CASE REPORT

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A rare case of placental mesenchymal dysplasia – case report and literature review

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Abstract

Described as a rare anomaly of the placenta, with a reported incidence of 0.02%, mesenchymal dysplasia is a benign condition characterized by placentomegaly, grape-like vesicles and by microscopic features resembling those of a molar pregnancy, such as hydropic villi, cistern formation and dysplastic blood vessels. We report a rare case of placental mesenchymal dysplasia diagnosed in a pregnancy with early symmetric fetal intrauterine growth restriction and a normal karyotype. Based on this case report, we discuss the particularities of this condition, emphasizing the ultrasonography and histopathological findings.

Keywords: placenta, mesenchymal dysplasia, ultrasonography, histopathology.

Introduction

Placental mesenchymal dysplasia is a rare condition, associated with high perinatal mortality and morbidity, and it can only be confirmed by histopathological (HP) evaluation [1]. This diagnosis was first termed in 1991 by Moscoso who describes a placental lesion previously reported in literature as "placentomegaly with massive hydrops of placental stem villi and pseudo-partial mole" [1, 2]. Its mechanism of occurrence involves a maternal nondisjunction error during the first meiotic division, which leads to an androgenic chimerism [2, 3]. Although the real incidence of this anomaly is poorly known due to its previous reporting under the name of pseudo-partial mole, its association with intrauterine growth restriction, as well as with Beckwith–Wiedemann syndrome and fetal demise is well-established [4]. In these patients, invasive tests can also reveal other chromosome abnormalities like Klinefelter syndrome, trisomy 13 or triploidies [4, 5]. However, in 78% of the cases, the tests showed a normal karyotype [5]. Moreover, it is demonstrated that it may mostly affect the female fetuses, with a predominance of up to 4:1 [5, 6]. At the moment, this placental lesion is described as a vascular anomaly characterized by multi-cystic lesions and abnormal dilated, tortuous blood vessels [6, 7]. The histological findings include abnormal dilation of the stem villi, with no trophoblastic proliferation and multiple dysplastic blood vessels, often displaying a chorangiomatosis-like appearance [7, 8]. First of all, a differential diagnosis with partial molar pregnancy should be made, especially considering the ultrasonographic resemblances of these two pathological entities [8]. Other differential diagnoses include confined placental mosaicism, chorangiomatosis, or subchorionic hematomas [8, 9]. Other complementary medical examinations are serological tests, as placental mesenchymal dysplasia is often associated with elevated maternal serum alpha-fetoprotein (AFP) levels and rarely with increased beta-human chorionic gonadotrophin (β-hCG) levels [9].

Aim

The aim of this paper was to gain further knowledge about the HP and immunohistochemical (IHC) features of placental mesenchymal dysplasia, as well as about the peculiarities of serology and ultrasound (US) findings in the matter of this condition, especially considering its rarity.

Case presentation

A 32-year-old woman, with a history of recurrent miscarriages, was referred for a routine US at 15 weeks of gestation. No complaints of vaginal bleeding or pelvic pain were reported by the patient. Also, the first trimester US and serological tests showed a normal sized fetus

(crown-rump length 64.6 mm) with no detectable anomalies. The level of β-hCG was equivalent to 0.773 median multiple of the median (MoM), while pregnancy-associated plasma protein A (PAPP-A) was 2.323.

Because of the personal history of first trimester miscarriages and the risk of preeclampsia showed by the combined first trimester screening test (1:180 risk), and despite quasi-normal thrombophilia profile with a low level of homocysteine (2.09 μmol/L), the patient underwent anticoagulant and antiplatelet treatment. Furthermore, a low dose prednisone treatment was given to prevent an abnormal immune response.

The US performed at 16 weeks of gestation revealed an early onset fetal growth restriction. Moreover, a hyperechogenic fetal bowel and a hypertrophic placenta with multiple anechoic cysts, with a maximum thickness of 4 cm (Figure 1) were detected.

