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SHORT REPORT

Usefulness of fetal autopsy in the diagnosis of blomstrand chondrodysplasia: a report of three cases

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Abstract

Blomstrand osteochondrodysplasia (BOCD) is a rare autosomal recessive sclerosing skeletal dysplasia characterized by accelerated chondrocyte differentiation. In this article, we discuss three cases where lethal skeletal dysplasia was suspected and Blomstrand dysplasia was diagnosed by autopsy. Antenatal ultrasound findings include increased nuchal translucency, tetramicromelia and polyhydramnios. Radiological hallmark is advanced skeletal maturation and bone sclerosis. Histology of long bones revealed narrow cartilagenous cap and changes in the physeal growth zone which showed severe hypoplasia and disorganization of proliferative phase and hypertrophic phase. Homozygous and compound heterozygous mutations in PTHR1 gene have been implicated in the pathogenesis of this chondrodysplasia.

Keywords

Blomstrand, chondrodysplasia, sclerosing

History

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Introduction

Blomstrand osteochondrodysplasia (BOCD) is a lethal autosomal recessive skeletal dysplasia caused by homozygous or compound heterozygous inactivating mutations encoding parathyroid hormone receptor – 1 gene. Clinically BOCD is characterized by polyhydramnios, hydrops, tetramicromelia, facial dysmorphism and abnormalities in the breast and tooth development. Characteristic radiological findings include increased bone density and advanced skeletal maturation. We present three fetuses with the Blomstrand chondrodysplasia, two of whom are siblings.

Case 1

This male fetus was delivered at 20 weeks and was evaluated in view of lethal skeletal dysplasia. The parents were second-degree consanguineous Indian couple and this was their first pregnancy. Ultrasound at 20 weeks revealed mild hydramnios, dysmorphic facies and short long bones. All long bones were short (<4SD) for gestational age with a lag of 9–10 weeks. Additional findings included abnormal shape of skull, narrow thorax and protuberant abdomen. Hence, a provisional diagnosis of thanatophoric dysplasia was considered. The couple opted to terminate the pregnancy and fetus was subjected to detailed autopsy. The male fetus weighed 440 g, Crown heel length was 21 cm and head circumference measured 22 cm. On examination the fetus appeared hydropic and markedly dysmorphic with facial hirsutism, bilateral proptosis, hypertelorism, short nose and micrognathia. Both upper and lower limbs were severely rhizomesoacromelic (Figure 1 -IA,IB). Internal organs were structurally normal. Fetogram revealed large vault with frontal bossing, absent nasal bone, maxillary and mandibular hypoplasia with harlequin orbits. Long bones were all markedly short and misshapen with bulbous ends. The most striking feature was osteosclerosis and advanced skeletal maturation in all long bones (Figure 1-IC,ID). Premature ossification of carpal and tarsal bones was seen. Vertebral bodies showed mild platyspondyly. All these features suggested a diagnosis of BOCD. Bone histology revealed a very narrow epiphyseal cartilage cap and the cartilage bone junction was abnormal and irregular (Figure 2). The proliferative and hypertrophic phase were completely absent in some foci and retarded and disorganized in others (Figure 3). Metaphysis was severely abnormal with broad and short trabeculae. The diaphyseal trabeculae were coarse, irregular and broad (Figure 4). In addition, the femoral diaphyseal margin was very irregular with scalloped margin.

Case 2

Case 2 and 3 are siblings born to a III consanguineous Indian couple. The couple's first pregnancy was terminated at 22 weeks of gestation in view of sonologically diagnosed lethal skeletal dysplasia. This pregnancy was complicated by polyhydramnios. The couple did not opt for autopsy of the fetus. In the second pregnancy, ultrasound revealed recurrence of tetramicromelia and polyhydramnios at 17–18 weeks of gestation. The couple opted to terminate the pregnancy and the fetus was subjected to detailed autopsy. External examination

