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Prenatal diagnosis of twins with thanatophoric dysplasia type I and Down syndrome: a case report

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We present a case of spontaneous dichorionic diamniotic twins, each affected by thanatophoric dysplasia type I and Down syndrome. Non-invasive prenatal screening revealed an increased level of chromosome 21 DNA. Ultrasound showed that twin A had short long bones and a bowed humerus, whereas twin B appeared phenotypically normal. Amniocentesis of twin A sent for quantitative fluorescent-polymerase chain reaction (QF-PCR), chromosome microarray, and sequence analysis of the fibroblast growth factor receptor 3 gene (*FGFR3*) identified a heterozygous variant in exon 7 of *FGFR3*, suggestive of autosomal dominant thanatophoric dysplasia type I (OMIM 187600). Amniocentesis of twin B sent for QF-PCR revealed trisomy 21, likely caused by meiotic nondisjunction, with normal chromosomes 13 and 18; karyotyping showed 47,XY,+21, suggestive of Down syndrome. At 22 weeks and 2 days of gestation, termination of pregnancy for both twins was performed.

Keywords: Down syndrome; Prenatal diagnosis; Thanatophoric dysplasia

Case presentation

In December 2024, a 41-year-old Chinese woman with a natural pregnancy presented for prenatal diagnosis after a positive non-invasive prenatal screening (NIPS). The couple had no family history of congenital or hereditary abnormalities. The woman had undergone two surgical terminations of unwanted pregnancies and had no live births. At 11 weeks and 6 days of gestation, ultrasound showed dichorionic diamniotic twins. At 12 weeks, NIPS using safeT21express showed a total fetal fraction of 13.8%, with a borderline increase in DNA from chromosome 21, suggestive of trisomy 21. The possibility of one affected fetus or fetal mosaicism could not be excluded. Invasive diagnostic testing by amniocentesis for karyotyping was recommended to confirm the findings.

At 18 weeks and 2 days of gestation, ultrasound showed two viable fetuses with estimated fetal weights appropriate for gestational age. Twin A had short long bones, a bowed humerus, and macrocephaly (Figure 1). The femur length measured 2.38 cm (16th centile), and the humerus length measured 1.56 cm (below the 1st centile). The biparietal diameter was 4.76 cm and the head circumference was 16.87 cm (both above the 99th centile[1]). Twin B had normal parameters: the biparietal diameter was 4.26 cm (74th centile), the femur length was 2.35 cm (14th centile), the abdominal circumference was 13.01 cm (57th centile), and the head circumference was 15.59 cm (82nd centile). The estimated fetal weight was 215.9 g, which was appropriate for gestational age. A uterine fibroid was also noted.

At 19 weeks and 2 days of gestation, a morphology scan showed that twin A had short and bowed long bones, with all parameters below the 1st centile. The thoracic circumference measured 10.94 cm (7th centile). The femur length-to-abdominal circumference ratio was low at 0.143 (2.01/14.15), consistent with severe skeletal dysplasia. In twin B, the long bones appeared normal. No abnormal morphology was identified; however, the face and heart were not well visualised due to fetal position. Amniocentesis of both twins was performed without complications.

At 21 weeks of gestation, ultrasound showed that twin A had short and bowed long bones. The femur length measured 1.83 cm, and the humerus length measured 1.71 cm (both below the 1st centile). The thoracic circumference was 12.19 cm (5th centile). In twin B, the humerus measured 2.94 cm (2nd centile) and the femur length measured 3.0 cm (5th centile). The face and heart were re-examined and appeared normal.

