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CASE REPORT

Pregnancy with concomitant chorangioma and placental vascular malformation with mesenchymal hyperplasia

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We present two pregnancies associated with normal live births and the unusual concomitance of chorangioma and placental vascular malformation with mesenchymal hyperplasia. The enlarged placenta had the characteristic findings of chorangioma, dilated and varicose chorionic vessels and multiple vesicle-like villi containing hyaluronic acid. The vesicle-like villi showed diploid cellular DNA contents. Molecular genetic analysis using the polymerase chain reaction amplification of polymorphic microsatellite markers confirmed genetic identity among the chorangioma, the vesicle-like villi and the fetus. Both pregnancies were complicated by polyhydramnios, preterm labour and prematurity. One neonate suffered from anaemia and thrombocytopenia. Another neonate suffered from haemangiomatosis. Our cases demonstrate that concomitant chorangioma and placental mesenchymal hyperplasia are genetically identical to the fetus and can coexist with a normal viable fetus. Since haemangiomas, chorangiomas, chorionic vessels and villi mesenchymal cells are all derived from the mesoderm, a combination of fetal haemangiomas, placental vascular malformation, chorangiomas and placental mesenchymal hyperplasia may represent a mixed form of congenital malformation of the mesoderm.

Key words: chorangioma/haemangioma/mesoderm/placental mesenchymal hyperplasia/placental vascular malformation

Introduction

Pregnancy with concomitant chorangioma and placental vascular malformation associated with mesenchymal hyperplasia and a live birth is very rare. To our knowledge, only one case of concomitant chorangioma and placental vascular malformation with mesenchymal hyperplasia has been reported. The enlarged placenta has grape-like vesicles similar to partial hydatidiform moles. The chorangioma coexists with dilated and tortuous chorionic vessels of the placenta. The rarity of this condition and the interest in its genetic origin and pregnancy outcome prompted this report.

Case 1

A 25 year old Chinese primigravida was referred at 36 weeks gestation because of polyhydramnios, intrauterine growth retardation, a bulky placenta with a placental tumour and a fetal intra-abdominal cyst. Her blood pressure was normal and routine obstetric urine investigations revealed neither protein nor glucose. The maternal serum syphilis screen result was negative. Ultrasound examinations confirmed a singleton inconsistent with the gestational age. The biparietal diameter measured 7.5 cm and femur length 5.1 cm, equal to 29 weeks gestation. The largest pocket of the amniotic cavity measured 10.2 cm. A bulky placenta with a thickness of 8.2 cm and a well-defined 7.3×7.3 cm mixed-echogenic mass and areas of multiple cystic echoes was noted. The fetus had a 5.5×4.1 cm intra-abdominal cystic mass. At 37 weeks gestation, as the result of premature rupture of the membranes and preterm labour, a 1500 g female was delivered vaginally, with Apgar scores of 5 and 9 at 1 min and 5 min, respectively. Physical examination showed a distended abdomen and a palpable mass in the right upper abdomen of the newborn. Haemangiomatosis was noted over the face, left ear auricle, left arm, both palms, right lower leg and left thigh. The initial blood count revealed: haemoglobin 14.4 g/dl; haematocrit 43.5%; white blood cell count 19 800/mm^3; and platelet count 243 000/mm^3. Other blood components and electrolytes were within normal ranges. The placenta measured 20 cm in diameter, 7 cm in thickness, and weighed 1150 g. The fetal surface of the placenta showed dilated and tortuous chorionic vessels penetrating into the maternal side. About one fourth of the area on the maternal surface of the placenta was occupied by varicose chorionic vessels and grape-like vesicles mimicking partial moles and a 9×6×4.5 cm concomitant chorangioma (Figure 1). Histological examination of the chorangioma showed the typical angiomatous pattern with numerous capillary vessels and focal infarctions. Microscopically, the enlarged stem villi contained central vessels and cellular ground substances which stained strongly with alcian blue stain (Figure 2). However, after hyaluronidase treatment, no staining with alcian blue was observed, indicating that the ground substance was hyaluronic acid, the acid mucopolysaccharide found in the connective tissue layers of the normal chorionic mesoderm. The distended villi manifested neither abnormal trophoblastic proliferation nor stromal trophoblastic inclusions. Peripheral blood karyo-

