Case Report

Dysosteosclerosis – A Rare Sclerosing Bone Dysplasia

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Abstract

Dysosteosclerosis (DOS) is a rare inherited sclerosing bone disorder caused by lack of osteoclast differentiation. A nine-month-old infant presented with a past history of pathological fracture, developmental delay and facial dysmorphisms. The sclerotic radiographic changes along with histologically observed increased bone deposition on clavicular bone biopsy led to the initial suspicion of osteopetrosis. However, a genetic analysis revealed a mutation in the *SLC29A3* gene confirming the diagnosis of DOS. Due to the close clinical and radiological resemblance most infants with DOS are misdiagnosed as osteopetrosis, a related skeletal dysplasia. The presence of purplish skin rash, platyspondyly on radiographs and absence of bone marrow involvement differentiates DOS from the latter. Treatment is supportive and overall prognosis is poor with the eventual neurological deterioration and recurrent fractures.

Keywords: Skeletal dysplasia, Osteopetrosis, Platyspondyly, *SLC29A3*

Introduction

Dysosteosclerosis (DOS) is a rare skeletal dysplasia presenting with recurrent fractures, deafness, blindness, and short stature. Facial dysmorphisms and radiographic changes such as metaphyseal widening of long bones and thickening of flat and tubular bones closely resemble osteopetrosis. We present an infant with history of a pathological fracture and sclerotic radiological features, clinically and histologically misdiagnosed as osteopetrosis but confirmed to be a case of DOS on genetic analysis.

Case Report

A nine-month-old boy, born of a non-consanguineous union was referred in view of a suspected metabolic bone disorder. His birth history was uneventful with a birth weight of 2.5 kg. He had suffered a single pathological fracture of the right humerus on day 10 of life. From three months of age a bulging anterior fontanelle was also noticed, without history suggestive of decreased vision or hearing. There was mild global developmental delay; he was unable to sit with support or babble. On examination, the boy was playful. His weight was 5.8 kg (-2.95 SD), length was 68 cm (-3.4 SD) and head circumference was 44 cm (0.12 SD). Pallor, wide (2 x 2 cm) bulging but pulsatile anterior fontanelle, frontal bossing, hypertelorism and saddle nose were observed; limb deformities were absent (Fig. 1). Dental examination revealed two lower incisors. A mild soft hepatosplenomegaly was also noted with otherwise unremarkable systemic examination.

Investigations revealed iron deficiency anemia along with normal serum calcium,

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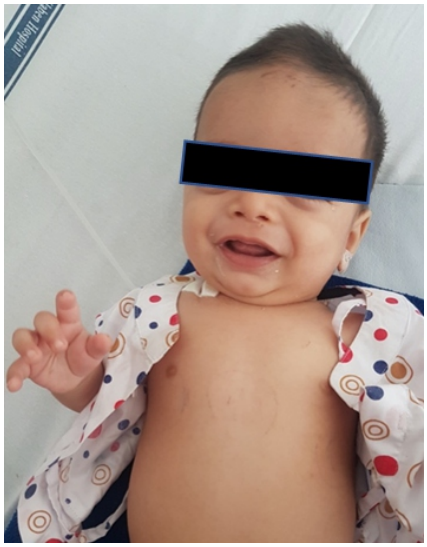

Figure 1: Clinical photograph showing facial dysmorphisms such as bulging anterior fontanelle, broad forehead, hypertelorism and depressed nasal bridge

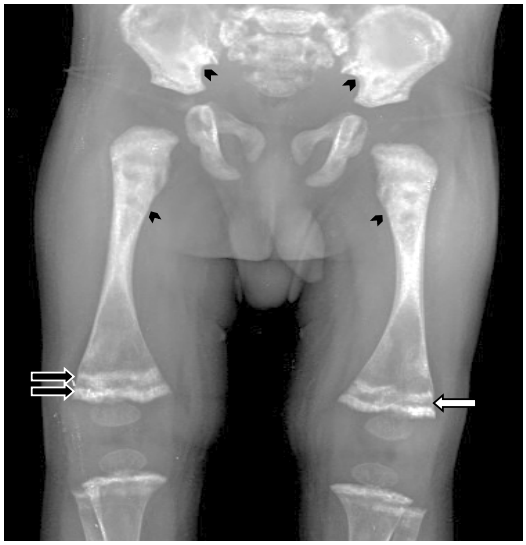

Figure 2: Radiograph of the pelvis with lower limbs showing patchy sclerosis of the iliac bones and femoral diaphyses (black arrowheads). Also seen is the evolving Erlenmeyer flask deformity of the femurs with lower metaphyseal sclerotic bands (black arrows) and submetaphyseal radiolucency (white arrow) typical of dysosteosclerosis. Similar changes can be seen in upper ends of the tibial bones.

