Dichorionic Twins Discordant for Massive Perivillous Fibrinoid Deposition: Report of a case and review of the literature

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A case of dichorionic twins discordant for massive perivillous fibrinoid deposition supports an immune etiology for fibrinoid formation.

Keywords: discordant twin growth; massive perivillous fibrinoid deposition; placental fibrinoid
Abstract:

Massive perivillous fibrinoid deposition (MFD) and maternal floor infarction (MFI) are lesions of unknown etiology associated with poor perinatal outcomes, including fetal intrauterine growth restriction and neurodevelopmental injury, and high risks of pregnancy loss and recurrence in subsequent gestations. Maternal floor infarction is comprised of massive intervillous fibrinoid deposition concentrated at the maternal floor. Massive perivillous fibrinoid deposition is a similar lesion, however is diffuse within the parenchyma. MFD/MFI lesions represent a spectrum of severity of cloak-like perivillous fibrinoid deposition and there is mounting evidence that, often, they represent sequelae of immune-mediated phenomena and/or an imbalance in factors that normally maintain the fluidity of blood in the maternal space. There are only a handful of reported instances of discordant MFD/MFI occurrence in twin placentas. We present a fourth such occurrence in a fused, dichorionic diamniotic twin placenta and submit that our dizygotic twin gestation case provides additional supportive evidence that immune-mediated mechanisms are involved in the formation of pathologic accumulations of fibrinoid, in at least some cases.
Introduction:

Massive perivillous fibrinoid deposition (MFD), and maternal floor infarction (MFI) are rare closely related placental pathologic conditions of unknown etiology estimated to occur in 0.28-0.5% of pregnancies that are associated with poor perinatal outcomes including preterm birth, fetal intrauterine growth restriction and/or death and neurodevelopmental injury, and gestational oligohydramnios. Maternal floor infarction is comprised of massive intervillous fibrinoid deposition concentrated at the maternal floor. Massive perivillous fibrinoid deposition is a similar lesion, however the fibrinoid deposited is diffuse within the parenchyma, not just confined to the maternal floor. The MFI/MFD lesional spectrum is characterized by cloak-like encasements of amorphous fibrinoid that surround chorionic villi and lead to progressive villous atrophy and agglutination. These findings are compatible with progressive loss of functional placental parenchyma and may well lead to disturbances of blood flow patterns in the immediate and more distant sites in the maternal space that supplies the remainder of the parenchyma. In MFI, the deposition is confined to the basal plate, in a grossly detectable, basal “rind-like” distribution of pale, dense fibrinoid (responsible for the misnomer, “infarction”) that microscopically is characterized by villous aggregates that are frequently matted together. In MFD, fibrinoid deposition diffusely extends into the mid-zonal and subchorial regions especially in placentas from later, third trimester deliveries. Diffuse and transmural involvement is compatible with a progressive process, especially since the subchorionic and peripherally oriented borders of the lesions generally show a graded deposition of fibrinoid suggestive of deposition on preexistent fibrinoid scaffolding. There is good evidence that MFD/MFI represents
sequelae of maternal immune-mediated processes (1) and/or a manifestation of anti-fetal rejection (2) in at least some cases. Rarely, discordant manifestation of MFD/MFI in only one twin’s placental domain in monochorionic (3) and dichorionic (3-6) gestations has been reported. We present a fourth such case of discordant occurrence in a dizygotic dichorionic diamniotic twin gestation and a review of the literature and propose that our case provides further evidence that immunologic processes likely contribute to the pathogenesis of this condition, in a subset of cases.

Case:
An African-American, 24-year old, G1P0 woman with type 2 diabetes mellitus, and obesity, and who is status post gastric sleeve placement was noted to have a spontaneous diamniotic dichorionic twin gestation. Subsequently she was found to be Group B streptococcus positive (cervical culture result). Discordant twin growth was detected early in gestation; Twin A, a female, showed poor growth and intrauterine fetal demise was noted at 22 weeks. The pregnancy continued, and the woman was given betamethasone at 32 weeks, but required admission to labor and delivery and cesarean section delivery at 34 1/7th weeks of gestation for complications of absent end-diastolic umbilical artery blood flow in the living twin.

