CASE STUDIES

Campomelic Dysplasia

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Campomelic dysplasia is a rare congenital skeletal disorder. It is an autosomal dominant condition caused by mutation of the SOX9 gene on chromosome 17. Many different body systems can be harmfully affected, resulting in a variety of skeletal and extraskeletal anomalies attributable to the gene mutation. The most evident characteristics of the condition are symmetrical shortening and anterior bowing of the femurs and tibias. For most affected fetuses, death occurs in the fetal period or in the neonatal period shortly after birth. The primary cause of death is respiratory distress due to many possible factors such as micrognathia and hypoplastic chest cavity, lungs, or airways. Fetal sonography is fundamental in the detection of related defects and the ultimate diagnosis of the disorder.

Key words: campomelic dysplasia, SOX9 gene, hypoplasia, micrognathia

Campomelic dysplasia is a rare hereditary skeletal disorder characterized by abnormal curving of the long bones. Commonly referred to as camptomelic dysplasia, campomelic syndrome, or camptomelic dwarfism, it received its name from the Greek words *campto*, meaning bent, and *melia*, meaning limb. It is inherited as an autosomal dominant genetic trait, affecting approximately 1 in 10,000 newborns.[1] Facial, cardiac, central nervous system, respiratory, and genitourinary anomalies are frequently associated with this disorder. Sonographic detection is imperative for accurate prenatal diagnosis.

Case Report

A woman in her early 20s, gravida 1, para 0, presented for a routine sonogram to determine fetal size and dates. The sonogram revealed a 16-week, 6-day-old fetus with bilateral bowed femurs and

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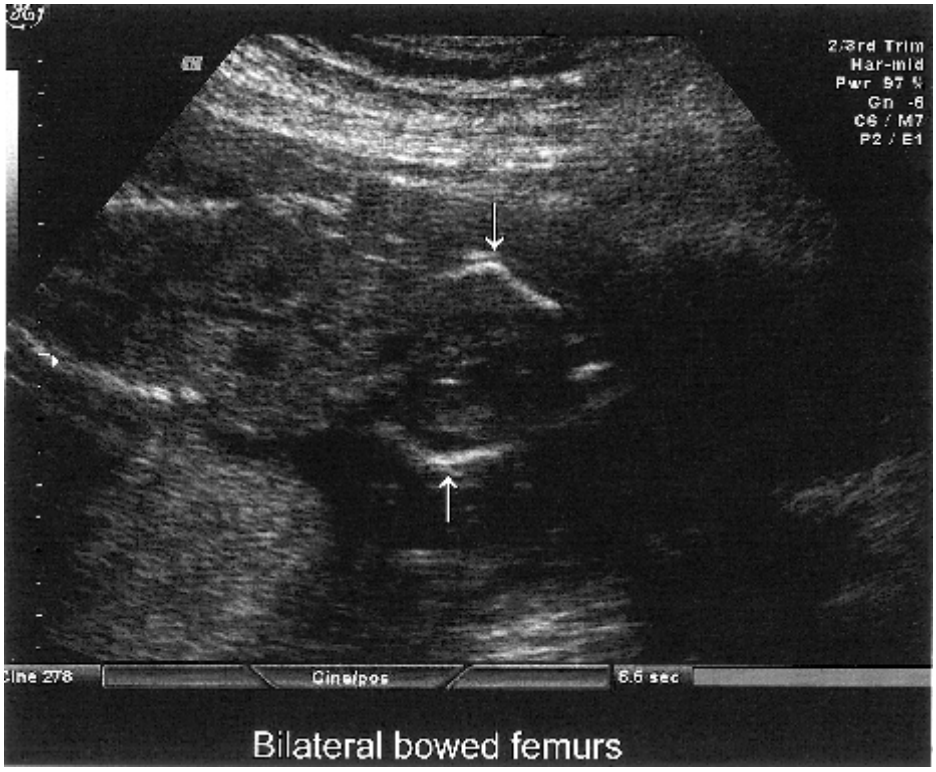

FIG. 1. Sonogram of a 16-week, 6-day-old fetus with bilateral bowed femurs.

tibias (Figs. 1-2), clubbed feet (Fig. 3), prominent c-spine curvature (Fig. 4), bell-shaped chest, pyelectasis in the right and left kidneys (Fig. 5), and micrognathia (Fig. 6). The findings were consistent with campomelic dysplasia.

