Campomelic dysplasia with dextrocardia and without sex-reversal

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Abstract

Campomelic dysplasia (CD) is a very rare, sporadic, autosomal dominant syndrome. CD is characterized by an association of skeletal (bowed long bones, pelvis and chest abnormalities, eleven rib pairs) and extraskeletal abnormalities (facial dysmorphism, sex-reversal in boy and visceral malformations). We report a case of a 3 days old male diagnosed by CD. At birth, the boy displayed severe asphyxia and therefore needed intensive care. Physical examination revealed short stature, a craniofacial dysmorphism, cleft palate, muscle hypotonia, skeletal anomalies (chest hypoplasia, curved short upper and lower limbs, *talipes equinovarus*) cardiac malformations, normal male genitalia. The X-ray examination showed bell-shaped, narrow thoracic cage, hypoplastic scapulae, reduced cranial, pelvic, tibial and fibular ossification, absence of nasal and sternal ossification, cervical kyphosis, 11 pairs of ribs, flat and short vertebral bodies, short humerus with widened distal epiphysis, anterolateral femoral and tibial bowing and ankle valgus deformity. Dextrocardia was identified on X-ray examination and on echocardiography. Karyotype was 46,XY. The particularities of cases are campomelic dysplasia with dextrocardia, but without sex-reversal.

Keywords: *campomelic dysplasia, plurimalformative syndrome, dextrocardia, absence of sex reversal*

Introduction

Campomelic dysplasia (CD) (OMIM #114290) is a very rare, sporadic, autosomal dominant syndrome with variable penetrance and expressivity. The term "campomelic", derived from the Greek word "campto" meaning bent and "melia" meaning limb; it refers to bowing of the long bones, primarily the tibiae and femur [1].

CD is characterized by a variable association of skeletal and extraskeletal abnormalities: bowed and fragile long bones, pelvis and chest abnormalities, eleven pairs of ribs, facial dysmorphism, cleft palate, sexual ambiguity in boys and heart, brain and kidney malformations [1-3].

Prevalence at birth ranges from 1/40,000 to 1/80,000 and the syndrome is associated with poor survival, primarily due to respiratory insufficiency [3-5]. Malformations such as micrognathia, retroglossia, cleft palate, narrow airways (caused by tracheobronchial cartilage defects), hypoplastic lungs, and a bell-shaped thorax are usually present and are the major cause of the severe respiratory problems that arise soon after birth, leading to death mostly during the neonatal period [6-8].

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Case report

We report a case of a 3 days old male with plurimalformative syndrome. He is the first child of normal, non-consanguineous, Caucasian parents without family history of congenital malformations, genetic disorders or reproductive trouble. The mother had 18 years old and the father had 21 years old at the moment of conception. The pregnancy course had been uneventful until 32 weeks of gestational age when a routine ultrasound scan showed polyhydramnios, protrusion of the parietal bones and predominantly mesoacromelic shortness of long bones. No known toxic, medical exposures or unusual events were reported during the gestation.

The child was delivered at term, by cesarean section, because of reduced fetal heart beats. Birth weight was 3700 g, length was 40 cm, head circumference was 39.5 cm and chest circumference was 33 cm. At birth, the boy displayed severe asphyxia and therefore needed intensive care.

Physical examination revealed disharmonic short stature (Figure 1), a craniofacial dysmorphism characterized by: macrocephaly with flat occiput, wide fontanels, high forehead, high anterior hairline, nevus flameus on forehead, hypertelorism, flat nasal bridge with anteverted nostrils and wide nasal base, short and deep philtrum, microretrognathia, microstomia, cleft palate, low-set and posteriorly rotated ears and short neck (Figure 2).