Twin A was noted to be mummified, and 92 g [280 – 760 g 10th to 90th centiles expected for 22 weeks of gestational age (wk GA) dichorionic twin] (7) but with no appreciable anomalies; a foot length of 3.0 cm was consistent with about 19-20 wk GA (233.8 – 311 g expected for 19 wk GA, 283.9 – 378 g expected for 20 wk GA dichorionic twin)(7). Other observations at an external pathologic examination were of questionable reliability due to the prolonged period of intrauterine retention. However, the fetus did appear excessively small for a 22 wk GA
dichorionic twin; crown heel length was 22 cm (23 – 27.2 cm expected), crown rump length 12.5 cm, head circumference 13 cm (~15.2 -17.1 cm 10th to 90th centiles expected for 19 wk GA)(7), chest circumference 11.8 cm, and abdominal circumference was 10 cm (~12.5 – 15.2 cm 10th to 90th centiles expected for 19 wk GA) with elevated head:abdominal circumference ratio supportive of asymmetric intrauterine growth restriction (1.3 observed versus 1.0 expected at 22 wk GA) (7).

The 423 g(trimmed weight without cords or membranes), fused, dichorionic diamniotic placenta (531 – 923 g expected)(9) was 12 x 7.5 cm and showed a thin, 0.6 cm in diameter, pale trivascular, eccentrically inserting umbilical cord of Twin A (total length received including that attached to the fetus, 35.4 cm). The placental parenchyma of Twin A was pale and diffusely dense appearing(fig1). Microscopic examination of the placental side corresponding to the mummified fetus, Twin A showed massive, transmural perivillous fibrinoid deposition involving the vast majority of the villous tissue present and represented pathology that could not simply be explained as features of prolonged retention (Fig 2,3). Because of the prolonged period of intrauterine retention following fetal demise, we could not reliably interpret C4d staining in the umbilical vein nor the chronic deciduitis in Twin A’s placenta; however, the chronic deciduitis with scattered plasma cells appeared relatively increased in the affected placenta and may well have reflected a difference in antemortem infiltration.

Twin B, a male, was 2020 g (2020g mean expected for dichorionic twin at 34 wk GA)(8) and had Apgar scores of 8 and 9, at one and five minutes, respectively, but had transient tachypnea of the newborn, followed by hyperbilirubinemia of prematurity, respiratory distress syndrome, and Vitamin D deficiency. The viable Twin B’s umbilical cord was three-vessel (18 cm length received; 1 cm diameter) and showed marginal insertion 1.0 cm from the placental margin(10).
The parenchyma of placenta B was grossly unremarkable, but showed evidence of malperfusion microscopically (figure 3). There were chorionic villous ischemic change with some villous hypoplasia, patchy perivillous fibrinoid, X-cell cysts and X-cell proliferation (10). If the pregnancy had been affected by the maternal diabetes, it is possible Twin B may have been small for gestational age if not macrosomic due to diabetes, however there was no evidence of villous dysmaturity associated with maternal diabetes.
Discussion:

MFD/MFI is a rare placental condition of unknown etiology with high rates of serious adverse pregnancy outcomes including fetal growth restriction and recurrent pregnancy loss. It is characterized by marked, lattice-like deposition of perivillous fibrinoid that is accompanied by villous atrophy, sclerosis, and agglutination. The intervening space is reduced in MFD, the space between the villi is filled with fibrinoid and X-cells, but the distance between the villi remains normal, this is in contrast to true ischemic infarct.

The amount of fibrinoid is generally more extensive in third trimester and/or late gestation placentas and the fibrinoid entrapment of chorionic villi is consistent with progressive loss of functional placental parenchyma, however early gestation MFD/MFI often results in fetal demise.

