Thanatophoric Dysplasia – Rare Fatal Skeletal Dysplasia Detected on Prenatal Ultrasound

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Abstract

Skeletal dysplasias form an assorted cluster of bone dysplasias that result in atypical and aberrant skeletal size and shape. The case discussed here was diagnosed as thanatophoric dysplasia during the second-trimester ultrasound examination and the medical termination of pregnancy was subsequently done. The fetus had shortening of the limbs (micromelia) with long bones (shaped like a telephone receiver), a small conical thorax, a protuberant abdomen, increased skin thickness with a cloverleaf skull, and macrocephaly. The relevant details and review of literature pertinent to the case are hereby discussed.

Keywords: Cloverleaf skull, micromelia, prenatal, thanatophoric dysplasia, ultrasound

Introduction

Thanatophoric dysplasia is one of the most common fatal congenital skeletal dysplasias having a prevalence of 1 in 20,000–50,000.[1-5] The initial description of thanatophoric dwarfism dates back to 1967 by MacDonald *et al*.[6] The present-day name of thanatophoric dysplasia was changed at the 2nd International Conference for Nomenclature of skeletal dysplasias back in 1977.[7] The condition is characterized by macrocephaly, platyspondyly, micromelia, and small conical thorax. It can be categorized into two subtypes: Types I (80%) and II (20%) with a considerable overlay of features in both subtypes. They can be distinguished based on the shape of the skull and the morphology of the femur. In Type I thanatophoric dysplasia, there is the presence of a short and curved femur seen in a telephone receiver-like configuration. In Type II thanatophoric dysplasia, the presence of a cloverleaf skull is the predominant morphology and there is an absence or reduced degree of shortening and bending of long bones as seen in Type I.[2] Cloverleaf skull in Type I thanatophoric dysplasia may or may not be present.[3]

The underlying cause for variable morphological presentations is gene alterations detected in the fibroblast growth factor receptor 3 (FGFR3) gene located on 4p16.3, with the most common mutations being Tyr373Cys, Arg248Cys, and Lys650Glu.[1] Fibroblast growth factors are related to cell growth and bind to the FGFR3 receptor resulting in the activation of the signal transduction pathway. This controls endochondral ossification by stopping cell division and commencement of cell differentiation and maturation. When mutations occur in the FGFR3 gene, it leads to the initiation of the receptor despite the absence of growth factors, consequently leading to uncharacteristic long-bone development.[2] Hence, the condition gets its typical features subsequent to disruption of the growth plates, presence of fibrous bands, and fibrous ossification.[8]

Case Report

A 25-year-old nonconsanguineously married woman presented for second-trimester targeted imaging for fetal anomalies ultrasound scan (TIFFA) at 23-week period of gestation as per her last menstrual period. The female had been married for 2 years with no history of previous abortions. The obstetric

Received: 04-03-2023 **Revised:** 09-05-2023 **Accepted:** 08-06-2023 **Available Online:** 02-09-2023

Access this article online

Quick Response Code:

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

DOI: 10.4103/jmu.jmu_20_23

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How to cite this article: Lahel RS, Kumar S, Mishra RK. Thanatophoric dysplasia – Rare fatal skeletal dysplasia detected on prenatal ultrasound. J Med Ultrasound 2024;32:341-4.

history of the patient was $G^1P^{0\ L0}A^0S^0$. Double marker maternal serum screening test to assess the risk of chromosomal abnormalities by evaluating free beta human chorionic gonadotrophin and pregnancy-associated plasma protein A was done early in pregnancy and was within normal limits. Nuchal translucency measured in the first-trimester scan was 1.4 mm (within the normal range). There was no positive history of pyrexia, skin rashes, bleeding per vaginum, any drug intake, or radiation exposure during this pregnancy. She was a nonalcoholic and nonsmoker with no drug addiction. There was no relevant past or family history of fetal congenital abnormalities, diabetes mellitus, hypertension, deranged thyroid profile, or infectious diseases such as tuberculosis.

On ultrasound, the biparietal diameter of the fetus was corresponding to 25 weeks of gestation whereas the long bones (femur and humerus) were very short and corresponded to 16–17 weeks of gestation. The fetus had a cloverleaf skull with macrocephaly and frontal bossing [Figures 1 and 2], shortening of the limbs (less than 3rd percentile) with long bones (shaped-like a telephone receiver) [Figures 3 and 4], small conical thorax, protuberant abdomen, and increased skin thickness [Figure 5]. A diagnosis of thanatophoric dysplasia was made and parents were counseled about the lethal condition. Subsequently, medical termination of pregnancy was done to abort the dysplastic fetus. On inspection [Figure 6], the fetus had a large head with frontal bossing, shortening of the neck, narrowing of the chest, protrusion of the abdomen, and shortening of limbs. The postabortion radiograph [Figure 7] showed short humeri, femora, forearm bones, tibiae, the presence of metaphyseal flaring, shortening of ribs, and narrowing of the thoracic cage. There was the presence of H-shaped platyspondyly in the vertebrae. Iliac bones had reduced height with increased horizontal width.

