



## Placental Mesenchymal Dysplasia with Fetal Mosaicism – A Case Report

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### Abstract

**Introduction:** Placental mesenchymal dysplasia (PMD) is a rare lesion, characterized by atypical placental development with placentomegaly, hydropic cystic stem villi formation and anomalous villous stroma and vessels. PMD fetuses are often normal. Because of this characteristics it is important to do the differential diagnosis among gestational trophoblastic disease, Beckwith-Wiedemann syndrome and other placental vascular anomalies. Although PMD is compatible with fetal life, there are more complicated pregnancies that can compromise obstetric outcome.

**Material and Methods:** We present a case of a 39-year-old female, nulliparous, diagnosed at 12 weeks gestation with a normal fetus and a multicystic placenta. Subsequent ultrasounds found a normal anatomical survey and appropriate fetal growth. Human chorionic gonadotropin ( $\beta$ -HCG) levels were in the usual levels. At 37 weeks, intra-uterine fetal death occurred unexpectedly.

**Results:** Pathological examination revealed placentomegaly with abnormally large stem villi with cysts and peripheric thick wall vessels with no trophoblast proliferation. Chorionic vessels presented thrombi and fibrinoid necrosis. Immunohistochemistry for p57<sup>kip2</sup> showed positivity in trophoblast cells and negativity in stromal villous cells. Necropsy study showed a normal female fetus with signs of anoxia. Mosaicism was diagnosed on amniotic fluid karyotype: 46,XY(18)/46,XX(10).

**Conclusion:** PMD is a rare entity, probably under diagnosed, but important to recognize in order to perform correct follow-up. It can be associated with adverse pregnancy outcome, IUGR (intra-uterine growth restriction), IUID (intra-uterine fetal death) and preterm delivery (PTD). Women should be counseled regarding these and surveillance heightened. Etiology remains uncertain, being androgenic/biparental mosaicism a possibility.

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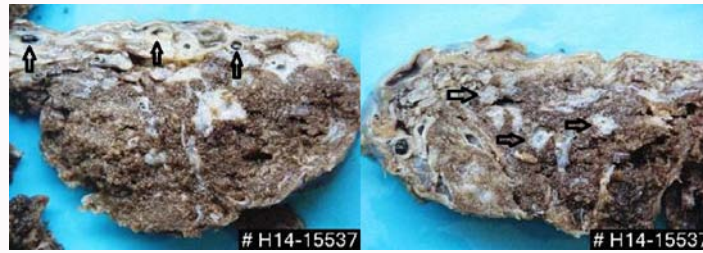
**Keywords:** Fetal growth restriction; Fetal intra-uterine death; Molar pregnancy; Placenta; Placental mesenchymal dysplasia; Stem villous hyperplasia; Mosaicism

### Introduction

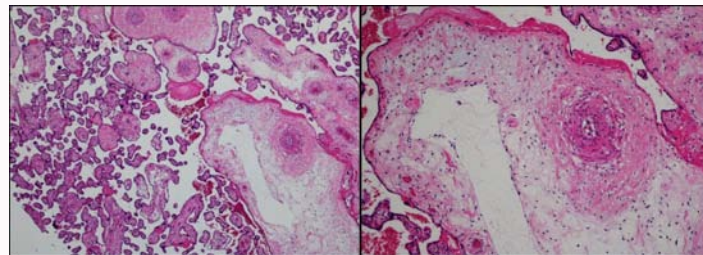
Placental mesenchymal dysplasia (PMD), also known as mesenchymal villous dysplasia or pseudopartial mole is defined as abnormal placental development with placentomegaly, hydropic cystic stem villi and abnormal villous stroma and vessels [1]. On ultrasound and gross examination it shows grape like vesicles that can mimic molar pregnancy [2], but histologically the absence of trophoblastic proliferation can distinguish PMD from moles [3]; additionally, blood flow is seen in placental cysts of PMD pregnancies and is absent in cysts of molar pregnancies [4].

