Painful periostitis in the setting of chronic voriconazole therapy

Margaret Skaug, MD, Cedric Spak, MD, MPH, and Umesh Oza, MD

A 72-year-old woman on chronic voriconazole therapy for recurrent histoplasmosis developed a painful forearm mass. Laboratory and imaging findings were consistent with a diffuse periostitis. Her symptoms resolved after discontinuation of voriconazole. To our knowledge, this is the first case of voriconazole-induced periostitis to be reported in a patient with chronic histoplasmosis.

Chronic voriconazole therapy can produce a syndrome of painful periostitis, the etiology of which is a subacute fluoride toxicity. Knowledge and recognition of this entity allows for discontinuation of voriconazole, which results in prompt symptom resolution.

CASE DESCRIPTION

A 72-year-old African American woman with past mixed connective tissue disease (MCTD) with scleroderma-type features and recurrent histoplasmosis presented with left forearm pain and mass. She previously had developed extrapulmonary histoplasmosis with colonic perforation while being treated with high-dose oral prednisone for her rheumatologic illness. After successful induction with amphotericin B, she was placed on maintenance voriconazole therapy at 4 mg/kg twice a day for 4 years. She was then lost to follow-up and discontinued voriconazole. Fifteen months later, she presented with a nontender breast mass, and biopsy showed it to be recurrence of histoplasmosis, confirmed by culture and positive antigenemia. Due to mild renal insufficiency, amphotericin was deferred, and she was treated with voriconazole at 4 mg/kg twice daily. In addition, low-dose prednisone was continued for MCTD. The breast mass resolved, and she had been maintained on voriconazole 4 mg/kg twice daily for 3 years. Examination on a routine follow-up disclosed a painful palpable mass on the distal left forearm. The alkaline phosphatase was 585 U/L (normal range 35–104 U/L), having increased from 173 U/L 3 months before and a remote value of 71 U/L.

Radiographs of her forearm demonstrated two irregular calcific deposits between the radius and ulna along the distribution of the interosseous membrane *(Figure 1)*. Nuclear bone scan images showed nonspecific multifocal increased radiotracer uptake involving the scapulae, left forearm, hips, and femoral diaphyses *(Figure 2)*. A background of degenerative uptake was present at the shoulders, spine, knees, and ankles. Single photon emission computed tomography/computed tomography (SPECT/CT) imaging of the chest localized the radiotracer uptake to sites of periosteal calcification, including exostoses, along ribs and the scapulae bilaterally *(Figure 3)*. Both voriconazole and prednisone were discontinued, and her symptoms improved. Her alkaline

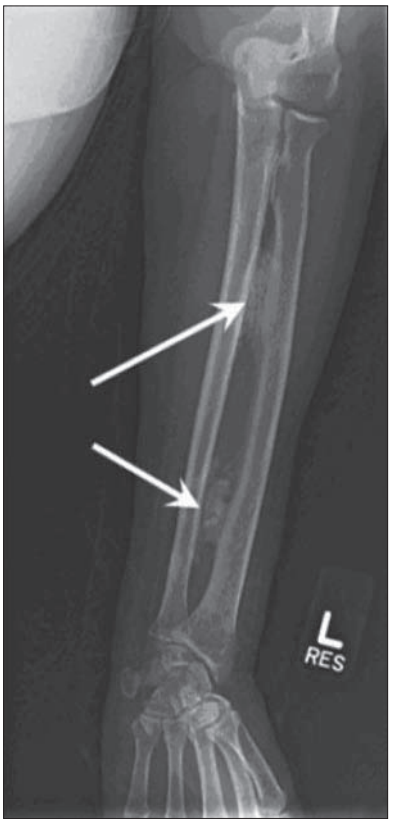

Figure 1. Nodular periostitis. Left forearm radiograph shows two regions of irregular, nodular calcification (arrows) along the interosseous membrane between the radius and ulna.

From the Department of Radiology (Skaug, Oza) and Division of Infectious Diseases, Department of Internal Medicine (Spak), Baylor University Medical Center at Dallas.

Corresponding author: Margaret Skaug, MD, Department of Radiology, Baylor University Medical Center at Dallas, 3500 Gaston Avenue, Dallas, TX 75246-2017 (e-mail: margaret.hotze@gmail.com).

