Placental mesenchymal disease: how to approach the diagnosis as early as the first trimester ? A case report and a review

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Key clinical message

Placental mesenchymal disease has to be evoked as a diagnosis when an unusual cystic appearing placenta is noticed on prenatal scans. The pathway to diagnosis is challenging since it includes trophoblastic disease with a concrete neoplastic risk for the mother and PMD with high rate of associated feto-maternal complications.

Title

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Introduction

Placental mesenchymal disease (PMD) is a rare and benign antenatal disorder affecting the placenta in 0,02-0,2% of pregnancies (1). It is predominantly seen in female fetuses with a male to female ratio of 1 : 3,6 - 8 (2).

Initially based on a sonographic evaluation, the differential diagnoses include partial hydatidiform molar pregnancy, complete mole and coexisting fetus, spontaneous miscarriage with hydropic changes and placental mosaicism (1).

Diagnosing PMD proves to be challenging since the ultrasound features resemble hydatidiform molar pregnancy (1-2). The clinical implications and management differ greatly. Even if PMD carries no risk of neoplastic disorder (1), only 9% of reported cases of PMD result in an uncomplicated pregnancy, while the vast majority is associated with feto-maternal complications (3).

The definitive diagnosis is only confirmed by gross and microscopic pathologic examination (3).

Detecting the disease to be able to correctly inform the patients on this rare disorder and to provide the best management is of utmost importance.

We report a case of PMD resulting in the birth of a healthy female baby with review of the literature.

Case history

A 35-year-old woman, gravida 2 and para 1, was referred to the Maternal Foetal Medicine (MFM) Unit of our hospital at 9 weeks and 6 days of gestational age (GA) to start the follow-up of her second pregnancy. Her first pregnancy was terminated at 25 weeks of GA because of a fetal hypoplastic left heart syndrome diagnosis. A comparative genomic hybridization-array (CGH) and exome sequencing in trio with the parents was normal. The patient was in good health, except for a Hashimoto thyroiditis, treated with a low dose of l-thyroxine. No other remarkable personal and/or family past history are to be reported.

Differential diagnosis, investigations and treatment

The first ultrasound of her second pregnancy performed at 9 weeks and 6 days showed an embryo measuring 36 mm with cardiac activity and two ventricular flows in power Doppler but the placenta exhibited cystic, grape-like features (Figure 1). On the same day, human chorionic gonadotropin (hCG) serum levels were obtained at 221 944 UI/L, significantly above the median value of 74 655 UI/L (97th percentile) expected for this GA (4). A meeting with the genetics department and Maternal Fetal Medicine unit (MFM) was held to discuss the findings. The first trimester ultrasound, at 11 weeks and 6 days, showed an anterior, thickened, and heterogeneous placenta with molar-like features, an embryo with a normal nuchal translucency and no anatomical anomaly, a normal amniotic fluid quantity and a crown rump length correlated to the gestational age. Based on ultrasound findings, differential diagnosis of a partial mole with an euploid fetus or a complete mole with coexisting twin and PMD were considered. No signs of an evanescent twin were visible on ultrasonogram.

The maternal serum alpha-fetoprotein (MSAFP) at 12 weeks and 5 days was at 179.6 mcg/L, the median value at 12 weeks of GA being 18.75 mcg/L (5).

After multidisciplinary discussion, it was decided to carry out, with the couple's information and consent, a transabdominal chorion villous sampling (CVS) at 13 weeks and 3 days. No triploidy was found and a PMD diagnosis was retained as most plausible after a thorough literature review. Consequently, a regimen of low-dose aspirin was initiated because of the high risk of early preeclampsia associated with PMD (3). Amniocentesis was carried out at 19 weeks and 4 days at parental demand due to the strong association with Beckwith Wiedemann Syndrome (BWS) (3). The results of microarray and molecular testing for BWS were normal as well as fetal anatomy scan at 20 weeks of GA. Subsequently the patient had a pathological oral glucose tolerance test at 26 weeks of GA and was diagnosed with gestational diabetes, which was kept under control with a diet throughout the pregnancy.

