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Case Report

Placental mesenchymal dysplasia: a case of a normal-appearing fetus with intrauterine growth restriction

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Abstract: In this paper, we described a placenta with vesicular lesions in a 23-year-old woman (1-gravid) who visited our hospital at 13 weeks of gestation on prenatal routine examination. Ultrasound findings showed multiple vesicular lesions which gradually increased as the pregnancy advanced, and a live normal-appearing fetus which was confirmed of IUGR at 30 weeks of gestation in her uterus. Throughout gestation, the maternal serum β-human chorionic gonadotropin level keeps normal, but the serum alpha-fetoprotein was higher than average. The patient delivered an 1800-g female without obvious anomalies at 35 weeks 5 days of gestation due to premature rupture of membrane. The diagnosis of placental mesenchymal dysplasia was determined on the pathological examination and androgenetic/biparental mosaicism in the placenta was identified by immunohistochemical staining of p57kip2.

Keywords: Placental mesenchymal dysplasia, molar pregnancy, Beckwith-Wiedemann syndrome

Introduction

Placental mesenchymal dysplasia (PMD) is a condition with quite low morbidity features placentomegaly and grapelike vesicles which is similar to molar pregnancy. To the best of our knowledge, 110 cases of PDM were presented in total, among them the incidence of PMD is estimated to 0.02% of pregnancies, with a definite female preponderance of 3.6-4.0: 1 (female: male) [1, 2]. The majority of the PMD cases are associated with intrauterine growth restriction (IUGR), intrauterine fetal death (IUFD) and Beckwith-Wiedemann syndrome (BWS) characterized by macrosomia, exomphalos, macroglossia, omphalocele, internal visceromegaly, placentomegaly, and increased susceptibility to childhood tumors, but can also occur with a normal appearing fetus [3]. Here, we report a case of Placental mesenchymal dysplasia with a normal appearing fetus with IUGR.

Case report

A 23-year-old G1P0 woman took her first routine ultrasonography examination at 13 weeks of gestation. Ultrasound identified a single live fetus compliant with the period of gestation without detectable anomalies. The placenta was unclear, but an area of multiple cystic echoes without vascular flow, measuring 88x42x76 mm, was detected in her uterus. Partial mole was initially suspected. As the pregnancy progressed, the area enlarged gradually to 116x48x66 mm at 16 weeks when the prenatal screen was carried out. The maternal serum β-human chorionic gonadotropin (β-hCG) level was normal, however maternal serum alpha-fetoprotein (AFP) was found to be 6.22 U/ml, moderately excess the average level. The screen suggested a high-risk of open neural tube defects (ONTD), but the patient declined amniocentesis. Close follow-up supersonic inspections revealed a normal amniotic fluid index, fetal anatomy and a gradual increase of size in placental vesicular lesions. At 18 weeks, the lesion was 121x50x101 mm and it grew to 112x78x93 mm 15 weeks later, while the IUGR was confirmed because of estimated fetal weight was below the 10th percentile at 30 weeks. The patient was admitted complaining of vaginal discharge without obvious predisposing cause at 35 weeks 5 days of gestation, and

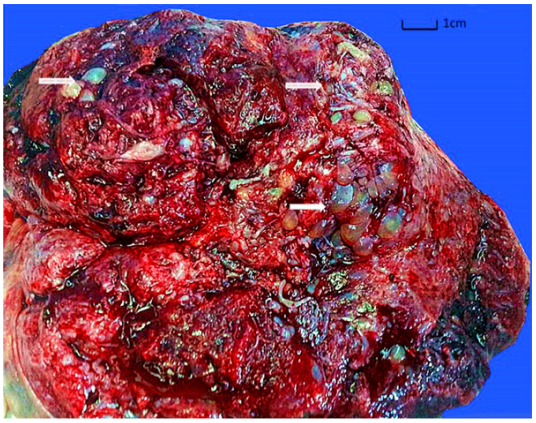

Figure 1. The maternal plate of the placenta shows multicystic, thin-walled, grape-like cysts ranging from 0.2 to 1.0 cm in diameter and with serous fluid distributed randomly (arrows).

premature rupture of membrane (PROM) was confirmed. An 1800 g female neonate was delivered vaginally without any definite anomalies and an Apgar score of 10 and 10 at 1 min and 5 min, respectively. After birth, the infant suffered from pathological jaundice of newborn. The maternal serum ThCG was 4335 mIU/ml at 2 days postpartum and was 7.5 mIU/ml at 3 weeks after delivery. Followup of neonate and mater was uneventful till 10 months.

