Case Report

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Congenital Disseminated Pyogenic Granuloma: A Case With Numerous Mucocutaneous and Visceral Lesions

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Abstract

Congenital disseminated pyogenic granuloma (CDPG) is characterized by eruptive disseminated or localized lesions, which may arise spontaneously or secondary to predisposing factors. Even rarer is the occurrence of CDPG with numerous lesions affecting variable organs, which develop during the fetal period. This report describes the case of a 32-week-old fetus presenting with severe hydrocephalus and vascular intracranial and right lung masses on magnetic resonance imaging. Preterm labor occurred at the 32nd week due to preterm premature rupture of membranes, and the newborn died due to cardiac dysfunction within 2 hours postpartum. The subsequent autopsy revealed multiple violaceous to dark red papules, nodules, pedunculated and un-pedunculated mucocutaneous masses, as well as two brain lesions, a lung lesion, a thoracic wall intramuscular mass, and a pyloric mass. Microscopic examination and immunohistochemical evaluation for glucose transporter 1 (GLUT1) confirmed the diagnosis of CDPG. CDPG represents a rare condition with an elusive etiology and limited reports in the literature. Differential diagnosis from multifocal infantile hemangioma, based on GLUT1 negativity of CDPG, is imperative due to differing clinical course and treatment modalities. This report underscores a severe case of CDPG characterized by preterm labor and demise shortly after delivery, notable for its extensive involvement across multiple organs, including the brain, lung, intestine, musculoskeletal system, mucosal, and numerous cutaneous sites.

Keywords: Pyogenic Granuloma; Congenital; Hemangioma

Introduction

Various benign and malignant conditions manifest with similar skin either at birth or within weeks after birth. The macroscopic characteristics of these lesions, including color (eg, reddish, violaceous, pinkish, bluish), appearance (eg, macular, nodular, sessile, pedunculated), integrity (eg, intact, ulcerated, crusted), consistency (eg, firmness, softness), distribution (eg, cutaneous, mucosal, and visceral), and associated signs and symptoms, serve as primary indicators for accurate diagnosis and management. However, histologic evaluation is often necessary in certain situations to establish a definite diagnosis. Pyogenic granuloma (PG), also known as lobular capillary hemangioma, presents one such scenario. The classic presentation typically involves a solitary mucocutaneous lesion on the face or extremities, which gradually develops over weeks, primarily in children and occasionally in infants. Several predisposing factors, including inflammation, trauma, medication, and irritation, have been proposed. According to the last revision (2018) of the International Society for the Study of Vascular Anomalies classification for vascular anomalies, PG is categorized as a benign vascular tumor.[1]

A rare variant of PG is eruptive disseminated or localized lesions, either spontaneously or secondary to predisposing factors, such as pregnancy, infection-induced irritation, heat trauma, or inflammatory skin conditions.[2] An even rarer form of this lesion, reported in a few case reports, is congenital disseminated PG (CDPG).[3] This condition can be similar to more common lesions, especially infantile hemangioma, necessitating differentiation due to its distinct course. Furthermore, considering the potential for visceral involvement, it may lead to permanent side effects and even fatalities due to thrombosis or hemorrhage in vital organs such as the brain or lungs.[4]

In this report, we present a severe case of CDPG with concomitant multiple large skin lesions, mucosal lesions, as well as several visceral, musculoskeletal, and brain lesions.

Case presentation

A 29-year-old primigravida was referred for fetal magnetic resonance imaging (MRI) at 30 weeks of gestation following the detection of marked bilateral hydrocephalus and a midline echogenic intracranial mass adjacent to the cerebellopontine