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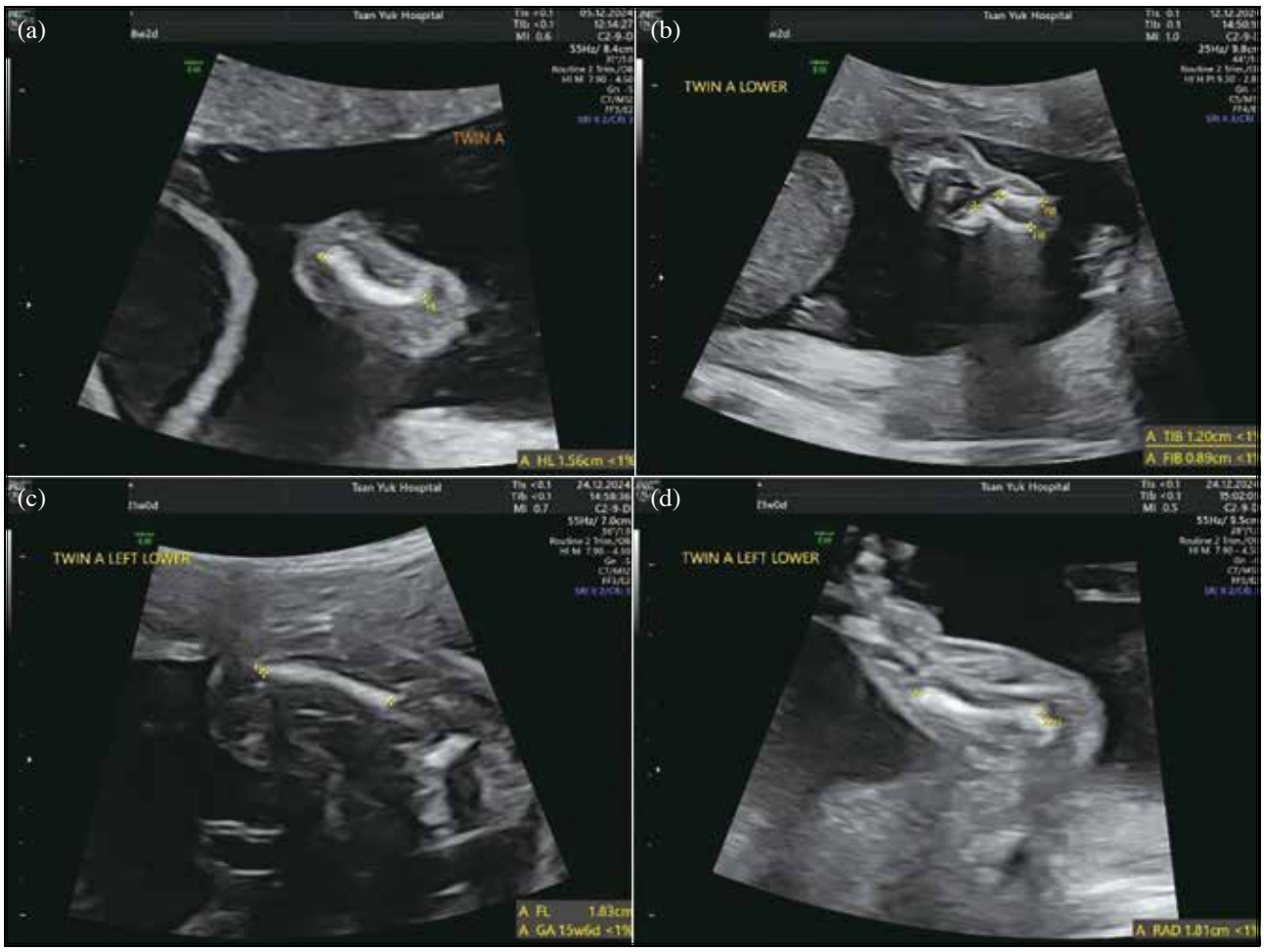

Figure 1. Ultrasonography of twin A showing (a) the humerus at 18 weeks and 2 days, (b) the tibia and fibula at 19 weeks and 2 days, (c) the femur at 21 weeks, and (d) the radius at 21 weeks.

