

# Co-occurrence of Massive Perivillous Fibrin Deposition and Chronic Intervillositis: Case Report

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## ABSTRACT

Chronic intervillositis (CI) and massive perivillous fibrin deposition (MFD), together 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. We report a patient who was found to have both MFD and CI in the same placenta, resulting in severe intrauterine fetal growth restriction and intrauterine fetal death at 37 weeks of gestation. Characteristic histological findings included both very extensive perivillous deposition of fibrinoid material and a heavy infiltrate of CD68-positive macrophages/monocytes in the maternal intervillous space. To our knowledge, this is the first time the co-occurrence of MFD and CI is reported in the literature.

**Key words:** chronic intervillositis, intrauterine fetal death, intrauterine growth restriction, massive perivillous fibrin deposition, maternal floor infarction

## INTRODUCTION

Massive perivillous fibrin deposition (MFD) and its related entity, maternal floor infarction (MFI),

are rare placental lesions [1]. Their cause and pathogenesis are unknown, and the histological criteria for diagnosis are poorly defined. Chronic intervillositis (CI), too, is an infrequently diagnosed placental disorder [2], and in most cases, the etiology is unknown. Both MFD/MFI and CI are associated with poor fetal outcome, and both conditions can recur [1,2].

We report a case of MFD and CI occurring in the same placenta. Although increased fibrin deposition is described in CI [2–4], to our knowledge, this is the first time that the co-occurrence of both MFD and CI is reported in the literature.

## CASE REPORT

The patient is a 22-year-old mother, gravida 5, para 1, with 1 previous apparently uncomplicated pregnancy resulting in a live birth at term. Three previous pregnancies had been terminated at her request. Her latest pregnancy was complicated by intrauterine growth restriction (IUGR), followed by intrauterine fetal death at 37 weeks of gestation. Microbiological investigations and maternal thrombophilia screen were not performed.

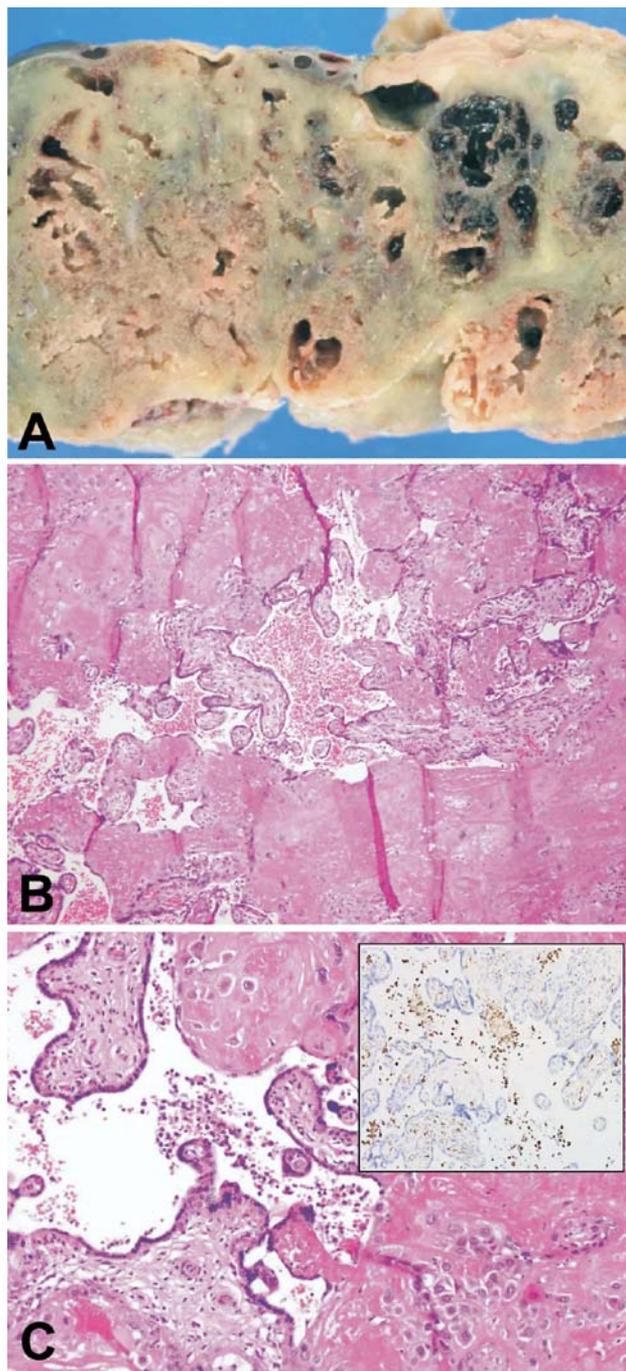
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A consented postmortem examination revealed a severely growth-restricted infant weighing 1450 g. There were no dysmorphic features or congenital abnormalities. Histological examination showed marked autolysis of the fetal tissues but was otherwise noncontributory. Consent was withheld for examination of the brain.