phosphorus, alkaline phosphatase, and vitamin D levels. Serial radiographs since early infancy showed sclerosis of the cranial base and clavicles as well as diaphyseal thickening, metaphyseal sclerotic bands and submetaphyseal radiolucency of the long bones (Fig. 2). Lateral radiograph of the spine revealed mildly thickened superior and inferior endplates of the vertebral bodies, without platyspondyly. A provisional diagnosis of a sclerosing bone disorder such as osteopetrosis was made. A clavicular bone biopsy showed calcified cartilage surrounded by dense woven bone with a "bone within bone" appearance, classical of osteopetrosis. Next generation sequencing revealed a homozygous pathogenic mutation in the exon 6 of the *SLC29A3* gene (c.1330G>T), responsible for dysosteosclerosis, a rare skeletal dysplasia.

Discussion

Dysosteosclerosis is an autosomal recessively inherited sclerosing bone disorder, although x-linked inheritance has also been rarely described. Until 2010, around 20 cases have been reported worldwide [1]. DOS is characterized by osteosclerosis and platyspondyly. Long bones as well as flat bones such as cranial base, clavicles and ribs demonstrate sclerosis. In addition, ends of tubular bones show widening with sclerotic bands along with a typical submetaphyseal radiolucency (Fig. 2). Basal skull bone sclerosis leads to progressive narrowing of cranial nerve foramina often resulting in optic atrophy, deafness, and facial nerve palsy. Facial dysmorphisms similar to those seen in our child, short stature, and intellectual disability are other features of DOS. Skin involvement in the form of purple-red macular atrophy as well as recurrent pathological fractures have been described with variable incidence [2]. Dental anomalies described include delayed tooth eruption, oligodontia and enamel hypoplasia.

Histologically, increased mineralization with a paucity of osteoclasts on immunohistochemistry favors the diagnosis of DOS. Although, in our case, the latter was not performed, histopathological examination revealed increased bone deposition. Interestingly, mutation in the gene implicated in DOS, *SLC29A3*, encoding a nucleoside transporter is also seen to be responsible for other conditions such as H syndrome (hypertrichosis, hyperpigmentation, low height, hyperglycemia, hallux valgus, hepatosplenomegaly, and hearing loss), Faisalabad histiocytosis, Rosai-Dorfman disease and pigmented hypertrichosis with insulin dependent diabetes mellitus (IDDM) [3]. All the latter, lack skeletal involvement and are grouped under the single entity histiocytosis-lymphadenopathy plus syndrome (OMIM#602782). The homozygous mutation found in our case has been previously reported in a child with hypertrichosis and IDDM, demonstrating a lack of genotype-phenotype correlation. On the other hand, the phenotype of DOS has also been seen to result from mutations of the *TNFRSF11A* and *TCIRG1* genes [4, 5]. Due to the striking resemblance of facial features and skeletal changes, most infants with DOS like our case, are initially misdiagnosed as infantile osteopetrosis. The clinical and radiological evolution of skin rash and platyspondyly respectively, along with absence of bone marrow involvement differentiates DOS from the latter [1]. Pyknodysostosis, another bone sclerosing condition is differentiated by the presence of resorbed terminal phalanges or acro-osteolysis; a normal alkaline phosphatase level rules out juvenile Paget's disease.

Treatment of DOS is mainly supportive. Bone marrow transplant has been reported in one case but was seen to be ineffective [6]. The overall prognosis of individuals with DOS is poor with blindness, deafness and recurrent fractures being the common comorbidities described.

Conclusion

In summary, DOS is a rare sclerosing bone dysplasia which can be easily mistaken for osteopetrosis, especially in infancy. A look-out for typical markers such as platyspondyly, metaphyseal sclerotic bands, submetaphyseal radiolucency and skin changes with absence of bone marrow involvement aid in its diagnosis.

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Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Conflict of interest: Nil; **Source of support:** None

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