Fetoplacental Hydrops: A Case of Recurrent Fetal Hydrops and Review of the Literature

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ABSTRACT

Recurrent fetal hydrops is a severe condition with a generally poor prognosis. The causes of fetal hydrops are diverse and mainly classified as immunological or non-immunological, although genetic and metabolic factors contribute to the recurrent form. Maternal prognosis is also at risk due to the association of this condition with severe preeclampsia. For women with a history of pregnancy complicated by fetal hydrops, subsequent pregnancies require special monitoring to detect early ultrasound signs of recurrence. We report a case of recurrent hydrops fetalis, which represents the fourth episode. This case emphasizes the importance of etiological diagnosis, particularly genetic causes, to provide appropriate genetic counseling and prevent transmission to future generations.

Keywords: Etiologies; Genetics; Hydrops fetalis; Prognosis

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Introduction

Fetal hydrops are defined as the presence of at least two abnormal fetal fluid collections (1). The recurrence of this anomaly strongly suggests a genetic cause that affects the functioning of the lymphatic system or certain metabolic deficiencies (2). The mutated genes implicated in the pathogenesis of fetal hydrops are numerous. However, identifying these genes requires advanced diagnostic techniques, such as sequencing and microarray analysis, which are limited in developing countries. These genetic abnormalities lead to early and severe hydrops with consequences for fetal development, making them incompatible with life. This condition is described here in both prenatal and postnatal contexts.

Case report

K.G., a 29-year-old gravida 7, para 4, abortus 2 (G7 P4 A2), presented with a complex obstetric history. Her obstetric history included three pregnancies complicated by unexplained hydrops fetalis and two early spontaneous abortions. The patient's blood group was A negative, and indirect Coombs test (IDC) results were negative.

Comprehensive laboratory investigations were performed during the current pregnancy, including a thrombophilia panel, TORCH screen (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex virus), syphilis serology, and parvovirus B19 testing, all of which were negative. Genetic testing was not performed in previous pregnancies. Additionally, the patient and her husband were not consanguineous and did not have a family history of genetic disorders.

At 20 weeks of gestation, hydrops fetalis was detected during routine ultrasonography. Fetal ultrasound findings included ascites, skin edema, pleural effusion, and pericardial effusion (Figure 1A and 1B). Middle cerebral artery peak systolic velocity (MCA PSV) value was normal, 25 cm/s to assess for fetal anemia. An amniocentesis was not performed as

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the patient declined the procedure after being informed of its risks and benefits.

At 32 weeks, the patient presented with symptoms of threatened preterm labor. By this time, there was no evidence of maternal mirror syndrome. Given the poor fetal prognosis, multidisciplinary consultation was undertaken with neonatologists, and it was decided not to proceed with tocolysis or corticosteroid administration for fetal lung maturation. Instead, a fetal cardiac puncture for genetic karyotyping was planned post-delivery.

The patient delivered vaginally a female fetus weighing 3750 g (Figure 2). Apgar scores were 2, 1, and 1 at 1, 5, and 10 minutes, respectively. The infant passed away 10 minutes after birth. Postmortem fetal cardiac puncture was performed, yielding only yellow, citrine-colored effusion. Genetic analysis was attempted, but the results were incomplete.