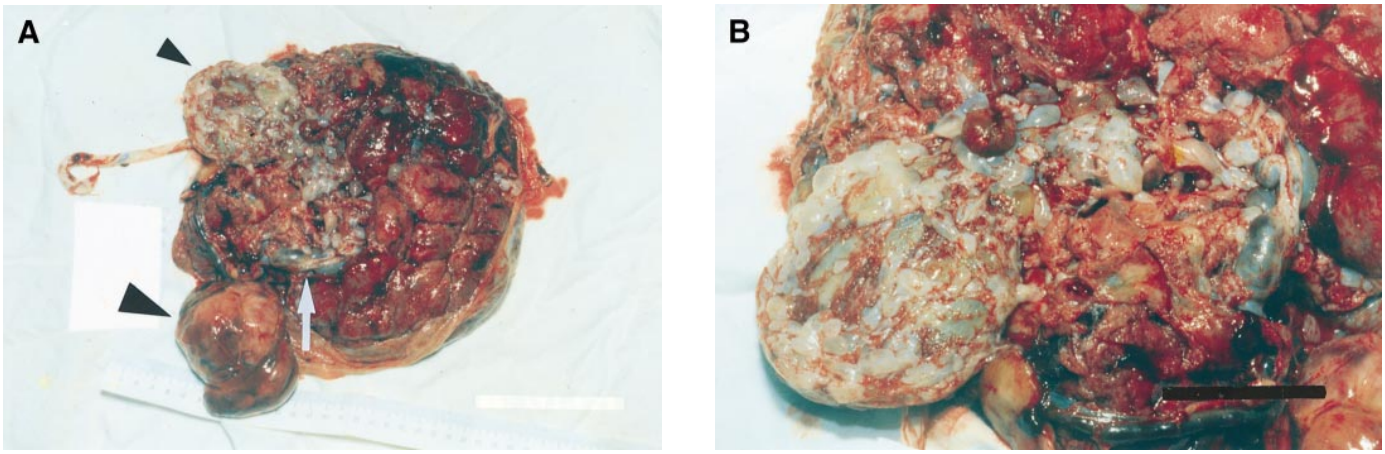

Figure 1. (A) The maternal plate of the placenta from case 1 showing a large chorangioma (large arrowheads), focal vesicle-like villi (small arrowhead) and varicose chorionic vessels (arrow). **(B)** A close up view of the vesicle-like villi and varicose chorionic vessels (magnification ×2.5).

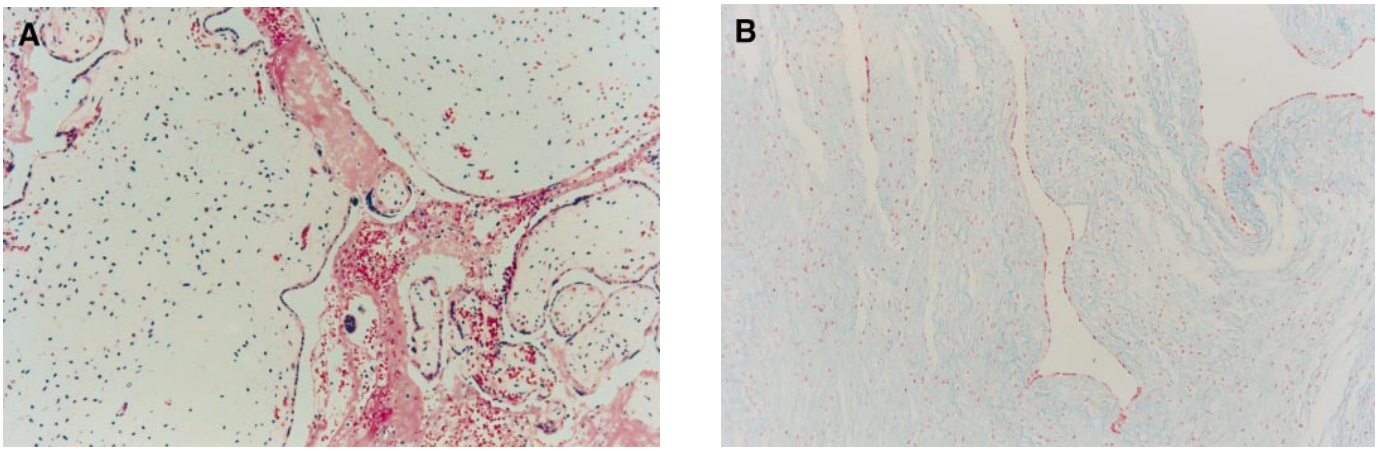

Figure 2. (A) A histological section through vesicle-like villi compared to normal villi (haematoxylin and eosin staining magnification ×100). **(B)** A histological section through vesicle-like villi showing strong staining with alcian blue stain (magnification ×100).

