Camptomelic Dysplasia Prenatally Diagnosed at 18 Week of Gestation: A Case Report and Review of the Literature

Prenatal 18. Gebelik Haftasında Tanı Koyulan Kamptomelik Displazi Olgusu ve Literatür Derlemesi

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ABSTRACT Camptomelic dysplasia (CD) is a rare skeletal disorder that is characterized by anterior bowing of the long bones. Ambiguous genitalia occurs in the majority of patients with an XY karyotype. Mutations in an SRY related gene, SOX9, are responsible for this disorder. Prenatal differential diagnosis of skeletal dysplasia includes asphyxiating thoracic dysplasia, thanatophoric dysplasia, hypophosphatasia, osteogenesis imperfecta types 2 and 3, and unclassified varieties of congenital bowing of the long bones. Since CD is a frequently lethal form of skeletal dysplasia, early diagnosis has at most importance in order to offer the option of termination to the expectant parents. Herein, we present one of the earliest reports of a prenatally diagnosed case of CD in a fetus without sex reversal leading to ambiguous genitalia at 18 weeks of gestation.

Key Words: Campomelic dysplasia; prenatal diagnosis; ultrasonography, prenatal; sex reversal, gonadal; SOX9 protein, human

ÖZET Kamptomelik displazi (KD) uzun kemiklerde öne doğru eğrilik ile karakterize nadir görülen bir iskelet displazisidir. XY karyotipine sahip hastaların çoğunluğunda kuşkulu dış genitalya mevcuttur. SRY ilişkili gendeki mutasyon, SOX9, bu hastalığın sorumlusudur. İskelet displazilerinin prenatal ayırıcı tanısı asfiktik torasik displazi, tanatoforik displazi, hipofosfatazya, osteogenezis imperfekta 2, 3 ve sınıflandırılmamış çeşitli konjenital uzun kemik eğriliklerini içermektedir. KD, iskelet displazilerinin sıklıkla ölümcül şekli olarak tanımlandığından dolayı, erken tanı gebeliğin sonlandırılması seçeneğini gelecekteki ebeveynlere sunabilmek için daha da önem kazanmaktadır. Burada, prenatal 18. gebelik haftasında tanı koyulan, belirsiz dış genitalyaya neden olmayan, KD olguları içinde en erken tanı alan olgulardan birini sunmaktayız.

Anahtar Kelimeler: Kamptomelik displazi; prenatal tanı; ultrasonografi, prenatal; seks zıtlığı, gonadal; SOX9 proteini, insan

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Camptomelic dysplasia (CD) is a congenital disorder characterized by development of abnormal curvature of the long bones, particularly of lower extremities, such as femur and tibiae.[1] It is a rare, frequently fatal skeletal dysplasia with a prevalence of 0.02/10.000.[2]

The gene associated with the disorder is located on chromosome 17 and is designated SOX-9 gene. In the early phase of the extremity development, differentiation of the mesenchymal cells to chondrocytes is needed and SOX-9 gene plays a major role in that process.[3] SOX9 is a member of the growing SOX-gene family, which is related by homology to the HMG-box

region of the testis-determining gene SRY ("SOX" is an acronym for "SRY-related HMG-box").[4,5] Camptomelic dysplasia is frequently associated with complete or partial XY sex reversal.[1] The abnormality of sexual development stems from abnormal gonadal development rather than a defect of gonadal function. The gonadal defects are observed in only XY patients, indicating a defect in testis determination rather than a generalised defect of gonadal development.[6] This further helps for the prenatal diagnosis of CD when there is a mismatch between the sonographic fetal sex and karyotype. However, the prenatal diagnosis is more challenging in a 46,XX female fetus which is a much more infrequent situation.

Herein, we present the sonographic, radiologic and morphologic features of a case of camptomelic dysplasia in a 46,XX female fetus which was diagnosed at 18 weeks of gestation.