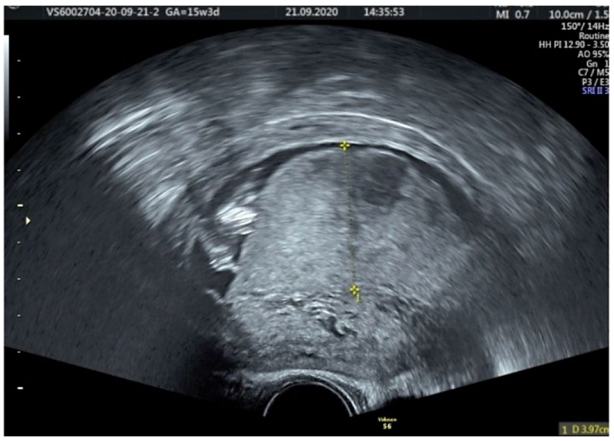

Figure 1 – ***Transvaginal ultrasound examination at 16 weeks of gestation: note the enlarged, low-lying, anteriorly placed placenta, with anechoic cysts.***

The patient was referred to the Department of Obstetrics and Gynecology, University Emergency Hospital, Bucharest, Romania, for further investigations at 19 weeks of gestation. Another US was performed, which showed a voluminous placental mass, with a bumpy fetal surface associated with severe oligoamnios and with an early-onset severe, symmetrical growth restriction (three weeks). Frequent episodes of fetal bradycardia were also observed throughout 30 minutes of continuous US evaluation. The Doppler study revealed normal umbilical, uterine, and ductus venosus flows. A non-invasive fetal membrane rupture test was performed, and it came back negative. Furthermore, the results of serologic tests that we obtained were negative and the panel of infectious diseases which had been chosen included parvovirus B19 and *Listeria monocytogenes*. Due to severe oligoamnios, the therapeutic conduct excluded the possibility of performing an amniocentesis which would have helped us rule out a genetic syndrome. Given the major risk of imminent intrauterine fetal death, associated with fetal cardiac rhythm anomalies, a medical commission, formed by specialists in maternal–fetal medicine, gathered and decided that a medically induced abortion was justified in our patient's case. Later on, the evaluation of the placenta showed an increased adhesion and an impregnated sponge appearance. While a fetal tissue fragment was also sent for genetic testing, the fetus (Figure 2) and fragmented placental tissue (measuring 13/15 cm) were sent for HP examination in the Department of Pathology, to clarify the diagnosis.

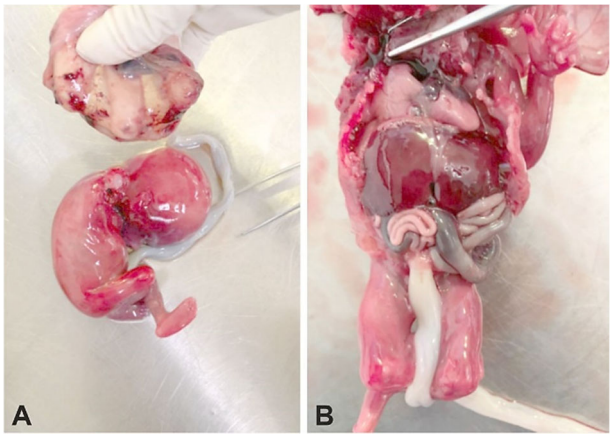

Figure 2 – ***Macroscopic aspect of the 400 g specimen: no malformations or abnormalities have been discovered during the necropsy.***

Specimen samples were fixed with 10% neutral buffered formalin for 24 hours and processed by conventional HP methods. HP examination revealed hydropic stem villi, with hemorrhagic suffusions in the intervillous space, abundant peri and intervillous fibrinoid deposits, and the focal presence of moderate mixed inflammatory infiltrate. Moreover, marked fibrinoid deposits adjacent to the necrobiotic villi were distinguished (Figure 3). The blood vessels of some stem villi exhibited marked fibromuscular hyperplasia and focal obliteration of the vascular lumina. There was no evidence of trophoblastic proliferation at the periphery of the abnormal villi, nor were stromal cell inclusions seen. Such HP findings suggested the diagnosis of placental mesenchymal dysplasia.

An IHC panel was also performed, using the standard procedure. The tissue section was deparaffinized and then rehydrated before applying the primary antibody. Enzyme-conjugated secondary antibodies were then applied so that specific staining could be visualized after adding the enzyme-specific substrate. Immunohistochemistry using anti-p57 (rabbit monoclonal antibody, clone SP118, 1:100 dilution) shows staining of the villous cytotrophoblast and stromal cells. Anti-cluster of differentiation (CD)34 (mouse monoclonal antibody, clone QBEnd/10, 1:100 dilution) and anti-podoplanin (mouse monoclonal antibody, clone D2-40, 1:100 dilution) showed multiple thick-walled blood vessels in the villi. The placental tissue was also investigated with anti-p53 (rabbit monoclonal antibody, clone EP9, 1:100 dilution) and the wild type expression of this protein was documented (Figure 4).

