Voriconazole-related periostitis presenting on magnetic resonance imaging

Derik L. Davis

Department of Diagnostic Radiology & Nuclear Medicine,
University of Maryland School of Medicine, Baltimore, Maryland, USA

Address for correspondence:
Derik L. Davis, MD
Assistant Professor
University of Maryland School of Medicine
Department of Diagnostic Radiology & Nuclear Medicine
22 S. Greene Street, Baltimore, Maryland 21201 - USA
Phone: +39 410 3283763
E-mail: ddavis7@umm.edu

Summary
Painful periostitis is a complication of long-term antifungal therapy with voriconazole. A high clinical suspicion coupled with imaging and laboratory assessment is useful to establish the diagnosis. Prompt discontinuance of voriconazole typically results in the resolution of symptoms and signs. This report describes the presentation of voriconazole-related periostitis on magnetic resonance imaging.

KEY WORDS: periostitis; MRI; voriconazole; pain; bone.

Introduction
Triazole medications are commonly prescribed to recipients of solid organ transplantation for the prevention and treatment of fungal infections. Recently, the potential risks of long-term antifungal therapy with fluorinated triazoles have become better understood. Prolonged use of voriconazole increasingly has been associated with painful periostitis (1). The clinical presentation is frequently nonspecific and insidious. Recognizing this medication-related complication requires a high level of clinical suspicion and a proper understanding of the association between voriconazole and bone pain. Diagnostic imaging plays a central role in confirmation of the bony periostitis, and has been described on radiographs, computed tomography and bone scintigraphy (1, 2).

Case report
A 39-year-old woman presented with a 2-week history of new-onset bone pain in the hips, thighs and knees. Her past medical history was significant for end-stage pulmonary sarcoidosis and a 2-year history of bilateral lung transplantation. She denied complaints of cough, fever, chills, dyspnea or injury. Her pain was worse with activity, but was not relieved fully by rest. On physical examination, the patient had no edema, erythema or tenderness to palpation in the lower extremities. She had normal range of motion of her joints, although pain was present with passive motion in the hips and knees. The patient had normal strength and muscular tone. She had no evidence of rash. She was afebrile and her lungs were clear to auscultation.

Despite multiple trials of narcotic and non-narcotic analgesics, her pain steadily increased over the next 4 weeks without relief. Due to her known history of sarcoidosis, magnetic resonance imaging (MRI) of the hips was ordered to rule out sarcoid granulomas as the cause of pain. Despite the initial suspicion for bony sarcoidosis, the MRI showed no granulomas. Instead, irregular and thick periosteal edema was present at both proximal femurs compatible with periostitis (Figure 1). The MRI also ruled out osteonecrosis and fracture, which were also in the differential diagnosis. Laboratory findings included a serum alkaline phosphatase of 332 units/L, serum aspartate aminotransferase of 23 IU/L, serum alanine phosphatase of 11 IU/L, total bilirubin of 0.1 mg/dL, serum calcium of 8.8 mg/dL, serum phosphorus 3.1 mg/dL, serum creatine kinase of 25 units/L, serum 25-hydroxyvitamin D of 10 ng/mL, white blood cell count of 7.0 x 10^9 cells, serum creatinine of 1.1 mg/dL, blood urea nitrogen of 37 mg/dL, and an estimated glomerular filtration rate of 70 mL/min/1.73m^2.

A review of the patient’s medications revealed a twice daily regimen of voriconazole 200mg, which was begun 5-months earlier for antifungal therapy following an abnormal bronchoalveolar lavage. Subsequently, follow up radiographs of the hips were obtained and showed multifocal areas of dense and irregular periostitis (Figure 2), which confirmed the diagnosis of this medication-related complication (2). There was no evidence of juxta-articular osteopenia. The radiographs were helpful for imaging correlation since no case of voriconazole-related periostitis presenting on MRI had been reported previously in the literature at the time of diagnosis.

Upon recognition of the association between periostitis and her medication regimen, the patient’s voriconazole was discontinued and she was prescribed twice daily itraconazole 100mg for antifungal prophylaxis. Her bone pain decreased at a rapid pace over the next two weeks, and she was pain free after one month. The patient’s serum alkaline phosphatase level returned to normal after four months.

Discussion
Voriconazole is a second generation triazole antifungal agent and has a broadened spectrum of activity compared to
Voriconazole-related periostitis presenting on magnetic resonance imaging

Figure 1 - (A) Axial T2-weighted turbo spin echo fat-suppressed and (B) coronal STIR-weighted magnetic resonance imaging of the hips demonstrate thick and irregular periosteal edema (white arrows) along the outer cortical surfaces of the bilateral proximal femoral shafts indicative of periostitis.

Figure 2 - (A) Anteroposterior radiograph of the right hip and (B) anteroposterior radiograph of the left hip demonstrate multifocal areas of irregular, dense and fluffy periostitis (black arrows) spanning the femoral necks to proximal shafts in both hips.
first generation antifungals such as fluconazole due to the attachment of an alpha-methyl group and the substitution of a fluorinated pyrimidine for a triazole ring (3). Voriconazole contains three fluoride atoms which constitute 16.3% (by weight) of the drug, and a standard prescription of daily oral 400 mg represents consumption of 65 mg of fluoride per day (4). The mechanism of action for voriconazole involves inhibition of cytochrome P450 (CYP 450)-dependent lanosterol 14 alpha-demethylation, which is an integral component of fungal cell membrane synthesis (3). The liver facilitates metabolism of voriconazole, with CYP2C19 representing the major hepatic pathway (3).

