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Case report

A case series of chorioangiomas in placentas with clinical indication for histological examination

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Summary

Chorioangiomas are benign angiomas arising from chorionic tissue and they are the most common non-trophoblastic tumors of the placenta, as they are observed in 1% of all placentas examined. Most chorioangiomas are small and asymptomatic, often undetected during a prenatal ultrasound, and their clinical significance is still unknown. Large chorioangiomas, measuring more than 4-5 cm in diameter, can usually be detected prenatally by gray-scale or color Doppler sonography, and may be associated with maternal or fetal complications, such as preeclampsia, maternal mirror syndrome, preterm delivery, non-immune fetal hydrops, fetal growth restriction and fetal demise. We herein describe the clinical-pathological features of a monocentric series of 30 placental chorioangiomas and discuss their clinical-pathological features and possible molecular mechanisms underlying their development.

Key words: chorioangioma, placental tumor, vascular lesions, pregnancy complication, histochemical evaluation

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Introduction

The human placenta is a disc-shaped, hemochorial organ and is the largest organ of fetal origin [1,2]. It regulates the exchanges between maternal and fetal circulations, by allowing the transport of nutrients and oxygen from the mother to the fetus and the removal of waste products from the fetal blood [3,4]. It releases hormones that affect pregnancy, maternal metabolism, fetal growth and parturition [2,4]. The placenta also acts as a selective barrier, protecting the fetus against xenobiotic molecules and infections. Therefore, proper placental development and function are essential to maintain pregnancy and preserve fetal health and growth. Abnormalities of the placental structure and function can cause fetal growth restriction, spontaneous preterm birth, and intrauterine fetal demise [5,6].

The histopathological examination of the placenta provides crucial information about the nature and cause of some pathological conditions affecting both the fetus and the mother. Placental lesions include a group of fetal-stromal vascular lesions, and a subgroup has been identified within it, defined as villus capillary lesions [5,7], which appear to be caused by excessive angiogenesis [5,8]. The villus capillary lesions include chorangiosis, chorangiomatosis, chorioangioma (CA) and multiple CA

syndrome [5,9,10]. A chorioangioma (CA) is a placental hemangioma and benign vascular tumor [11]. It arises from chorionic tissue and is the most common benign non-trophoblastic tumors of the placenta, occurring in 1% of all placentas examined [12]. It is observed with a higher incidence in cases of maternal hypertension, diabetes, twin pregnancies and female fetal sex [13].

In most cases, a chorioangioma is small, less than 4 cm in diameter, and asymptomatic. It is generally not considered clinically significant, although its relevance remains unknown [14]. A CA measuring more than 4-5 cm in diameter is rare, affecting approximately 1 in 10,000 pregnancies [15], and can be associated with maternal and fetal complications [16-19]. Early prenatal diagnosis, close surveillance and appropriate intervention may prevent the severe complications caused by large chorioangiomas [12].

The mechanisms underlying the development of a CA are poorly understood; some studies suggest that the environment for life at higher-altitudes and genetic factors could be involved in the pathogenesis of CA [20,21].

In this study, we describe a series of 30 large and small placental CA with related pregnancy complications, and we discuss their pathological features and the possible molecular mechanisms underlying their development.

Materials and methods

Placental sample collection and immunohistochemical analysis

Thirty cases of histologically confirmed placental solitary CAs diagnosed from 2011 to 2021 were retrospectively selected from the archive of the Section of Pathology, Department of Health Sciences, University of Florence, Italy, after excluding cases of major fetal malformations and twin pregnancies. The indications for referral of placentas for pathological examination were those defined by the SIAPEC/SIGO-AOGOI recommendations [22].

Most CAs examined (27 out of 30) were small and measured less than 1 cm in diameter. Three cases were greater in size and measured between 5.5 and 12 cm in diameter. These three CAs had been detected during prenatal ultrasounds at the Ultrasound Unit of the Department of Obstetrics and Gynecology of Careggi Hospital, where the patients received sonographic follow-up over the course of their pregnancy. The medical records and clinical data of the pregnancy for each case were also reviewed, and the incidence of pregnancy complications was retrospectively evaluated.