As it was mentioned earlier, a fetal tissue sample was sent for genetic testing. The karyotype showed a normal female fetus. Twenty metaphases were analyzed, of which 10 were karyotyped. Cytogenetic analysis did not reveal numerical or structural changes in the analyzed chromosomes. Chromosomes were banded by hydride generation technique (banding score >4), while tissue cells were cultured in two independent cultures (two flasks).

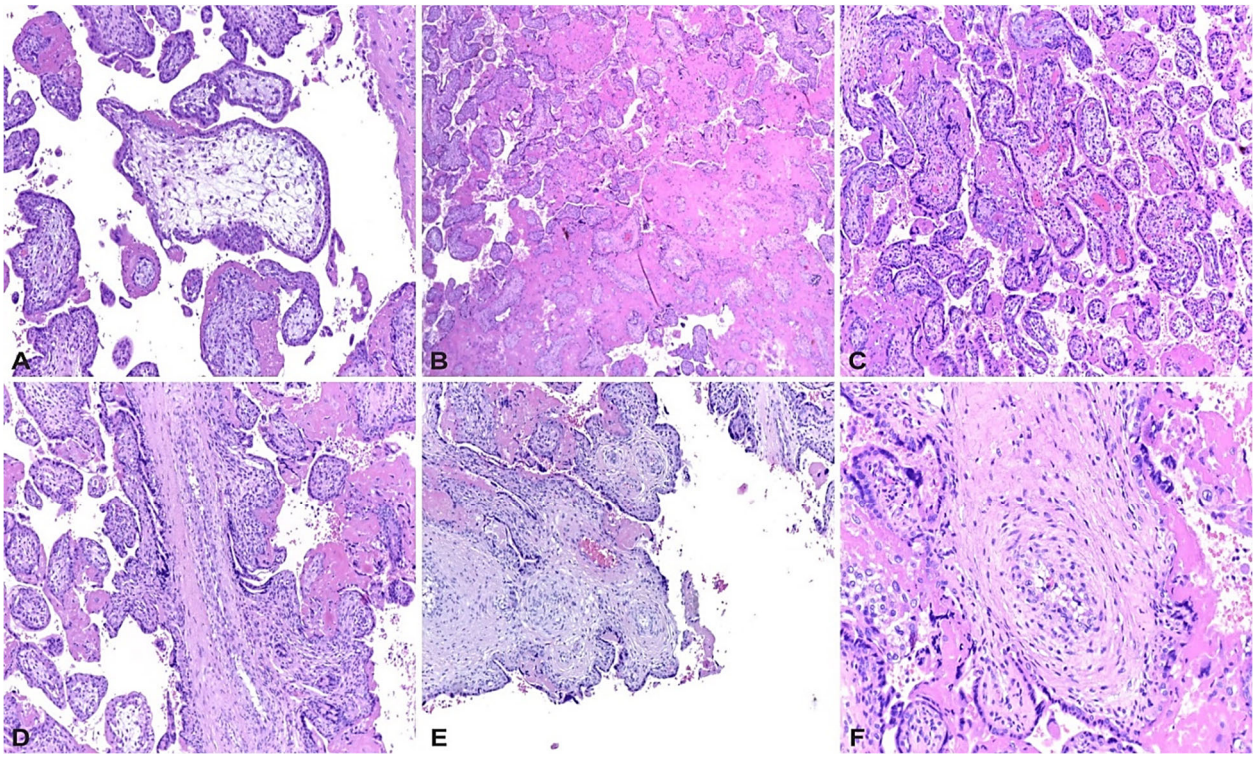

Figure 3 – ***(A) Hydropic stem cell villi with hemorrhagic suffusions in the intervillous space; (B) Extensive deposits of inter- and perivillous fibrinoid; (C) Multiple congested vessels in the stroma of hydropic stem cell villi; no trophoblast proliferation; (D) Chorionic blood vessels exhibiting fibromuscular hyperplasia; (E) Marked fibromuscular hyperplasia of the chorionic blood vessels; (F) Thick-walled chorionic vessel and perivillous fibrinoid deposits. Hematoxylin–Eosin (HE) staining: (A, C, E) ×100; (B and F) ×40; (D) ×200.***

