Primary Hypertrophic Osteoarthropathy and successful treatment with Oral Bisphosphonates: A Case Report with Literature Review

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Abstract

Primary hypertrophic osteoarthropathy (PHOA) is a rare syndrome with diverse radiological and clinical features. Though the diagnosis can be easily made on the basis of the classic clinical and radiological features, it is often missed due to its variable presentations. Medical management of this rare condition is mainly palliative and it includes usage of NSAIDS, steroids, tamoxifen citrate, retinoids, octreotides, and bisphosphonates and so on. Each group of drug acts differently, as there are many theories postulated towards cause of joint related symptoms. Recently, high amount of interest has been shown with usage of bisphosphonates, which act by inhibition of osteoclasts, as well as by their action against angiogenesis and against vEGF. Isolated case reports of management of PHOA by intravenous pamidronate and zolidronic acid are available. Very few reports show the effects of oral bisphosphonates in the management of PHOA. Here we present a rare case of PHOA who presented with complaints of joint pain and with thickened lesions over the skin and hyperhidrosis. It was successfully and symptomatically treated with oral alendronate.

Introduction

PHOA is a syndrome characterized by abnormal proliferation of the skin and osseous tissues at the distal parts of the extremities. Three features are primarily required to make a diagnosis of PHOA: **Clubbing, periostosis of the tubular bones** and **pachydermia**. Though may present with varied clinical features, a presentation with pain in the joints of extremities seem **consistent** with the case reports reviewed. It is a rare condition in itself, and primarily a diagnosis by exclusion. The pathogenesis of the disease has many postulates, the recent one and best proven of them being VEGF mediated. Treatment suggested includes NSAIDS, steroids, octreotide, retinoid, VEGF inhibitors and more recently bisphosphonates. Most of the case reports use intravenous bisphosphonates. Very rare case reports of successful treatment with oral bisphosphonates cited.

Case Report

A 20 year old male presented to our OPD with complaints of continuous pain presenting over both wrist joints for the previous 6 months. He had no history of other joint involvement or history of morning stiffness. The patient also reported skin lesions on his palms. Occasional history of fever was present. He had no other constitutional symptoms. He was unemployed, not a smoker and not an alcoholic. No similar history in the family.

He was already on treatment for the same complaints for the previous 3 months elsewhere on an outpatient basis. Diagnosed provisionally as a case **sero-negative rheumatoid arthritis** and was given various **NSAIDs**, **Chloroquine** and **steroids** in optimal doses without any effect. Earlier lab results showed increased ESR (40mm/hr), minimal increase in C Reactive protein and RF negative.

On general examination, there was grade IV clubbing which was pan digital in both upper and lower limbs. **(Fig. 1)**

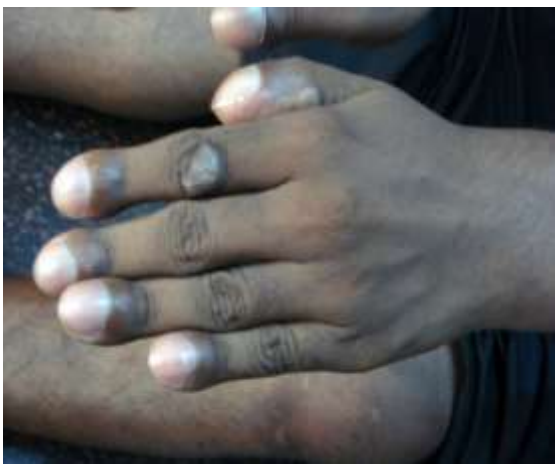

Fig. 1

He also had bilateral symmetrical enlargement of wrist joint. His systemic examination was unremarkable with no cardiac murmurs or thyroid enlargement.

Local Examination of the wrist: Though the clinical picture resembled arthritis of the wrist joints, on careful examination, the swelling was confined to the juxta articular area and not the joint itself. **(Fig. 2**)

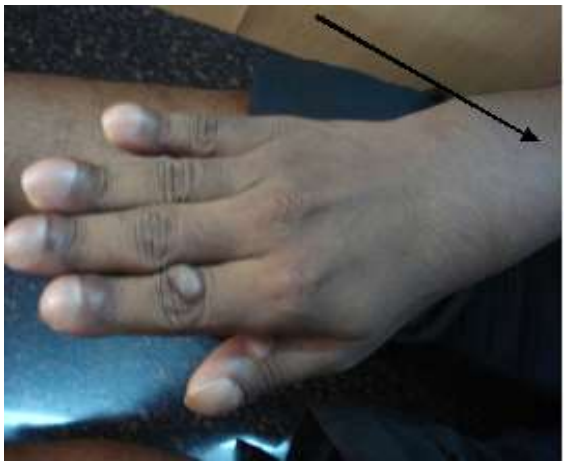

Fig. 2

The swelling was diffuse, bony hard with warmth and there was tenderness on palpation near the articular ends. There was terminal restriction of palmar and dorsiflexion due to pain. Similar juxta articular swelling over both ankle joints was present. (**Fig. 3)**