Hematoxylin and eosin-stained slides were reviewed, and representative formalin-fixed and paraffin-embedded (FFPE) tissues were selected for additional immunohistochemical analyses. FFPE sections 4 µm in thickness were immunostained with anti-CD34 antibody (Ventana; Roche Tissue Diagnostics, Indianapolis, USA), on a Ventana automated slide stainer.

Results

Pregnancy characteristics and outcomes

Clinical information, pregnancy complications and neonatal outcomes of the 30 cases are reported in Table I. The mean maternal age was 36.30 ± 4.75 years, and the mean gestational age at delivery was 36.1 weeks ± 3.40. Overall, we observed a 13.3% incidence of hypertensive pregnancy disorders, a 33% incidence of fetal growth restriction (FGR), and a 10% incidence of preterm premature rupture of the membranes (pPROM). All the cases were live births, but in one case the child died of sepsis at 8 months of age. This was a case of extremely preterm birth due to maternal preeclampsia, and the child developed sepsis in the postnatal period, which was the cause of death. 11/30 neonates (37%) were admitted to the neonatal intensive care unit (Tab. I).

The presence of a large CA did not affect pregnancy outcome in two of the cases, because both mothers and fetuses did not present any specific complication - in particular, no signs of fetal anemia, cardiac failure, hydrops, or intrauterine growth restriction were detected. In one of our cases, fetal anemia was suspected antenatally, and confirmed after birth.

Ultrasound characteristics of the large chorioangioma

Figure 1 shows the sonographic images of case #30, in which the diagnosis of a large CA was made during an antenatal ultrasound. The diagnosis was first suspected at the 20-weeks anatomy scan, which showed a vascularized hypoechoic mass measuring 56x39x36 mm underneath the chorionic plate, near the placental insertion of the umbilical cord. An ultrasound follow-up was performed every two weeks until 27+6 weeks of gestation (Fig. 1B), and the size of the mass remained stable over time. Afterwards, a scan was conducted once a week to detect possible signs of fetal anemia. The size of the mass remained unchanged (Fig. 1C), but signs of fetal anemia were observed at 34+5 weeks of gestation, when the MCA-PSV was 79.01 cm/sec (1.57 MoM, Fig. 1D). Based on the suspicion of fetal anemia and given the gestational age, delivery

Table I. Clinical information, pregnancy complications and neonatal outcome of placental chorioangioma (n = 30).

Case	Maternal age (years)	Gestational weeks at delivery	Baby weight/ Sex	Indications for referral of placenta	Pregnancy complications	Neonatal complications
1	27	39+5	2900 g/F	FGR	FRG	-
2	41	37+1	2400 g/F	Small for gestational age newborn	-	Small for gestational age
3	40	38+3	2500 g/M	Small for gestational age newborn	Intrahepatic cholestasis of pregnancy	Small for gestational age
4	31	39+4	3340 g/M	Suspected intraamniotic infection	Maternal intrapartum fever, purulent cervical drainage	Admission to NICU
5	32	33+1	1440 g/M	Small for gestational age newborn	Gestational hypertension, FGR, iatrogenic preterm delivery	Low birth weight due to preterm birth Admission to NICU Small for gestational age newborn
6	37	37+5	2350 g/M	Small for gestational age newborn Preeclampsia	Preeclampsia, FGR	Admission to NICU Low birth-weight Small for gestational age
7	33	30+0	715 g /F	Small for gestational age newborn Very preterm birth	Gestational diabetes, FGR, iatrogenic preterm delivery	Admission to NICU Small for gestational age Low birth-weight due to preterm birth. Lost at follow-up due to transfer to a different hospital
8	43	37+2	2510 g/F	Preeclampsia	Preeclampsia	None
9	42	32+3	2230 g/M	pPROM,	pPROM, preterm delivery	Admission to NICU Low birth-weight due to preterm birth
10	38	40+2	3350 g/F	Suspected intraamniotic infection	Gestational diabetes Maternal intrapartum fever, fetal tachycardia	Admission to NICU
11	36	32+6	1720 g/M	pPROM, Small for gestationa age newborn	pPROM, preterm delivery	Admission to NICU Small for gestational age Low birth-weight due to preterm birth
12	34	26+5	750 g/M	pPROM, Small for gestational age newborn Very preterm birth	pPROM, FGR, iatrogenic preterm delivery	Admission to NICU Small for gestational age newborn Low birth-weight due to preterm birth
13	37	37+1	2910 g/F	Suspected intraamniotc infection	Maternal intrapartum fever, fetal tachycardia	Admission to NICU Neonatal jaundice
14	37	39+1	2410 g/M	Small fo gestationa age newborn	Oligohydramnios	Low birth-weight Small for gestational age
15	28	36+6	2010 g/F	Small for gestational age newborn	FGR, iatrogenic preterm delivery	Admission to NICU Low birth-weight Small for gestational age
16	35	37+0	2150 g/M	Small for gestational age newborn	-	Admission to NICU Low birth-weight Small for gestational age; neonatal jaundice
17	26	38+3	2310 g/F	Small for gestational age newborn	Gestational diabetes, FGR	Low birth-weight Small for gestational age

