Rare Discordant Genetic and Structural Anomaly in Monochorionic Twins – A Challenging Approach

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Section 2 - Answer

Case Description

A primigravidae was referred at 13 weeks of gestation due to a diamniotic monochorionic pregnancy [Figure 1] with discordant fetal malformation. Fetuses had a 17% crown–rump length (CRL) and a 75% nuchal translucency (NT) discordance. NT of twin A was normal and twin B had an NT of 7.1 mm (>99th centile), with septated structures, compatible with suspected nuchal cystic hygroma [Figures 2 and 3]. Combined first-trimester screening revealed an increased average risk for trisomy 21 (1:102) and a low risk for trisomies 18 and 13. At 16 weeks of gestation, the following anomalies were identified in twin B: occipital encephalocele, hydrocephalus, bilateral renal dysplasia, and oligohydramnios [Figures 4 and 5]. Both fetuses had female genitalia.

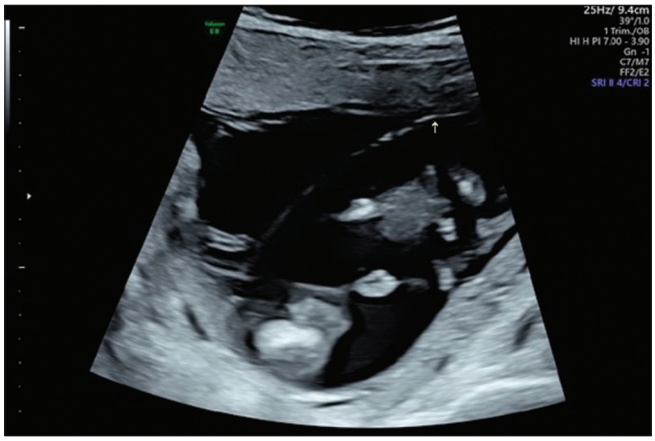

Figure 1: First-trimester ultrasound: Chorionicity determination at 12 weeks of gestation - T-sign (arrow) and a single placental mass are observed, compatible with monochorionic diamniotic twin pregnancy

Amniocentesis was performed at 17 weeks, sampling both amniotic sacs individually. Fetal karyotype, comparative genomic hybridization (CGH) array test, and next-generation sequencing (NGS) panel analysis for ciliopathies were requested. The couple also agreed on the genetic evaluation of both parents. After a discussion of the probable diagnosis and likely prognosis, the couple refused selective termination of the affected twin. In subsequent scans, the following anomalies were identified in twin B: dextrocardia [Figure 6], interventricular communication, bilateral postaxial polydactyly [Figures 7 and 8], hydrocephalus, and occipital encephalocele were progressively increasing in severity and ventriculomegaly was identified [Figures 9 and 10]. Fetal Dopplers were normal. At

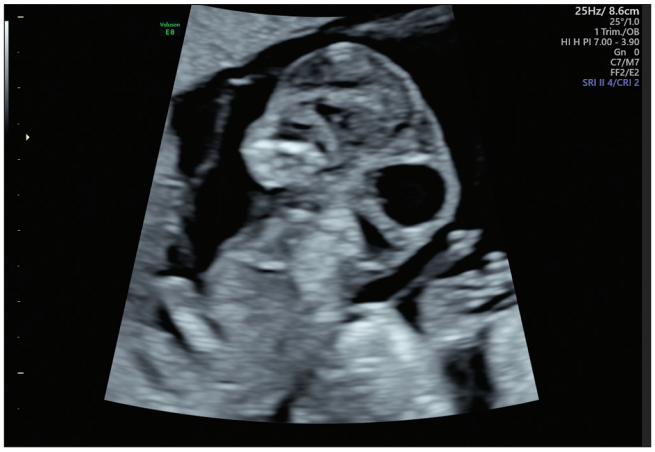

Figure 2: First-trimester ultrasound of twin B (mid-sagittal plane), showing nuchal translucency evaluation, which was above the 99th centile and showed septated internal structures, suggesting cystic hygroma

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Received: 23-06-2023 **Revised:** 31-08-2023 **Accepted:** 12-09-2023 **Available Online:** 26-02-2024

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jmut

DOI: 10.4103/jmu.jmu_76_23

How to cite this article: Coelho ML, Castro F, Soares E, Carvalho AP, Rocha J, Marinho C, *et al*. Rare discordant genetic and structural anomaly in monochorionic twins – A challenging approach. J Med Ultrasound 2025;33:88-91.