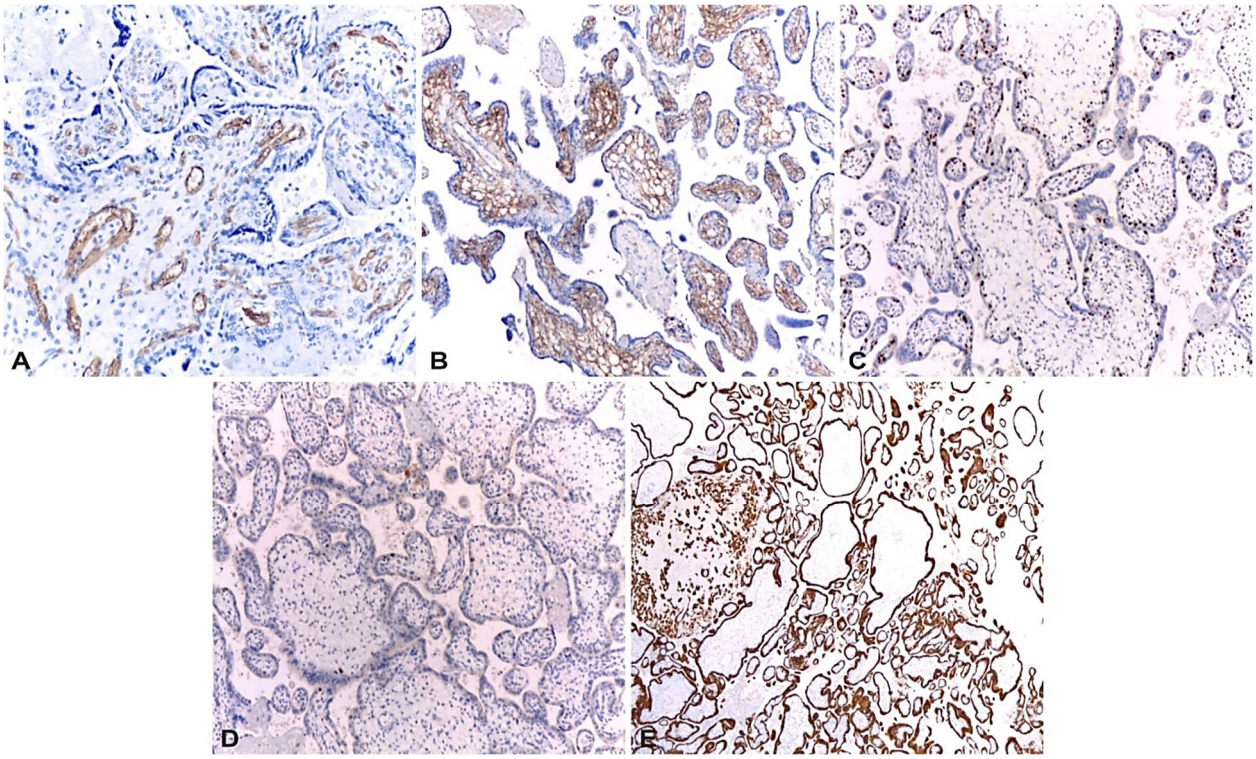

Figure 4 – ***(A) Tortuous intravillous vascular proliferation, highlighted by CD34 (IHC staining with anti-CD34 antibody, clone QBEnd/10, 1:100 dilution, mouse monoclonal, ×100); (B) Podoplanin shows vascular proliferation in the chorionic villi (IHC staining with anti-podoplanin antibody, clone D2-40, 1:100 dilution, mouse monoclonal, ×100); (C) Normal p57 immunoexpression in the trophoblast, but absent stromal immunostaining in placental mesenchymal dysplasia (IHC staining with anti-p57 antibody, clone SP118, rabbit monoclonal, ×100); (D) Wild-type immunoexpression in the nuclei of trophoblastic cells (IHC staining with anti-p53 antibody, clone EP9, 1:100 dilution, rabbit monoclonal, ×100); (E) Intense positive CK7 immunostaining of the villous trophoblastic cells (IHC staining with anti-CK7 antibody, clone BC, 1:100 dilution, rabbit monoclonal, ×100). CD34: Cluster of differentiation 34; CK7: Cytokeratin 7; IHC: Immunohistochemical.***

