ADULT ONSET OSTEOPETROSIS (ALBERS SCHONBERG DISEASE) -
A CASE REPORT

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Abstract:
Osteopetrosis is a rare genetic disease that occurs due to defective bone modelling, with an approximate incidence of 1 in 100,000 to 1 in 500,000 adults as quoted in literature. The underlying pathology is an impaired function of osteoclasts and their role in bone resorption. A 24 year old male presented with severe chronic anaemia, pancytopenia and hepatosplenomegaly with history of receiving recurrent blood transfusions. Laboratory investigations revealed normocytic hypochromic anaemia. The bone marrow examination showed a hypocellular picture with fibrosis. Radiologic examination showed presence of sclerosis of the base of the skull, generalised sclerosis of the pelvis and thickened lower ends of femur and tibia. It was diagnosed as adult onset benign form of autosomal dominant osteopetrosis. We report this case in view of its rare incidence.

Keyword: Osteopetrosis, anemia, osteoclast, sclerosis, pathological fracture.

Introduction
German radiologist, Albers Schonberg, first described osteopetrosis in 1904 in a 26 year old man with generalised sclerosis of bones associated with multiple fractures.  Osteopetrosis refers to a dysplastic condition associated with abnormal bone modelling and generalised increase in bone density. The disease is referred to by a myriad of names including chalky bone disease, marble bone disease, osteosclerosis fragilis generalisata and osteopetrosis generalisata.

Case Report
A 24 year old male presented with chronic anaemia with repeated attack of lower respiratory tract infection for 3 years. He had history of repeated blood transfusion. The patient had a history of jaundice at 2 years of age. There was no history of gastrointestinal blood loss, no history of repeated attacks of jaundice or abdominal pain. Patient also did not give any history of bone pains. He was born to third degree consanguineous parents and there was no family history of anemia, jaundice or gallstones. On examination the patient had severe pallor, anicteric with mild growth...
retardation with no significant superficial lymphadenopathy. The patient also had thickened lower ends of tibia bilaterally. Cardiovascular examination was unremarkable except for the presence of functional murmur. Abdominal examination revealed mild hepatosplenomegaly. Direct ophthalmoscopic examination of the fundus showed haemorrhages and Roth spots. Laboratory investigation revealed hemoglobin of 3.5gm%, normocytic hypochromic anaemia with pancytopenia on peripheral smear study. His ESR was 170mm/hr. Special investigations like LE cell test, Direct Coombs test, Hams test for PNH, stool for occult blood were all negative. Osmotic fragility test and Red cell G6PD enzyme activity were normal. Liver function tests, renal function tests, Serum alkaline phosphatase and urinalysis for urobilinogen was normal. Urinary hemosiderin was also negative. Haemoglobin electrophoresis showed no abnormal bands. Iron studies revealed serum Iron levels of 50µg/dL (Ref 41-141µg/dL), TIBC 220 µg/dL (Ref 251-406 µg/dL), and serum LDH 205 IU/L (Ref 115-221 IU/L). Bone marrow aspiration from the right posterior superior iliac spine showed hypocellular marrow with significant reduction in erythroid and granulocyte progenitors and megakaryocytes with few osteoblast and osteoclast. The Myeloid: Erythroid ratio observed was 17:1. Bone marrow biopsy showed cortical and trabecular bony spicules and interspersed marrow. The bony trabeculae showed prominent cement lines with focal irregularity. Mild focal irregular fibrosis was seen. Bone marrow biopsy was predominantly hypocellular with fibrosis.