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revealed a male fetus with tetramicromelia with the upper limbs affected more than lower limbs. Crown rump length was 13 cm, crown heel length was 14.5 cm. The foot length was 2.0 cm, which corresponded to 16–17 weeks of gestation. Fetus was edematous and dysmorphic with prominent forehead protruberant eyes, short-flat nose, micrognathia and protruberant tongue. Palate was intact. Thorax was narrow and there was no nipple dimple noted. Mild thoracolumbar lordosis noted. Upper limbs were symmetrically shortened with brachydactyly. Both the lowerlimbs were severely and symmetrically shortened (Figure 1-II A,B). The feet appeared relatively normal. Internal examination revealed no major abnormality. Fetogram showed marked sclerosis and advanced skeletal maturation in this fetus also. The clavicles were abnormally thick, everted. The scapulae were also osteosclerotic (Figure 1-IIC,D). The long bones were extremely short and metaphyses appeared flared. The vertebrae were mildly platyspondylic. Carpal and two tarsal bones were seen. The above features were consistent with BOCD. Histology of sections from femur and humerus showed that the cartilagenous cap was narrow. The physeal growth zone showed severe hypoplasia and disorganization of proliferative phase and hypertrophic phase (Figure 5). The bone cartilage junction was convex. Metaphysis was narrow. Diaphyseal trabeculae were broad, misshapen, irregular and showed reduced mineralization (Figure 6). The couple had two subsequent pregnancies unfortunately both with recurrence of BOCD. The fourth pregnancy was terminated and the fetus was subjected to autopsy.

Case 3

This female fetus was the sibling of the fetus presented earlier. Ultrasound at 12–13 weeks showed increased nuchal translucency – 4.75 mm (>95th centile for gestational age),

