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Case Report

Thanatophoric dysplasia: A case report with probable recurrence

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ABSTRACT

Thanatophoric dysplasia (TD) is a congenital, sporadic, and the most lethal skeletal dysplasia caused by new mutation in the fibroblast growth factor receptor 3 gene. At birth, it is characterized by shortening of the limbs (micromelia), small conical thorax, platyspondyly (flat vertebral bodies), and macrocephaly. TD is divided into two clinically defined subtypes: Type I and II which can be differentiated by the skull shape and femur morphology. Ultrasound examination in the second trimester is often straight forward in diagnosing the congenital anomaly. We report a case of preterm stillborn female baby with dysmorphic facies, macrocephaly, micromelia with short stubby fingers and deep skin creases, short limbs, narrow thorax, and protuberant abdomen delivered at our hospital to a 24-year-old multigravida mother with the previous history of first-trimester abortion. The antenatal ultrasound examination showed shortening of long bones with femur-shaped like a telephone receiver. Dysmorphic facial feature, skeletal abnormalities, and histopathological examination lead us to make the diagnosis of TD Type I. We report this case of TD in view of recurrence risk of around 1%, occurring mostly through autosomal dominant mode of inheritance, which may be the possibility in this case.

Key words: *Congenital, Platyspondyly, Thanatophoric dysplasia, Recurrence, Autosomal dominant inheritance*

Thanatophoric dysplasia (TD) is a congenital, sporadic, and usually lethal skeletal dysplasia at birth characterized by micromelia, small conical thorax, platyspondyly (flat vertebral bodies), and macrocephaly. Its incidence is 1 in 20,000 to 1 in 50,000 of live births [1]. It is caused by *de novo* mutations [2] in the fibroblast growth factor receptor 3 (FGFR3) genes, which has been mapped to chromosome band 4p16.3. There are two subtypes with relative incidence**:** Type I - 80% and Type II - 20%. The two subtypes can be differentiated by the skull shape and femur morphology [3,4]. We report a stillborn female baby with TD with probable recurrence which merits importance.

CASE REPORT

A 24-year-old female, a multigravida with 5 months amenorrhea, visited our hospital for antenatal checkup. She had a history of one previous spontaneous abortion at 12 weeks of gestation. She was an unbooked case. She married for the last 3 years and was a second-degree consanguineous marriage. She was a non-smoker, non-alcoholic, and not addicted to any drug. There was no history of fever, rashes, spotting per vaginum, and drug intake and radiation exposure during this pregnancy. There was no past or family history of congenital abnormalities. At the time of admission, her vitals were within normal limits. No abnormality was detected on respiratory, cardiovascular, or central nervous system examination. On per abdomen examination - fundal height was 22 weeks with fetus in the longitudinal lie, with increased liquor volume. Fetal heart rate was 144/min and uterus was relaxed.

Complete blood count of the mother showed raised leukocyte count. Her urine routine, blood sugar, liver, and renal function tests were within normal range. Human immunodeficiency virus, hepatitis-B surface antigen, and venereal disease research laboratory were non-reactive. Her C-reactive protein was negative. Ultrasound examination showed a single live intrauterine fetus with unstable presentation of around 20 weeks gestation. Placenta was anterior. Fetal skull was normal with no ventriculomegaly. Fetal thorax was abnormally small with reduced circumference, and abdomen showed gross ascites with no gastric bubble. Fetal limbs showed diffuse shortening of long bones, and femur was shaped like telephone receiver. Ribs were shorter and curved. Foot length was 3.2 cm on either side. Bilateral kidney showed pyelectasis (Figs. 1 and 2).

Her labor was induced in view of skeletal dysplasia in the fetus, most probably TD, a lethal condition, as suspected in antenatal ultrasonography. Patient delivered a preterm female baby of 340 grams vaginally, a still born with phenotypic dysmorphism. The baby had macrocephaly with head circumference 30.2 cm (>3 standard deviation). Anterior and posterior fontanelles were wide and open, and sutures were separated. Face was coarse and edematous with frontal bossing, midfacial hypoplasia, depressed nasal bridge, low-set ears, and short neck. Upper and lower limbs

were shortened with short stubby fingers and deep skin creases. Thorax was narrow with protruberant abdomen and spine was normal (Fig. 3a and b).

