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Case Report
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OSTEOPETROSIS CONGENITA IN A 2 MONTHS OLD MALE PATIENT, A CASE REPORT & LITERATURE REVIEW

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Introduction

Osteopetrosis is a rare hereditary bone disorder which may present in one of three forms: osteopetrosis tarda, osteopetrosis congenita and "marble bone" disease. Osteopetrosis tarda, is a benign form, & usually presents in adulthood, while the two more malignant variants, osteopetrosis congenita and marble bone disease, present in infancy and childhood, respectively. In all three forms, the principal pathology is alteration of osteoclastic bone resorption with consequent thickening of both cortical and lamellar bones. Osteopetrosis tarda is usually discovered accidentally on routine radiographs and is often asymptomatic; however, patients may present because of related degenerative joint disease. Osteopetrosis congenita results in bone marrow failure and is almost always fatal. Marble bone disease causes short stature, cerebral calcification and mental retardation. Bone marrow transplant is the only chance for survival in patients with osteopetrosis congenita.

We describe a case of osteopetrosis congenita in a 2 months old boy from Thi-Qar City.

Case description

A two-months aged male baby from Thi-Qar, presented with progressive pallor, susceptibility to infections, failure to thrive & failure to achieve normal mile stones since birth that necessitated repeated blood transfusions. On examination, the baby was quite pale, despite normal & good feeding, he had a protruded tongue, distended abdomen, & he was feverish, dyspneic, not jaundiced & not cyanosed. Chest examination revealed scattered rale (crackles) here & there of active chest infection, normal cardiac double rhythm & palpable both liver & spleen. There was no neurological deficit, no other abnormality. Family history was negative.

Haematological investigations revealed: a low hemoglobin (46 g/L), HTC (0.13), leucocytosis (18.9 x 10^9/L), slightly elevated ESR (37 mm/1st hr), & normal platelets count (234 x10^9/L). His blood film morphology showed red cell normochromia with neucleated cells seen, leucocytosis with a myeloid left-shift & normal platelets morphology with absence of any malignant cell. The picture was of a severe leuco-erythroblastic anemia. (Figure-1)

Figure 1: Peripheral blood film of the patient showing leuco-erythroblastic blood picture

His biochemical values were: T.S.bilirubin 1.4 mg/dl, S. alkaline phosphatase 188 IU/L, ALT 24 IU/L, AST: 34 IU/L, LDH: 342 IU/L, calcium: 9.8 mg/dl, phosphorus 2.3 mg/dl, urea; 34 mg/dl, creatinine 0.8 mg/dl, total proteins 76.6 g/L, s albumin 45.1 g/L & globulins 31.5 g/L. His prothrombin & partial thromboplasin times were both normal & plasma fibrinogen level was 187 mg/dl. An X-ray skeletal survey showed an overall increased density of axial & peripheral skeleton with almost total obliteration of medulla & increased cortical thickening (Figures-2-5).

Figure 2: Skeletal X-ray shows calcification of almost all bones with obliteration of medulla

Figure 3: Skeletal X-ray shows medullary obliteration & cortical thickening of axial skeleton

Figure 4: Skull X-ray, AP view shows cortical thickening, obliteration of medulla. Cervical spine is showing the same changes.

Figure 5: Skull X-ray, lateral view showing the same changes seen in previous films.

Bone marrow aspiration was done & it revealed a moderately hypocellular marrow with all normal cellular elements seen in normal maturational stages. However, a striking feature is the abundance of osteoclasts allover the marrow (Fig. 6,7).