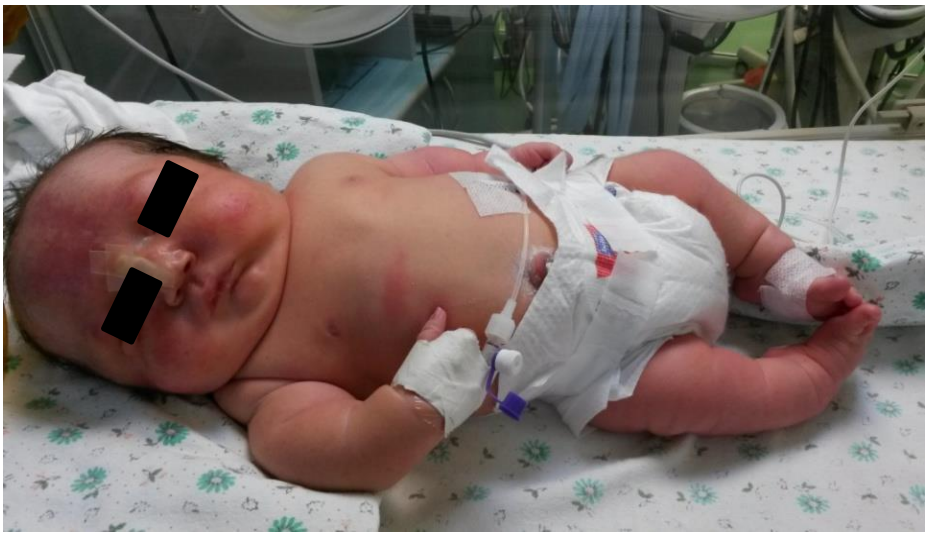

Fig. 1. General aspect with disharmonic short stature.

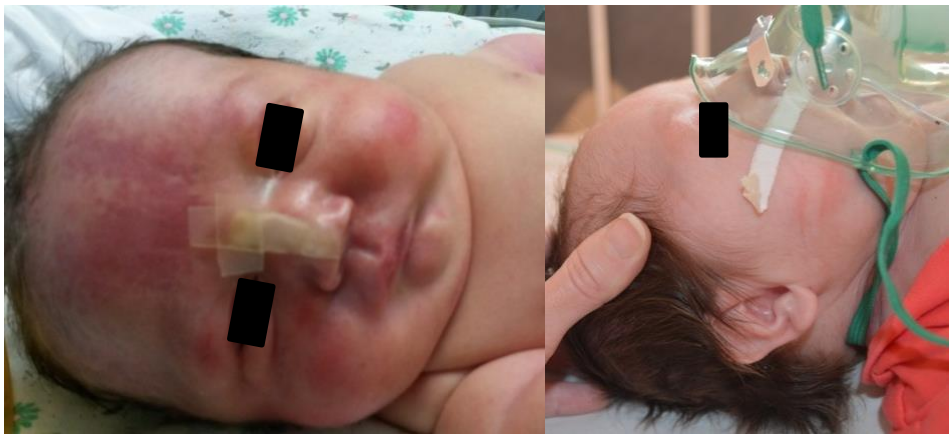

Fig. 2. Flat-appearing small face with high forehead, anterior frontal hair upsweep, low-set and posteriorly rotated ears.

Also we identified severe muscle hypotonia associated with skeletal anomalies: severe chest hypoplasia, curved short upper and lower limbs, talipes equinovarus. Genitalia was normal male (Figure 3).

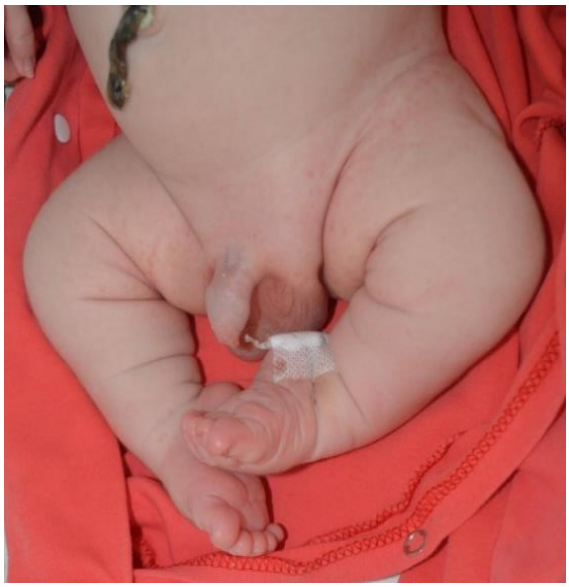

Fig. 3. Curved and short lower limbs, male normal external genitalia.

Cardiac examination and auscultation indicated the presence of dextrocardia. Echocardiography revealed dextrocardia, patent foramen ovale, persistent common atrioventricular canal, reduced left-to-right shunt, abnormal left ventricle relaxation, tricuspid aortic valve.

The abdominal ultrasound revealed hepatomegaly.