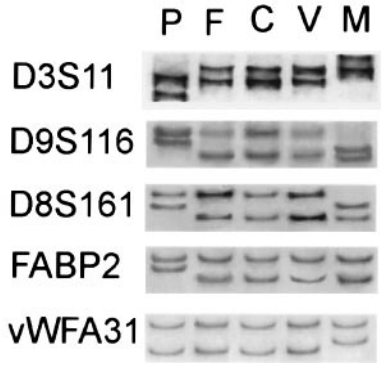

Figure 3. Linkage analysis of the microsatellite polymorphisms (D3S11, D9S116, D8S161, FABP2, vWFA31) in the samples of paternal blood (P), neonatal blood (F), chorangioma (C), vesicle-like villi (V) and maternal blood (M), revealing genetic identity and heterozygosity in the fetus, chorangioma and vesicle-like villi.

typing of the neonate revealed a 46,XX karyotype. The neonate was doing well after surgical excision of the hepatic cyst, the hepatic haemangioma and cutaneous haemangiomas. Maternal serum beta-human chorionic gonadotrophin (β-HCG) was undetectable 3 weeks after delivery. The chest roentgenography *post partum* showed negative findings. The mother was followed up for more than 1 year and showed no sign of trophoblastic disease. Flow cytometric analysis of the enlarged stem villi and the chorangioma revealed diploid DNA contents. DNA was extracted from the whole blood samples obtained from the neonate and her parents, and from the paraffin tissue blocks of the vesicle-like stem villi and the chorangioma. Five genetic marker loci vWFA31, FABP2, D9S116, D3S11 and D8S161 including tandem repeat regions were amplified by the polymerase chain reaction (PCR). A total of 200 ng of genomic DNA was amplified in a 50 µl reaction mixture by each of five PCR assays according to the condition noted in the references (Brett *et al.*, 1991; Couch *et al.*, 1991; Kwiatowski and Gusella, 1992; Kimpton *et al.*, 1992; Edwards *et al.*, 1992). The PCR products were resolved on 10% sequencing gels. After electrophoresis, gels were stained by silver, visualized, and analysed with a GAS-6000 gel analysis system (Evergene, UK). Genotypic information obtained from the infant, her parents, the enlarged stem villi, and the