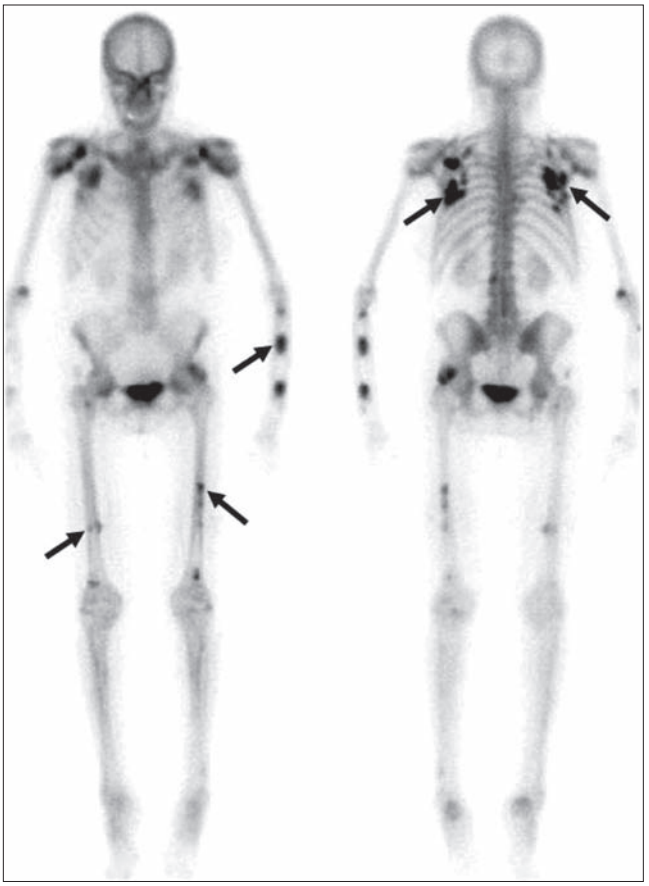

Figure 2. Whole-body bone scan images in the anterior and posterior projection show multiple foci of abnormal radiotracer uptake involving the scapulae, left forearm, hips, and femoral diaphyses (arrows). Ultimately, these findings are nonspecific, requiring correlation with radiographs or CT and clinical history. The bone scan provides a skeletal survey of the osseous abnormalities and can serve as a baseline study prior to voriconazole therapy being withheld and subsequent follow-up. A background of degenerative uptake is present at the shoulders, spine, knees, and ankles. Tracer overlying the right elbow is related to injection of tracer in a right antecubital vein.