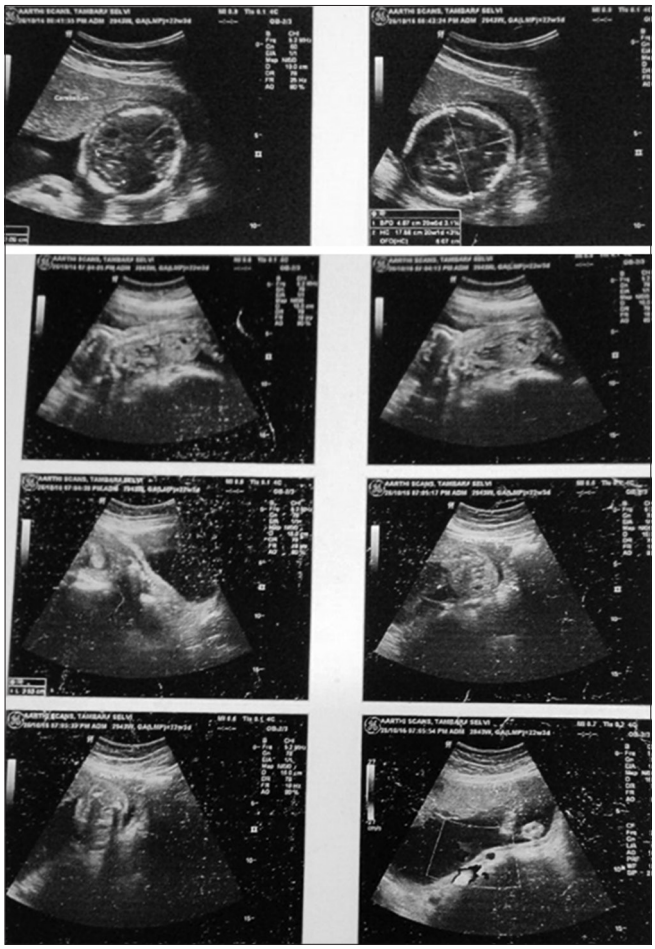

Figure 1: Fetal biometry showing increased biparietal diameter (macrocephaly)

Skeletal survey was done, which showed severe platyspondyly, short ribs, small ilia, markedly shortened limb bones with telephone receiver-like curved femoral and curved clavicles resembling bicycle handlebar (Figs. 4 and 5). Histopathological examination of the temporal bones showed non-specific disturbance of enchondral ossification with preservation of periosteal ossification. There was retardation of growth zone with disordered proliferative, hypertrophic chondrocytes (Fig. 6). The diagnosis of TD Type I was made based on antenatal ultrasonography, clinical dysmorphism, skeletal deformities, and histopathological examination. In this case, the previous spontaneous abortion may be most probably due to the same cause, which is rare autosomal dominant inheritance (recurrence risk-1%), as TD usually occurs sporadically.

DISCUSSION

TD is a congenital, sporadic, and usually lethal skeletal dysplasia at birth characterized by micromelia, small conical thorax, platyspondyly (flat vertebral bodies), and macrocephaly. Its incidence is 1 in 20,000 to 1 in 50,000 of live births [1]. TD or dwarfism literally meaning death bearing dwarf was first described by Maroteaux et al. [5]. It is caused by *de novo* mutations [2] in the FGFR3 genes, which has been mapped to chromosome band 4p16.3. Fibroblast growth factors, which are associated with cell growth, bind to the FGFR3 receptor and activate a signal transduction pathway that regulates endochondral ossification by inhibition of cell division and stimulation of cell maturation and differentiation. Mutations in the FGFR3 gene give rise to activation of the receptor in the absence of growth factors, thus causing abnormal long bone development [6]. It has been recently proposed that mutated FGFR3 induces premature exit of proliferative cells from the cell cycle and their differentiation into