The X-ray examination showed bell-shaped, narrow thoracic cage, dextrocardia, hypoplastic scapulae, reduced cranial, pelvic, tibial and fibular ossification, absence of nasal and sternal ossification, cervical kyphosis, 11 pairs of ribs, flat and short vertebral bodies, short humerus with widened distal epiphysis, anterolateral femoral and tibial bowing and ankle valgus deformity (Figure 4).

Because of the multiple anomalies found, chromosomal analysis was performed and revealed, by GTG-banding, a normal male karyotype (Figure 5).

On the basis of characteristic clinical and radiologic features, we established the diagnosis of campomelic dysplasia without sex reversal.

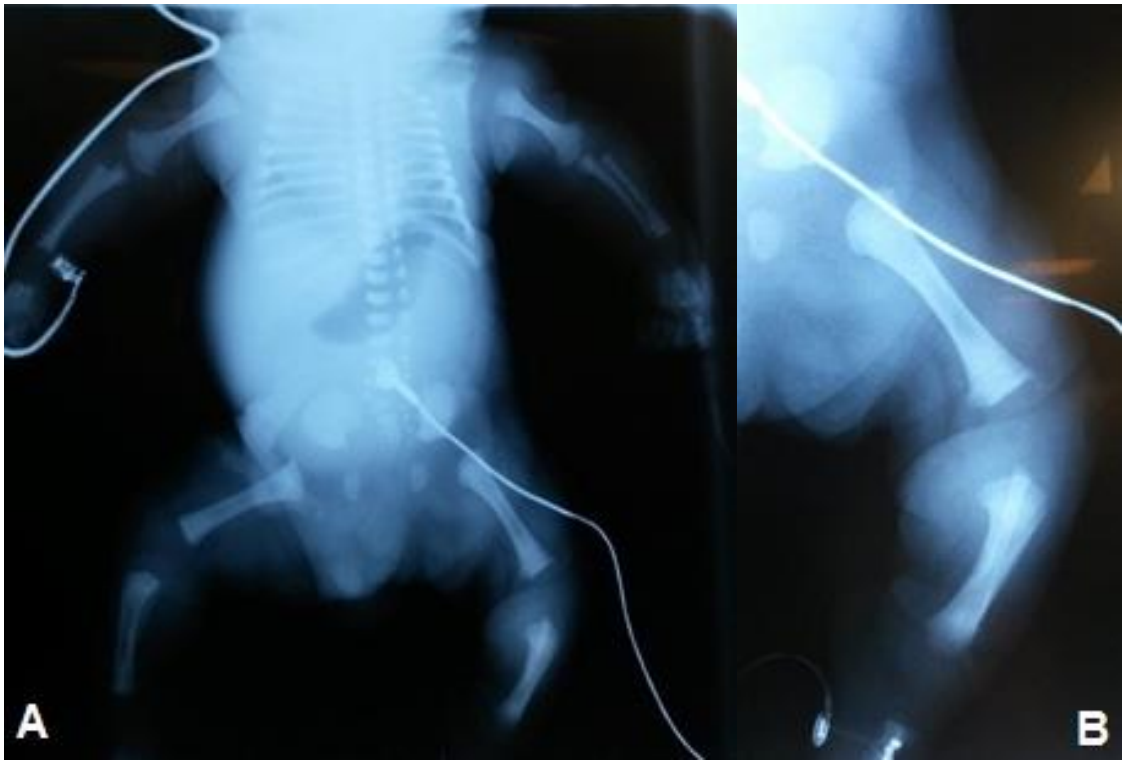

Fig. 4. (A) X-ray show bell-shaped, narrow thoracic cage, 11 pairs of ribs; (B) anterolateral femoral and tibial bowing.