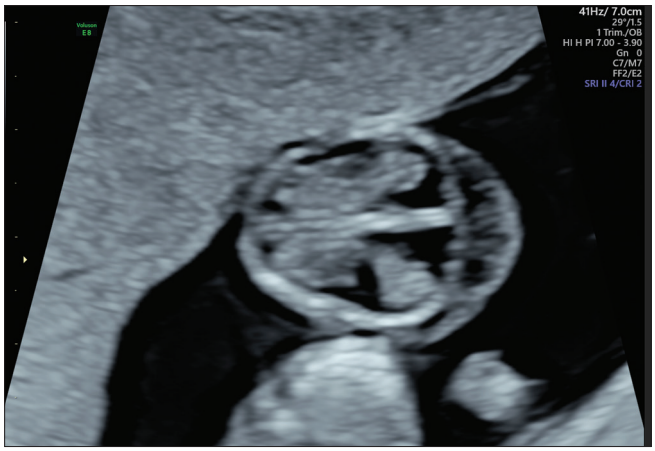

Figure 3: First-trimester ultrasound of twin B (axial plane), showing nuchal translucency evaluation, which was above the 99th centile and showed septated internal structures, suggesting cystic hygroma

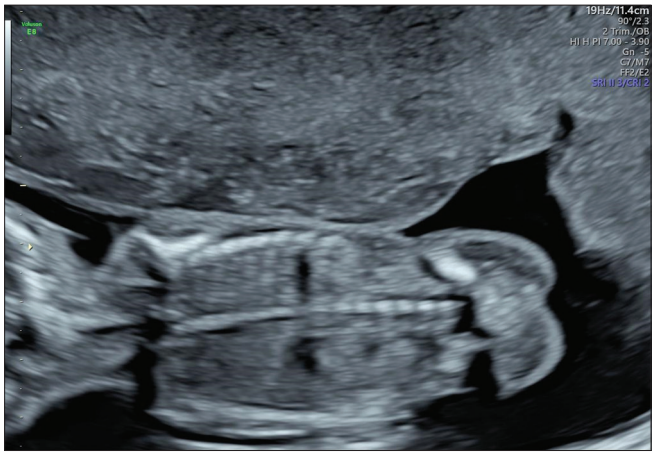

Figure 5: Second-trimester ultrasound of twin B (coronal plane), showing bilateral renal dysplasia

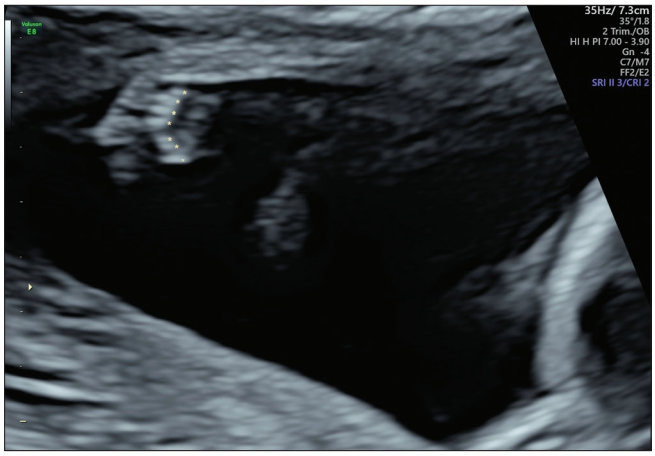

Figure 7: Second-trimester ultrasound of twin B, showing foot postaxial polydactyly

28 weeks of gestation, the patient was admitted due to preterm prelabor rupture of membranes. Fetal lung maturation and tocolysis were administered after excluding signs of maternal

