

Case Report

Hypertrophic pulmonary osteoarthropathy as the presenting symptom of non-small cell lung cancer: A case report

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Hypertrophic pulmonary osteoarthropathy (HOA) is a disabling condition that may occur secondarily to primary lung carcinoma. Management of joint pain in patients with HOA is challenging, and treatment options are experimental. Here we report an unusual case of HOA in a 54 year-old man who presented with fever, rash and arthralgia as initial symptoms of an underlying non-small cell lung cancer. He did not respond to various treatment modalities including non-steroidal anti-inflammatory drugs (NSAIDs), pamidronate, and octreotide. His pain symptoms only improved once chemotherapy was administered. This case exemplifies the diagnostic and therapeutic challenge in patients with HOA, and underlines the need for further research to better define this disease and appropriately direct therapy.

Key words: Osteoarthropathy, secondary hypertrophic; carcinoma, non-small-cell lung; therapy; pamidronate; octreotide

INTRODUCTION

Hypertrophic pulmonary osteoarthropathy (HOA) is a rare but disabling condition associated with a wide spectrum of diseases most notably pulmonary malignancies. It is a syndrome characterized by digital clubbing, periostosis of the tubular bones and joint pain (Yao et al., 2009). HOA can either occur as a primary familial autosomal dominant condition known as pachydermoperiostosis (Bazar et al., 2004), or more commonly secondary to conditions characterized by arterio-venous shunts such as bronchogenic carcinoma, pulmonary metastasis, primary intrathoracic neoplasms, and cystic fibrosis (Ntaioset al., 2008). HOA represents a dilemma in medicine in which diagnosis is relatively simple while management is exceedingly difficult due to obscure pathogenesis mechanism, various treatment modalities, and individualized treatment response (Nguyen and Hojjati, 2011). In this

report, we present a case of refractory HOA as an initial manifestation of an underlying non-small cell lung cancer (NSCLC) and further discuss various treatment modalities.

CASE REPORT

A 54-year-old Chinese man with 30 years of smoking was referred to Rheumatology clinic for evaluation of fevers, diffuse rash and arthralgia of 4 weeks duration. His outpatient course for pain management included naproxen, oxycodone/acetaminophen. He was also treated with prednisone 40 mg daily and colchicine for suspected gout with no improvement. Outside workup was remarkable for elevated C-reactive protein (CRP) at 205 mg/L, erythrocyte

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Figure 1. Photographs of patient's hands and feet. Panel A demonstrates clubbing of his digits and panel B demonstrates synovitis of the ankles.



Figure 2. X-ray image shows nonspecific areas of periosteal new bone formation adjacent to the diaphysis of tibia.

sedimentation rate (ESR) of 115 mm/hr, and elevated alkaline phosphatase 436 IU/L. Physical examination was significant for a diffuse erythematous maculopapular rash over his trunk and extremities, cervical lymphadenopathy, decreased breath sounds, grade 3 clubbing of his digits and 2+ pitting edema of the lower extremities. Musculo-skeletal examination revealed exquisite tenderness and swelling of his wrists, knees, and ankles (Figure 1). Differential diagnosis included an unusual infectious process, systemic vasculitis, or a paraneoplastic process. A comprehensive infectious and rheumatologic workup including blood cultures, Mantoux test, rheumatoid factor, antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), anti-cyclic citrullinated peptide antibodies (anti-CCP), and cryoglobulins were all negative. Knee synovial fluid analysis was non-inflammatory with no crystals. A skin biopsy showed non-specific inflammation.

His chest X-ray and CT scan revealed a mass-like consolidation in the left upper lobe of the lung. Patient was treated with ceftriaxone and azithromycin for suspected pneumonia and morphine was administered for pain control. Given his presentation with arthropathy in the setting of new lung findings, hypertrophic pulmonary osteoarthropathy (HOA) was suspected. Bilateral hip, femur, tibia, and fibula X-rays were obtained and showed scattered periosteal new bone formation adjacent to the diaphysis (Figure 2). A whole body bone scan showed increased uptake along the cortex of the bilateral lower extremities (Figure 3). Patient was started on IV pamidronate, which resulted in only minimal improvement of his arthralgia.

