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Prenatal Diagnosis and Management of Thanatophoric Dysplasia Type 1: A Case Report and Literature Review

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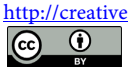

Abstract

Thanatophoric dysplasia (TD) is a rare and lethal skeletal disorder caused by fibroblast growth factor receptor 3 (FGFR3) gene mutations, leading to severe skeletal abnormalities and neonatal mortality. We report a prenatal diagnosis of TD Type 1 (TD1) in a 38-year-old gravida 6 para 3 with a history of two neonatal deaths, highlighting the importance of early detection and empathetic counseling. At 24 weeks of gestation, prenatal imaging revealed profound micromelia, curved femurs, and a narrow thoracic cavity, consistent with TD1. Despite the poor prognosis, the patient continued the pregnancy. At 34 weeks and 2 days, she delivered a severely malformed newborn who died shortly after birth due to respiratory failure secondary to pulmonary hypoplasia. Molecular confirmation was declined by the family. This case underscores the critical role of prenatal ultrasound in diagnosing TD1 early, enabling informed decision-making and compassionate counseling. It emphasizes the need for multidisciplinary support and clear communication when managing lethal fetal anomalies.

Subject Areas

Gynecology & Obstetrics

Keywords

Thanatophoric Dysplasia, FGFR3 Gene, Prenatal Diagnosis, Micromelia, Pulmonary Hypoplasia, Lethal Skeletal Dysplasia

1. Introduction

Thanatophoric dysplasia (TD) is an exceedingly rare and lethal skeletal dysplasia

caused by mutations in the fibroblast growth factor receptor 3 (FGFR3) gene, located on the short arm of chromosome 4. It is the most common form of lethal neonatal skeletal dysplasia, with an estimated incidence of 1 in 20,000 to 50,000 births [1]. The condition is characterized by severe skeletal abnormalities, including marked limb shortening (micromelia), a narrow thoracic cavity, and curved femurs, which lead to pulmonary hypoplasia and neonatal death [2]. Two distinct types of TD have been identified: Type 1 (TD1), characterized by curved femurs and a normal skull, and Type 2 (TD2), associated with straight femurs and a cloverleaf skull [3].

Prenatal diagnosis of TD is primarily based on ultrasound findings, which typically reveal shortened long bones, a narrow chest, and other skeletal anomalies. Early detection is crucial for providing accurate counseling to families and discussing management options, including the possibility of medical termination of pregnancy in cases of confirmed lethal anomalies [4]. Molecular genetic testing can confirm the diagnosis by identifying mutations in the FGFR3 gene, which plays a critical role in regulating bone growth [5].

We present a case of Thanatophoric Dysplasia Type 1 (TD1) diagnosed prenatally in a 38-year-old woman with a history of two neonatal deaths. This case highlights the importance of early prenatal imaging, the challenges of managing lethal fetal anomalies, and the need for compassionate counseling and multidisciplinary support for affected families.

2. Case Presentation

The reported case is that of a 38-year-old woman, G6P3, with no history of consanguinity or significant pathological background. She presented at 24 weeks of gestation for evaluation of suspected congenital malformations. The patient had no known family history of congenital anomalies, genetic disorders, or consanguinity. She denied exposure to teratogens, such as alcohol, tobacco, or medications, and had no history of diabetes or nutritional deficiencies. Her obstetric history included three living children delivered vaginally and two neonatal deaths, with the infants succumbing to asphyxia shortly after birth. No congenital malformations were noted in those cases.

The obstetrical ultrasound performed at 24 weeks of gestation revealed a single viable fetus in transverse presentation with normal amniotic fluid volume. The ultrasound also identified several morphological abnormalities, including marked shortening of the long bones "micromelia" (**Figure 1**), curved femurs (**Figure 2**), a narrow thoracic cavity and Mild retrognathia (**Figure 3**), however, there was no prominent frontal bossing nor cloverleaf skull appearance (**Figure 4**), spinal, cardiac, or cleft lip/palate abnormalities were observed. Overall, These collective findings are most consistent with a diagnosis of four-limb achondrodysplasia associated with mild retrognathia, in the absence of other facial dysmorphic features.

After detailed counseling regarding the condition and its prognosis, the patient decided to continue the pregnancy. She underwent rigorous prenatal monitoring

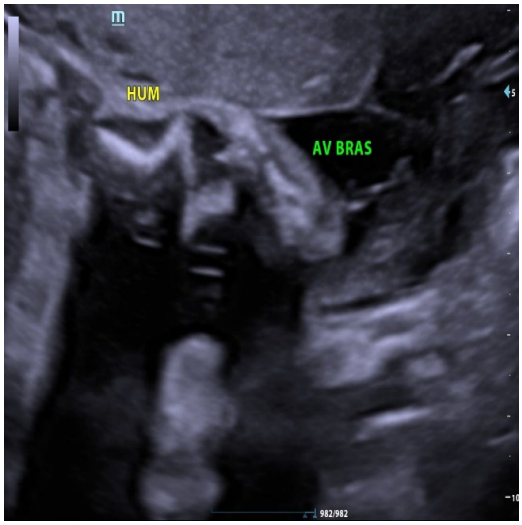

Figure 1. Sonographic appearance of a shortened upper limb.

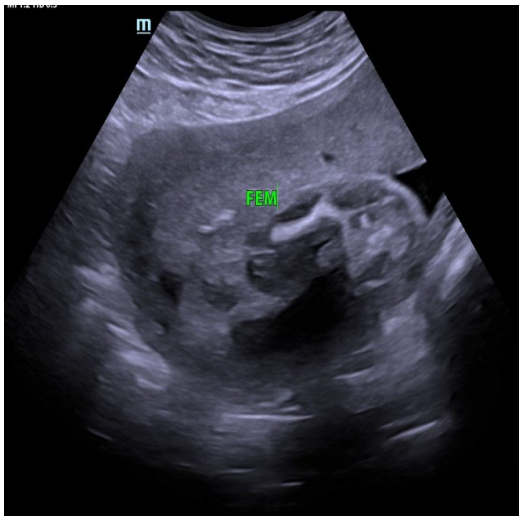

Figure 2. Short and curved femur.

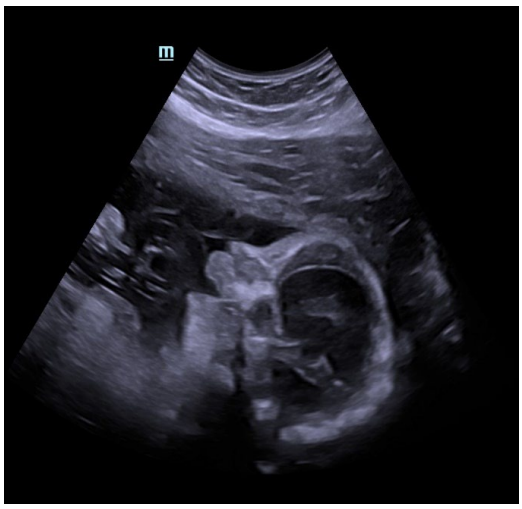

Figure 3. Retrognathism on ultrasound.

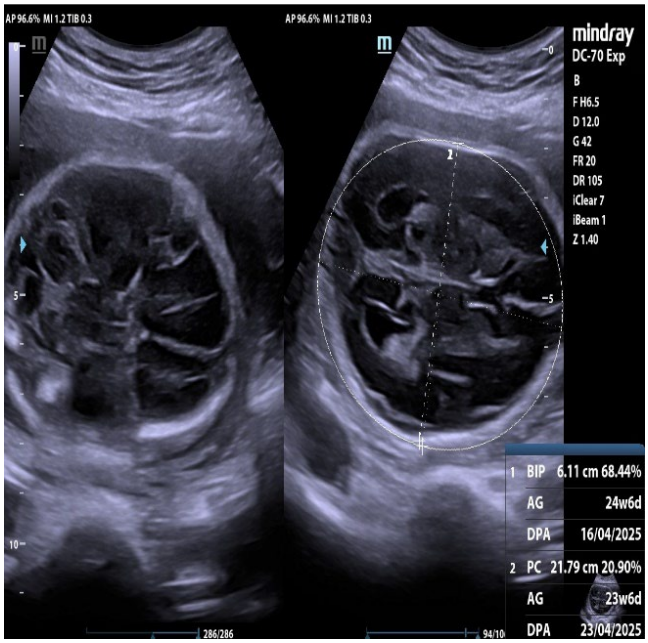

Figure 4. A normal skull.

throughout the remainder of her pregnancy. At 34 weeks and 2 days of gestation, she went into spontaneous labor and delivered a polymalformed newborn. The newborn exhibited severe micromelia, curved femurs with a "telephone receiver" appearance, a narrow thoracic cavity, platyspondyly (**Figure 6**), and square iliac bones. Craniofacial abnormalities included a prominent forehead, a flattened nose, and mild retrognathia. Visceral abnormalities included pulmonary hypoplasia and a protruding abdomen (**Figure 5**). Following the delivery, the diagnosis of Thanatophoric Dysplasia Type 1 (TD1) was confirmed. The newborn died shortly after birth due to respiratory failure secondary to pulmonary hypoplasia.

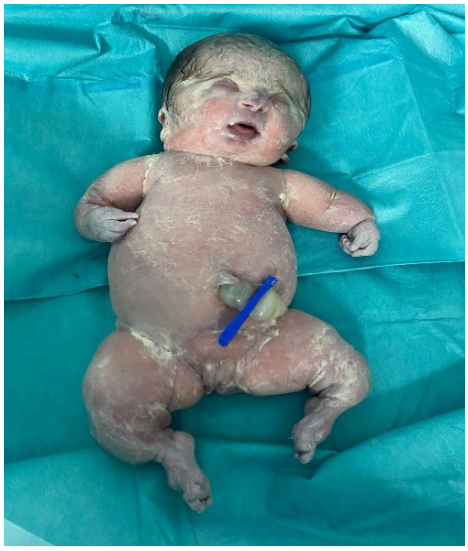

Figure 5. Thanatophoric Dwarfism Micromelia, Narrow Thoracic, protruding abdomen Cavity, Square Iliac Bones, Prominent Forehead, and Flattened Nose.

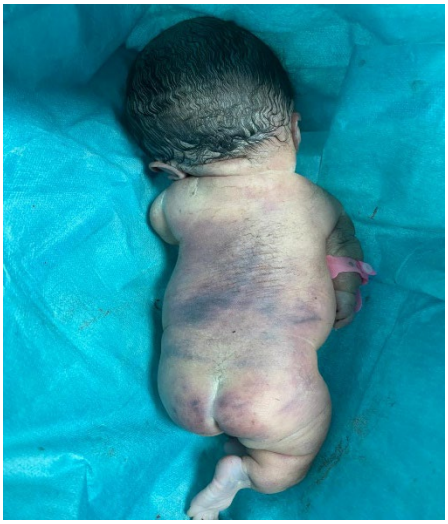

Figure 6. Platyspondyly.

Molecular biology, autopsy, and radiography of the fetus were not performed due to the family's refusal. This case underscores the importance of early prenatal imaging in diagnosing TD1 and the challenges of managing lethal fetal anomalies.

3. Discussion

Thanatophoric dysplasia (TD) is the most common lethal skeletal dysplasia, characterized by severe skeletal abnormalities and neonatal mortality due to pulmonary hypoplasia. The term "thanatophoric," meaning "death-bearing", reflects the devastating prognosis of this condition, which is caused by mutations in the FGFR3 gene located on chromosome 4. These mutations disrupt bone growth, leading to micromelia, curved femurs ("telephone receiver" appearance), and a narrow thoracic cavity [1] [2]. Although rare cases of survival into adulthood have been reported, they remain exceptional and are often associated with significant complications [3]. Our case of TD Type 1 (TD1) in a 38-year-old woman with a history of two neonatal deaths underscores the critical role of prenatal ultrasound in early diagnosis. At 24 weeks of gestation, characteristic findings such as micromelia, curved femurs, and a narrow thoracic cavity were identified, consistent with established diagnostic criteria [4] [5]. The absence of cranial or spinal anomalies further supported the diagnosis of TD1, distinguishing it from TD2, which is associated with a cloverleaf skull [5].

Prenatal diagnosis of thanatophoric dysplasia relies on well-established sonographic markers. First-trimester findings may include increased nuchal translucency (≥3.5 mm) and early-onset femoral shortening [6]. (Schramm *et al.*, 2009). Second-trimester pathognomonic features include severe micromelia (<5th percentile), femoral bowing angle (>40˚), (characteristic "telephone receiver" appearance), and narrow thorax, demonstrating 85% - 90% detection rates in experienced centers [7]. (Krakow *et al.*, 2009). Fetal MRI provides prognostic information through lung volumetry, with pulmonary volumes < 15% of gestational

age norms predicting lethal pulmonary hypoplasia [8] (Cassart *et al.*, 2011). While 3D ultrasound and molecular testing (FGFR3 analysis) offer complementary information, systematic ultrasound evaluation remains the diagnostic cornerstone. Current guidelines emphasize sequential assessment combining standardized sonographic evaluation, advanced imaging when indicated, and genetic confirmation (ISUOG Practice Guidelines, 2020).

The biparietal diameter-to-femur length (BPD/FL) ratio has emerged as a valuable sonographic marker for detecting TD, even in the first trimester. A BPD/FL ratio greater than 3.5 is highly suggestive of TD and warrants further investigation [9]. In our case, ultrasound findings were sufficient to establish a strong suspicion of TD1, although molecular confirmation was not pursued due to the family's refusal. This aligns with previous reports highlighting the reliability of prenatal ultrasound in diagnosing TD and enabling early counseling [10]. Early diagnosis is crucial, as it allows families to consider management options, including medical termination of pregnancy (MTP) in cases of confirmed lethal anomalies.

In our case report, although thanatophoric dysplasia is recognized as a lethal condition, several particular factors influenced the decision-making process: On one hand, the absence of typical facial features (no prominent frontal bossing or characteristic dysmorphism); On the other hand, the expressed will of both the patient and her spouse to continue the pregnancy despite having received thorough counseling about the poor prognosis [11] [12].

Following an in-depth multidisciplinary discussion incorporating medical, ethical, and psychosocial considerations, a shared decision was made not to pursue medical termination of pregnancy. This decision highlights the importance of patient-centered care and empathetic counseling, particularly for families with a history of neonatal loss.

The management of TD raises significant ethical and emotional dilemmas. In our case, the patient's decision was influenced by her previous experiences and her desire to have a living child. This underscores the need for comprehensive genetic counseling, which helps families understand the implications of the diagnosis and the likelihood of recurrence in future pregnancies [13] [14]. The FGFR3 gene mutation responsible for TD is typically sporadic, as seen in our case, where there was no family history of congenital anomalies or consanguinity [15]. This sporadic nature emphasizes the importance of routine prenatal screening and genetic counseling for all pregnant women, particularly those with a history of fetal anomalies or neonatal loss [16].

In conclusion, our case highlights the critical role of early prenatal diagnosis in managing TD1 and the need for multidisciplinary support for affected families. Prenatal ultrasound remains the primary diagnostic tool, with advanced imaging modalities such as MRI offering additional insights in complex cases [17] [18]. Future research into genetic therapies and standardized protocols for prenatal screening and counseling may improve outcomes for families facing this devastating condition. Empathy, clear communication, and comprehensive counseling

remain essential in helping families navigate the emotional and ethical complexities of TD.

4. Conclusion

Thanatophoric dysplasia (TD) is the most common lethal neonatal skeletal dysplasia. Early prenatal diagnosis through ultrasound is imperative, as it assists obstetricians and parents in making informed decisions regarding the option of medical termination of pregnancy (MTP). This case highlights the critical role of prenatal ultrasound in the early identification of characteristic skeletal abnormalities in TD1, enabling comprehensive counseling and informed decision-making. Empathetic support and multidisciplinary care are essential for families facing such challenging diagnoses. Future advancements in genetic therapies and standardized prenatal screening protocols may offer hope for improved management of this devastating condition.

Conflicts of Interest

The authors declare no conflicts of interest.

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