Table I. *Follows.*

Case	Maternal age (years)	Gestational weeks at delivery	Baby weight/ Sex	Indications for referral of placenta	Pregnancy complications	Neonatal complications
18	43	39+1	3710 g/M	Suspected intraamniotic infection	Maternal intrapartum fever, purulent cervical drainage	Neonatal jaundice
19	41	38+5	2720 g/F	Cord pH ≤ 7.05	-	Admission to NICU Cord pH ≤ 7.05 Neonatal jaundice
20	35	40+4	2860 g/F	Small for gestational age newborn	Symptomatic COVID infection during delivery	Small for gestational age
21	43	37+0	2600 g/F	Cord arterial pH ≤ 7.05	Placenta previa Placenta accreta spectrum	Admission to NICU Cord arterial pH ≤ 7.05 Neonatal jaundice, neonatal weight loss
22	40	27+6	900 g/F	Small for gestation age newborn Extremely preterm birth	Intrahepatic cholestasis of pregnancy; iatrogenic preterm delivery	Admission to NICU Small for gestational age Low birth-weight due to preterm birth Respiratory distress Anemia Bronchodysplasia
23	37	37+4	2180 g/F	Small for gestational age newborn	FGR	Low birth-weight Small for gestational age
24	38	40+3	2852 g/F	Small for gestational age newborn Cord arterial pH ≤ 7.05	Gestational diabetes	Admission to NICU Small for gestational age
25	31	27+1	580 g/F	Small for gestational age newborn Extremely preterm birth Preeclampsia	Gestational diabetes, preeclampsia, iatrogenic preterm delivery	Admission to NICU Admission to NICU Low birth-weight due to preterm birth Small for gestational age Premature birth complications and postnatal death at 8 months of age due to sepsis
26	36	37+3	1930 g/F	Small for gestational age newborn	FGR, oligohydramnios	Low birth-weight Small for gestational age
27	34	39+5	2220 g/M	Small for gestational age newborn	PROM; FGR	Low birth-weight Small for gestational age
28*	41	34+1	2140 g/F	Prenatal diagnosis of large chorioangioma	Intrahepatic cholestasis of pregnancy, iatrogenic preterm delivery	Low birth-weight due to preterm birth
29*	33	38+6	3560 g/F	Prenatal diagnosis of large chorioangioma	Prenatal diagnosis of large chorioangioma	None
30*	40	34+6	2360 g/F	Prenatal diagnosis of large chorioangioma	Iatrogenic preterm delivery	Admission to NICU Low birth-weight due to preterm birth **Neonatal anemia**

F: female; M: male; FGR: fetal growth restriction; (p)PROM: (preterm) premature rupture of the membranes; * These cases had a prenatal diagnosis of large chorioangioma.

