CASE REPORTS

Bisphosphonates use in Pachydermoperiostosis

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Abstract

Pachydermoperiostosis is a rare genetic disorder which commonly presents with clubbing, bone pains and skin changes. The treatment is mostly unsatisfactory. We tried bisphosphonates in our case with encouraging results. We suggest that parenteral bisphosphonates should be tried early in treatment of Pachydermoperiostosis.

Introduction

Pachydermoperiostosis is also known as Touraine-Solente-Gole´ syndrome, primary or idiopathic Hypertrophic osteoarthropathy(HOAP). It is a rare autosomal disorder with variable expression. Pachydermoperiostosis is characterised by bilateral symmetrical grade IV clubbing, periosteal new bone formation, thickening of skin (pachyderma), and excessive sweating (hyperhydrosis). No treatment is curative. Symptomatic treatment such as NSAIDS, steroids, Colchicine are used. There are case reports of bisphosphonate (Pamidronate) use with good results in secondary[2] HOAP. The reports about use of bisphosphonates[3] in primary HOAP/Pachydermoperiostosis are only few.

Case Report

A 31 years old, male patient, non smoker, non alcoholic, resident of Bihar, presented to us with history of pain and swelling in hands and feet, followed by involvement of ankle, knee and wrist joints, of 15 years duration. This was associated with hyperhydrosis of palms and soles. There was no history of fever, palpitation, bluish discolouration, backache, haemoptysis, haemetemesis, hematuria, haematochezia, cough, expectorations, dyspnea, oral ulcers, weight loss or bleeding tendency. Family history of similar complains positive in paternal cousin brother.

On physical Examination, He was afebrile, pulse-70/min, respiratory rate-16/min, BP-122/80 mm Hg,SpO2-98% at room air. There was no cyanosis, pallor, lymphadenopathy, oedema. On systemic examination, respiratory, cardiovascular, abdominal and neurological examination were normal. On skin examination, there was furrowing on the forehead, skin as oily and shiny in appearance (Figure 1) and hyperhydrosis of hands and feet. Musculoskeletal examination showed grade IV clubbing along with widening of wrist and ankle joint, swelling of both the knee joint (Figures 5a, 6a, 7a and 8a).

Fig. 1: Facial features-furrowing on the forehead with oily and shiny skin

On investigation his haemoglobin, ESR,CRP, leukocyte counts and platelet counts were within normal limits. Peripheral blood film showed normocytic normochromic picture. Liver, kidney and thyroid function tests were normal. Blood sugar was within normal range. Urine examination was also within normal range. Stool for occult blood, chest X-ray PA view, Contrast enhanced CT chest, 2 D echocardiography, USG abdomen and pelvis were normal. Other radiological investigations, X- ray of ulna, radius, tibia and fibula showed wavy periosteal reaction along the distal meta-diaphyses (Figures 2, 3 and 4). On the basis of history, physical examination and investigations, we made diagnosis of Primary HOAP (Pachydermoperiostosis).

His main problem was of bony pains and swelling, We started him on NSAID, steroids, colchicine, added one after the other to relieve pain over six months without much relief. We gave bisphosphonates infusion (Pamidronic acid) 60 mg over 2 hours slowly, after hydration with 500 ml normal saline. Patient responded well in the form of pain relief in 3-4 days of treatment and decrease in swelling of hands, feet and knee in 7-10 days. Patient is still feeling better after 30 days of follow up. Oral glycopyrrolate was given for hyperhydrosis with good result.

Images comparing before bisphosphonates (Pamidronate)

