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# Thanatophoric dysplasia: case report of an autopsy complemented by postmortem computed tomographic study

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## ABSTRACT

Thanatophoric dysplasia (TD) is one of the most common lethal skeletal dysplasias, which was first designated as thanatophoric dwarfism and described in 1967. The authors report a case of a Caucasian girl with TD, born to a 31-year-old woman without comorbidities. The newborn presented respiratory distress immediately after delivery, progressing to death in less than 2 hours. An autopsy was carried out after postmortem tomographic examination. The autopsy findings depicted extensive malformations of the skeletal system and the brain. The aim of this report is to discuss the pathogenesis and correlate the morphologic features of TD that were disclosed at the tomography and the autopsy.

### Keywords
Thanatophoric Dysplasia; Tomography, Spiral Computed; Autopsy.

## CASE REPORT

A Caucasian girl was born through cesarean section because of her breech presentation at an ultrasonographic gestation age of 38 weeks and 1 day. She weighed 3,188 g, and had an APGAR score of 2/1/1 at 1/5/10 minutes. This was the second pregnancy of a 31-year-old woman without comorbidities. Serologic tests were undertaken during the prenatal examination and were negative for syphilis, HIV, hepatitis B and C, and toxoplasmosis. Immediately after delivery, the newborn presented respiratory distress and required high titers of oxygen supplementation. The newborn progressed to bradycardia, apnea, and died 1 hour and 38 minutes after birth.

## POSTMORTEM TOMOGRAPHIC EXAMINATION

Before the autopsy was performed, the newborn's entire body was submitted to postmortem tomographic examination, which showed a large skull with cranium-facial disproportion, large fontanels (Figure 1) and a depressed nasal bridge. The trunk was narrow and long with very short ribs.

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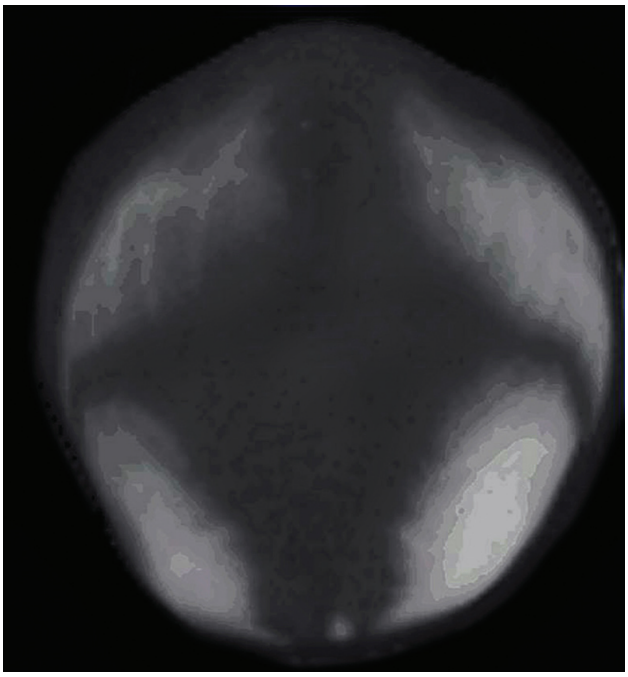

**Figure 1.** 3D reconstruction in maximum intensity projection (MIP). Note a very large anterior fontanel.

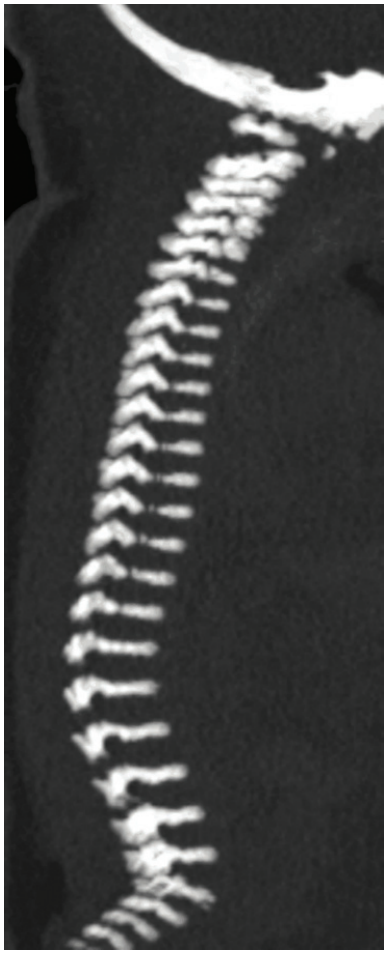

**Figure 2.** Computed tomography of the vertebral spine showing marked reduction of the central and posterior regions of the vertebral bodies (platyspondyly) and broad and rounded anterior aspect.

