Case Report

Unusual presentation of osteopetrosis in a young female with anemia and hepatosplenomegaly

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ABSTRACT

Osteopetrosis (or Albers-Schonberg disease) is a rare, hereditary bone disorder that is characterised by increased bone density caused by osteoclast dysfunction. Bones become sclerotic and thick, but their abnormal structure results in them being both weak and brittle. Excessive bone density can lead to associated problems which may be life threatening. Nerves in the skull may be compressed and cause vision loss, hearing loss, or paralysis of facial muscles. Crowding of the bone marrow can lead to low levels of cells and platelets needed to fight infection, carry oxygen to the body’s cells, or control bleeding. Clinicians managing patients with osteopetrosis face a difficult task of treating the complications. Although advances in molecular genetics have led to an improved understanding of the cellular basis of the disease, clinical management has still remained unchanged. The characteristic radiological findings are usually sufficient for diagnosis of the disease. This article presents a case of autosomal dominant osteopetrosis type II in a young female. Most of the cases present clinically with fracture because of the weakened bones. Fractures are often transverse with multiple areas of callus formation and normal healing. In this case there was no evidence of any fracture in the bones and patient presented with symptoms of anemia. In addition, the literature is reviewed with a comparative discussion of the difficulties associated with osteopetrosis.

Key words: osteopetrosis, bone dysplasia, autosomal dominant

INTRODUCTION

Osteopetrosis is a group of rare sclerosing bone dysplasias that share the common pathogenesis of diminished osteoclast-mediated skeletal resorption. There is a reduction in bone resorption relative to bone formation, which leads to generalized increased bone mass. Imbalanced bone turnover is a consequence of inadequate osteoclastic bone resorption, despite normal osteoblastic function. The estimated incidence of the disease is 1 in 100,000–500,000 of the population. The characteristic radiological findings are usually sufficient for diagnosis of the disease. The patients usually present to the the clinicians with the complications of the disease and diagnosis is usually made after radiological investigation. Bone biopsy is not recommended in Osteopetrosis. In this particular case the patient presented with gross anaemia with hepatosplenomegaly and was diagnosed later as a case of osteopetrosis after X-Rays.

CASE REPORT

A 35 years old house wife presented with history of easy fatigue and abdominal discomfort since 9 to
10 years and low grade fever off and on since 1 year. There was no history of active bleeding from any site. Patient gave a past history of blood transfusion 3 units of packed red blood cells during last 2 years. Her menstrual cycle was regular and she had no issue. There was no significant past history or family history. On examination she had severe pallor, no icterus cyanosis, clubbing, edema or lymphadenopathy. She was short stature with pulse 84 beats per minute, blood pressure 130/84 mmHg. Respiratory rate 22 per minute regular and afebrile. On per abdomen examination abdomen was distended, with grossly enlarged spleen crossing umbilicus, firm and nontender. Liver was palpable 2 cms below costal margin, firm and nontender. All other systems were normal. Haematological examination revealed Hb: 7.3 g/dl, TLC - 5700 c/mm, DLC %: P56, L42, E02, MCV 81.7, MCH 24.7, MCHC 30.3, Plat- 1.24 lac, ESR- 65. Peripheral Smear: RBC microcytic hypochromic with anisocytosis, platelets adequate, no immature cell or malaria parasite seen. Reticulocyte counts- 3%. Other blood findings were as follows: Serum bilirubin - 0.8 mg/dl, SGOT- 15 IU, SGPT- 10 IU ,Serum. alkaline phosphatase - 144 IU, Serum Protein - 7.0 gm%, Serum Albumin- 4.0 gm%, Globulin - 3.0 gm%, Urea16 mg/dl, Creatinine. 0.4 mg/dl, FBS- 87 mg/dl, Na+ 136 mEq / L, K+ 3.4 mEq / L, Serum.Calcium 6.9 mg/dl, phosphate 4.2 mg/dl, magnesium- 1.23 mEq /L, PTH -116.9, Vit. D, 25 Hydroxy- 10.12 nmol/L, Hb electrophoresis: HbA - 96.2%, HbA 2 - 3.0, Hbf - 0.8%, S. Iron - 87.0 mg/dl, TIBC 320S, ferritin - 2.1 mg/dl, S. LDH 230 IU, Malaria antigen negative, rk-39 - negative, VGM Typhoid- negative. Urine exam(R/M) NAD, TSH 3.0, ANA (anti nuclear antibody) Negative, HIV Negative. ECG was within normal limits. Ultrasound abdomen revealed: Liver: mildly enlarged with normal echotexture, Spleen: Grossly enlarged, 23 cm. showing tiny echogenic foci suggestive of gamma - gandy bodies. No ascites, no retroperitoneal lymphadenopathy, Kidney, uterus and adnexa NAD. A diagnosis of Anaemia with Hepatomegaly, massive splenomegaly with growth retardation was made.