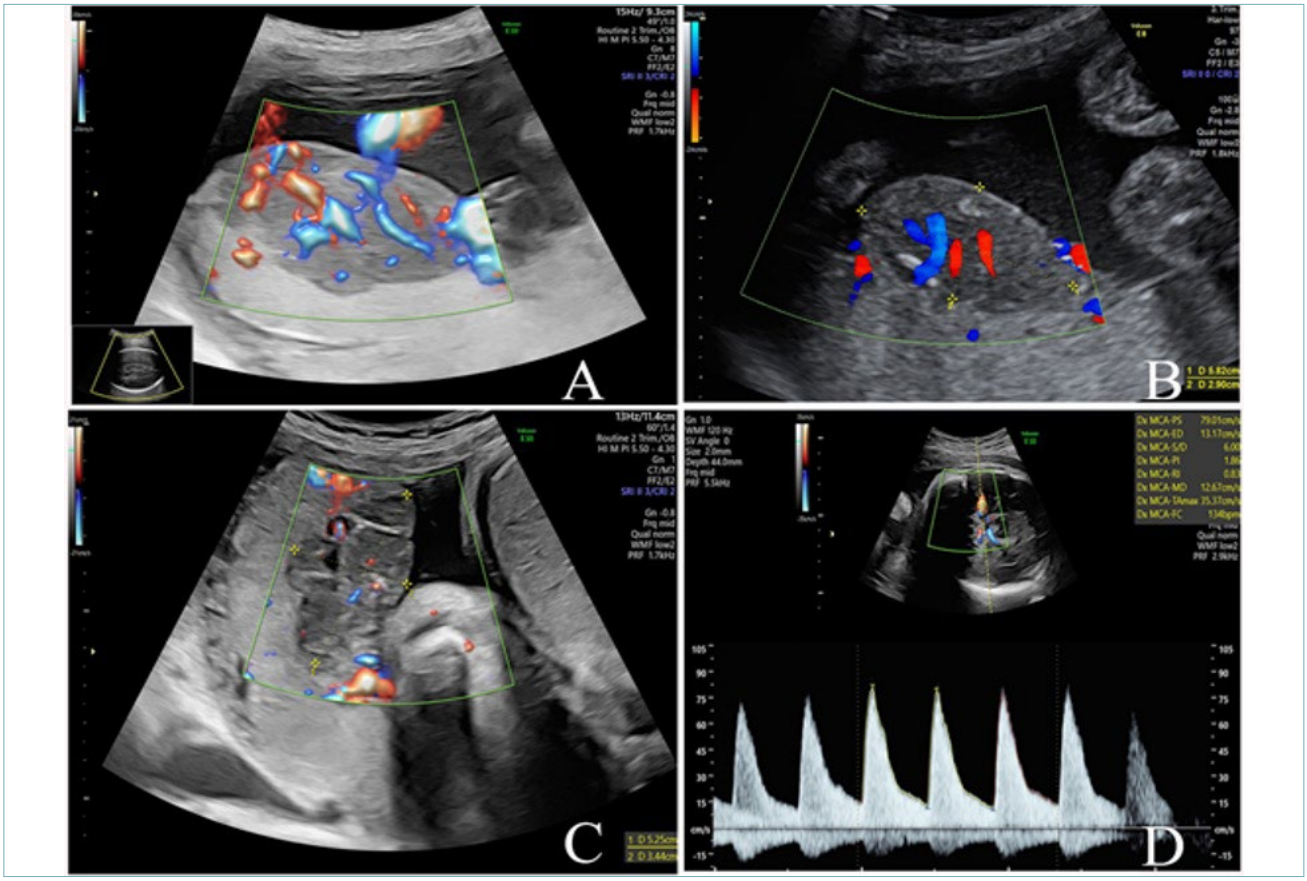

Figure 1. Sonographic features of a large chorioangioma. (A) 25+3 weeks: color Doppler flow imaging demonstrates large vascular channels within the tumor; (B) Size of the mass at 27+ 6 weeks; (C) Size of the mass at 34+5 weeks. (D) Pulsed-wave Doppler of the middle cerebral artery demonstrating increased peak systolic velocity.

by C-section was indicated. The diagnosis of anemia was confirmed in the newborn.

Histopathological and immunohistochemical analysis

Tissues were sampled, macroscopically evaluated, and examined by conventional histopathology following the Amsterdam Placental Workshop Consensus Statement [23]. Placental weight, funicle insertion and membrane color were recorded. (Tab. II).

Then, for each placenta we submitted a minimum of 4 blocks: one block included a roll of the extraplacental membranes and 2 cross sections of the umbilical cord, the other blocks contained a full-thickness section of normal-appearing placenta parenchyma. If gross lesions were identified, they were described and sampled for histological evaluation.

In the three cases where the chorioangioma was identified macroscopically, it was described and measured, and subsequently, samples were taken for its histological evaluation.

Macroscopically, the three large CAs were described as solid, well circumscribed masses. Histopathological examination showed the presence of placental chorioangioma in all cases. Both small and large chorioangiomas appeared as well-circumscribed vascular proliferations arising in and protruding from large stem villi (Fig. 2). In addition, the follow-

Table II. Macroscopic placental examination.

	Number of cases (%)
Weight ≤ 350 g > 350 g	9 (33.3%) 18 (66.7%)
Funicle insertion Eccentric Marginal Velamentous	 18 (66.6%) 7 (26.0%) 2 (7.4%)
Membrane color Shiny transparent Opaque Yellowish	 21 (75.0%) 4 (14.3%) 3 (10.7%)

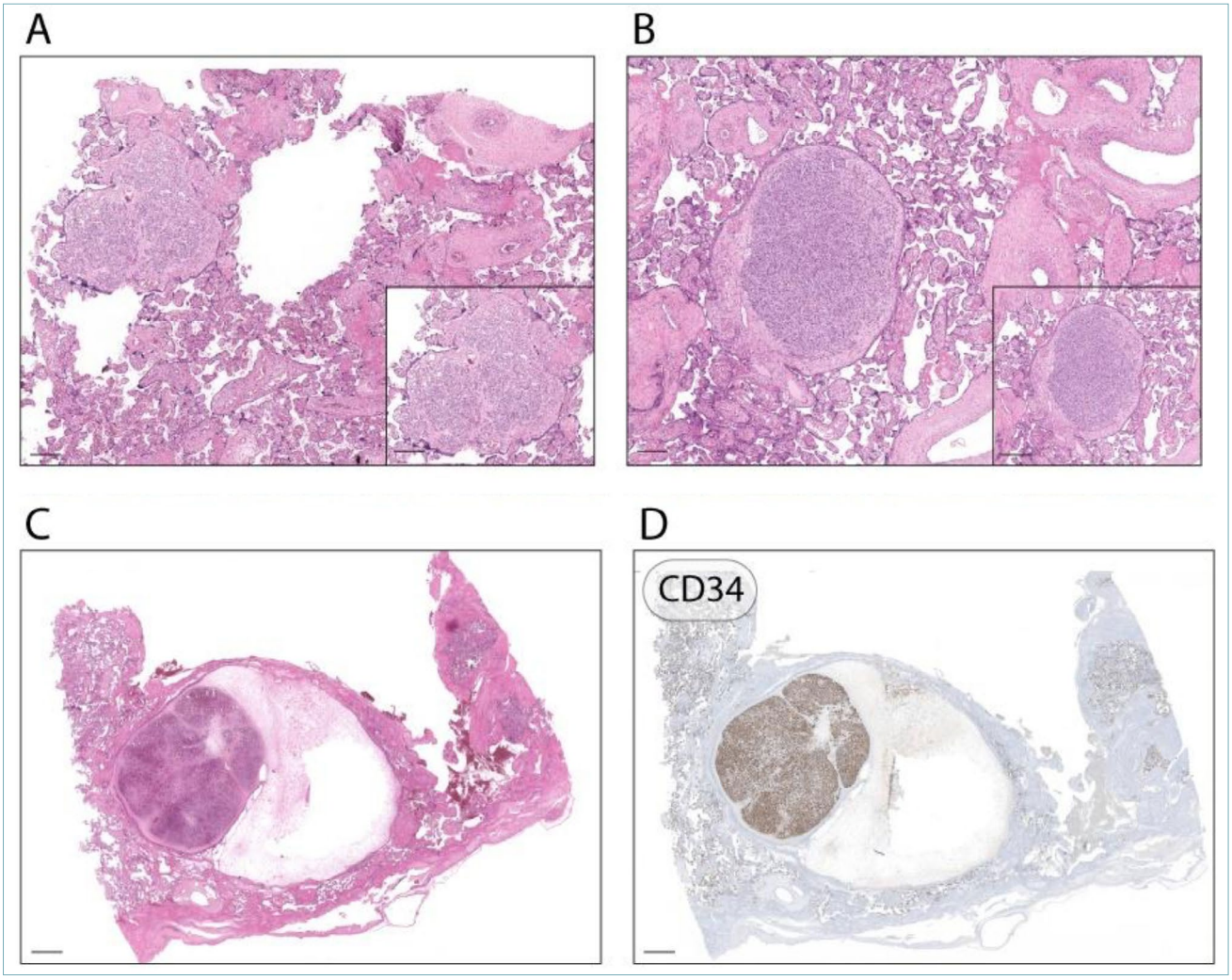

Figure 2. Histopathology of small placental chorioangioma. (A, B, C and E) Representative H&E images of well-demarcated solitary tumor mass within placental parenchyma. The tumor is composed of a capillary vascular proliferation decorated by cytologically bland endothelial cells. (D, F). Immunohistochemical stain of anti-CD34 in small placental chorioangioma shows strong positivity in endothelial cells. (A-B) magnification x3, inset x7; (C, D) magnification 0.5;(E, F) magnification x2.