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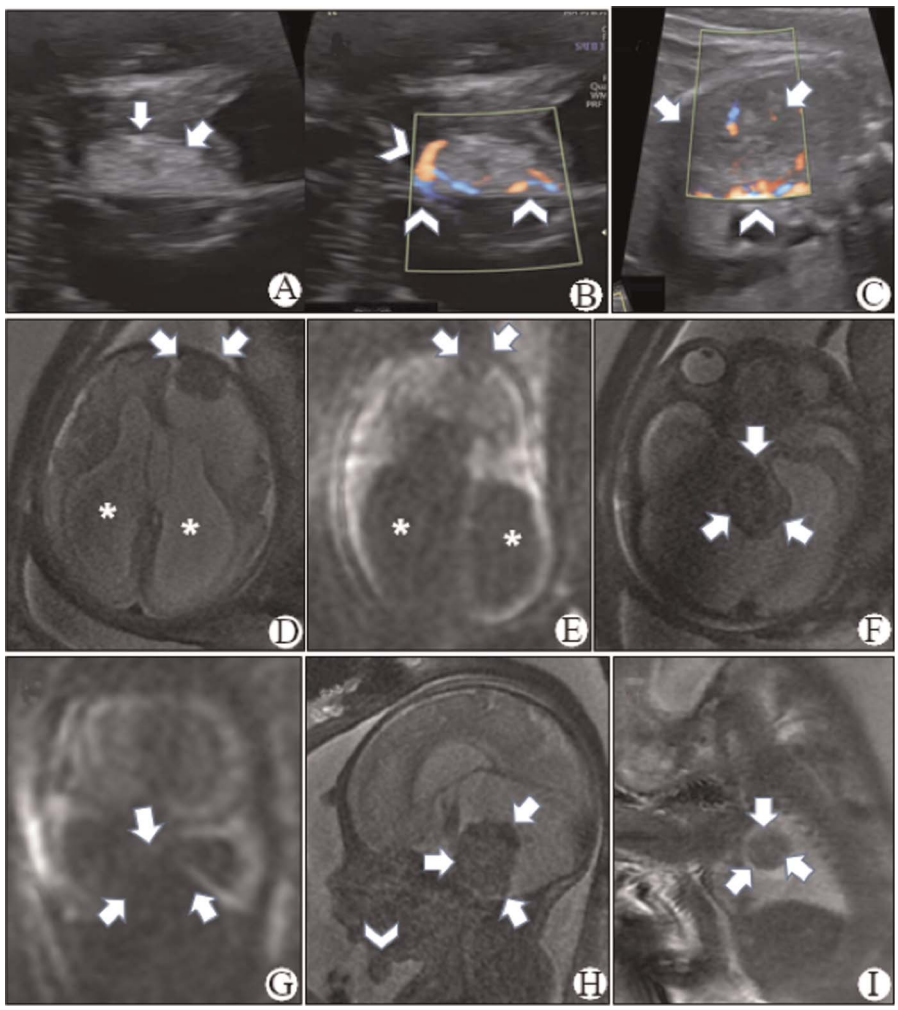

Figure 1. Diffuse hemangiomatosis in a 30-week fetus. A&B Abdominal transverse scan showing a hyperechoic mass (arrows in A) in the posterior fossa, with hypervascularity shown on color Doppler (arrowheads in B). C Color Doppler image of the fetus' right lung upper lobe showing blood flow (arrowhead) within the mass (arrows). D&E Axial fetal MRI indicating a cortical hemangioma on right frontal lobe (arrows in D), with no restriction observed on DWI sequence (arrows in E). Hydrocephalus and significant parenchymal edema are also noted (asterisks in D and E). F&G Axial fetal MRI displaying a right cerebellar hemangioma (arrows in F), without restriction on DWI sequence (arrows in G). H Sagittal fetal MRI showing a right cerebellar hemangioma (arrows) compressing the fourth ventricle and causing hydrocephalus. A mass is visible on the chin (arrowhead), initially unnoticed but later observed during postmortem examination. I Fetal MRI of the thoracic region showing a hemangioma of the right lung upper lobe with peripheral edema (arrows). DWI: Diffusion-weighted imaging; MRI: Magnetic resonance imaging.

angle (CPA) during a routine second-trimester scan. The personal, familial, and medical histories of the unrelated parents were unremarkable.

During simultaneous sonography, homogenous echogenic masses with internal vascularity were observed (Figs. 1A–C). Differential diagnoses such as metastatic lesions such as lung blastoma with metastasis to the brain, cerebral primitive neuroectodermal tumors with metastasis to the lung, or masses of unknown origin were considered based on the signal characteristics of the lesions on MRI, edematous changes surrounding the lesions, and the presence of multiple vascular masses.