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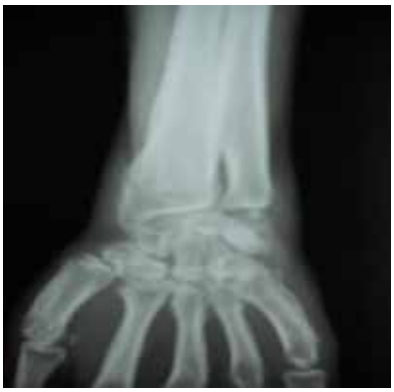
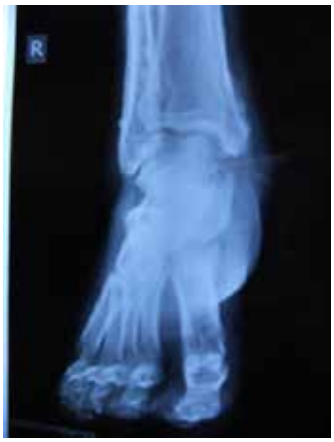
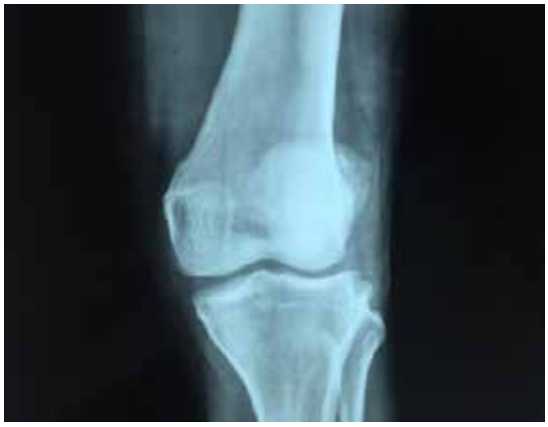


(2) Wrist Joint

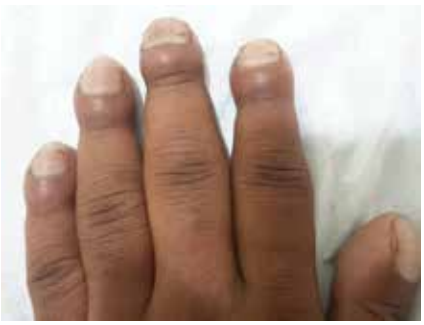


(3) Ankle joint

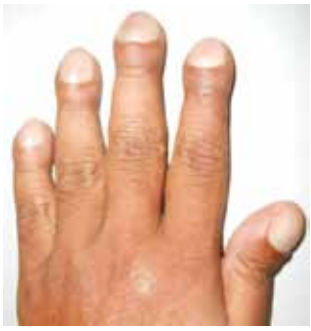


(4) Knee joint

Fig. 2, 3, 4: Periosteal reaction –wavy periosteal reaction along the distal meta-diaphyses of ulna, radius, tibia and fibula and around knee joint. (image-2,3 and 4)

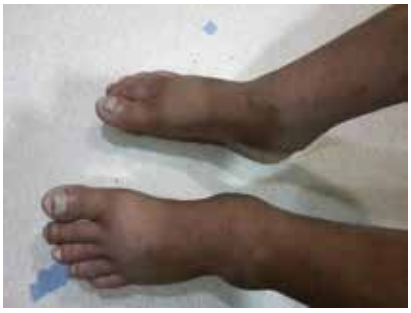


(5a) Before Pamidronate injection

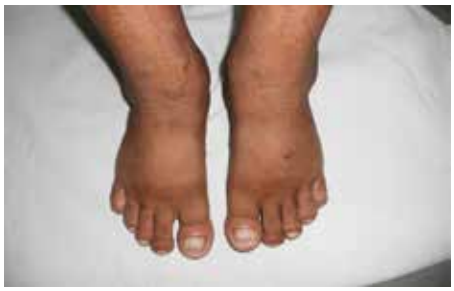


(5b) After Pamidronate injection

Fig. 5: Hands-Soft tissue swelling significantly reduced post treatment



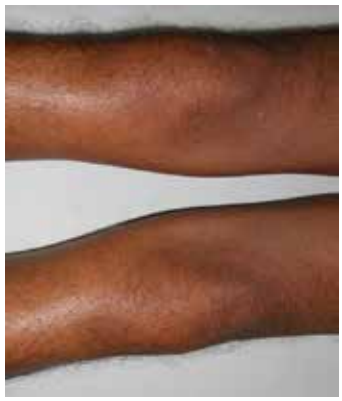
(6a) Before Pamidronate injection



(6b) After Pamidronate injection

Fig. 6: Feet and ankle swelling reduced significantly post treatment.

