



# Voriconazole-induced periostitis: A radiographic progression

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## ABSTRACT

The present study is a case of incidentally discovered voriconazole-induced periostitis in a patient on long-term anti-fungal prophylaxis due to chronic lymphocytic leukemia. Voriconazole was initiated approximately 2 years before the periostitis discovery on a chest computed tomography (CT). There was no documented report of bone pain during the multiple medical visits since medication initiation. Due to the asymptomatic nature of the periostitis and its slow development over time, it was not reported on imaging for over 2 years' time. The patient underwent scheduled, serial CT imaging to evaluate disease burden, allowing for retrospective evaluation of periostitis progression. The admission that led to its discovery was for acute on chronic respiratory failure and ultimately ended in his demise. Although there are several cases of periostitis from chronic voriconazole use in literature, this case is made unique in its asymptomatic presentation, allowing for a visual display of periostitis progression over 2 years. This case highlights the fact that voriconazole-induced periostitis can be asymptomatic and should, therefore, be readily recognized and include a comprehensive differential. Discontinuation of voriconazole has been shown in previous studies to resolve the periostitis, also emphasizing the importance of its recognition.

**KEY WORDS:** Voriconazole, periostitis, CT, radiographs

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## INTRODUCTION

Periostitis is a nonspecific imaging and clinical entity due to inflammation of the periosteum that usually manifests as bone pain. A rare cause of periostitis is voriconazole, an anti-fungal medication that most often affects immunosuppressed transplant patients who require antifungal therapy. The patient presented here had chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma with computed tomography (CT) and radiographs showing worsening periostitis over 2 years coinciding with the onset of voriconazole therapy. This case is unique in its demonstration of a 2-year progression of periostitis on imaging in an asymptomatic patient. Awareness and recognition of voriconazole-induced periostitis by radiologists is important as symptoms may not always be present; however, this case will highlight that progression will still occur [1,2].

## CASE REPORT

The presented patient was a 54-year-old male with a history of CLL/small lymphocytic lymphoma status post-cord blood stem cell transplant (SCT) complicated by graft versus host disease (GVHD) of GI tract and lungs, chronic respiratory failure from GVHD/bronchiolitis obliterans. Due to the GVHD complication, he had been on long-term prophylactic oral voriconazole for approximately 2 years prior to presenting for acute on chronic respiratory failure. The immunocompromised

state from CLL/small lymphocytic lymphoma, SCT, and chronic graft versus host disease prompted the initiation of anti-bacterial, anti-fungal, and anti-viral prophylactic medications including Bactrim, voriconazole, and Valtrex, respectively. At the time of admission, the patient was started on voriconazole 252 mg PO q 12 h and remained on this dose for 21 days. It was escalated to intravenous administration at the same dose and frequency on admission day 21 for 2 days due to worsening respiratory status and pneumonia suspicion. The route was then reverted back to PO until his passing 8 days later. He was additionally treated with steroids and weekly photopheresis treatments, which did not improve his respiratory status. He eventually expired from acute on chronic hypoxemic respiratory failure.

CT of the chest was initially performed on admission for acute dyspnea in the setting of chronic lung disease. The CT revealed centrilobular emphysema with multiple new <4 mm nodules that were nonspecific in etiology. A subsequent chest CT was done 3 weeks later for worsening respiratory failure. Diffuse periostitis was incidentally reported most prominently in both proximal humeri, clavicles, and along the posterior aspect of ribs, with a nodular and irregular pattern. At this time, the periosteal changes were retrospectively seen on prior CTs [Figures 1-4]. There was no documented bone pain during his 1-month admission or on prior oncology appointments since the onset of voriconazole use. He did complain of long-term lower extremity numbness and tingling; however, no imaging of the lower extremities was obtained. Given the lack of bone pain or

note of periostitis on imaging until 5 days prior to expiration, no bone scan or serum fluoride level was performed.

A retrospective review of the patient’s CT examinations performed during his 2-year prophylactic voriconazole use was performed. CT of the abdomen/pelvis done approximately 4 months after starting voriconazole did not show evidence of periostitis [Figures 1a, 2a, 4a]. However, subsequent CT of the chest performed approximately 7 months later, 11 months after initiation, did reveal periostitis for the first time [Figures 1b and 2b]. Two subsequent CTs of the chest/abdomen/pelvis were performed over the following year, which showed gradually worsening periostitis [Figures 1c, 2c, 2d, 3a, 3b, 3c, 4b].