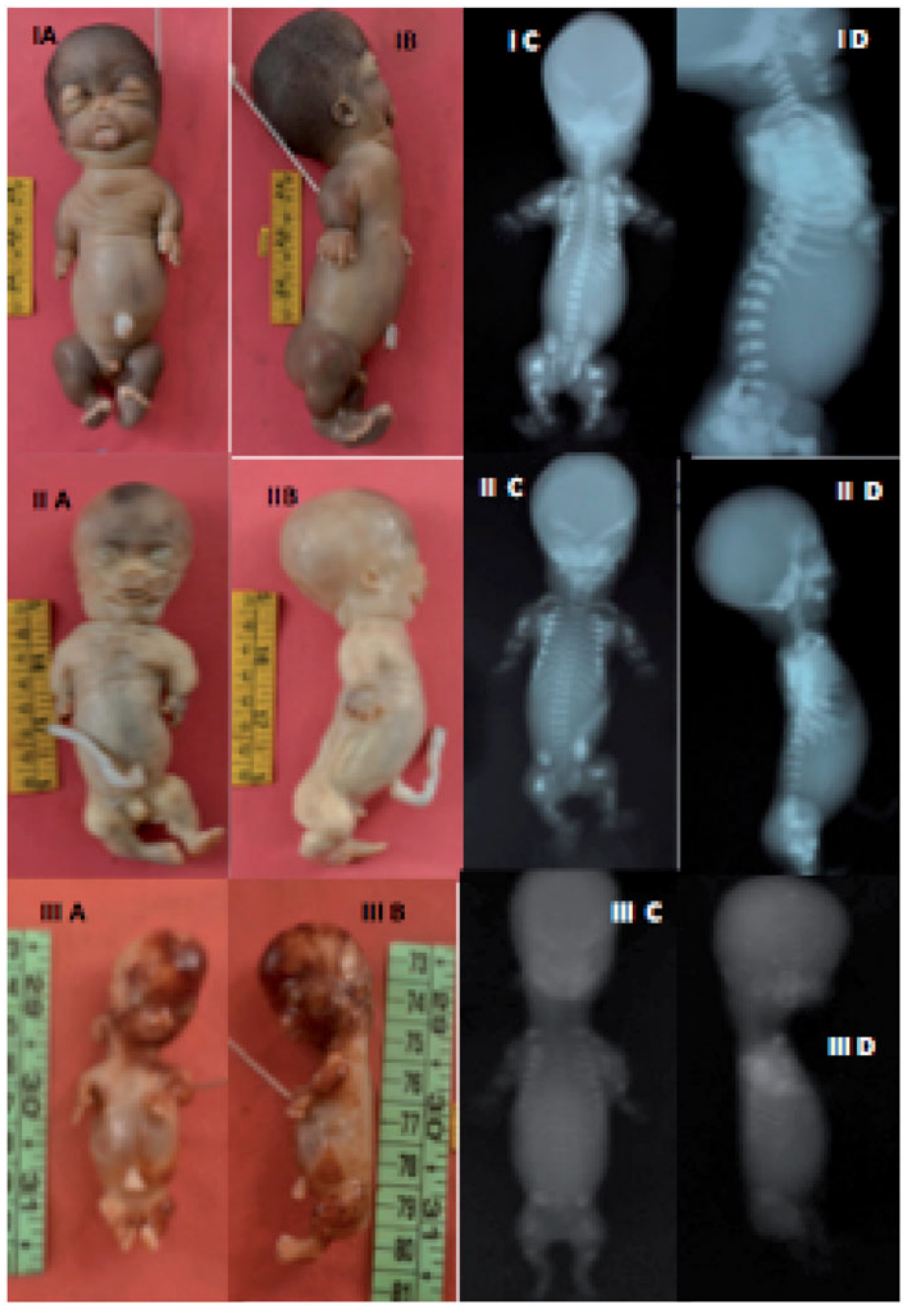

Figure 1. Photographs and fetograms of all the three fetuses. Facial features show significant dysmorphism and fetograms reveal shortening of all long bones and sclerosis (IC,ID,IIC,IID).

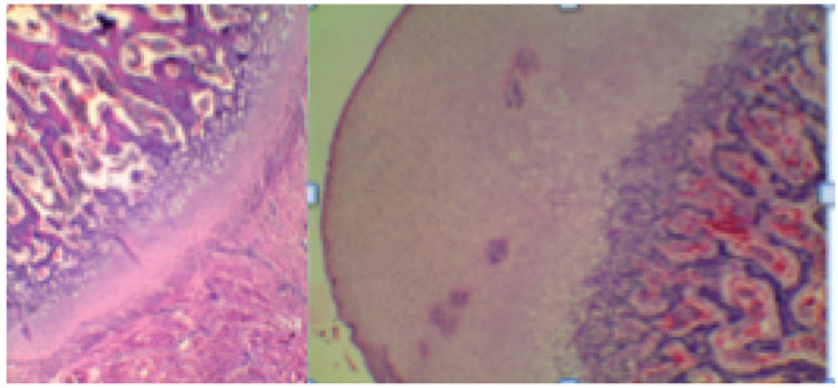

Figure 2. Histology of sections from femur and humerus showing narrow cartilaginous cap. The physeal growth zone shows severe hypoplasia and disorganization of proliferative phase and hypertrophic phase. The bone cartilage junction is convex.

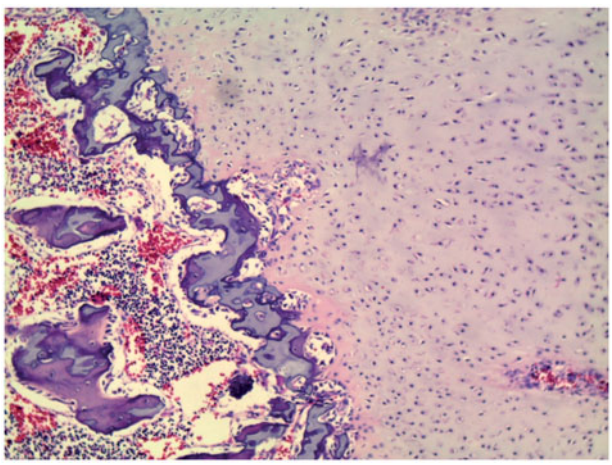

Figure 3. Histopathology of shaft of femur showing broad misshapen diaphyseal trabeculae.