Amniocentesis of twin A was sent for quantitative fluorescent-polymerase chain reaction (QF-PCR), chromosome microarray, and sequence analysis of the fibroblast growth factor receptor 3 gene (*FGFR3*). A heterozygous NM_000142.4:c.742C>T p.(Arg248Cys) variant in exon 7 of *FGFR3* was detected, suggestive of thanatophoric dysplasia (TD) type I (OMIM: 187600). The variant was considered pathogenic according to the American College of Medical Genetics and Genomics guidelines. The genetic findings were consistent with the phenotypic features of TD type I, an autosomal dominant disorder. Amniocentesis of twin B was sent for QF-PCR and revealed trisomy 21, likely caused by meiotic nondisjunction, with normal chromosomes 13 and 18. Karyotyping showed 47,XY,+21, suggestive of Down syndrome. The recurrence risk was low but would increase with maternal age.

Options of continuing the pregnancy or terminating the pregnancy for twin A or both twins were discussed. At 22 weeks and 2 days of gestation, the woman underwent termination of pregnancy for both twins.

Gross examination of twin A showed short and bowed limbs and a narrow thorax (Figure 2). A babygram showed markedly shortened, deformed, and bowed upper and lower limbs. The thoracic cage was narrow, and all vertebrae were markedly shortened. The skull was relatively large with frontal bossing. The overall findings were consistent with TD type I. Gross examination of twin B was unremarkable. A babygram showed that both upper and lower limbs were slightly short, without deformity or bowing. Vertebral pedicles were intact, and skull size was normal.

Discussion

TD is the most common lethal skeletal dysplasia[2]. Babies with TD usually die during the early neonatal period due to pulmonary hypoplasia leading to respiratory distress, although some survive into childhood[3]. Features of TD include marked rhizomelic limb shortening with skin redundancy, a narrow thorax with short ribs but normal trunk

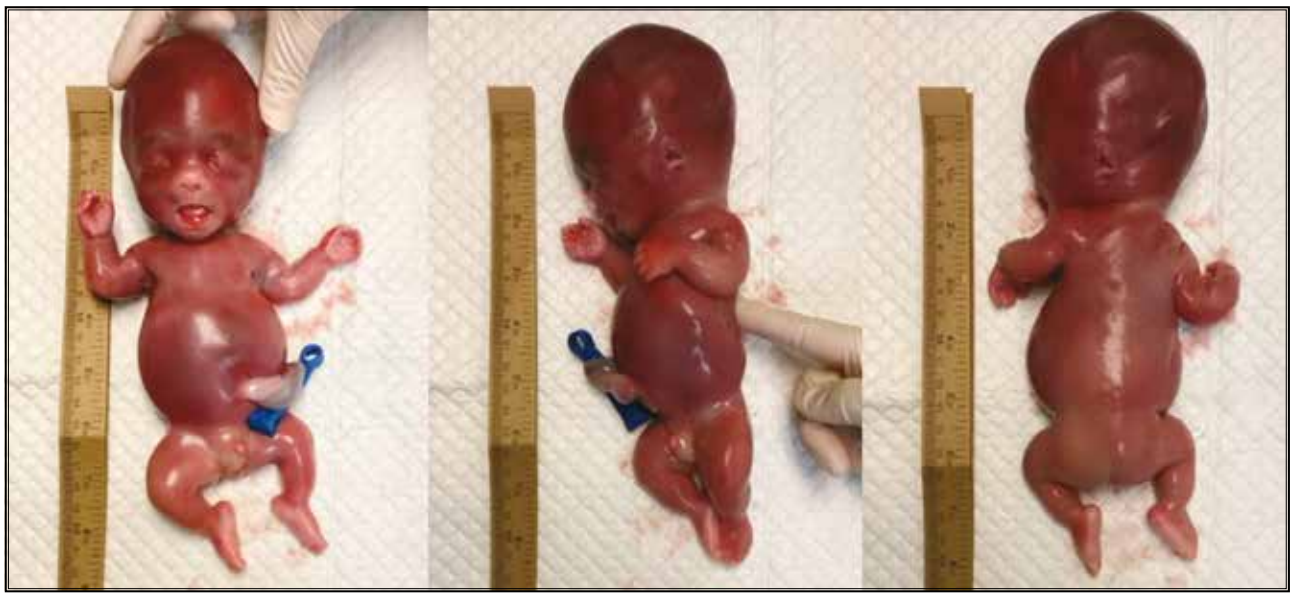

Figure 2. Gross examination of twin A showing short and bowed limbs and a narrow thorax.