The posterior ribs had prominent grooves and the scapula was malformed. The lung was small and hypoplastic. The vertebral bodies had marked reduction in the central and posterior regions (platyspondyly) and broad and rounded anterior aspect (Figure 2). In the coronal plane, the vertebral body had an "H"-shaped configuration and a marked decrease of the interpedicular distance. The iliac bones were small and the acetabular roof was dysplastic and flat. Very narrow sacrosciatic notches were also noted. The long bones of the upper and lower limbs were short and curved, especially the femur, with an old-fashioned telephone-receiver-like configuration.

The metaphysis of the long bones was enlarged and had a cup-shaped configuration (Figure 3). The phalanges of the hands and feet were also short. There was a discreet increase of subcutaneous thickness over the body. The liver, spleen, kidney, and bladder were unremarkable.

## AUTOPSY

The external examination findings revealed a large cranium with frontal bossing, large fontanels posterior and anterior, hypertelorism, and a depressed nasal bridge with cranium-facial disproportion. The thorax was narrow and shortened with a protruding abdomen. The upper limbs were symmetrically short. The lower limbs were also short with curved femurs (Figure 4).

On opening the skull, the brain volume was increased to its chronological age with partial agenesis of the *corpus callosum*, the ventricles in "Bat Wing" formation, and the temporal lobes medially rotated (Figure 5A). The light microscopy did not show alterations in neuronal migration, which was consistent with a normal brain.

Gross examination of the skeletal system showed the presence of short ribs and long bones that were also shortened with a prominent curved form of the femurs like an old-fashioned telephone receiver (Figure 5B).

Slides from the femur showed femoral epiphyseal cartilage irregularity with hypertrophic chondrocytes forming a disorganized arrangement (Figure 6A), increased periosteal ossification (Figure 6B), and no clear differentiation between proliferation and rest

