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Case Report

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A Twin Pregnancy With Undiagnosed Hereditary Hemorrhagic Telangiectasia With Severe Hypoxia

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Abstract

During pregnancies with hereditary hemorrhagic telangiectasia (HHT), rare severe complications could be fatal. This study presents a Chinese immigrant with twin gestation with asymptomatic hypoxia. The pregnancy was complicated with fetal growth discordance, placental insufficiency, and preterm labor, which she delivered at 34 weeks via a primary cesarean section. The series of images showed multifocal bilateral pulmonary arteriovenous malformations and evidence of pulmonary hypertension. Postoperatively, the patient required high-flow oxygen and nitrogen oxide supply due to severe hypoxia. HHT was diagnosed with positive genetic testing of the ENG variant. She received pulmonary artery embolization and the hypoxia improved. The further workup of brain and liver arteriovenous malformations was negative. This study reviewed literature about HHT and its effects on pregnancies. The disease onset, the diagnostic process, and the management experience might provide clinical value for care providers and for future reference.

Keywords: Hereditary hemorrhagic telangiectasia; Asymptomatic hypoxia; Pulmonary arteriovenous malformation; Twin pregnancy; Preeclampsia; Placental insufficiency

Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is a rare autosomal dominant disease with a prevalence of approximately 1 in 2,300 to 1 in 39,000 among different European populations [1]. During pregnancies, worsening epistaxis (17-31%) is the most commonly reported symptom, while severe HHT complications, though very rare, could be fatal [2, 3]. Undiagnosed HHT without preconceptional counsel might lead to poorer outcomes [2]. Therefore, we decided to present an undiagnosed HHT in a Chinese immigrant with twin gestation presenting with asymptomatic hypoxia. The disease onset, the diagnostic process, and the management experience might provide clinical value for care providers and for future reference.

Case Report

The case was a 29-year-old G2P1001 Chinese female with no significant past medical history with di/di twin gestation. Due to a 21% fetal growth discordance diagnosed at 27 weeks gestation, the patient received antepartum testing with a nonstress test (NST) biophysical profile (BPP), and umbilical artery Doppler (UAD). She presented for antepartum testing at 34 weeks gestation and was found to have persistently mildly elevated blood pressure (> 140/90 mm Hg), and oxygen saturation (SpO_2) of 90%, which was improved to 94% with 3 L of oxygen supplement via nasal cannula. She denied shortness of breath, fatigue, headache, epigastric pain, or any other symptoms of preeclampsia with severe features. Physical exam was positive for brisk deep tendon reflux. She had a urine protein/creatinine ratio of 6.68 mg/mg and a platelet count of 115,000/µL on presentation. Her blood counts and the comprehensive metabolic panel were otherwise not significant. Both fetuses had reactive NST and BPP 8/8. UAD of twin A was normal. However, the umbilical arterial systolic/diastolic ratio of twin B was 9.94 with intermittent absent umbilical arterial diastolic flow. The plan was to proceed to a primary cesarean section after the betamethasone course.

After the first dose of betamethasone, a primary cesarean section was performed due to preterm labor and malpresentation. During her recovery, persistent hypoxia on room air was noted. Magnesium intravenous infusion was started for suspected preeclampsia with severe features. Chest X-ray showed cardiomegaly, bilateral lung hyperinflation, biapical fibrobullous lung changes, and increased interstitial markings. Further computed tomography angiogram (CTA) revealed multifocal bilateral pulmonary arteriovenous malformations (PAVMs) and evidence of pulmonary hypertension. Vital signs during prenatal visits were carefully reviewed. Her SpO_2 was found to have been at 90-94% since her initial prenatal visit at 10 weeks gestation. Magnesium was held for low suspicion of preeclampsia with severe features and a high risk of respiratory complications of magnesium toxicity.

Upon pulmonologist evaluation, the patient denied a his-

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tory of frequent nose bleeding or related family history. A physical exam was significant for finger clubbing. No telangiectasia was found. An echocardiogram with saline contrast revealed right ventricular and left atrial dilation, a consequence of pulmonary hypertension with right to left shunt resulting from chronic hypoxia due to multiple PAVM. The patient was transferred to another center for pulmonary artery embolization on postoperative day 3.

During her hospital course, she required a high flow of 45 - 60 L of oxygen supplement with nitrogen oxide (NO) to keep SpO_2 above 92%. Pulmonary artery embolization was performed twice. A transesophageal echocardiogram showed no patent foramen ovale. The patient was weaned off NO and could keep her SpO_2 above 88% with 1 L of oxygen by nasal cannula while walking. She was discharged in post-cesarean section week 3 with home oxygen supplementation.

