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CASE REPORT

Osteopetrosis: trephine biopsy an essential tool

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ABSTRACT

Osteopetrosis is a group of rare genetic diseases, consequent on absent or defective osteoclasts. A large number of genes have been found to be associated with the defect, each of which results in a clinically variable phenotype with regards to age at presentation and severity of disease. This makes the disease a clinical diagnostic challenge. We present one such case which was diagnosed on trephine biopsy performed to understand the cause of the presence of blast cells in peripheral blood of an 8-month-old infant.

Key words: Osteoclasts, osteopetrosis, trephine biopsy

Introduction

Osteopetrosis (OP), also known as the Marble bone disease or Albers Schönberg disease is a group of rare genetic diseases consequent on the defect in osteoclast function or formation. Osteoclasts may be increased, decreased or present in normal numbers, but are always qualitatively abnormal. The result is osteosclerosis with gradual obliteration of the marrow cavity by both bony encroachment and associated fibrosis [1]. Very few cases of OP have been reported in infants until date. We present a case of this rare disease, which was diagnosed on trephine biopsy performed to investigate the presence of blast cells seen on peripheral blood smear of an 8-month-old infant, with clinically significant hepatosplenomegaly and lymphadenopathy.

Case Report

A first born child of a non-consanguineous couple presented at 8 months of age with abdominal distension for 1 month and bulging anterior fontanelle of 10 days duration. His developmental milestones were delayed, as he had started neck holding at 6 months of age. Furthermore, the infant was not able to change side from supine to prone position. His physical examination revealed an increased head circumference of 45 cm, macrognathia, squint and a bulging anterior fontanelle. A palpable liver 4 cm below right costal margin and an enlarged spleen of 6 cm below left costal margin was noted. His vitals and motor and sensory examination were within normal limits. The preliminary clinical impression was storage disorder.

A complete blood picture revealed hemoglobin 8.2 g% and platelets 1,30,000/µL. The total leukocyte count was 23.37 thousand/µL and differential showed neutrophils 39%, lymphocytes 28%, eosinophils 5%, monocytes 02%, nucleated red blood cells 20% and blast cells 06% respectively. Considering these findings, vitamin B_{12}/folate deficiency and juvenile acute myeloid leukemia were added to the differential diagnoses.

His biochemical parameters were alanine aminotransferase 57 U/L, a mildly raised alkaline phosphatase 179 U/L, markedly raised lactate dehydrogenase 1757 U/L, normal serum iron 105 µg/dL and mildly raised total iron binding capacity 478 µg/dL. Vitamin B_{12} and folate assay were performed, which were normal at 447 pg/mL and 7.51 ng/mL, respectively. Serum calcium was normal at 9.8 mg/dL and phosphate was mildly raised at 6.0 mg/dL. Serum vitamin D levels were 27 ng/mL (normal).

Without a definitive diagnosis and because of the curious presence of blast cells seen on peripheral smear, a bone marrow aspirate and trephine biopsy was performed. The aspirate was a dry tap. The procedure was repeated and dry tap was encountered again. Flow cytometric immunophenotyping carried out on peripheral blood ruled out any hematological malignancy. The trephine biopsy, however, revealed the presence of markedly increased woven bone which lead to thickening of the trabeculae and thus, obliteration of the marrow spaces [Figure 1]. There was no marrow seen within the marrow cavity. The trabeculae were lined with active osteoblasts and a reduced number of osteoclasts were noted with obliterated ruffled borders. A diagnosis of OP was established on trephine biopsy and further tests were carried out to support the diagnosis. X-ray of the chest was carried out, which showed spatula shaped ribs with thickening of ends [Figure 2a]. X-ray femur and tibia showed bone within bone appearance. His creatine phosphokinase-brain (CPK-BB) isoenzyme electrophoresis showed raised CPK-BB level 77.05% of total CPK. Genetic studies could not be carried out as these are performed in a reference laboratory and the parents had financial constraints.

The parents were advised to consider stem cell transplant

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CASE REPORT

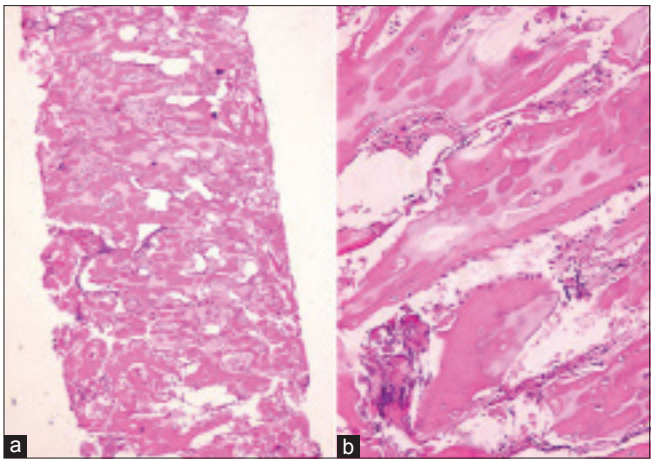

Figure 1 (a) Trephine biopsy showing markedly increased woven bone with thickened trabeculae and obliteration of the marrow spaces (H and E, ×100); (b) Active osteoblasts lining the trabeculae (H and E, ×400)

therapy from a higher center; however, they could not afford the treatment and took their ward home against medical advice.