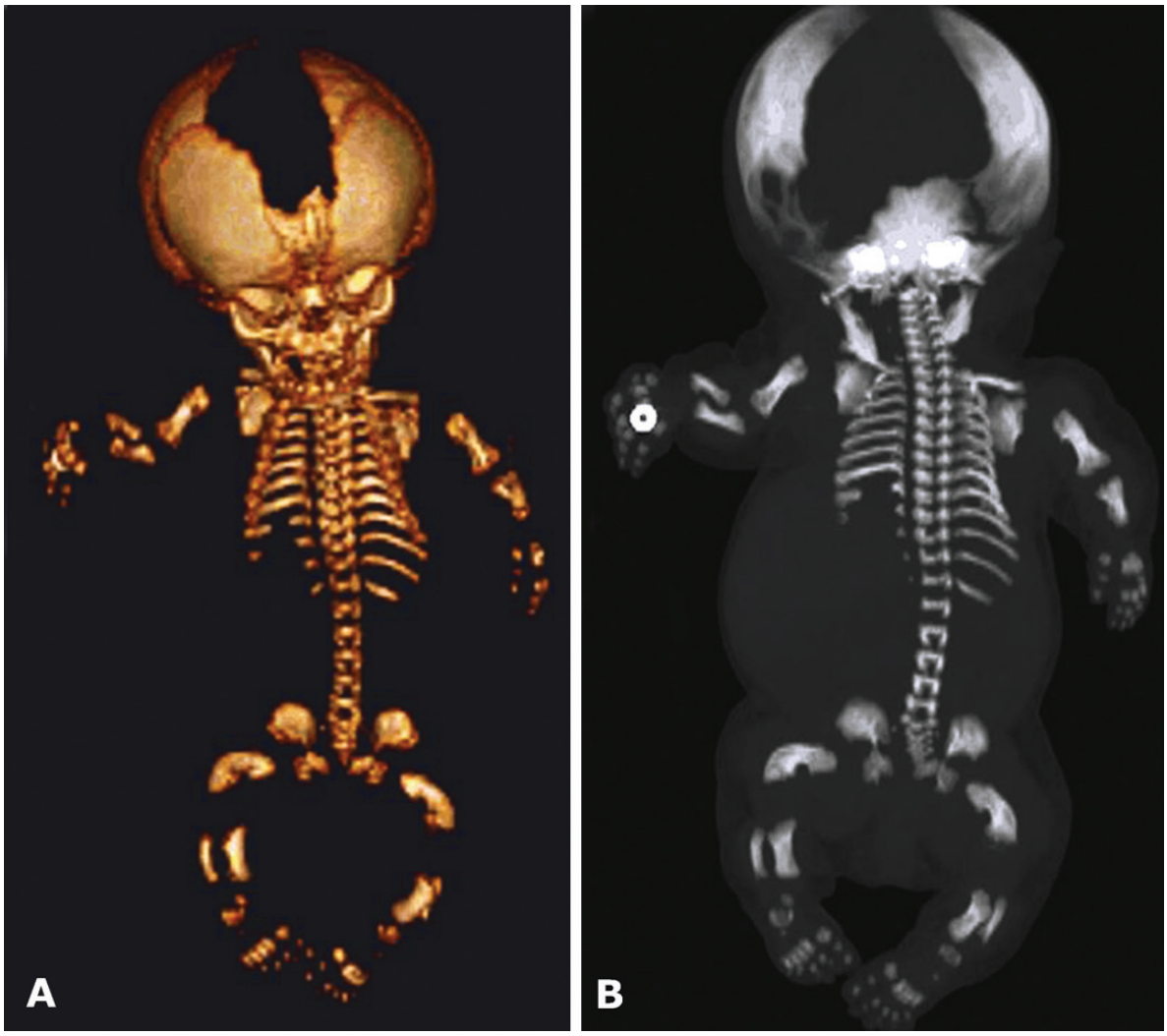


**Figure 3. A** and **B** - Computed tomography of the whole body - Coronal 3D reconstructions showing long and narrow trunk, "H"-shaped vertebral bodies, small iliac bones, dysplastic and flat acetabular roof, very narrow sacrosciatic notches, shortened long bones of the upper and lower limbs, and curved with old-fashioned telephone-receiver-like configuration of the femur.

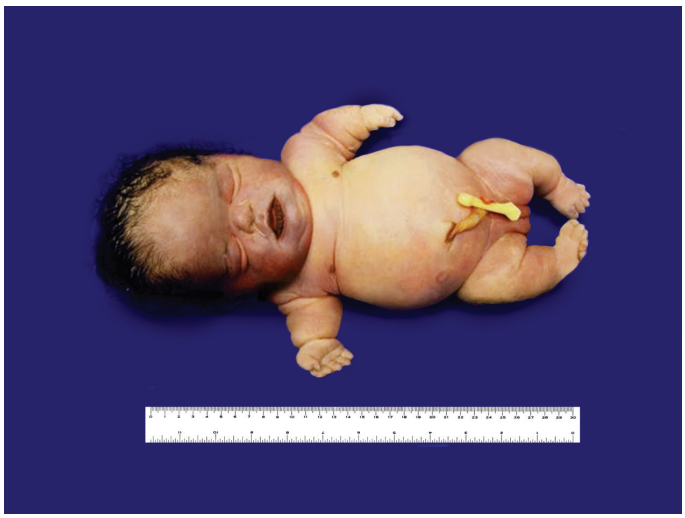

**Figure 4.** Gross findings of the newborn, showing hypertelorism, a depressed nasal bridge with cranium-facial disproportion. Note the short thorax, protruding abdomen and short and curved limbs.

zones. The analysis with specific stains for collagen showed islands of fibrosis in the epiphyseal cartilage (Figure 6C).