CASE REPORT

A 20-year-old woman, gravida 1, para 0, was evaluated at 18 weeks of gestation, because skeletal dysplasia was suspected in the fetus. The family history was noncontributory whereas the parents were consanguineous (first degree cousins). Two-dimensional ultrasound revealed a single viable female fetus with a biparietal diameter of 39.8 mm, consistent with a gestational age of 18 weeks. The bone density was normal (Figure 1). The femurs and the humerus were severely short (18.1 mm and 19.4 mm), consistent with a gestational age of 15 weeks. There was marked anterior bowing and angulation of both femora, tibia and humeri with bilateral talipes equinovarus, hypoechogenity of the mid-thoracic vertebral bodies and polyhydramnios (Figure 1). The long-bone angulation in conjunction with normal head development concordant

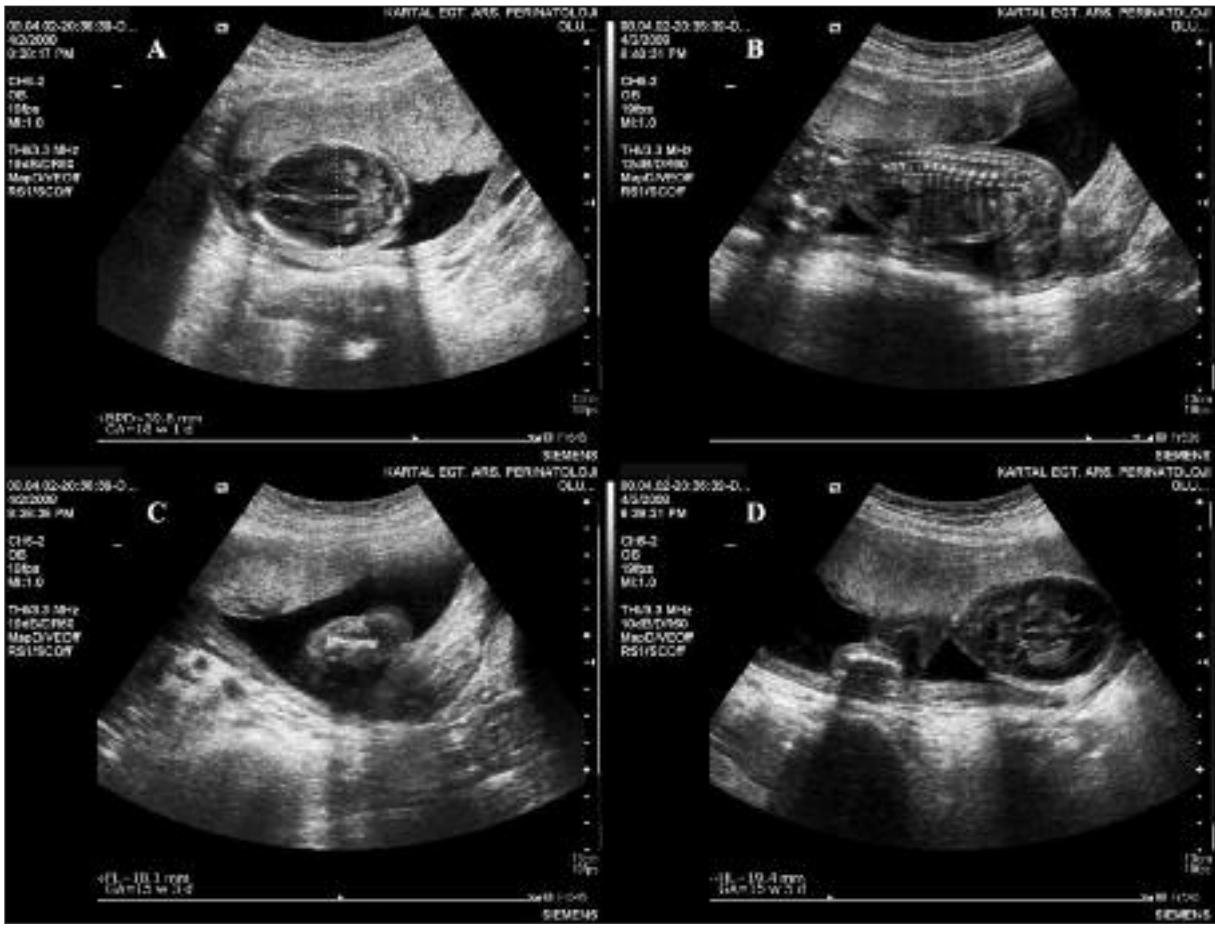

FIGURE 1: Ultrasonographic images showing A) the normal cranium B) hypoechogenic thoracic vertebral bodies C), D) anteriorly bowed femur and humerus.

