Placental Mesenchymal Dysplasia
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- **Context.**—Placental mesenchymal dysplasia is characterized by placentomegaly and may be mistaken for molar pregnancy both clinically and macroscopically because of the presence of “grapelike vesicles.” It may be associated with a completely normal fetus, a fetus with growth restriction, or a fetus with features of Beckwith-Wiedemann syndrome.

- **Objective.**—To review the etiology, molecular pathology, gross and microscopic features, clinical presentation, complications, and differential diagnosis of placental mesenchymal dysplasia.

- **Data Sources.**—The PubMed and the Medline databases were systematically searched for articles between 1970 and 2006. The following keywords were used: placental mesenchymal dysplasia, mesenchymal hyperplasia, molar pregnancy, pseudomolar pregnancy, Beckwith-Wiedemann syndrome, and placentomegaly. Relevant references from review articles were also searched.

- **Conclusions.**—Placental mesenchymal dysplasia should be considered in the differential diagnosis when the ultrasonographic findings show a cystic placenta. Close attention should be paid to fetal morphology for early recognition of fetal complications and to prevent unnecessary termination of pregnancy in cases associated with a normal fetus.

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Placental mesenchymal dysplasia (PMD) is a relatively recently recognized, rare placental vascular anomaly characterized by placentomegaly and grapelike vesicles resembling partial molar pregnancy by ultrasonography and by gross placental examination. Placental mesenchymal dysplasia was initially described by Moscoso et al1 as stem villous hyperplasia in 1991 when they identified 2 cases with elevated maternal serum alpha fetoprotein levels and enlarged placentas with corresponding ultrasonographic features suggestive of partial mole. There were aneurysmally dilated vessels on the fetal surfaces of the placentas and dilated stem villi filled with clear gelatinous material in the subchorionic region. Histologically, however, these placentas could be distinguished from partial moles because of the absence of trophoblastic proliferation.2 Since then, this entity is being increasingly recognized. Several authors have preferred to use the term placental mesenchymal hyperplasia rather than dysplasia.2-5

The true incidence of PMD is unknown because it has been previously reported under a variety of names such as “placentomegaly with massive hydrops of placental stem villi” and “pseudopartial moles.”6-7 In addition, PMD remains unfamiliar to many pathologists and for these reasons it is believed that PMD is both underdiagnosed and underreported. According to 1 publication, the incidence of PMD is 0.02%.8 To date, 66 cases of PMD have been reported in the literature with a definite female preponderance of 3.6:1 (female-male).9

This review intends to highlight the salient features of PMD and the importance of distinguishing PMD from its mimickers, the most important of which is a partial mole. Placental mesenchymal dysplasia is associated with Beckwith-Wiedemann syndrome (BWS) and fetal growth restriction in the majority of the cases but can also be associated with normal-appearing fetuses. Placental mesenchymal dysplasia should be included in the differential diagnosis of cystic lesions of a placenta by sonography especially when a phenotypically normal-appearing fetus can be identified.

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**ETOLOGY**

The underlying cause of PMD is currently unknown. Some speculate that PMD is a congenital malformation of the mesoderm. This theory is based on observations of mesenchymal hyperplasia in stem villi along with other placental mesenchymal proliferative disorders such as chorangiomas and chorionic vessel dilatation as well as hemangiomas of the fetus.2 In addition, the enlarged stem villi contain acid mucopolysaccharide, which is found in the connective tissue layers of the normal chorionic mesoderm.2

There is a definite association of PMD with BWS, which is characterized by macrosomia, exomphalos, macroglossia, omphalocoele, and internal visceromegaly in addition to placentomegaly and increased susceptibility to childhood tumors.6,10 According to a recent article, 23% of PMD cases are associated with BWS.9 Because of highly variable penetrance in BWS, PMD and BWS are considered a spectrum of phenotypic changes of common etiology. At one end of the spectrum, PMD exhibits phenotypic changes limited to the placenta and BWS at the opposite end with phenotypic changes affecting both placenta and fetus. The...
molecular pathogenesis of BWS has been extensively studied and there is strong evidence that abnormal expression or disruption of 1 or more of the imprinting gene(s) on chromosome 11p15.5 (the so-called BWS candidate gene) is thought to be the major underlying defect.7,11