Routine X-Ray Chest PA [figure 1] showed diffuse osteosclerosis of the visualized bones. On skeletal survey [figures 2-5] all bones showed diffuse osteosclerosis with cortical thickening. There were medullary encroachment and longitudinal metaphyseal striations. Vertebra showed bone within the bone appearance. Clinical findings and radiological findings confirmed the diagnosis of Osteopetrosis. The detailed family history of the patient was unclear and it was not possible to examine her family members for determination of the exact hereditary pattern.

DISCUSSION

Osteopetrosis is a rare, hereditary bone dysplasias is diagnosed by increase in the bone density caused by osteoclast dysfunction. It can manifest in wide ranging forms from asymptomatic benign form to malignant neonatal form with life-threatening complications.

Osteopetrosis has been classified into three broad types. The first is an autosomal-recessive type. It occurs during infancy or early childhood and is also termed as malignant as it is frequently fatal.

This type of osteopetrosis present with numerous neurological symptoms (eg, blindness, facial palsy, and deafness) and hematologic abnormalities (eg, anemia and thrombocytopenia). Patients most often die from complications with in the first few decades of life. A gene for the autosomal-recessive type of osteopetrosis has been localized to chromosome 11q13. The second type is autosomal-dominant osteopetrosis. Patients with autosomal-dominant osteopetrosis usually lead a normal life but may
develop cranial nerve compression (with subsequent deafness, vision loss, or facial nerve palsy), mandibular osteomyelitis, and multiple orthopedic problems.\textsuperscript{[1,2,4,7]}

An intermediate form of osteopetrosis has been described with an autosomal-recessive pattern of inheritance with a milder course. A subtype of this form is associated with renal tubular acidosis and cerebral calcification secondary to a deficiency of carbonic anhydrase.\textsuperscript{[9]}

Anderson and Bollerslev described two types of benign osteopetrosis compatible with a normal life span on the basis of radiological and clinical differences. They include: ADO Type I and ADO Type II. ADO Type I is associated with a low fracture rate. Radiographs reveal that sclerosis was more pronounced at the cranial vault, with acid phosphatase levels being normal. ADO Type II, also called as Albers-Schonberg disease, typically has onset in late childhood or adolescence. Clinical manifestations include spontaneous fractures, scoliosis, hip osteoarthritis and osteomyelitis, particularly affecting the mandible in association with dental abscess or caries.\textsuperscript{[10]}

Neuropathies related to cranial nerve entrapment occur, leading to visual and hearing deterioration. Radiographs display diffuse osteosclerosis, vertebral end plate thickening showing Rugger-jersey or sandwich appearance of vertebra, bone in bone appearance and sclerosis of the skull base. In contrast to ADO I, in ADO II, acid phosphatase levels are elevated. Doctors may use other tests to diagnose and gain additional information about specific problems related to osteopetrosis. These may include hearing and vision tests, blood tests, computerized axial tomography (CAT) scans, and magnetic resonance imaging (MRI).

