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Hepatic mesenchymal hamartoma and placental mesenchymal dysplasia: an association ever less rare; a focus on current Knowledge

A. Cordisco[1], M. Di Tommaso[2], A.M. Buccoliero[3], R. Biagiotti[4]

[1]Division of Prenatal Diagnosis, P. Palagi Hospital, Florence, Italy
[2]Division of Obstetrics and Gynecology, Department of Health Sciences, University of Florence, Florence, Italy
[3]Division of Pathology Unit, Meyer Children's Hospital, Florence, Italy
[4]Division of Prenatal Diagnosis, Meyer Children's Hospital, Florence, Italy

ABSTRACT

Objectives. Hepatic mesenchymal hamartoma (HMH) is a lesion that originates from the mesenchymal tissue of the portal tract and that in most cases manifests itself in the first three years of life. The placental mesenchymal dysplasia (PMD) is a rare anomaly characterized by placentomegaly with the presence of hydropic chorionic villous that resemble those of hydatiform mole. In literature there is only a few number of cases characterized by this association that have led to formulate the hypothesis of a common pathogenetic pathway to the two pathologies. This report wants to offer tools for a correct prenatal diagnosis and management of similar cases.
Methods. We report a detailed description of the prenatal signs of association of a voluminous HMH and a PMD. Histological studies have been conducted on fetal tissues of hepatic and placental origin.
Results. The large size of the abdominal mass resulted in a severe impairment of respiratory function and the neonatal death. Histological study confirmed the prenatal diagnosis. The understanding of the etiopathogenetic mechanism of the association was negatively affected by the failure to carry out molecular genetic investigations on the affected tissues.
Conclusion. In light of current scientific findings, we recommend to always study the placenta very carefully in case of detection of fetal abdominal cystic masses, to plan molecular genetic investigations on affected tissues and to be very cautious considering the high incidence of neonatal complications and adverse outcomes.

SOMMARIO

Obiettivo. L'amartoma mesenchimale epatico (HMH) è una lesione che origina dal tessuto mesenchimale del tratto portale e che nella maggior parte dei casi si manifesta nei primi tre anni di vita. La displasia mesenchimale della placenta (PMD) è una rara anomalia caratterizzata da placentomegalia con la presenza di villi coriali idropici che assomigliano a quelli della mola idatiforme. In letteratura c'è solo un numero limitato di casi caratterizzati da questa associazione che ha portato a formulare l'ipotesi di una via patogenetica comune alle due patologie. Questo report vuole offrire strumenti per una corretta diagnosi prenatale e la gestione di casi simili.
Metodi. Riportiamo una descrizione dettagliata dei segni prenatali di associazione di un voluminoso HMH e un PMD. Sono stati condotti studi istologici su tessuti fetali di origine epatica e placentare.
Risultati. La grande dimensione della massa addominale ha provocato una grave compromissione della funzione respiratoria e la morte neonatale. Lo studio istologico ha confermato la diagnosi prenatale. Sulla comprensione del meccanismo eziopatogenetico dell'associazione nosologica ha influito negativamente il mancato allestimento di indagini genetiche molecolari sui tessuti coinvolti.
Conclusione. Alla luce delle attuali acquisizioni scientifiche raccomandiamo di studiare sempre con molta attenzione la placenta in caso di riscontro di masse cistiche addominali fetali; pianificare le indagini genetiche molecolari sui tessuti affetti e avere un comportamento molto prudente considerata l'alta incidenza di complicazioni e esiti avversi neonatali.

Corresponding Author: Adalgisa Cordisco
adalgisa.cordisco@uslcentro.toscana.it

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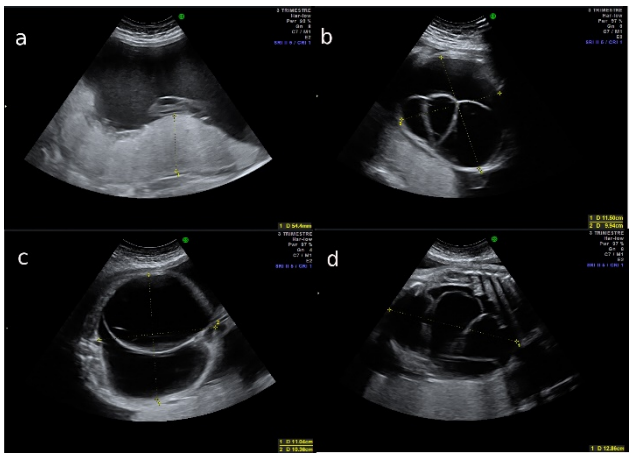
INTRODUCTION

