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Concise report

Hypertrophic pulmonary osteoarthropathy: an unusual presentation

Pooja Kumari[1], Paul Yeung[1], Abuzaid Medani[1] and Adnan N. Kiani[1]

Abstract

Objectives. Hypertrophic pulmonary osteoarthropathy (HPOA) is a syndrome characterized by the triad of periostitis, digital clubbing and painful arthropathy of the large joints, especially involving the lower limbs. HPOA without clubbing of the digits is considered an incomplete form of HPOA and has been rarely reported. We are presenting here a case of HPOA without clubbing in a patient with lung cancer.

Methods. A 52-year-old female active smoker presented with a complaint of multiple joint pains with associated morning stiffness, swelling and weight loss for 3 months. On examination, the patient had tenderness to palpation over the anterior shin, but no obvious clubbing was noted. X-rays of the lower extremities revealed periosteal thickening compatible with HPOA.

Results. A bone scan showed increased uptake along the periosteum and cortex of the long bones. In view of her smoking history and weight loss, a chest X-ray was done that revealed an upper lung mass. A diagnosis of lung carcinoma was made on biopsy.

Conclusion. Our case demonstrates that the unusual finding of HPOA in the absence of clubbing is a rare entity and can often be missed. Once diagnosed, a prompt search of other associated conditions should be conducted.

Key words: clubbing, hypertrophic pulmonary osteoarthropathy, malignancy

CONCISE REPORT

Key message

- Once diagnosis of hypertrophic pulmonary osteoarthropathy is made, a search for other conditions, including pulmonary malignancy, should be conducted.

Introduction

Hypertrophic pulmonary osteoarthropathy (HPOA) is a syndrome characterized by the triad of periostitis, digital clubbing and painful arthropathy of the large joints, especially involving the lower limbs. HPOA without clubbing of the digits is considered an incomplete form of HPOA and has been rarely reported [1]. Clubbing is characterized by bulbous enlargement of terminal segments of the fingers and toes due to proliferation of subungual connective tissue [2]. Clubbing was first described by Hippocrates in the 5th century BC [3]. The association of clubbing, arthralgia and periostitis as a distinct clinical syndrome known as HPOA was not recognized until 1889 by Bamberger [4] and 1890 by Marie [5], so it is also known as Bamberger–Marie syndrome. HPOA without clubbing of the digits is a rare entity and can easily be missed. Bone scintigraphy is the most sensitive method to detect HPOA.

Case report

A 52-year-old female with a medical history of asthma and seasonal allergies and an active smoker with a 30

[1]*Marshfield Clinic/St. Joseph Hospital Marshfield, Marshfield, WI, USA*

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Correspondence to: Adnan N. Kiani, Marshfield Clinic/St. Joseph Hospital, 522 West Ives Street, Marshfield, WI 54449, USA.
E-mail: adnan051@yahoo.com

packs/year smoking history presented with a 3 month history of progressively worsening joint pains affecting the hands, wrists, elbows, knees, ankles and toes, associated swelling and morning stiffness. The patient also reported weight loss of 35 pounds within the last 3 months. The patient reported recent travel to Vermont. She denied any symptoms of sore throat, abdominal discomfort, nausea, vomiting or dysuria. She denied any fevers at home, however, she was febrile upon presentation. She denied any history of skin psoriasis or IBD, inflammatory low back pain, dactylitis, enthesitis or uveitis. She also denied any history of photosensitive skin rash, malar rash or oral or nasal ulcers. There was no recent use of any antibiotics, any hospitalizations or i.v. drug use.

On physical examination, the patient had a temperature of 99.1°F, pulse 104 bpm, blood pressure 104/57 mmHg, respiratory rate 18 and oxygen saturation 96–97% on room air. A musculoskeletal exam was positive for findings of tenderness over her anterior leg over the shin and tenderness on palpation across multiple joints. No obvious clubbing in her fingers was noted. She had swelling with mild synovitis across her wrists, MCP joints, PIP joints, knees, ankle and MTP and IP joints. The patient's blood work showed elevated acute phase reactions, namely ESR at 39 mm/h and CRP at 11.2 mg/L. She had a normal complete blood count, with a white count of 9.5×10^9/L, haemoglobin 12.6 g/dL and platelets 323×10^9/L. Her albumin was 3.3 g/dL, which is suppressed. Her kidney function was normal. She had mild elevation in procalcitonin at 0.68 μg/L.

