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Unusual association of diseases/symptoms

Campomelic dysplasia and malignant hyperthermia

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Summary

Campomelic dysplasia (CD) is a rare clinical entity, usually fatal in the first year of life. It is characterised by bowing and angulations of long bones, along with other congenital anomalies. The occurrence of malignant hyperthermia is rare, but it has been associated with skeletal dysplasias. The authors present the case of a boy, born at 40 weeks of gestational age, with multiple congenital anomalies and subsequently diagnosed with CD, who died at 16 months of age as a consequence of malignant hyperthermia.

BACKGROUND

Campomelic dysplasia (CD) is a rare clinical entity affecting approximately 1 in 200 000 live births. Usually fatal in the first year of life, this severe osteochondrodysplasia is characterised by congenital bowing and angulations of long bones.[1] Several other anomalies compromise the normal orofacial, cardiopulmonary, neurological and genitourinary development. There is a reported prevalence of hydronephrosis in 38% of CD patients and 21% have ventricular septal defects.[1 2]

Different mutations of SOX9 gene in chromosome 17q24-q25 have been implied in the pathogenesis of CD through an abnormal expression of gene COL2A1, generating an anomalous collagen. It is inherited in an autosomal dominant manner but is most commonly the result of a de novo dominant mutation, with variable penetrance and expressivity.[3 4] The prognosis is variable, ranging from high risk of neonatal mortality to rare cases of survival till adolescence.[5] The management of a newborn with prenatal or presumptive neonatal diagnosis of CD raises several

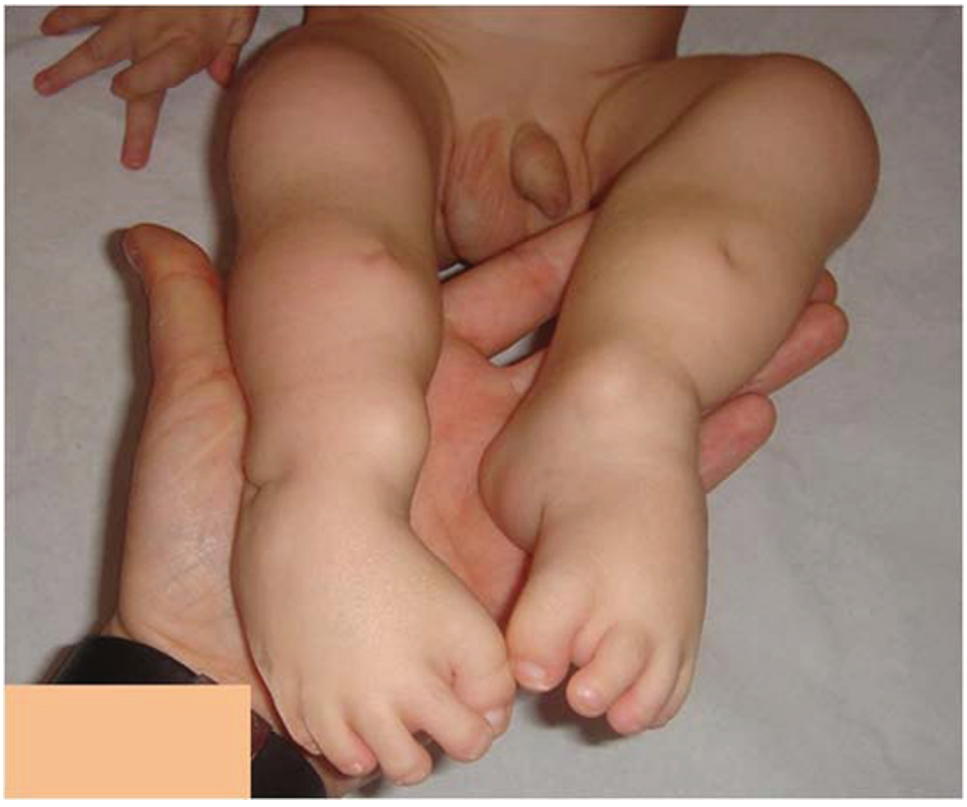

Figure 1 Lower extremities with clinical features of CD, including cutaneous dimples, tibial bowing and feet deformation.

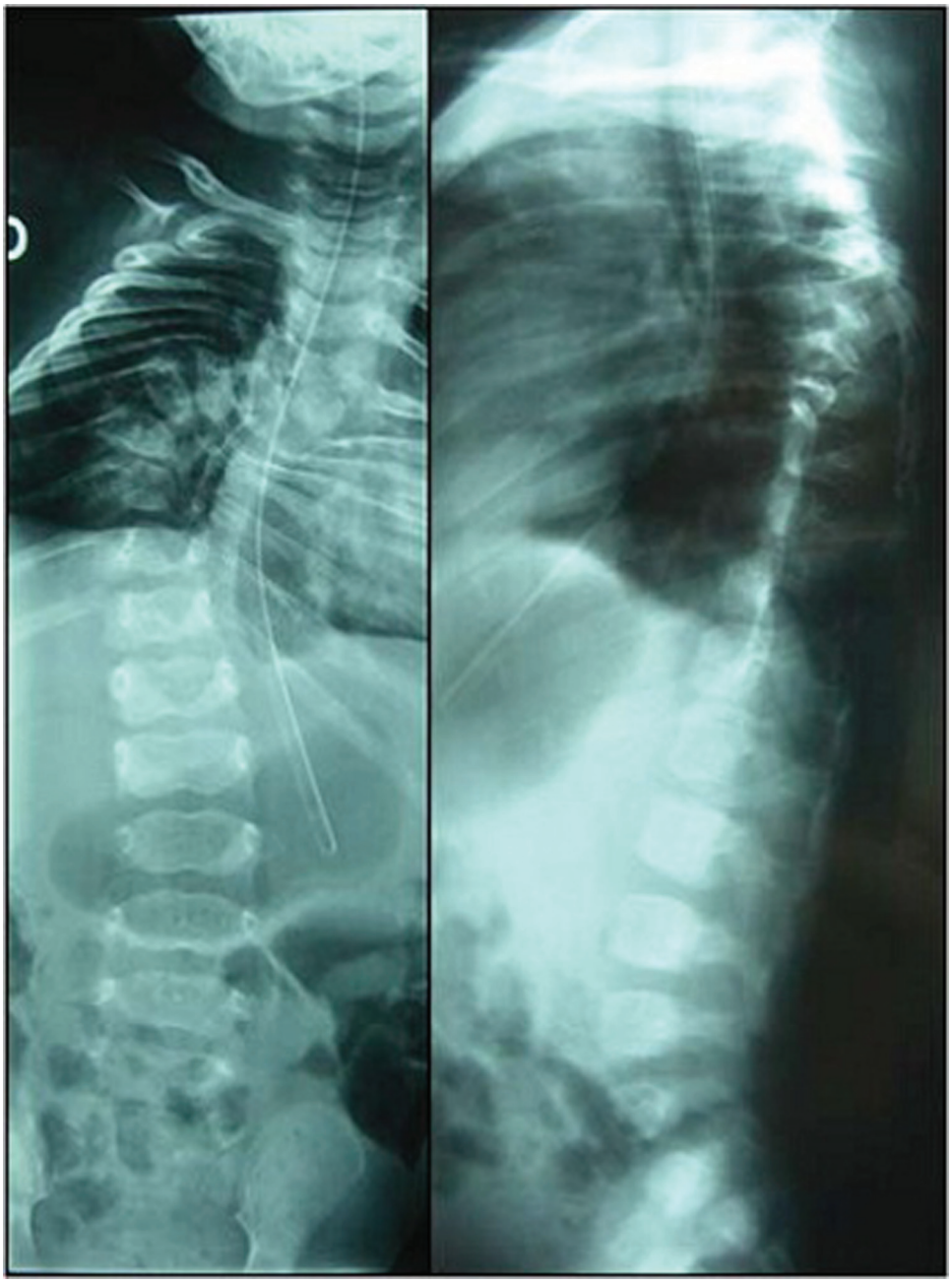

Figure 2 Spine radiographs showing a small thoracic cage, 11 pairs of ribs and marked thoracic scoliosis.

ethical questions, particularly regarding heroic maneuvers in situations of imminent death.

The authors describe the case of an infant with postnatal diagnosis of CD, who died at 16 months of age from malignant hyperthermia and multiorgan failure.

CASE PRESENTATION

The authors report the case of a newborn, male, third son of unrelated parents, with two previously healthy daughters. The mother was 31 years old, with obstetric index 5233 and no history of congenital malformations or medical disease. The pregnancy had been uneventful and the foetal sonograms were reported as normal. He was born at 40 weeks postconception age by normal vaginal delivery. Apgar score was 8/9 (1'/5'). At birth, his weight was 2965 g (25th percentile), length 45 cm (<5th percentile) and head circumference 38 cm (>95th percentile). Physical examination of the neonate revealed dysmorphic features: facial dysmorphias (low set ears, long philtrum, micrognathia and cleft palate), dolicocephaly, small thoracic cavity, shortening of all four limbs, tibial bowing, multiple cutaneous dimples and bilateral feet deformation (figure 1). External genitalia were of normal male appearance.

