Medication induced periostitis resembling hypertrophic osteoarthropathy in lung transplant patients

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Learning objectives

To review the current literature on the clinical and radiologic manifestations of medication induced periostitis resembling hypertrophic osteoarthropathy in lung transplant patients. To illustrate the variety of imaging characteristics of this entity so that interpreting radiologists can make accurate diagnosis and avoid unnecessary work up.

We report five cases of diffuse periostitis resembling hypertrophic osteoarthropathy in lung transplantation patients on chronic voriconazole prophylaxis. To our knowledge detailed imaging characteristics of this complication have not been previously reported in the radiology literature.
Hypertrophic osteoarthropathy (HOA) is characterized by periostitis of the long tubular bones and digital clubbing. HOA is classified into primary and secondary types. Primary form is hereditary due to mutation in the 15-hydroxyprostaglandin dehydrogenase (HPGD) gene that encodes the primary enzyme degrading prostaglandin. Secondary HOA is associated with a variety of disease entities. Approximately 80% of secondary HOA is found with primary or metastatic pulmonary malignancies. Other HOA associated conditions include cyanotic congenital heart disease, chronic lung disease such as cystic fibrosis and chronic infection.

Although drug related periostitis including prostaglandin, vitamin A and fluoride have long been known, the association of lung transplant medication with periostitis was only recently introduced in the literature. Yao et al described a female patient with history of chronic lung transplant rejection who presented with polyarthritis and limb pain (1). This patient had periostitis of primarily the lower extremities and the radius and ulna without clubbing. Wang et al. reported five cases (three female and two male patients) of long term voriconazole induced periostitis in patients following lung transplantation (2). Voriconazole is a widely used medication in lung transplantation patients for both prophylaxis and treatment of aspergillus infection. The distinguishing features according to their case series include diffuse periostitis, absence of clubbing and elevated alkaline phosphatase. Commonly involved sites according their study include the radius, ulna, tibia, fibula and femur. Other involved sites by at least one patient include ribs, shoulder, manubrium spine, sacral iliac joint and ischium.

The pathogenesis of HOA is still unknown. Earlier theories suggest a role for neural reflex and neuroendocrine mechanisms. More recently megakaryocytes or large clump of platelets are thought to be involved. This is substantiated by a recent report of 5 cases of reversible periostitis occurring in 24 pediatric patients in a phase I/II trial of interleukin-11, a thrombopoietic growth factor that stimulates production, differentiation, and maturation of megakaryocytes and platelets (3). Voriconazole or Vfend belongs to the triazole class of antifungals similar to fluconazole. Whether or not there is interaction between triazole and megakaryocyte or platelet function is yet to be elucidated.

Regarding treatment of HOA, removal of tumor was reported to improve or resolve clubbing in cancer associated HOA (4). Interestingly lung transplantation was reported to improve HOA in cystic fibrosis patients (5). Pharmacologic treatment includes conventional analgesic medication such as nonsteroidal anti-inflammatory. In refractory cases, bisphosphonates such as pamidronade or octreotide may be useful for symptomatic relief. According to TF Wang et al., all patients in their series had rapid resolution of symptoms after discontinuation of voriconazole.
The five cases reported here resemble HOA in that diffuse periosteal reaction is the hallmark of osseous manifestation. However, two of our five patients were documented to have absence of clubbing. In all of our patients the periosteal reaction is dense and irregular, as opposed to the smooth and single layer periostitis described in lung-cancer associated HOA. Previous study also reported irregular periostitis to represent the minority (one-third) of patients with primary and cyanotic congenital heart disease associated HOA (6). In addition to involvement of tubular bones characteristic of classic HOA, our patients also had variable involvement of the clavicles, ribs, scapulas and pelvis.
Case 1

First patient was a 64 year old African-American female with history of COPD and left lung transplant 9 months prior to presentation. She presented with muscle pain that was sharp and aching in her legs, left arm and shoulder. Her medications at presentation included voriconazole 200 mg daily. On physical examination she was afebrile and had no clubbing and no adenopathy. Her shoulders, wrists, thighs, knees and ankles were tender to palpation. Her laboratory evaluation showed normal white blood cell count and normal thyroid stimulating hormone. On her presenting chest radiograph, there was diffuse periosteal reaction involving the medial shaft of the left proximal humerus and ribs, new since her pre-transplant radiograph 9 months prior (Figure 1A-B). Her hand radiographs showed symmetric diffuse fluffy periosteal reaction involving middle and proximal phalanges of both hands and limited involvement of 5th metacarpal (Figure 1C-E). Her voriconazole was discontinued upon hospital discharge.

Case 2

Second patient was a 67 year old man with history of idiopathic pulmonary fibrosis and left lung transplant 2 ½ years prior to presentation. Bronchoscopy prior to presentation showed evidence of chronic rejection. He was on voriconazole since transplant. His presenting chief complaints were fatigue, anorexia, weight loss and diffuse abdominal pain. His chest radiograph showed symmetric and diffuse periosteal reaction of bilateral proximal humerus, inferior aspect of the clavicles, and multiple ribs, and these findings were new from his pre-transplant radiographs 2 ½ years prior. CT scan of the chest, abdomen and pelvis again demonstrated these findings and additionally show involvement of bilateral acetabuli and proximal femurs (Figures 2). He had a complicated hospital course and eventually succumbed to pneumonia.

