CASE REPORT

UNIQUE PRESENTATION OF OSTEOPETROSIS

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Osteopetrosis is a rare hereditary disorder of osteoclast dysfunction leading to abnormally dense and sclerotic bones that are fragile and break easily. It can be inherited in various patterns like autosomal-dominant, autosomal-recessive or as X-linked traits, but the most grievous forms of its inheritance are the autosomal-recessive ones, which show early onset and are associated with very poor prognosis. We report here the case of an asymptomatic young boy, who was diagnosed as the case of autosomal recessive osteopetrosis on the basis of his genetic studies. The reason for his unusual asymptomatic disease was the location of mutation in TCIRG1 gene that was revealed from his genetic studies. Another unusual point about him was his survival at this age, which is surprisingly rewarding as patients with autosomal recessive osteopetrosis usually die earlier by the age of 2–3 years.

Keywords: Osteopetrosis, hereditary disorder, autosomal recessive, X-linked, Osteoblast, Osteoclast

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INTRODUCTION

Osteopetrosis (OP), also known as Albers Schonberg disease, is a rare hereditary disorder of osteoclast dysfunction leading to skeletal abnormalities.[1] It is also known as "marble bone disease" because the bones become abnormally dense and sclerotic, secondary to defective bone resorption by osteoclasts.[2]

This disorder can be inherited in various patterns like autosomal-dominant, autosomal-recessive or as X-linked traits, but the most grievous forms of its inheritance are the autosomal-recessive ones.[3] Osteopetrosis is classified into following types based on the severity of clinical profile, age of onset and type of inheritance as follows: malignant OP, intermediate OP, benign OP and carbonic anhydrase type-II (CA-II) deficiency.[4] The first two types characteristically have early onset of disease and are associated with very poor prognosis. The benign type, on the other hand, usually presents later in life and is associated with favourable prognosis, with individuals living a longer life span.[5] Despite all these differences, used to classify OP, all of these forms typically show an increased bone density on radiographic findings as a hall mark feature. Consent was taken by parents of patients.

CASE

An 11 years old boy visited the emergency of Abbasi Shaheed Hospital with chief complaint of severe lower back pain. After taking a detailed history, we found that family history was positive for bone disease on his father side with his first cousin diagnosed with osteopetrosis. On examination, GCS was 15/15, chest was clear with normal vesicular breathing, cardiovascular examination was insignificant and abdomen was soft with positive gut sounds. He has normal hearing and vision except left eye squint since birth which showed a pale optic disc. His height, weight and other anthropometric measurements were also normal as per his age other than he had a short stature.

All the developmental milestones were also achieved timely. He had no previous records of his illness and neither was he previously admitted in any hospital. We suspected septic arthritis and had his blood work and radiography of the back done. The blood labs were perfectly alright with no signs of anaemia, infection or bleeding disorder. His X-rays (Figure-1, 2) were found to be highly radio-dense for which CT scan was done, changing the provisional diagnosis from septic arthritis to skeletal dysplasias such as osteopetrosis and pyknodysostosisas. He was discharged on ibuprofen that relieved his pain in a day.

In order to confirm the type of skeletal dysplasias his genetic testing was done. A panel deletion/duplication test (HDT array) for osteopetrosis was done which revealed a c.630G> a transition in exon 6 of the TCIRG1 gene (T-cell, ATPase, lysosomal V0 subunit A3, H+ transporting, immune regulator 1). This change does not alter the amino acid Thr210 as both ACG and ACA are codons for threonine. However, this change occurs at the last nucleotide of exon 6 and

is predicted to disrupt splicing and result in aberrant mRNA processing. Additionally, this change is not listed in either the dbSNP or ESP database. We have previously detected the change, compound heterozygous with a definitive TCIRG1 mutation, in a patient with sclerotic bones and metaphyseal flaring. These findings suggest that this change is most likely pathogenic; however, the biological significance of this change is not known for certain and clinical correlation is ultimately required.

The patient was homozygous for this alternation. In summary, the genetic studies revealed the mutations at the junction of intron and exon supporting the diagnosis of osteopetrosis.

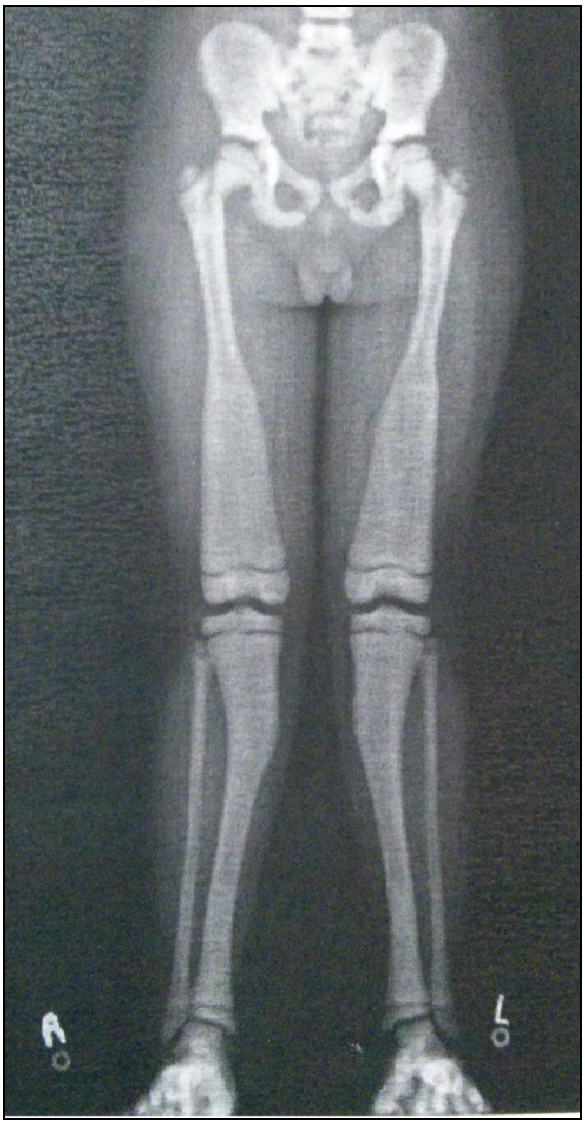

Figure-1: X-ray full-length lower limbs

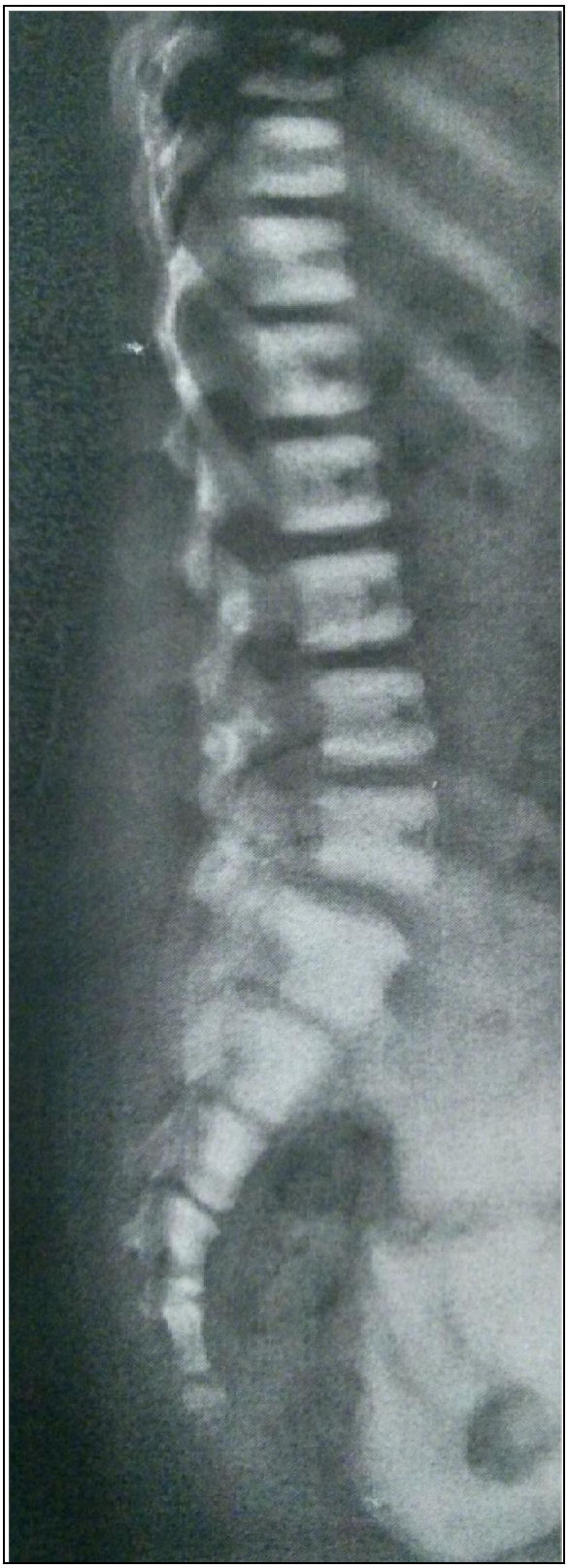

Figure-2: X-ray of spine

DISCUSSION

Osteopetrosis especially infantile type carries a malignant course whereas the intermediate and autosomal dominant has shown to have full life expectancy but with many orthopaedic issues such as increased fractures, coxa vara, long-bone bowing, mandibular and long-bone osteomyelitis, degenerative arthritis of hip and knee, and cranial nerve compression.[6] The mortality rate in these patients is mostly due to bone marrow failure and overwhelming infections.[7] All the patients with osteopetrosis have characteristic roentgenographic bony change and they commonly presents with nasal obstruction and adenoid expression[8] in contrast to our case where patient has no classical presentation but was diagnosed as a case of osteopetrosis on the radiological and biopsy basis.