Radiographs showed dorsal scoliosis, 11 pairs of ribs and severe hypoplastic scapulae (figure 2), bilateral hip dislocation, abnormally vertical iliac bones, bowing of the long bones, fibular hemimelia and clubfeet (figure 3). The diagnosis of CD was confirmed in consultation with an orthopaedic surgeon and geneticist. Other skeletal dysplasias were excluded, based on clinical and radiological

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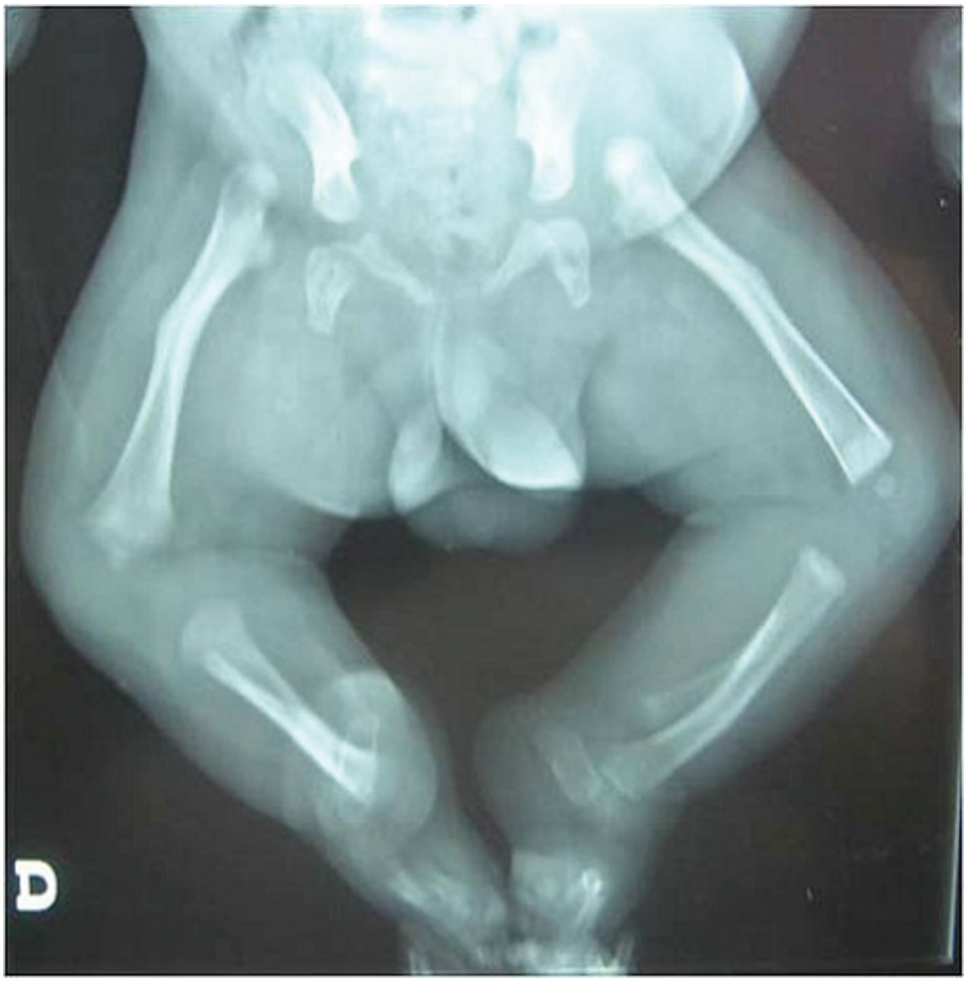

Figure 3 Lower extremities radiograph denoting hip displacement, vertical iliac bones and shortened and bowed long bones.

features (table 1). Karyotype revealed 46XY with a pericentric inversion at the polymorphic region of chromosome 9. The mother's karyotype presented the same inversion and the father's was normal.

The patient's breathing pattern was consistent with laryngomalacia and he required supplemental oxygen in the first 2 days of life. Respiratory support at discharge was not required.

Echocardiography revealed a large interventricular communication, with spontaneous resolution by the age of 5 months. A cranial ultrasound (US) detected a subependymal pseudocyst without ventricular ectasia and renal US was normal.

Nasogastric feeding (bolus) was maintained until 2 weeks of age. He presented with persistent hypotonia, neurodevelopment delay and feeding difficulties. Surgical correction of cleft palate was programmed for the second year of life. The parents consented to a gastrostomy. Orthopaedic interventions were also considered and discussed with the parents.

At 9 months, he was admitted to the paediatric intensive care unit with upper gastrointestinal bleeding, community acquired pneumonia and cardiorespiratory arrest, requiring cardiopulmonary resuscitation and invasive mechanical ventilation. He was discharged home on day 7, without oxygen support.