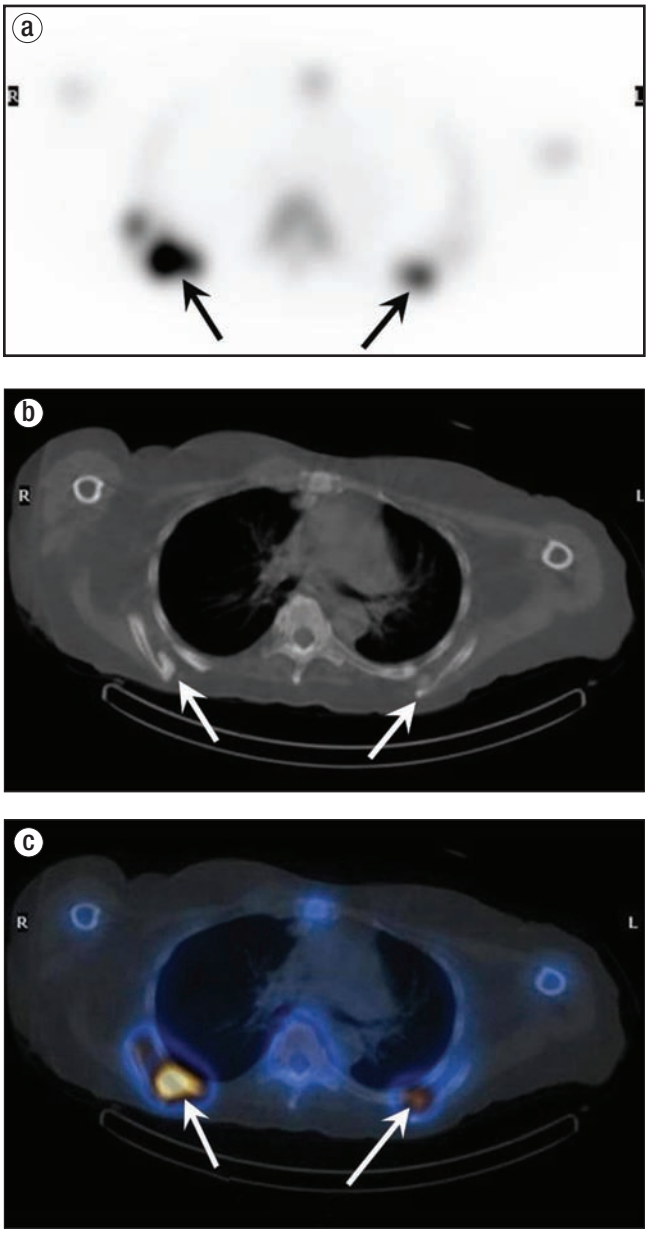

Figure 3. (a) Transversal SPECT, **(b)** low-dose CT, and **(c)** fusion images from SPECT/CT through the chest at the level of the scapulae demonstrate areas of increased tracer activity corresponding to osseous projections, or exostoses, off the scapulae (arrows) in this patient with voriconazole-induced periostitis.

phosphatase level fell to 73 U/L within 3 months of discontinuing voriconazole. Since that time, her MCTD has been quiescent.

DISCUSSION

Voriconazole is a second-generation azole antifungal agent. It is generally well tolerated and has a broadened antifungal spectrum as compared to first-generation azoles (1). Since voriconazole's approval in 2002, an iatrogenic painful periostitis has been reported in patients on voriconazole long term. Many are lung transplant patients taking voriconazole for treatment of or prophylaxis for aspergillosis (2–5). Cases have also been seen in immunosuppressed patients with other solid organ transplants (6) and in patients with hematologic malignancies (7). A case report of a patient who developed periostitis while on voriconazole for fungal endophthalmitis did not remark on whether the patient was immunocompromised (8). Common to the cases are a history of long-term voriconazole use and prompt resolution of musculoskeletal symptoms within days to weeks of discontinuation of the medication.

In these cases, periostitis was evidenced by musculoskeletal pain, elevated alkaline phosphatase, radiographic abnormalities, and/or multifocal radiotracer uptake on nuclear medicine bone scan. In the case series presented by Wang and colleagues (2) reviewing radiologic findings in five patients, the plain film and CT findings were described as irregular, dense, and undulating or feathery. Bone scans show multifocal intense radiotracer uptake. Distribution of radiographic and bone scan abnormalities were diffuse, involving both the axial and appendicular skeleton with involvement most commonly of the rib, clavicle, and proximal medial humerus; other common sites included the hands, scapulae, proximal femurs, acetabulae, and pubic

bones. Imaging follow-up has been infrequently reported. In the study by Wang et al, follow-up bone scans were obtained in two patients after discontinuation of voriconazole; one was performed 2 months after and the other, 6 months after. These examinations showed marked improvement of the abnormal multifocal radiotracer uptake (2). Partial resolution of imaging findings on follow-up imaging has been described in two case reports (3, 8).

Although the process remains to be fully characterized, the radiographic appearance and developing laboratory evidence support a subacute fluoride toxicity from chronic therapy with voriconazole, a fluoride-containing compound. Fluoride toxicity has been recognized as a cause of a bone disease called periostitis deformans since the mid 20th century (9). First described in those who drank wine with a fluoride preservative, it has since been described in a number of other scenarios, including fluorinated medications. Serum fluoride is distributed throughout the body, with the greatest amount retained in calcium-rich bone and teeth (10). Fluoride acts on bone by stimulating osteoblasts, with a corresponding increase in serum alkaline phosphatase (11). Fluorosis results in osteosclerosis followed later by osteoporosis, periosteal changes including pathognomonic tumor-like zones of periosteal hyperostosis, and osteophytes at tendon, fascial, and muscle insertions (12).

Voriconazole contains three fluoride molecules, and 5% of voriconazole is metabolized to free fluoride (13), which is primarily excreted by the kidneys (10). A small study comparing post-lung transplant patients on voriconazole for 6 months versus controls not on voriconazole found that all patients on voriconazole had elevated plasma fluoride levels, while none of the patients in the control group did (14). In a small retrospective study comparing voriconazole to other azoles (itraconazole and posaconazole), elevated fluoride levels were present only with voriconazole; additionally, the presence of an elevated fluoride level with voriconazole was independent of treatment duration (15). Although both studies show elevated fluoride levels in patients on voriconazole, it remains to be demonstrated why some patients develop symptomatic periostitis and others do not. The role of renal insufficiency remains unclear, with one study finding it significant (15), while the other found that it was not predictive of fluoride levels (14).

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