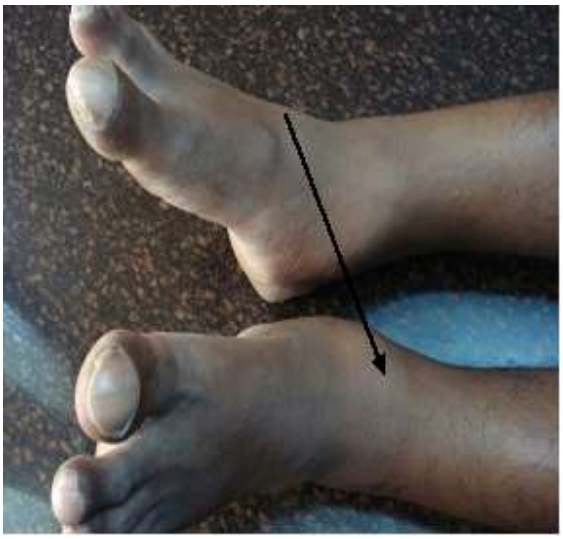

Fig. 3

On careful examination, on the dorsum of the index finger and thumb two cutaneous lesions 2x1 cm size with indurations and hyper pigmented, raised margins seen. **(Fig. 4)**

Fig. 4

There was hyperhidrosis and local warmth over both palms.

His recent blood investigations showed elevated ESR (40mm/ hr), CRP + ve with mild elevation and RF negative. X-Ray Chest and CT Chest were normal. USG Abdomen and Pelvis did not show any abnormalities. ECG and ECHO were normal. X-ray of the wrist and ankle showed widening of the articular ends. Symmetric, irregular periosteal reaction seen. Corticomedullary differentiation is maintained. No remarkable features of arthritis (**Fig. 5, 6)**

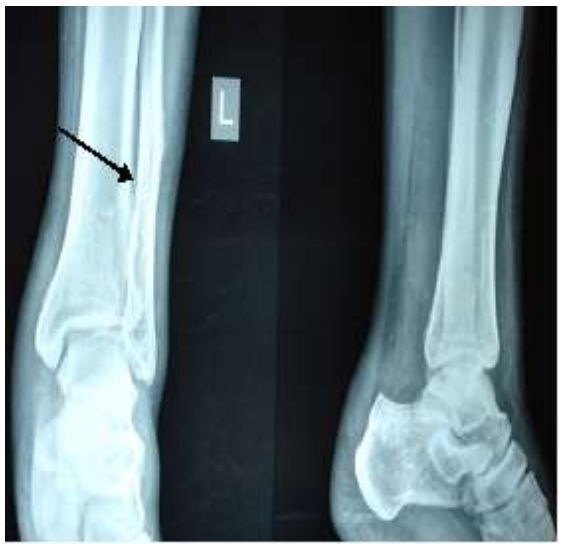

Fig. 5

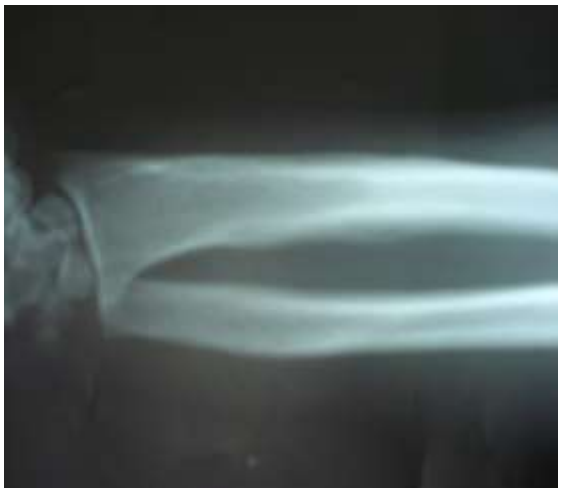

Fig. 6

With all these diagnostic features and by ruling out other systemic illnesses in respiratory system, abdomen and CVS we made a diagnosis of PHOA with the classical **triad of clubbing, periostitis and pachydermia.** Dermatologist opinion also obtained.