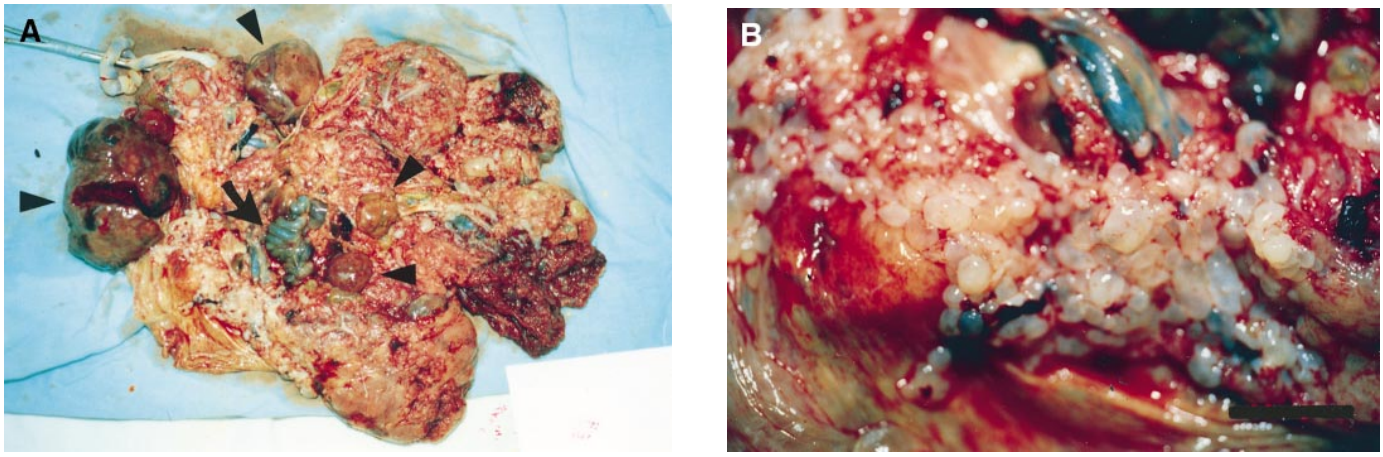

Figure 4. (A) The maternal plate of the placenta from case 2 showing multiple chorangiomas (arrowheads), diffuse vesicle-like villi and varicose chorionic vessels (arrows). **(B)** A close up view of the vesicle-like villi and varicose chorionic vessels (magnification ×5).

chorangioma for all five PCR assays showed that the enlarged stem villi were of biparental origin and heterozygous. The genotypes of the enlarged stem villi, the neonate and the chorangioma were genetically identical (Figure 3).

Case 2

A 24 year old Chinese primigravida was referred at 27 weeks gestation due to preterm labour, polyhydramnios and a bulky placenta with multiple placental tumours. Her blood pressure and urinalysis were normal. The maternal syphilis test was negative. A level-II ultrasound examination revealed polyhydramnios with an amniotic fluid index equal to 25.5 cm and a structurally normal fetus whose sonographic biometry was consistent with 27 weeks gestation. The bulky placenta contained several echogenic masses measuring 4–9 cm in diameter and diffuse cystic echoes. Pulsed Doppler investigations and colour flow mapping revealed a pulsatile blood flow within the intrauterine masses, indicating the vascular origin. The mother was admitted for tocolysis management. However, rupture of the membranes occurred 3 days after admission. A 976 g female was delivered vaginally with Apgar scores of 6 and 6 at 1 min and 5 min, respectively. The neonate was anaemic at birth. The initial blood count revealed: red blood cell count $1.96\times10^6/mm^3$; haemoglobin 7.9 g/dl; haematocrit 25.3%; white blood cell count $7300/mm^3$; and platelet count $90\,000/mm^3$. The placenta measured 24 cm in diameter and 5 cm in thickness and weighed 1100 g. The fetal plate showed enlarged varicose chorionic vessels. The maternal plate was filled with diffuse vesicle-like structures and four chorangiomas with the largest one measuring up to 9 cm in diameter (Figure 4). Placental histology confirmed the presence of multiple chorangiomas and the diffusely mesenchymal hyperplasia. The distended stem villi contained alcian blue positive hyaluronic acid and the same microscopic features as case 1. Cytogenetic studies performed on the neonate and the vesicle-like stem villi revealed a 46,XX karyotype. The infant had an uneventful neonatal course. She was discharged at the age of 3 months with a body weight of 2200 g. The maternal serum β-HCG concentration was below the limit of detectability at 3 weeks *post partum*. Follow-up of the mother for more than 1 year showed no trophoblastic disease. Flow cytometric analysis of the enlarged stem villi and the chorangioma revealed diploid DNA contents. Genetic analysis of the neonatal blood and paraffin-embedded vesicle-like villi, and chorangioma using the same PCR method as employed in case 1, proved genetic identity among the chorangioma, the vesicle-like villi and the neonate.