Bone resorption and remodeling requires the function of osteoclasts which is an intricately controlled, physiological process.[9] In osteopetrosis osteoclast dysfunction cause inadequate bone resoprtion. Many molecular defects have been reported as a cause of osteoclast dysfunction but in most of the cases the gene is unknown.[10] In our case, TCIRG1 gene (T-cell, ATPase, lysosomal V0 subunit A3, H+ transporting, immune regulator 1) was found to be the defective which is a frequent cause of autosomal recessive type of osteopetrosis.[10] In a similar study it was found that the most common cause of osteopetrosis in 50–60% of patients is defects in the A3 subunit of the osteoclast vacuolar H+–ATPase proton pump.[11]

Autosomal recessive ("malignant") osteopetrosis is a life-threatening condition, classically manifests in the first few months of life[12] but in our case the patient presented after 9 years with only lower back pain. The longitudinal growth of bones is impaired, resulting in short stature of varying degrees.[6] The disease should be distinguished from myelofibrosis, malignancies, Paget's disease, lead and bismuth poisoning etc.

At present, effective medical treatment for osteopetrosis does not exists. Treatment is largely supportive and is aimed at providing symptomatic management and multidisciplinary surveillance of complications.[6] The only curative treatment for malignant osteopetrosis is bone marrow transplantation. It has been found that infants transplanted with marrow from an HLA-identical sibling or unrelated volunteer donor have an actuarian five-year survival with a functioning graft of 50–70%.[12]

Competing interest Declaration: The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

HAD: Main concept, drafting, critical revision, compilation. AAM: Designing, compilation, drafting, critical revision. SMM &: Data collection, drafting, typing data. AI: paper writing. SMAA: Technical support, illustration designing in manuscript. SAA: Designing and paper writing.

Consent: Written informed consent was obtained from the patient's guardian for publication of this Case report and accompanying images.

REFERENCES

1. Kant P, Sharda N, Bhowate RR. Clinical and Radiological Findings of Autosomal Dominant Osteopetrosis Type II: A Case Report. Case Rep Dent 2013;707343–9.
2. Sit C, Agrawal K, Fogelman I, Gnanasegaran G. Osteopetrosis: radiological & radionuclide imaging. Indian J Nucl Med 2014;30(1):55–8.
3. Rajathi M, Austin RD, Mathew P, Bharathi CS, Srivastava KC. Autosomal-dominant osteopetrosis: an incidental finding. Indian J Dent Res 2009;21(4):611–4.
4. Essabar L, Meskini T, Ettair S, Erreimi N, Mouane N. Malignant infantile osteopetrosis: case report with review of literature. Pan Afr Med J 2013;17:63.
5. García CM, García MA, García RG, Gil FM. Osteomyelitis of the Mandible in a Patient with Osteopetrosis. Case Report and Review of the Literature. J Maxillofac Oral Surg 2013;12(1):94–9.
6. Stark Z, Savarirayan R. Osteopetrosis. Orphanet J Rare Dis 2009;4:5.
7. Yu T, Yu Y, Wang J, Yin L, Zhou Y, Ying D, *et al*. "Identification of TCIRG1 and CLCN7 gene mutations in a patient with autosomal recessive osteopetrosis." Mol Med Rep 2014;9(4):1191–6.
8. Loría-Cortés R, Quesada-Calvo E, Cordero-Chaverri C. Osteopetrosis in children: a report of 26 cases. J Pediatr 1977;91(1):43–7.
9. Lomaga MA, Yeh WC, Sarosi I, Duncan GS, Furlonger C, Ho A, *et al*. TRAF6 deficiency results in osteopetrosis and defective interleukin-1, CD40, and LPS signaling. Genes Dev 1999;13(8):1015–24.
10. Frattini A, Orchard PJ, Sobacchi C, Giliani S, Abinun M, Mattsson JP, *et al*. Defects in TCIRG1 subunit of the vacuolar proton pump are responsible for a subset of human autosomal recessive osteopetrosis. Nat Genet 2000;25(3):343–6.
11. Tolar J, Teitelbaum SL, Orchard PJ. Osteopetrosis. N Engl J Med 2004;351(27):2839–49.
12. Fasth A, Porras O. Human malignant osteopetrosis: pathophysiology, management and the role of bone marrow transplantation. Pediatr Transplant 1999;3(Suppl 1):102–7.

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