He was treated with Oral alendronate 70 mg per week. To our surprise, the symptoms immediately responded and he felt better within 3 weeks. Initial 2 weeks he was asked to continue the previous NSAID, tab. Etoricoxib 60 mg OD which was later stopped at the end of 2 weeks. His blood investigations including ESR and CRP were monitored. The dose was continued for 3 months (total 12 doses) later tapered to 35 mg/ week for the next 3 months. The investigations normalized gradually and the patient felt completely symptom free at the end of 3 months of reduced dosage. He is currently under follow-up and has not reported of pain or swelling since then.

Discussion

Primary HOA or pachydermoperiostosis is a genetically inherited phenomenon mostly affecting males in childhood. Although it shares many of the same clinical manifestations as secondary HOA, the onset of disease and presence of associated systemic symptoms make the two relatively easy to differentiate.

It was first described by Friedreich as 'excessive growth of bone of the entire skeleton' in 1868. Touraine, Solente and Golé described this condition as the primary form of bone disease in 1935 and distinguished its three known forms. Till date, at least 250 cases of PHOA have been reported. The precise incidence and prevalence of this rare condition is still unknown. The ratio between primary and secondary forms is 1:35.

Male: Female ratio is 8:1. Familial: 35%., Autosomal dominant in majority of the cases hence family history and charting is essential in diagnosed cases.

The characteristic features in PHOA are **Pachydermia, Finger Clubbing, and Periostitis.** Though **o**ther associated features like skin thickening, hyperhidrosis, arthralgia, ptosis, Cutis Vertis Gyrata, hypertrophic gastritis may be present; they need not be present always to diagnose PHOA.

There are **3 types** mainly, **complete, incomplete and Frustre** types. The exact distribution of these types among the diagnosed cases is not known. Complete form: All three essential features present

Incomplete form: No pachydermia. Frustre: Prominent pachydermia with few skeletal manifestations.

Etiopathogenesis: There are many theories postulated toward etiology of this rare condition.

a. **Theory of alteration in Lung Function** as suggested by **Stoller J, Moodie D et al**[1]. This was also supported by **Martinez-Lavin M.**[2] who demonstrated that patients with PDA complicated by pulmonary hypertension have acropachy limited to the cyanotic limbs alone.
b. **Theory of improper removal of fibroblast growth factor** as suggested by **Martinez-Lavin m.**[3] He described that a fibroblast growth factor could be at the epicenter of the syndrome. This FGF is normally present in venous circulation and removed by the lungs. Incapability of the lungs to remove FGF or increased production of FGF could be the cause for clubbing.
c. **Theory of Von Willebrand factor antigen: Matucci-Cerinic M, Martinez-Lavin M et al**[4] Measured plasma levels of von Willebrand Factor Antigen by ELISA assay as a marker of platelet and/or endothelial activation and found statistically significantly higher levels.
d. **Mutations in HGPD and resulting impaired metabolism of PGE2**: **Uppal et al**[5] identified mutations in HPGD, which encodes 15-hydroxyprostaglandin dehydrogenase (15-PGDH), a prostaglandin E2 catabolizing enzyme in three families with PHO. High levels of urine PGE2 was also observed in these patients as well as some heterozygous carriers.
e. **Theory of VEGF excess**: **Silveria LH, Martinez-Lavin M, Pineda C et al**[6] suggested that VEGF is responsible for all the symptoms of HOA. It is one of the platelet derived factors released during activation. It is induced mainly by hypoxia. It can also be produced by malignant tumors as a mechanism of growth. It induces vascular hyperplasia, new bone formation and edema. Its plasma and serum concentrations were significantly higher in patients with PHOA. Over expression in stroma of clubbed digits was also seen.

A more recent study by **Atkinson S, Fox SB** evaluated the hypothesis that platelet clusters impacting

in the distal vasculature mediates clubbing. The researchers used immunohistochemistry to evaluate eight different parameters in the stroma of clubbed digits and compared them to control. These digits demonstrated **statistically significant** increase in 5 of the 8 parameters: VEGF, PDGF, micro vessel density, hypoxia-inducible factor (HIF)-1 alpha, and HIF-2 alpha.