There are two subtypes of autosomal-dominant osteopetrosis that can be differentiated by radiographic characteristics. In autosomal-dominant osteopetrosis type I, radiographic sclerosis is most notable in the cranial vault, while autosomal-dominant osteopetrosis type II is characterized by skull base sclerosis, vertebral end-plate thickening (Rugger-jersey spine), and pelvic end bones.\textsuperscript{[11]} Our patient belong to autosomal-dominant osteopetrosis type II category. In this patient the bone marrow spaces were decreased due to cortical thickening, leading to hematological failure resulting in anemia and pancytopenia. Long term marrow compromised condition resulted in hepatosplenomegaly due to extramedullary haematopoiesis. But the bones did not show any evidence of any fracture.

Fractures in autosomal-dominant osteopetrosis are common, and fracture management have to be modified in view of variable healing process. The anatomic regions most prone to fracture in osteopetrotic patients include the inferior border of the femoral neck as well as the proximal femoral shaft\textsuperscript{[1]} although other references suggest other areas of the skeleton are affected just as commonly.\textsuperscript{[10]} Orthopedic concerns in osteopetrosis include periodic back pain, bone pain, and recurrent fractures, which may be easily induced by relatively low-energy mechanisms.\textsuperscript{[10]} Osteopetrosis fracture requires specific preoperative planning and caution during operative procedures like drilling and plating and post-operative management to avoid further injury.

Mapping of the Albers-Schoenberg gene,\textsuperscript{[10]} will result in new insights into the regulation of osteoclast function and the development of a gene-based therapy for osteopetrosis. A gene for autosomal-dominant osteopetrosis has been localized to chromosome 1p21 but targeted therapies are not yet available.\textsuperscript{[13]} Interferon gamma-1b delays the progression of the disease. Calcitriol reduces bone density & Orthopaedic care for fractures. Monitoring of the eye, ear, nose, and
throat along with good dental care to decrease the chance of dental infections. In Malignant osteopetrosis a bone marrow transplant may be performed where abnormal osteoclasts are replaced with normal ones but it cannot reverse damage that has already occurred.

**SUMMARY**

Extensive research in molecular biology has been successful in identifying the chromosome responsible for Osteopetrosis but there are limitations to the treatment and management. The cases are usually diagnosed after they have presented to the clinicians with complications related to the disease process. Osteopetrosis fractures and dental caries management requires caution. Osteopetrosis patient may be asymptomatic or present with anaemia and require a proper clinical and radiographic investigation for diagnosis. Radiological and clinical features are sufficient to make a definite diagnosis and there is no need to perform a genetic study to confirm the disease. Biopsy must be avoided because of a marked infection risk. There is need to examine the genetic and molecular mechanisms of abnormal bone formation and breakdown to find new targets for therapy, stopping the disease and preventing its complications.

![Figure 1: 35yrs old female with anemia and hepatosplenomegaly diagnosed with osteopetrosis. Chest radiograph shows diffuse increase in density of bones. Cortical thickening of humerus is also noted.](image1.jpg)

![Figure 2: 35yrs old female with anemia and hepatosplenomegaly diagnosed with osteopetrosis. Radiograph of pelvis shows diffusely increased density of bones with cortical thickening and medullary encroachment. No evidence of any fracture. No evidence of any ligament calcification is noted.](image2.jpg)

![Figure 3: 35yrs old female with anemia and hepatosplenomegaly diagnosed with osteopetrosis. Skull radiograph AP and lateral view shows increased bone density of base of skull.](image3.jpg)
Figure 4: 35yrs old female with anemia and hepatosplenomegaly diagnosed with osteopetrosis. Lumbo-sacral spine radiograph AP and lateral view shows increased bone density of end-plates giving "Sandwich" vertebrae appearance.

Figure 5: 35yrs old female with anemia and hepatosplenomegaly diagnosed with osteopetrosis. AP radiograph of wrist and forearm shows increased bone density and cortical thickening. No evidence of interosseous membrane calcification.

REFERENCES:

