CASE REPORT

A giant early second-trimester placental chorioangioma associated with isolated proteinuria and histopathologically confirmed placental insufficiency, a novel association: A case report

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Funding information
None.

Abstract

We present a case of giant chorioangioma at 18 weeks of gestation leading to fetal hypertrophic cardiomyopathy without other evidences of fetal volume overload and late-onset isolated proteinuria. Oligohydramnios developed at term and placental insufficiency was confirmed on histopathological examination and a non-anemic nonthrombocytopenic normal weight healthy baby was delivered.

KEYWORDS
cardiomyopathy, chorioangioma, oligohydramnios, placental abruption, proteinuria

1 | INTRODUCTION

Chorioangiomas are the most common placental nontrophoblastic tumors with an incidence rate of 0.6%.[1] Maternal and fetal complications are more frequent in tumors larger than 4 cm,[2] although giant chorioangioma occurs 1 in 10,000 pregnancies.[3] These complications include intrauterine growth restriction (IUGR), polyhydramnios and preterm labor, fetal anemia, fetal cardiomegaly and congestive heart failure, nonimmune hydrops, fetal demise,[2,4] neonatal cardiomyopathy,[5] disseminated intravascular coagulation (DIC) and neonatal death,[6] maternal thrombocytopenia and hemolytic anemia,[7] and/or sudden maternal collapse.[8]

A placental chorioangioma often appears as a solid hypoechoic and heterogeneous mass, most frequently found on fetal surface of the placenta. On Doppler study, chorioangioma is often hypervascular, which can help physicians to differentiate it from other nonvascularized tumors such as hematoma, teratoma, and myoma.[9]

Different risk factors have been associated with occurrence of placental chorioangioma like advanced maternal age, maternal hypertension and diabetes, primiparity, and multiple gestation.[10] Additionally, carrying a female fetus has also been linked to higher incidence of these benign tumors.[10,11]

The presence of vascular shunts of low pressure inside the tumor can result in reduced perfusion of chorionic villus and subsequent decrease in nutrients and oxygen transport to fetal circulation. Moreover, hemolysis can occur inside tumor vessels, which per se disturbs fetal perfusion due to induced fetal hemolytic anemia.[12] These pathologic changes will diminish fetal cardiac afterload. Hence, fetal heart should compensate to maintain fetal tissue perfusion and nutrients and oxygen exchange properly. If fetal heart cannot compensate properly, this will lead to cardiac failure and occurrence of fetal hydrops.[13,14]

In other words, less vascularized chorioangioma may have more favorable outcomes.[15] In fact, if tumors are more echogenic than the surrounding tissue, it may testify tumor fibrous degeneration, which may be associated with less serious pregnancy adverse events.[16] In line with this finding, Sepulveda et al. reported a case of poorly vascularized chorioangioma that had undergone degenerative changes and the mother experienced an uneventful gestation except for polyhydramnios.[17,18]

Here, a case of very rare manifestation of a giant placental chorioangioma in a primiparous woman at the age of 18 weeks and its unusual subsequent course during gestation is fully presented.

2 | CASE REPORT

An 18-year-old primigravid at gestational age of 37 weeks was referred to our hospital due to a placental mass at her prenatal sonography report. Her first-trimester combined aneuploidy screening was low-risk, and fetal nuchal translucency (NT) measurement was normal. Maternal serum pregnancy-associated plasma protein A (PAPPA) level and beta human chorionic gonadotropin (BHCG) concentration were 0.99 MoM and 1.46 MoM (37,732 mIU/ml), respectively. Due to an increase in approximately 15 mm Hg in her diastolic pressure compared to her previous prenatal visit (as seen in delta hypertension), a physician had prescribed her 250 mg methyldopa and 80 mg ASA daily. She had undergone mid-trimester anomaly scan, which
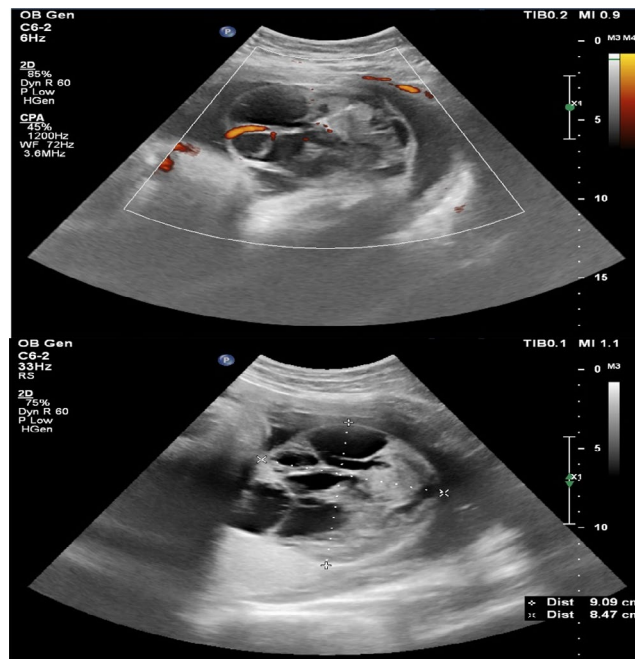

FIGURE 1 Sonographic appearance of the placental mass showing a small feeding vessel in a septa

revealed a placental cystic lesion with maximum diameter of 54 mm and multiple septations and internal echo. The patient was lost to follow-up till around 33 weeks of gestation. At that time, fetal biometry and Doppler indices were all in normal limits and just a 70 × 76 mm cystic structure with multiple septations and calcified foci was found in fetal surface of placenta protruding into amniotic cavity near the umbilical cord insertion site; however, color Doppler study of the placental lesion was not mentioned in the sonography report. Subsequently, fetal echocardiography had been performed and septal hypertrophy in excess of 6 mm and mild ventricular discrepancy were discovered. Next follow-up visit after birth and fetal surveillance was highly recommended. Additionally, her obstetrician had discontinued methyldopa intake due to all self-reported blood pressure measurements of ranging 100/60 to 110/70 mm Hg. Unfortunately, the patient did not have appropriate prenatal care until week 37 of gestation. She referred to Yas Hospital (referral hospital for fetal malformations, Tehran, Iran). According to sonography results, the estimated fetal weight was 2930 grams, amniotic fluid index (AFI) was 10 cm, and the aforementioned complex placental mass was observed measuring 91*87 mm. In color Doppler study, the mass hardly showed a feeding vessel with low resistance and pulsatile indices (Figure 1). The middle cerebral arterial (MCA) velocity was 68.9 cm/s (1–1.3 MoM), and umbilical artery Doppler study was unremarkable. In four-chamber view of fetal chest, mild septal hypertrophy was evident. According to the characteristics of the tumor on sonography, two

main differential diagnoses were chorioangioma and less probably placental teratoma and not just a simple placental cyst. To further rule out gestational trophoblastic tumors and teratoma, we measured maternal serum BhCG, alpha-fetoprotein (AFTP), and carbohydrate antigen 19–19 (CA19-9), which were 52,741 mIU/ml, 142 ng/ml, and 2.2 U/ml, respectively. Since all blood pressure measurements were in normal range, the fetal biophysical profile score was 10 out of 10, and there was no sonographic sign of severe anemia or hydrops fetalis, and fetal surveillance was continued. On her next visit (six days later), biophysical profile score was 10/10 but borderline oligohydramnios was found (AFI of 6.1 cm). Also, since she complained of vague abdominal pain, she was referred to our obstetric emergency department for further investigations. Her blood pressure was 123/70 mm Hg on admission, and she had no complaints of eminent signs (headache, nausea, vomiting, etc.). She had been admitted due to the presence of spontaneous regular uterine contractions and onset of spotting. Her initial vaginal examination revealed that her cervix was 3 cm dilated and 30% effaced. Initial laboratory tests are summarized in Table 1. All blood pressure results were unremarkable, but her vaginal bleeding suddenly aggregated and she experienced fresh clot passage and uterine hypertonia. Subsequently, she was urgently transferred to the operating room by impression of placental abruption, and finally, a female baby weighting 3350 g with Apgar score of 8 and 10 at first and fifth minute and respiratory acidosis was born through cesarean section. Umbilical cord blood gas study was as follows: PH: 7.2, PCO$_2$: 62 mm Hg, HCO$_3$: 24 mMol/L, and base excess: −5 mMol/L. Placenta was exploded manually weighting 853 g with dimensions of 22 × 17 × 5 cm (Figure 2). There was a 7 × 3.5 × 3.5 cm solid–cystic mass at its periphery, which seemed to contain yellowish fluid. The placenta was sent for histopathological examination, and finally, angiomatous chorioangioma of placenta with foci of degenerative changes was confirmed. Also, perivillous fibrin deposition and distal villous hypoplasia in favor of

maternal vascular malperfusion were also documented (Figure 2). The baby underwent echocardiography 24 h after birth, which showed no abnormality except for previously detected mild left ventricular hypertrophy (septal thickness of 5 mm). The baby's complete blood cell count (CBC) revealed hemoglobin (Hb) of 16.6 g/dl and platelet count of 165,000/ml, and she was discharged home by her mother 48 hours after birth. The mother was highly recommended to come back for a second echocardiography of her newborn two months later.

3 | DISCUSSION

As seen in our case, chorioangioma is the most common nontrophoblastic tumor of the placenta.[1] Our patient was misdiagnosed with placental cyst initially, which emphasizes the importance of precious color or power Doppler study to help the definite diagnosis. Our patient's placental mass was poorly vascularized, and we could find a small feeding vessel in one of its septations, which had maximum velocity of 15–20 cm/s. However, resistance and pulsatile indices were 0.48 and 0.72, respectively, which were so similar to umbilical artery indices. Misdiagnosis of this placental lesion with a simple placental cyst may lead to serious adverse effects and even fetal or maternal mortality. Additionally, our 18-year-old patient had been misdiagnosed with hypertension in her late first trimester and was taking antihypertensive drug even though her blood pressure was not in hypertensive range. In contrast to previous very rare reports of early second-trimester chorioangioma[15] and despite the presence of a giant chorioangioma since early second trimester, the patient remained normotensive and the pregnancy did not complicate with preeclampsia, preterm delivery, or polyhydramnios. Kirstie et al.[15] reported a case of early-onset small chorioangioma, which was misinterpreted a venous lake up to 27 weeks of gestation after the presence of a giant hypervascular chorioangioma. At that time, the patient had developed

TABLE 1 Patient's laboratory test results

Laboratory test		Laboratory test			Laboratory test	
WBC	9600/ml	AST	22 IU/L	23 IU/L	BHCG	41089 mIU/ml
Hb	14.4 g/dl					
RBC	4.4 × 10^6/μl	ALT	12 IU/L	10 IU/L	ANA	Negative
MCV	91	ALK-P	324 U/L		Anti dsDNA	Negative
HCT	42.8%	LDH	430	428	Urine analysis	2+ proteinuria
Plt	150 × 10^3/ml	Urea	24 mg/dl			Negative hemoglubinuria
Urine protein/Cr ratio	0.94 1.63	Cr	0.8 mg/dl	0.65 mg/dl		Negative hematuria

Abbreviations: ALK-P, alkaline phosphatase; ALT, alanine aminotransferase; ANA, anti-nuclear antibody; Anti ds-DNA, anti double strand-deoxyribonucleic acid; AST, aspartate aminotransferase; BHCG, beta human chorionic gonadotropin; Cr, creatinine; Hb, hemoglobin; HCT, hematocrit; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; Plt, platelet; RBC, red blood cell; WBC, white blood cell.
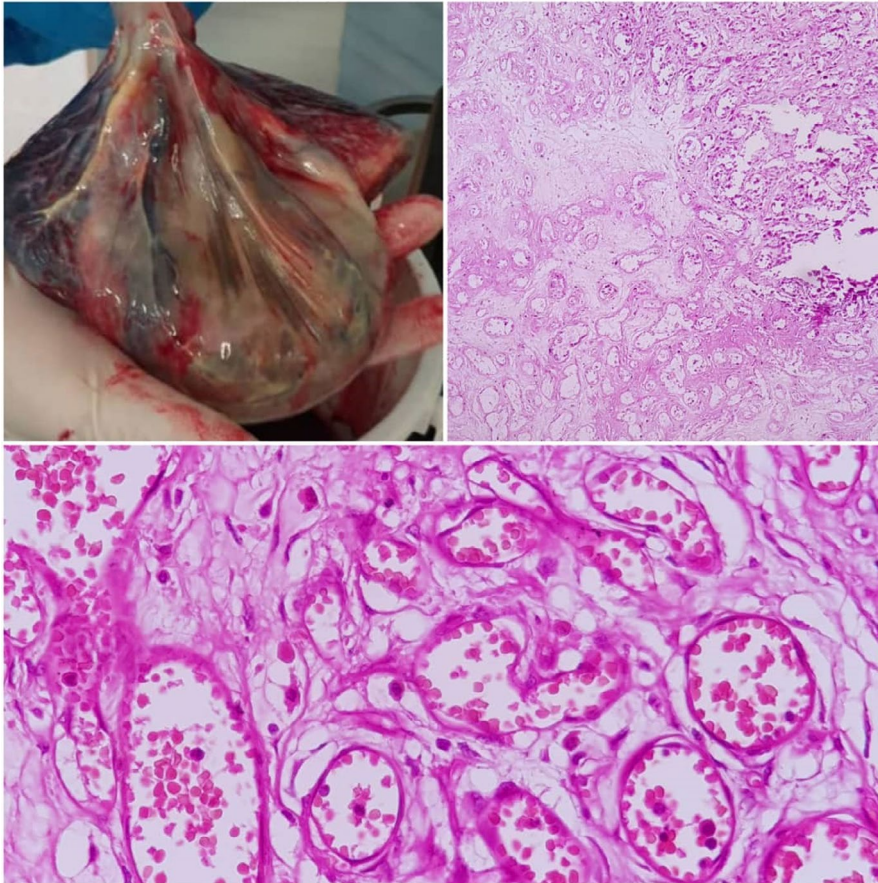
FIGURE 2 Left upper image shows macroscopic appearance of the placenta. Right upper and also lower images both show microscopic examination of the tumor in which capillary formation, calcification, and necrosis are all evident

severe polyhydramnios, which underwent multiple amnioreductions but finally polyhydramnios had resulted in preterm delivery at 33 weeks of gestation. Their patient had developed a 1.7 × 1.9 × 2 cm cystic hypoechoic lesion at 19 weeks of gestation, which reached to 4.4 cm at 23 weeks, and at 27 weeks it showed significant hypervascularity causing severe polyhydramnios. In fact, chorioangioma may undergo temporal changes such as necrosis, calcification, and hemorrhage during pregnancy, which can differ the tumor appearance on ultra-sonographic imaging,[19] as happened in their patient after approximately six weeks and tumor vascularity significantly increased. In contrary to their report, as our patient's previous available images were reviewed, and there was no significant change in sonographic characteristics of tumor except for its gradual growth and appearance of a small feeding vessel. Also, in a six-year retrospective study, Zanardini et al.[4] pointed out that mean gestational age at the time of diagnosis was 28.4 weeks (range: 23.2–35.1 weeks), but placental tumor was diagnosed in our case at gestational age of 18 weeks. Although her first-trimester sonography was unremarkable and the placenta was located posteriorly and completely previa and no other placental abnormality was reported, we reviewed the images to further investigate the precise onset of placental chorioangioma. It seems that at that time, there had been a very

small hypoechoic lesion inside the placenta, which may be a very early developmental stage of chorioangioma. However, this hypothesis cannot be confirmed as access to those saved sonographic images with proper quality were limited. Moreover, despite minimal vascularity on sonography but confirmed angiomatous subtype on histopathologic examination, the pregnancy did not complicate with polyhydramnios or preterm delivery.

On the other hand, although the patient had no abnormalities in liver or kidney function tests, her platelet count was at lower limit of normal and any blood pressure measurement over 120/80 mmHg was not detected during pregnancy or admission period, but random urinary protein/creatinine ratio was high in two subsequent measurements (0.9 then 1.6). According to a late first-trimester negative 24-h urinary protein and subsequent negative random urinary dipsticks, this was considered new-onset proteinuria. In fact, suddenly during a one-week period, the patient developed both borderline oligohydramnios and new-onset proteinuria. Despite reports of preeclampsia in context of chorioangioma,[20] there is no report on coincidence of isolated gestational proteinuria and placental chorioangioma. Our case seems to be the first in this regard. However, confirming this association needs further investigations. Indeed, our patient's kidney sonography was unremarkable and

antinuclear antibodies (ANA) and anti-double-strand deoxyribonucleic acid (anti-dsDNA) tests were both negative, and at the time of discharge, proteinuria had been resolved completely.

It is worthy to note that despite the presence of confirmed fetal hypertrophic cardiomyopathy and also perivascular fibrin deposits and distal villous hypoplasia on placental histopathology of this early-onset large chorioangioma, all serial prenatal sonographic examinations had documented appropriate fetal weight gain and the baby was born in normal weight too. Moreover, we could not find a similar histopathology report in literature. Undiagnosed gestational diabetes may prevent establishment of fetal growth restriction, but our patient had negative diabetes screening test and random blood sugar was also in normal range. So, it is not the case in our patient and its reason remains unknown.

Moreover, there is a report of neonatal cardiomyopathy[5] diagnosed retrospectively after birth when other etiologies were ruled out and the presence of multiple small chorioangiomas in placental histologic examination was confirmed. Our case may be the first case of isolated fetal hypertrophic cardiomyopathy proved by postnatal echocardiography in context of an early second-trimester slowly growing giant chorioangioma.

Another interesting point is that although the tumor was poorly vascularized on prenatal sonography examinations and middle cerebral arterial (MCA) peak systolic velocity (PSV) did not show any significant fetal anemia and/or even histopathological examinations revealed angiomatous subtype, but the fetus developed cardiomyopathy. An explanation for this issue may be concurrent hypoxic-induced cardiomyopathy, although on postnatal echocardiography no other sign of hypoxia was evident. Another reason may be the prolonged presence of a poorly vascularized giant chorioangioma since early mid-trimester.

A novelty in our case is that serum BHCG, CA19-9, and AFTP were all checked. Her BHCG significantly decreased (approximately 25%) during a week interval, and normal CA19-9 and the presence of a feeding vessel could help us to put more emphasis on chorioangioma instead of placental teratoma. Additionally, AFTP was not elevated according to gestational age-specific nomogram of Bredaki.[21] Thus, despite the presence of a giant chorioangioma, lack of significant fetomaternal hemorrhage may lead to no increase in maternal serum AFTP at term, even though we could not rule out second trimester elevation of AFTP since no measurement was carried out.

It is also interesting to point out that it is more common to see polyhydramnios in case of the presence of giant chorioangiomas. On the other hand, in pregnancies complicated by chorioangioma, polyhydramnios is the most common adverse effect,[22] which itself may be associated with preterm delivery and placental abruption.[23] Surprisingly, in our case despite the presence of a 9 cm chorioangioma, the patient developed a sudden decrease in AFI to 6 cm in a 6-day interval at her late third trimester, and subsequently, she experienced placental abruption. As maternal malperfusion was confirmed on histopathological examinations, it might had prevented the occurrence of polyhydramnios, and this insufficiency along with a giant chorioangioma might had led to placental abruption after initiation of spontaneous uterine contractions.

Another point to be discussed is that the appearance of proteinuria and sudden abruption of placenta could be early signs of initial phase of preeclampsia as seen in atypical preeclampsia. In fact, in atypical preeclampsia proteinuria may precede the onset of hypertension [24]. But as all blood pressure measurements of our patient were normal during admission and on 5-day postpartum follow-up visit, proteinuria could not be considered as a consequence of preeclampsia.

In conclusion, detailed color Doppler study of any placental mass is recommended to help diagnose the cases precisely and prevent any unpredictable adverse events. Also, we should highlight the importance of performing fetal echocardiography and pay more attention to four-chamber view on each prenatal visit even in the absence of overt fetal anemia or other early sings of volume overload. It also seems that even if a giant chorioangioma does not lead to fetal growth disturbance, subclinical placental insufficiency can have still occurred and may subsequently result in sudden ominous events such as placental abruption. Furthermore, the coincidence of late third-trimester onset isolated proteinuria in context of giant chorioangioma warrants further investigations.

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS
Fatemeh Rahimi-Sharbaf, Seyedeh Noushin Ghalandarpoor-Attar, Farnaz Moravej-Salehi, and Seyedeh Mojgan Ghalandarpoor-Attar made substantial contributions to conception, design, acquisition, and interpretation of data. They all were involved in drafting and revising the manuscript. All the authors read, corrected, and approved the final manuscript.

ETHICAL APPROVAL

The manuscript does not contain any direct patient identification details, and hence, ethics committee approval was waived.

CONSENT

Witten informed consent was obtained from the patient to publish this record in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were generated or analyzed in this study.

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