Figure 6: Bone marrow aspirate shows a hypocellular marrow with multiple osteoclasts (arrows). Leishman stain, 250X

Figure 7: Bone marrow aspirate showing single multinucleated osteoclast(arrow)with a markedly hypocellular background, Leish-man stain, 400X

Bone marrow trephine biopsy was intended to be done but the parents didn't accept that & discharged their patient on their own responsibility. All above findings were conclusive of osteopetrosis congenita

Review of literatures

Osteopetrosis is a rare bone disease that may present in one of three distinct forms (osteopetrosis tarda, osteo-petrosis congenita & marble bone disease). Osteopetrosis tarda, is the most benign form, & usually presents in adulthood and is often diagnosed incidentally on routine radiographs, whereas the two more malignant variants, osteopetrosis congenita and marble bone disease, present in infancy and childhood. In all the three forms, the principal pathology is reduction of osteoclastic bone resorption and thickening of cortical and lamellar bones[1]. However, despite that, there is normal bone formation. As a consequence, bone modeling and remodeling processes are impaired, resulting in the presence of excessive calcified tissue. The abnormal resorption results in a grossly altered structural pattern of bone: so that the cortices are thickened, individual bony trabeculae are increased, and the marrow spaces are encroached upon, leading to a paucity of hemopoietic tissue, with consequent secondary anemia[2].

Pathophysiology

The main reason behind all forms of osteopetrosis is the failure of normal osteoclastic bone resorption. This results in dense, deformed sclerotic bones that show typical and diagnostic patterns on radiograph[1]. The defect in bone turnover characteristically results in skeletal fragility despite increased bone mass, and it may also cause hemopoietic insufficiency, disturbed tooth eruption, nerve entrapment syndromes, and growth impairment. So it is a heterogeneous disorder involving different molecular lesions and a wide range of clinical features[3,4].

Osteopetrosis tarda, the benign adult form, is inherited as an autosomal dominant trait. Patients typically are asymptomatic and have good long-term survival rates because bone marrow failure rarely occurs[1].

Osteopetrosis congenita, is a more common and malignant form, & presents in infancy resulting in bone marrow failure. It is caused by complete replacement of the marrow spaces with osteoclasts[1].

An extremely rare form occurs in childhood and is inherited as an autosomal recessive disorder. The syndrome results from the absence of carbonic anhydrase isoenzyme II enzyme necessary for normal osteoclastic bone resorption. The major characteristics of this disorder include cerebral calcification, osteopetrosis and distal renal tubular acidosis[5]. This form has been called marble bone disease. Genetically, two forms of this type exist: an autosomal recessive form which can present as either a severe or intermediate form[6].

The severe autosomal recessive, (sometimes called malignant form) is a rare congenital disorder of bone resorption, occurring in less than 1 in 200 000 births. It shows an insufficient bone marrow hemopoiesis leading to extramedullary hemopoiesis (which subsequently results in hepato-splenomegaly); pancytopenia with all its consequences. Patients may also show cranial-nerve dysfunction, deafness and visual deficits[7].

The intermediate autosomal recessive form is usually diagnosed in the first decade and patients tend to survive into adulthood; with increased bone density, recurrent fractures, macrocephaly, and mild-moderate anemia. Disturbances in osteoclast functions have been attributed to mutations in a gene encoding an osteoclast-specific unit of the vascular proton pump (TCIRG1)[7].

The other genetic form is an autosomal dominant form which can present in two forms both of which are mild & patients may have normal life expectancy, but may suffer from recurrent fractures; It can present in one of 2 types: type I: is associated with sclerosis of the cranial vault; & type II: is characterized with rugger jersey spine and pelvic endobones; & defects in the chloride channel (CLCN7) gene. Some patients may show spondylolisthesis in the cervical and/or lumbar spine. Most of these patients can be managed non-operatively. The dominant form has been genetically mapped to chromosome 1p21[7].

Clinical Presentation

The clinical manifestations run a spectrum from the severe form which is detected earlier in infancy to the milder form which even sometimes is detected incidentally by the characteristic radiographic finding. The severe form usually presents with failure to thrive, the development of macrocephaly, severe anemia, hepato-splenomegaly, deafness, blindness (due to entrapment neuropathies). With time patients show psychomotor delay & worsening of cranial neuropathies & anemia. The development of dental problems, osteomyelitis of the mandible and pathological fractures are common. Severely affected patients die during infancy, while less severely affected ones, rarely survive beyond the second decade of life.

