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CASE REPORT

Prenatal Diagnosis of Osteogenesis Imperfecta Type III

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Case Presentation

A 30-year-old woman in her second pregnancy attended routine prenatal visits. Her first pregnancy was uneventful, and she has a 4-year-old healthy daughter now. The parents were not-consanguineous, and their genetic histories did not indicate any abnormality. Nuchal translucency was normal in the first-trimester screening with a present nasal bone. At a routine prenatal visit at 17th gestational weeks, ultrasound revealed: marked shortening (< 5 percentile) with angulations and bowing of both femurs; the other limb bones were slightly short (Fig. 1). Fetal foot length was at the 5th percentile, and the fetal femur/foot ratio was 0.73 (< 1). The inferior facial angle was 53 degrees showing no sign of retrognathia. Fetal skull, spine, thorax, ribs, clavicles, hands and amniotic fluid were also normal. She was offered amniocentesis with sequencing analysis for the possible diagnosis of OI type III/IV and campomelic dysplasia. The amniocentesis revealed normal 46, XY chromosomes, but the further sequencing analysis with Illumina MiSeq next-generation sequencer showed single nucleotide missense variant NM_000088.3(COL1A1):c.1588G>A (p.Gly530Ser) heterozygous mutation for COL1A1 gene coding collagen type 1 alpha chain 1 on 17q21.33 chromosome, whereas COL1A2 gene and SOX 9 gene found normal. The results of the genetic testing with sequencing and ultrasound scans pointed out OI type III. After the genetics consultation, the family chose to terminate the pregnancy. At the 23 weeks of gestation, feticide was performed by potassium chloride injection in the umbilical cord and labor was induced by prostaglandin induction. A 524-g male fetus delivered through vaginal route. The fetal X-ray sonograms showed deformity of all extremities and ribs due to vaginal delivery as well as bilateral bowing of the femurs. Post-termination pathologic findings showed blue and white cartilaginous nodules on the femur and tibia. Irregularities were observed in the growth plate and trabecular bones of all extremities. Osteoid increase and necrosis in trabecular bone, as well as changes like fracture healing, were detected (Fig. 2).

Discussion and Conclusions

The prenatal diagnosis of the short femur in the early second trimester depends on the pattern of shortening (< 5th percentile), the structure of the femur (fractured, bowed or straight) and whether it is isolated or not. Additionally, accompanying abnormalities affecting other organs, particularly the skull, spine, chest, and ribs should be assessed. The short femur in the second trimester may be wrongly measured, it can be constitutional, or it can be a sign of intrauterine growth restriction, aneuploidy or skeletal dysplasia. In the case of skeletal dysplasia, the differential diagnosis for second trimester bilaterally short and symmetrically bowed femur includes OI types, particularly type III or IV, thanatophoric dysplasia, achondrogenesis, and campomelic dysplasia [1]. In the present case, the femurs are bilaterally short (< 5th percentile) and symmetrically bowed, and sequential scans showed shortening of all long bones; the face profile is normal, fetal karyotyping showed normal chromosomes, but further analysis showed heterozygous mutation for COL1A1 gene. The X-ray sonograms after delivery showed fractures

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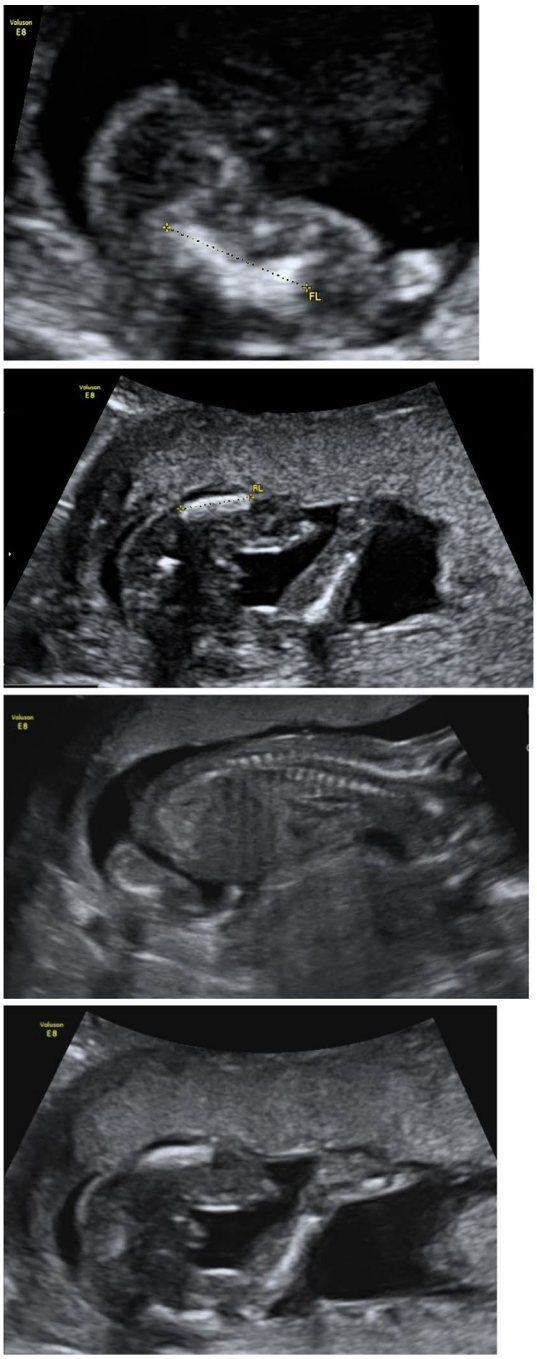

Fig. 1 Ultrasonographic view of bowed and angulated femur in different positions at 17th gestational week

in all bones and ribs with bilaterally bowed femurs. As a result of all these data, the final diagnosis concluded as OI type III, which is also known as progressively deforming OI.

