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Case Report

Primary hypertrophic osteoarthropathy presenting as juvenile idiopathic arthritis: a case report

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ABSTRACT

Primary hypertrophic osteoarthropathy (PHO) is an inherited disorder, characterised by skin thickening of face and extremities, and periosteal proliferation of the long bones. It is caused by HPGD or SLCO2A1 gene mutations, inherited in an autosomal dominant or recessive pattern. It presents with characteristic skin changes and musculoskeletal pain. We present the case of an adolescent male patient with hypertrophic osteoarthropathy. We managed him successfully with zolendronic acid.

Keywords: Pachydermoperiosteitis, Bisphosphonates, Zolendronic acid, Proliferative bone disease

INTRODUCTION

Primary hypertrophic osteoarthropathy (PHO) is a rare inherited disorder, characterized by abnormal skin proliferation at the distal parts of the extremities as well as periosteal proliferation of the long bones - leading to the alternative term pachydermoperiostosis. Inherited in an autosomal dominant or recessive pattern, it is caused by HPGD or SLCO2A1 gene mutations. Pathogenesis is mediated by excess prostaglandin E2 (PGE2) and vascular endothelial growth factor (VEGF).[1] This entity needs to be considered in the differential diagnosis of any patient presenting with clubbing with or without musculoskeletal symptoms. We present a case of an adolescent male patient with PHO, managed with zolendronic acid.

CASE REPORT

A 17-year-old male patient, born to parents of third degree consanguineous marriage, presented with complaints of joint pains for the past 5 years, involving the ankles, knees, wrists and elbows in a symmetric fashion. He had developed restricted movements of both elbows since the past 1 year. He also had history of excessive sweating from both palms and soles for 5 years. There was no history of recurrent fever, back pain, psoriasis, visual disturbances, altered bowel habits, or failure to thrive. He had sought treatment for the above complaints 5 years ago, when he was told to have polyarticular juvenile idiopathic arthritis, and started on low dose steroids and methotrexate, which he took for a year and then discontinued in view of poor response. He did not have any comorbid illnesses. There was no history of similar symptoms in the family.

On examination, he had pan-digital clubbing, palmoplantar hyperhidrosis and skin thickening involving the fingers and forehead. Musculoskeletal exam revealed fusiform bony swelling of the distal end of both forearms and legs (Figure 1). Bilateral elbows had fixed flexion deformity of 20 degrees. Pronation and supination of both elbows were impaired. Bilateral wrists, elbows and ankles were tender.

A complete blood count, renal and liver function tests, calcium, phosphate, alkaline phosphatase levels, thyroid function test and urinalysis were normal. Stool examination was normal and testing for occult blood was negative. Erythrocyte sedimentation rate (ESR) was 4

mm/hour and C-reactive protein (CRP) was 0.2 mg/dl. Rheumatoid factor and antinuclear antibody tests were negative. Radiographs revealed periosteal thickening predominantly involving the shaft of radius, ulna, tibia and fibula bilaterally. There was acro-osteolysis of distal phalanges of the hand. Chest radiograph and 2D-echocardiogram were normal. 99Tc MDP bone scintigraphy showed diffusely increased and symmetrical uptake in the periosteal surface of the shaft of long bones (Figure 2). We made a diagnosis of hypertrophic osteoarthropathy.

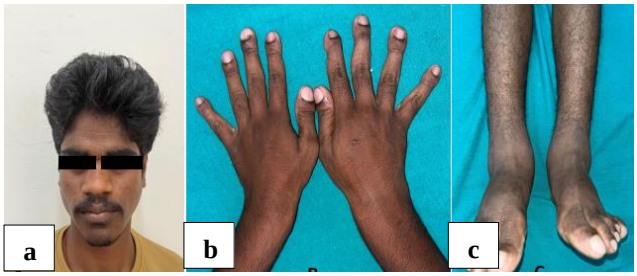

Figure 1: (a) Thickening and furrowing of forehead skin, (b and c) pan-digital clubbing and swelling of distal forearms and legs.

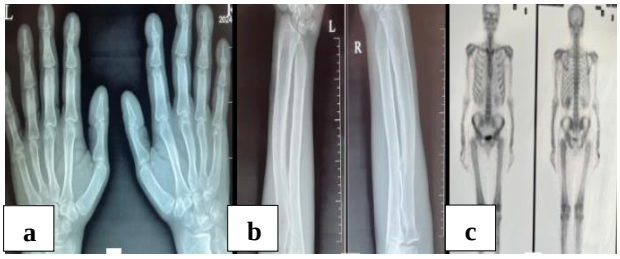

Figure 2: (a) Acro-osteolysis of distal phalanges, (b) periosteal thickening of shaft of radius and ulna, and (c) diffuse symmetrical increase in uptake in periosteal surface of long bones.

We started him on indomethacin 25 mg twice a day for 3 months, following which, pain reduced by 5 points on pain visual analogue scale (VAS), but hyperhidrosis and swelling persisted. In view of inadequate response, we treated him with a single dose of intravenous zolenronic acid 5 mg. Following this, he had complete resolution of pain. Indomethacin was discontinued. There was a partial improvement in hyperhidrosis. He also reported that his finger ring had become loose, reflecting a decrease in skin thickening. He remained pain-free at 6 months' follow-up.