The heart showed no malformation. To evaluate the pulmonary hypoplasia we calculated lung weight/body weight ratios (LW/BW) and the morphometry was determined by the radial alveolar count (RAC) at a microscopical magnification of 40x, using a modification of the method of Emery and Mithal.[1] When weighed together the lungs were 20.8 g for an expected value of 52 ± 15.6 g. The LW/BW ratio was 0.0065 for a normal expected value of 0.0081 according to the tables of Maroun and Graem.[2] The mean RAC was 2.8; the normal expected value is 4.1-6.3. These findings were compatible with lung hypoplasia. At the histological examination,

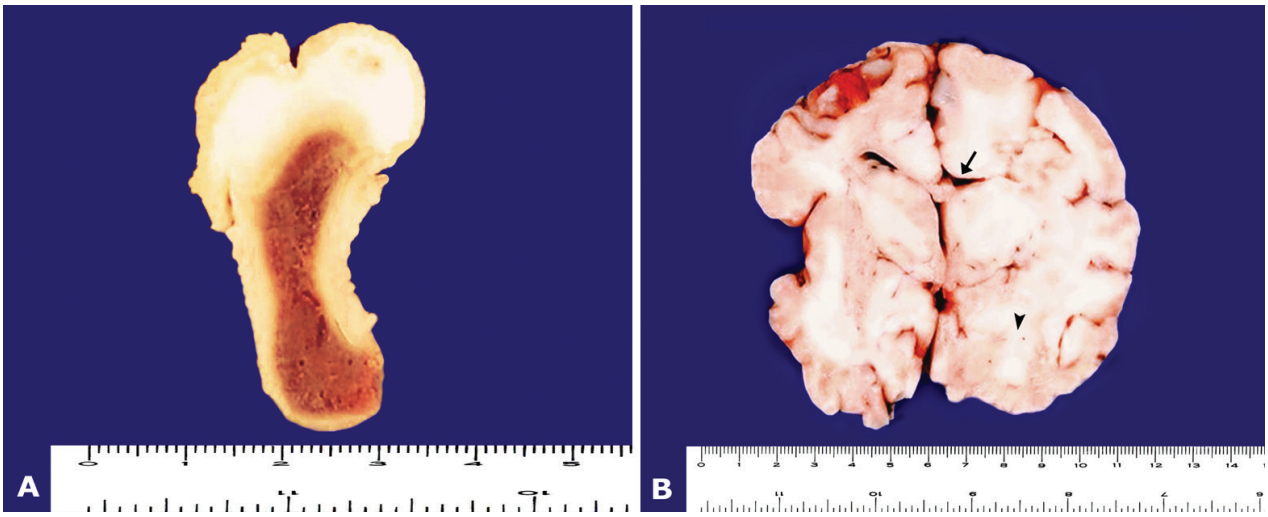


**Figure 5. A** - Panoramic macroscopic view of the right femur; **B** - The frontal section of the brain showing partial agenesis of the corpus callosum and ventricles in "Bat Wing" formation (arrow) and temporal lobes medially rotated (arrowhead).