with the last menstrual period raised the suspicion of a number of possible diagnoses, such as osteogenesis imperfecta type II/III or hypophosphatasia, and thanatophoric dysplasia type I2 in which bowed femora are commonly found. The normal bone density ruled out osteogenesis imperfecta and hypophosphatasia.[1] Thanatophoric dysplasia was excluded due to absence of very narrow chest expanding into a bell-shaped abdomen and cloverleaf deformity of the abdomen, was considered unlikely. Achondroplasia was also excluded because it is characterized by rhizomelic shortening without angulation of the long bones.[1] Amniocentesis was performed, normal female karyotype was revealed but mutation analysis of the SOX9 gene was not performed because of unavailability of the test at our hospital. Following counseling, the parents opted for termination of the pregnancy. Postnatal radiograph and autopsy findings confirmed the expected skeletal abnormalities as well as 11 pairs of unfractured ribs; however the scapulae were not hypoplastic (Figures 2, 3).

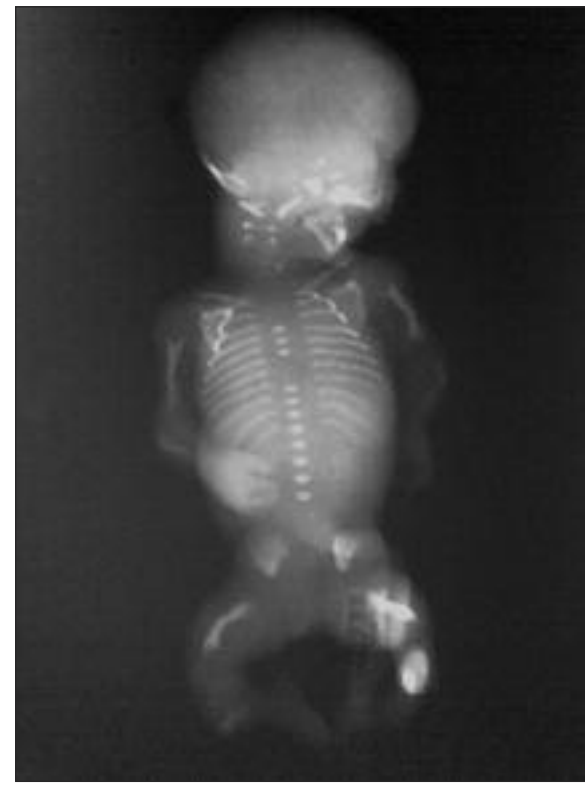

FIGURE 2: Postnatal X-ray showing hypomineralization of the thoracic vertebrae, 11 pair of ribs, bowing of the long bones.

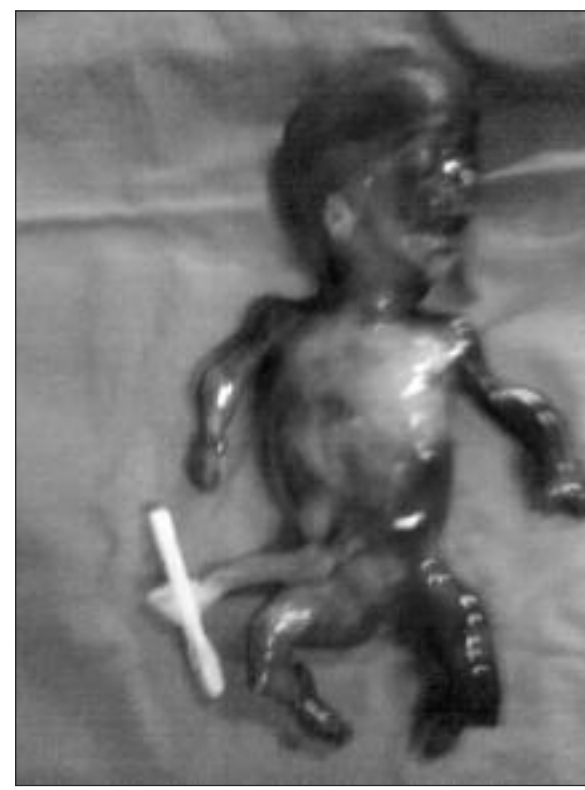

FIGURE 3: Clinical photograph of the abortus showing the bowed extremities and club feet.