At 16 months of age, he was admitted with respiratory distress and developed prolonged fever (>41°C) with hypercarbia (92 mm Hg) and high serum creatine kinase (1.619 IU/l). This was consistent with malignant hyperthermia, not reverted with either the usual antipyretic drugs nor with dantrolene, resulting in cardiorespiratory arrest and death.

DISCUSSION

Fatal skeletal dysplasias are a rare, but important, group of heterogeneous disorders identified by abnormal growth of bone and cartilage. CD is a condition characterised by bowing of the long bones (particularly the lower extremities) and a wide variety of associated abnormalities, including hydrocephalus, congenital heart disease and hydronephrosis. Dysplasias can be suspected antenatally, especially if bowing of long bones is seen. However, such hallmarks can be mild, even absent in acampomelic forms of CD or present in other skeletal dysplasia.[6 7] Recent studies[6] report CD to be responsible for 3–8% of prenatal sonographic diagnosis of skeletal dysplasias.

In this particular case, all the clinical findings and musculoskeletal manifestations supported the diagnosis of CD after birth. Other skeletal dysplasias should be considered, since bowed bones are not exclusive to CD (table 1).[1 7 8] Mansour *et al* suggested clinical and radiological criteria

Table 1 Differential diagnosis of bent bones skeletal dysplasia

Bent bones dysplasia		
Campomelic dysplasia	Antley-Bixler syndrome	Dysegmental dysplasia
Stüve-Wiedmann dysplasia	Cartilage hair hypoplasia	Hypophosphatasia
Cumming syndrome	Kyphomelic dysplasia	Osteogenesis imperfecta

for CD. The presence of three of the five radiologic features helps to establish the diagnosis: hypoplastic scapulas, bowed femurs, bowed tibias, vertically narrow iliac wings and non-mineralised thoracic pedicles.[2]

The patient's karyotype revealed 46 XY and pericentric inversion at the polymorphic region of chromosome 9. This inversion, also present in the mother, has been considered a normal variant and is present in 3% of the general population.[9] There was no sex reversal as described in some patients. Genetic test for the specific mutation was not available.

Severe respiratory insufficiency is the most common cause of death in the neonatal period. It arises from several anomalies such as tracheobronchial and lung hypoplasia, craniofacial anomalies and hypotonia.[2 5] Patients with milder forms of CD can survive longer periods. Better neonatal and respiratory care have also prolonged survival.

The associated spinal anomalies include craniocervical junction instability, hypoplastic thoracic pedicles and progressive cervicothoracic and lumbar kyphoscoliosis.[4] Several attempts have been made to prevent the progressive kyphoscoliosis responsible for respiratory and neurological compromise. Initial treatments with braces (Milwaukee type) or early aggressive surgical correction have been prescribed, despite a 50% risk of pseudoarthosis.[4] In this case report, orthopaedic intervention (cervical stabilisation) was considered. Feeding facilitation was also discussed with the parents and gastrostomy was considered. Surgical correction of the cleft palate was programmed for the second year of life.

These patients pose true challenges and need a multidisciplinary team. They require orthopaedic, gastroenterology, pulmonary, neurosurgery and plastic surgery care in order to achieve a satisfactory quality of life.

Malignant hyperthermia is usually associated with inhaled anaesthetics and succinylcholine.[10] There are a few reports of malignant hyperthermia in skeletal dysplasia.[11 12] There are also several genes responsible for malignant hyperthermia susceptibility, such as the MHS2 gene located in chromosome 17q11.1-24,[11] near to the SOX9 gene. In this case, the absence of genetic testing prevented any conclusion. Nonetheless, in a patient with CD and possible malignant hyperthermia, it is important to establish an early diagnosis, treatment with dantrolene and eviction of potential inciting agents on future occasions.

Several ethical question are posed when assisting a CD patient and their family. Difficult questions arise, from the neonatal care specialist in assisting a newborn with no prenatal diagnosis, to the intensive care specialist upon cardiorespiratory arrest scenario and to the surgeons in proceeding with aggressive, non–risk-free interventions. These decisions require a multidisciplinary team and discussion with the parents in order to offer the best treatment and quality of life to CD patients.

Learning points

- CD is a rare and usually fatal skeletal dysplasia in the neonatal period. It should be suspected prenatally, especially if bowing of long bones is seen.[13]
- Milder forms have longer survival rates and require a multidisciplinary team to search for the best treatment in respiratory, orthopaedic, gastroenterology and plastic surgery care.
- In a patient with CD and suspicious of malignant hyperthermia, it is important to establish an early diagnosis and treatment with dantrolene.
- Eviction of potential inciting agents for malignant hyperthermia is mandatory.

Competing interests None.

Patient consent Obtained.

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