The placenta measured 23x20x4 cm and weighed 760 g. The fetal plate was glossy without vascular anomaly. The maternal plate showed multiple grapelike cysts with serous fluid ranging from 0.2 to 1.0 cm in diameter interspersed among normal-appearing villous tissue (**Figure 1**). A cross section of the placenta indicated a cystic dilate in the parenchyma, the diameter was approximately 2-3 cm. The umbilical cord was eccentrically inserted, measured 50 cm long and 1 cm in diameter with three vessels. The gross features were suggestive of a partial hydatidiform mole. Microscopically, enlarged stem villi demonstrated hydropic changes with central cistern formation and thick-walled vessels at the periphery, and showed loose and myxoid stroma with an overgrowth of fibroblastoid, which were surround by normal-appearing tertiary villi (**Figure 2A-C**). Immunohistochemical examination demonstrated that desmin and vimentin were strongly expressed in stromal cells of both normal and abnormal villi, whereas the smooth muscle actin was merely present in normal villous stromal cells. The cells lining the cistern were negative for D2-40 and CD34, but labeled with vimentin (**Figure 3A**). The expression of p57kip2 was discovered in all villous cytotrophoblast cells as well as normal villous stromal cells, but absent in abnormal villous stromal cells (**Figure 3B**, **3C**). There was low detectable Ki-67 expression in either tissue. Those changes and the absence of trophoblastic proliferation and inclusion were evaluated to compatible with PMD.

Discussion

Firstly introduced by Moscoso et al. [4], Placental mesenchymal dysplasia (PMD) is considered as a placental vascular anomaly characterized by placentomegaly and stem villous hyperplasia. But the exact statistics of this lesion and scientific researches are still in confusion for the ever-changing terms used to describe it, including “placentomegaly with massive hydrops of placental stem villi”, “mesenchymal stem villous hyperplasia”, and “pseudopartial moles” [5-7]. Recent studies show that the presentations of the placenta vary with gestational age and typically accompanied with cystic changes and chorionic vascular malformations. According to Satoshi Ohira et al. [1] approximately 70% of cases were diagnosed as multicystic placenta at 13-20 weeks of gestation, as in the current case, which was recorded at 13 weeks, while rare case were detected prior to 13 weeks of gestation. Besides, our case shows that cystic changes progressively enlarged with gestation proceeding [8]. A total of 90% of cases were diagnosed as placenta with dilated fetal chorionic vessels in the third trimester and barely any case with such feature were detected prior to 25 weeks of gestation. These findings suggest the progressive development of vascular malformations secondary to circulatory disorders of the dysplastic villi. Furthermore, umbilical cord anomalies were found in PMD placentas, for example an excessively long cord, a single umbilical artery, and tortuous, marked twisted cord and abnormal insertion like eccentrically insertion which was observed in our case [3, 9]. Moreover, chorioangioma might also co-exist occasionally in PMD placentas and sometimes consisted with chorioangioma [10].

The clinical symptoms of PMD remain inconspicuous as most cases are diagnosed by prenatal ultrasonography for routine prenatal

