

CASE DISCUSSIONS (CASES 21-24 FRITSCH)

CASE 21

PLACENTAL MESENCHYMAL DYSPLASIA

Background: Placental mesenchymal dysplasia (PMD) is a rare disorder (estimated incidence of 0.02% of deliveries) of poorly understood pathogenesis and characterized by placentomegaly, dilated vesicular villi reminiscent of a partial mole, and aberrant fetal vasculature. The fetus is usually normal, although there can be IUGR, and 80% of reported cases occur in female fetuses. Ultrasound often reveals subchorionic or localized cystic (hyperechoic) areas and an enlarged placenta. These abnormal appearing villi seem to become progressively worse with gestational age.

Pathology: Grossly the placenta is usually very large for gestational age with ectatic tortuous thick-walled chorionic plate vessels and occasionally umbilical cord varices. Many enlarged villi consisting of edematous or fibrotic myxoid stroma with abnormally dilated or increased numbers of thick-walled vessels are seen. These vascular abnormalities are a hallmark feature of PMD. Thrombi and focal areas of hemorrhage are common. The histologic features of fetal thrombotic vasculopathy can be seen. There is focal cistern-like or hydropic dilatation of villi similar to a partial mole, however, there is no trophoblast proliferation. These abnormal villi are intermixed with relatively normal appearing villi. On molecular studies the placental parenchyma is diploid but shows confined placental androgenetic/biparental mosaicism with an imbalance of imprinted genes in the abnormal villi. The abnormal villi show evidence of uniparental disomy (paternally derived) and the normal villi show biparental derivation. P57kip IHC is helpful, as the abnormally dilated villi show positive staining in cytotrophoblast cells but absence of staining in stromal/endothelial cells (biallelic imprinted p57 paternal gene is not expressed in these cells), whereas the normal appearing villi show p57 expression in both the cytotrophoblast and stromal cells. Increased circulating nucleated fetal red blood cells are often present. The main differential diagnosis is with a partial hydatidiform mole.

Summary of the features of PMD:

1. Abnormal vasculature including focal tortuous ectatic chorionic plate and umbilical cord vessels. Villous stromal vessels with increased numbers, thickened walls or abnormally dilated, often with thrombi.
2. Dilated cistern-like villi with edematous or fibrotic stroma intermixed with normal age appropriate villi. No trophoblast proliferation.
3. Diploid karyotype (partial mole is triploid), 80% female 46,XX, androgenetic/biparental mosaicism in most cases (use of p57 expression very helpful; best assessed by (short tandem repeat (STR) analysis - usually performed in selected laboratories)).
4. Fetus usually normal but often with IUGR.
5. Associated with Beckwith-Wiedemann syndrome.

There can be a spectrum of findings in any given case of PMD (i.e. they do not all present grossly or microscopically exactly alike).

Clinical associations: The progressive vascular abnormalities of PMD can result in thrombi within the fetal circulation, IUGR and an increased risk for IUFD or post-delivery morbidity. PMD is strongly associated with Beckwith-Wiedemann syndrome (BWS) in 25-33% of cases. BWS is a disorder of imprinting of a locus of genes on chromosome 11p15.5 including IGF2 and p57. A variety of mechanisms can result in imprinting defects in BWS, the most common being aberrant methylation of the regulatory region for these genes. Only a small number of patients with BWS present with PMD. Despite the clear association between PMD and BWS the molecular events linking these two imprinting disorders remain to be resolved. There is also a weak association between confined placental mosaicism for trisomy 13 and PMD. Various forms of villous vascular proliferations including chorangiomas, chorangiosis, and chorangioma are associated with PMD. An increased incidence of hemangiomas of the skin and liver are seen in patients with PMD. Various fetal hamartomas including hepatic mesenchymal hamartomas and hamartomas of the lung are associated with PMD, some (but not all) of which have also been shown to demonstrate androgenetic/biparental mosaicism. Detailed follow-up studies of infants born with PMD are needed to determine the long-term effects of this placental pathology.

