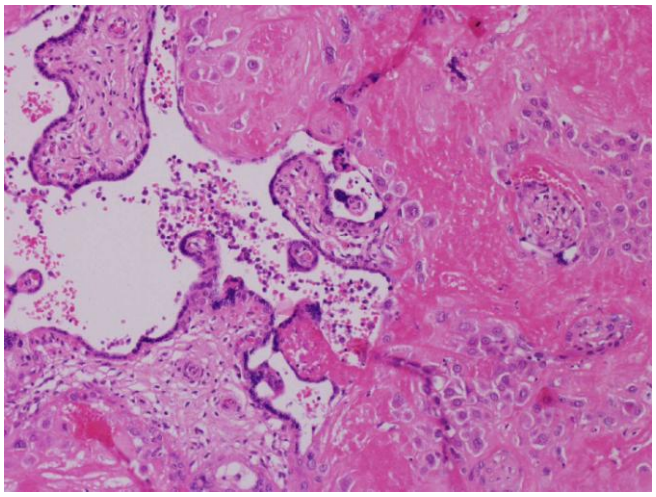

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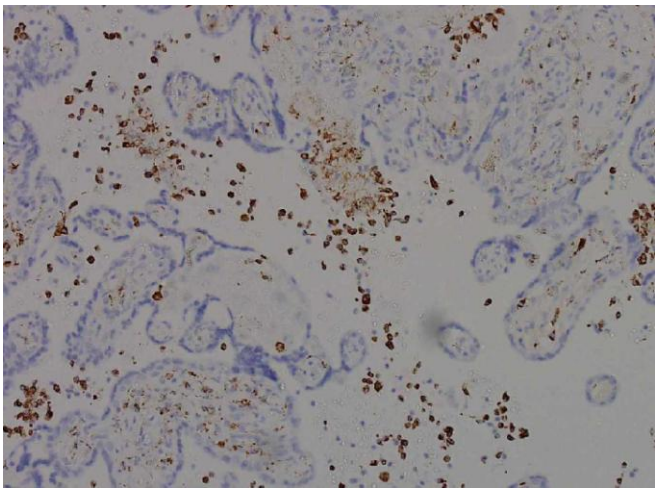

Figure 4

Figure 1: Macroscopical appearances of MFD, also known as Gitterinfarkt. The grey deposits consist of perivillous fibrinoid material.

Figure 2: The histological appearances of MFD. The chorionic villi are encased in eosinophilic fibrinoid material. The entrapped villi are sclerotic and avascular (H&E x 40).

Figure 3: MFD is often accompanied by extravillous trophoblast proliferation within the fibrinoid material. Also note the chronic inflammatory cell infiltrate in the intervillous space, in keeping with chronic intervillositis (H&E x 100).

Figure 4: Chronic intervillositis with CD68-positive macrophages and monocytes in the intervillous space (PGM1, 1:200, Dako x 100).

Massive perivillous fibrin deposition and maternal floor infarction

MFD and MFI are rare disorders of pregnancy and are associated with significant fetal morbidity and mortality.[2 9] Both conditions are characterised by an excessive deposition of fibrinoid material: in the latter, excessive fibrinoid material is deposited within or around the basal plate,[5 6] encasing the basally situated chorionic villi; in the former, fibrinoid material obliterates the intervillous space throughout the placenta.[5 12 13] In the German literature, MFD has been referred to as Gitterinfarkt or Netzinfarkt,[6 12] owing to its macroscopic appearances of a diffuse whitish mottled net-like consolidation of the placental parenchyma (Figure 1). The entrapped chorionic villi become sclerotic and avascular,[6] and often lose their surrounding syncytiotrophoblast.[4 5] There may be associated cytotrophoblast[5] or extravillous trophoblast (X cell)[6 12] proliferation within the surrounding fibrinoid material. Although the encased villi show degenerative changes, there is no true infarction[3 5]; the term MFI is misleading, and Fox[5] proposes that "massive basal plate fibrin deposition" would be a more appropriate term.

There is considerable clinical and pathological overlap between MFI and MFD, and it is probable that these two conditions share a common pathophysiological mechanism.[3 4 5 12] In other words, it seems likely that MFI and MFD represent

slightly different expressions of the same disease process rather than two separate disease entities.