Hypoxia and hypoperfusion of unknown etiology may give rise to the phenotypic findings in the placenta with PMD. During hypoxia, fibroblasts are stimulated to produce increased connective tissue fibers with subsequent increased production of vascular endothelial growth factor by villous macrophages leading to angiogenesis.12

More recently, androgenetic/biparental mosaicism has been suggested by Kaiser-Roger et al13 as the underlying cause of PMD, supported by the finding of 2 separate cell lines in PMD placental tissue. In this condition, the androgenetic cell line is thought to arise from endoreduplication of the haploid paternal genome, whereas the biparental cell line arises from the combination of the haploid maternal and the paternal genomes. However, the presence of the same paternal haploid complement in both cell lines suggests paternal uniparental disomy and involvement of only a single egg and sperm nucleus.13 The abnormal androgenetic cells are confined to chorion, meconium, membranes, and vessels, whereas the trophoblastic cells are normal with no evidence of androgenetic cells.13 This explains the absence of trophoblast overgrowth in PMD in contrast to complete moles in which androgenetic cells are identified in the trophoblastic cell layer. Studies have shown a female predominance in cases of PMD and it is speculated that there is a relationship to the X chromosome, although an exact underlying mechanism is not yet fully known.8 Female predominance can also be explained by androgenetic/biparental mosaicism.13 Because the androgenetic cell line has arisen from duplication of the haploid paternal genome, it is likely that this would give rise to the 46,XX cell line because 46,XY cell lines are incompatible with life.13 However, because cases of PMD with male fetuses have been reported, it seems that the etiology of PMD is heterogenous.

MOLECULAR PATHOGENESIS

Placental mesenchymal dysplasia is characterized by overgrowth of placental tissue. The mechanisms for this overgrowth are only partially understood at this time. Chen et al13 analyzed DNA from the fetus and different parts of the placenta from 2 cases of PMD and confirmed genetic identity among the chorangioma, vesicle-like villi, and the fetus. Much of the information on the molecular genetics of PMD comes from studies done on BWS cases and it is thought that defects in the genes controlling cell cycle lead to overgrowth of placental tissue and are described here briefly.

Imprinted Genes Cluster at Chromosome 11p15.5

Beckwith-Wiedemann syndrome imprinting genes cluster is traced to chromosome 11p15.5 with disruption of 1 or more genes.14 The most commonly involved genes are CDKN1C (p57kip2), H19, IGF-II, and KVLQ. There have been no major analyses of how frequently these molecular alterations are observed in PMD, but it is thought that, in PMD without fetal anomalies, the underlying 11p15 abnormality is confined to the placenta. The genomic imprinting of these genes is influenced by parent of origin. The CDKN1C (p57kip2) gene is expressed in the maternal genome, whereas the paternal allele is transcriptionally silenced.15 It belongs to the family of cell-cycle regulators and encodes a cyclin dependent kinase inhibitor. The underlying abnormality is thought to be the loss of activity of the p57kip2 gene causing loss of cell-cycle inhibition and overgrowth.16,17 Insulin-like growth factor II (IGF-II) encodes a fetal-specific growth factor that is paternally expressed.18 It has been suggested that abnormalities of IGF-II gene or IGF-II receptor gene lead to up-regulation of IGF-II resulting in overgrowth of the placental tissue.19,20 Molecular studies have shown that IGF-II overproduction is the result of an aberration in normal maternal suppression or, in rare cases, because of the presence of 2 paternal copies of the IGF-II gene.7 It is suggested that IGF-II and p57kip2 act in the same pathway but in an opposing manner to control the cell cycle. A gain in function of IGF-II or a loss in the function of p57kip2 would have similar consequences, that is, somatic overgrowth.21