ing histopathological parameters were evaluated and recorded (Tab. III): funisitis (absent/present), chorioamnionitis (absent/present), infarcts (absent/present), hemorrhage (absent/present), and chorangiosis (absent/present).

All the CAs were identified as solitary lesions. The tumors were composed of numerous predominantly small capillary sized vascular channels decorated by endothelial cells embedded within connective tissue. Endothelial cells did not show signs of cytological atypia or mitotic activity. There was no necrosis. The adjacent villi were normal or slightly enlarged and covered by a trophoblast layer.

Table III. Microscopic placental examination.

	Number of cases (%)
Funisitis	
- Absent	28 (93.3%)
- Present	2 (6.7%)
Chorioamnionitis	
- Absent	25 (83.3%)
- Present	5 (16.7%)
Infarcts	
- Absent	20 (66.7%)
- Present	10 (33.3%)
Hemorrhages	
- Absent	27 (90%)
- Present	3 (10%)
Chorangiosis	
- Absent	25 (83.3%)
- Present	5 (16.7%)

Discussion

Placental CA is a benign tumor derived from non-trophoblast cells in the placenta with predominantly vascular involvement [11]. The estimated incidence of CA is about 1% in microscopically examined placentas [24]. Most CAs are less than 0.5 cm at their point of greatest dimension and are incidental findings during microscopic evaluation. In contrast, larger lesions can be identified by gross examination of the placenta as single, well-circumscribed, solid, nodular lesions, most often found just below the chorionic plate or at the placental margin [12-25]. The color varies from red-brown to tan-white depending on the ratio of the vascular and stromal components.

During the prenatal period, sonography can be used to diagnose a large CA. In most cases, it appears as a hypoechoic mass bulging on the fetal surface of the placenta, underneath the chorionic plate near the umbilical cord insertion. Some studies have described only arterial blood flow within the mass, others have found only venous waveforms, while a few studies have demonstrated both arterial and venous waveforms [26]. A large CA may have clinical implications, as it can be associated with maternal or fetal complications including fetal growth restriction, polyhydramnios, fetal hydrops, preeclampsia, maternal mirror syndrome, preterm delivery and fetal demise [16-19,27-29]. No data in the literature has correlated the presence of a CA with the occurrence of pPROM. These pathological conditions are associated with poor pregnancy outcomes.

Because of the lack of a control group in our case series, we could not evaluate if the presence of a subcentimetric CA is associated with adverse maternal, fetal and neonatal outcomes related to placental dysfunction. We chose to not include normal placentas as controls because the placentas sent to the Pathology Service, including those used in this study, come from pregnancies that had pathological conditions, during the course of the pregnancy or at the time of birth, requiring placental histological analysis (such as intrauterine growth restriction, preeclampsia, suspicion of intraamniotic infection). Therefore, comparing outcomes of our selected cases with those of placentas from normal pregnancies would have led to a selection bias. Although we have reported the outcomes of pregnancy for the cases studied, the main aim of the study was to describe the diagnosis and histological characteristics of placental chorioangiomas.

Chorangiosis, multifocal chorangiomatosis, and CA are three histological entities characterized by excessive vascularity in the placental villi, and the diagnosis of CA must be differentiated from these other villus capillary lesions, as they share overlapping similarities with CA, and similar clinical implications [30]. The exact causes of these villus capillary lesions are poorly understood but they probably involve abnormal angiogenesis [31-33].

Chorangiosis is characterised by an increase in the number of capillary cross sections per villus and is defined as 10 or more villi containing 10 or more capillary cross sections in different regions of the placenta [34]. Chorangiosis is the most common of these three lesions [30,35]. Histopathologically, capillaries in villus chorangiosis are lined by a single layer of endothelium, a continuous basement membrane and lack surrounding pericytes. This lesion can involve the entire placenta but most commonly has a patchy distribution. Immunohistochemistry does not play a central role in the diagnosis as CD31 and CD34 may overestimate the density of the capillaries [30,35]. Generally, CD31 and CD34 are also not required for the diagnosis of CA, but they can be helpful in highlighting endothelial cells [11].