The placenta weighed 520 g (untrimmed) and showed a centrally inserted, 3-vessel umbilical cord. The cut surfaces of the placental disc had a variegated red and pale gray appearance. The gray deposits were present throughout the entire placenta, extending from maternal to fetal surface and occupying more than 50% of the total placental volume (Fig. 1A). Histological examination revealed MFD (Fig. 1B), the perivillous eosinophilic fibrinoid material corresponding to the pale gray deposits observed macroscopically. In addition, there was marked CI characterized by a prominent infiltrate of CD68-positive macrophages and monocytes in the maternal intervillous space in all sections examined, involving areas both with and without perivillous fibrin, equaling grade 2 [2] (Fig. 1C). No evidence of infarction or villitis was seen. There was delayed villous maturation; numerous nucleated fetal red blood cells were noted in villous vessels; and an acute chorioamnionitis, but no funisitis, was also present.

## DISCUSSION

Massive perivillous fibrin deposition and MFI are rare disorders of pregnancy and are associated with significant fetal morbidity and mortality [1]. There is considerable clinical and pathological overlap between these 2 conditions, indicating a common underlying pathophysiological mechanism [1]. Both conditions are characterized by an excessive deposition of fibrinoid material: in the latter, excessive fibrinoid material is deposited within or around the basal plate, encasing the basally situated chorionic villi; in the former, fibrinoid material obliterates the intervillous space throughout the placenta. In the German literature, MFD is referred to as Gitterinfarkt or Netzinfarkt [5], owing to its macroscopic appearances of a diffuse net-like consolidation of the placental parenchyma (Fig. 1A). Although the encased villi show degenerative changes, there is no true infarction; the term MFI is misleading, and Fox [6] proposes “massive basal plate fibrin deposition” as a more appropriate term.



**Figure 1.** A. Macroscopic appearance of massive perivillous fibrin deposition (MFD), also known as Gitterinfarkt. The gray deposits consist of perivillous fibrinoid material. B. Histological appearance of MFD. The chorionic villi are encased in eosinophilic fibrinoid material. Many of the entrapped villi are sclerotic and avascular (hematoxylin and eosin (H&E), ×40). C. MFD is often accompanied by extravillous trophoblast proliferation within the fibrinoid material. Note the chronic inflammatory infiltrate in the intervillous space, the hallmark of chronic intervillitis (H&E, ×100). Inset: Immunohistochemical staining with CD68, confirming the presence of macrophages and monocytes in the maternal intervillous space (PGM1, 1:200; DAKO, ×100). A color version of this figure is available in the online journal.

The reported frequency of MFI and/or MFD ranges between 0.028% and 0.5% [1,7–9]. Both MFI and MFD are associated with IUGR and intrauterine fetal death, and both conditions can recur [1,7,8,10]. Andres and others [8] report recurrence of MFI in 39% of subsequent pregnancies; Katzman and Genest [1] document recurrence of MFI/MFD in only 14% of 2nd and 3rd-trimester pregnancies, but they document recurrence of MFI/MFD in 50% of 1st-trimester miscarriages. The cause(s) of MFI or MFD, however, are unknown. Various hypotheses have been proposed, including maternal autoimmune disease [11] and cytotoxicity mediated by pregnancy-associated major basic protein [12]. Naeye [7], on the other hand, suggests that MFI/MFD may represent the “final common pathway” for a number of different placental insults. Any discussion on potential etiologies and/or pathogeneses is further complicated by the inability to discriminate, on routine light microscopy, between the different types of fibrinoid material that may occur in the placenta. Kaufmann and others [13] have grouped these types into (1) “fibrin-type fibrinoid,” largely composed of fibrin and believed to be derived from maternal blood, and (2) “matrix-type fibrinoid,” secreted by extravillous trophoblast or X cells and consisting of extracellular matrix-like material, containing variable amounts of collagen IV, laminin, and specific proteoglycans and fibronectins. While in the case of MFI/MFD there is an increase in extravillous trophoblast cells [5,12], it appears that the eosinophilic material that obliterates the intervillous space in patients with these conditions is predominantly composed of “fibrin-type fibrinoid” [5,9,13]. It is therefore possible that the etiology for “true” MFD (i.e., those placentas characterized by massive “fibrin-type fibrinoid” deposition) is different for “MFD-like” placental lesions in which the fibrin-like deposits are actually exclusively composed of “matrix-type fibrinoid.” However, to our knowledge, there is no evidence in the literature to support the existence of separate “types” of MFD, and as routine microscopy fails to discriminate between the 2 forms of fibrinoid, the potential distinction between “true MFD” and “matrix-type MFD” seems largely an academic one.

