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Case report

Coexistence of hypertrophic osteoarthropathy and myelofibrosis☆

Coexistência de osteoartropatia hipertrófica e mielofibrose

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Introduction

Hypertrophic osteoarthropathy (HOA) is a condition presented by arthralgia/arthritis, clubbing, and periosteal proliferation (periostitis) in long bones. It is classified as primary (hereditary or idiopathic) and secondary. Primary HOA is a rare and hereditary condition observed mainly in children and adolescents.[1] Secondary HOA may be seen in the various systemic disorders including inflammatory and malign diseases. Clinical findings develop as a result of an increase in peripheral blood flow as well as abnormal fibroblast activity and proliferation.[2–4]

Myelofibrosis is a chronic myeloproliferative disease characterized by clonal expansion of an abnormal hematopoietic stem/progenitor cell.[5] There are a few case reports regarding the coexistence of myelofibrosis with HOA. Here we present a case of HOA coexisted with myelofibrosis.

Case report

Sixty-five years old male admitted to Physical Medicine and Rehabilitation Outpatient Clinic due to increased pain at both lower extremities for the preceeding year. He was diagnosed myelofibrosis as a result after medical history, routine blood tests and bone marrow biopsy 6 years ago. Bone marrow aspiration was dry, and examination of the biopsy revealed a hypoplastic marrow with myelofibrosis (Fig. 1A and B). Patient received interferon (IFN) alfa 2A during 2 years and his bone marrow was in remission after this treatment. Although

☆ This study was originated in Cukurova University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Adana, Turkey.

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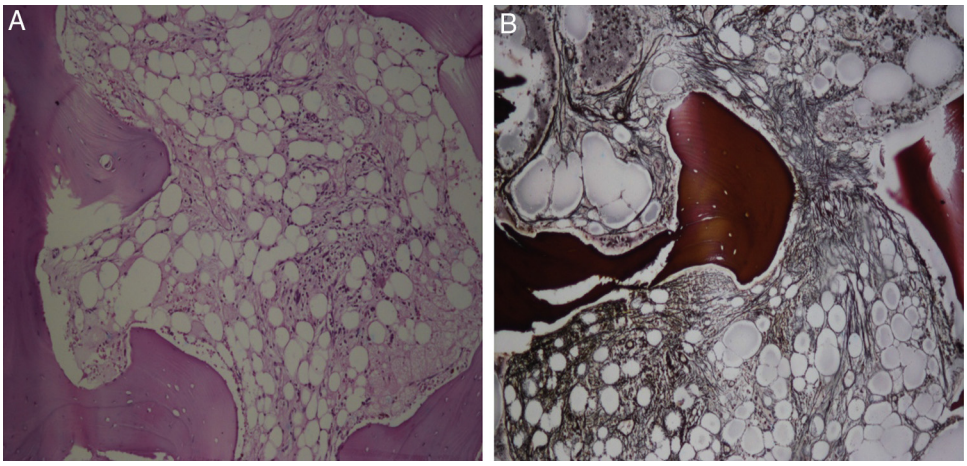

Fig. 1 – Bone marrow biopsy shows reticulin-type myelofibrosis (hematoxylin and eosin, 100×). Bone marrow biopsy shows reticulin-type myelofibrosis (reticulin, 100×).

patient's pain has increased while moving, it has also persisted at rest. Patient had benefited from analgesic medication initially but he stated that his pain increased over time, and not resolved with analgesics. On the physical examination, patient's general status was well. Blood pressure was measured as 125/75 mmHg, and pulse rate was 78 min^{-1}. Clubbing was observed at both hands. Both tibias were painful by percussion, and tibial margins were palpated as irregular. Although pain was present at ankles and knees, no temperature rise or synovitis were detected. Range of motion for bilateral hip, knee and ankle joints were within the normal limits.

Conventional X-ray of the cruris region demonstrated periosteal reaction at both tibial bone which is more prominent on the left side (Fig. 2). Whole body bone scintigraphy demonstrated increased uptake at distal part of left tibia. In laboratory analysis, hemoglobin, white blood cell and platelet counts were within normal limits, while MCV was decreased [69.5 fL – (N: 80–97–)]. Peripheral blood smear was assessed as normal. There was not an increase in acute phase reactants. Erythrocyte sedimentation rate was 20 mm/h (N: 0–15) and CRP was within normal range [<0.5 ng/L (N: 0–0.8)]. Parathyroid hormone, calcium and 25-hydroxyvitamin D_3 levels were within normal limits. Serum IL-6 and TNF alfa levels were within normal range.