Fetal growth and well-being were followed closely every two weeks before 28 weeks of GA and on a weekly basis further. The growth was at about the 30th percentile (Intergrowth 21st curves) during the second trimester and the placenta maintained a thickened, hypo-echoic multicystic and heterogenous aspect. At 27 weeks of GA, an apical cystic zone evoking a thrombotic formation of 30x22x20 mm was detected on US. An additional investigation by MRI performed at 30 weeks showed a fundal placenta with dysplastic lesions measuring 5x9x3.9 cm consistent with the diagnosis of PMD (Figure 2). No fetal hepatic lesions were detected on MRI. From 32 weeks, the MFM team noted a slight decrease in fetal growth (11th percentile) and a few episodes of decreased subjective fetal movements were indicated by the mother with satisfactory ultrasound evaluation and monitoring. At 34 weeks and 5 days of GA, an additional thrombosis zone was observed in one of the dilated vessels of the chorionic plate with a central location, proximal to umbilical cord insertion.

Outcome and follow-up

The team decided to induce the labor at 35 weeks and 2 days, by vaginal prostin E2 tablets. Labour was uncomplicated and a healthy girl of 2160 g and 46 cm, Apgar score 8-9-10, born the day after. The placenta was delivered spontaneously.

The female infant was admitted to the neonatal unit due to induced prematurity.

The adaptation to extrauterine life went smoothly. A transitory hypoglycemia was noted as well as a neonatal jaundice requiring phototherapy. No anemia and no thrombocytopenia were detected.

The placenta was sent for pathological examination. The macroscopic report found the placenta to be enlarged and thickened, weighing 530g (90th percentile). Near cord insertion on the fetal surface, vessels were dilated, tortuous with varicose like aspect and abnormal branching (Figure 3, left). A fibrinoid deposition was found on one third of the maternal surface. On the cut sections, organized thrombi were found in the macroscopically dilated vessels that also exhibited a microscopically thickened wall. Histological examination found enlarged villi with cisterns with hypercellularity and stromal fibrosis (Figure 3, right). No trophoblastic proliferation nor stromal trophoblastic inclusions were found. Therefore, a PMD diagnosis was established with certainty after pathologic examination. Additionally, only a limited portion of the placenta did not exhibit any histological abnormality, showing typical aged matched terminal villi.

Discussion

Placental mesenchymal disorder is an uncommon vascular anomaly affecting the placenta and its development (6). PMD is mainly detected after 13 weeks of GA when the placenta appears multicystic (1). Its etiology and pathogenesis are yet to be fully characterized (6).

Due to the low incidence of this disease as well as the lack of sizable studies preventing from issuing guidelines, diagnosis, management and follow-up might prove to be challenging for the medical team and the parents.

Here, we present a case where PMD was considered as a diagnosis since the earliest stages of the pregnancy, at only 9 weeks and 6 days, resulting in prompt management and eventually leading to the delivery of a

healthy female baby.

When morphological placental anomaly is identified on ultrasound during the first trimester, the differential diagnosis must include partial molar pregnancy, complete mole with a coexisting normal fetus and PMD. These entities share similar ultrasound features such as enlarged or thickened placenta with multi cystic and grape-like hypo echoic lesions (1).

Anatomopathology

Macroscopically, pathologic examination of PMD reveals placentomegaly associated with dilatation of fetal chorionic vessels. Microscopically, the analysis shows thrombosis and oedematous stem villi without trophoblastic proliferation or hyperplasia, this last characteristic formally excluding a molar pregnancy (6).

Since the diagnosis is only confirmed by the pathologist's team after birth, an early antenatal rigorous diagnostic approach should be adopted by the multidisciplinary medical team.

Firstly, invasive testing with CVS should be performed for genetic analysis.

Genetic testing

On a genetic level, a complete mole is characterized by an androgenetic diploid conception where the ovum is either fertilized by one duplicated sperm or, more rarely, by two sperms and has lost its maternal DNA (7). A partial mole originates from a diandric triploid conception where one ovum is fertilized by two sperms or one duplicated sperm, thus the genetic arrangement is built by two paternal and one maternal chromosomal complements (7). Therefore, PCR based DNA genotyping (STR) compared to the maternal and paternal, when possible, genomes can also be useful to distinguish complete moles, thanks to their androgenetic constitution, from the diandric triploidy nature of partial moles and both of these from the biparental allelic balance of non molar pregnancies like PMD (7).

As shown in the review of 66 cases of PMD conducted by Cohen et al, the majority of fetuses had a normal karyotype (78%), while 23% were affected by BWS and finally only 3 cases of chromosomal anomalies were reported, one triploidy (69, XXX), one Klinefelter Syndrome (47, XXY) and one trisomy 13 (8).

Therefore, if a normal karyotype is obtained, the differential diagnosis should rule out a partial hydatidiform mole.