The woman returned the following day and underwent a single-tap amniocentesis, where clear amniotic fluid was aspirated and sent for alpha-fetoprotein and karyotype testing. The results of the amniocentesis revealed a normal genetically female (XX) karyotype. The parents received genetic counseling and were thoroughly educated in the possible associated anomalies and lethalness of campomelic dysplasia. The patient was sent home with no risk to her own health. The physician's report stated that the ultrasound findings were consistent with campomelic dysplasia. A cesarean section was scheduled to be performed at 37 weeks of gestation. At birth, the baby weighed 6 lbs, 7 oz, and was 19.5 inches in length. This weight and height are in the 60th and 75th percentiles, respectively, and are impressive as they are in the upper limits for a child with campomelic dysplasia. The baby received oxygen in the delivery room and was moved to a special care nursery and put on continuous positive airway pressure (C-PAP) to assist with breathing. Initial radiographs revealed bowing of the femurs, less severe bowing of the tibias, and only 11 pairs of ribs. An echocardiogram was also performed shortly after birth; the report stated there was slight cardiac rotation with normal connections, function, and apical location. Physical examination confirmed the bilateral clubbed feet, micrognathia, and bell-shaped chest discovered by the ultrasound. Approximately 24 hours after birth, the baby girl's condition was improving. She was off the C-PAP, breathing normally, and successfully feeding from a bottle.

Discussion

Campomelic dysplasia is a rare and often lethal genetic disorder. It is caused by a variation in the SOX9 gene, located on chromosome 17. Normally, there are two copies of the SOX9 gene, one from the mother and one from the father. In the case of autosomal dominant disorders, such as campomelic dysplasia, only one altered gene copy

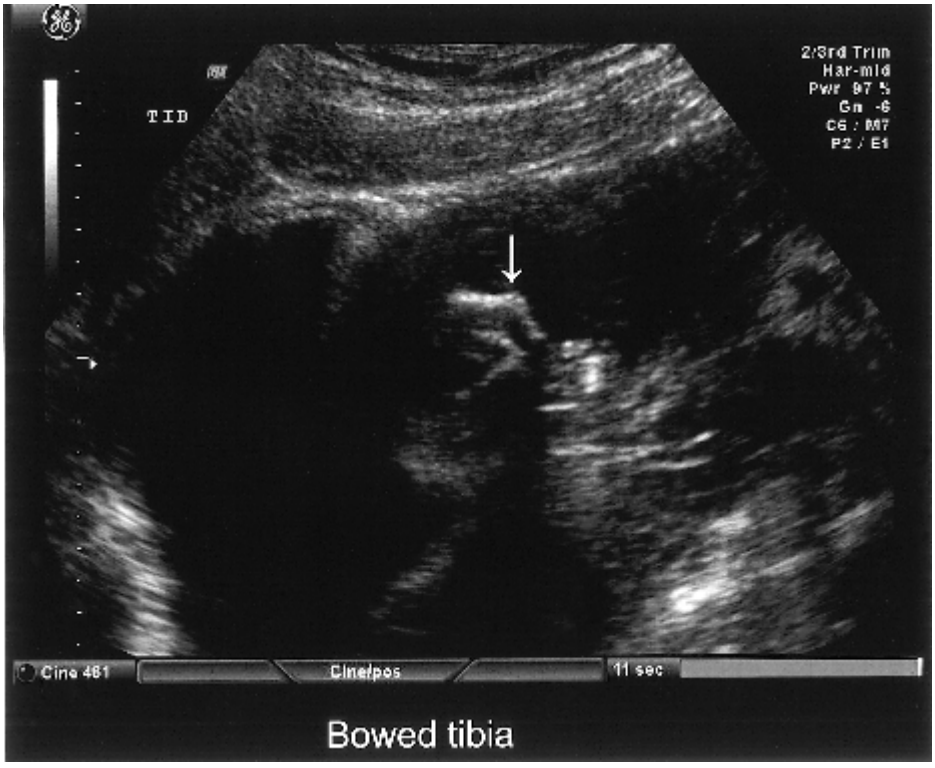

FIG. 2. Sonogram of a 16-week, 6-day-old fetus with bilateral bowed tibias.