Rheumatology was consulted with concern of inflammatory polyarthritis and the patient was started on fentanyl for pain relief and Solu-Medrol. Subsequently joint aspiration of the left knee was performed and joint fluid analysis revealed a total neutrophil count of 197/mm^3, RBC 20 353/μL, neutrophils 30%, lymphocytes 6%, negative Gram stain and culture, no crystals, negative RF <1:40 and anti-CCP antibody as well as normal C3 and C4, negative ANCA and negative viral hepatitis and Lyme serology.

X-rays of the lower extremities (Fig. 1) demonstrated periosteal thickening compatible with hypertrophic osteoarthropathy and MRI of the lower extremities (Fig. 2) confirmed the findings. A bone scan demonstrated increased periosteal and cortical uptake seen in the lower end of the femur. A chest X-ray was done in view of the weight loss and her history of smoking that showed a 6 × 9 cm posteromedial right lung mass. Bronchoscopy with endobronchial ultrasound biopsy was performed and the pathology report revealed adenocarcinoma. The patient was referred to the haematology-oncology service for further management of her lung cancer.

Discussion

There are two forms of HPOA: primary and secondary.

Primary, also known as pachydermoperiostosis, is a rare hereditary condition with variable expression, with a male:female ratio of 9:1. A majority of cases (>90%) of secondary HPOA are associated with pulmonary malignancies [6] or chronic suppurative pulmonary diseases. Pulmonary malignancies, including primary [7], metastatic lung cancer and intrathoracic lymphoma, account for 80% of cases of secondary HPOA. Adenocarcinoma of the lung is the most frequent and small cell carcinoma is the least frequent histopathologic type of lung cancer associated with HPOA [7].

Other associated extrathoracic malignancies include nasopharyngeal carcinoma, renal cell carcinoma, oesophageal cancer, gastric tumour [8], pancreatic cancer, breast phyllodes tumour [9], melanoma, thyroid cancer, osteosarcoma and intestinal lymphoma.

Various rheumatologic conditions, including RA [10], AS [11], polyarteritis nodosa, SLE [12], Takayasu disease [13], sarcoidosis, APS and Mediterranean fever are known to be associated with this condition as well.

Pulmonary conditions such as cystic fibrosis, tuberculosis, idiopathic pulmonary fibrosis [14] and lung transplantation have also been associated with HPOA.

Other associated conditions include hepatic cholestatic disease, hepatopulmonary syndrome, cryptogenic cirrhosis, celiac disease, IBD, cyanotic congenital disease, subacute bacterial endocarditis and interstitial lung disease with a right to left shunt.

Regardless of the aetiology, clubbing is the most common manifestation of this syndrome and periostitis

Fig. 1 X-ray of the left femur: periosteal thickening at the regions of the arrows

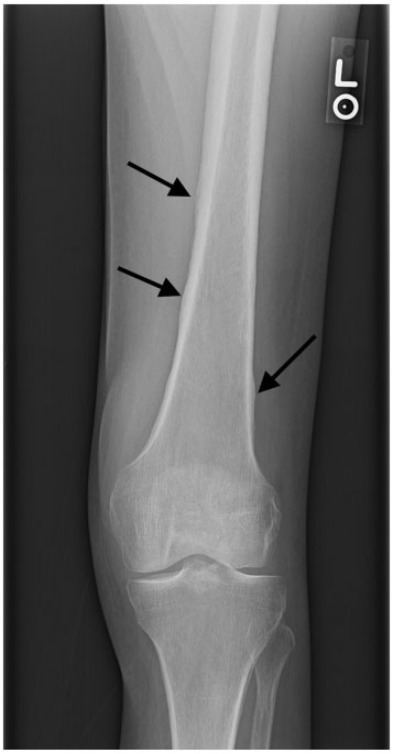
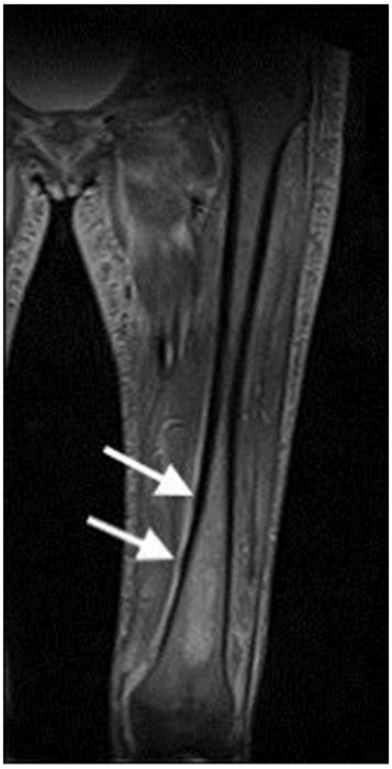