Discussion

OP is a family of extremely rare bone disorders caused due to defective osteoclast function, leading to reduced bone resorption and a diffused symmetric skeletal sclerosis. It is also known as the marble bone disease because the bones have a stone like quality, but they are abnormally brittle and fracture easily [2]. X-rays of long bones show the Erlenmeyer flask deformity and bone within bone appearance as was seen in this case [Figure 2b]. Vertebrae show dense end plates at upper and lower border producing a sandwich appearance. Differential diagnoses of radiographic appearance of OP include conditions which produce general increase in bone density such as fluorosis, myelosclerosis, Engelmann's disease and sclerosing form of Paget's disease, melorheostoses, lymphoma and osteoblatic metastases [3]. Histologically, the osteopetrotic bone lacks a medullary canal and is filled with primary spongiosa. Osteoclasts may be normal, increased or decreased, depending on the underlying genetic defect. Deposited bone is not remodeled and tends to be woven instead of forming mature trabeculae in architecture [2]. In the severe infantile form of OP, there is increasingly severe leukoerythroblastic anemia and thrombocytopenia associated with extramedullary hematopoiesis. Occasionally, the white cell count is increased and immature granulocytes are present in the blood. In the milder adult form of the disease, there is only a minor degree of anemia [1].

The mutations underlying OP interfere with the process of acidification of the osteoclast resorption pit, which is required for dissolution of the calcium hydroxyapatite within the matrix [4].

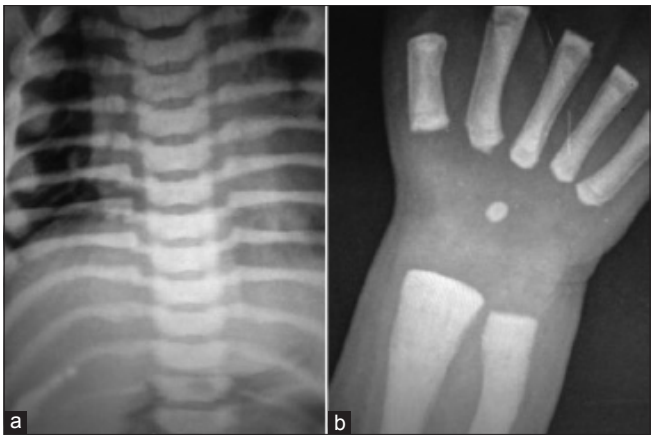

Figure 2 (a) X-ray chest showing spatula shaped ribs with thickening of ends; (b) Erlenmeyer flask deformity of distal ends of Radius and Ulna

Classification scheme of OP: It has classically been classified into variants based on the mode of inheritance and clinical findings into: (a) infantile malignant (severe autosomal recessive) form, (b) intermediate (autosomal dominant or recessive) form and (c) adult onset (benign autosomal dominant) form [5,6]. Others have divided OP according to the presence and absence of osteoclasts as osteoclast-rich and osteoclast-poor forms. The osteoclast-rich forms are associated with an effector dysfunction of osteoclasts, the genetic basis of which lies in the carbonic anhydrase Type II (CAII) gene, T-cell immune regulator 1 (TCIRG1), chloride channel 7 (CLCN7), osteopetrosis-associated transmembrane protein 1 (OSTM1) and pleckstrin homology domain-containing family M member 1 (PLEKHM1) genes. Most of the osteoclast-rich forms show a good response to hematopoietic stem cell therapy, except the form associated with OSTM1 gene defect [6]. The osteoclast-poor forms are associated with a defect in differentiation of osteoclast precursors. The genes identified for the defect are receptor activator of nuclear factor-kappa B ligand (RANKL) and receptor activator of nuclear factor-kappa B (RANK). The osteoclast poor OP caused by RANKL defect does not respond to hematopoietic stem cell transplant (HSCT) since RANKL is expressed on osteoblasts. However, these patients could benefit from mesenchymal stem cell transplant and/or soluble RANKL therapy [7].

Analysis of bone marrow is required to detect osteoclast poor forms and speed genetic analysis. In atypical and milder forms, the extent of reduced hematopoiesis in the marrow should help to determine indication and time point for HSCT. In rare cases, open bone biopsy may even be required [6]. Some other authors also share the opinion that trephine biopsy has a bearing on deciding the treatment strategies and is important in the complete work-up of OP [8].

Conclusion

Trephine biopsy clearly has a very important role in reaching

the diagnosis of OP. The osteoclast morphology and numbers are of immense help in prognostication of the disease and in selecting the right candidate likely to show response to the HSCT. Thus, we strongly recommend that trephine biopsy should be included in the diagnostic work-up of suspected OP.

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Authors' Contributions

HW, RJ and RN conceptualized the paper. HW and RJ contributed to the literature and data search whereas HW was involved in the preparation and editing of the manuscript. RKB participated in the clinical care. GNG made critical contributions to the laboratory studies. RN, RKB and GNG helped revise the paper. RKB and GNG are the guarantors of the manuscript. All authors contributed to the intellectual content of the manuscript and have read and approved the final version of the manuscript for publication.

Consent

The authors certify that a written informed consent was obtained from the parents of the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.

Competing Interests

The authors declare that they have no competing interests.

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