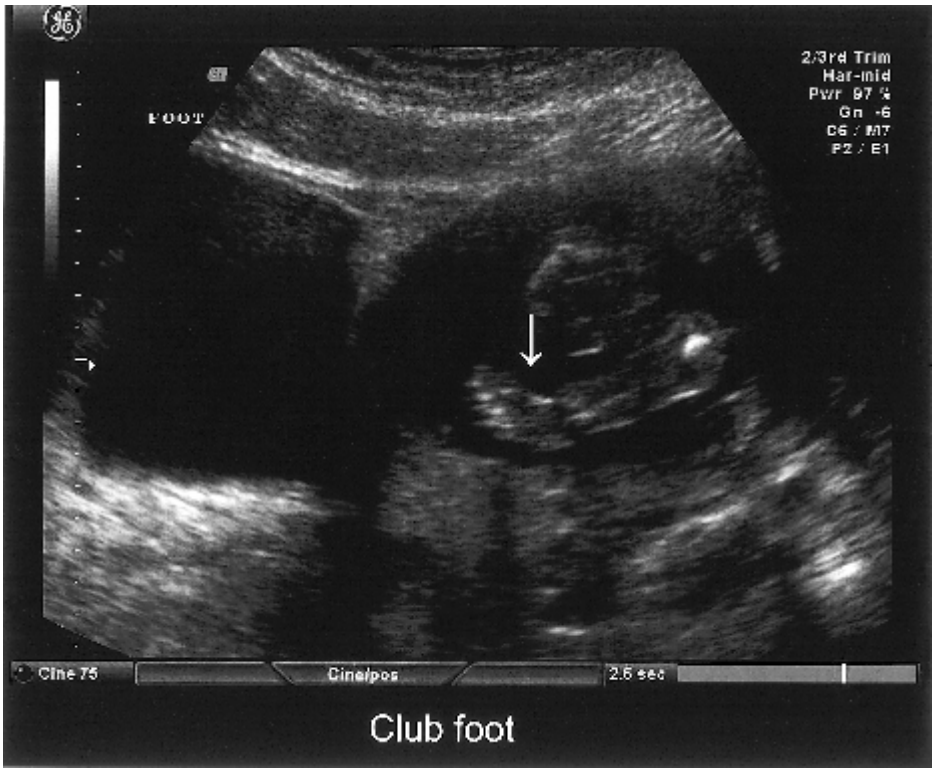

FIG. 3. Sonogram of a 16-week, 6-day-old fetus with clubbed feet.

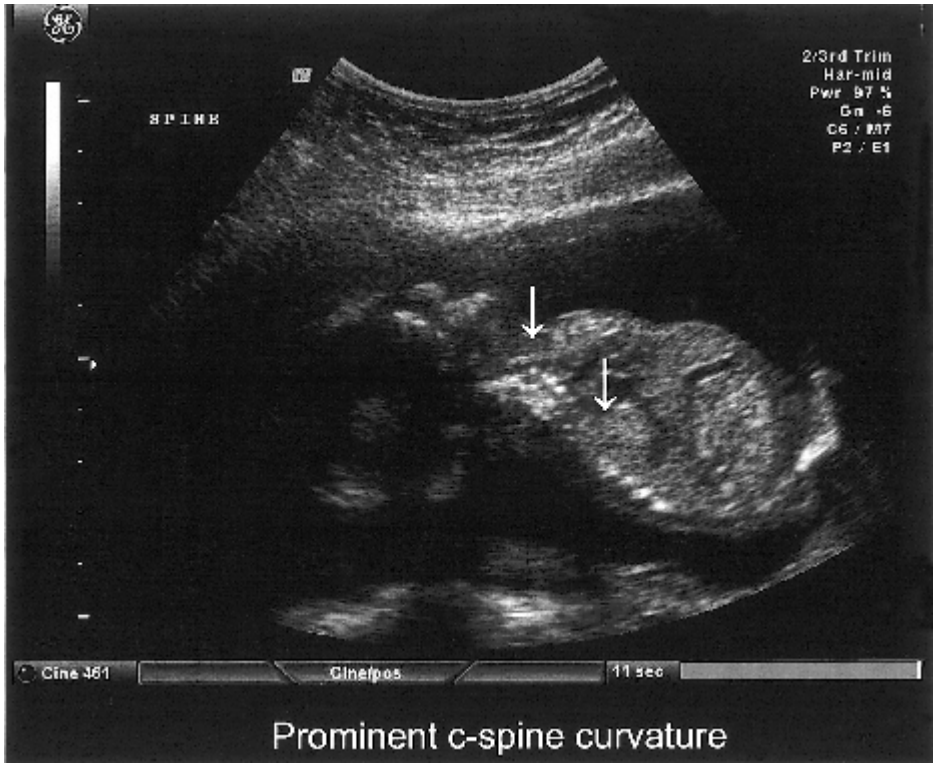

FIG. 4. Sonogram of a 16-week, 6-day-old fetus with prominent c-spine curvature.

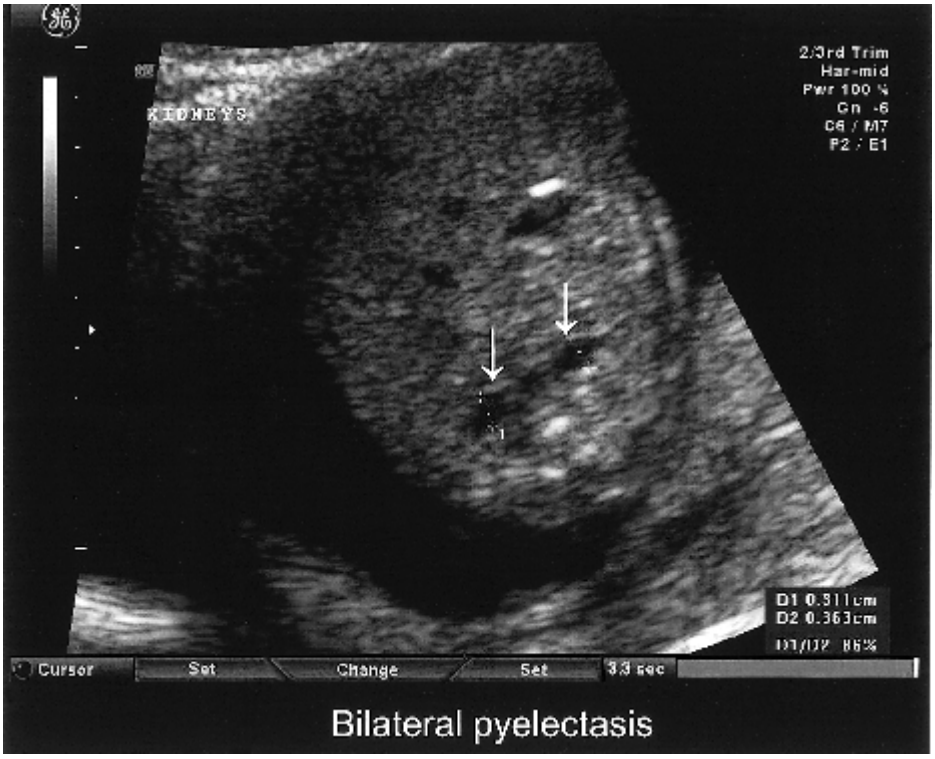

FIG. 5. Sonogram of a 16-week, 6-day-old fetus with pyelectasis in right and left kidneys.

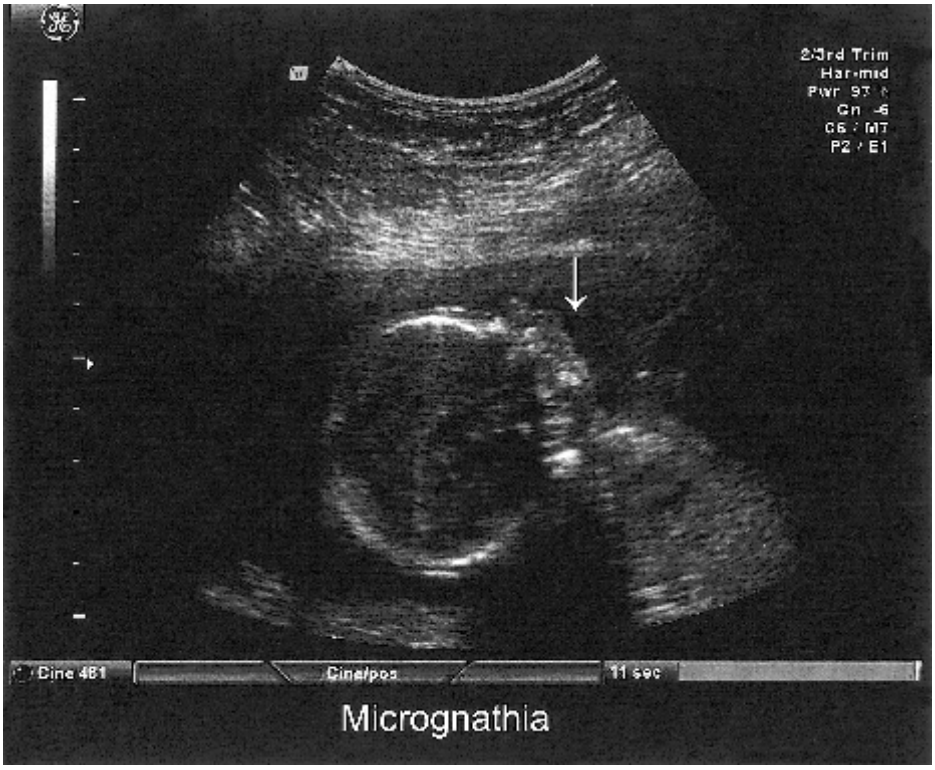

FIG. 6. Sonogram of a 16-week, 6-day-old fetus with micrognathia.

is needed to develop the condition. The actual cause of the alteration in the gene is random and therefore unknown. The probability for recurrence in siblings is only 5%.[2] It is possible for the altered gene to be passed on to offspring; however, there are no reported cases of people with campomelic dysplasia reproducing.

The SOX9 gene plays a role in both bone formation and testes development, which accounts for various skeletal and sex organ abnormalities associated with campomelic dysplasia. The incomplete bone formation can cause skeletal features such as small scapulae, small chest, curved or twisted spine, narrow iliac wings, poorly developed pubic bone, clubfoot, dislocated hips, short fingers and toes, and often only 11 pairs of ribs. The most prominent effects are of the appendicular skeleton, causing short limb bones and anterior bowing of the femurs and tibias. The facial anomalies caused by bone hypoplasia include cleft palate, flat nasal bridge, and micrognathia.

There are numerous extraskeletal anomalies associated with campomelic dysplasia. In addition to the facial anomalies caused by the bone deformation, other distinctive facial features are high forehead, small mouth, long philtrum, low-set ears, and widely spaced eyes. The central nervous system can be adversely affected in many ways. There can be absence of the olfactory tract or bulbs, hydrocephalus, polygyria, and/or macrocephaly. Polygyria is a condition in which the brain has an excessive number of gyri in the cerebral or cerebellar cortex. Otitis media, inflammation of the middle ear, can also occur, resulting in pain and deafness. The heart is another of the many organs that can be affected by the disorder. One-third of patients with campomelic dysplasia have cardiac defects such as ventricular and atrial septal defects, tetralogy of Fallot, and a patent ductus arteriosus.[3] The respiratory system abnormalities associated with campomelic dysplasia are small lungs, narrow airways, tracheomalacia, and laryngomalacia. These are from defective laryngotracheobronchial cartilage development and can result in apnea, atelectasis, aspiration, and pneumonia.

The involvement of the genitourinary system can result in renal anomalies in male or female patients and sex reversal in some male patients. Renal anomalies that can be present are hydronephrosis, pyelectasis, hydroureter, renal hypoplasia, and renal cortical and medullary cysts. Pyelectasis is dilatation of the renal pelvis, and progression of the dilatation into the renal calyces is considered hydronephrosis. The mutation of the SOX9 gene can cause the testes to form improperly, and male hormones are not produced. In the absence of the male hormones, a genetically male (XY) individual can grow as a normal female with ovarian, mullerian duct, and vaginal development. The male-to-female ratio of campomelic dysplasia is 1:1, and approximately 75% of genotypic XY males will exhibit female or ambiguous genitalia.[4]