Case 3

Third patient was a 69 year old man with history of bilateral lung transplant for hypersensitivity pneumonitis and pulmonary fibrosis 3 years prior to presentation. He had acute rejection 1 ½ years prior to presentation. He presented to the hospital with increasing shortness of breath with exertion. His admission medications also included voriconazole. His admission chest radiograph showed symmetric, dense and irregular periostitis involving bilateral clavicles and ribs that was not present on pre-transplant radiograph 3 years prior. CT of the chest showed marked periostitis of these areas (Figure
3). His bone scan (not available) showed diffuse uptake in the sternum costochondral regions, inferior margins of the scapula, shoulders, knees, acetabuli and sacroiliac joints bilaterally. Long bones were unremarkable. During his hospital stay he developed respiratory distress secondary to aspiration pneumonia and eventually succumbed to cardiac arrest.

Case 4

Fourth patient was a 64 year old woman with history of right lung transplant for chronic obstructive pulmonary disease 3 years prior to presentation. Her presenting symptom was altered mental status, therefore her review of systems and musculoskeletal physical exam were limited. Extremity exam showed diffuse soft tissue swelling but no clubbing. Her admission chest radiograph showed periostitis involving bilateral proximal medial shaft of the humerus and ribs that was not present on pre-transplant radiograph 4 years prior. CT of the chest confirmed marked periostitis of these areas (Figure 4). She succumbed to posterior encephalopathy during her admission.

Case 5

Fifth patient was a 68 year old woman with history of bilateral lung transplant 3 years prior to presentation. She developed graft failure and underwent a second bilateral lung transplant 2 years prior. She was on chronic voriconazole prophylactic therapy and had chronic respiratory failure. Her post-transplant chest radiograph showed periostitis involving bilateral proximal medial shaft of the humerus that was not present on her pre-transplant radiograph 6 years prior. CT of the chest confirmed periostitis of the humerus and also show involvement of the ribs, clavicles and scapula. Sequential CT images of the pelvis show periosteal reaction in the bilateral acetabuli, proximal femurs, and inferior pubic rami (Figure 5). She eventually succumbed to pneumonia during her most recent hospital admission.
Fig. 0: 64 year old African-American female with history of COPD and left lung transplant 9 months prior to presentation. A. Pre-transplant radiograph 9 months prior to presentation show no osseous changes. B. Post-transplant radiograph show interval development of periosteal thickening along the left humeral medial shaft and left 7th rib (arrows). C and D. Left and right hand radiographs at presentation show fluffy periosteal reaction involving middle and proximal phalanges of both hands in a fairly symmetric pattern. There is also involvement of the left 5th metacarpal (arrows). E. Lateral radiograph of the distal fingers show no radiographic evidence of clubbing, concordant with clinical examination.
Fig. 0: 67 year old man with history of idiopathic pulmonary fibrosis and left lung transplant 2 ½ years prior to presentation. A. Pre-transplant radiograph 2 ½ years prior to presentation showed no osseous changes. B. Presenting chest radiograph show new periosteal reaction involving the inferior aspect of bilateral clavicles, medial shaft of the proximal humerus, and multiple ribs (arrows). C and D. CT images of the chest also show these changes (arrows). E and F. Axial pelvic CT images of patient 2 demonstrate symmetric periosteal reaction involving bilateral acetabuli and femoral necks (arrows).
Fig. 0: 69 year old man with history of bilateral lung transplant for hypersensitivity pneumonitis and pulmonary fibrosis 3 years prior to presentation. A. Pre-transplant radiograph 3 years prior to presentation show no osseous changes. B. Presenting chest radiograph show dense periosteal reaction of bilateral clavicles and ribs (arrows). C though F. Sequential CT images of the chest confirm these findings (arrows).

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Fig. 0: 64 year old woman with history of right lung transplant for chronic obstructive pulmonary disease 3 years prior to presentation. A. Pre-transplant radiograph 4 years prior to presentation show no osseous changes. B. Presenting chest radiograph show periosteal reaction of bilateral proximal medial shafts of the humerus and ribs (arrows). C and D. Sequential CT images of the chest confirm these findings (arrows).

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**Fig. 0:** 68 year old woman with history of bilateral lung transplant 3 years prior to presentation. She developed graft failure and underwent a second bilateral lung transplant 2 years prior. A. Pre-transplant radiograph 6 years prior to presentation show no osseous changes. B. Post-transplant chest radiograph show periosteal reaction of bilateral proximal medial shafts of the humerus (arrows). C and D. Sequential CT images of the chest confirm this finding and also show periosteal reaction in the ribs, clavicles and scapula (arrows). E and F. Sequential CT images of the pelvis show periosteal reaction in the bilateral acetabuli, proximal femurs, and inferior pubic rami (arrows).
Conclusion

In this article we report five cases of periostitis in lung transplant patients on chronic voriconazole (two male and three female). One of our patients developed osseous changes as soon as 9 months following transplant. All patients had bilateral and diffuse bony changes, with dense undulating or feathery periosteal reaction. Rib, clavicle and proximal medial humerus were common sites of involvement. Additional sites of involvement include phalanges of the hand, scapula, proximal femur, acetabulum and pubic bone. Imaging features along with clinical history help to distinguish this benign condition from other differential considerations including tumor, trauma, infection, and rheumatologic or metabolic diseases. Accurate diagnosis of this condition is important to avoid unnecessary further diagnostic evaluation.
Personal Information

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