length, flattened vertebral bodies, and macrocephaly with frontal bossing[4]. There are two major forms of TD, both caused by mutations in *FGFR3*. TD type I is characterised by curved femurs and variable craniosynostosis; the responsible mutations include p.Arg248Cys (55%), p.Tyr373Cys (24%), p.Ser249Cys (6%), and stop codon mutations (10%). TD type II is characterised by straight femurs and severe craniosynostosis, known as cloverleaf skull, and is associated with the p.Lys650Glu mutation[5].

Two-dimensional ultrasound is the primary imaging modality for prenatal diagnosis of TD type I[6]. Three-dimensional ultrasound can enhance visualisation of fetal structural abnormalities[7]. The most distinctive features of TD type I include shortening of the long bones (below the 5th centile), a narrow chest cavity with short ribs, bowed femurs, and platyspondyly[4]. Prenatal diagnosis of TD type I is based on ultrasound assessment and identification of a pathogenic or likely pathogenic variant in *FGFR3*, which should be confirmed by sequence analysis. If the phenotype is indistinguishable from other skeletal dysplasias, a multigene panel that includes *FGFR3* and other genes of interest can be used to identify the underlying genetic cause[8].

Our patient was initially referred for abnormal NIPS owing to increased chromosome 21. NIPS for trisomies 21, 13, and 18 has equivalent screening sensitivity and specificity in both twin and singleton pregnancies[9]. The American College of Medical Genetics and Genomics recommends NIPS over conventional trisomy screening in twin pregnancies[10]. Although NIPS is accurate in the detection of trisomies 21, 18, and 13, as well as sex chromosome aneuploidies, its performance in identifying rare autosomal trisomies and copy number variants is variable[9].

Next-generation sequencing panels to detect *FGFR3* mutations are available for pregnancies at risk of *FGFR3*-related skeletal dysplasia. Cases of NIPS for lethal skeletal dysplasia by targeted capture sequencing of maternal plasma have been reported[11]. Next-generation sequencing is accurate for detecting *de novo* and paternally inherited mutations in *FGFR3*-related skeletal dysplasia[12]. NIPS for *FGFR3*-related skeletal dysplasia is available in the United Kingdom for women carrying fetuses with suspected *FGFR3*-related skeletal dysplasia, for pregnancies at risk due to paternal *FGFR3*-related skeletal dysplasia, and for those with a previous pregnancy confirmed with *FGFR3*-related skeletal dysplasia. It can be performed after 8 weeks of gestation. It uses a next-generation sequencing panel and detects pathogenic variants of the *FGFR3* gene[13]. Given accurate sonographic phenotyping, the diagnostic yield of NIPS in fetuses with suspected *FGFR3*-related skeletal dysplasia can be maximised[14]. Although NIPS demonstrates high sensitivity and specificity for detecting *FGFR3* mutations, it is primarily used as a screening tool rather than a definitive diagnostic test[12]. A positive NIPS result typically warrants confirmation through invasive testing (amniocentesis or chorionic villus sampling)[15,16]. In patients exhibiting ultrasound abnormalities consistent with TD type I, the role of NIPS may be limited. The

primary diagnostic approach remains targeted ultrasound evaluation combined with invasive testing for molecular confirmation.