Many of the abnormalities associated with campomelic dysplasia can be seen sonographically and are used in the definitive diagnosis. The most outstanding deformities are the bowed femurs and tibias with consequential symmetrical shortening. Those also detectable by sonography include cleft palate, micrognathia, pyelectasis or hydronephrosis, curved or twisted spine, small bell-shaped chest, clubfeet, cardiac defects, macrocephaly, and hydrocephalus. Polyhydramnios has been reported in 25% to 48% of affected cases.[5]

Differential diagnoses for campomelic dysplasia include thanatophoric dysplasia, hypophosphatasia, mesomelic dysplasia, Roberts syndrome, diastrophic dysplasia, and osteogenesis imperfecta. All of these disorders display similar abnormalities to those of campomelic dysplasia. Thanatophoric dysplasia is the most common form of skeletal dysplasia and is characterized by severe shortening of the limbs, a narrow thorax, macrocephaly, and a normal trunk length. Hypophosphatasia is a rare, inherited metabolic disease of decreased tissue nonspecific alkaline phosphatase and defective bone mineralization. These patients have skin-covered spurs extending from the forearms or legs, appear with short stature, and suffer from respiratory complications. Mesomelic dysplasia is a skeletal disorder characterized by hypoplasia or shortening of the ulna, radius, tibia, and fibula. Roberts syndrome is a rare developmental disorder characterized by symmetrical short limbs, bilateral cleft lip and palate, nose and ear anomalies, and severe mental and growth retardation. Diastrophic dysplasia is a rare growth disorder in which patients are usually short, have clubfeet, and have malformed joints. Osteogenesis imperfecta is a condition resulting from an abnormality in the type I collagen, which most commonly manifests as fragility of bones. Much like campomelic dysplasia, this condition can present with bowing of the lower limbs, but the tibial bowing is much more pronounced in campomelic dysplasia and accompanied by the bowing of the femurs.

The prognosis for patients diagnosed with campomelic dysplasia is poor, resulting in fetal or early neonatal death due to respiratory complications. These complications usually develop from the small chest size, hypoplastic lungs, narrow airway passages, micrognathia, or a combination of these abnormalities. Micrognathia is fatal in many cases due to the anterior attachment of the tongue being displaced posterior, therefore falling back into the pharynx and obstructing the airway. This increases the patient's risk for regurgitation and aspiration due to difficulties in breathing and feeding simultaneously. Because of the high mortality rate of fetuses with campomelic dysplasia, termination of pregnancy is offered if the disorder is detected early. In cases of termination, the placenta should be sampled to acquire DNA for SOX9 mutation analysis to assist in determining recurrence rates for future pregnancies.

Parents who choose to continue with the pregnancy should prepare to deliver the baby at a tertiary care center to ensure extensive medical treatment. Upon delivery, the infant should undergo a complete physical examination and radiograph to confirm diagnosis. Once diagnosis is confirmed, the infant's hearing should be assessed and heart evaluated because of the increased risk for hearing loss and heart defects. All affected infants, due to respiratory distress, require oxygen or a mechanical ventilator to assist with breathing. An orthopedist should be consulted to advise the parents about potential treatments such as bracing or surgery for the curved spine, clubfeet, dislocated hip, and bowed legs. In cases of sex reversal, it is recommended that the gonads be removed because of the increased risk for tumor growth.

A study conducted by Mansour et al[5] in 1995 evaluated 36 cases and reported that 77% died in

the neonatal period. Although the majority of infants die within a few hours after birth, rare survivors of campomelic dysplasia have been reported. Survival beyond the first year of life improves the prognosis somewhat, but feeding, respiratory, and auditory problems will most likely remain. The oldest reported campomelic dysplasia survivor was 17 years old with an IQ of 45.[6] Little People of America is a nonprofit organization that provides information and support for campomelic dysplasia survivors and their families.

Conclusion

Campomelic dysplasia is a rare, genetic skeletal condition caused by mutation of the SOX9 gene located on chromosome 17. It comprises various anomalies, affecting many areas of the body with the signature characteristic being shortening and anterior bowing of the femurs and tibias. Respiratory distress is the cause of death in most cases, occurring shortly after birth. A thorough fetal sonogram is essential for the visualization of associated abnormalities and the precise prenatal diagnosis of the disorder.

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