PMD is a rare lesion, occurring in 0.002% to 0.02% of pregnancies and is predominantly seen in female fetuses [5]. It was first described in 1991 [6] with about 100 cases reported since then [7]. Jauniaux et al. [8] in 1997 stated six cases of PMD, in which placenta's karyotype was normal in all cases, suggesting that the placental anomaly is more commonly associated with a 46, XX karyotype.

Ultrasonographically complete molar pregnancies usually have absent fetuses and PMD resembles more partial moles, as fetus is present and initially can present with no gross malformations [9]. Fetuses of PMD are often normal and pregnancy can reach term. However, in some cases, intrauterine growth restriction, preterm delivery or prenatal demise can occur. Beckwith-Wiedemann Syndrome (BWS) may be associated with PMD; even with a normal fetus, BWS can occur [10]. As so, ultrasound evaluation, placental histology and karyotype determination are essential to perform the correct diagnosis.



**Figure 1:** Gross inspection: chorionic thick and tortuous vessels, with thrombi – upward arrows (A) and small cysts in the parenchyma – rightward arrows (B).



**Figure 2:** Admixture of intermediate villi and stem villi with central dilation, H&E 40x (A); stem villi were hypervascular with peripheral thick walled vessels, H&E 100x (B).

## Material and Methods

### Histology evaluation

Examination was performed on haematoxylin and eosin (H&E) stained slides observed in light microscope – Nikon Eclipse 50i<sup>®</sup>, and images obtained using a Nikon-Digital Sight DS-Fi1<sup>®</sup> camera.

### Ancillary techniques/Immunohistochemistry

Studies were performed on one representative block of the lesion, resorting to avidin-biotin-peroxidase complex detection system and performed on Ventana Marker Platform Bench Mark ULTRA IHC/ISH<sup>®</sup> using the following antibodies: p57<sup>kip2</sup> (C-20, Santa Cruz, CA-USA), CD3 (Policlonal, Dako, Denmark) and CD20 (L26, Leica, Germany).

## Case Report

### Clinical data

A 39-year-old female, with no pathological background, first pregnancy, with first ultrasound scan at 12 weeks gestation that showed abnormal multicystic placenta (several round hypoechoic areas resembling «Swiss cheese») with a normal fetus. Ultrasound was repeated at 15 weeks gestation revealing adequate growing fetus without morphologic anomalies. She was institutionalized at 16 weeks due to suspected infection for *Listeria monocytogenes*, treated successfully with ampicillin and gentamicin. In the subsequent ultrasounds, at 22, 28 and 32 weeks, fetal anatomical surveys and growth patterns were normal. Human chorionic gonadotropin (B-HCG) serum levels were also within normal range. At 37 weeks, fetal death was documented in emergency, after complaints of absent quickening for some hours. Amniocentesis was performed, after the initial refusal of the pregnant woman, with the purpose of clarifying anomalies of the karyotype and possible diagnosis. Therapeutic protocol for fetal expulsion was engaged.

### Pathologic findings – Placenta

Gross examination revealed an enlarged placenta with 17 cm × 15 cm, weighting 680 g with tortuous and dilated chorionic plate vessels; on cut section with maximum thickness of 5.5 cm. Maternal plate

was unremarkable. The parenchyma had multiple and disperse cysts, the biggest with 1 cm, between spongy and red villous parenchyma (Figure 1A and 1B). Membranes and umbilical cord did not have pathological alterations.

Histological examination showed predominance of intermediate villi, sometimes with interstitial hemorrhage (Figure 2A); the stem villi have central cistern and peripheric hypervascular stroma with anomalous thick walled vessels (Figure 2B). There is fetal thrombotic vasculopathy with dilation of chorionic vessels and mural thrombus (Figure 3A and 3B), also seen in stem villi. These features were frequent and associated with fibrinous necrosis (Figure 3C). No trophoblastic proliferation was registered and immunostaining for p57<sup>kip2</sup> revealed nuclear positivity in the trophoblast cells and negativity in stromal cells (Figure 4).