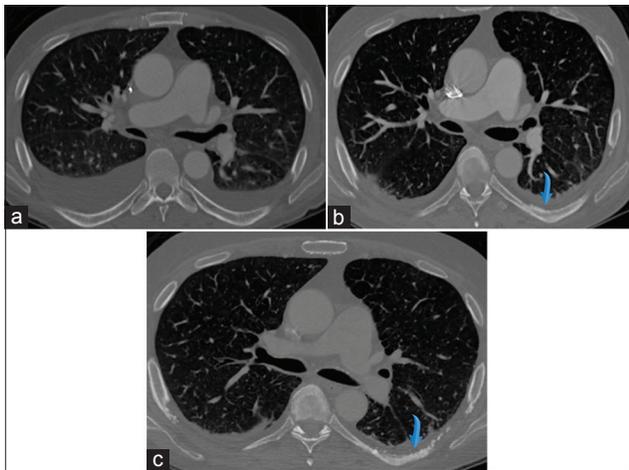
**DISCUSSION**

Voriconazole-induced periostitis is becoming a recently recognized entity, predominantly based on case reports in

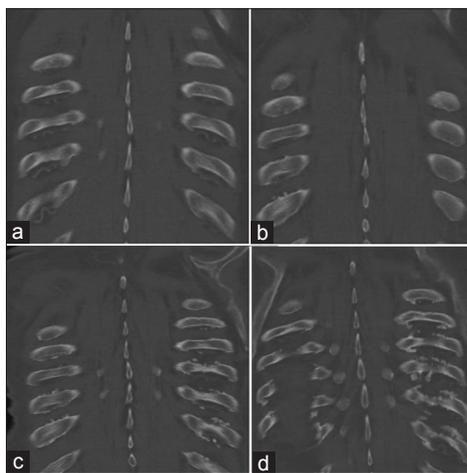
transplant patients [2-12]. Voriconazole is a second-generation antifungal medication used primarily for the treatment or prophylaxis of fungal infections such as *Aspergillus* in high-risk populations [3,13,14]. Fluoride is becoming increasingly common in medications as the exchange of hydrogen and other functional groups with fluoride increases molecular lipophilicity, advantageously affecting its clearance and metabolism [4]. Despite the added benefits fluoride provides to the medication profile, hepatic metabolism of the drug elevates unbound serum fluoride levels, which are thought to cause periostitis with long-term use in as much as 50% of treated patients [1-5,13,15].

The chemical structure of voriconazole contains three fluoride atoms [4,13]. Although many azole antifungals contain fluorine, it is the tri-fluorinated chemical structure of voriconazole that is felt to be the cause of the periosteal reaction. Azole antifungals containing two or fewer fluorine atoms, such as posaconazole, itraconazole, and fluconazole, have not been shown to demonstrate periostitis [1,16,17]. Of the azole antifungals, only voriconazole has been associated with bone pain and radiographic evidence of periostitis [17]. Although it appears that the tri-fluorinated structure plays a significant role in the development of periostitis, there may also be fluoride-independent mechanisms affecting osteogenic activity by stimulating vascular endothelial growth factor and platelet-derived growth factor [18].

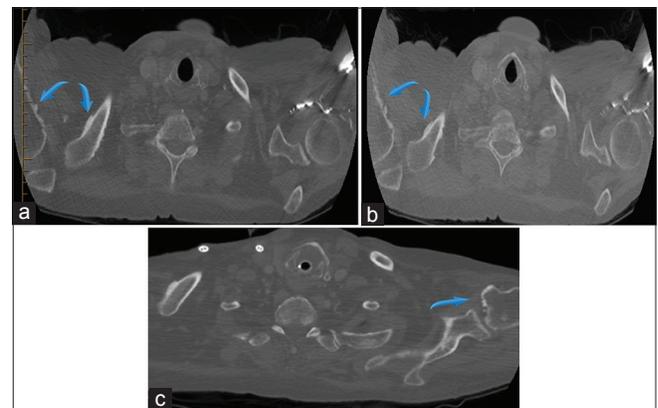
Fluoride assimilates into the crystal structure of bone as fluorapatite and promotes bone formation by stimulating



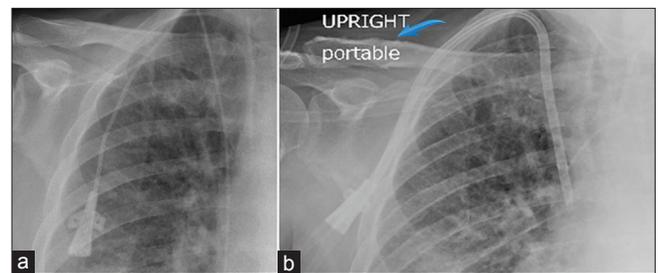
**Figure 1:** Progression of periostitis in the posterior ribs on axial computed tomography (CT) of the chest/abdomen/pelvis. (a) No CT evidence for periostitis on March 2014. (b) First signs of periostitis on January 2015, which was seen only retrospectively. (c) Worsening periostitis on January 2016 at the time of initial reporting