The process almost certainly leads to disturbances of blood flow patterns in the maternal space adjacent to regions of involvement and abnormal channeling or restriction of flow to the rest of the parenchyma(1). The degree of fibrinoid deposition and its distribution has also been scored semi-quantitatively as “classic MFI”(maternal floor infarction)(basal villous deposition of entire maternal floor), “borderline MFD” (essentially transmural fibrinoid deposition affecting >25% but < 50% of villi on at least one slide), and “transmural MFD” (transmural with ≥50% villous encasement)(11). In some cases, there is proliferation of extravillous cytotrophoblast (X-cell) with formations of large interconnected aggregates of cells and associated reduction of intervening maternal space. These bulky masses could create or exacerbate the generation of abnormal blood flow patterns in the maternal space. Indeed, sites of villous ischemic change and
infarction, intervillous thrombohematomas(1) and villous hypoplasia(12) can be found in cases of MFD/MFI, including some from gestations without maternal hypertension. In combination, these features likely correlate with the progressive development of the abnormally dense, hypoechogenic placenta typically seen on serial prenatal ultrasonograms that is accompanied by fetal growth deficiency and, in many cases, oligohydramnios(1,13).

The etiology of MFD/MFI remains unknown. Despite the observation that damage to syncytiotrophoblast is the first detectable histopathologic villous change, it is unclear whether this feature represents direct damage to the syncytiotrophoblast or whether the initiating event in the pathogenesis of the condition begins in the perivillous space. In addition, part of the challenge of elucidating the cause of MFD/MFI, in addition to its rarity, may be that the initiation of formation and composition of the amorphous, perivillous material is not uniform among individual cases. Immunohistochemically and ultrastructurally the material appears to be an amalgam of fibrinoid of maternal coagulation origin(3) (laminated fibrin-type fibrinoid) and trophoblast-derived extracellular substance (matrix-predominant type fibrinoid)(1,4,11) but the relative proportions of these elements may be different among individual cases, underlying cause, and periods of gestation. A variety of factors may adversely affect the normal homeostasis between elements in the maternal blood and trophoblast-generated procoagulant and anticoagulant molecules and matrix that contribute to maintenance of a fluid perivillous space. Thus, the accumulations in MFD/MFI likely represent a similar appearing pathologic outcome of activations of converging pathways that have many triggers or exacerbating risk factors(1,6).

For example, maternal conditions such as heritable disorders of coagulation and long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency(14) and mutations in LCHAD gene(15) have been associated with MFD. Other maternal disorders such as hypertension/preeclampsia
could be exacerbating conditions since they have been associated with imbalances in angiogenic and antiangiogenic factors(2,12). In addition, specific ratio patterns of imbalances between angiogenic factor, placental growth factor (PIGF) and anti-angiogenic factors soluble vascular endothelial growth factor receptor (sVEGFR)-1 and -2 and soluble endoglin (sEng) have been found in MFD/MFI(16) and treatment with pravastatin has been associated with an improved gestational outcome in one patient with recurrent pregnancy loss and MVFD/MFI(12). In addition, environmental factors have been postulated to be contributory in gestations resulting from in vitro fertilization(6).

There is mounting evidence, however, that maternal alloimmune or autoimmune mechanisms are involved, in at least a subset of cases. MFD/MFI occurs more commonly in women with autoimmune disorders with or without thrombophilia(1,12,17) and pregnancies achieved by egg donation (e.g. total allograft);(18,19) has high recurrence risks of 12% to 78%; may exhibit co-existent massive chronic histiocytic (monocytic) intervillositis;(1) and may be associated with earlier and more rapid progression when it does recur(13). While it did not eradicate the recurrence of MFD/MFI, IUGR, or preterm birth, a few cases of women with a history of prior MFI/MFD and primary anticardiolipin autoantibody (3 patients)(20) and one without evidence of autoimmune disease or preeclampsia,(21) who were treated with aspirin and low dose heparin, and one patient treated with intravenous immunoglobulin,(22) have been observed to have improved outcomes in subsequent pregnancies and generally less extensive MFD. Romero, et al(2), in their recent study of 10 pregnancies complicated by placental MFD/MFI, compared to 175 uncomplicated term gestations, reported finding significant increases in prevalence of plasma cell deciduitis; abnormal circulating plasma levels of maternal anti-HLA class I antibodies in the second trimester as well as elevated mean concentrations of the inducible Th1-
chemokine CXCL-10 (which, through binding to its CXCR3 receptor regulates leukocyte immune responses and is elevated in autoimmune diseases); strongly positive C4d deposition on umbilical vein endothelium (indicative of localized complement activation); and a uniform presence of specific maternal antibody against fetal HLA antigen class I or II. These authors submitted their findings were evidence of an antifetal response (2).