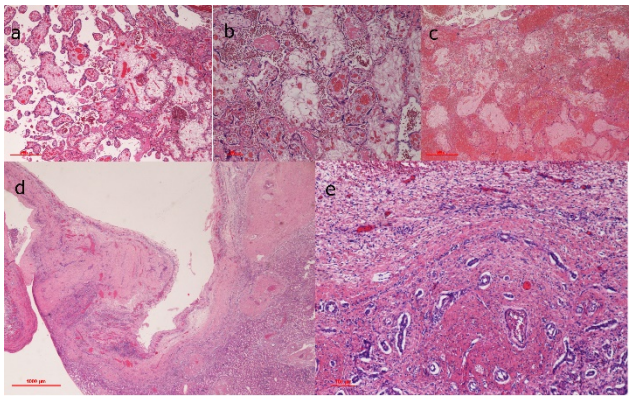
A thirty years old woman, gravida 2 para 1, came to our observation at thirty weeks' gestation for the presence of a massive multicystic lesion in the fetal abdomen. The ultrasound examination showed a multiloculated cystic lesion of 128x115x99 mm which almost entirely occupied the fetal abdomen, extending from the inferior margin of the liver up to the pelvis. Ascites were not present. The color doppler examination did not show significant vascularization. It was associated with polydramnios and the placenta appeared thick and hyperechogenic (**figure 1a**). At the follow-up of the next week the mass was further increased in volume and the diagnosis of a HMH was suspected although the mainly exophitic development from the liver made difficult the differential diagnosis with other abdominal multiloculated lesions, such as mesenteric and omental cystic lymphangiomas (**figures 1b, c, d**).

***Figure 1**. 2D image at 31 weeks' gestation showing a thickened and hyperechogenic placenta; (b-c) transverse and (d) parasagittal prenatal ultrasound image at 31 weeks' gestation showing a subphrenic multiloculated abdominal lesion.*



At 32 weeks a mirror syndrome occurred for which it was decided to carry out the delivery by caesarean section. The large size of the mass resulted in severe impairment of respiratory function and despite intubation the newborn of female sex died three hours after birth. The autopsy was requested. Macroscopic examination of the placenta showed enlarged size (24x20x4,5 cm; 780 grams), eccentric insertion of the umbilical cord and an intraplacental hematoma (10 cm). Microscopically hydropic villous with dilated central cisterns (**figures 2a, b**), thick-walled fibromuscular vessels, loose myxoid stroma and chorangioma like vasculature (**figures 2a, b**) were present. Moreover, intra and intervillous hemorrhage was appreciable (**figure 2c**). Autopsy revealed a wide (11x9 cm) multicystic lesion in the left lobe of the liver. Microscopically, the cystic walls were unlined, focally hemorrhagic and consisted of an admixture of mesenchyme and bile ducts (**figures 2d, e**).

***Figure 2.** Hydropic villi with dilated central cisterns and chorangioma-like vasculature. Hematoxylin-Eosin. Original magnification a: 2X, b:10X; (c) intra and intervillous hemorrhage. Hematoxylin-Eosin; original magnification 4X; (d-e) unlined cystic walls consisting of an admixture of mesenchyme and bile ducts. Original magnification a: 2X, b:10X.*



DISCUSSION

HMH represents the second most common benign hepatic lesion of childhood (first two years of life) after hemangioma / hemangioendothelioma and clinically manifests itself with abdominal distension and / or as a mass of the upper abdomen. However, this condition is quite rare. There is a predominance in the male sex and about 75% of cases originate from the right lobe of the liver. Up to 20% develops from the lower surface of the liver therefore its hepatic origin could be difficult to determine as in the reported case. The HMH can reach considerable dimensions in childhood (1). It generally has a benign behavior and is susceptible to complete postnatal removal; however, rare cases of highly malignant tumor onset such as undifferentiated hepatic sarcoma on a previous HMH are reported. The origin of HMH is uncertain, although recent studies of molecular biology seem to indicate that it should be considered a benign neoplastic lesion ab initio (1). It has been diagnosed prenatally since the 19th week (2) but in most cases it manifests itself in the third