Vascular Endothelial Growth Factors

Vascular endothelial growth factors (VEGFs) have a major role in normal angiogenesis. The VEGF-D gene is encoded on chromosome Xp22.31 and because of the predominance of female fetuses affected by PMD, some authors have suggested a relationship between abnormal angiogenesis and chromosome X.8 This relationship has not been confirmed or studied by other investigators. Vascular endothelial growth factors interact with tyrosine kinase receptors on the endothelial cell surfaces. Flt-4, a tyrosine kinase receptor expressed on placental endothelial cells, interacts with VEGF-C and, because of structural similarities between VEGF-C and VEGF-D, Flt-4 may also interact with VEGF-D.22,23 It is quite possible that this interaction causes increased angiogenesis and may play a role in the development of vascular malformations seen in PMD.

CLINICAL PRESENTATION

There is no specific clinical symptomatology associated with PMD. Most cases of PMD in early pregnancy are diagnosed by prenatal ultrasonography done either for routine prenatal checkup or because of an abnormal amniocentesis result. The most common abnormal laboratory test includes increased level of maternal serum alpha fetoprotein, which is thought to be of fetal origin. It is speculated that the increase in the surface transfer area because of increased placental volume and increased vessels within the stem villi may lead to increased transfer of alpha fetoprotein into the maternal circulation.1 The level of beta-human chorionic gonadotropin is normal to slightly increased but returns to normal levels soon after delivery.7,9 Later in the pregnancy, the patient usually presents with intrauterine growth restriction or fetal demise. Patients may also present with polyhydramnios if the fetus has swallowing difficulty as part of BWS. Many cases are asymptomatic and are diagnosed postpartum because of delivery of an abnormally large placenta.

The sonographic features of PMD are very similar to those of partial moles.1 A thickened placenta with hypoechoic spaces are classical sonographic findings of both PMD and molar pregnancies. The other differential diagnoses of these ultrasonographic findings include chorionic angiomas and subchorionic hematomas. However, these findings are less diffuse than in PMD.24 A few small anechoic spaces can be present in the placental tissue without any clinical significance.25 However, if the process is diffuse, close monitoring of the pregnancy is required. Jau-
niaux et al\textsuperscript{10} evaluated 6 suspected cases of PMD with serial prenatal ultrasonography and Doppler imaging that showed cystic spaces located deep in the placental parenchyma and increased placental thickness early in gestation. As the pregnancy advanced, the cystic spaces moved toward the chorionic plate. The chorionic plate vessels, including both the arteries and veins, became progressively dilated and aneurysmal. No abnormal chorionic vessels were seen before midgestation. The ultrasonographic finding of a large cystic placenta along with a phenotypically well-formed fetus is highly unlikely in molar pregnancy and should raise the possibility of PMD.

**MACROSCOPIC FEATURES**

Grossly, the placenta is usually extremely large for gestational age. In the cases described so far, more than 90% of the cases exhibited placental weights of more than the 90th percentile.\textsuperscript{9} The gross placental findings in PMD vary with gestational age. In third trimester PMD placenta, the chorionic plate vessels are aneurysmally dilated and tortuous (Figure 1, A and B), measuring up to 2.5 cm in diameter, and show abnormal branching.\textsuperscript{7} The dilated chorionic plate vessels may show luminal thrombosis or can rupture giving rise to subamniotic hemorrhage, which can further compromise the growth restricted fetus.\textsuperscript{3,7} In both early and late gestation PMD, placental parenchyma may have pale and friable areas with streaks of prominent stem villi and multiple cysts oriented perpendicular to the chorionic plate.\textsuperscript{6} These grapelike cystic vesicles, which are similar grossly to those of molar pregnancy, range in size from 0.3 to 2.5 cm and are usually visible grossly (Figure 2, A and B). In rare cases, the vesicle formation is minimal or absent.\textsuperscript{3} In cases terminated before 20 weeks of gestation, the chorionic plate vessels are not dilated and the normal and abnormal areas are not clearly delineated suggesting that the vascular malformations develop progressively secondary to circulatory imbalance and poor vascularization of the dysplastic villi.\textsuperscript{10} As the pregnancy advances, tangled congested vessels grossly resembling gray-white or dark-red wormlike structures may be identified within the parenchyma (Figure 2, A and B) and are often most prominent in the subchorionic plate region near the fetal surface.\textsuperscript{26,27} Amniotic bands have also been described in rare cases.\textsuperscript{28}
**MICROSCOPIC FEATURES**