Multifocal chorangiomatosis is characterized by small anastomosing capillaries affecting immature intermediate and small stem villi. Unlike chorangiosis, capillaries in this lesion lack a continuous basement membrane [36].

CA also need to be differentiated from multiple chorioangioma syndrome, a rare phenomenon characterized by the presence of multiple vascular tumors, from small and early lesions to well-developed chorioangiomas [37].

This syndrome has similar adverse maternal and fetal outcomes as the ones described in large chorioangiomas [38].

Furthermore, CA needs to be distinguished from choriocarcinoma, a trophoblastic malignant lesion. This is a very rare tumor characterized by abnormal trophoblastic proliferation associated with a hypervascular chorangiosis, nuclear atypia, large areas of necrosis and high mitotic activity [39,40]. A high proliferative rate (> 90%) detected by Ki-67/MIB-1 is generally observed.

Histopathologically, CA and chorangiomatosis are distinguished from chorangiosis by the presence of capillary-vascular spaces, that are surrounded by a continuous layer of muscle specific actin (MSA)-positive pericytes and by a high stromal collagenization and cellularity, which increase the spacing of the capillary vascular channels [11,30].

Endothelial cells are positively stained for both CD31 and CD34 in CA, chorangiosis and chorangiomatosis, while macrophages are rarely found [11].

The villi with chorangiosis show structural features similar to the normal terminal villi, including uniformly CD31/34-positive endothelium and a thin, well-cir-

cumscribed basement membrane. The lack of Ki-67 positive cells suggests that capillaries in chorangiosis are not in a phase of active endothelial proliferation. The number of smooth muscle actin-positive pericytes is slightly higher compared to the normal villi but does not form the continuous perivascular layer observed in cases of CA and chorangiomatosis [11].

The molecular mechanisms underlying the development of a CA are still poorly understood. Indeed, few data are available on genetic analysis and on protein expression of CAs [8,11,21,41]. Changes in gene expression levels between recurrent multiple chorioangioma and normal placenta using angiogenesis tissue array were evaluated by Gallot et al. The authors demonstrated that the transforming growth factor receptor 3 (TGFR3), epidermal growth factor receptor (EGFR), Integrin-V (ITG5), tyrosine kinase VEGF receptor 2 (FLK1) and the tissue inhibitor of metalloproteinase 2 (TIMP2) are lower, whereas the angiotensin 2 (ANGPT2) and osteopontin (SPP1) are higher in recurrent multiple chorioangioma compared to the normal placenta [8]. Sirtotikna et al. [21], investigated the deletions and duplications in the CA genome using an array comparative genomic hybridization method. Their analyses did not reveal any rare or novel structural change involving gain or loss of genetic material in the CA samples compared with either standard control DNA or unaffected placenta DNA.

Conclusion

During the prenatal period, ultrasound can be used to diagnose a large CA, which may have clinical implications as it may be associated with adverse maternal or fetal outcomes. On the other hand, a subcentimeter CA might not be evident in ultrasound scans, but only be detected through placental histologic examination. It is unknown if a small CA can cause adverse maternal, fetal, or neonatal outcomes, and further study including larger cohorts and control groups should investigate the association with placental-related complications.

The genetic basis and the protein expression of CAs is an open field of investigation and, for this reason, further molecular studies are desirable. In particular, future research should aim to better characterize the molecular mechanisms underlying the CA. The analysis of our case series involved both the clinician and the pathologist. Multidisciplinarity is an essential aspect of studies on the placenta, as it allows the evaluation of the morpho-phenotypic profile in relation to clinical outcomes.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Authors' contribution

Conceptualization: EN, FC; Data acquisition: AS, IA, EN, EO; Writing: EN, AS, IA; Funding acquisition: DM; Supervision: FC, VS, MDT, DM; Review: FC, VS, MDT, DM.

Ethical consideration

The present study complied with the Ethical Principles for Medical Research Involving Human Subjects according to the World Medical Association Declaration of Helsinki; all samples were anonymized before histology and immunohistochemistry; no futher ethical approval was necessary to perform the retrospective study.

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