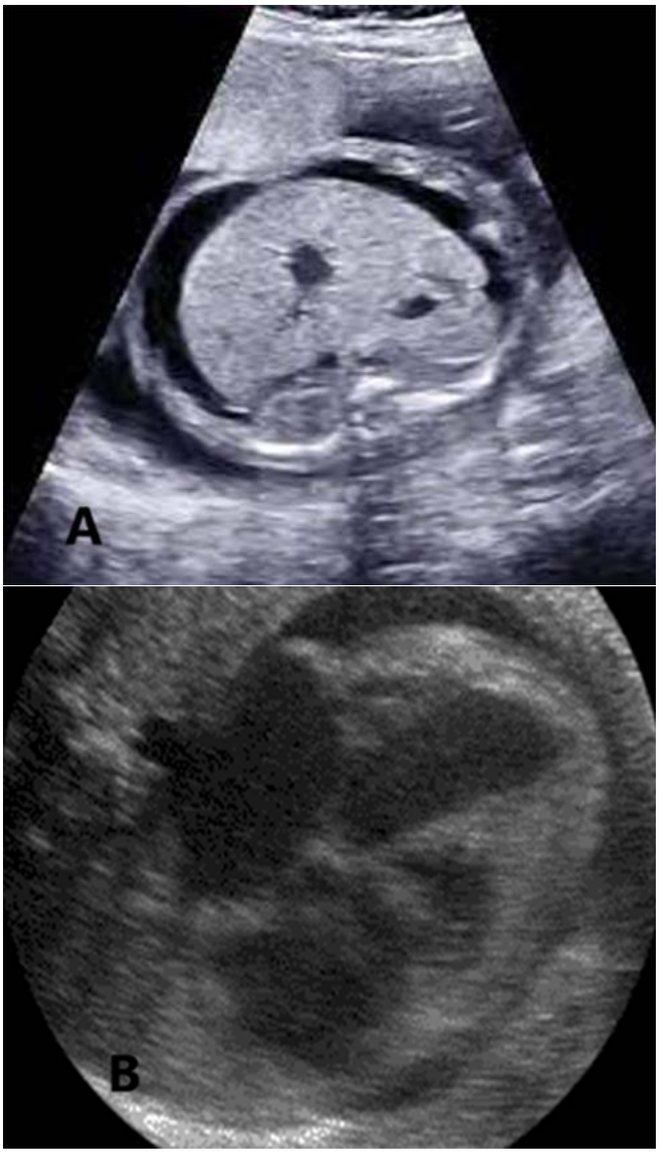

Figure 1A: *Fetal Hydrothorax, 1B: Fetal Pericardial effusion*

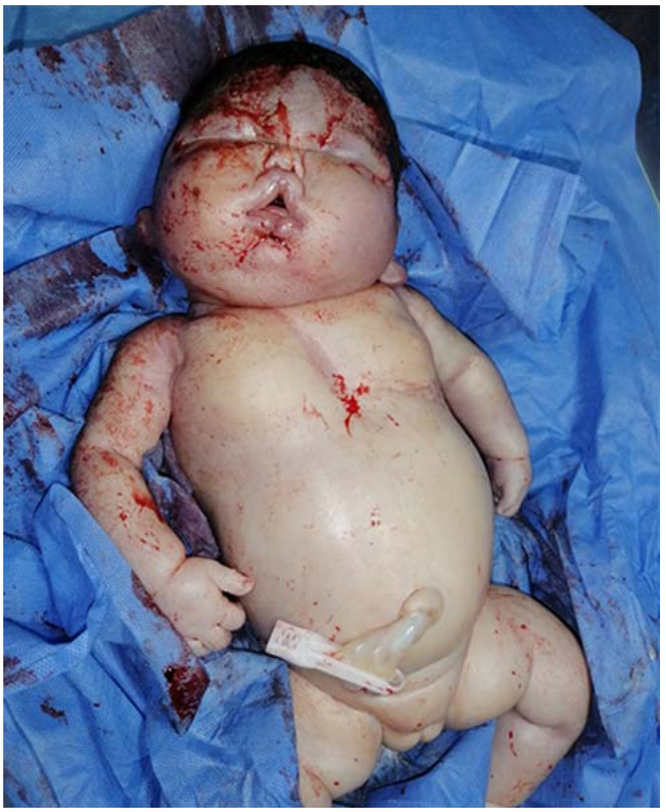

Figure 2: *Neonate with Hydrops Fetalis*

Discussion

Fetal hydrops is a rare pathology. In 10% of cases, the cause is immunological (3). Maternal-fetal rhesus incompatibility is responsible for the passage of maternal antibodies to the fetus and the destruction of its red blood cells, leading to severe fetal anemia, heart failure, and consequently, hydrops fetalis (4). If immunological origin is suspected, a positive indirect Coombs test in the mother makes the diagnosis. However, the association between rhesus immunization and hydrops fetalis is regressing with the advent of anti-D (1).