DISCUSSION

The prenatal diagnosis of skeletal dysplasia is suspected initially on two dimensional (2D) ultrasound, however only 65% of cases can be diagnosed correctly by 2D ultrasound.[5,6]

When we made a MEDLINE search with the keywords of "camptomelic dysplasia" and "camptomelic dysplasia" we identified 160 and 27 cases, respectively. Among them, only 12 cases were found to have been suspected and diagnosed prenatally.[7-15] Besides, 21 fetuses were reported to be diagnosed as CD among 264 fetuses with angulated femurs according to the radiographic database of the International Skeletal Dysplasia Registry (ISDR) between the years 1988-2006.[16]

Prenatal differential diagnosis of skeletal dysplasia includes asphyxiating thoracic dysplasia, thanatophoric dysplasia, hypophosphatasia, osteogenesis imperfecta types 2 and 3, and unclassified varieties of congenital bowing of the long bones. Asphyxiating thoracic dysplasia is characterized by extremely severe thoracic hypoplasia; thanatopho-

ric dysplasia by severe thoracic hypoplasia, very short ribs, frontal bossing and cloverleaf skull; hypophosphatasia by hypomineralization involving all of the bones without clavicles; osteogenesis imperfecta type 2 by hypomineralization of the calvarium, diffuse and early fractures; type 3 by late onset bowing. All of these differential diagnoses were excluded due to the absence of the abovementioned anomalies. However, the absence of sex reversal was an unexpected and rare finding which further complexed the final diagnosis. Therefore, it seems to be worth emphasizing that sex reversal leading to ambiguous genitalia is not a *sine qua non* for the diagnosis of CD. In the developing gonad, SOX9 is known to show differential expression after the period of SRY expression. Expression is maintained throughout testis differentiation, but is extinguished in the developing ovary.[17] Although mutations or translocations in the gene SOX9 on the long arm of chromosome 17, result in the syndrome of CD, we could not perform SOX9 gene analysis for our case. SOX9 is known to play an important role in chondrogenesis and testogenesis. Three important domains on it, HMG domain, proline/glutamine/serine-rich C-terminal transcription activation domain, and dimerization domain, are needed for its function.[18] Since a dominant mode of inheritance for this syndrome is suggested and most cases are sporadic, the availability of the mutation analysis would help to confirm the diagnosis; rather than adding much to the genetic counseling for the consangineous couple. Although it is difficult to give an accurate recurrence risk in CD, it is suggested to screen subsequent pregnancies with ultrasound paying particular attention to the appearance of the long bones and the size of the thorax.[6]

Since CD is a frequently lethal form of skeletal dysplasia, early diagnosis has utmost importance in order to offer the option of termination to the expectant parents. However, the diagnosis is not usually made until the mid-second trimester or later. The earliest reported diagnosis was at 14^{+3} gestational weeks suspected in a fetus with cystic hygroma and lower limb anomalies.[14] In their report, the authors have also described another case of CD diagnosed at 20^{+6} weeks in a fetus with first-trimester hygroma colli accompanied by lower limb anomalies. Furthermore, Michel-Calemard et al. described the first report affected with CD presenting with increased nuchal translucency of 5.6 mm thickness at 13 gestational weeks.[19] However, the definitive diagnosis could only be made following termination of pregnancy at the 33rd gestational week since the femoral length had remained normal until 32 weeks of gestation. Since, the pregnancy was already over 14 weeks' of gestation when the patient applied to our prenatal unit, it was not possible to perform first-trimester screening test. Nuchal translucency (NT) screening for chromosomal abnormalities has been used successfully worlwide due to its effectiveness and capacity for early diagnosis since proposed by Nicolaides in 1992.[20] Increased NT thickness is also associated with numerous fetal anomalies; including skeletal defects and genetic syndromes in chromosomally normal fetuses.[21] Therefore, NT screening at 11-14 weeks' gestation may lead to early diagnosis of CD and early sonographic criteria for CD may be identified in the first trimester. We believe that the clear visibility of femora at 13-14 weeks should enable the clinician to make the diagnosis earlier especially when associated with increased NT measurement.

As a conclusion, CD is a severe skeletal dysplasia which can potentially be diagnosed during the first and the early second-trimester. On the other hand, sex reversal leading to ambiguous genitalia is not a *sine qua non* for the diagnosis of CD.

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