On subsequent workup, PET scan showed increased uptake in the left upper lobe with a consolidation measuring 11.2 x 7.1 x 8.2 cm and positive mediastinal lymph nodes. Patient underwent a transbronchial needle biopsy of the lung mass and pathology came back consistent with stage IIIB NSCLC, deemed unresectable.

He continued to complain of severe diffuse joint pains and his arthralgia remained unresponsive to different NSAIDs and narcotics. A second dose of pamidronate did not alleviate his joint pains. He then received octreotide for 5 days, again with minimal response. Eventually patient was started on chemotherapy (docetaxel) and had significant improvement of his joint pains over the course of the following month and all other pain medications were discontinued. His chemotherapy regimen was later switched to carboplatin/abraxane, and finally to oncarboplatin/pemetrexed. Three months later patient started on palliative radiation given the poor response of his lung cancer to chemotherapy. He eventually expired due to respiratory failure, pneumonia, and severe malnutrition 3 months after his initial diagnosis.

DISCUSSION

Here we describe a patient who presented with HOA as

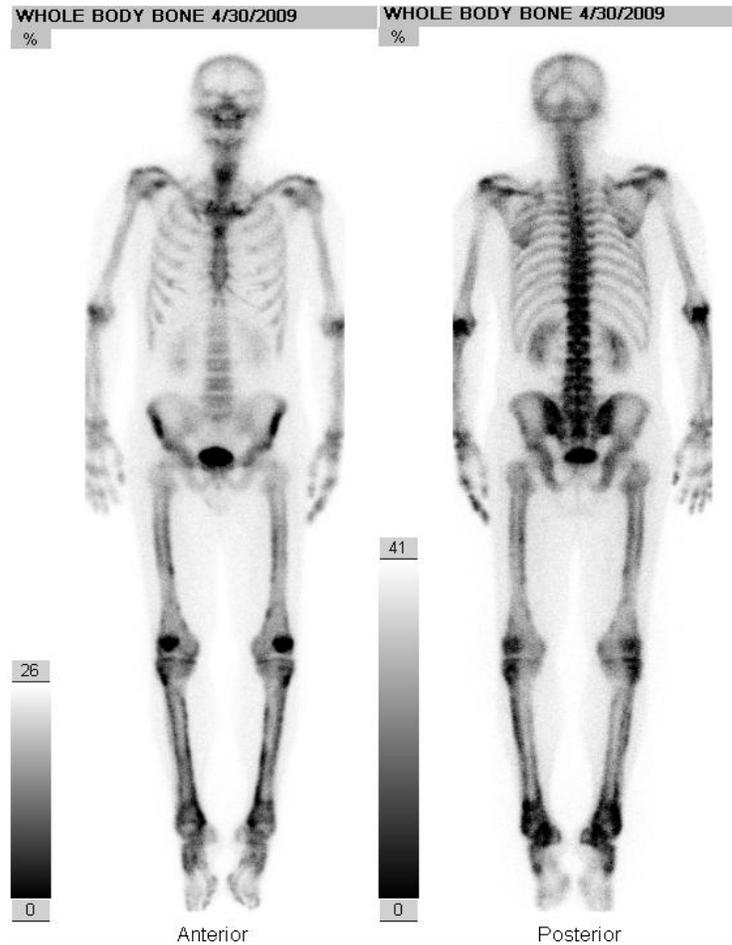


Figure 3. Bone scan showing increased uptake along the cortex of the bilateral lower extremities.

a paraneoplastic presentation of an underlying malignancy. His arthritis was severe, disabling, and refractory to steroids, NSAIDs, pamidronate, and octreotide. His pain improved only after initiation of chemotherapy. HOA is difficult to recognize due to its clinical resemblance to other rheumatic diseases such as gouty arthritis, rheumatoid arthritis, and osteoarthritis. Even when recognized, the challenge lies in treatment of symptoms. As early as 1890, the association of HOA with chronic lung and heart diseases was established and to date, there is still no known cure for HOA (Ooi et al., 2007). The prevalence of HOA in lung cancer ranges from 4 to 32% (Yao et al., 2009). In adulthood, HOA most commonly presents in NSCLC and mesothelioma, primarily affecting joints of distal inter-phalanges and long bones (Ooi et al., 2007).