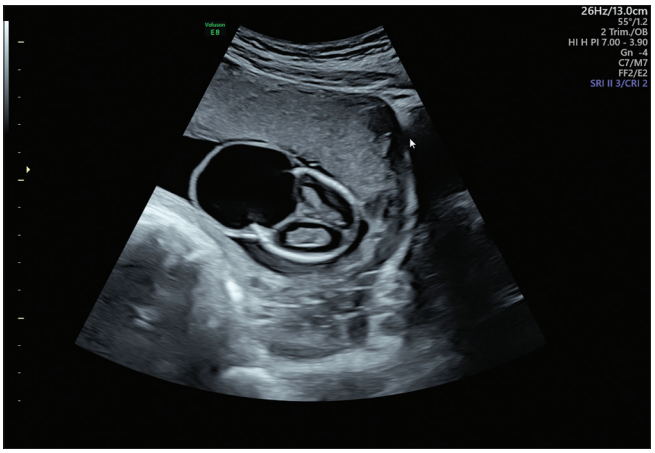

Figure 4: Second-trimester ultrasound of twin B (axial plane), showing occipital encephalocele and hydrocephalus

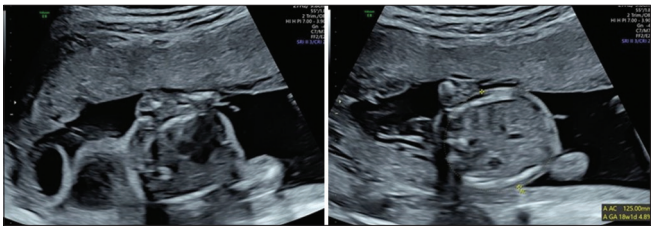

Figure 6: Second-trimester ultrasound showing dextrocardia in twin B

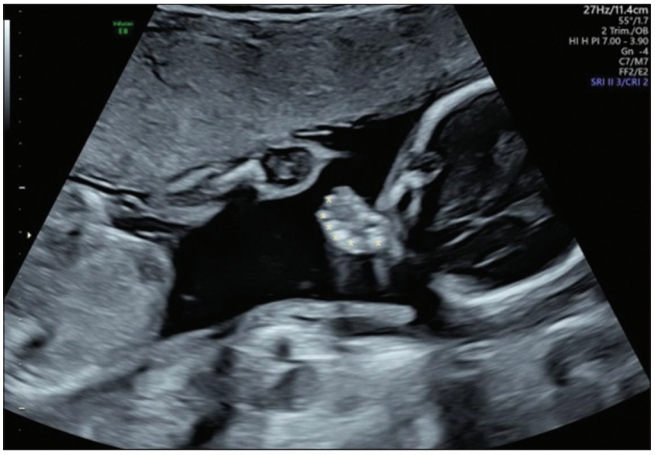

Figure 8: Second-trimester ultrasound of twin B, showing hand postaxial polydactyly

infection. Prophylactic antibiotic therapy was started, and after a 2-week latency period, the patient had an eutocic delivery at 30 weeks. The first newborn (twin A) weighed 1670 g and had the Apgar score of 6/8. The second newborn (twin B) weighed 1200 g and had the Apgar score of 1/1 and died moments after birth. Fetal autopsy was refused by the couple. At 6, 12, and 18 months of age, the surviving infant presented normal development.

Interpretation

Considering the significant discrepancy in the monochorionic

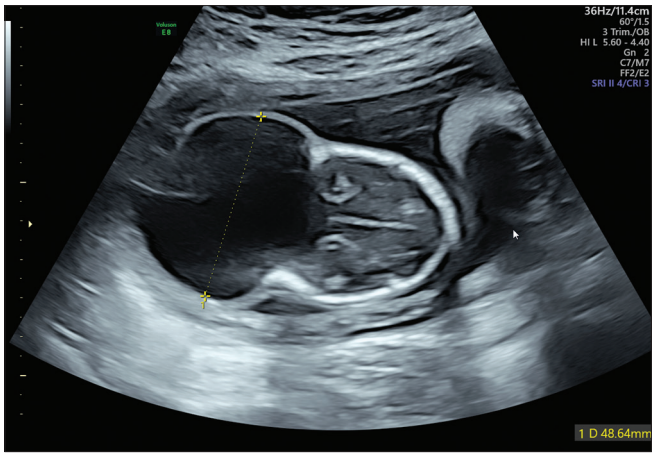

Figure 9: Second-trimester ultrasound (axial plane), showing progressively severe encephalocele at 19 weeks of gestation

