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Case Report

Thoracic periosteal reaction secondary to voriconazole use in an adult transplant patient ☆

Anisha N. Shetty, MD, Kristopher W. Cummings, MD, Michael B. Gotway, MD, Eric A. Jensen, MD, Clinton E. Jokerst, MD, Prasad M. Panse, MD, Carlos A. Rojas, MD*

Department of Radiology, Mayo Clinic Arizona, 5777 E. Mayo Blvd, Phoenix, AZ, 85054 USA

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ABSTRACT

Periosteal reaction may result from multiple causes including infection, trauma, medications, and neoplasms. One important etiology that must be considered in the differential diagnosis of symmetric periosteal reaction, especially in immunocompromised patients, is voriconazole use. We present a case of a 65-year-old man who underwent liver transplantation complicated by acute hypoxic respiratory failure and *Aspergillus* infection. Long term voriconazole therapy was initiated with resultant development of thoracic periosteal reaction which improved following discontinuation of the medication. Given the preferential upper body distribution of periosteal reaction induced by voriconazole, chest radiologists might be the first ones to recognize this adverse effect.

Introduction

Periosteal reaction is a nonspecific imaging finding that may be encountered incidentally. The appearance, extent of involvement, anatomic distribution, and clinical context of periosteal reaction must be integrated with an understanding of the various etiologies for this imaging finding, particularly rare causes, to allow proper diagnosis. In the immunocompromised population, a rare but important etiology for periostitis is long term voriconazole use. Awareness of this association avoids further potentially costly evaluation as the periosteal reaction resolves with medication discontinuation.

Case report

A 65-year-old man with end stage liver disease secondary to hepatitis C complicated by development of hepatocellular carcinoma underwent liver transplantation. His postoperative course was complicated by hemorrhagic shock, acute metabolic encephalopathy and acute hypoxic respiratory failure with continued need for mechanical ventilation and circulatory support through postoperative day 8. CT was obtained as part of an evaluation for sepsis secondary to infection and showed centrilobular ground glass opacities (not shown). Bronchoscopy was positive for *Pseudomonas Aeruginosa* and

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* Corresponding author.
E-mail address: Shetty.anisha@mayo.edu (A.N. Shetty).

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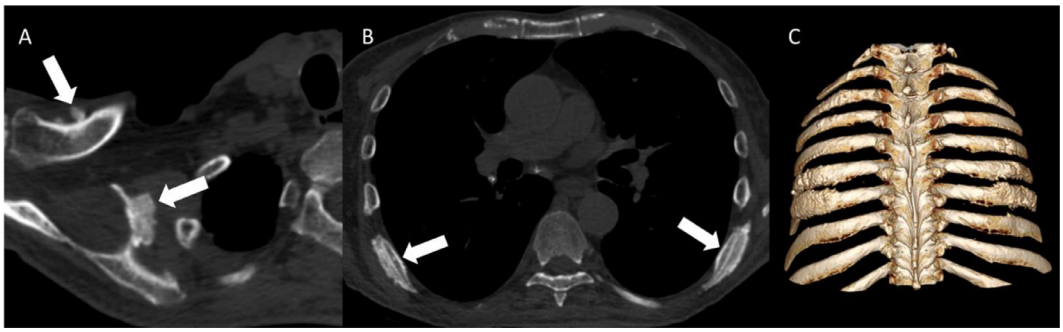

Fig. 1 – Unenhanced chest CT 4 months after initiation of voriconazole. Axial images (A, B) and 3D reconstruction (C) demonstrate symmetric periosteal reaction along the clavicle, scapula and bilateral mid posterior ribs (arrows).

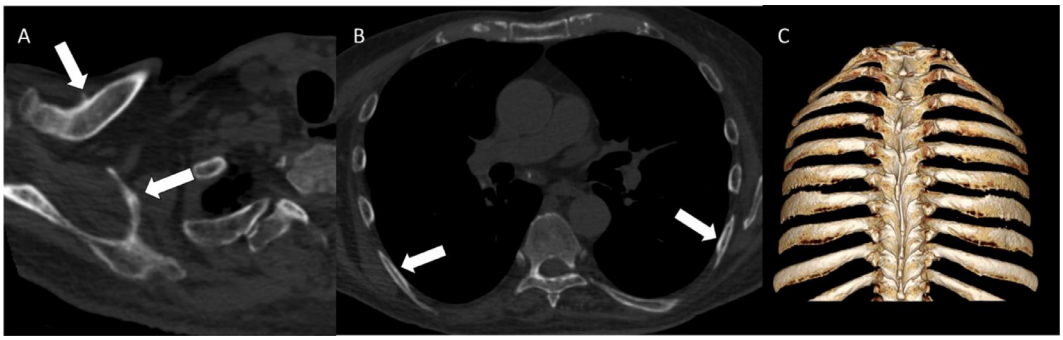

Fig. 2 – Unenhanced chest CT Axial image 7 months after discontinuation of voriconazole. Axial images (A, B) and 3D reconstruction (C) demonstrate significant interval reduction in periosteal reaction previously seen along the clavicle, scapula and bilateral mid posterior ribs (arrows).