Despite its resemblance to partial moles on gross examination, PMD can be distinguished from the former by careful histologic examination. The histopathologic findings in placentas with PMD are similar irrespective of fetal association with BWS and vary with the gestational age. Third trimester PMD placentas have dilated thick-walled chorionic plate vessels with fibromuscular hyperplasia and may have fresh or organizing thrombosis (Figure 3, A) with varying degrees of luminal obliteration.27,29 Thrombosis may be present in both the veins and arteries of the chorionic plate.3 The vessel walls usually show some degree of fibrinoid necrosis (Figure 3, B). The parenchymal vascular malformations dilate vessels and may have fresh or organizing thrombosis (Figure 3, C). The stem villi are enlarged in both early and late gestation PMD placentas and, at times, may be up to 10 times the size of normal stem villi late in gestation. These enlarged stem villi have central cisterns filled with gelatinous material and fibromuscular vessels at the periphery (Figure 4, A).27 These thick-walled vessels develop during time as pregnancy advances and may show fibrinoid necrosis and degenerative changes in the vessel wall (Figure 4, B). Irrespective of gestational age, the stem villi in PMD have loose and myxoid stroma with an overgrowth of fibroblasts (Figure 4, B) and foci of myxoid degeneration unlike the normal stem villi, which are mostly fibrous.1,27 Similar to the stem villi, the terminal villi may also show mesenchymal cell hypercellularity and stromal fibrosis (Figure 4, C).8,26 However, scattered between dilated stem villi may be a mixture of normal-appearing and hydropic secondary and tertiary villi.9 Early in gestation these changes are not as well-developed and the stem villi show dilated cisterns surrounded by loose myxomatous stroma, which has delicate vessels under the trophoblastic layer (Figure 5, A and B). Some stem villi reveal intravillous fibrin deposition and lack distinct fetal vessels because of fetal vessel thrombosis.9 Recanalization of stem villus thrombosed vessels has also been described.8 The important diagnostic features of PMD include the absence of trophoblastic proliferation, stromal trophoblastic inclusions, and scalloping of the villous surface, which are characteristics of a molar pregnancy.1,3,5,7,26,28 Discrete chorangiomas may be identified.31 In rare cases, extramedullary hematopoiesis is identified.28 Nucleated red cells are seen mostly in areas of chorangioma or chorangiomas at a stage when nucleated red cells are not normally seen in the fetal vessels. These changes are thought to represent a consequence of placental hypoxia.9 Villous hemorrhage has been identified in some cases.8

**IMMUNOHISTOCHEMICAL AND SPECIAL STAINS**

Stromal cells in the large stem villi of PMD placentas are positive for vimentin and desmin and negative for alpha-smooth muscle actin, whereas the stromal cells in the surrounding normal-appearing stem villi are positive for vimentin, desmin, and α-smooth muscle actin.27 In a normally developing placenta, mesenchymal cells (stromal cells in the villi) acquire vimentin and desmin at the end of the second month of gestation, at which stage these cells are called reticular cells or fibroblasts. With further cell differentiation, these fibroblasts would acquire alpha-smooth muscle actin and would then be called myofibroblasts. In PMD, the staining characteristics of the dilated stem villi stromal cells is that of fibroblasts and it appears that these cells cease to differentiate beyond the fibroblast stage.32

The ground substance shows a strong reaction to Alcian blue stains indicating the presence of large amounts of acid mucopolysaccharides.27 Macrophages in the stroma also contain Alcian blue positive vacuoles in their cytoplasm.1 The p57KIP2 protein is a potential marker that may prove helpful in distinguishing PMD from molar pregnancy. Castrillon et al7 utilized the p57KIP2 diagnostic marker to distinguish normal placential tissue, spontaneous abortion with hydropic changes, and partial moles from complete molar pregnancies. Unfortunately, there have been no studies done to see the utilization of this marker in PMD, but, with increased awareness of PMD, it is hoped that studies in the future will demonstrate the significance of this marker.