The majority of cases of hydrops fetalis are non-immunological (3). The most frequent etiology is cardiovascular anomalies (1). These pathologies may be related to a structural abnormality of the heart, arrhythmia, cardiac tumor, cardiomyopathy, or vascular anomaly (2,5). Chromosomal origins are dominated by trisomies 13, 18, and 21, Turner 45 X syndrome, and triploidies. Other causes include hematological pathologies such as myelodysplasias and hemoglobinopathies, mainly alpha-thalassemia (6).

Urinary, digestive, and especially thoracic fetal malformations have been incriminated in the genesis of fetal hydrops (7,8). Infections during pregnancy, by viruses such as HPV and CMV, herpes HSV type 2 (9), parasites such as toxoplasmosis, or bacteria such as syphilis, can damage the endothelium of fetal vessels, leading to myocarditis or severe anemia (9).

The origin of fetal hydrops can also be placental, such as a

chorioangioma or a vascular aneurysm (1). A fetal tumor can cause fetal hydrops, including lymphangioma, hemangioma, teratoma, or neuroblastoma (1). Genetic and metabolic causes of fetoplacental hydrops reported in the literature account for 2 to 3% of the etiologies of fetoplacental hydrops (3). The investigation of these abnormalities is based on karyotype analysis, FISH, and microarray analysis.

In the karyotype, one may find uniparental disomy of chromosome 16 (5), trisomy 21, 18, or 13, Turner syndrome 45 X, or triploidy. In FISH studies, the PIEZO1 variant can be investigated through exome sequencing in the presence of lymphatic dysplasia (10), as well as the hemizygous mutation of the FOXP3 gene (IPEX syndrome) (11). These two abnormalities can be responsible for recurrent fetal hydrops. The RASA1 mutation causes associated arteriovenous and lymphatic malformations, while the CCBE1 mutation is implicated in lymphangiectasia syndrome (12).

If the cause of fetal hydrops is not identified, an autopsy is recommended to search for alterations in the structure and function of the lymphatic system in the fetus (11). This involves immunohistochemical analysis, including CD31: an adhesion molecule for endothelial cells of lymphatic and blood vessels; CD34: expressed by embryonic cells of blood vessels; CD2-40 (podoplanin): a selective marker of endothelium, specifically the lymphatic endothelium; SMA (smooth muscle actin) to identify myofibroblasts and smooth muscle cells in the intima and media of lymphatic vessels; and anti-LYVE-1 antibodies, which target lymphatic endothelium (13).

The prognostic factors mainly include the etiology, the response to treatment if a rescue intervention is feasible, a gestational age of less than 20 weeks, and the timing of delivery (1-3). Early hydramnios is associated with a very high mortality rate.

Preterm delivery is justified only if there is a compelling obstetric indication, particularly in cases of mirror syndrome, defined as the association of severe preeclampsia with fetal hydrops (1,3).

Antenatal management is based on two main steps: identifying the etiology and performing in-utero transfusions. Postnatal management involves invasive ventilatory support, inotropic medications, and transfusions (3,4).

Conclusion

This case highlights the importance of an etiological diagnosis of hydrops fetalis, particularly genetic, to provide appropriate genetic counseling and prevent transmission to future generations.

Declarations

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: KB and MM raised the presented idea. KB, CC, and SG designed the study. MM conducted the analyses. KB and DT developed the first draft of the manuscript. All authors contributed to the writing of the paper, and have read and approved the final manuscript. RF designed the study and critically revised the manuscript. All authors read and approved the final manuscript.

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