Aspergillus antigen, the latter prompting initiating of voriconazole 300mg twice daily. Three months later, repeat CT chest revealed multifocal, symmetric periosteal reaction involving the bilateral mid to upper posterior ribs as well as the peripheral right clavicle and medial bilateral scapulae (Fig. 1). The skeletal abnormalities were asymptomatic; however, voriconazole therapy was discontinued. Follow up CT chest 6 months later showed significant improvement in periosteal reaction (Fig. 2).

Discussion

Periosteal reaction is a nonspecific imaging finding associated with a broad range of etiologies including infection, trauma, medications, neoplasms and physiologic stressor. A rare but important etiology for symmetric periosteal reaction that practitioners must be aware of is long term voriconazole use.

Antifungal treatments are often used for immunocompromised patients at risk for invasive fungal infection. Voriconazole, an azole targeting cytochrome P450, is considered first-line therapy for treating a number of fungal infections, including invasive *Aspergillus,* and may be employed for prophylaxis or treatment. In some circumstances, long-term therapy is required for effective fungal eradication. Recognized adverse effects of voriconazole use that can lead to discontinuation of the medication include hepatotoxicity, hormone-related effects, visual changes, and rashes [1,2]. Periosteal reaction from chronic voriconazole use occurs in approximately 5-10% of patients, described mostly in case reports [1].

Voriconazole is unique among the azoles in that it is trifluorinated, and it has been shown that voriconazole use leads to an increase in circulating plasma fluoride levels [3–8]. It is thought that the mechanism of voriconazole-induced periosteal reaction is similar to fluorosis, a metabolic disease caused by excessive ingestion of fluoride. Increased fluoride levels are thought to lead to osteoblast stimulation and increased osteogenic activity [1].

Periosteal reaction can manifest anywhere from 6 weeks following therapy initiation to as long as eight years later [3–9]. Patients can be asymptomatic, as in our patient, but often patients present with focal or diffuse skeletal pain prompting further evaluation [3–9]. Laboratory evaluation may reveal elevated alkaline phosphate levels [4–9].

Imaging of voriconazole-induced periosteal reaction typically shows multifocal, bilateral abnormalities that tend to affect the upper more than the lower body; therefore, chest radiologists may be the first to recognize these abnormalities. Periosteal reaction commonly involves the ribs, clavicles, scapula, and extremities, particularly the forearms. Radiographs and CT often demonstrate new, nodular or smooth bone formation and thickening bilaterally, occasionally with evidence of associated enthesopathy [3–10]. Periostitis

manifests with tracer uptake on Technetium-99m methylene diphosphonate bone scintigraphy [3,5–8]. MRI performed for patients with voriconazole-induced periosteal reaction shows increased T2 signal indicative of periosteal edema [7]. Incidentally noted periosteal reaction can be observed on PET/CT where affected sites demonstrate hypermetabolic activity [7]. Of note, other disease processes, such as hypertrophic osteoarthropathy, thyroid acropachy, hypervitaminosis A and venous stasis can also mimic voriconazole-induced periosteal reaction [10]. Nodular growth, reaction in the flat bones, lack of digital clubbing, lack of subcutaneous edema, and presence bilaterally all support voriconazole as the most likely etiology [10].

In the immunocompromised patient population, heightened suspicion for infection may cause medication-induced phenomena to be overlooked, and hence physicians must be vigilant for such reactions. Awareness of the potential for voriconazole to induce periostitis is important to avoid misdiagnosis and because dose reduction or discontinuation of this medication may lead to improvement or resolution of both periosteal reaction and associated symptoms [3–9]. A study by Moon et al. demonstrated that 25 of 28 patients with skeletal pain due to voriconazole-induced periostitis experienced a reduction in symptoms upon drug discontinuation or dosage reduction [8]. Chest radiologist's awareness of the potential for voriconazole to produce periosteal reaction involving the thoracic osseous structures should facilitate accurate diagnosis and appropriate management.

Patient consent

Written, informed consent for publication of this case was obtained from the patient.

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