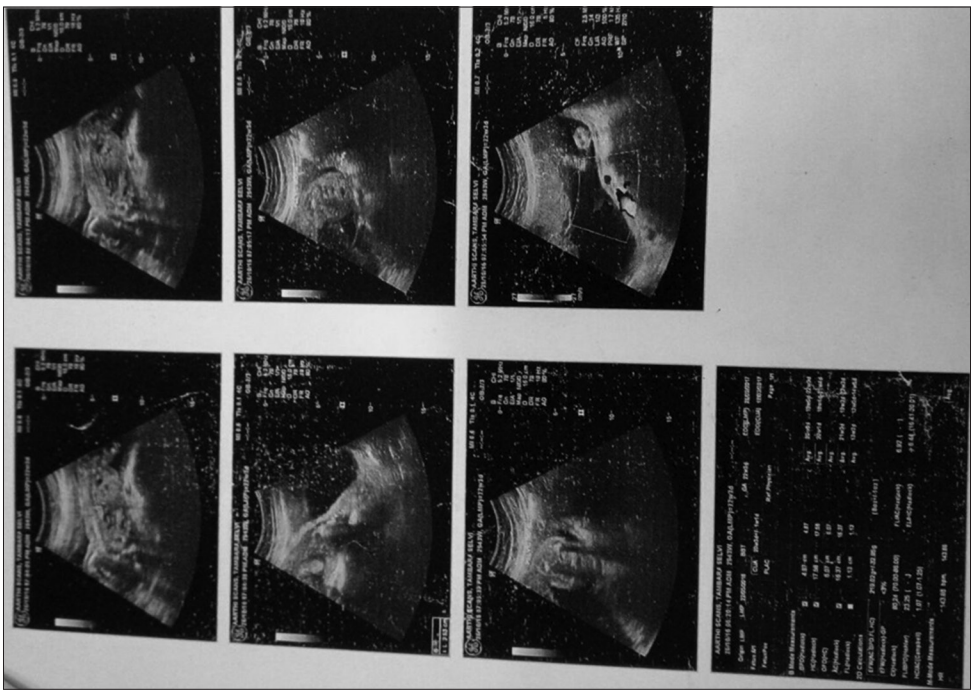

Figure 2: Fetal biometry showing small thorax with increased abdominal circumference and shortened long bones

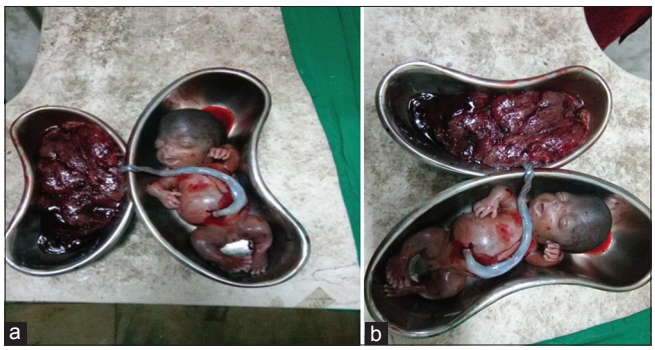

Figure 3: (a and b) Preterm stillborn female baby with dysmorphic facies, macrocephaly, micromelia with short stubby fingers, deep skin creases, short limbs, narrow thorax, and protuberant abdomen

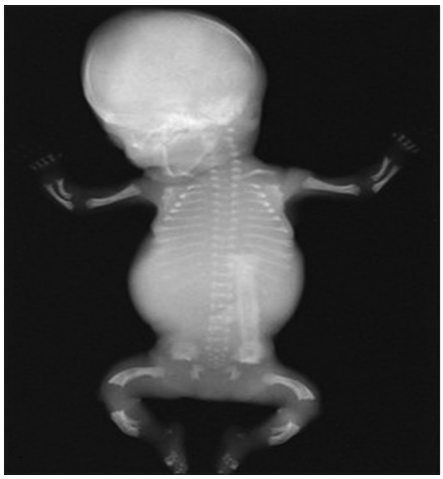

Figure 4: Skeletal survey showing severe platyspondyly, short ribs, small ilia, markedly shortened limb bones

pre-hypertrophic chondrocytes, thus ascribing to the defective differentiation of chondrocytes, the main cause of long bone growth defects in TD Type I [7].

There are two subtypes with relative incidence: Type I - 80% and Type II - 20%. The two subtypes can be differentiated by the skull shape and femur morphology [4,6]. TD Type I, the most common subtype, is characterized by curved and short femur which is in a telephone receiver-like configuration and no cloverleaf-shaped skull. Furthermore, the abdomen appears protuberant in comparison with the chest which is narrow and small [4]. The fetuses with Type II TD are reported to have cloverleaf skull which means a trilobed skull. The premature closure of coronal and lambdoid sutures is commonly seen with the cloverleaf skull [8]. Other features common to both types include small narrow thorax with horizontally placed short ribs, macrocephaly, large anterior fontanel, a small foramen magnum, distinctive facial features (frontal bossing, low nasal bridge, flat faces), severe platyspondyly, marked shortening and bowing of long bones, brachydactyly (short broad tubular bones in hands and feet), redundant skin folds along the limbs [4]. Dysmorphic facial features and skeletal abnormalities such as macrocephaly, wide open anterior and posterior fontanels with suture separation but absence of cloverleaf skull deformity, short upper and lower limbs, shape of femur as telephone receiver, short stubby fingers,

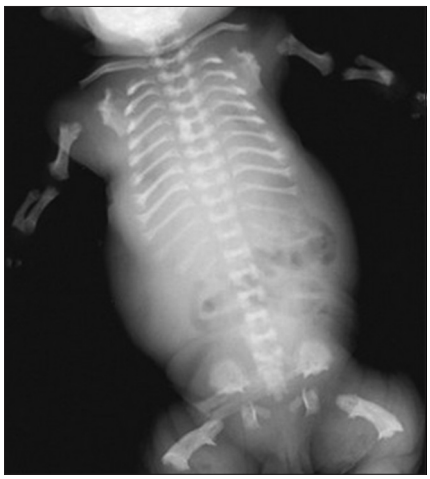

Figure 5: Skeletal survey showing telephone receiver-like curved femoral and curved clavicles resembling bicycle handlebars