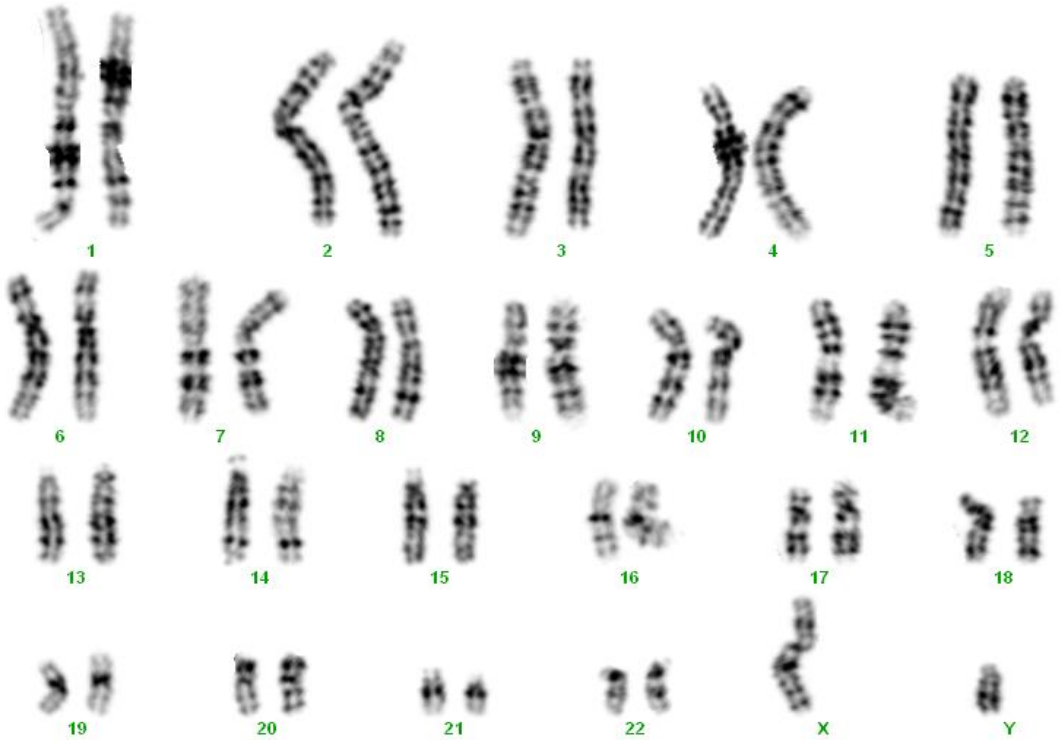

Fig. 5. Normal male karyotype 46,XY.

Discussions

CD is a rare plurimalformative syndrome that could be identified in prenatal period or immediately after birth.

The identification of a skeletal dysplasia in a prenatal setting generates a dilemma for both the physician and the family. Usually, prenatal diagnosis is made by ultrasound examination, completed by IRM. However, it is often difficult to establish a specific diagnosis before birth, and X ray examination after birth confirms the clinical supposition. The prenatal specific diagnosis is important to provide the informations about future prognosis and obstetrical management. Also, these data allow calculating the appropriate risk of recurrence in future pregnancies [6, 8, 9].

The prenatal diagnosis of CD by ultrasound examination is difficult, especially in cases when limbs are not bowed. Repeated prenatal ultrasound examinations could identify additional signs that allow a differential diagnosis with other skeletal dysplasia [9, 10].

In the presence of bowed limbs, the prenatal differential diagnosis of CD must consider Cummings syndrome, osteogenesis imperfecta type 2, hypophosphatasia, and thanatophoric dysplasia. Cummings syndrome is an autosomal recessive form of campomelic dysplasia that associate to skeletal malformations other anomalies like cystic disease (with renal, hepatic and pancreatic localization) cervical lymphocele or defects in laterality, manifested by polyasplenia complex, severe congenital heart disease and dextrocardia [11]. In our case, we exclude the diagnosis of Cumming syndrome because cystic disease, lymphocele and other defects of laterality (except dextrocardia) are missing. Osteogenesis imperfecta type 2 is a perinatal lethal form of an autosomal dominant skeletal dysplasia produced by mutation in *COL1A1* or *COL1A2* genes. The patients present severe skeletal deformations produced prenatally, secondary to multiple prenatal fractures that imply ribs and femur [12]. The absence of fractures in our patient can exclude the diagnosis of osteogenesis imperfecta type 2. The perinatal form of hypophosphatasia associates respiratory insufficiency and hypercalcemia [13]. The presence of dysmorphic features in our patient can exclude the diagnosis of hypophosphatasia. Thanatophoric dysplasia (TD) is a skeletal dysplasia characterized by association

between short limbs (most affected being humerus and femur), narrow thorax, and macrocephaly. Type I TD presents also bowed femurs and cloverleaf skull deformity. The majority of cases died in utero or immediately after birth by respiratory insufficiency. The disease is sporadic and is produced by autosomal dominant mutation in *FGFR3* gene [14]. The presence of dysmorphic features, the missing ribs and the cardiac malformation in our patient can exclude the diagnosis of thanatophoric dysplasia, type I.