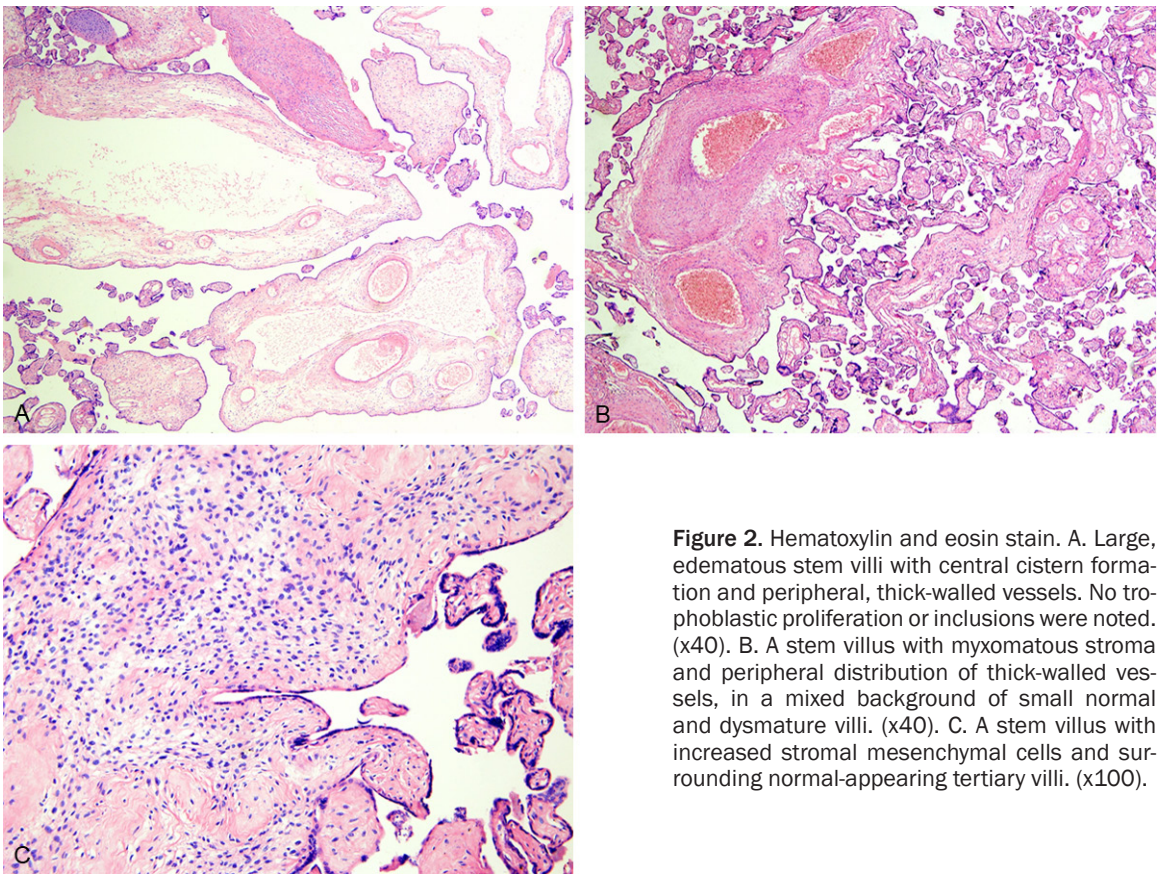

Figure 2. Hematoxylin and eosin stain. A. Large, edematous stem villi with central cistern formation and peripheral, thick-walled vessels. No trophoblastic proliferation or inclusions were noted. (x40). B. A stem villus with myxomatous stroma and peripheral distribution of thick-walled vessels, in a mixed background of small normal and dysmature villi. (x40). C. A stem villus with increased stromal mesenchymal cells and surrounding normal-appearing tertiary villi. (x100).

checkup in early pregnancy. Laboratory test indicates an increasing level of maternal serum AFP, the major characteristic of PMD. The increased surface transfer area as a consequence of enlarged placental volume and the abnormal thin-walled vessels within the stem villi is determined as main contribution to the anomalously rising transfer of AFP into the maternal circulation [4]. On the other hand, the contents of hCG may remains normal or increasing slightly throughout gestation and returns to normal soon after delivery [5]. In our case, both were confirmed and distinguished from moles. However, PMD has distinct clinicopathological complications including IUGR, IUFD and BWS, and the rate of them are 50%, 43% and 25%-33%, respectively [2]. The reason of IUGR and IUFD is currently unknown and may be heterogeneous. The inappropriate circulation of fetal blood within the vascular malformations and a potentially chronic hypoxia as a result of stem villi blood vessel thrombosis and greater reduction in villous functional capacity are deemed to be potential causes of IUGR or IUFD. Umbilical cord anomalies or thrombosis of chorionic vessels may also be concerned with them [9, 11]. In addition, the hemorrhage as a consequence of the rupture of the fragile and dilated cirsoid chorionic vessels may contribute to the sudden death of the fetus [8]. Our case presented the existence of placental multicystic lesions and absence of fetal vascular anomaly simultaneously, which resulting in the outcome of IUGR instead of IUFD, it is worth noted that those findings may convince much of the fetal and neonatal deaths were not associated with IUGR as others mentioned [9, 12].