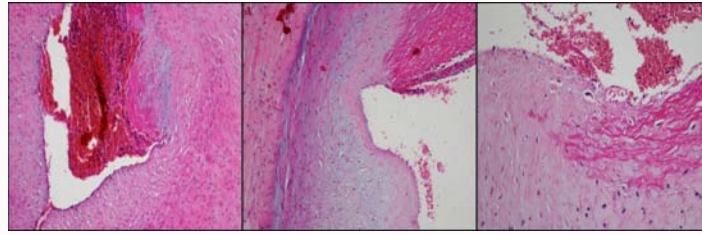
Immuno histochemistry for CD3 and CD20 were negative and helped ruling out vilitis.

### Pathologic findings – Autopsy

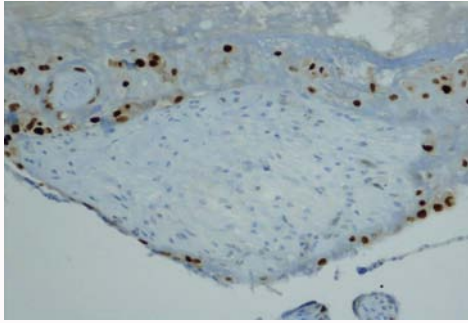
Autopsy study of the 37-week-old female fetus, weighting 2,800 g, exhibited no gross morphologic alterations with anthropometric measures in percentile 50 (Crown-Heel=49.5 cm, Crown-Rump=35.5 cm, Toe-Heel=7.5 cm, Cephalic Perimeter=32 cm, Thoracic Perimeter=30.6 cm, Abdominal Perimeter=26 cm). There was neither macroglossy nor abdominal wall defects. Female external genitalia did not show alterations and ovaries were located in abdominal cavity, without changes (Figure 5). There was not cardiomegaly - 16.6 g, pancreatic hyperplasia, adrenal gland was normal - 5.1 g, and there was no renal dysplasia - 25.4 g. Lungs, spleen, thymus and liver with normal weights.

Microscopically there were findings suggestive of fetal suffering/anoxia: amniotic fluid aspiration, adrenal gland lipidic pattern inversion, without cytomegaly, and meningeal vascular congestion.

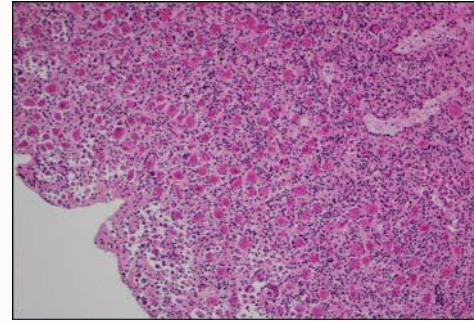
Karyotype done on amniotic fluid revealed a mosaic pattern presenting two different cell lines: 46,XY(18)/46,XX(10). Possible maternal contamination was excluded.



**Figure 3:** Chorionic vessels were dilated and had thrombi, H&E 40x (A and B); fibrinous necrosis was present in a majority of chorionic blood vessels, H&E 100x (C).



**Figure 4:** Immunostaining with p57<sup>kip2</sup> with a discording profile – positive in the trophoblastic cells and negative in the stromal cells, 200x.



**Figure 5:** Ovarian normal morphology, H&E 100x.

## Discussion

PMD is rare, but usually a benign condition that has to be part of the differential diagnosis when ultrasound reveals a cystic placenta with a normal fetus [2]. Due to the fact that in the past PMD was reported under several names, such as “pseudopartial mole” and to the fact that it is still unfamiliar to several pathologists, it is believed to be under diagnosed, so it’s true incidence is unknown [3].