Finally, an exceptionally rare case of MFD/MFI deposition may be due to infection with Coxsackievirus and immune-mediated pathways(23).

Although extremely rare, discordant occurrence of MFD/MFI in twin gestations is also supportive evidence of an immune-mediated etiology(s) for this entity. Only five cases have been reported since 2003 (3-6); four were dichorionic diamniotic (DiDi) gestations(3-6) and one was monochorionic(3), but all had correlative growth deficiency of the twin with the affected placental region (Table 2). While Bane and Gillian(3) stated that the occurrence in their monochorionic twin placenta excluded simple Mendelian genetic inheritance of an autosomal dominant or recessive factor as immunologic basis for the discrepancy, placental epigenetic factors may be involved in discordant placental pathology of MFD/MFI since discordant IUGR in monozygotic twins has been found to have different placental epigenetic dysregulations(24). Our case of dizygotic twins with discrepant presence of MFD/MFI is the third such report of spontaneous DiDi gestation and the fourth such report of DiDi twins in general (3-6), and also provides evidence that specific genetic differences between mother and fetus/placenta likely have a role in triggering the process that leads to the pathologic deposition of fibrinoid. Based on the criteria of Katzman and Genest, our affected placenta exhibited transmural MFD.

Because of the prolonged period of intrauterine retention following fetal demise, we could not reliably interpret C4d staining in the umbilical vein nor the chronic deciduitis in Twin A’s
placenta; however, the chronic deciduitis appeared relatively increased in the affected placenta and may well have reflected a difference in antemortem infiltration.

Although Feist, et al(6) did not find evidence of overexpression of humoral rejection marker C4d in the umbilical venous endothelium of the affected twin’s cord, it is the opinion of these authors that this does not exclude an immunologic etiology for the discordant presence of MFV/MFI in their case of dizygotic twins.

There can be fibrinoid deposition associated with intrauterine retention after demise, however extensive fibrinoid deposition was not a criteria for evaluating and timing intrauterine retention in Genest’s or Jacque’s studies(25,26). The degree and distribution of fibrinoid deposition seen in twin A exceeds what one would expect due only to intrauterine retention. In addition, Twin A had a greater degree of chronic deciduitis with scattered plasma cells(27), which may reflect a difference in antenatal influx. We thus interpreted the findings as true MFD.

In summary, there may well be as yet undiscovered immunologic triggers and components in the likely complex mechanisms involved in the pathogenesis of MFD/MFI, and further studies are needed to elucidate their contributions, overall. Such elucidation may explain why some outcomes of recurrent MFD/MFI associated with maternal anti-cardiolipin antibody can be improved with anticoagulant or immunoglobulin therapies and others not, and why maternal plasma levels of angiogenic and antiangiogenic factors are elevated or may not exhibit consistent response to agents such as pravastatin during gestation. In addition, further studies are necessary to determine if the IUGR associated with MFD/MFI represents epigenetic placental dysregulation of lipid metabolism and transcriptional regulation and cadherin and Wnt signaling pathways. Also, it is unknown whether these or other such aberrations are consistently expressed throughout gestation, since MFD/MFI shows greater severity in late gestation. The rarity of
MFD/MFI pathology impedes study efforts, but the uniqueness of twin gestations is that they represent instances of a temporally shared maternal environment. Thus, retrospective genome-wide DNA methylation analysis of case tissues of singleton and twin placentas, including cases of dizygosity, may provide new pathogenetic information and lead to improved and patient-specific therapies to prevent progression or recurrence of this spectrum of pathology. Thus, we recommend that a combined clinicopathologic effort be instituted to collect tissue from individual maternofetal dyad cases of MFD/MFI to facilitate such studies.
References:


**Figure Legends:**

Figure 1-comparison of placenta with massive perivillous fibrinoid (bottom) and unaffected twin placenta (top).