Selected References:

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CASE 22

CHRONIC (HISTIOCYTIC) INTERVILLOSITIS (massive chronic intervillitis)

Background: Chronic histiocytic intervillitis is defined histologically as a diffuse infiltration of the intervillous space by a monomorphic population of CD68 positive maternal histiocytes accompanied by increased perivillous fibrinoid and extravillous trophoblast. A small number of intervillous T-cells may also be present. The villi are not involved by the histiocytes (this is not chronic villitis). This lesion occurs more commonly in spontaneous abortions (about 10 per 1000) especially in the first trimester and is rare in later pregnancy (<1 in 1000). The

incidence is reported to be much higher in women with recurrent spontaneous abortions (80 per 1000). The recurrence rate is high (67-100% in selected studies). The differential diagnosis includes placental malaria, which is exceedingly rare in the US. Other infectious etiologies should also be considered, especially if any inflammation involves villi. The etiology remains unknown, but it is proposed to be related to an underlying immunologic dysfunction, as the number of Treg lymphocytes have been reported to be elevated in both the basal plate and intervillous space.

Pathology: The placentas involved by chronic histiocytic intervillositis are usually small for gestational age. The histologic findings as described above define this entity. If chronic villitis or a polymorphous intervillous inflammatory infiltrate is present then this entity is excluded. Malaria should be considered with the clinical history reviewed and malaria organisms should be sought (only present in 40% of infected placentas) as well as the black malaria pigment (only present about 35% of the time). A note should probably be added that malaria cannot be excluded based on the absence of diagnostic findings. There is a histologic grading system for chronic histiocytic intervillositis proposed by Rota et al.:
Grade 1: Inflammatory infiltrate (histiocytes) and fibrin occupy less than 10% of the intervillous space.

Grade 2: 10-50% of the intervillous space is occupied by inflammatory cells and fibrin.

Grade 3: greater than 50% of the intervillous space is affected.

The severity of some outcomes have correlated with the histologic grade.

Clinical associations: Chronic histiocytic intervillositis is associated with recurrent spontaneous abortion, IUGR, and intrauterine fetal demise. Overall perinatal mortality rate has been reported to be as high as 77%. The death rate is lower in the third trimester (18%). A recent review of treatments for this disorder failed to show any significant improvement in outcome with treatment and there was a small trend (not statistically significant) that treatment resulted in a lower incidence of live birth than no treatment.

Selected References:

1. In: Atlas of Nontumor Pathology – Placental Pathology. Kraus FT et al. eds. American Registry of Pathology, Washington DC, 2004.
2. In: Manual of Pathology of the Human Placenta, 2nd ed. Baergen RN. Springer, New York, 2011.
3. In: Pathology of the Placenta – Major Problems in Pathology, 3rd ed. Fox H and Sebire NJ. Saunders-Elsevier, China, 2007.
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CASE 23

MASSIVE PERIVILLOUS FIBRIN DEPOSITION (and maternal floor infarct):

Background: In massive perivillous fibrin deposition (MPVFD) (considered in the spectrum with maternal floor infarction (MFI)) there is markedly increased perivillous fibrin and extracellular matrix fibrinoid surrounding distal villi in the lower 2/3 of the placenta usually including the basal plate. Regionally increased perivillous fibrin can occur in the setting of maternal vascular underperfusion but rarely affects a large percentage of the placenta and definitive villous infarcts can be identified histologically with MVU. MPVFD is a rare disorder affecting 0.03 to 0.5% of deliveries. The etiology for MPVFD remains unknown but it can recur in future pregnancies (12-78% reported). There is an association of this disorder in patients with autoimmune diseases, preeclampsia/maternal hypertension, thrombophilias, long-chain 3-hydroxyacyl-CoA (LCHAD) deficiency or mutations, and in patients with an imbalance in angiogenic and anti-angiogenic factors. More recently MPVFD has also been associated with an increased risk of renal tubular dysgenesis in a small number of cases. Prenatal ultrasound usually shows IUGR, oligohydramnios and a dense hyperechoic placenta in cases of MPVFD.

Pathology: Placentas affected by MPVFD are usually small for gestational age and often tongues of firm fibrinoid material can be seen grossly, often best after fixation. There are two histologic patterns of presentation one being a rind-like basal plate-associated deposition of fibrin which was originally called maternal floor infarction. The second presentation is diffuse lacy strands of fibrin marbling the lower 2/3 of the parenchyma. These strands can extend to the chorionic plate. Histologically there is extensive perivillous fibrin surrounding but not displacing distal villi with large numbers of associated intermediate trophoblast cells. The entrapped villi can become infarcted due to diminished perfusion. Localized lesions should not be confused with this more diffuse process. Perivillous fibrin occupying >30-50% of the intervillous space has been proposed to be potentially lethal to the fetus. Care must be taken with stillbirths as increased perivillous fibrin can occur as part of involutational changes. A semiquantitative scoring system has been proposed by Katzman and Genest for making the diagnosis of MPVFD:

1. Classic pattern: basal villous involvement by fibrinoid along the entire maternal floor (MFI) and of >3mm thickness on at least one slide.
2. Borderline MPVFD: 25-50% of villi encased by fibrinoid in a transmural distribution on at least one slide.
3. Transmural MPVFD: >50% of villi encased by fibrinoid material with transmural extension on at least one slide.