Osteogenesis imperfecta is an inherited disorder of the connective tissue affecting mostly the bone tissue resulting in fragility and fractures. In most of the OI cases, type I collagen synthesis is affected due to a mutation in either the gene COL1A1 or COL1A2 (2). Autosomal dominant

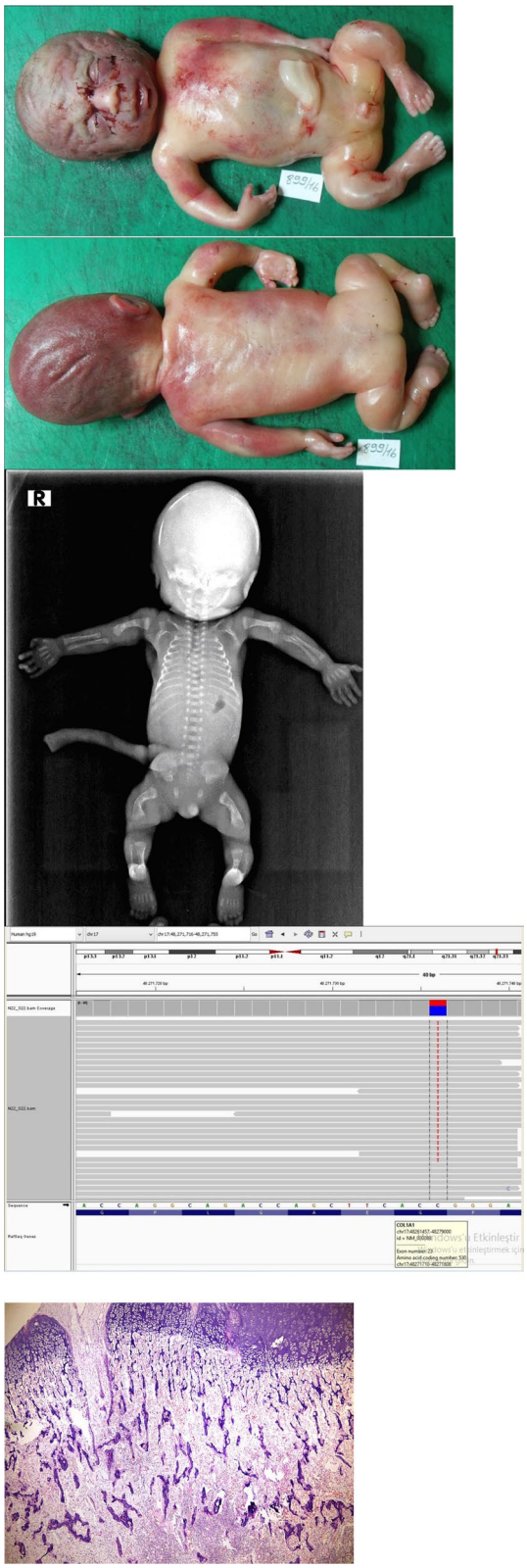

Fig. 2 Post-termination views of the fetus (front and back), post-termination X-ray sonogram of the fetus, COL1A1 gene mutation view and autopsy microscopic view of the femur showing irregularities in the growth plate and osteoid increase and necrosis in the trabecular bones

inheritance is common in most of the OI cases, besides de novo mutations can be detected, and recessive inheritance can occur. It favors female gender with an incidence of one in 25.000–30.000 pregnancies. In OI type III mutations resulted in the production of an abnormal quality of collagen type I. In the present case, this mutation is caused by a mutation in COL1A1 gene that resulted in serine substitution for glycine, which is quite common. Further DNA analysis of the parents showed no causative variants in COL1A1 and COL1A2 genes. In this case, the reported empirical recurrence risk of OI is between 1.3 and 2% for the subsequent pregnancy [2].

The pathologic reflections of the production of an abnormal quality of collagen type I in OI type III fetus in the light microscope showed thickened and disorganized osteoid with thinned osteoblasts with a mixture of lamellar and woven bones as reported previously [3].

Skeletal abnormalities can be detected as early as 14 weeks in the presence or absence of a family history. Increased NT, which is normal in the present case, may serve as an early sign for some cases of skeletal dysplasia, including OI type III in the early prenatal diagnosis [4]. Short and bowed femurs with short extremities are the most common prenatal findings distinguishable from mid-second trimester associated with OI type III.

Prenatal detection and classification of OI are challenging for the obstetrician. Gene mutation analysis is of paramount importance for the accurate classification and diagnosis of OI along with sonographic, radiological and pathological findings. If there is no related family history of skeletal dysplasia, parents should be supported to authorize for medical termination and autopsy for further radiological and pathological examinations to make a proper diagnosis and genetic counseling for future pregnancy.

Compliance with Ethical Standards

Conflict of interest Mehmet Tunc Canda, Serdar Ceylaner, Latife Doganay Caglayan, Ayşe Banu Demir and Namik Demir declare that they have no conflict of interest.

Ethical Standard All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed Consent Informed consent was obtained from the patient being included in the study.

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About the Author

Mehmet Tunc Canda is an Assoc. Prof. of Obstetrics and Gynecology. He has a deep interest in maternal and fetal medicine. He works full time in Kent Hospital, Izmir, Turkey. He along with Prof. Dr. Namik Demir made the interventions and management of this particular case.