Fig 1
fig-2 : X Ray Skull, lateral view showing generalised sclerosis of the vault Xray cervical spine lat view showing sclerosis of vertebrae
Discussion

Osteopetrosis refers to a group of genetic diseases characterized by reduced bone resorption and diffuse symmetric skeletal sclerosis as a consequence of impaired formation or function of osteoclasts. Osteopetrosis reflects the stone like quality of the bones; however, the bones are abnormally brittle and fracture easily, like a piece of chalk.\(^3\) It occurs due to the inability to produce Macrophage Colony Stimulating Factor (M-CSF) as a consequence of which there is defective osteoclast production and function. Osteoclasts are multinucleated giant cells derived from fusion of progenitor cells of the monocyte/macrophage lineage of the hematopoietic stem cells [HSC].\(^4\) They resorb and remodel bone, regulate osteoblast activity, and help control the HSC entry into and exit from the marrow.\(^5\) Osteoprotegrin (OPG) is a soluble decoy receptor that binds osteoblast derived RANK (receptor activator of NFB ) ligand which mediates osteoclast differentiation and activation. Transgenic mice that over express OPG have been shown to develop osteopetrosis by blocking RANK ligand. Mice deficient in RANK lack osteoclast and develop osteopetrosis.\(^6\) Osteopetrosis has been classified into the following clinico-pathologic types.\(^7,8\)

An **Infantile malignant form of osteopetrosis** with an autosomal recessive pattern of inheritance. Its manifestations include fractures, hydrocephaly, anemia, and infections due to decreased hematopoiesis, and hepatosplenomegaly as a consequence of extramedullary hematopoiesis.

**Autosomal dominant type I and type II.** These have similar clinical features. Clinical presentation may be in the form of pathological fractures, anemia, and mild cranial nerve deficits due to impingement.

**Osteopetrosis secondary to Carbonic anhydrase II deficiency** due to effect of mutation resulting in the inability to excrete hydrogen ions, thus impairing osteoclast function.
Various clinical presentations of osteopetrosis have been recognized. The severe (malignant) form usually causes death in utero or in early infancy, is inherited as an autosomal recessive trait. In this severe form of the disease, marrow cavities fail to develop, leading to extramedullary hematopoiesis, anemia, leukoerythroblastosis, and progressive hypersplenism. Obstruction of the cranial foramina results in increased intracranial pressure, optic atrophy, deafness, and cranial nerve palsies. These children can present with developmental delay, and death usually occurs during the first years of life secondary to anemia, bleeding, or infection. Microscopic examination may reveal extremely dense and irregular bone trabeculae, nearly all of which may have a central core of cartilage. A paucity of osteoclasts has sometimes been reported in patients with osteopetrosis, but this finding cannot be extended to all cases. In other words, osteoclasts though present do not appear to be functioning normally. This disturbed microarchitecture results in multiple fractures, while the anemia results from the marked reduction in the marrow space. Three mutations have been known to cause defects in osteoclast function: carbonic anhydrase II deficiency, osteoclast proton pump deficiency, and defects in the chloride channel. The most common of these, found in 50% to 60% of patients, results from defects the osteoclast vacuolar H+ -ATPase proton pump. Adult onset osteopetrosis or osteopetrosis tarda is a benign autosomal dominant disease. It is usually diagnosed by characteristic radiological features during the course of evaluation of pathological fracture or may be a discovery of chance during a routine evaluation of a patient or anapatent with anemia. There is generalised symmetrical increase in bone mass with thickening of both cortical and trabecular bone. The course of the disease is associated with loss of vision, deafness, psychomotor delay and mandibular osteomyelitis. The clinical, biochemical, bone marrow studies and radiological picture of our patient was adult onset osteopetrosis. For infantile malignant osteopetrosis only curative treatment is haematopoietic stem cell transplantation [HSCT]. Allogenic HLA-identical bone marrow transplantation may prove useful in some. Random studies in small populations of patients have yielded variable results following treatment with agents like interferon gamma -1, methyl prednisolone, Vitamin D3, and a low calcium/high phosphate diet. Surgical care may be required for treatment of complications. In the near future gene therapy could be the treatment of choice for carefully selected patients with osteopetrosis.

Conclusion

Adult onset osteopetrosis though a rare entity, is a differential that has to be considered in a young adult with anemia and in an adult with pathological fracture.

References

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