Discussion

Moscoso *et al.* (1991), Jauniaux *et al.* (1989) and Jauniaux and Campbell (1990) described two cases of placental vascular anomaly with diffuse mesenchymal stem villous hyperplasia. The two pregnancies resulted in healthy female neonates despite the associated enlarged placentas with aneurysmal and varicose chorionic vessels and semitranslucent lobulated stem villi. Højberg *et al.* (1994) reported another case of placental vascular malformation with mesenchymal hyperplasia and a localized chorangioma. This pregnancy also resulted in a healthy female neonate. We report two additional cases with living non-malformed female neonates. However, our cases were complicated by polyhydramnios, preterm labour and prematurity. The neonate in the pregnancy with diffuse placental mesenchymal hyperplasia and multiple chorangiomas suffered from severe anaemia and thrombocytopenia. The neonate in the pregnancy with a large chorangioma suffered from haemangiomatosis. The maternal and fetal complications associated with large chorangiomas include polyhydramnios, oligohydramnios, hydrops fetalis, intrauterine growth retardation, prematurity, stillbirth, fetal thrombocytopenia and microangiopathic haemolytic anaemia, maternal thrombocytopenia and consumptive coagulopathy, pre-eclampsia, abruptio placentae, fetomaternal transfusion, haemolysis and haemoglobinuria (Benirschke and Kaufmann, 1995; Quintero *et al.*, 1996). Our cases demonstrate that pregnancy with concomitant chorangioma, placental vascular malformation and mesenchymal hyperplasia can be at risk for complications caused by chorangiomas. In addition to the two previous reports, our cases also showed a female predominance. The female

predominance in placental vascular malformation and mesenchymal hyperplasia will require more studies for confirmation.

The present report concerns a differential diagnosis with gestational trophoblastic disease with a coexistent normal fetus. The morphologically differential diagnosis between complete hydatidiform moles, partial hydatidiform moles and non-molar products of conception such as diffuse mesenchymal hyperplasia or hydropic degeneration of the placenta can be difficult. In cases of gestational trophoblastic disease, the classic 'snowstorm' features of molar pregnancies seen in the B-mode static scanning may not appear in current ultrasonography (Kuhlmann and Warsof, 1996). The sonographic appearances of hydropic degeneration of retained placenta or placental mesenchymal hyperplasia may simulate the images seen in gestational trophoblastic disease (Buschi *et al.*, 1979; Jauniaux *et al.*, 1989, 1990). Histologically, complete hydatidiform moles are characterized by generalized macroscopic swelling of all chorionic villi, diffuse trophoblastic hyperplasia and lack a fetus, while partial hydatidiform moles are characterized by focal trophoblastic hyperplasia with stromal trophoblastic inclusions, focal swelling of chorionic villi and have a fetus (Szulman and Surti, 1978a, b). However, the histological criteria for the diagnosis of gestational trophoblastic disease are subject to inter- and intrapathologist variability (Messerli *et al.*, 1987; Howat *et al.*, 1993). The majority of complete hydatidiform moles are diploid/tetraploid, consisting of paternal complements only. Most complete hydatidiform moles are homozygous, being a product of one endoreduplicated sperm. A few hydatidiform moles are heterozygous, being a product of dispermy. The majority of partial hydatidiform moles are triploid, consisting of one maternal and two paternal complements. Awareness of DNA ploidy alone is not sufficient for establishing a diagnosis of gestational trophoblastic disease, because hydropic abortions can also be DNA diploid, triploid, tetraploid or aneuploid (Lage and Bagg, 1996). Currently, DNA polymorphism analysis is a possible diagnostic tool for determining the genetic origin of hydatidiform moles and the non-molar products of conception (Fisher *et al.*, 1992; Fisher and Newlands, 1993; Fujita *et al.*, 1994; Højberg *et al.*, 1994; Hoshi *et al.*, 1994; Jinno *et al.*, 1994; Osada *et al.*, 1995; Ikeda *et al.*, 1996). In the present cases, molecular genetic analysis using polymerase chain reaction amplification of polymorphic microsatellite markers confirmed the genetical identity among the chorangioma, the vesicle-like villi and the fetus with the same maternal and paternal contributions. There was neither trophoblastic proliferation nor stromal trophoblastic inclusions. The enlarged villi contained a great amount of hyaluronic acid due to abnormal mesenchymal growth. Furthermore, there were associated venous anomalies of the placenta, neonatal haemangiomatosis and multiple chorangiomas. These findings led us to exclude the possibility of dizygotic twins with a complete hydatidiform mole and a normal fetus, partial hydatidiform moles, or the coexistence of a blighted dizygotic ovum with diffuse hydropic change and a normal fetus. Since haemangiomas, chorangiomas, chorionic vessels and villi mesenchymal cells are all derived from the mesoderm, a combination of fetal haemangiomas, placental vascular malformations, chorangiomas, and mesenchymal hyperplasia may represent a mixed form of congenital malformation of the mesoderm.

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