Case Report

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Malignant infantile osteopetrosis presenting as failure to thrive

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Malignant infantile osteopetrosis presenting as failure to thrive

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ABSTRACT

Osteopetrosis or marble bone disease is a heterogeneous group of hereditary disorders in which deficient or altered function of osteoclasts results into defective resorption of bone with resultant sclerosis. We report a case of infantile osteopetrosis who presented to us as failure to thrive, severe anemia and developmental delay. This case report highlights the importance of this rare disease as a differential diagnosis in infants with failure to thrive, to avoid the potentially treatable entity.

Key words: *Failure to thrive, Infant, Osteopetrosis, Osteosclerosis*

Osteopetrosis or marble bone disease discovered by Albin Schonberg in 1904, also called by his name, is a heterogeneous group of hereditary disorders in which deficient or altered function of osteoclasts results into defective resorption of bone and sclerosis, with uncertain etiology. Osteopetrosis is very rare in most populations; estimated incidence is less than 1:200,000 births [1]. Osteopetrosis is characterized by the bone marrow fibrosis, bicytopenia, and compensatory hepatosplenomegaly. Because of failure of osteoclasts to resorb bone, bone modeling and remodeling are impaired and this defect in bone turnover characteristically results in skeletal fragility despite increased bone mass. It may also cause hematopoietic insufficiency, disturbed tooth eruption, nerve entrapment syndromes, and growth impairment.

Disturbances of osteoclast function due to mutations in a gene encoding an osteoclast-specific subunit of the vacuolar proton pump (TCIRG1) are found in most patients with the recessive form of osteopetrosis. Mutations of the gene encoding the chloride channel protein, CLCN7, are observed in the dominant form of osteopetrosis [2]. Being a rare disease one needs to have a high index of suspicion in any infant with severe anemia, failure to thrive, and organomegaly.

CASE REPORT

Nine and half month old female infant, a product of non-consanguineous marriage, with no remarkable antenatal, natal and post natal history, was presented by parents with complaints of not gaining weight despite being adequately fed. There was no history of recurrent chest infections, recurrent vomiting, chronic diarrhoea, previous hospitalizations or neuro-developmental delay. Baby had birth weight of 2.7 Kg, was breast fed till 7 months, and then weaning was started.

Anthropometry at this age revealed weight 4.3 kg (< 3rd percentile), length 58 cm (< 3rd percentile), and mid arm circumference 10 cm (< 3rd percentile). Clinical examination revealed wasted infant, with severe pallor, gum hyperplasia, high arched palate, open anterior fontanels, significant hepatosplenomegaly without lymphadenopathy (Fig. 1) with normal ophthalmalogical and otolaryngological examination. There were no other remarkable clinical findings including neurodevelopmental assessment. She had 4.5 cm of hepatomegaly and 3 cm splenomegaly below the costal margin. It was the initial chest radiography that delineated the increased bone density, a pointer towards the osteopetrosis.

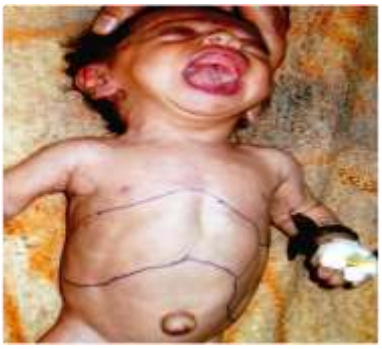

Figure 1 - Gum hyperplasia, high arched palate, hepatosplenomegaly and umbilical hernia

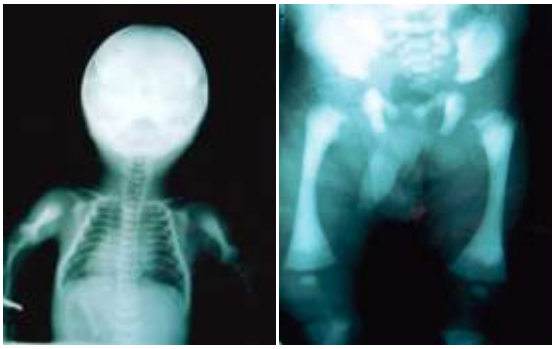

Figure 2 - Showing diffuse sclerosis, modeling and hyperdensity of upper and lower limbs

Laboratory findings revealed hemoglobin of 6.5 g/dl (11-13g/dl), hematocrit of 29.5 % (40-55%), white blood cells of 14000/mm^3 (5000-11000/mm^3), polymorphs 70% (35-70%), lymphocytes 25% (25-50), platelets 80,000/mm^3 (150,000-300,000/mm^3), serum bilirubin 0.8mg/dL, aspartate amino transferase (AST) 88 U/L (10-40), alanine amino transferase (ALT) 53 U/L (5-40), alkaline phosphatase 553 U/L, serum calcium 9.2 mg/dL, phosphorus 4.5 mg/dL. Peripheral blood smear revealed anisocytosis, and thrombocytopenia; urine analysis, C-reactive protein and erythrocyte sedimentation rate (ESR) was within normal limits.