**Figure 2:** Periostitis of the posterior ribs on coronal chest computed tomography progressing from, (a) No periostitis on November 2014, (b) first signs of periostitis on January 2015, (c) May 2015, (d) January 2016



**Figure 3:** Progression of periostitis on the bilateral humeri on axial computed tomography chest. (a) December 2015, (b) January 2016, (c) January 2016



**Figure 4:** Radiographic evidence of periostitis of the right clavicle over 2 years’ time. (a) No signs of periostitis on March 2014, (b) periostitis developed on January 2016

osteoblasts [4]. Prolonged exposure of excess fluoride can lead to osteosclerosis followed by osteoporosis and periosteal changes [3]. Given these developing findings, if a patient on voriconazole develops bone pain and/or periostitis, a serum fluoride level or bone scan is recommended along with the discontinuation of voriconazole therapy [2,13].

In addition to voriconazole, several differential diagnoses must be considered in a patient with periostitis including hypertrophic osteoarthropathy, metastatic disease, and leukemia, which are important entities to differentiate in our patient with known CLL. Additional diagnoses include thyroid acropachy and multifocal osteomyelitis, which although less likely, are also important to consider. Voriconazole-induced periostitis on imaging has been described as having a fluffy, feathery, nodular, or irregular morphology with an asymmetric distribution. Typical locations include the clavicles, ribs, and proximal long bones, as in our patient, as well as the scapula, hands, and acetabula [16]. Elevation of alkaline phosphatase may also be seen [7]. In contrast, leukemia-induced periostitis characteristically is associated with marrow expansion and thinning of the cortex, findings that were not seen in our case and are not characteristic of voriconazole-induced periostitis [19]. Periosteal reaction in hypertrophic osteoarthropathy can be differentiated based on morphology and location, appearing more smooth and linear, with a predilection for the metaphyses and diaphysis of long bones in a symmetric distribution. This is in contrast to our patient's case, which demonstrated an irregular periosteal reaction in an asymmetric distribution of both the axial and appendicular skeleton. There is also usually associated digital clubbing with hypertrophic osteoarthropathy, of which there was no mention on documented physical examinations [9,16,19]. Thyroid acropachy is a rare phenomenon seen with hyperthyroidism, which predominantly affects the metatarsals and metacarpals in a "lace-like" or "bubbly" morphology, presenting clinically with digital clubbing, exophthalmos, and myxedema [20]. Multifocal osteomyelitis and metastatic disease would have associated bone marrow and/or cortex changes, as white blood cell count elevation in osteomyelitis. Another important cause to consider is periostitis provoked from another medication. Upon review of our patient's medication list, he was not on any medications that have been shown to cause periostitis to the best of our literature review [21-25]. Overall, the clinical context of periosteal changes on imaging is likely to be most helpful in distinguishing the etiology.

One of the indications for voriconazole is anti-fungal prophylaxis following allogeneic hematopoietic SCT or following a possible complication of GVHD as in this patient [26,27]. The time course requiring prophylaxis post-transplant varies according to the degree of immunodeficiency and if complicated by GVHD. Immune system rebuilding may take over a year after allogeneic hematologic SCT and many years, if ever, in chronic graft versus host disease [26]. Therefore, it is the standard practice to continue long-term anti-fungal prophylaxis as was in this patient's case of developing chronic graft versus host disease. The patient started voriconazole, coinciding with his bone marrow transplant, approximately 2 years before his

periostitis was mentioned on imaging. Retrospectively, first signs of periostitis were noted on a CT performed 11 months after voriconazole initiation, which is consistent with the development of periostitis with chronic use of >6 months. Imaging findings were subsequently noted to progress over the next 2 years.

Most cases in the literature report early recognition and immediate discontinuation of voriconazole with subsequent resolution of pain as well as normalization of fluoride levels and imaging findings [1,2,6-12]. This case is unique in that lack of bone pain or recognition of periostitis on early imaging led to continued use of the drug and progression of imaging changes over a period of 2 years. It highlights the need for increased radiologist awareness and suspicion of this entity on any imaging examination in the appropriate patient population, particularly since bone pain may not be present. Discontinuation of voriconazole has been shown to be effective at reversing its early bone side effects, emphasizing the need for its recognition on imaging studies with or without clinical clues to prevent further progression of skeletal fluorosis and/or development of symptoms [3,13].

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