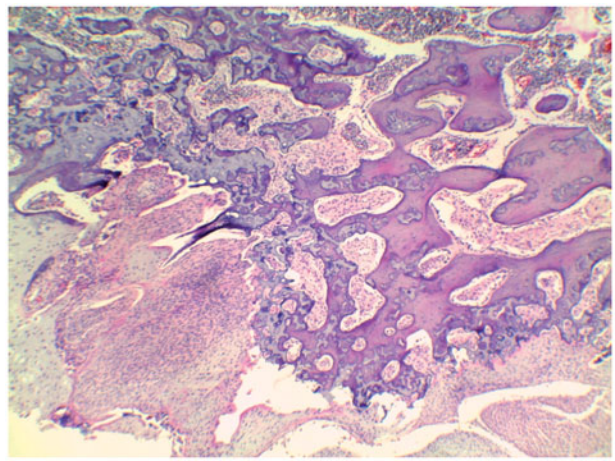

Figure 4. Histopathology of shaft of femur showing broad misshapen diaphyseal trabeculae.

tetramicromelia, narrow thorax and micrognathia. In view of recurrence, the couple opted to terminate the pregnancy and the fetus was sent for autopsy. On examination, the fetus had tetramicromelia and dysmorphic face with hypertelorism, broad nose with depressed nasal bridge, low set ears and micrognathia. Upperlimbs showed rhizomesomelic shortening, bowing of both arms and forearms. Lowerlimbs similarly showed severe rhizomesomelic shortening with bowing of both legs (Figure 1 -III A,B). Fetogram revealed severely shortened humerus and femur with proximal club like enlargement and distal widening. Other long bones such as radius, ulna, tibia and fibula were severely shortened (Figure 1- III C,D). Histopathology revealed flattened epiphyseal cartilage with some vacuolated chondrocytes, severely retarded and disorganized proliferative and hypertrophic phases and disorganized hypertrophic phases. The bone cartilage junction was narrow and showed side by side arrangement of bone and cartilage. Metaphyseal growth plate was completely lacking and the diaphysis was severely shortened with broad trabeculae. This autopsy helped us to gain an insight into the early presentation of BOCD.

Discussion

The PTH/PTHrP receptor type 1 (PTHR1) and its ligand PTHrP have a key role in endochondral bone formation during embryonic development. Mutations in the PTHR1 can be divided into dominant and recessive mutations. Dominant mutations are found in the Jansen-type metaphyseal chondrodysplasia (JMC) and Ollier's disease [1]. Recessive mutations in the PTHR1 have been identified in the Eiken syndrome and in BOCD [1]. BOCD, OMIM 215045 is an autosomal recessive disorder due to homozygous or compound heterozygous inactivating mutations in parathyroid hormone receptor 1 gene (PTHR 1).This gene encodes parathyroid hormone(PTH)/parathyroid hormone-related peptide(PTHrP) receptor (PTH1R) [2]. These mutations result in decreased binding or response to PTH and PTHrP leading to the characteristic clinical features of extremely accelerated skeletal maturation and mineralization at sites of enchondral bone formation. Mutations resulting in complete inactivation result in severe phenotype or type 1 BOCD. Those mutations resulting in partial activity result in a less severe variant or type 2 BOCD [3]. This syndrome was first reported in 1985 by Blomstrand et al. in a neonate with skeletal dysplasia who died shortly after birth [4]. Subsequently, case reports of BOCD have been published, but less than 10 cases have been reported worldover [5]. The most characteristic finding was advanced skeletal maturation [6]. During antenatal period the striking feature of tetramicromelia can be identified as early as 12–13 weeks as was evident in the third patient. This fetus also had increased nuchal translucency. Subsequently, at later gestation polyhydramnios and hydrops may develop. Hence, the diagnosis of BOCD should be kept in mind when sonological diagnosis of teramicromelia with increased nuchal transclucency and polyhydramnios, is made. Other features include facial

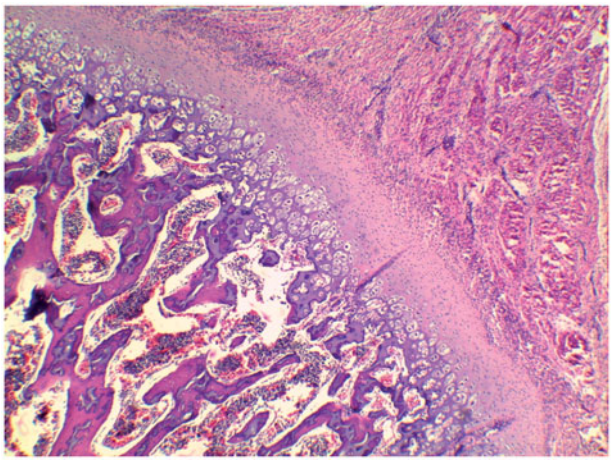

Figure 5. HPE of femur showing narrow cartilagenous cap and abnormal physeal growth zone.