The pathogenesis of PMD is still unclear, with some authors initially theorizing that it was a mesoderm congenital malformation [11]. Recently, others suggested that a mosaic pattern of normal and androgenetic cell types is the only recognized etiology for PMD, which results from the failure of the maternal genome to duplicate, concluding that the placental anomaly is more commonly associated with a 46, XX karyotype [12]. Because of the association of PMD with BWS, characterized by macrosomia, organomegaly, macroglossia, omphalocele and increased risk of pediatric tumors [1], PMD and BWS are considered a spectrum of phenotypic alterations of the same etiology, being PMD one end of the spectrum, where the phenotypic changes are confined to the placenta and BWS the opposite edge, with modifications in fetus and placenta [3]. Molecular pathogenesis of BWS has been widely studied and is traced to chromosome 11p15.5 with disruption of 1 or more genes, more commonly Cyclin-Dependent Kinase Inhibitor 1C-CDKN1C (p57<sup>kip2</sup>), H19, Insulin Growth Factor II (IGF-II) and potassium channels, voltage dependent (KVOLT) [3]. The abnormal expression of imprinted genes as also been raised as a possible etiology for PMD [12]. In the last years, the androgenetic/biparental mosaicism proposed as the cause for PMD, supports the existence of two separate cell lines in PMD placental tissue – one in chorionic mesoderm, membranes and vessels and the other in the trophoblast layer [12]. In 2006, Kaiser-Rogers et al. [12] reported that a mosaic pattern of normal and androgenetic cell types is the only recognized etiology for PMD. They suggested that this mosaicism results from the failure of the maternal genome to duplicate before

the first cleavage, with normal duplication and segregation of the paternal genome, resulting in two daughter cells: one with normal biparental genes and the other one with only paternal genes. This new hypothesis may account for the marked female predominance in PMD (because an androgenic 46, YY cell line is presumably non-viable). The abnormal androgenetic cells would be confined to the chorionic mesoderm, membranes and vessels, whereas the trophoblastic cells would be normal with no evidence of androgenetic cells. These characteristics are also in the origin of a p57 discording immune profile between the trophoblast and stromal cells [13]. This feature would explain the absence of trophoblast overgrowth in PMD, contrasting to complete moles, in which androgenetic cells are identified in the trophoblastic cell layer. This could be a possible explanation for the fact that we had a phenotypic female fetus with a mosaic karyotype: 46,XY(18)/46,XX(10), although the possibility of a reabsorbed twin fetus with the male karyotype, could not be excluded.

The main ultrasound differential diagnosis of PMD is partial molar pregnancy, but the presence of a normal fetus does not discard the latter hypothesis, only confirmed by triploidy, trophoblast proliferation and mixture of normal and abnormal villi [2]. Heightened surveillance with serial growth evaluations and assessment of fetal wellbeing in the third trimester should be considered. However, there is no evidence to suggest that Doppler evaluation of fetal and uteroplacental vessels would help to identify cases of PMD, but it may be important in cases complicated by IUGR.

Grossly placentas with PMD are overweighed with numerous cysts in the parenchyma and varicose dilation of chorionic vessels [1,10], as verified in our case. Histologically, placental parenchyma shows abnormally enlarged stem villi, with stromal cystic degeneration forming cysterns, and vascular and stromal proliferation [10]. As for chorionic vessels, fetal thrombotic vasculopathy is often present [1]. These characteristics were also identified in our specimen, as well as the discording p57 profile.

Due to strong association with BWS, that would motivate a



genetic counseling about increased risk in future pregnancies [2], this situation had to be excluded. The necropsy study reported a fetus without the morphologic alterations identified in BWS, namely cardiomegaly, macroglossy, cytomegalia and abdominal wall alterations. Fetus death was identified to be in relation with hypoxia, probably in tight relationship with the fetal thrombotic vasculopathy identified in the placenta. It must be noticed that even in fetus without BWS, 50% usually show IUGR and 43% had intrauterine fetal demise or neonatal premature death, many of them without IUGR, suggesting other factors for the fatal event [10].

In conclusion, PMD is a rare entity, important to recognize in order not to terminate pregnancy unnecessarily and to consider close follow-up of these pregnancies, especially in cases of IUGR or fetus over growth. It is thought that IUGR and IUFD occur due to the higher probability of vascular events, such as obstructive thrombosis and consequent decreased maternal-fetal gas exchange. It is suggested an intensive monitoring of women with PMD in order to improve pregnancy outcome, although this has not yet been verified [5,14]. In cases with PMD and a normal anatomical fetus, having uncomplicated maternal clinical histories, mothers can be reassured about a normal live birth [5].

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