Discussion

A large proportion of fetuses with thanatophoric dysplasia decease *in utero* with the reason for death being respiratory insufficiency as an outcome of narrowing of the chest cavity and the presence of hypoplastic lungs. The other prominent cause is brain stem compression due to narrow foramen magnum, or it can be a combination of both these factors to varying extents.[2] The relevant differential diagnoses to be considered for thanatophoric dysplasia includes rhizomelic chondrodysplasia punctata (has characteristic stippling and punctuate calcification in cartilage), campomelic dwarfism (involves bowing of long bones with immature ossification), achondroplasia/achondrogenesis (the calvarium and vertebral bodies demonstrate demineralization of bones and shortening of trunk length), severe hypophosphatasia, and osteogenesis imperfecta (multiple bone fractures and generalized hypomineralization of bones).

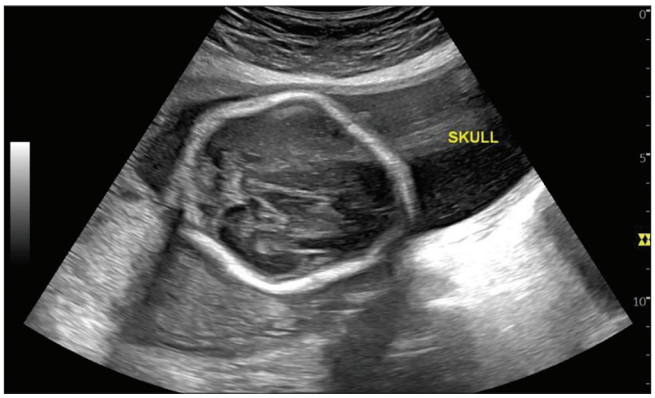

Figure 1: Cloverleaf skull

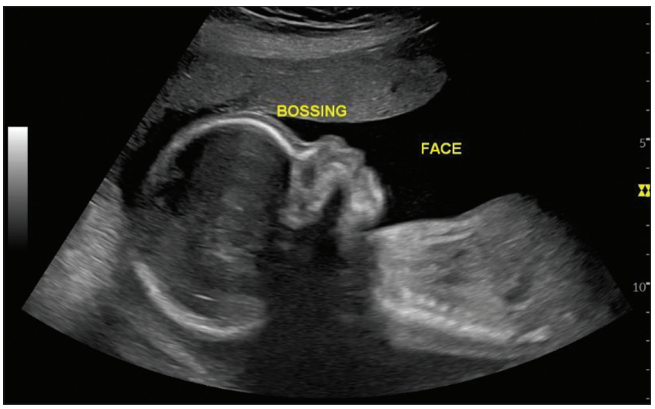

Figure 2: Frontal bossing

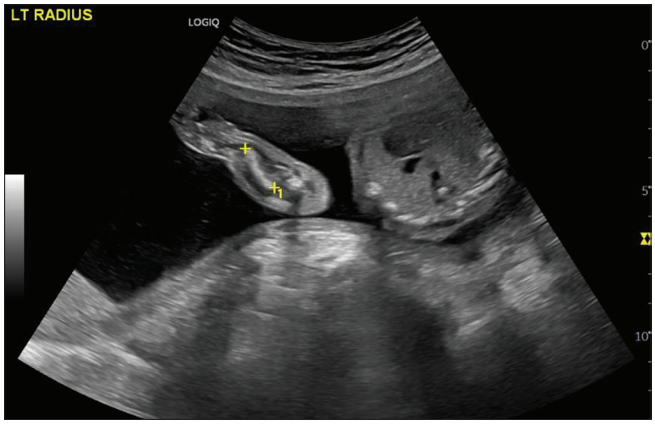

Figure 3: Shortened left radius with bowing

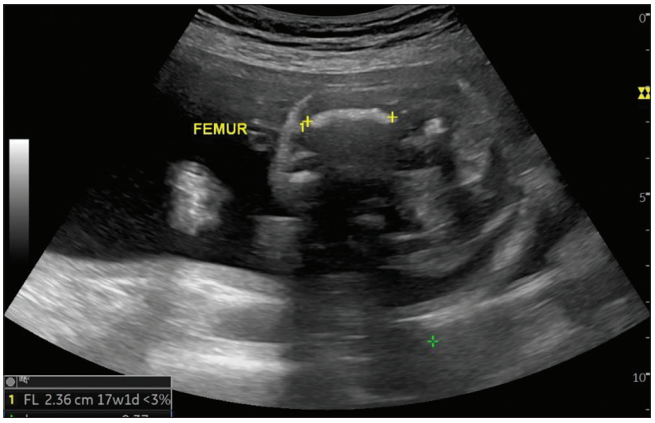

Figure 4: Shortened femur with bowing

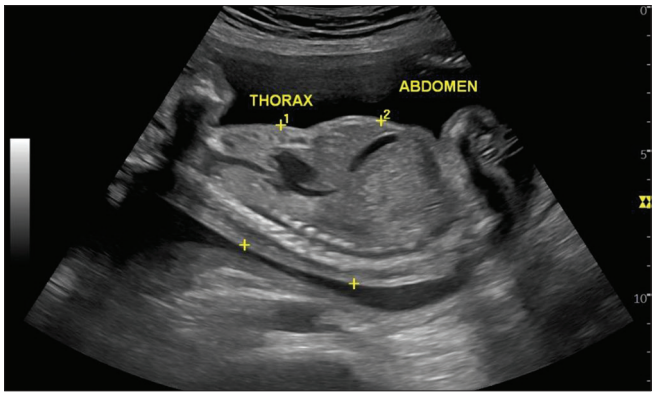

Figure 5: Small thoracic cavity with protuberant abdomen

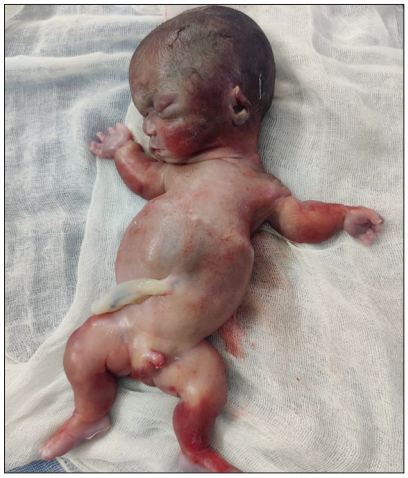

Figure 6: Postabortion fetus

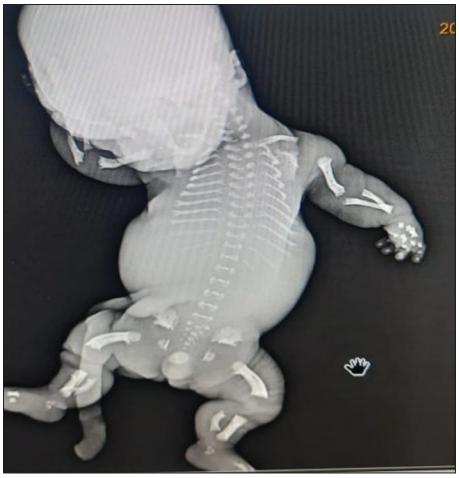

Figure 7: Postabortion radiograph of the fetus

The most common findings elucidated by Chitty *et al*. in a retrospective study of 42 cases included short limbs seen in 100% of cases, shortening of ribs and narrowing of chest described in 95% of cases, frontal bossing observed in 80%, bowing of the femora seen in 67% of the cases, presence of cloverleaf skull in 31%, shortening of fingers in 52%, and polyhydramnios in 31% of the cases.[1] Cloverleaf skull is characteristically seen on ultrasound. Its connotations with other skeletal anomalies such as Pfeiffer, Apert, and other craniosynostosis syndromes, as well as generalized bone dysplasias, are well established, and hence, the diagnosis "thanatophoric dysplasia with cloverleaf deformity" needs to be stringently used for only those sporadic cases of the cloverleaf skull that also demonstrates bone changes representative for the syndrome.[9] The sonographic criteria concerning the long bones include rhizomelic micromelia with associated bowing and the length of limbs being lesser than the 3rd percentile for the given gestational age.[10]

Skeletal dysplasia is considered to be fatal with the presence of a femur length (FL) –abdominal circumference (AC) ratio of <0.16.[4] In the present case, the FL/AC ratio was 0.12.

Further, definitive diagnosis as an adjunct to prenatal ultrasound findings can be done by either invasive testing or molecular analysis (obtaining fetal cells through chorionic villous sampling/amniocentesis) or by noninvasive prenatal diagnosis using cell-free fetal DNA removed from maternal blood to confirm the existence of mutation in FGFR3 gene.[1]

Conclusion

In the present case, the occurrence of a distinctive cloverleaf skull, macrocephaly with frontal bossing, shortened long bones with the telephone receiver-like presence of humerus and femur, shortening of the neck, platyspondyly, small conical thorax, protuberant abdomen, short stubby fingers, increased skin thickness, and dysmorphic facies clinched diagnosis in favor of Type I thanatophoric dysplasia.

As the condition is associated with lethality *in utero* or shortly after birth, it becomes clinically important to diagnose the dysplasia early during ultrasound scans to minimize the mental suffering to the parents of having to face the unfavorable outcome as a surprise at the end of the gestation period. Further, the couple needs to be reassured to relieve them of apprehensions regarding future pregnancies as the condition is sporadic with *de novo* mutations and the overall empirical risk of recurrence for this condition is assessed at a mere 2%.[3]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for the 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 identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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