Despite an increased awareness of MFI and MFD among pathologists, the diagnosis of these disorders is still subjective, as there are no accepted

diagnostic criteria. Perivillous fibrin is seen in virtually every placenta [6], and at present, there are no clear guidelines with regard to what truly represents excessive/massive intervillous fibrinoid material. Fox [6] claims that the placenta can withstand a loss of up to 30% of its functioning villi without any evidence of adverse effects, but 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 fibrin. Others appear to be more conservative, applying the term MFD if  $\geq 30\%$  of chorionic villi in the central (nonbasal) region of the placenta are encased in fibrinoid material [14] or if  $>40\%$  of the placenta is affected [15]. In our present case, the diagnosis of MFD is based on our observation that  $>50\%$  of the placenta was obliterated by fibrin.

Maternal floor infarction, too, shows a variable spectrum of pathological changes, as the fibrin deposits may not necessarily involve the entire maternal floor [5]. In addition, there is uncertainty about the relative contributions of the macroscopic and/or microscopic placental appearances to the diagnosis of MFI and MFD with regard to whether the diagnosis can be made on histological examination alone [1]. To address the lack of standardized diagnostic criteria, Katzman and Genest [1] propose stringent histological definitions for both disorders; however, as Redline [16] aptly points out, these somewhat arbitrarily defined categories (classic MFI, borderline MFD, and transmural MFD) fail to separate “patients with high perinatal morbidity and mortality in the affected pregnancy and a high probability of recurrence from those without.” In contrast, Redline [16] suggests a more practical approach to the diagnosis of MFI/MFD, comprising the need for clinicopathological correlation, recommending that the diagnosis should not be made on pathological examination alone but rather that it requires a pertinent (current and past) obstetric history, including preterm delivery, severe IUGR or fetal distress, and/or evidence of recurrence (with possible review of former placental specimens). However, while emphasizing the importance of the characteristic macroscopic appearances—and the histological features, including exclusion of histological mimics—Redline makes no attempt to quantify the minimum amount of fibrin deposition required to make a diagnosis of MFI or MFD.

Instead, he appears to suggest that even a “patchy” lesion (as opposed to a “diffuse” involvement) may occasionally warrant the diagnosis of MFI/MFD, provided that all of the other diagnostic criteria (appropriate histology, obstetric history) are met.

Chronic intervillitis, too, is a rare lesion and is characterized by an intervillous mononuclear inflammatory cell infiltrate [4], in contrast to chronic villitis, in which 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. Chronic intervillitis has been associated with a poor pregnancy outcome, including spontaneous abortion, IUGR, and perinatal death [2–4]. Recurrence has been reported [2,3], with Boyd and Redline [2] documenting a recurrence rate of 67% in their sample of 9 patients who had more than 1 placenta available for assessment.

The cause of CI is unknown in most cases, although malaria must be excluded [2]. An immunological pathogenesis has been suggested, partly because CI shares clinical and pathological features with chronic villitis of unknown etiology [3], an idiopathic placental lesion characterized by patchy or diffuse chronic inflammatory changes within chorionic villi. In our case there was also a concomitant acute chorioamnionitis; although it is doubtful that this is related to the pathogenesis of CI, it has been previously described in occasional cases [3,4].

Interestingly, several authors [2,3,17] have previously commented on the possible association of CI and MFI. The typical histological changes in CI, described above, are usually associated with prominent perivillous fibrin deposition [2–4], and—as outlined above—both conditions share similar clinical features. However, to our knowledge, the co-occurrence of MFI/MFD and CI in the same placenta has not yet been reported in the literature. While Boyd and Redline [2] seem to suggest that the presence of inflammation negates the diagnosis of MFI/MFD, our case report supports the hypothesis that CI and MFI/MFD may share a common pathogenesis.

In conclusion, both MFI/MFD and CI, albeit rare, are associated with significant fetal morbidity, fetal mortality, and recurrence. Pathologists must be familiar with these entities, and standardization of the diagnostic criteria, especially for MFI/MFD,

will undoubtedly improve the reliability and reproducibility of their diagnosis. The diagnosis of MFI/MFD and CI has significant implications for obstetrical care, and obstetricians must be alerted to the risk of recurrence in future pregnancies of women previously diagnosed with these placental lesions. There have been successful attempts to diagnose MFI antenatally, prompting delivery before the onset of critical fetal distress [18]. Fuke and others [10] 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 babies in previous pregnancies. Similarly, Doss and others [3] report a diminution in the severity of recurrent massive CI with maternal immunosuppressive therapy in a patient with repeated abortions, leading to a successful pregnancy outcome. Awareness of MFI/MFD must also be raised among neonatologists and pediatricians, thus enabling them to provide adequate follow-up to surviving infants and appropriate counseling to parents, as babies born to mothers with MFI were recently shown to have a higher incidence of abnormal cranial ultrasound findings compared to gestational age-matched controls, with a greater likelihood of neurodevelopmental impairment [19]. Finally, the co-occurrence of both MFD and CI in our case would indicate a possible common etiology and/or pathogenesis for these placental disorders. Further critical research is required, not only to elucidate the cause(s) of these diseases but, importantly, to establish criteria for reliable antenatal diagnosis and to develop suitable intervention strategies to reduce the severity and/or prevent recurrence of these unusual but significant placental disorders.

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