Fig. 2 Fluid-sensitive MRI sequence: oedema-like signal along the medial femur, including along the periosteum, with areas of periosteal thickening along the medial left femur (white arrows)



is the hallmark of HPOA. Our case demonstrates the unusual presentation of HPOA without clubbing reported in only a few case reports.

The signs and symptoms of HPOA include asymptomatic disease or burning sensation of the fingers and excruciating deep joint pain. Physical examination is particularly important to look for clubbing and skin hypertrophy in primary HPOA, with coarse facial features and cylindrical soft tissue swelling of the soft tissues of the legs (elephant legs). Periostitis is a radiographic finding that clinically manifests as tenderness on palpation of the involved anatomic area. Effusions of the large joints are frequently observed and the range of motion is slightly decreased [15].

Differentials for causes of periostitis are tumours, drug-related periostitis and periostitis related to chronic venous insufficiency and infection-related periostitis. There were no signs of underlying malignancy on imaging in our patient. The patient was not on any drugs that could cause periostitis, such as variconazole, vitamin A, prostaglandins or fluoride. MRI and physical exam showed signs of oedema, but on X-ray, periostitis caused by chronic venous stasis would typically show a solid undulating reaction that is separated from the cortex. Periostitis can been seen in osteomyelitis, but this patient's MRI did not show signs of osteomyelitis.

Bone scintigraphy is the most sensitive test showing periosteal involvement. Characteristic findings on bone scans are bilateral symmetrical linear uptake of the tracer along the cortical margins of the long bones, which is also known as tram line or double stripe sign [6, 16].

The pathophysiology of this condition demonstrates increased vascular permeability and stimulation of smooth muscle cells and fibroblasts. The exact mechanism of clubbing in HPOA is unknown, but several theories have been proposed. Dickinson [17] proposed a megakaryocyte–platelet clumping hypothesis, stating that normally megakaryocytes and platelets are destroyed in the lung and any process that destroys the pulmonary vasculature in turn leads to transfer of whole megakaryocyte and platelet clumps to gain access to the periphery, where it releases the PDGF, which is a general growth promoter leading to fibroblast proliferation.

VEGF is a cytokine that induces vascular hyperplasia, new bone formation and oedema. It has also been proposed to be involved in the pathogenesis of HPOA [18]. Silveira *et al.* [19] studied 24 patients with HPOA and found an increased level of VEGF in patients with primary and secondary HPOA due to lung cancer. Olan *et al.* [20] described a case of HPOA in a patient with lung cancer with high levels of VEGF and a dramatic disappearance of skeletal abnormalities and a decreased level of VEGF after tumour removal. Prostaglandin E also induces periostitis, Lette *et al.* observed five infants who developed limb pain and swelling associated with periostitis after chronic infusion of PGE for congenital ductal-dependent heart disease [21].

The management of HPOA includes treatment of the underlying condition. Pharmacologic therapy for HPOA includes traditional NSAIDs, opiates, bisphosphonates, octreotide and palliative radiation.

Conclusion

HPOA without clubbing is a rare entity. Due to its association with various other conditions, the importance of recognizing this condition cannot be overemphasized. Once diagnosed, a prompt search of those conditions, especially pulmonary malignancy, should be conducted.

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