Thyroid stimulating hormone, parathyroid hormone level, and lactate dehydrogenase (LDH) levels were also normal. Work up for intrauterine infections as well as inborn errors of metabolism including TORCH titers, tandem mass spectrometry (TMS) and urine organic acid levels were in normal limits. Bone marrow aspiration revealed a dry tap. Ultrasonography cranium was normal, while abdominal scan showed hepatic and splenic enlargement. Findings of gum hyperplasia, high arched palate, hepatosplenomegaly, anemia, thrombocytopenia and dry bone marrow tap lead us to suspect of osteopetrosis. Subsequent whole body X-rays depicted generalized osteosclerosis (Fig 2).

The diagnosis of malignant infantile osteopetrosis (MIOP) was made on the basis of all these clinical and laboratory findings. However, we could not confirm the diagnosis by genetic analysis due to unavailability of the testing in our setup. We started treatment with methylprednisolone 2 mg/kg/day for 3 days followed by prednisolone 1.5 mg/kg/day in 2 divided doses. Clinical improvement was obviousand marginal improvement was also noted in hematological parameters. We could not administer or interferon due to financial constraints. Bone marrow transplantation although forms an important treatment modality could not be administered in our patient, that could have changed the course of disease [3].

DISCUSSION

Developmental delay, growth retardation, anemia, thrombocytopenia with hepatosplenomegaly and bony sclerosis at this age suggests malignant infantile osteopetrosis (MIOP), an autosomal recessively inherited disease. Apart from these findings, blindness and deafness can occur as a result of compression of cranial nerves [4]. Our patient had all these features except optic nerve and vestibulocochlear nerve involvement. Striking point was dry bony tap, and sclerotic bony changes that led us to think of MIOP.

Differential diagnosis is very important in this situation because these findings are nonspecific and may also exist in case of infectious diseases and inborn errors of metabolism. Therefore, detailed history, thorough clinical examination along with routine tests like blood counts, peripheral smear examination, reticulocyte count, C-reactive protein, ESR, arterial blood gas analysis, liver and kidney function tests, urine analysis, aided by level second tests like USG cranium, and abdomen, blood and urine culture, TMS, whole body x-ray, along with bone marrow aspiration should be carried out, as in our case.

Other conditions that can present in similar way include: renal osteodystrophy, osteosclerosis like pyknodysostosis, osteomyelofibrosis, Gaucher's

disease, hypoparathyroidism, pseudohypoparathyroidism, Caffey's disease, chemical poisoning (fluoride, lead, and beryllium), hypervitaminosis D, and chronic hypervitaminosis A. Absence of other relevant clinical and laboratory features in these entities, did not favor possibility of these conditions. Prognosis in MIOP is poor without treatment as a result of bone marrow failure. The natural course of the disease results in survival of about 30% of patients at six years of age. Some may live till 2nd or 3rd decade but the quality of life is mostly poor [5-6].

Drug therapies only decrease symptoms. Steroids at high doses only decrease bone density and bone marrow thickness [7]. This is due to direct thinning effect of steroids on bone. Other treatment modalities include interferon gamma-1b that slows down the progression, increase bone resorption and hematopoiesis, and improve leukocyte functions [8]. Although, calcitriol stimulates dormant osteoclasts and thus stimulate bone resorption; however, it is not the routine treatment modality. Usually, modest improvement is seen which is not sustained after cessation of therapy. Erythropoietin can be used to correct anemia. Nutritional support, vitamin D and calcium supplementation are necessary to treat malnutrition. Bone marrow transplantation provides the only curative treatment for AR osteopetrosis. Successful results have been achieved in patients transplanted with HLA matched sibling donor stem cells [9].

CONCLUSION

Malignant infantile osteopetrosis should be kept as a differential diagnosis in infants with failure to thrive, organomegaly and anemia. Cases might have escaped diagnosis, and faced untimely demise, that could have been prevented by heightening the sensitivity regarding the early diagnosis of this condition, in particular to our region where rate of consanguinity is very high.

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