Investigations: As such there is no useful serological test for HPOA. As this is primarily a disease of exclusion, most of the tests done are to rule out secondary causes mainly. ESR and CRP may be elevated as in other inflammatory conditions. X rays will show the typical hyperostosis and periosteal thickening. Technetium Bone scan will be of use to find out other joint involvement with high amount of tracer uptake. Electron microscopic studies show structural vessel damage by presence of **Wiebel Palade bodies** and **prominence of Golgi Complexes.**

Differential Diagnosis: Generating a differential diagnosis for HOA first requires determining whether it is a primary or secondary process. As discussed previously it a **diagnosis of exclusion** of all other causes of HOA, mainly cardiac, abdominal, and other associated conditions

Treatment: As there are many theories postulated for etiopathogenesis of HPOA, many drug therapies also suggested for effective treatment. **NSAIDs** reduce inflammation by inhibiting cyclooxygenase, an enzyme necessary for the biosynthesis of prostaglandins, thromboxanes, and leukotrienes. Certain NSAIDs, such as coxibs, ketorolac, and indomethacin have been shown to be more effective.

SA Johnson A Spiller, C M Faul[7]: demonstrated usage of subcutaneous octreotide in HPOA based on the possibility of hormonal etiology of the HPOA.

Role of Bisphosphonates: After their introduction to clinical practice more than 3 decades ago, bisphosphonates have been increasingly used for many skeletal disorders. They are used mainly in osteoclast-mediated bone loss due to osteoporosis, Paget disease of bone, malignancies metastatic to bone, multiple myeloma, and hypercalcemia of malignancy.

They also have **some lesser known actions** which have not been studied in great detail. **Wood et al** reported that zoledronic acid produced a **dose-dependent inhibition of cell proliferation** in human umbilical vein **endothelial cells**. This effect counteracts stimulation by fetal calf serum, basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). They also have demonstrated that it was able to reduce vessel sprouting in cultured aortic rings and in the chicken egg chorioallantoic membrane assay.

B. Vincenzi, D. Santini, L. Rocci and G. Tonini[8]: For the first time in humans, showed a significant decrease of circulating VEGF levels in patients with advanced solid cancer and bone metastases receiving a single dose of pamidronate administration (90mg). This decrease which was significant on day 1 persisted on day 7. Hence the research was extended to the potential antiangiogenic properties of a single zoledronic acid infusion (4 mg) in cancer patients with bone metastases. Differently from pamidronate, zoledronic acid with 40 to 850 fold greater potency than pamidronate induced a more prolonged decrease in serum VEGF levels lasting 21 days from the infusion. Moreover, it was able to induce a significant, though transient, decrease in serum platelet-derived growth factor levels. Many case reports have demonstrated support for the usage of iv pamidronate as well as zoledronic acid in reducing or resolving symptoms from HOA as well as decreasing radiological evidence of periostitis on bone scan.[9,10]

Newer Therapy: VEGF Inhibitors[11,12] With supporting evidence for the importance of VEGF in the pathogenesis of HOA and its correlation with disease activity, targeted antibodies, such as **bevacizumab**, and EDFR tyrosine kinase inhibitor, **gefetinib** used alongside first-line chemotherapies can alleviate pain symptoms in patients with HOA

Having all these theories and postulates in mind and with the proven role of bisphosphonates, we wanted to treat our patient with oral bisphosphonates. The reason being it scores over IV infusion in some aspects like **standard regimen**, **easy once a week dosing** which can be taken by the patient. **Better compliance** and is **cheaper** and can be used as outpatient treatment. Also, parenteral infusion of all bisphosphonates is associated with dose- and infusion-rate-dependent effects on renal function as evidenced by increases in serum creatinine[13]. This can be avoided by oral therapy. Dose was completely stopped after six months. The patient reported complete resolution of pain by the end of therapy. ESR, CRP started coming down from 2nd week of starting the therapy and showed normalization on subsequent follow-up. Now the patient on 2 years follow-up is not on any drugs and is symptom free.

Follow-up: Possibility exists that it could be an undiagnosed pulmonary malignancy presenting as HOA. PHOA is also said to predispose to lung malignancies by a reciprocal relationship. Investigations and careful examination of the patient is done every time he visits.

Conclusion

PHOA is rare condition. With its clinical presentation can mimic RA, and this can frequently lead to misdiagnosis. Most of the times family history cannot be elicited accurately, because at times clubbing is the only presentation without pain of any kind. This results in the acceptance as a part of the body image of

the patient. Simple examination can reveal pan digital clubbing. The diagnosis is by exclusion and there are no definite tests available. In relevance with our current clinical scenario, Oral alendronate is as efficacious in treatment as IV preparations with all the above mentioned advantages. Follow-up is mandatory for these patients, as PHOA can lead to malignancies by a reciprocal relationship and it can also be the presenting feature of an undiagnosed primary malignancy.

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