trimester. Ultrasound generally reveals a multicystic lesion with thick septa, more rarely with a mixed structure (solid and cystic) or completely solid. All lesions diagnosed during the prenatal period are hypovascular to the color doppler. This feature allows the differential diagnosis from the hepatic hemangiomas. Approximately 50% of cases have rapid growth in utero, the remaining tend to remain stable and in about 10-15% of cases may also undergo partial regression. The prognosis of the HMH diagnosed in the prenatal age is worse than those diagnosed in postnatal age. In the larger hamartomas the occurrence of fetal hydrops is frequent and is associated with a high perinatal mortality, as in the reported case. The pathogenetic mechanism of hydrops is unclear because, as we have already pointed out, hypervascular hamartomas have not been found in prenatal age. Kamata et al. (3) suggested that hydrops could depend on circulatory insufficiency due to rapid accumulation of fluid in cysts but is more likely to be related to compression of the inferior vena cava and / or umbilical vein. There is also an increase in the risk of preterm birth linked to the polydramnios which may require an amnioreduction (4). Intrauterine therapy may be indicated in selected cases as the appearance of hydrops at early gestational age. In these cases, the aspiration of the larger cysts can be performed. As the liquid tends to quickly regenerate it is often necessary to repeat the procedure in order to postpone the delivery. Alternatively, a cystic-amniotic shunt can be inserted which allows partial decompression of the lesion.

In our case the association between a HMH and a rare placental pathology represented by the PMD has been observed. This pathology was described for the first time by Moscoso et al in 1991 (5) and is characterized by placentomegaly and by the presence of cluster vesicles similar to those of the hydatiform mole. In rare cases the formation of the vesicles is minimal or absent. Differently from the hydatiform mole there is no trophoblastic proliferation. In the third trimester the chorial plate reveals dilated and thick-walled vessels and various degrees of endoluminal thrombotic obliteration. Ultrasound in the second trimester shows a thickened placenta with multiple hypoechoic areas, similar to those of the hydatiform mole. As the pregnancy proceeds, the cystic spaces are superficialized towards the chorial plate and may not be evident on the ultrasound examination. In the described case the pregnant woman has come to our observation belatedly and we were not able to indicate how the placental structure was in the second trimester. The placenta in the third trimester appeared thickened and hyperechogenic but there were no cystic spaces in its context. Differently from the partial molar pregnancy, PMD is associated in most cases with a phenotypically normal fetus and pregnancy continues until the third trimester. PMD is associated with an increased risk of growth restriction, intrauterine death, preterm birth and some genetic abnormalities. In literature the incidence of intrauterine growth restriction ranges from 33% (6) to 50% (7), the intrauterine mortality from 13% to 40%. In about 50% of cases a preterm birth occurs (6) In about 20% of cases PMD is associated with the Beckwith-Wiedemann syndrome. More rarely chromosomal abnormalities, especially on the X chromosome (about 3%), were observed (8). To our Knowledge there are nine other reported cases characterized by this association that led to formulate the hypothesis of a common pathogenetic pathway to the two entities (2, 9, 10, 11, 12, 13, 14, 15). The most accredited theories are: (i) a congenital malformation of mesoderma; (ii) a dysregulation of genes implicated in the Beckwith-Wiedemann syndrome and (iii) an androgenic/biparental mosaicism (12, 16). According to the first main hypothesis PMD could originate from an inadequate blood supply which results in both aneurysmal dilatation of the chorionic vessels and a placental stem villous hyperplasia. As a result of thrombosis of the chorionic vessels, hepatic ischemic lesions would occur with a proliferative response of the bile ducts. Placental alterations arise during the second trimester and precede the development of the hepatic ones. On the basis of these observations, PMD would therefore represent a congenital anomaly of the mesoderm.

Recent literature also suggests the presence of multiples molecular mechanisms for C19MC gene activation on chromosome band 19q 13.4 in HMH and the existence of a placental imprinting pattern in mesenchymal cells (17). C19MC is maternally imprinted, so the placental expression is due to the paternal allele. C19MC is normally

expressed in the placental stroma and in case of androgenic/biparental mosaicism an association with the proliferation of stromal cells, similar to that of the HMH, has been noted (17).

The really incidence of androgenic/biparental mosaicism is unknown. Several mechanisms have been proposed to explain its origin in humans. Phenotypic manifestations can be very different due to the variable degrees of mosaicism and the combinations of uniparental disomy phenotypes.

A recent work emphasizes the importance of carrying out molecular genetic investigations, such as nucleotide polymorphism microarray and short-tandem repeat analysis, on the affected tissues to formulate an accurate genetic diagnosis (16).

In our case the anatomo-pathological and histological diagnosis were not supported by molecular genetic investigations targeted on the sample tissues. This has perhaps subtracted information from the etiological understanding of the desease.

CONCLUSION

To date in literature there are only a few reports of association between the HMH and the PMD. Immunohistochemical and cytogenetic studies have led to formulate the hypothesis of a common causal association between the two pathologies. In light of the current acquisitions we can recommend to always study very carefully the placenta in case of finding of fetal abdominal cystic masses; not to stop at the conventional karyotype surveys but to plan molecular genetic investigations on affected tissues and to have a very heedful behavior considering the high incidence of complications and adverse outcomes.

CONFLICT OF INTEREST

The authors report no conflict of interests.

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