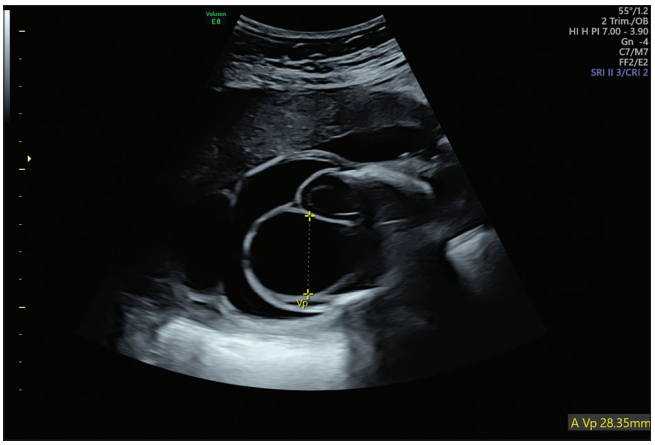

Figure 10: Second-trimester ultrasound (axial plane), showing posterior atrium measuring 28.35 mm at 25 weeks of gestation, compatible with ventriculomegaly

twin's CRL, NT, and amniotic fluid, it was not possible to exclude an early twin-to-twin transfusion syndrome (TTTS). Nevertheless, with CRL discordance ≥10% and NT discordance ≥20%, the risk of fetal abnormalities is approximately 25%, and detailed ultrasound assessment and genetic testing are indicated.[1]

The subsequent scans revealed discordant anomalies and, despite the persistent amniotic fluid discrepancy, fetal Dopplers remained normal, as well as twin A's development, making the diagnosis of TTTS less likely. Bilateral postaxial polydactyly diagnosis, along with previous findings of central nervous system (CNS) malformation and bilateral renal dysplasia, raised the suspicion of Meckel–Gruber Syndrome (MKS).

MKS is a rare genetically heterogeneous lethal disorder, classified as a ciliopathy, with an estimated incidence of 1:13000–1:400000 individuals.[2,3] Diagnostic criteria consist of at least two of three characteristic features: CNS anomalies (most commonly occipital encephalocele), renal dysplasia, and postaxial polydactyly.[3] Due to its phenotypic variability, additional anomalies are often present, such as cardiovascular defects and orofacial clefts.[2,3] Differential includes trisomy 13, Smith–Lemli–Opitz, Joubert, and Bardet–Biedl syndromes.[3]

Genetic mutations associated with MKS were identified in various genes, including MKS, TMEM, CEP, RPGRIP1L, and others.[3] Identification of genetic mutations not only confirms the diagnosis but also allows genetic counseling. This is particularly significant considering a recurrence rate of 25%.[2] Most prenatally detected cases are terminated due to the presence of severe anomalies, resulting in a reduced rate of live births, most of which die within a few hours or days after birth.[3] In this case, the NGS panel for ciliopathies revealed a pathogenic mutation in the CEP83 gene in the male parent. Despite the paternal inheritance, the twins, who theoretically share an identical genetic heritage, exhibited significantly discrepant phenotypic traits, which prompt inquiries into the true genetic origin of the identified malformation. Fetal karyotype was 46, XX and CGH-array showed no imbalances for both fetuses.

Discussion

Twin pregnancies will have a discordant anomaly in 1%–2% of cases, originating a challenging decision concerning its management.[1] Selective termination of the affected fetus may be associated with loss of the entire pregnancy, preterm delivery, and neurological injury.[1,4] Some studies suggest that there is no significant difference in the live-birth rate of the healthy fetuses between selective feticide and expectant management.[4] Thus, in the presence of a serious and lethal malformation, selective termination is controversial.

The reported clinical case posed a significant challenge, as it involved a monochorionic twin pregnancy with discordant anomalies, with one of the fetuses exhibiting a nonviable syndrome, and the diagnosis of a severe lethal anomaly with a high recurrence rate was established. It also highlighted the importance of prenatal ultrasound and genetic testing for both twins in pregnancies with theoretically genetically identical twins, as it provided information about the inheritance pattern of MKS, risks of recurrence in future pregnancies, and options available for subsequent pregnancies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent form. In that form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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