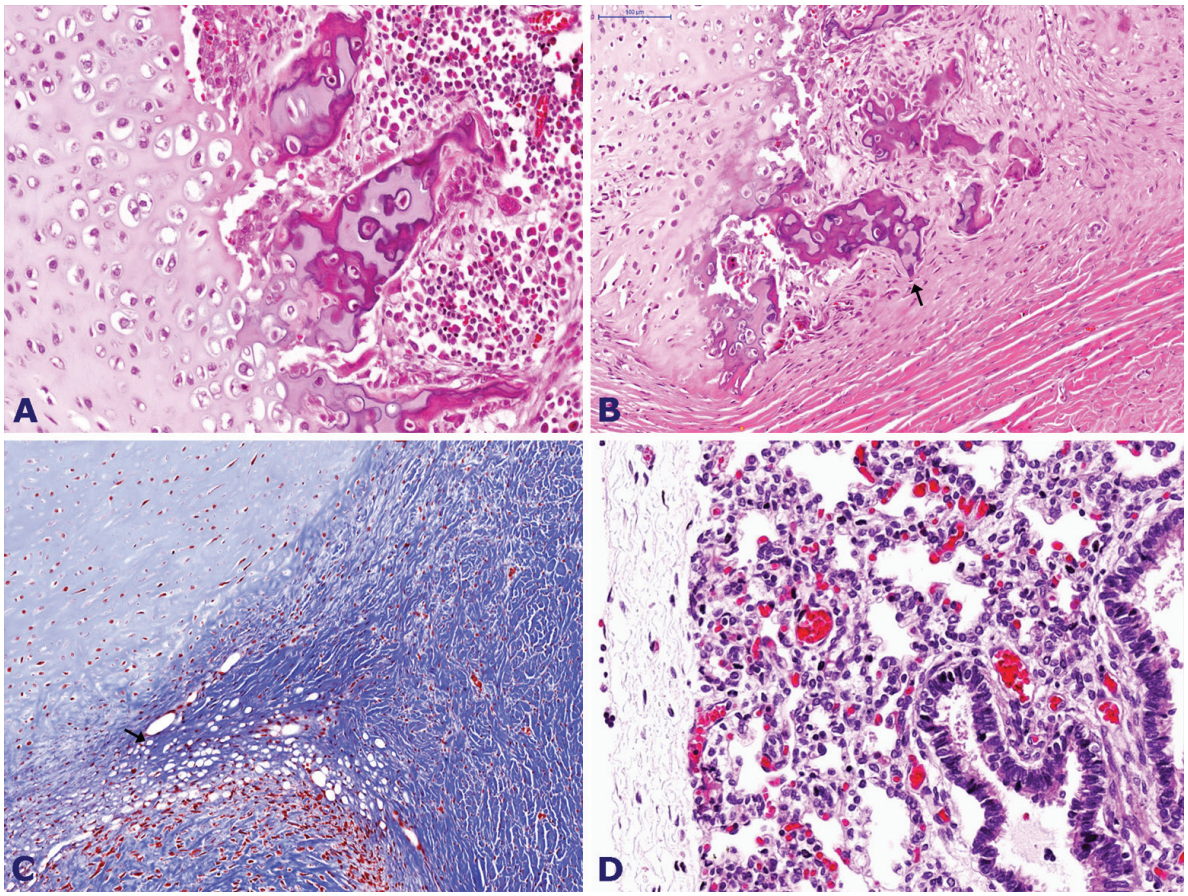


**Figure 6.** Photomicrography of the distal femur showing in **A** - hypertrophic chondrocytes forming a disorganized arrangement (HE, 20x); **B** - expanded epiphyseal cartilage, irregular endochondral ossification, and prominent periosteal bony spurs (arrow) (HE, 20x); **C** - islands of fibrosis in the epiphyseal cartilage (arrow) (Masson, 20x); **D** - Photomicrography of the lung depicting a bronchial presence near the pleura with a radial account of three air spaces, confirming pulmonary hypoplasia (HE, 40x).

the parenchyma showed an immature pattern with decreased airway caliber, a bronchial presence close to the pleura, and a decreased radial count (Figure 6D).

Microscopic evidence of prematurity was found in the thyroid, spleen, and liver with extramedullary hematopoiesis. The kidneys showed nephrogenic zones. The intensity of all these findings was consistent with the gestational age.

The placental examination was in accordance with the gestational age depicting a small villous infarction and a normal umbilical cord.

## DISCUSSION

In 1967, Maroteaux et al.,[3] described a specific chondrodystrophy calling thanatophoric dwarfism. In 1977, this term was changed to thanatophoric dysplasia at the Second International Conference of the Nomenclature of Skeletal dysplasias.[4] Currently, according to international nomenclature; TD is classified in group 1, FGFR3 (fibroblast growth factor receptor 3) chondrodysplasia group, and subclassified in TD types 1 and 2.[5]

TD is one of the most common lethal skeletal dysplasias. In a population study, Andersen and Hauge[6] found a prevalence of 3.8 per 100,000 births. Other population studies have reported the prevalence around 1.7[7] and 2.8[8] per 100,000 births. The term thanatophoric is derived from the Greek "thanatophoros" meaning "death-bearing," since early death is inevitable.[9] TD types II and I are diagnosed prenatally or in the immediate neonatal period.[10]