Conclusion

This case report highlights the rarity of discordant genetic abnormalities in dichorionic diamniotic twins and the role of prenatal diagnosis in identifying genetic conditions. The combination of ultrasound findings and genetic testing facilitates decision making.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, PWH was not involved in the peer review process. Other authors have no conflict of interest to disclose.

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Data availability

All data generated or analysed during the present study are available from the corresponding author upon reasonable request.

Ethics approval

The patient was treated in accordance with the tenets of the Declaration of Helsinki.

References

1. Liu F, Lu J, Kwan AHW, Yeung YK, et al. Consolidated and updated ultrasonographic fetal biometry and estimated fetal weight references for the Hong Kong Chinese population. Hong Kong Med J 2024;30:444-51. Crossref
2. Richards AJ, McNinch A, Martin H, et al. Stickler syndrome and the vitreous phenotype: mutations in COL2A1 and COL11A1. Hum Mutat 2010;31:E1461-71. Crossref
3. Baker KM, Olson DS, Harding CO, Pauli RM. Long-term survival in typical thanatophoric dysplasia type 1. Am J Med Genetics 1997;70:427-36. Crossref
4. Burgel PR, Paillasseur JL, Durieu I, et al. Multisystemic effects of elexacaftor-tezacaftor-ivacaftor in adults with cystic fibrosis and advanced lung disease. Ann Am Thorac Soc 2024;21:1053-64. Crossref
5. Hatzaki A, Sifakis S, Apostolopoulou D, et al. FGFR3 related skeletal dysplasias diagnosed prenatally by ultrasonography and molecular analysis: presentation of 17 cases. Am J Med Genet A 2011;155A:2426-35. Crossref
6. Schild RL, Hunt GH, Moore J, Davies H, Horwell DH. Antenatal sonographic diagnosis of thanatophoric dysplasia: a report of three cases and a review of the literature with special emphasis on the differential diagnosis. Ultrasound Obstet Gynecol 1996;8:62-7. Crossref
7. Chen CP, Chern SR, Shih JC, et al. Prenatal diagnosis and genetic analysis of type I and type II thanatophoric dysplasia. Prenat Diagn 2001;21:89-95. Crossref
8. MacCarrick G, Aradhya S, Bailey M, et al. Clinical utility of comprehensive gene panel testing for common and rare causes of skeletal dysplasia and other skeletal disorders: results from the largest cohort to date. Am J Med Genet A 2024;194:e63646. Crossref
9. Delezoide AL, Narcy F, Larroche JC. Cerebral midline developmental anomalies: spectrum and associated features. Genet Couns 1990;1:197-210.
10. Dungan JS, Klugman S, Darilek S, et al. Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2023;25:100336. Crossref
11. Dan S, Yuan Y, Wang Y, et al. Non-invasive prenatal diagnosis of lethal skeletal dysplasia by targeted capture sequencing of maternal plasma. PLoS One 2016;11:e0159355. Crossref
12. Chitty LS, Mason S, Barrett AN, et al. Non-invasive prenatal diagnosis of achondroplasia and thanatophoric dysplasia: next-generation sequencing allows for a safer, more accurate, and comprehensive approach. Prenat Diagn 2015;35:656-62. Crossref
13. Verhoef TI, Hill M, Drury S, et al. Non-invasive prenatal diagnosis (NIPD) for single gene disorders: cost analysis of NIPD and invasive testing pathways. Prenat Diagn 2016;36:636-42. Crossref
14. Mellis R, Chandler N, Jenkins L, Chitty LS. The role of sonographic phenotyping in delivering an efficient noninvasive prenatal diagnosis service for FGFR3-related skeletal dysplasias. Prenat Diagn 2020;40:785-91. Crossref
15. Gregg AR, Skotko BG, Benkendorf JL, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. Genet Med 2016;18:1056-65. Crossref
16. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal-Fetal Medicine. Screening for fetal chromosomal abnormalities: ACOG Practice Bulletin, Number 226. Obstet Gynecol 2020;136:e48-69. Crossref