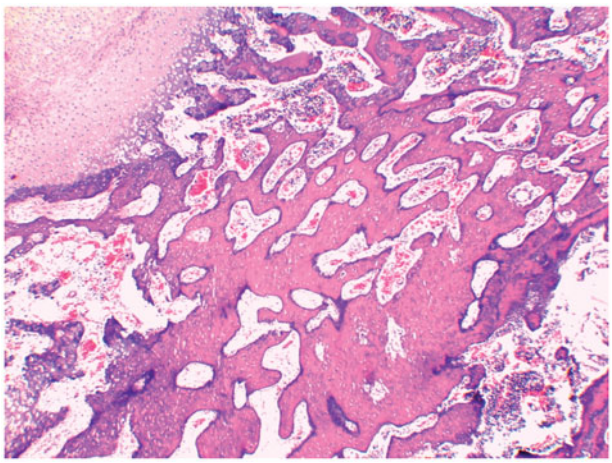

Figure 6. Histopathology of humerus showing narrow cartilagenous cap, hypoplasia of physeal growth zone and disorganisation of proliferative and hypertrophic phase.

dysmorphism due to low set and posteriorly rotated ears, macroglossia, micro or retrognathia, presence of natal teeth, exophthalmos, cataracts, defects in mammary gland, preductal aortic coarctation, hypoplastic lungs or even agenesis [3]. In our case series we noted polyhydramnios in Case 1 and 2. In the third case we did not notice polyhydramnios possibly due to early detection (12–13 weeks of gestation) and termination. Though the exact etiology is unknown, the narrow chest wall apparently leads to increased intrathoracic pressure which in turn obstructs the venous flow leading to increased interstitial fluid accumulation and hydrops [7].

Dysmorphism was marked in all three fetuses more in the the first two fetuses. Hypertelorism, broad nasal bridge and macroglossia were seen in Case 1 and 2. Nipples and breast appeared hypoplastic in the first two fetuses and, however, it could not be commented in Case 3. Radiologically the characteristic feature is advanced skeletal maturation and premature ossification, which was seen in all three fetuses. In general, bone density is increased, tubular bones are short with wide ends and there is ossification of tarsal bones [8]. Metaphyseal growth plates are undetectable [3]. The epiphyseal cartilage is markedly reduced with fusiform and occasionally vacuolated chondrocytes. The epiphyseal metaphyseal junction was wide and irregular; the zone of proliferating cartilage was narrow but also irregular. Irregular columnization was seen in the hypertrophic zone. Bone remodeling was deficient [1,6]. Hoogendam et al. reported a decrease in resting chondrocytes and a near complete absence of column-wise orientated proliferating chondrocytes [1]. These features were seen in our fetuses also.

PTH/PTHrP receptors are members of subclass of G protein-coupled receptors. They have extracellular N terminus, seven transmembrane domains and an intracellular C terminus. The intracellular components activate two signaling pathways adenylate cyclase and protein C that are important for calcium and phosphorus homeostasis and thereby cartilage and bone development. Several homozygous and compound heterozygous inactivating mutations in PTHR 1gene (nonsense, splice site defect, missense and frameshift mutations) have been reported as pathogenic in BOCD. Many of these mutations result in the formation of a truncated protein with no functional domain [1].

This disease follows an autosomal recessive pattern with 25% recurrence risk in every pregnancy. This chondrodysplasia manifests itself early in pregnancy and hence can be identified as early as 12–13 weeks (Case 3).If disease causing mutation is idenitified in the family, preimplantation genetic diagnosis can be planned. Thus, when a sonological diagnosis of lethal skeletal dysplasia is arrived, it is important to have a complete external examination and radiological imaging to come to a conclusive diagnosis. The characteristic radiological features in addition to the dysmorphism will help to differentiate BOCD from other skeletal dysplasias [9].

Declaration of interest

The authors reports no conflict of interest. The authors alone are responsible for the content and writing of this article.

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