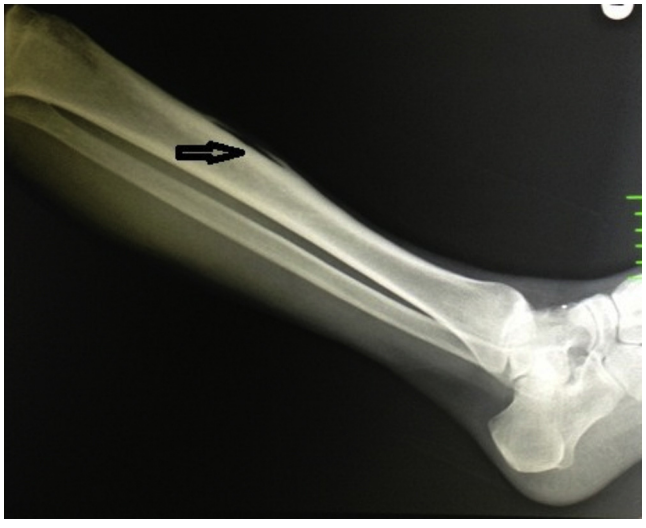

Fig. 2 – Periosteal reaction (periostitis) at the tibial margin (black arrow).

Diagnosis was made as secondary HOA associated with myelofibrosis. Patient was recommended to receive oral meloxicam 15 mg daily. Because of the incomplete response after seven days, colchicine 1 mg/day was added to the treatment, and significant decrease of pain was detected after one week.

Discussion

HOA is a clinical syndrome characterized by digital clubbing and periostal proliferation especially in the tibial bone.[1] HOA includes skin manifestations such as thickened skin on face and scalp, and coarse facial features along with clubbing, periostosis, acroosteolysis, and painful joint motion.[6]

HOA may be associated with various disorders including intrathoracic malignancies, cyanotic heart diseases, gastrointestinal tumors and inflammatory bowel diseases.[1] One of the rare causes of secondary HOA is myelofibrosis.

Mechanism of HOA formation is not fully understood. Recent studies suggest the role of platelets.[3] Platelet fragmentation and aggregation as well as endothelial cell activation lead to release of platelet derived growth factor (PDGF) and other factors which induce connective tissue and periosteal proliferation.[3,7] PDGF plays an important role in the pathogenesis of both myelofibrosis and HOA.[8] Increased levels of PDGF, transforming growth factor beta (TGF-β) and epidermal growth factor (EGF) are present in alfa granules of megakaryocytes in the myelofibrosis. Increased levels of TGF and EGF cause excess production of collagen type III. This increase in collagen type III causes clubbing and periostitis.[7] Plasma levels of pro-inflammatory cytokines such as tumor necrosis factor-alfa (TNF-alfa), interleukin-6 (IL-6), and vascular endothelial growth factor (VEGF) were also reported to be increased.[9] One

of the limitations of this case report was the lack of laboratory tests including PDGF, TGF and VEGF. Nevertheless, TNF-alfa and IL-6 levels were negative in our patient.

HOA associated with myelofibrosis is observed rarely and a limited number of case reports are presented in the literature. Yu et al. presented two male with HOA associated with myelofibrosis. They suggested that periostitis, when associated with fever and bone pain, is indicative of more aggressive disease.[10] In several case reports of HOA associated with myelofibrosis it has been reported that the acute phase *reactants* were higher.[2,3,7] Our patient had not fever and there was no evidence of increased acute phase proteins. These points may be associated with the milder disease course of our case.

There is no evidence in the literature regarding that IFN causes clinically overt HOA. But IFN therapy may cause clubbing in some patients. There was only a published report consisting two patients who had clubbing associated with the use of IFN treatment.[11] It was reported that IFN treatment causes abnormal fibroblast activation and this condition may be the cause clubbing. In this case report two patients were presented who received IFN alfa 2A for hepatitis C virus. Digital clubbing was developed after the 2nd and 4th months of medication in these patients, respectively. In contrast, our patient was developed digital clubbing and tibial bone pain after 2 years of medication. Nevertheless, there was a periosteal reaction in both tibial bones in addition to clubbing in the current case which provided the diagnosis of HOA.

There is no consensus on the standard treatment regimen of HOA. A favorable result to the combination of colchicine and meloxicam was observed in the present case. In the literature, it has been reported that pamidronate has been found to be effective in osteoarthropaties not responding to nonsteroidal anti-inflammatory drugs. Octreotide treatment has also yielded similar results.[12]

In conclusion, patients who had diffuse joint pain with unknown cause should be checked for comorbid conditions and additional diseases. In addition, HOA should be suggestive in cases presented with atypical localized pain and clubbing already who had myelofibrosis either in active or remission period. However, it should be noted that all clinical findings may not be observed in cases of secondary or associated HOA.

Conflicts of interest

The authors declare no conflicts of interest.

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