Painful periostitis after lung transplantation is a rare complication encountered following long-term antifungal therapy with voriconazole, and patients present with bone pain and an elevated serum alkaline phosphatase (1). In addition to solid organ transplantation recipients, voriconazole-related periostitis has been reported in other patient populations including those with hematologic malignancies, connective tissue diseases and autoimmune disorders (5-8). Patients typically present with symptoms after three or more months of continuous voriconazole therapy (6).

The most common side effect of voriconazole is visual disturbance, and rash is the second most common. These adverse outcomes are usually mild and reversible, and severe complications are uncommon (3). Other known side effects of voriconazole include an elevation of hepatic enzyme levels, including alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase (1, 3). Most patients are asymptomatic, but severe hepatitis has also been described with elevated serum voriconazole levels. Bone-related complications of voriconazole are rare and occur in < 2% of patients (1). Fluoride ions bond with bone in the form of fluorapatite and produce bone formation through the stimulation of osteoblasts (5). Serum alkaline phosphatase levels are a marker for new bone formation, and elevations are a result of the ensuing painful periostitis in voriconazole toxicity (4). Elevation of bone-specific alkaline phosphatase has also been described (6).

This case illustrates the first report of bony voriconazole-related periostitis presenting on MRI as the initial imaging study to the best of the Author's knowledge. Recognition of isolated periostitis on MRI in a patient on voriconazole therapy is important to establish the diagnosis, especially in those cases without prior radiographs or computed tomography available for comparison. Only one other recent report in the literature discusses MRI in the context of voriconazole, with a focus on soft tissue ossification and enthesis (9).

The diagnosis of voriconazole-related periostitis most often involves the recognition of periostitis on an imaging study in the setting of unexplained bone pain and long-term use of voriconazole for antifungal therapy. Elevation of serum alkaline phosphatase is an associated finding. The mainstay of effective treatment is simply to discontinue voriconazole therapy (6). Bone pain and elevation of serum alkaline phosphatase typically resolve over the following weeks to months (4, 6). Following the discontinuance of voriconazole, patients are prescribed a different antifungal agent if continued therapy is needed. Itraconazole is an alternative nonfluorinated triazole antifungal medication commonly prescribed in this setting, since this triazole has no association with painful periostitis or fluoride toxicity (10).

The differential diagnosis for medication-related periostitis includes hypertrophic osteoarthropathy (HOA), periostitis due to vitamin A toxicity, prostaglandin use and other sources of fluoride toxicity (such as excessive black tea consumption, toothpaste swallowing, fluoride supplementation or occupational exposure) (2, 4, 6). The patient in this case did not have a past medical history consistent with primary HOA nor did she have a pulmonary malignancy responsible for the secondary form of HOA. Although chronic lung infection has been associated with secondary HOA, drug toxicity is favored in this case since her symptoms mirrored the temporal relationship of the voriconazole therapy. Her painful periostitis had begun after the start of voriconazole and resolved shortly after discontinuance of the drug. Prostaglandin and vitamin A toxicity are excluded since the patient was not prescribed these medications. Periostitis deformans and other sources of fluoride toxicity resemble the presentation of voriconazole-related periostitis due to the central role of the fluoride ion in bone pathogenesis. Periostitis deformans was first described in association with drinking Spanish wine which contained fluoride additives (2, 4). Although various causes of fluoride toxicity have been described, voriconazole is the most likely source of fluoride toxicity for the patient in this case.

The clinical presentation of voriconazole-related periostitis also initially may be confused with a rheumatologic or endocrinologic disorder. However, rheumatologic tests such as C reactive protein, antinuclear antibody, Jo-1 antibody, complement levels (C3, C4), and creatinine kinase are usually normal in patients with voriconazole-related periostitis (1). Vitamin D deficiency has been described in the setting of fluorosis, although normal levels may also be present (5, 6). Calcium, phosphate, parathyroid hormone and thyroid stimulating hormone also may be normal in voriconazole-related periostitis (1, 6).

Two theorized mechanisms for voriconazole-related periostitis include 1) the direct toxic effect of the drug or 2) an indirect effect from elevated circulating levels of fluoride ion released during the drug’s hepatic metabolism (2, 4). Metabolism of voriconazole also has been shown to be nonuniform among different populations, and this heterogeneity among individuals is related to genetic differences (3, 5). Certain populations have been shown to have reduced CYP2C19 activity, and these individuals present with much higher serum voriconazole levels compared to individuals with “normal” CYP2C19 activity despite receiving the same dose (3).

In clinical practice, patients with known liver dysfunction are prescribed a reduced dose of voriconazole to prevent abnormally elevated serum fluoride levels, but a similar approach to dose reduction in renal insufficiency is not universally undertaken (3). Fluoride is excreted by the kidneys, and patients with chronic renal disease may be at increased risk for fluoride toxicity (5). Whether or not patients with renal insufficiency (creatinine clearance < 50mL/min) require a dose adjustment is controversial since the oral form has been touted as a beneficial alternative to intravenous medication for patients in renal failure and also because no definite consensus exists for the toxicity of voriconazole in the setting of renal insufficiency (3, 4, 6). Further research is needed to clarify the relationship of chronic renal disease and fluoride toxicity (5). Liver dysfunction is an unlikely explanation for the patient’s fluoride toxicity in this case since her alanine aminotransferase and aspartate aminotransferase levels were normal. Her elevated serum alkaline phosphatase was most likely the result of her medication-related periostitis. Renal insufficiency was also not likely a major factor since her creatinine...
clearance was > 50 mL/min. In conclusion, this case describes the first report of bony voriconazole-related periostitis presenting initially on MRI. A high clinical suspicion is necessary for timely diagnosis. Prompt discontinuance of voriconazole results in resolution of this disorder.

Conflicts of interest and source funding

The Author has no conflicts of interest to declare. There is no source of funding to disclose.

References