A rare case of lethal campomelic dysplasia

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Abstract

Campomelic dysplasia is a rare and mostly lethal congenital malformation. It is known as an autosomal dominant disorder due to mutations in SOX9, a member of the SOX (SRY-related HMG box) gene family. Here we report a case of a 26 years old primigravida married for 3 years with a history of consanguinity. She was impregnated by intracytoplasmic sperm injection (ICSI) due to male factor infertility. This mostly lethal skeletal anomaly was diagnosed by detailed ultrasonography in the late second trimester. She underwent an induction of labor termination due to intrauterine fetal demise.

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Introduction

Campomelic dysplasia (CD) is mostly lethal skeletal malformation syndrome characterized by abnormal curving of the long bones.[1] It is believed to be an autosomal dominant genetic trait and the mutation is located at 17 q 24.3 – q 25.1.[2]

It is characterized by macrocephaly, mid-face hypoplasia, hip dislocation, bowed femora and tibiae (i.e., campomelia), talipes, missing pairs of ribs, narrow thorax and respiratory distress. In addition, hydrocephalus, hydronephrosis, and congenital heart disease (ventriculoseptal defect, atrioseptal defect, aortic stenosis, and/or tetralogy of Fallot) are also present.[3] Another feature of CD is male-to-female sex reversal, which occurs in about two-thirds of patients with an XY karyotype.[3] Antenatal ultrasound scanning at about 18 to 20 weeks of gestation permits the

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detection of large number of major fetal structural anomalies.[4]

A considerable proportion of males requiring intracytoplasmic sperm injection (ICSI) have a very low sperm count, which is associated with a greater risk of chromosomal abnormalities.[5] Spermatozoa selection for ICSI is typically based on motility and morphology attributes, without information about the chromosomal status.[6]

In children born after standard in vitro fertilization (IVF) and ICSI, the rate of major congenital malformations is around 4%.[7] The most common congenital malformations associated with ICSI conceived children are urogenital malformations, especially hypospadias, as well as cardiac defects, tracheo-esophageal fistula, and renal malformations.[8]

Herein, we present a rare case of campomelic dysplasia diagnosed at 27 weeks in pregnancy achieved by ICSI.

Case presentation

A 26-year-old primigravida married for 3 year with a history of consanguinity (first cousin) conceived after ICSI due to male factor infertility. The patient was referred to our tertiary fetal medicine unit for a sonogram at 27 weeks gestation. The ultrasound scan revealed the presence of shortened fetal extremities with possible fractures in all four distal long bones.

The patient had regular prenatal care visits at a primary health care unit, where her obstetrician suspected fetal congenital anomalies and referred her to our specialized unit.

Ultrasound findings showed a male fetus with average biometry for 27 weeks gestation. The fetus showed short radius and ulna (Figure 1A), hypoplastic scapula, small thoracic cavity (Figure 1B), bilateral bowing of the femurs (Figure 1C), mild unilateral ventriculomegaly, low-set ears and kyphoscoliosis. The umbilical cord showed an umbilical vein varix by Doppler evaluation (Figure 1D).

One week later, the patient presented with absent fetal movement. Ultrasound examination revealed occurrence of intrauterine fetal death (IUFD). After counseling, the patient elected to undergo induction of labor. Informed written consent was obtained from the patient and her husband, and medical induction of labor was done at 28 weeks using vaginal misoprostol, 50 mcg every 6 hours, until delivery occurred.

Physical examination of the neonate revealed dysmorphic features including four shortened limbs with prominent bowing of the lower extremities. Distortion of the cervical vertebral bodies was also noted, as were hypoplastic scapula and small chest cavity. A medical genetic consultation was obtained and a preliminary diagnosis of CD was made. Cytogenetic study was not possible as the fetus was too macerated.