Fetal MRI revealed three solid masses with low signal intensity on T1-weighted images and low to iso signal intensity on T2-weighted images. Two solid masses were intracranial, including a 22.7 × 16-mm mass at the cortex of the right frontal lobe with peripheral edema (Figs. 1D, E) and a 30.4 × 23.1-mm mass at the right CPA, exerting compression on the fourth ventricle, resulting in marked hydrocephalus and dilatation of the aqueduct (Figs. 1F–H). Another solid mass was also observed in the upper lobe of the right lung, measuring approximately 23.5 × 21.4 mm (Fig. 1I). No lesions exhibited obvious restriction on diffusion-weighted imaging.

Preterm labor occurred at 32 weeks of gestation due to preterm premature rupture of membranes, resulting in the vaginal delivery of a male baby weighing 2406 g (98^{th} percentile) (large for gestational age) with a head circumference of 37.5 cm (99^{th} percentile). The baby had an Apgar score of 0 and 2 at 1 and 5 minutes, respectively, and died 2 hours after birth due to poor cardiac function.

Autopsy examination revealed an overweight fetus with macrocephaly and hydrocephaly, characterized by the

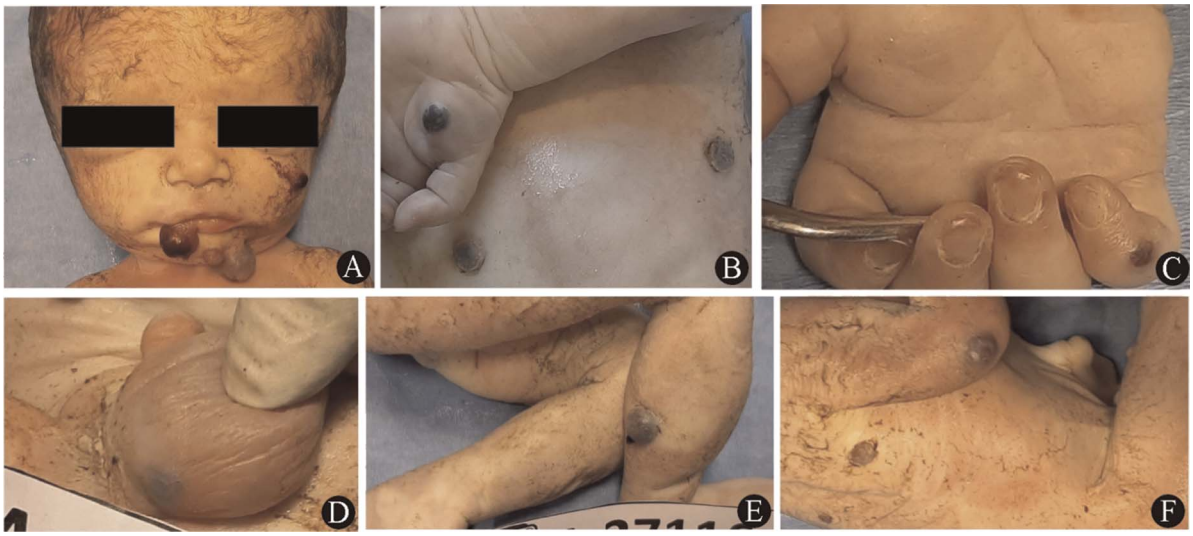

Figure 2. Clinical presentation of cutaneous lesions. A Pedunculated and nodular lesions with erosive hemorrhagic surface concentrated around the mouth. B Nodular lesions on the trunk and palm. C Macular lesion on the fifth finger. D Papular lesion on the scrotum. E Nodular lesion on the lower leg. F Nodular lesions on the right elbow and back.

dilation of the third and lateral ventricles and the aqueduct of Sylvius. Multiple mucocutaneous and internal organ lesions were identified as follows:

Skin

Twenty maculopapular to pedunculated masses with violaceous dark appearance in small lesions to dark red fragile hemorrhagic surface on large lesions were observed. The largest lesions, measuring up to 2.7 cm in diameter, were located on the face area as pedunculated fragile erosive masses around the mouth. These lesions were distributed throughout the body, including the fingers, palm, foot, forearm, leg, scrotum, abdomen, thorax, back, face, and scalp (Figs. 2A–F).

Mucosa

A large violaceous nodule was observed on the right buccal area (Fig. 3A).

Musculoskeletal system

An intramuscular mass was located at the back of the left thoracic cavity between the sixth and seventh ribs (Fig. 3B).