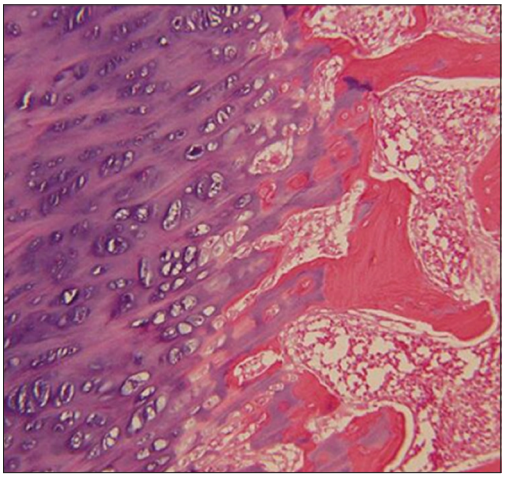

Figure 6: Histopathological examination of the temporal bones showing non-specific disturbance of enchondral ossification with preservation of periosteal ossification. There was retardation of growth zone with disordered proliferative, hypertrophic chondrocytes

deep skin creases, narrow thorax, and protuberant abdomen with ascites suggested a diagnosis of TD Type I in the baby that delivered in our hospital.

Although identification of a lethal skeletal dysplasia in the second trimester is often straight forward, establishing its specific diagnosis can be difficult. A three-dimensional ultrasound examination aids in visualizing facial features and other soft tissue findings such as cloverleaf skull, very short extremities, and small thorax, which are suggestive of TD [9]. Since our patient did not have antenatal checkup in the second trimester, early diagnosis could not be made. Diagnosis was made by ultrasonography when she reported to the hospital in early third trimester. Final diagnosis in our case was made by detecting the clinical features at birth - dysmorphic facial features and skeletal abnormalities through skeletal survey and histopathological examination.

Prenatal diagnosis can be confirmed by molecular analysis of the mutation in FGFR3 gene extracted from fetal cells obtained by amniocentesis usually performed at 15-18 weeks gestation or chorionic villous sampling at about 10-12 weeks gestation [10].

Chromosomal analysis and DNA molecular testing for FGFR3 can be done in suspected cases of TD. Almost all cases are caused by new mutation in the FGFR3 gene and occur in people with no history of the disorder in their family. Affected individuals never survive, so disorder never passes to next generation [8]. Recurrence risk is also not increased over that of the general population as it is a *de novo* mutation [2].

Our case is reported for two specific reasons. Early abortion in first trimester in the first pregnancy and late detection in early third trimester in the second pregnancy occurred in the same patient. As TD is usually sporadic in occurrence, recurrence in this patient suggests the possibility of autosomal dominant mode of inheritance, which is relatively rare (recurrence risk-1%). Most of the fetuses with TD die *in utero*. The cause of death is due to respiratory insufficiency which may be secondary to the narrow chest cavity and hypoplastic lungs, brainstem compression by the narrow foramen magnum, or a combination of both. Surviving neonate is almost always ventilator dependent and mentally deficient [8,11]. Postnatal autopsy of the affected fetus shows disorganized chondrocyte columns, poor cellular proliferation, lateral overgrowth of metaphyses, and increased vascularity of cartilage [1,11].

Differential diagnosis of TD includes homozygous achondroplasia (both parents suffer from the achondroplasia), achondrogenesis (bones demineralization that are most marked in the calvarium and vertebral bodies, shortened trunk length), campomelic dwarfism (bowing and angulation of long bones with immature ossification), rhizomelic chondrodysplasia punctata (micromelia is rhizomelic with characteristic stippling radiologically and punctuate calcification in cartilage), severe hypophosphatasia, and severe osteogenesis imperfecta (generalized hypomineralization of bones with multiple bone fractures) [11,12]. The presence of a characteristic cloverleaf skull with telephone receiver appearance of humerus and femur with platyspondyly, small conical thorax, and a very high mortality differentiates TD from other causes of severe short stature with micromelia.

CONCLUSION

TD is a congenital, sporadic, and the most lethal skeletal dysplasia at birth. Ultrasonography highly indicates the diagnosis, but confirmation is done by molecular analysis in the prenatal period, clinical features at birth, skeletal survey, or by autopsy. Features such as macrocephaly, wide fontanels, micromelia, and telephone receiver-like femur, short stubby fingers, deep skin creases, narrow thorax, and protuberant abdomen are highly suggestive of TD Type I.

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