Scattered acute and/or chronic inflammation can be present including intervillitis or villitis. However, the predominant pattern should be massive perivillous fibrin deposition for a diagnosis of MPVFD. The differential diagnosis includes normal perivillous fibrin deposition, chorionic villous ischemia/infarction, fetal thrombotic vasculopathy, diffuse chronic villitis (VUE), and massive histiocytic chronic intervillitis.

Clinical associations: This is a serious disease that can recur and is associated with recurrent pregnancy loss (both spontaneous abortions and stillbirths (13-50%)), severe IUGR (24-100%), preterm delivery (26-60%), and neurologic impairment. It often begins in late second trimester or early third trimester. If suspected clinically early delivery is recommended. Therapy using anticoagulants remains controversial. While the exact cause for this disorder remains unknown, several possibilities have been proposed (see reference 9 for discussion).

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CASE 24

TRANSIENT ABNORMAL MYELOPOIESIS (TAM) IN A PATIENT WITH DOWN SYNDROME

The objective of this slide is to highlight the need to look closely in the placenta at all "compartments" including the fetal circulation for possible pathology. The presence of circulating nucleated fetal red blood cells (usually indicative of hypoxic/ischemic stress including fetal anemias) is the most common abnormality of the fetal circulation, however, other fetal disorders, especially neoplasms, can be detected if sought.

Background: Patients with Down syndrome (DS) (Trisomy 21) often demonstrate a spectrum of clinical findings including varying degrees of mental retardation, congenital heart disease, gastrointestinal disorders, hematologic abnormalities, and a characteristic facies (often subtle in the neonate). Hematologic abnormalities occur frequently in newborns with Down syndrome including transient thrombocytopenia (66%), polycythemia (34%), or neutrophilia (80%), all of which spontaneously resolve usually in the first 3 weeks of life. Transient abnormal myelopoiesis (TAM, also known as transient leukemia or transient myeloproliferative disorder) associated with Down syndrome is relatively rare affecting 4-10% of newborns with Down syndrome. TAM is defined as the presence of blasts (usually megakaryocytic in origin) in the peripheral circulation with spontaneous remission within three months of life. There is no significant morphologic distinction between TAM and acute megakaryoblastic leukemia, except that TAM spontaneously resolves. Patients with TAM demonstrate a variable presentation including no clinical symptoms, hepatosplenomegaly, effusions, diffuse lobular liver fibrosis, fetal hydrops, or TAM can be detected during assessment of other complications of DS.

Pathology: The blasts in TAM are thought to arise from a peripheral organ of fetal hematopoiesis such as the liver. The bone marrow may not contain blasts even in the presence of high numbers of blasts in the peripheral circulation. The liver can demonstrate extramedullary hematopoiesis, megakaryoblasts, dysplastic megakaryocytes, and in some cases diffuse lobular fibrosis. The circulating blasts in TAM are difficult to discern from blasts seen in AML or ALL. TAM blasts are medium to large with little basophilic cytoplasm, and scattered fine granules with occasional cytoplasmic blebbing. When assessed by flow cytometry the blasts usually demonstrate a megakaryoblastic phenotype including being positive for CD45, CD34, CD33, Cd38, CD36, CD56, HLA-DR, CD7 and a megakaryocytic marker (CD41, CD42a, or CD61). Specific lymphoid markers CD3, CD5, CD19, and CD20 are usually negative. The blasts in TAM demonstrate trisomy 21 and may contain other cytogenetic abnormalities. In addition, all TAM have been shown to contain a somatic mutation in GATA1 gene.

Clinical associations: TAM is difficult to distinguish from acute lymphoid or myeloid leukemia. Myelodysplastic syndrome must also be considered. In most cases of TAM the blasts disappear within 3 months of age. Neonatal death occurs in 11-52% of DS neonates affected by TAM, from a variety of causes, but many are directly related to the TAM. Even in DS patients with resolution of TAM, 13-29% will eventually go on to develop acute megakaryoblastic leukemia after 6 months of age.

Selected References:

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