**CYTOGENETICS AND DNA PLOIDY STUDIES**

In the cases described in which karyotyping has been performed, the majority of the cases are diploid.29 Most are karyotypically and phenotypically normal females (46,XX). With rare exceptions, no major chromosomal abnormalities are identified.29 Four cases described exhibited chromosomal abnormalities including trisomy 13, Klinefelter syndrome (47,XY), triploidy (69,XXX), and 46,XXp-.8 However, scattered between dilated stem villi may be a mixture of normal-appearing and hydropic secondary and tertiary villi.9 Early in gestation these changes are not as well-developed and the stem villi show dilated cisterns surrounded by loose myxomatous stroma, which has delicate vessels under the trophoblastic layer (Figure 5, A and B). Some stem villi reveal intravillous fibrin deposition and lack distinct fetal vessels because of fetal vessel thrombosis.9 Recanalization of stem villus thrombosed vessels has also been described.8 The important diagnostic features of PMD include the absence of trophoblastic proliferation, stromal trophoblastic inclusions, and scalloping of the villous surface, which are characteristics of a molar pregnancy.1,3,5,7,26,28 Discrete chorangiomas may be identified.31 In rare cases, extramedullary hematopoiesis is identified.28 Nucleated red cells are seen mostly in areas of chorangioma or chorangiomas at a stage when nucleated red cells are not normally seen in the fetal vessels. These changes are thought to represent a consequence of placental hypoxia.9 Villous hemorrhage has been identified in some cases.8

**DIFFERENTIAL DIAGNOSIS**

It is important to distinguish PMD from molar pregnancy because it may avoid unnecessary termination of pregnancy especially if prenatal ultrasonographic examination shows features suggestive of molar pregnancy in the presence of a normal-appearing fetus. The main differential diagnoses of PMD, both clinically and pathologically, are partial hydatiform moles, a twin gestation with complete mole, spontaneous abortion with hydropic changes, and confined placental mosaicism. Unlike partial moles, the placenta in PMD is almost always diploid (except in rare instances), and histologically the villi do not show proliferation of trophoblasts or stromal trophoblastic inclusions. The triploid fetus associated with a partial mole shows growth restriction with a variety of external and internal defects. In twin gestations with complete moles, the abnormal fetal vessels in the stem villi characteristic of PMD are absent even though the fetus may have a diploid karyotype. Complete hydatidiform moles may also exhibit high levels of IGF-II expression and loss of expression of p57KIP2, but these are purely androgenetic and the entire genome is paternally derived.34 Spontaneous abortion with hydropic change may have vesicle formation and can be confused with early PMD. The vesicles in hydropic spontaneous abortion, if present, are usually
Figure 3.  A, Dilated subchorionic vessel with acute and organizing thrombosis. B, Fibrinoid necrosis of the subchorionic vessel wall. C, Vascular malformations with fibrinoid necrosis of the vessel wall and thrombosis (hematoxylin-eosin, original magnification ×40).

Figure 4.  A, Placental mesenchymal dysplasia, 36 weeks’ gestation. Stem villus demonstrating a central cistern with peripheral, thick-walled vessels and surrounding normal-appearing tertiary villi. B, Higher magnification showing a fibromuscular vessel and increased stromal mesenchymal cells (fibroblasts). C, Tertiary villi with increased stromal mesenchymal cells. Note the absence of trophoblastic proliferation (hematoxylin-eosin, original magnifications ×40 [A], ×100 [B], and ×200 [C]).
Intrauterine growth restriction, and intrauterine fetal demise. Severe intrauterine growth restriction may be related to diversion of fetal blood within the vascular malformations or stem villi blood vessel thrombosis resulting in hypoperfusion and hypoxia that ultimately leads to intrauterine growth restriction.