DISCUSSION

Digital clubbing is one of the oldest signs to be recognized: Hippocrates described it in the 5th century BC, lending the term Hippocratic fingers. Clubbing and hypertrophic osteoarthropathy are now understood to represent different stages of the same disease process. In 1935, Albert Touraine, Gabriel Solente, and Laurent Golé distinguished PHO from the secondary form and detailed three subtypes: the complete form, with the full-blown phenotype; the incomplete form, with isolated bone involvement; and the fruste form, with pachydermia alone. More recently, Lu and colleagues classified it into: autosomal recessive 1 (PHOAR1); autosomal recessive 2 (PHOAR2); and autosomal dominant (PHOAD). PHOAR1 is caused by HPGD gene mutation, while PHOAR2 and PHOAD are caused by SLCO2A1 gene mutation.

The epidemiology of PHO is not well characterized. According to one study, it has a prevalence of 0.16%. Onset is during childhood (PHOAR1) or adolescence (PHOAR2 and PHOAD). Overall male-to-female ratio is approximately 7:1. However PHOAR1 affects males and females equally and PHOAR2 and PHOAD almost exclusively affect males. PHO is more common in African Americans.[2]

HPGD gene, encodes the 15-hydroxy prostaglandin dehydrogenase (15PGDH) enzyme that inactivates PGE2 to PGE-M. The SLCO2A1 gene, encodes OATP2A1, which is a prostaglandin transporter (PGT). PGT facilitates transport of PGE2 into the cell, which is necessary for catabolism of PGE2 by 15PGDH. Deficiency of either of the above proteins, leads to impaired prostaglandin degradation, causing elevated prostaglandin levels. Elevated PGE2 levels mediates its pathogenic effect through increased vascular endothelial growth factor (VEGF) which can promote angiogenesis, increase vascular wall permeability, promote endothelial bone formation and activate osteoblast function and migration.[3]

Clubbing is usually the initial symptom. Skin manifestations include pachydermia, hyperhidrosis, seborrhea and acne. Pachydermia manifests as thickening, furrowing and wrinkling of the skin, especially on the face and forehead. Severe scalp involvement manifests as cutis verticis gyrata. Articular manifestations include joint effusion and stiffness, involving the knee, ankle and wrist. Gastrointestinal abnormalities include diarrhea, chronic gastritis, peptic ulcer disease and gastrointestinal adenomas. Another peculiar manifestation is myelofibrosis, which is more common in PHOAR2. Anemia, which might be caused by gastrointestinal hemorrhage or myelofibrosis, is a major complication.

Radiography shows periostosis of shafts of tubular bones, namely, the tibia, fibula, radius, and ulna. Joint space narrowing, erosions, or periarticular osteopenia are absent. Acro-osteolysis can result from resorption of terminal phalanges of fingers and toes. 99mTc–methylene diphosphonate (MDP) bone scintigraphy, is more sensitive than radiography. Increased tracer uptake at the periosteum in a linear fashion along the cortical margins of the diaphysis and metaphysis of the tubular bones (tram line or double stripe sign) is the typical feature. Bone-formation marker levels, such as total alkaline phosphatase, bone alkaline phosphatase, the amino terminal propeptide of type I procollagen, and osteocalcin are elevated. Differential diagnoses include, thyroid

acropachy, voriconazole-induced periostosis and hypervitaminosis A. It is important to rule out secondary hypertrophic osteoarthropathy, which may be of generalized or localized forms. Generalized forms are caused by pulmonary, cardiac, hepatic or intestinal disorders, and localized forms are caused by arterial abnormalities of the involved limb.

NSAIDs, especially the COX-2 selective etoricoxib, form the first line of management. They mediate their effect by decreasing levels of PGE2. This leads to reduction in clubbing, pachydermia and arthritic symptoms, but not in periostosis. Based on the evidence in secondary hypertrophic osteoarthropathy, bisphosphonates have been successfully tried in primary hypertrophic osteoarthropathy.[4-7] Bisphosphonates are postulated to exert benefit due to their VEGF-inhibitory action. A recent systematic review noted the safety and effectiveness of bisphosphonates in both the primary and secondary forms of the disease.[8]

In spite of recent advances in the pathogenesis of primary hypertrophic osteoarthropathy, there remain many lacunae in our knowledge. There are many patients who are negative for the known genetic mutations. Whole-genome sequencing may help us find other genes that are responsible for this disease. Newer therapeutic targets such as E-prostanoid 4 receptor need to be explored, with a view to treat periostosis.

CONCLUSION

Primary hypertrophic osteoarthropathy is a rare genetic disorder with pathognomonic clinical and radiological features. However, it can present diagnostic and therapeutic challenges as exemplified by our case. NSAIDs, particularly COX-2 inhibitors, provide symptomatic relief. Bisphosphonates have emerged as a promising therapeutic option. Initially used in secondary hypertrophic osteoarthropathy, bisphosphonates have been successfully adapted for PHO. Well-designed prospective studies are needed to establish evidence of long term outcomes as well as optimal duration of therapy.

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