Mutation in the activation of the FGR3 gene located on chromosomal locus 4p 16.3 is responsible for a group of skeletal dysplasias that affect the growth of long bones and the formation of the cerebral cortex, of which TD is one, and is considered to be caused by a dominant mutation.[11-14] However, the differentiation between types 1 and 2 is made by the presence or not of cloverleaf skull and morphology of the femur. The presence of craniosynostosis causes the characteristic cloverleaf skull and is typical of type 2, which also shows less pronounced curvature of the long bones. Type 1 usually has a large head with facial asymmetry and short femurs with typical curvature like a telephone receiver. In both types, the vertebral bodies may have the format "U" or "H"; the ribs are thin and small decreasing the chest's volume, and lead to pulmonary hypoplasia. Usually, the liver is large and becomes the major site of hematopoiesis.[12,14]

The cerebral abnormalities were first reported in 1971 by Goutières et al.,[15] and since then, the cerebral alterations have been the subject of several research studies.[13] The most frequent cerebral abnormalities are posterior fossa hypoplasia, megalencephaly, hippocampal malformation, gyral disorganization, neuronal heterotopias, and inferior olivary dysplasia—but they are non-specific.[9] Currently, the association of brain malformations with skull growth defects are no longer accepted because of the compelling evidence that the neural changes originate before the ossification process entail restrictions on the size of the braincase. It is probable that the observed neural abnormalities are intrinsic defects of the nervous system.[13,16]

In this report, all the morphologic features were correlated and complemented with radiologic images acquired after the patient's death. Over the years, radiology has been gaining more space in several medical disciplines, but postmortem imaging only began in the year 2000 focusing more on forensic medicine.[17] The radiological images show details of alterations in the skeleton that would be unfeasible during the autopsy due to the impossibility of accessing all bones. Pulmonary findings are consistent with the autopsy findings. Comparing the imaging findings of the postmortem tomography with those of the autopsy, we conclude that in this case report, all the findings were similar and complementary.

The pathogenesis of morphologic alterations in TD is related to fibroblast growth factor signaling, which plays an important role in neural development, such as cell proliferation and apoptosis in the cortex and other areas of the brain. However, the link between FGFR3 and brain malformation remains unclear.[13,16,18] Furthermore, the extent of temporal lobe findings differs from case to case, and there are several cases where these alterations are only seen with thorough inspection.[14]

The fibroblast growth factor, specifically FGFR3, is also important for the development of the bones

where it regulates chondrocyte differentiation and proliferation.[13] The abnormalities are present in all grown plates. The decreased chondrocyte proliferation is responsible for irregular chondrocyte columns.[12] In a typical endochondral ossification, the bone matrix is deposited by osteoblasts on cores of calcified cartilage that extend from the hypertrophic zone of the growth plate into the subchondral bone. The ossification in TD has similarities of membranous ossification; cells with morphological characteristics of osteoblasts become surrounded by a matrix composed mainly of type I collagen that becomes mineralized.[19] The growth alterations of long bones in TD could result from defective chondrocyte proliferation, premature terminal differentiation, or both. However, FGFR 3 mutations are more related to an abnormal cell differentiation than to a lack of chondrocyte proliferation during fetal development. This is probably because terminally differentiating hypertrophic chondrocytes is controlled by apoptosis and these mutations increase chondrocyte apoptosis, which produces an increase in receptor function that results in a decrease of bone elongation.[20]

Most infants affected with TD die of respiratory insufficiency in the first few hours or days of life. Respiratory insufficiency may be secondary to a small chest cavity and consequently lung hypoplasia, or compression of the brain stem by the small foramen magnum, or a combination of both. Some affected children have survived until childhood by means of ventilatory support.[10]

## CONCLUSION

The radiologic, morphologic, and histologic features, herein described, were compatible with TD Type I. These findings helped us to correlate them with their pathogenesis and realize the reason why this disease usually has a poor prognosis. As far as we know, this report is the first one to describe the correlation between conventional autopsy and the realization of tomography postmortem in a case of TD. It is important to compare the traditional method of autopsy with this new method using images, which allows an interdisciplinary analysis of the disease and therefore contributes to the further acquisition of knowledge.

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