Brain

Two well-defined dark red soft masses were identified, including a lesion on the surface of the right parietal lobe adjacent to the occipital lobe, measuring 2.7 × 2.5 cm in

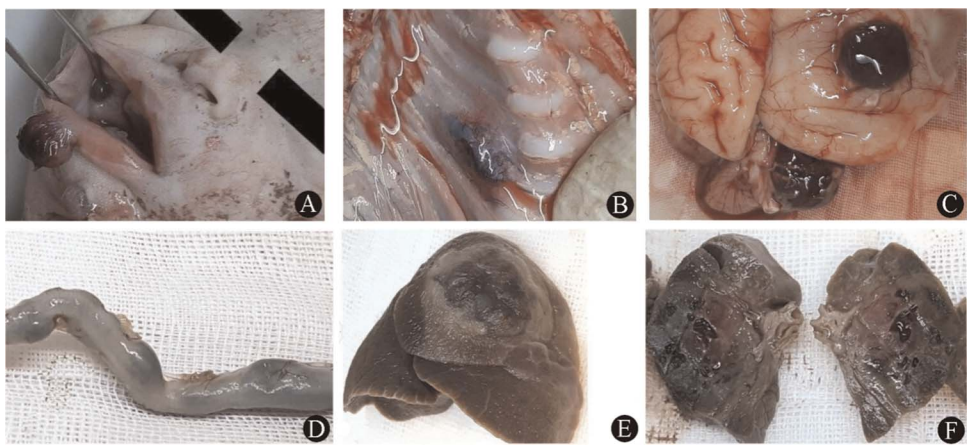

Figure 3. Clinical manifestations of lesions. A Intraoral mucosal lesion observed as a dark red nodule on right buccal area. B Intercostal lesion located between the 6th and 7th right ribs. C Brain lesions present on the surface of the right parietal lobe and right cerebellopontine angle and over the right cerebellar lobe. D Multiple intramural small violaceous lesions observed in the intestinal wall. E&F Masses detected in the upper lobe of the right lung showing a solid cystic and hemorrhagic appearance in cross section.

diameter, and a lesion at the CPA and over the right cerebellar lobe, measuring 2.8 × 2.5 × 2 cm in dimension. These masses were confined to the arachnoid space with no macroscopic invasion of the underlying brain tissue. Due to pressure from the CPA mass on the brain stem and mechanical obstruction, dilation of the aqueduct of Sylvius and the third and lateral ventricles were noted (Fig. 3C).

Intestine

Multiple intramural small violaceous lesions were observed in the duodenum, jejunum, and colon, along with a large intramural lesion in the pyloric canal (Fig. 3D).

Lung

A mass was observed in the upper lobe of the right lung, measuring 2.5 × 2.2 × 1.9 cm, with a fairly well-defined appearance. Upon sectioning, it was found to be solid cystic and hemorrhagic with a soft consistency (Figs. 3E&F).

Microscopic examination revealed vascular lesions with variable histology, predominantly exhibiting a lobular appearance composed of numerous capillaries, occasional large cavernous spaces filled with blood, and areas showing a retiform appearance lined by prominent endothelial cells. Larger lesions exhibited more diverse histological features, including areas of hemorrhagic cystic degeneration. Small skin lesions demonstrated a more regular lobular pattern, whereas larger lesions extended into subcutaneous fatty tissue, resulting in obscured lobularity with large vascular spaces and hemorrhage. The overlying skin was elevated with a peripheral collar and surface erosion in large lesions. Brain lesions showed variable histology, with a predominant retiform appearance. Endothelial cells, particularly in areas with atypical architecture and in visceral lesions, appeared moderately enlarged, with round to elongated nuclei and fine chromatin (Figs. 4A-F).

The pyloric canal lesion demonstrated a fairly infiltrative pattern, primarily located in the serosa and between the muscular layers, with extension into the submucosa. It consisted of dilated capillaries with a retiform appearance (Fig. 5A). The immunohistochemistry showed no glucose transporter 1 (GLUT1) expression in endothelial cells of the lesions (Fig. 5B). Structurally and histologically, all other organs and placenta were normal.

Based on histologic appearance and immunohistochemistry (IHC) findings, CDPG was diagnosed. Array comparative genomic hybridization was also conducted, revealing no aneuploidy and no genomic imbalance exceeding 1.0 Mb.

Whole exome sequencing was performed, identifying a heterozygous missense variant chr7:100420201C > T; c.500G > A (p. Gly167Glu) in the *EPHB4* gene. Confirmation of this variant was conducted via conventional Sanger sequencing in the patient and his parents, revealing the heterozygous state in the fetus and the mother. Consequently, this variant does not segregate with the disease in this family.

Discussion

Disseminated congenital/neonatal vascular lesions present rare disorders with similar clinical manifestations, necessitating accurate differentiation due to distinct treatments and potential outcomes. The spectrum of differential diagnosis encompasses multifocal infantile hemangiomas (MIHs), diffuse neonatal hemangiomatosis, cutaneovisceral angiomatosis with thrombocytopenia, capillary malformation/arteriovenous malformation (CM-AVM), and multiple venous malformations. Distinguishing CDPG from MIH poses a particular challenge due to the critical implications associated with CDPG, including brain and other internal organ hemorrhage. Additionally, CDPG does not respond to conventional MIH treatments involving propranolol and corticosteroids.

MIH typically manifests with numerous skin lesions with similar appearances; however, CDPG presents with more pronounced surface friability and hemorrhage. Although visceral involvement may occur in MIH, it predominantly affects the liver. Conversely, brain involvement is more prevalent in CDPG, often resulting in hemorrhagic complications. Microscopically, the lobular capillary appearance is identical in both conditions, making differentiation based on histology challenging. Two key distinguishing factors are GLUT1 negativity in CDPG and its congenital presentation if diagnosed accurately.[5]

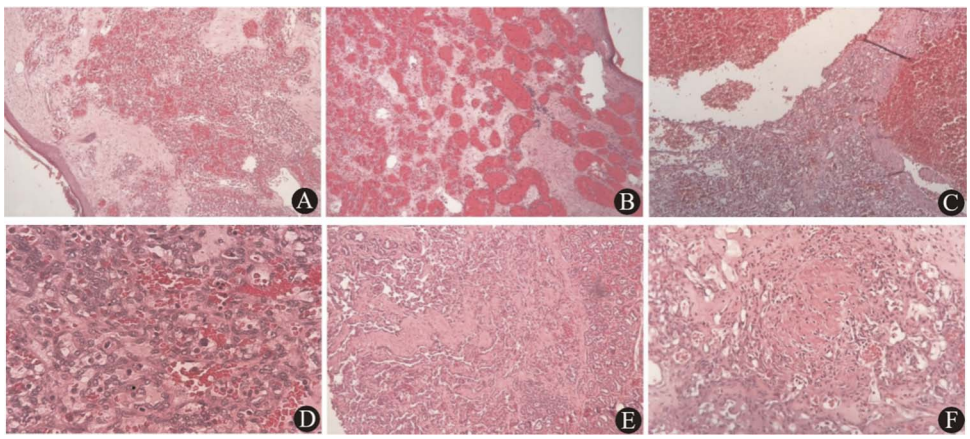

Figure 4. Vascular lesion variations (H&E staining). A Skin lesions exhibiting with small vessels arranged in a lobular pattern (H&E, ×200). B Skin lesions showing with dilated congested vessels of various sizes (H&E, ×200). C Brain lesion characterized by large cavernous spaces and hemorrhage (H&E, ×200). D Regions with a more solid appearance (H&E, ×400). E Lung lesion showing a retiform vascular appearance (H&E, × 200). F A locus indicating old thrombosis (H&E, × 400). H&E: Hematoxylin and eosin.