(7a) Before Pamidronate injection



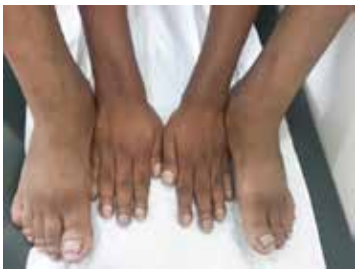
(7b) After Pamidronate injection

Fig. 7: Knee Effusion – decreased significantly post treatment

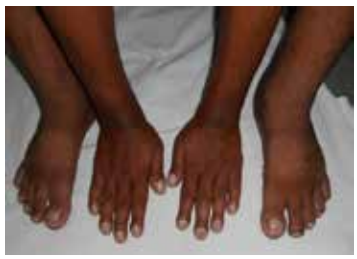
treatment and after bisphosphonates treatment are given below.

Disscussion

Primary HOAP / Pachydermoperiostosis is an autosomal dominant disease with incomplete penetrance and variable expression, in few cases autosomal recessive and X-linked inheritance can be there[1] and family history is present in 1/3rd of cases only. The disease begins insidiously at puberty and is nine times more common in males. Symptoms usually disappear at adulthood but in our patient symptoms persisted and patient did not respond to usual treatment. Exact pathology is unclear but it is suggested that abnormal production of growth factors[2] like VEGF (vascular endothelial growth factor) and PDGF (platelet derived growth factor) are playing central role. It is a rare disease and should be differentiated from other causes of clubbing like chronic suppurative pulmonary diseases, bronchogenic carcinoma and lung metastases, cystic fibrosis, and cyanotic congenital malformations of the heart, thyroid acropachy, acromegaly, and chronic inflammatory rheumatic diseases.[2] Long term prognosis of Pachydermoperiostosis is generally non fatal.No treatment is curative. Various symptomatic treatment strategies are there for Pachydermoperiostosis, including NSAIDS, Steroids, colchicine, vagotomy for skeletal symptoms,botulinium toxin type A, Isotretinoin[4] and plastic surgery for dermatological manifestation,Beta blockers, glycopyrolate or neurotoxins for hyperhydrosis. Newer therapies[2]



(8a) Before Pamidronate injection



(8b) After Pamidronate injection

Fig. 8: Hands,Wrist, Feet and Ankle swelling significantly reduced post treatment

are emerging like octreotide, gefetinib (EGFR inhibiotor) and bisphoshphonates (pamidronate or zoledronate).[2,3] Bishphosphonates exert their theraupatic effects through potent inhibition of osteoclastic bone resorption. They also have antiinflammatory, antiangiogenic effects and also reduce vascular endothelial growth factor.[7] Bisphosphonates[3] has also been tried in painful bony conditions in RA, SpA[2,4,5] bony metastasis, bone pain in secondary HOAP,[6,7] multiple myeloma.

Conclusion

We have earlier experience of using injectable bisphosphonates (Pamidronate) in painful Ankylosing Spondylitis (AS) patients. In primary HOAP,[3] there are few case report of use of bisphosphonates therapy with good result. We tried bisphosphonates in its treatment with encouraging results. We suggest that injectable bisphosphonates should be tried early in pachydermoperiostosis.

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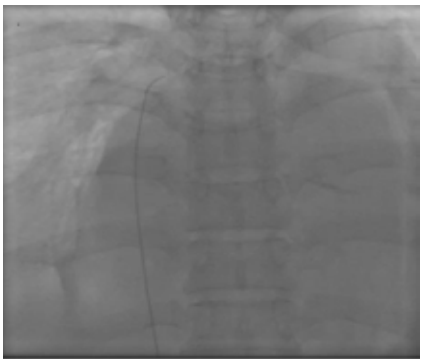

Fig. 1: Plane AP view showing terumo wire (0.035 inch and 150 cm) that negotiated past the IVC stenosis and passed into the RA