The next challenge is to differentiate PMD and complete mole with a coexisting normal fetus with a normal karyotype and a multi-cystic appearing placenta. A molar pregnancy with a live fetus carries a high malignancy risk with a significant maternal morbidity (3). Persistent gestational trophoblastic disease can occur in up to 20% of these pregnancies (3), and this is why it is important to correctly diagnose the disease.

While CVS is primarily performed for a genetic analysis, it could also be used to obtain larger villi samples for a histological examination. A well known marker, p57, is a cyclin-dependent kinase inhibitor, derived from the maternally expressed and paternally imprinted *CDKN1C* gene located on chromosome 11p15.5 (9).

Due to the lack of contribution of maternal DNA in complete moles, the p57 expression is absent in villous stromal cells and cytotrophoblast and this characteristic may be exploited in an immunohistochemistry analysis to differentiate between PMD and complete mole (7, 9). These two entities can therefore be distinguished by p57 immunostaining combined with DNA genotyping. This is not performed as a matter of routine, but could be an extra option in some complicated cases.

Biological data

Along with the early invasive testing, hCG and MSAFP dosage performed right after the first trimester ultrasound had a valuable role for the PMD diagnosis. MSAFP levels have been shown to be elevated in PMD. It is hypothesized that the enlarged placental volume resulting in a substantial surface area combined with thin walled arteries, enables an increased transfer of AFP into the maternal circulation, while HCG levels can be normal to slightly elevated for GA (7).

Imaging

Magnetic Resonance Imaging (MRI) is an additional diagnostic tool allowing a thorough and wider placental evaluation as well as obtaining a more detailed fetal view, thanks to its relative independence from the patient's body mass index (BMI) and high contrast resolution (10). MRI findings of PMD include an enlarged placenta with dilated vessels as well as heterogeneous signals (10, 11). Hemorrhage within the cystic part of the placenta might be associated with a molar pregnancy although it is not a specific sign (11). In our case, a large cystic area in the apical zone of the placenta was noted, supporting a PMD diagnosis.

Maternal and fetal complications

In the review of 64 reported cases conducted by Nayeri et al. it is reported that only a small number of pregnancies (9%) affected by PMD are free from feto-maternal complications (3). Maternal complications include gestational hypertension, preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) and eclampsia (1-3, 6).

Thus, a daily regimen of low dose aspirin was introduced at only 13 weeks of GA by our team to lower our patient's risk of developing preeclampsia. In our current knowledge, no other team has done the same.

Fetal complications consist of induced premature labor, spontaneous preterm delivery, in utero fetal growth restriction (IUGR), in utero fetal demise (IUFD) and BWS (1-3, 6). Neonatal complications include hematological disorders, such as anemia and thrombocytopenia and liver tumors, specifically mesenchymal hamartomas (1).

Up to 23% of fetuses can be affected by BWS (8), a multisystem genomic imprinting disorder characterized by mosaic genetic and epigenetic defects within the 11p15.5 region, which contains genes such as *CDKN1C* and *IGF2* , regulators of fetal growth (12). Fetal clinical expression of BWS may be wide, with macrosomia, macroglossia, exomphalos and organomegaly as main suggestive features, if present (12). Although molecular testing is possible with CVS and amniocentesis, a negative result should not falsely reassure the medical team due to the genetic mosaicism of BWS.

Lastly, the rate of IUFD in a review of 109 cases was found to be as high as 29,4% at the median age of 31 weeks of GA (13). It is theorized that the combination of vascular malformations of the placental vessels and thrombosis in the stem villi blood vessels as well as their decreased functional capacity, leads to chronic hypoxia (14).

Joined to the high risk of hemorrhage secondary to the rupture of thin walled and dilated chorionic vessels, PMD ultimately might conduct to IUFD (1).

Hence our team's decision to induce labor as soon as a novel thrombotic zone was noted in association with a subjective decrease in fetal movements.

PMD is a rare condition affecting the placenta's histology, anatomy and function, altering the exchanges' quality between mother and fetus and leading to a multitude of feto-maternal complications.

While it is essential to include PMD in the differential diagnosis when the placenta appears enlarged, thick and multicystic with a normal fetus to avoid an unnecessary pregnancy termination, it is also of the utmost importance to rule out gestational trophoblastic disease in light of the high maternal malignancy risk.

A multidisciplinary team involving obstetricians, pediatricians, MFM specialists, geneticists, radiologists, pathologists, midwives and psychologists is key to the diagnosis and a tailored management of the pregnancy in order to minimize fetal and/or maternal adverse outcomes.

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