The reported frequency of MFI ranges from almost 0.5%[9] to 0.09%[2]; Katzman and Genest[3] report a prevalence of only 0.005% for MFI/MFD. Both MFI and MFD are associated with IUGR.[2 3 9 14] MFI has been shown to be associated with a high incidence of fetal death, ranging from 17%[9] to 40%.[2] Infants born to mothers with MFI have recently been found to have a higher incidence of central nervous system abnormalities on neonatal head ultrasound examinations, and infants born to mothers with MFI are more likely to be neurodevelopmentally impaired.[15]

Recurrence of MFI has been documented in successive pregnancies. Andres et al[2] report a recurrence of MFI in 39% of patients, whereas Katzman and Genest[3] found a recurrence of MFI/MFD in only 14% of second and third trimester pregnancies. Naeye[9] found that previous unsuccessful pregnancies were twice as frequent in multiparous women with MFI than for women without this lesion.

The cause of MFI/MFD is unknown. Various hypotheses have been proposed, including an unknown abnormal host-placental interaction though not necessarily an immunological one,[6] a cytotoxic insult mediated by pregnancy-associated major basic protein,[12] abnormal intervillous blood flow,[5] and/or abnormalities of the trophoblast predisposing to coagulation.[16] Naeye[9] suggests that MFI represents the "final common pathway" for a number of different insults. Sebire et al[13 16] document three pregnancies in which MFI/MFD occurred in patients with primary antiphospholipid antibody syndrome who had been treated with low dose aspirin and heparin,

suggesting a possible immunological aetiology. Katz et al[17] report a case of MFI associated with activated protein C resistance. Whatever the initial insult, the deposition of fibrinoid material is believed to interfere with the perfusion of the intervillous space, causing growth restriction and fetal death.[2 18] Interestingly, there is some clinical evidence to suggest that the deposition of fibrinoid material may develop relatively rapidly.[1 6]

Summary points

Chronic intervillositis (CI) and massive perivillous fibrin deposition (MFD) with its related entity maternal floor infarction (MFI) are rare and poorly understood placental lesions.

Both MFD/MFI and CI are associated with poor fetal outcome and high risk of recurrence.

MFD is characterised by very extensive perivillous deposition of fibrinoid material.

CI is characterised by a heavy infiltrate of macrophages and monocytes in the maternal intervillous space.

Both MFD/MFI and CI may have significant implications for pathologists and obstetrical and neonatal care.

Deposition of perivillous fibrinoid material is seen in virtually every placenta[5 19] with the amount of deposited fibrinoid material increasing the closer the pregnancy reaches term. At what point then does fibrin/fibrinoid deposition become excessive/massive?

Fox[5] claims that the placenta can withstand a loss of up to 30% of its functioning villi without any evidence of adverse effects. He seems to suggest that a diagnosis of MFD should be reserved for those placentas in which 80 to 90% of the placental parenchyma is obliterated by this fibrinoid material. Other researchers appear to be more conservative, applying the term MFD if ≥ 30% of chorionic villi in the central (non-basal) region of the placenta are encased in fibrinoid material[20] or if >40% of the placenta is involved.[21] Some researchers, on the other hand, appear to rely on the typical macroscopic appearances described above.[12] MFI, too, shows a variable spectrum of pathological changes in that in some placentas the fibrin deposition may not necessarily involve the entire maternal floor.[6] The assessment of what constitutes excessive fibrin deposition is clearly subjective. To address this lack of standardised diagnostic criteria, Katzman and Genest[3] proposed strict histological definitions for MFI and MFD. These somewhat arbitrarily constructed categories (classic MFI, borderline MFD and transmural MFD), however, fail to separate those patients with a "high perinatal morbidity and mortality in the affected pregnancy and a high probability of recurrence from those without."[4]

In their study of placental diagnostic discrepancies between general histopathologists and a paediatric pathologist, Sun et al[20] found that general pathologists had missed the diagnosis of MFI and MFD in 66.7% and 68.4% of cases respectively. This was in part explained by the rarity of these disorders, general pathologists therefore being

"less familiar"[20] with these lesions, but the subjectivity of these diagnoses and the lack of standardisation of diagnostic criteria may also have played a contributory role. Redline[4] consequently proposes a more practical approach to the diagnosis of MFI/MFD which is not limited to histological examination alone, emphasising the typical macroscopic appearances, the associated clinical features of preterm delivery, fetal distress and IUGR, the previous obstetric history including previous placental specimens, and finally, the need for all pathologists to be familiar with the histological features of MFI/MFD and its mimics.