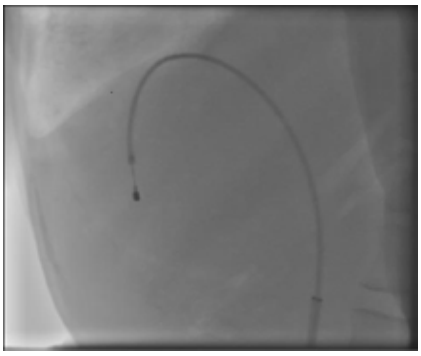

Fig. 2: Lateral view showing the 6F armoured sheath (distal end) in IVC with 6F pacing lead distal electrode at RV apex

there was difficulty advancing the pacing lead beyond the L3 vertebral level. Subsequently 5F pacing lead was used but it could be passed till D8 level only (drainage site of IVC into right atrium). Repeated manipulations were attempted but neither the pacing lead nor a diagnostic 0.032 inch wire could pass into the right atrium (RA). Stenosis of the IVC at the D8 level was confirmed by a contrast venogram. A Terumo wire (0.035 inch and 150 cm) was advanced into the IVC and then negotiated past the stenosis through gentle manipulation and passed into the RA (Figure 1). A 6F armoured sheath (24 cm length) was advanced over the Terumo wire into the RA and then after removal of the wire, a 6F pacing lead with its proximal end shaped into a more curved manner was inserted through the armoured sheath and advanced into the RA. The armoured sheath was then pulled back into the IVC and the lead was positioned into right ventricle (RV) apex (Figure 2). Adequate pacing and sensing thresholds were obtained and lack of diaphragmatic stimulation at high output was noted. Armoured sheath and pacing lead were anchored to the thigh with sutures. Procedure was successful and uneventful and pacing lead and sheaths were removed after 4 days when rhythm had reverted to sinus rhythm. Patient was given heparin till the time the temporary pacing lead was in situ. Abdominal ultrasonography revealed no evidence of extrinsic compression on IVC suggesting a membranous or a web like obstruction at drainage site into RA. Patient was advised further workup and treatment for mitral stenosis and IVC stenosis but she declined for the same. Patient was discharged on 7th post procedure day in a stable condition.

Discussion

Intracardiac temporary pacing by placement of electrode catheter into RV for management of bradyarrhythmias was first described by Furman and Robinson in 1958. It can be attempted through femoral, jugular, subclavian or brachial vein. IVC obstruction occurs in 3% of congenital heart diseases, especially heterotaxy. Isolated obstruction of caval veins is rare, usually iatrogenic and may be detected during right heart catheterization, percutaneous balloon mitral valvotomy (PBMV) or temporary pacing through femoral vein as in our case. Congenital membranous obstruction of the IVC at junction with RA or a restrictive eustachian valve has been described.[2] In Asian countries, the most common cause of acquired IVC obstruction is Budd-Chiari syndrome which presents as membrane occlusion or stricture of IVC.[3] In the west, thrombotic and proliferative disorders, post hepatic transplantation and post IVC filter placement are the predominant causes of acquired IVC obstruction. External compression by a tumor, aneurysmal dilation of aorta, pseudoaneurysm of a venous coronary graft,[4] goiter, mediastinal fibrosis, constrictive pericarditis, bile bladder distention, polycystic kidneys, hydatid cyst, and hematoma after blunt liver trauma have been reported. Vasculitis such as Behcet's disease may lead to shrinkage and obstruction of caval veins. Our patient denied history of any surgical intervention or blunt trauma to the abdomen in past.

In presence of IVC obstruction, the conventional transfemoral approach may not be feasible. In such situations, options are to use a transjugular or subclavian approach. But these approaches can be time consuming and requires considerable instrumentation and surgical skills. Moreover, manipulation of pacing lead from this site into right atrium is not always easy, especially in older people and use of subclavian route compromises later plans for permanent pacemaker implantation.

A transfemoral approach has several advantages: it can be accomplished quickly in 3-13 minutes and is particularly valuable in management of patients with cardiogenic shock where expediency is of paramount importance.[5] With the use of fluoroscope, placement of the pacing lead is precise, and the repositioning or replacement of lead can be done quickly. It does not compromise later plans for permanent pacemaker implantation. It is a simple and safe technique and has a short learning curve. A long armoured sheath is helpful in not only these situations but also in procedures attempted through femoral arterial route where the aorta might be tortuous.

Conclusion

Cost efficacy is a concern in developing countries. This novel technique of using an armoured sheath over a terumo wire to cross the IVC stenosis is a safe alternative and could be of help to interventionist to provide successful outcome when faced with similar difficult situation without significant increase in the procedural cost.

References

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