

**IMAGES IN HOSPITAL MEDICINE****Voriconazole-induced Periostitis**Ana Wilden<sup>1</sup>, Andres Bran<sup>2</sup><sup>1</sup>School of Medicine, University of Missouri, Columbia, MO<sup>2</sup>Division of Infectious Disease, University of Missouri, Columbia, MO

Corresponding author: Ana Wilden. Email: wildenae@health.missouri.edu

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**CASE**

A woman in her 60s presented with complaints of severe multifocal bone pain, including the shoulders, sternum, and hips, which had persisted for several months. Two years earlier, the patient had undergone heart transplant for ischemic cardiomyopathy. She had a history of post-transplant AKI on CKD, hypertension, hyperlipidemia, osteoporosis, hypothyroidism and COPD. She was on maintenance immunosuppression with azathioprine, tacrolimus and prednisone. She was on voriconazole for chronic suppression of *Bipolaris sp.* mediastinitis diagnosed shortly after transplantation and had remained on the antifungal.

The patient reported bone pain and a lump on the left clavicle that was palpable on physical examination. Radiograph of the left clavicle can be seen below (Figure 1). Laboratory values demonstrated an elevated creatinine (2.28mg/dL), BUN (35 mg/dL), TSH (2.77 mcunit/mL), alkaline phosphatase (616 units/L), ALT (62 units/L), and AST (67 units/L).

**DISCUSSION**

Voriconazole is a triazole antifungal agent used prophylactically or for the treatment of invasive fungal infections.<sup>4</sup> Voriconazole is similar to other triazole antifungals, in that it exerts its antifungal effect through the inhibition of cytochrome P450 enzymes, which decreases ergosterol biosynthesis, and ultimately results in fungal cell wall abnormalities.<sup>4</sup>

Unlike itraconazole, another triazole antifungal medication, voriconazole contains three fluoride atoms.<sup>1</sup> The trifluorinated structure of voriconazole suggests a possible relationship between excessive fluoride levels and periostitis.<sup>3</sup>

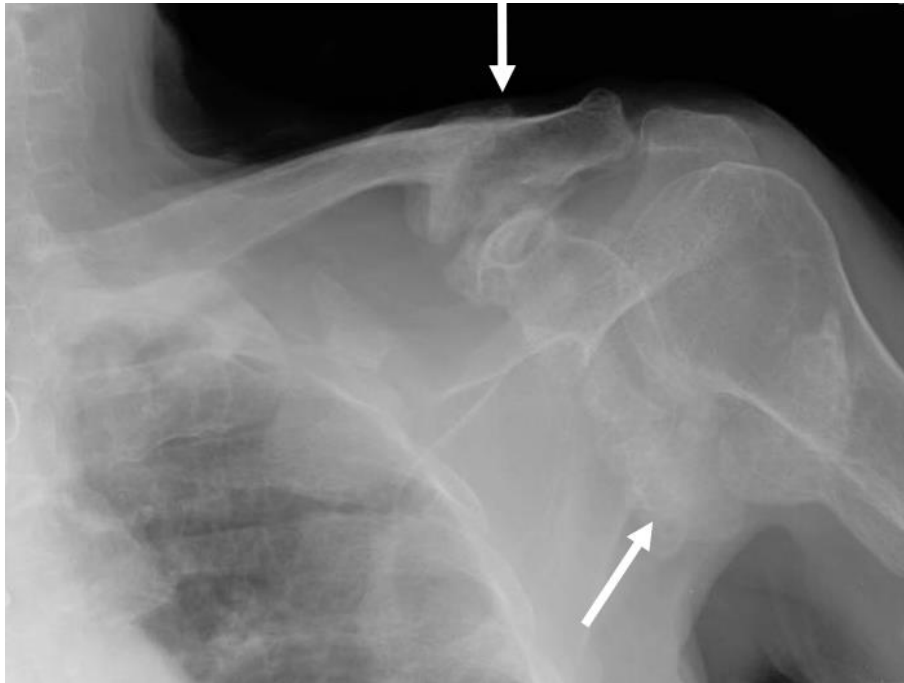
In multiple studies, patients on long-term voriconazole therapy had elevated plasma fluoride and alkaline phosphatase levels.<sup>1,2,3</sup> Current research hypothesizes that the accumulation of excess fluoride from long-term use of voriconazole stimulates osteoblasts, leading to increased bone formation evident by elevated levels of alkaline phosphatase.<sup>1</sup>

Additional bone formation can be seen in skeletal imaging of both the axial and appendicular skeleton with multiple areas

showing periosteal ossification on the cortical surface of bones.<sup>1</sup> Voriconazole-induced periostitis is most common in the ribs and ulna, and less common in the clavicle, scapula, humerus, radius, femur, tibia, and fibula.<sup>3</sup>

As providers, we need to be aware of the potential effect that long-term voriconazole therapy can have on patients. If a patient presents with severe diffuse bone

pain, elevated plasma fluoride and alkaline phosphatase levels, and long-term use of voriconazole, reduction or discontinuation of voriconazole therapy and/or transition to a non-fluoride antifungal medication is recommended. Discontinuation or replacement of voriconazole reduces bone pain and the levels of alkaline phosphatase and plasma fluoride in the body.<sup>1,2,3</sup>



**Figure 1:** Radiograph of the left clavicle demonstrating extensive deformity of the glenohumeral and cortical clavicular regions with heterotopic ossification in these locations, which are indicated by the arrows. There is also osseous expansion of several ribs, and some appear to be periosteal ossification.

#### NOTES

Potential conflicts of interest: None declared.

#### REFERENCES

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