The genetic testing showed a heterozygotic ENG gene (c.1646G>A, p.Cys549Tyr), a likely pathogenic ENG variant supportive of HHT. The further workup with head and neck CTA, and hepatic ultrasound were normal. At the 5-week follow-up, CTA showed significantly decreased prominence of the previously dominant medial right lower lobe PAVM. Her SpO_2 was above 92% on room air.

Discussion

HHT, also known as Osler-Weber-Rendu syndrome, is a rare autosomal dominant disease with a prevalence of approximately 1 in 2,300 to 1 in 39,000 people among different European populations [1]. Several gene mutations have been linked to HHT. The majority is associated with ENG (endoglin, 39-59%) and ACVRL1 (ALK1, 25-57%) mutations. Less commonly, HHT is related to MADH4 and GDF2 mutations [4]. In the described patient, an ENG mutation was identified.

HHT is clinically diagnosed using the Curacao criteria, which include recurrent epistaxis, telangiectasia, family history, and visceral arteriovenous malformations. The diagnosis is definite if three criteria are present and possible in patients who only meet two criteria [5]. The most common clinical manifestations of HHT are epistaxis (90-95%) and telangiectasis (95%). Of the patients with HHT, 15-50% present with PAVM and 1-5% have pulmonary hypertension [4]. Genetic testing is also confirmatory on asymptomatic or highly suspicious patients who do not meet the criteria. In fact, according to Anderson et al [6], one-quarter of adult patients with PAVMs and genetically confirmed HHT did not meet clinical diagnostic criteria for HHT. Conversely, the majority of PAVMs are associated with HHT, which is believed to be genetically related (58% with mutations in ENG versus 18% with mutations in ACVRL1) [7, 8]. In this patient, the only criterion she met was the PAVM. The physiological changes during pregnancy masked the manifestation of worsening right to left shunt from PAVM, which also posed an additional challenge to the diagnosis.

The ethnic and demographic distribution of HHT is wide. The conditions are especially prevalent in the Netherlands Antilles [9]. Only a few clinical trials were conducted on the Chinese population [10, 11]. Different from data collected in Western society and inconsistent with the findings in this patient, studies on the Chinese population noted that mutations on the ACVRL1, compared to ENG, are more prevalent. According to Yusuf et al [12], Asians are at a 2.3-fold increased risk of PAVMs compared with White patients.

The symptoms of HHT tend to be worse due to the increased cardiac output as pregnancies progress, among which worsening epistaxis (17-31%) is the most commonly reported symptom. On the other hand, pregnancies with severe HHT complications are rare [2, 3]. These complications, according to previous retrospective studies [2, 3, 13, 14], which include hemothorax, hemoptysis, hypoxia, cerebrovascular attack, and heart failure, are hugely related to PAVM. Undiagnosed HHT without preconceptional counsel might lead to poorer outcomes [2]. In this patient, the exaggerated maternal physiological change for twin gestation results in not only maternal deterioration but also placental insufficiency. Similar to a case reported by Worda et al [15], a transient worsening oxygen desaturation was observed in this patient. In this case, NO was given with high-flow oxygen to maintain SpO_2 for several days. This could be explained by the fluid overload from the fluid shift back to the intravascular space.

The care of patients with HHT is often multidisciplinary, and the managements are usually based on patients' phenotypes [16]. PAVMs are usually treated with coil embolization. During pregnancies, however, the treatment recommendations remained unclear [2, 14, 16, 17]. Some of the studies argue that the treatment of asymptomatic patients is not associated with improved outcomes. Hammill et al [16] suggest treatment during the second trimester if necessary.

In conclusion, undiagnosed HHT during pregnancy is a rare situation that might lead to adverse outcomes. The physiological changes during gestation might mask the symptoms of significant PAVM. The geographic and ethnic distribution is wide. Care providers should keep this potentially life-threatening disease in the list of differential diagnoses when the clinical presentation is ambiguous.

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Conflict of Interest

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Informed Consent

The patient's informed consent for the publication of this re-

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Author Contributions

Jessica Hao-Chen Wu, MD: manuscript writing, literature review; , Edward Charles Lampley Jr., MD: maternal-fetal medicine care, supervising faculty, manuscript review and finalization.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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