Chronic intervillositis

Chronic intervillositis, too, is a rare lesion, and is characterised by an intervillous mononuclear inflammatory cell infiltrate,[7 8] in contrast to chronic villitis where chronic inflammatory cells are situated within the villous stroma. The inflammatory cell infiltrate in CI is predominantly composed of macrophages and monocytes, and is believed to be maternal in origin.[7] CI has been associated with a poor pregnancy outcome, including spontaneous abortion, IUGR and perinatal death.[7 8 10 22] Other associations include pregnancy-induced hypertension, maternal autoimmune disease and decidual vascular atherosis.[7 22 23] A risk of recurrence has been reported[8 10] with Boyd and Redline[10] documenting a recurrence of 67% in their series.

The cause of CI is unknown in most cases,[7 8] although massive CI has been reported in placental malarial infection.[11 24] An immunological pathogenesis has been suggested, partly because CI shares clinical and pathological features with chronic villitis of unknown aetiology (CVUA),[7 8 22] an idiopathic placental lesion characterised by patchy or diffuse chronic inflammatory changes within chorionic

villi. Massive CI has been described in CVUA, leading some to suggest that massive CI may represent an extreme variant of CVUA.[22] Ordi et al[11] believe that massive CI may " represent a common histologic change secondary to different causes."

Interestingly, both Doss et al[8] and Boyd and Redline[10] comment on the possible association of CI and MFI. The typical histological changes in CI described above are usually associated with prominent perivillous fibrin deposition,[7 8 10 11] although, to our knowledge, the co-occurrence of MFI/MFD and CI has not yet been described in the English literature. Both conditions are associated with IUGR, fetal death and recurrence, and both conditions have been associated with elevated levels of maternal alpha-fetoprotein.[3 5 6 8 17 25] Our case report would support the hypothesis that CI and MFI/MFD may share a common pathogenesis.

Implications for pathologists, obstetricians and neonatologists

In conclusion, our case report highlights some important issues. Firstly, both MFI/MFD and CI are rare placental disorders that are associated with significant fetal morbidity, fetal mortality and recurrence. It is therefore important that general pathologists are familiar with these conditions. Standardisation of histological criteria, especially with respect to MFI/MFD, will undoubtedly improve the reliability of the diagnosis of these conditions and may help to reduce the discrepancy rate between pathologists.[20] Secondly, the diagnosis of MFI/MFD and CI has significant implications for obstetrical care, and obstetricians should be aware of the risk of recurrence in future pregnancies of women previously diagnosed with these placental disorders. There have been successful attempts to diagnose MFI antenatally, prompting delivery before the onset of critical fetal distress.[1 26] Fuke et al[14] claim that

antiplatelet drugs and/or heparin may prevent recurrence of MFD and IUGR in patients with a history of both MFD and small-for-dates infants in previous pregnancies. Similarly, Doss et al[8] report a diminution in the severity of recurrent massive CI with maternal immunosuppression in a patient with repeated abortions, leading to a successful pregnancy outcome. Thirdly, awareness of MFI/MFD and CI needs to be increased amongst neonatologists and paediatricians to enable them to provide adequate follow-up to surviving infants and appropriate counselling to parents. Adams-Chapman et al,[15] for example, recommend that infants born to mothers with MFI should have serial cranial ultrasound studies after birth and neurodevelopmental follow-up throughout early childhood. Finally, the co-occurrence of both MFD and CI in our case would suggest a possible common aetiology and/or pathogenesis for these placental disorders. Further critical research is needed into both of these conditions, not only to elucidate the causes of these diseases but also, importantly, to establish criteria for reliable antenatal diagnosis and to develop suitable intervention strategies to reduce the severity or prevent the recurrence of these unusual but significant placental disorders.

Competing interests:

All authors declare that the answer to the questions on your competing interest form are all No and therefore have nothing to declare.

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