Although many obstetrical complications such as polyhydramnios, fetal hydrops, gestational diabetes, and pre-eclampsia may be associated with a large placenta, placentomegaly in PMD, in and of itself, is thought not to be the cause of fetal complications. No direct association of placental weight and fetal or maternal complications have been identified. Rather, the complications are thought to be related to the degree of vascularity and excessive vascular shunting into the chorangiomatous areas. Cases associated with chorangiomas are thought to be associated with a higher rate of fetal complications including anemia and thrombocytopenia, which in turn are thought to be secondary to microangiopathic hemolytic anemia because of abnormal shunting of the blood. Chromosomal abnormalities may be found in a few fetuses, but most are karyotypically and phenotypically normal females. Rare cases of fetal congenital adrenal hyperplasia, vascular malformations or stem villi blood vessel thrombosis resulting in hyperinsulinemic hyperglycemia seen in neonates with PMD is secondary to BWS, but some of the complications seen in fetuses born with PMD are secondary to BWS without fully developed phenotypic features. For example, hyperinsulinemic hypoglycemia seen in neonates with PMD is secondary to islet cell hyperplasia of the pancreas, which is a frequent finding in BWS.

The common fetal complications reported in phenotypically normal fetuses associated with PMD are prematurity, intrauterine growth restriction, and intrauterine fetal demise. Severe intrauterine growth restriction may be related to diversion of fetal blood within the vascular malformations or stem villi blood vessel thrombosis resulting in hypoperfusion and hypoxia that ultimately leads to intrauterine growth restriction.

Although many obstetrical complications such as polyhydramnios, fetal hydrops, gestational diabetes, and pre-eclampsia may be associated with a large placenta, placentomegaly in PMD, in and of itself, is thought not to be the cause of fetal complications. No direct association of placental weight and fetal or maternal complications have been identified. Rather, the complications are thought to be related to the degree of vascularity and excessive vascular shunting into the chorangiomatous areas. Cases associated with chorangiomas are thought to be associated with a higher rate of fetal complications including anemia and thrombocytopenia, which in turn are thought to be secondary to microangiopathic hemolytic anemia because of abnormal shunting of the blood. Chromosomal abnormalities may be found in a few fetuses, but most are karyotypically and phenotypically normal females. Rare cases of fetal congenital adrenal hyperplasia, vascular malformations or other mesenchymal tumors. Follow-up of most of the normal-appearing infants has shown no developmental problems.

Maternal complications associated with PMD are comparatively rare. Gestational proteinuric hypertension has been reported, but it is believed that hypertension in these cases is probably a coincidental finding rather than any specific association with PMD. Similarly, polyhydramnios may occur as a result of swallowing-related problems because of macroglossia in a BWS fetus. A 5-year follow-up of mothers with PMD showed no sign of trophoblastic disease or recurrence of PMD in subsequent pregnancies. However, it should be noted that 15% of BWS cases are familial, and theoretically there is a small increased chance of having recurrence of PMD in such families.

CONCLUSIONS

Although PMD may be associated with fetal growth restriction or paradoxically with features of overgrowth, it is important to identify these cases prenatally to reduce fetal morbidity and mortality. It is also important to recognize the detailed gross and histopathologic features of this rare disease entity and be able to differentiate this condition from cases presenting as possible partial hydatidiform moles especially in the first half of pregnancy. Prenatal recognition of PMD during early as well as late gestation could prevent unnecessary termination of pregnancy. Placental mesenchymal dysplasia in early pregnancy is more likely to be mistaken for a partial mole especially by ultrasonographic examination. Ultrasonographic findings suggestive of a molar pregnancy because of hypoechoic spaces in the placenta in the presence of an apparently normal fetus, a fetus with growth restriction, or a fetus with features of overgrowth should raise the possibility of PMD.

References

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