The pain associated with HOA is often disabling and refractory to conventional analgesics, and effective management is primarily dependent on the underlying disease (Ooi et al., 2007). Since 1991, it has been established as a well-known phenomenon that resection of the primary tumor alleviates HOA symptoms (Akizuki

and Homma, 1991). Up to date, primary treatment of underlying disease is still the most widely reported modality to be efficacious (Nguyen and Hojjati, 2011). The challenge lies in symptomatic treatment of HOA when the primary cause cannot be eliminated. Many symptomatic treatment modalities including vagotomy, adrenergic antagonist such as propranolol and phenoxybenzamine, COX-2 inhibition with rofecoxib, other NSAIDs such as ketorolac and indomethacin, bisphosphonates, and octreotide have been tried, with varying degree of success (Nguyen and Hojjati, 2011). Unfortunately there has been no randomized controlled trial, to evaluate and compare the efficacy and safety profile of these therapeutic modalities.

Recent proposed therapy involves the use of bisphosphonates, a potent inhibitor of osteoclastic bone resorption found to be beneficial in treating osteoporosis, hypercalcemia of malignancy, and bone metastases (Suzuma et al., 2001). There are at least 5 cases reported in the literature on successful treatment of HOA with pamidronate and zoledronic acid (Speden et al., 1997;

Suzuma et al., 2001; Garske and Bell, 2002; Amital et al., 2004; King and Nelson, 2008). Another promising treatment outcome for HOA was reported with octreotide (Johnson et al., 1997). It has been suggested that the pain-relieving efficacy of octreotide for HOA may partly be attributed to its inhibitory effects on the production of vascular endothelial growth factor (VEGF) and endothelial proliferation (Angel et al., 2005; Yao et al., 2009).

In 1987, Dickenson and Martin observed that HOA is commonly found in conditions with pathologic shunting around the pulmonary vasculature permitting many circulating factors such as platelet derived growth factor (PDGF) and VEGF, which are normally inactivated in the lungs, to directly enter the systemic vasculature (Kozak et al., 2006). The local release of these growth factors leads to fibroblast proliferation with increased vascularity and permeability resulting in connective tissue changes that are the hallmark of clubbing (Dickinson and Martin, 1987). Furthermore, VEGF has been identified as an osteogenic-angiogenic coupling factor involved in new bone formation, vascular hyperplasia, and edema, all are typical symptoms of HOA (Towler, 2007; Atkinson and Fox, 2004). Both VEGF plasma levels and tissue expression have been reported in the majority of the diseases associated with HOA (Olán et al., 2004). Most recently, reports on reversal of HOA symptoms in surgically treated lung cancer, wherein the preoperative observed high levels of serum VEGF and interleukin 6 (IL-6) normalize 1 month post-operation (Hara et al., 2010). This discovery of VEGF's role in the development of HOA potentiates the use of agents with VEGF inhibition such as bevacizumab in the treatment of HOA.

Interestingly, growth factor inhibition in the treatment of HOA is illustrated in a recent case report wherein selective epidermal growth factor receptor tyrosine kinase (EGFR) inhibitor known as gefitinib induced disappearance of periostosis on bone scintigraphy and resolution of HOA symptoms in a patient with advanced stage lung adenocarcinoma (Hayashi et al., 2005).

In this paper, we report an interesting case of HOA as the initial presenting feature of a primary lung cancer. Despite its well-known association with primary lung tumor, HOA as a presenting symptom is a rare phenomenon that may complicate the diagnostic picture and delay identification of a more malignant process. Furthermore, our patient remained symptomatic despite administration of several reported HOA therapies including pamidronate and octreotide. Only chemotherapy resulted in partial relief of his joint pains.

Conclusion

Our case report exemplifies the diagnostic and therapeutic challenge in patients with HOA and underlines the need for further research, to better define the disease process and appropriately direct therapy.

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