After birth, the differential diagnosis is made with syndromes that present bone dysplasia. Spondyloepiphyseal dysplasia congenita is characterized by a very short stature with shortening of all bones. The mainly differences in our case are: dysmorphic feature and eleven pairs of ribs. Stüve-Wiedemann syndrome is a rare autosomal recessive dwarfism with bowed long bones, respiratory and feeding problems. The differences in our case are cardiac anomalies and thoracic dysplasia. Schwartz-Jampel syndrome is a rare disease that associate short stature, myotonia, chondrodysplasia and bowed long bones. We can exclude this condition in our case because our patient presents dysmorphic features, cardiac anomalies and thoracic dysplasia. Antley-Bixler syndrome is also a rare condition that associate craniosynostosis, radiohumeral synostosis, joint contractures and bowed long bones. The differences in our case are dysmorphic features, cardiac anomalies and absence of craniosynostosis. Diastrophic dysplasia is a form of dwarfism characterized by shortening of limbs, deformities of spine, contractures of joints, hitchhiker's thumb. The last feature is pathognomonic for diastrophic dysplasia and its absence in our case allows the exclusion [15-17].

The survival in CD is not long and the majority of patients die shortly after birth by respiratory insufficiency. In these cases the respiratory problems are secondary to tracheobronchomalacia or cervical spine instability. Such feature is different by comparison with other lethal skeletal dysplasias, where the cause of death is link to thoracic cage hypoplasia. The patients with CD that survived after neonatal period developed a progressive kyphoscoliosis [8]. Some survivors have mental retardation, but others have normal intelligence. The probability to survive in CD is estimated around 5-10 % [18].

Other characteristic of CD is ambiguous external genitalia. Approximately 75% of individuals with CD and 46,XY karyotype have intersex or even a normal female external genitalia. The internal genitalia are variable, often with a mixture of Müllerian and Wolffian duct structures. Our case is one of rare cases characterized by the absence of sexual ambiguity in a male newborn. The abnormal development of external and internal genitalia is linked to a de novo mutation in *SOX9* gene. This gene encodes a member of the sex-determining region Y (SRY)-related high-mobility group box family of transcription factors. The gene is located on human chromosome 17 (17q24.3-q25.1) and in some patients could be identified unbalanced or balanced rearrangements of chromosome 17. The presence of balanced translocations usually is associated with mild form of campomelic dysplasia, called acampomelic campomelic dysplasia [19-21].

The majority of cases are sporadic and affected individuals are heterozygotes for monogenic mutation in gene *SOX9*. The *SOX9* gene is a small gene, containing only three exons, but this gene is encompassed by a genomic region that contains regulatory elements located both upstream and downstream from the *SOX9* gene. The presence of this complex regulatory system explains the high variability of disease, characterized by campomelic dysplasia or acampomelic campomelic dysplasia with or without sex-reversal in 46,XY individuals [22, 23].

The abnormal development of skeleton in CD is induced by SOX9 gene's implication in chondrogenesis. The abnormal bone formation generates the main clinical features of CD: thoracic cage anomalies, poorly developed pelvian bone, delayed ossification of different bones, missing of ribs, shortening and bowing of femurs and tibias or facial/cranial anomalies [19, 24].

The confirmation of diagnosis in CD imposes molecular genetic testing of SOX9

gene and chromosomal analyses to detect rearrangements on chromosome 17. Application of both methods allows the confirmation of diagnosis in approximately 95% of affected individuals [3, 25].

As part of the family work up it is important to test the parents of the affected individual for the mutation detected, as there have been reports of somatic mosaicism and cases of parent-to-child transmission with a more severe phenotype in the affected offspring [16, 26].

Conclusions

CD is a rare skeletal dysplasia resulting from either autosomal dominant inheritance or gonadal mosaicism. Mutations in the *SOX9* gene located at 17q24–q25 locus have been implicated in the etiology of CD and have shown an association with both CD and sex reversal. When a skeletal dysplasia is suspected on ultrasound, a multidisciplinary team including maternal–fetal medicine, radiology, genetics and neonatology should be assembled to provide optimal care and complex management. The particularities of our case consist in the absence of sexual ambiguity and the presence of dextrocardia.

Conflict of interest

Authors declare no conflicts of interest.

Consent

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

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