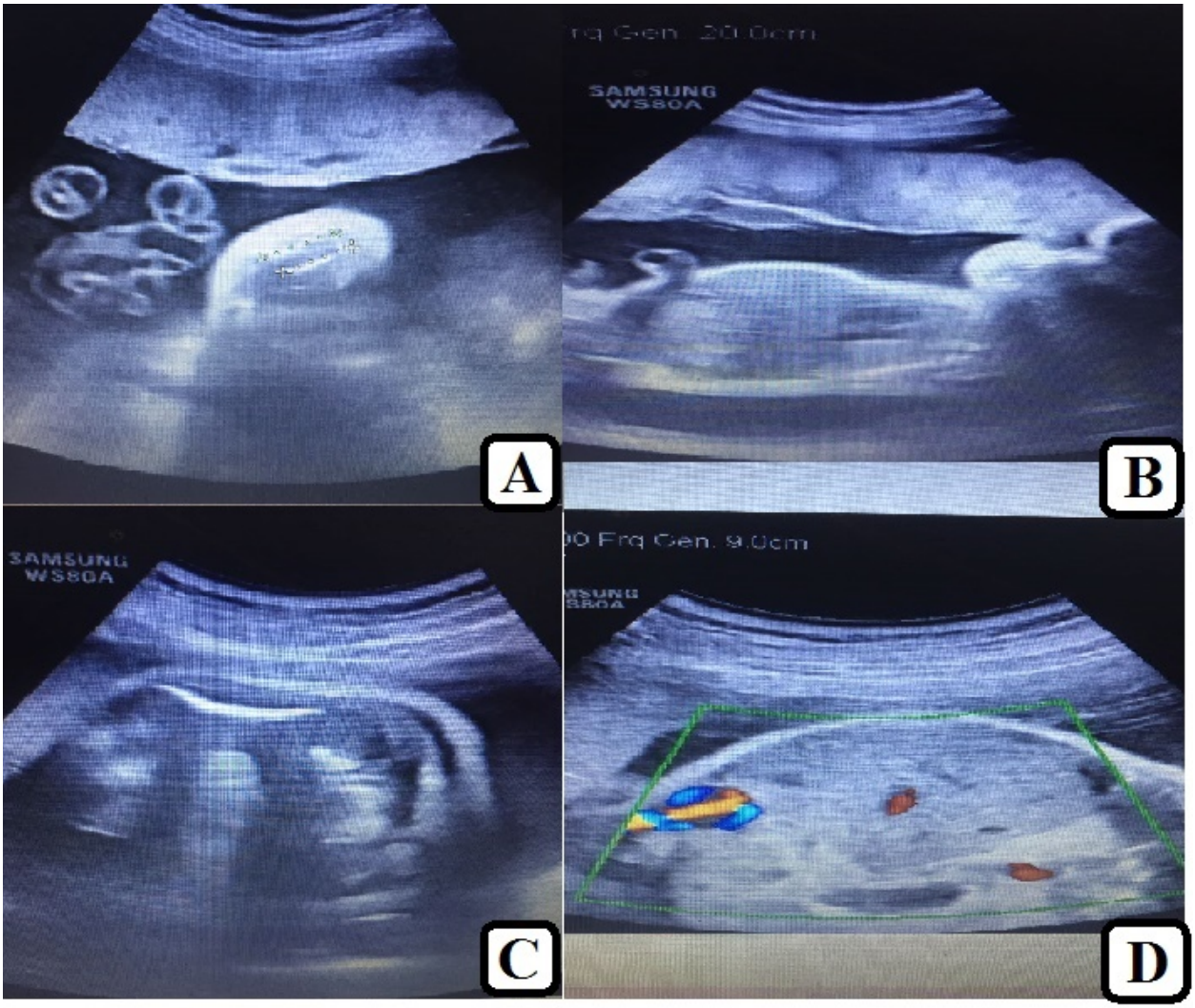

Figure 1: Ultrasound and Doppler evaluation of the fetus at 27 weeks gestation showing the following abnormalities. 1A: Short radius and ulna, 1B: Small bell shaped thorax, 1C: Short bowed femur and 1D: Umbilical vein varix.

Discussion

In several countries, prenatal diagnosis achieved by ultrasound scan is now a regular part of prenatal care. Ultrasonographic evaluation has been reported to identify 26.2% of fetuses having isolated malformations and 66.0% of fetuses having multiple malformations.[9]

One type of skeletal dysplasia, CD is a rare and mostly lethal condition observed with an incidence of 0.05-1.6 in 10,000 live births. It is known as an autosomal dominant disorder.[10] A definitive reason why this alteration happens in the gene is still unknown. The term “campomelic” refers to the angulations of long bones.

Characteristic features of CD are

skeletal hypoplasia and anomalies affecting the face, head, scapulae, spine, pelvis, and upper and lower limbs. The head is macrocephalic with a flattened face and nasal bridge, high forehead, low-set ears often with associated deafness, hypertelorism, long philtrum, small mouth, and micrognathia.[3] Cardiac diseases like ventricular and atrial septal defects, tetralogy of Fallot, and patent ductus arteriosus can also be detected. In addition, a group of respiratory anomalies that includes lungs and chest of a small size, narrow air-passages, tracheomalacia, laryngomalacia associated with cleft palate, micrognathia, and hypotonia may be present.[11]

The skeletal features that were the most prominent characteristics of CD as presented in our case including hypoplastic scapula, bilateral bowing of femurs, a small thoracic cavity and kyphoscoliosis.

Most cases of CD are caused by heterozygous de novo mutations of the SOX9 gene at the chromosome 17q24.3-q25.1.[2] The modification of the SOX9 gene may cause defected development of the testes and undersupplied male hormones. There is no sex discrimination, as the male-to-female ratio of campomelic dysplasia incidence is 1:1; however, 75% of genotypic XY males show female or indefinite genitalia.[3]

To date there are only a few reports on the skeletal features of campomelic syndrome in the literature.[12] To our knowledge, all reported cases of CD are the results of natural conception while in our case this pregnancy was achieved by assisted reproductive technology. Even though the rate of congenital malformations after ICSI (and standard IVF) is somewhat increased, no increased risk of dominant mutations has been described. CD seems not previously to have been reported in infants conceived by ICSI.[13] The most common congenital malformations associated with children born by ART techniques are urogenital malformations, especially hypospadias, as well as by cardiac defects, tracheo-esophageal fistula, and renal malformations.[8] Campomelic dysplasia has not previously been reported in ICSI conceived children.

With the diagnosis of this lethal malformation, couples and physicians are faced with both medical and moral decisions. Furthermore, newborn prognosis may be compromised by the timing of the diagnosis. These problems are common with the detection of any severe and potentially lethal malformation. How the news of a lethal malformation is handled depends on the moral and religious views of the parents as well as the legal and cultural mores concerning induced abortion in the society in which they live.

A high percentage of neonates with CD will die tragically from respiratory compromise in the neonatal period. If an infant survives the first 28 days, it may additionally be plagued by feeding problems, failure to grow normally and central nervous system developmental disorders, including developmental delay and mental retardation .[14] The decision to terminate may be difficult for parents, especially in cases in which

pregnancy was achieved after a long period of infertility and by using ICSI techniques. However, in our case the decision to terminate was simplified by the occurrence of IUFD.

Conclusion

To our knowledge, ours is the first case of campomelic dysplasia after ICSI conception reported in literature.

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