The autosomal dominant form (Albers-Schoberg disease, osteopetrosis tarda, benign osteopetrosis, marble bone disease), usually presents during childhood or adolescence with fractures & mild anemia & less frequently, a cranial nerve dysfunction, dental abnormalities[7]. It is usually detected by a family history of bone disease or as an incidental radiological finding, and

is asymptomatic in about 50 percent of cases. About 40 percent of patients present with fractures related to brittle osteopetrotic bones or with osteomyelitis, especially of the mandible[8]. There is sufficient retention of marrow cavity for normal hemopoiesis to occur. In some cases, there is an elevated acid phosphatase level[8]. Although patients with osteopetrosis tarda have an increased susceptibility to fractures, healing appears to proceed normally[1].

Osteopetrosis congenita (malignant osteopetrosis) presents in infancy and is associated with failure to thrive and growth retardation[4]. This form of osteopetrosis is very severe and usually results in death by age two years[1]. Proptosis, blindness, deafness and hydrocephalus occur in these patients as bone encroaches on the cranial foramina[9]. A critical feature of osteopetrosis congenita is severe bone marrow failure, resulting in pancytopenia. Extramedullary hemo-poiesis, results in hepatosplenomegaly and hypersplenism, may occur but cannot compensate for bone marrow failure. Thrombocytopenia, leuko-erythroblastic anemia and elevated serum acid and alkaline phosphatase levels are also usually present. Hypocalcemia may or may not be present. Death from osteopetrosis congenita occurs as a result of severe anemia, bleeding and/or infection[4]. In rare instances patients survive into adulthood. They present with severe anemia, recurrent fractures, growth retardation, deafness, blindness and massive hepatosplenomegaly[1].

Marble bone disease, the other infantile form of osteopetrosis, is not characterized by bone marrow failure. Although survival rates are better for patients with marble bone disease than for patients with osteopetrosis congenita, the consequences of renal tubular acidosis may shorten life expectancy. Patients with marble bone disease are usually of short stature and present with intracranial calcifications, sensorineural hearing loss and psychomotor retardation[10].

Radilogically radiographs show diffuse bone sclerosis. Later films show a"bone within a bone" which is characteristic. There is clubbing of metaphyses & alternating bands of lucent & dense bands producing a sandwich appearance to vertebral bodies[11].

Management

Osteopetrosis congenita is associated with failure to thrive and severe bone marrow failure; death occurs by two years of age.

Osteopetrosis tarda requires no treatment, except in patients who present with surgical or medical complications. Surgical treatment is sometimes essential in order to obtain the functional results, such as in cases of significant alterations of facial profile[11] and recurrent fractures with subsequent deformity. Surgical intervention is also necessary in some cases of severe related degenerative joint disease. Both internal[12] and external fixations have been used with excellent results[13].

Several treatment modalities have been under investigation for the infantile malignant variant of osteopetrosis. However, bone marrow (stem cell) transplantation is the only curative treatment for this autosomal recessive variant. Oral and external nutritional support has also been used to improve growth and enhance patient response to other treatment modalities[13,14]. Treatment with 1,25-dihydroxy vitamin D in an effort to provoke non-resorbing osteoclasts to resorb bone or to cause a differentiation of mononuclear cell precursors into mature normal osteoclasts, has been experimentally adopted[3]. Although no

clinical improvements were noted, bone biopsy specimens showed evidence of increased osteoclastic bone resorption[1].

Erythropoietin was found to correct anemia in osteopetrosis congenita presenting with myelophthisic anemia resistant to nandrolone and low-dose corticosteroid therapy[12]. Human interferon gamma therapy for 6 months showed a significant increase in bone resorption, hematopoiesis (medullary) and leukocytic function[15-17].

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