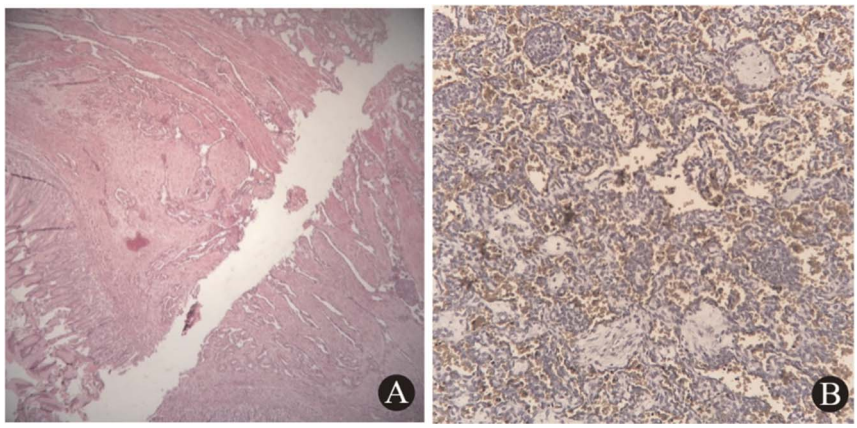

Figure 5. Pyloric canal lesion pathology images. A Lesion in the pyloric canal lesion showing an infiltrative pattern mainly located in serosa and between muscular layers, with extension into the submucosa (H&E, ×200). B Absence of GLUT1 expression in endothelial cells of the lesion. GLUT1: Glucose transporter 1; H&E: Hematoxylin and eosin.

Prior to 2000, the IHC marker of GLUT1 was not accessible. It is possible that some cases of MIH might be misinterpreted due to the absence of GLUT1 or the pathologist's unfamiliarity with this rare condition and its characteristic diagnostic features. Rothe *et al.*[6] reported the first case of numerous friable angiomatous skin lesions in 1991. Initially, they likened these to disseminated PGs, but ultimately favored a diagnosis of neonatal hemangiomatosis, as the diagnosis of MIH had not yet been established at that time.

GLUT1, a protein involved in glucose transportation, is expressed in microvascular endothelium and serves as a useful marker for distinguishing vascular tumors, particularly PG, from infantile hemangioma. Studies have consistently shown negative staining for GLUT1 in various types of PGs, including CDPG.[4] However, GLUT1 expression can be observed in other vascular lesions such as AVM and some isolated congenital hemangioma.[4] Despite this, clinical presentation and histologic findings remain informative in these cases. The disseminated PG, which was accepted as a different entity by the GLUT1 negativity, is mostly recognized as eruptive lesions in young or adults after a trauma (mostly burning).[2,7]

The congenital form of disseminated PG is rare, with limited cases reported in the literature. Initially described by North *et al.*[8] in 2001, this entity involves both cutaneous and visceral tissues, with GLUT1 negativity distinguishing it from infantile hemangiomas. Subsequent reports by Uyama *et al.*[9] in 2008 and Browning *et al.*[7] in 2009 further elucidated the presentation and features of cutaneous CDPG.

Our case stands out for its severe presentation during fetal development, ultimately leading to preterm labor and fetal loss. Detection of hydrocephaly on sonography, confirmed by MRI revealing intracranial masses, prompted further investigation. Postmortem examination showed a multiorgan phenomenon with the involvement of skin, mucosa, musculoskeletal system, lung, brain, and intestinal tract with the special infiltrative feature in the pyloric canal. To the best of our knowledge, there is only one report (by Uyama *et al.*) with such extensive involvement as mentioned above.[9] Another considerable feature, in this case, is its histologic diversity with its classic lobular appearance in mucocutaneous lesions and more solid and retiform appearance in viscera. Its unique infiltrative feature in the pyloric canal is another remarkable finding.

Furthermore, the next-generation sequencing analysis, a procedure not previously conducted in analogous studies, identified a variant of uncertain significance within the *EPHB4* gene. The protein encoded by this gene binds to ephrin-B2 and plays an essential role in vascular development.[10] Despite examining this gene in the parents, we did not observe any discernible causal relationship. Nonetheless, this discovery may serve as a preliminary step toward elucidating the etiology of this congenital abnormality.

Conclusion

CDPG represents a rare condition that should be considered in cases of fetal and/or neonatal vascular lesions with the potential to affect multiple organs. In such instances, GLUT1 staining is imperative for confirming the diagnosis, as its presentation differs from that of other differential diagnoses and may entail severe morbidity or even mortality due to internal organ hemorrhage.

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Author Contributions

Siavash Ghaderi-Sohi: Pathology workup and writing of the manuscript; Behnaz Moradi: Radiology workup and writing of the manuscript; Mahboobeh Shirazi: Gynecology workup and gathering clinical data; Rahil Rahimi: Gathering data; Romina Ravanbakhsh: Performing cesarean section and gathering clinical data; Ariana Kariminejad: Molecular workup and gathering data; Elham Feizabad: Coordinator, methodology consultant, and submission of the manuscript.

Conflicts of Interest

None.

Data Availability

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

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