Figure 2-Histology of the placenta associated with the fetal demise showed massive perivillous fibrinoid with encasement of chorionic villi with maintenance of architecture. The stem villous vessel changes of intrauterine retention after demise are seen to the left.

Figure 3-Histology of the unaffected twin, showing changes consistent with malperfusion, with villous hypoplasia, patchy perivillous fibrinoid, and X-cell proliferation at the top.
Table 1-Clinical and pathological findings of Twins A and B

<table>
<thead>
<tr>
<th>Significant clinical findings</th>
<th>Twin A</th>
<th>Twin B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signficant gross pathology</td>
<td>Poor growth, fetal demise 22 weeks</td>
<td>Absent end diastolic flow, Cesarean delivery 34 1/7 week</td>
</tr>
<tr>
<td>Signficant microscopic pathology</td>
<td>92 gm mummified female small for age. Placenta pale and dense</td>
<td>2020gm male, Apgars 8,9, with mild sequelae of prematurity</td>
</tr>
<tr>
<td>Massive perivillous fibrinoid</td>
<td>chorionic villous ischemic change with some villous hypoplasia, patchy perivillous fibrinoid), X-cell cysts and X-cell proliferation</td>
<td></td>
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</tbody>
</table>
Table 2-Reported cases of discordant massive perivillous fibrinoid/maternal floor infarction in twins

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient age/parity</th>
<th>Clinical presentation</th>
<th>Gestational age at delivery</th>
<th>Chorionicity/Gender</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Bane AL and Gillian, JE</td>
<td>33 yo, G1P0, smoker 36 yo, G2P1</td>
<td>one twin with growth restriction and demise one IUGR live born</td>
<td>33 weeks 36 weeks</td>
<td>One twin set reported as DiDi and one reported monochorionic; but which twin set MoDi not specified; no genders stated</td>
<td>Only one twin’s placental region in each case affected</td>
</tr>
<tr>
<td>2-Redline RW et al</td>
<td>19 yo G2P0010 with Class C diabetes, severe preeclampsia</td>
<td>Discordant fetal growth</td>
<td>30 3/7 weeks</td>
<td>DiDi; larger female smaller male,</td>
<td>Maternal floor infarction of smaller twin placenta</td>
</tr>
<tr>
<td>3-Gupta N, et al</td>
<td>30 yo G1P0 mildly elevated blood pressure, proteinuria</td>
<td>Discordant growth</td>
<td>33 weeks</td>
<td>DiDi; Both female, one with IUGR</td>
<td>Massive perivillous fibrinoid in smaller twin’s placenta</td>
</tr>
<tr>
<td>4-Feist H, et al</td>
<td>34yo G3P1112</td>
<td>IVF, Growth restriction of one twin</td>
<td>34 weeks</td>
<td>DiDi; Both female, one with IUGR</td>
<td>Massive perivillous fibrinoid in smaller twin’s placenta</td>
</tr>
<tr>
<td>Current case</td>
<td>24 yo G1P0, obese, type 2 diabetes mellitus, status post gastric sleeve placement</td>
<td>Demise of one twin at 22 weeks, delivery at 34 weeks</td>
<td>34 1/7 weeks</td>
<td>DiDi; Male, liveborn, 34 weeks; female stillborn estimated gestational age 22 weeks</td>
<td>Massive perivillous fibrinoid associated with mummified female’s placenta</td>
</tr>
</tbody>
</table>

Abbreviations: DiDi- Dichorionic diamniotic; MoDi- Monochorionic diamniotic; IVF- *in vitro* fertilization; IUGR- fetal intrauterine growth restriction