Nichetargeting therapeutic regimens rely on more specific distinguish of PMD among diverse differential diagnoses of cystic placenta. The principal differential diagnoses of PMD are partial hydatidiform mole, a twin gestation with complete mole, and confined placental mosaicism [3]. Partial mole displays proliferation of trophoblasts or stromal trophoblastic inclusions with high level of maternal serum hCG and triploid karyotype. Whereas PMD mostly show diploid karyotype and the dysplastic villi in it did not have a high proliferative rate, as

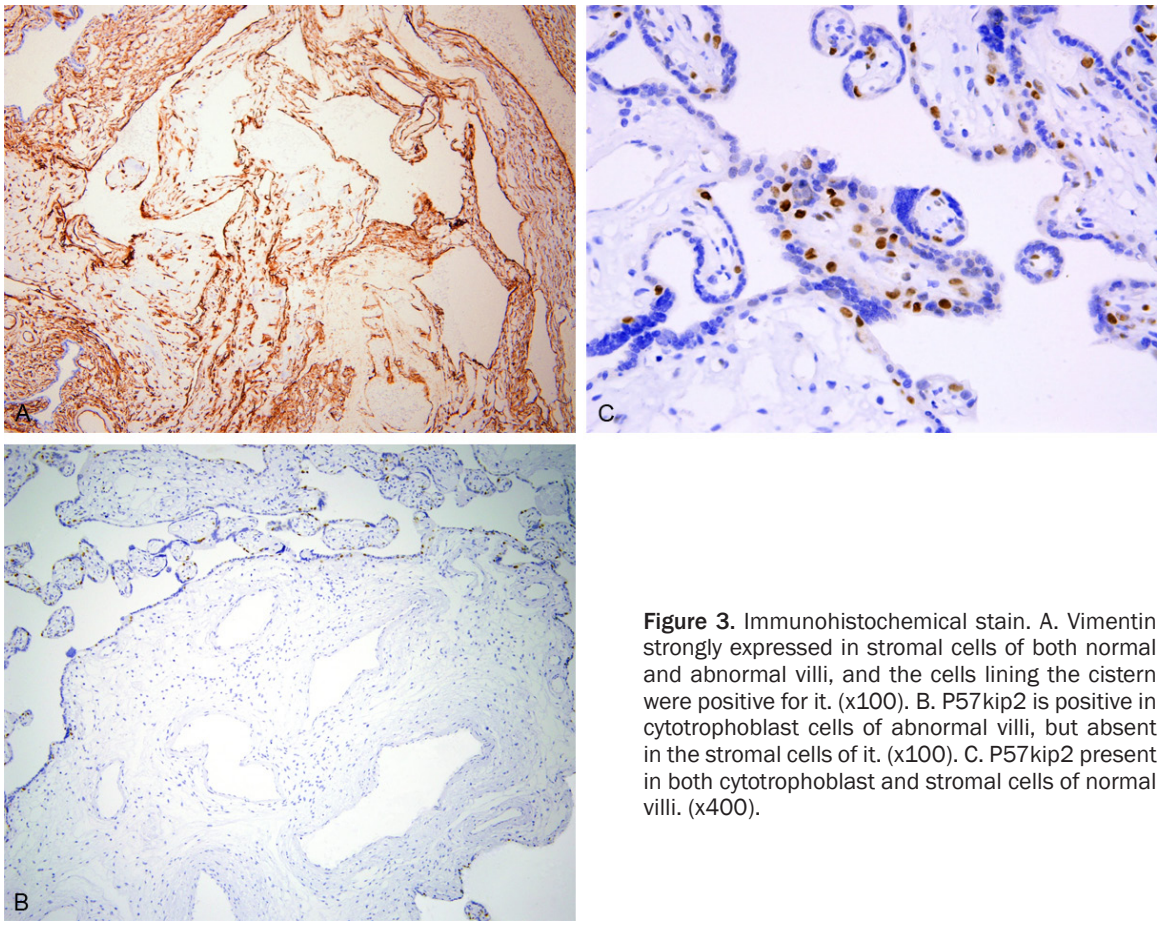

Figure 3. Immunohistochemical stain. A. Vimentin strongly expressed in stromal cells of both normal and abnormal villi, and the cells lining the cistern were positive for it. (x100). B. P57kip2 is positive in cytotrophoblast cells of abnormal villi, but absent in the stromal cells of it. (x100). C. P57kip2 present in both cytotrophoblast and stromal cells of normal villi. (x400).