Discussions

Mesenchymal dysplasia is a benign placental condition which poses a diagnostic challenge especially because it is exceptionally rare and poorly understood [9, 10]. In the University Emergency Hospital, Bucharest, this is the first known case of a woman with mesenchymal dysplasia, presenting with a normal karyotype and a morphologically normal fetus. The differential diagnosis implies other pathological entities, especially partial hydatidiform mole [10]. Medical investigation such as ultrasonography and serological tests are very useful, but the diagnosis can only be confirmed by HP examination of the tissue samples obtained from the placenta and fetus [5, 10, 11]. It is well-known from the available data that US findings consisting of a hypertrophic placenta, associating cystic lesions and a normally developed fetus, should raise a suspicion of partial molar pregnancy, but the possibility of mesenchymal placental dysplasia also must be considered [5, 11]. In our patient's case, US findings included a thickened placenta with multiple cystic or hypoechoic areas, associated with low-velocity blood flow in the first two trimesters. Upon gross examination of the placenta, there could be identified cystic areas of the parenchyma; the subsequent microscopic examination revealed several pathological changes, including cistern formation and edematous stem cell villi. Although these pathological findings would have been highly suggestive for partial hydatidiform mole, there was no microscopic evidence of trophoblastic proliferation.

The IHC study of anti-p57 antibody is helpful in analyzing the cytotrophoblast [12]. In our patient's case, a normal staining of the trophoblast and decidua was noted, helping the pathologist rule out the diagnosis of a partial molar pregnancy and of a complete hydatidiform mole. To go on, the differential diagnosis with chorangiomatosis is justified, as multiple chorionic blood vessels were seen and abundant inter- and perivillous fibrinoid deposits were also noted, suggesting hypoxic–ischemic tissular injuries [11–13]. Chorangiomatosis is characterized by a proliferation of chorionic capillaries surrounded by a circumferential layer of pericytes and reticulin fibers [8, 13]. Moreover, the gross aspect of chorangiomatosis consists of placentomegaly, the same as in mesenchymal dysplasia [8, 14]. The vascular structures can be better visualized using a CD34 or CD31 immunostaining [10, 14]. In contrast with chorangiomatosis, on the samples that we analyzed, the chorionic blood vessels were dilated and thick-walled, exhibiting fibromuscular hyperplasia and focal obliteration of the lumina, with the concomitant presence of edematous villi and cisterns. Using the IHC study with CD34 and podoplanin, a better visualization of the vascular structures was obtained, confirming the HP aspects discovered. As the p53 tumor suppressor gene can be expressed in human placenta, due to the extensive trophoblast proliferation, further IHC studies that we performed included p53 immunostaining. The results showed expression of this protein in the nuclei of some cytotrophoblastic cells (p53 wild type), a normal aspect for a second trimester placenta. Cytokeratin 7 (CK7) expression was also analyzed and intense immunostaining of the cytoplasm of trophoblastic cells was noted. As it was mentioned earlier, serological tests can be helpful during the diagnosis of mesenchymal placental dysplasia [2, 15]. The differential diagnosis also refers mainly to a partial mole, as it does in the HP and imaging studies, but either an abnormal triploid fetus or a complete mole with cotwin should be considered [15, 16]. Unlike partial mole pregnancies, in mesenchymal dysplasia the levels of β-hCG are within normal limits, as seen in our case, or slightly increased, and most of the fetuses are of normal karyotype [17, 18]. This condition is frequently associated with intrauterine growth restriction, stillbirth, Beckwith–Wiedemann syndrome (25% of the cases reported associated with paternal isodisomy of the 11p15.5 region), Klinefelter syndrome (the additional X chromosome is thought to allow male survival), transient neonatal diabetes mellitus and paternal uniparental disomy 6, trisomy 13 [1, 17–19]. However, a normal karyotype was identified in our patient's case after genetic analysis, ruling out a placental mosaicism. Despite the association between placental mesenchymal dysplasia and genetic anomalies, a normal karyotype was documented in 78% of the cases reported [15, 16, 20].

Conclusions

The early diagnosis and management of placental mesenchymal dysplasia can be challenging, especially considering the rarity of the condition. However, the aforementioned anomaly should be considered during the examination of high-risk pregnancies associated with intrauterine fetal growth restriction. We emphasize the importance of thorough correlations between the HP features and immunophenotype of these trophoblastic/placental lesions and the serology and imaging studies and genetic analysis, to identify specific diagnosis criteria. Moreover, we underline the importance of an adequate medical report, to provide more important data which may facilitate the positive and differential diagnosis of this condition and increase the number of case reports that may be helpful in avoiding the severe consequences of this rare disease.

Conflict of interests

The authors declare that they have no conflict of interests.

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