demonstrated by low expression of Ki-67 in our case. Additionally, the presence of a phenotypically well-formed fetus provides priority to PMD. As for twin gestation with complete mole, with normal fetal vessels in the stem villi and loss of expression of p57kip2, it was distinctly distinguished from PMD. The diagnosis of the confined placental mosaicism can be determined by karyotyping the neonatal and the placenta. Other different diagnoses include multiple cholangiomas, multiple large subchorionic cysts and spontaneous abortion with hydropic changes should also be taken into account. The 2-dimensional, 3-dimensional and color Doppler sonography are proposed by Edi et al. [12] to be beneficial in distinguishing them from PMD.

Currently, the underlying cause of PMD is still in dispute. Plenty of theories are proposed by different research groups. Among them, Some believe that PMD is a congenital malformation of the extraembryonic mesoderm [3, 10]. The theory is based on observations of mesenchymal hyperplasia in stem villi along with other placental mesenchymal proliferative disorders consist of chorioangiomas and chorionic vessel dilatation as well as hemangiomas of the fetus. Hypoxia and hypoperfusion of unknown etiology stimulate the fibroblasts to produce increased connective tissue with subsequent increased production of vascular endothelial growth factor resulting in angiogenesis and vascular malformations. The malformations as well as the associated circulatory imbalance are considered contributing to cisternal accumulations within villi [11]. Heazell et al. [13] described that cells lining the cistern in PMD were labeled with D2-40, and suggested the placental vesicular lesions may be caused by abnormally lymphangiogenesis. On the contrary, this study proves the existence of vimentin instead of D2-40 and CD34 on the cells of the cistern. It is persuasive that the formation of cistern is due to the highly edema of villi rather than the lymphangiogenesis. Furthermore, our immunohistochemical stains showed that stromal cells in the dysplastic villi are positive

for vimentin and desmin but negative for smooth muscle actin, while the stromal cells in the surrounding normal-appearing villi are positive for vimentin, desmin and smooth muscle actin. Our results confirm the findings of a great deal of the previous work on this view that the stromal cells in abnormal villi in PMD cease to differentiate beyond the fibroblast stage [9].

Recently, Kaiser-Rogers et al. [14] proposed an androgenetic/biparental mosaicism as the etiological factor of PMD. They assumed that the phenotype of androgenetic mosaicism range from mild PMD to a complete hydatidiform mole, depending on the extent and distribution of the androgenetic lineage. The androgenetic cell line is thought to inherit from endoreduplication of the haploid paternal genome, and those cells were confined predominantly to chorionic mesoderm, membranes, and vessels, but absent in the trophoblast. This explains the absence of trophoblast overgrowth in PMD in contrast to complete mole in which androgenetic cells were identified in the trophoblastic cell layer. This mechanism introduced in [14] also elaborate the female preponderance and the association with BWS exhaustively. With sufficient proof of genes on chromosome 11p15.5, the pathogeneses of BWS and PMD are speculated to be similar [3]. The most commonly involved genes are CDKN1C (p57kip2), H19, IGF-II, and KVLQT. The p57kip2 gene, which encodes a cyclin-dependent kinase inhibitor, is expressed in the maternal genome, but silenced on the paternally inherited genome. Our immunohistochemical staining of p57kip2 showed that abnormal villous stromal cells were negative for it, but positive in the villous trophoblasts. Nondysmorphic villi exhibit nuclear staining within the stroma and trophoblast. These findings are consistent with the androgenetic/biparental mosaicism of PMD. Insulin-like growth factor (IGF-II) encodes a fetal-specific growth factor that is paternally expressed, which has been confirmed related to the BWS. Thus, the abnormalities of IGF-II genes have been suggested resulting in overgrowth of the placental tissue. Besides ,With the high propensity of PMD in female infants, the speculation that the X chromosome may contribute to the development of PMD has also been raised, but the exact underlying mechanism is not fully recognized [3].

In conclusion, PMD is a rare anomaly and its ultrasonographic findings are more likely suggestive of a partial mole. With high rates of IUGR, IUFD and BWS, it is strongly recommended to identify PMD prenatally in order to reduce fetal morbidity and mortality. Further investigation is needed to clarify its etiology and pathogenesis.

Disclosure of conflict of interest

None.

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