Case Report

Voriconazole-Induced Diffuse Periostitis

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A B S T R A C T

Background/Objective: Voriconazole treatment has been associated with diffuse periostitis, especially in immunocompromised patients who had transplants or are on immunosuppressants. Here, we present a case of diffuse periostitis induced by prophylactic low-dose voriconazole for pulmonary aspergillosis.

Case Report: A 66-year-old woman presented with 1 year of progressive, diffuse bone pain most prominent over the left shoulder and bilateral hips. She had a history of sarcoidosis requiring a single orthotopic lung transplant. Left phalangeal soft tissue swelling and painful nodules without clubbing were noted on examination. Prophylactic voriconazole 200 mg twice a day for pulmonary aspergillosis was prescribed for over 7 years. Elevated levels of alkaline phosphatase (469 units/L [reference range, 38-126]), bone-specific alkaline phosphatase (125 μg/L [0-20]), and parathyroid hormone (137 pg/mL [8-54]) and normal c-telopeptide level (842 pg/mL [34-1037]) were noted. Radiographs showed “multifocal periostitis” in both hip joints and bilateral proximal femurs, findings suggestive of voriconazole-induced periostitis deformans. Voriconazole was discontinued, and the patient improved symptomatically, despite persistent bone deformities on imaging.

Discussion: Diffuse bone pain can be due to various pathologies, including metabolic or inflammatory diseases and bone tumors. Voriconazole-induced periostitis is caused by skeletal fluorosis, which can result in diffuse bone pain. It is a clinical diagnosis that is supported with radiologic findings, including focal, nodular, dense, and irregular periosteal reactions. Biochemical evaluation may reveal elevated alkaline phosphatase levels, but it is usually related to normal voriconazole trough levels. Periostitis is a benign condition, and discontinuation of the drug usually leads to clinical improvement.

Conclusion: Voriconazole-induced periostitis should be considered as a diagnosis in elderly, immunosuppressed patients with diffuse bone pain on antifungal treatment. Early recognition of voriconazole-induced periostitis may result in both improved patient clinical outcomes and avoidance of unnecessary diagnostic testing.

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Introduction

Voriconazole has been linked to the development of diffuse periostitis especially in immunocompromised patients who have had transplants or are on immunosuppressants. Voriconazole is an antifungal that is commonly used in the treatment of invasive aspergillosis. It is also used as a prophylactic antifungal in patients with solid organ and hematopoietic stem cell transplant. We present a case of periostitis caused by voriconazole with symptomatic improvement after discontinuation of the drug.

Case Report

A 66-year-old woman presented with 1 year of progressive, diffuse bone pain, most prominently in the left shoulder and bilateral hips. She had a history of pulmonary sarcoidosis requiring a single orthotopic lung transplant. She had been on pulmonary aspergillosis prophylaxis for 7 years with voriconazole 200 mg twice a day for 7 years. She presented with 1 year of progressive, diffuse bone pain, most prominently in the left shoulder and bilateral hips.
Imaging on admission demonstrated a creatinine level of 1.45 mg/dL (reference range, 0.52-1.04), calcium level of 7.8 mg/dL (8.6-10.2), albumin level of 3.2 g/dL (3.2-4.6), alkaline phosphatase (ALP) level of 125 units/L (0-20), c-telopeptide level of 842 pg/mL (34-1037), parathyroid hormone level of 137 pg/mL (38-126), bone-specific ALP level of 125 µg/L (0-20), and 25-hydroxyvitamin D level of 25 ng/mL (20-80). Laboratory evaluation revealed a creatinine level of 1.45 mg/dL (reference range, 0.52-1.04), calcium level of 7.8 mg/dL (8.6-10.2), albumin level of 3.2 g/dL (3.2-4.6), alkaline phosphatase (ALP) level of 469 units/L (0-20), c-telopeptide level of 842 pg/mL (34-1037), parathyroid hormone level of 137 pg/mL (38-126), bone-specific ALP level of 125 µg/L (0-20), and 25-hydroxyvitamin D level of 25 ng/mL (20-80). Imaging on admission demonstrated “multifocal periostitis” in both the hips and bilateral proximal femurs and avascular necrosis of bilateral hips. Hand radiographs showed numerous areas of well-defined calcification/ossification along the phalanges and metacarpals (Fig. 2A). Subsequently, computed tomography of the abdomen/pelvis showed a new periosteal reaction surrounding the hips and femurs (Fig. 3). The patient had been on voriconazole for pulmonary aspergillosis prophylaxis for over 7 years. Laboratory and imaging findings were characteristic of voriconazole-induced periostitis. Voriconazole was discontinued, and despite the persistent bone deformities, symptomatic improvement was noted over the next 6 months (decrease in joint pain), and the ALP level normalized to 74 units/L. No further fungal prophylaxis was given. Her x-ray changes progressed over 8 months’ time (Fig. 2B).

Discussion

Voriconazole-induced periostitis is a clinical diagnosis supported by laboratory and radiologic findings. It presents with localized diffuse bone pain, mainly affecting the lower extremity joints, but may also affect the upper extremity joints. Recommended biochemical testing includes bone-specific ALP, which is consistently elevated. Despite higher doses being related to periostitis, voriconazole trough levels are typically within the normal range (1-5.5 mg/L).1 While higher levels of plasma fluoride would strongly support the diagnosis, low or normal plasma fluoride levels do not exclude it.2 The majority of cases are reported in immunocompromised patients.1 Because a higher dose or longer duration of voriconazole is often needed in immunocompromised patients for fungal prophylaxis or treatment, exposure to the drug level is higher, thereby increasing the risk of periostitis as a complication. In addition, drug-drug interactions and genetic CYP2C19 polymorphism may result in faster metabolism of voriconazole, necessitating higher doses to maintain target trough levels. In this case, periostitis developed with the use of a relatively lower dose of voriconazole (200 mg twice a day) for prophylaxis, whereas it is more prevalent when using higher doses for invasive pulmonary aspergillosis in patients with lung transplant.

In the context of immunosuppression, voriconazole-induced periostitis must be differentiated from hypertrophic osteoarthropathy. Periostitis owing to voriconazole is asymmetrical and affects flat bones (eg, ribs, clavicle, scapula, acetabulum, and hands), whereas, hypertrophic osteoarthropathy is symmetrical with a predilection for a tubular portion of long bones with digital clubbing.4 The perioseal reaction in voriconazole-induced periostitis is focal, nodular, dense, and irregular compared with the linear reaction in hypertrophic osteoarthropathy.5 It is postulated that voriconazole is a trifluorinated molecule and the elevation of fluoride blood content is responsible for the fluoride-induced osteoblastic proliferation and skeletal fluorosis.1 The main clinical manifestation of skeletal fluorosis is diffuse...
bone pain. Both upper and lower extremity joints are commonly affected. The symptoms of periostitis improve upon discontinuation of voriconazole, which supports the diagnosis, as in this case. However, radiographic findings do not usually improve after stopping the medication. If clinically warranted, transition to nonfluorinated antifungals will reduce the risk of periostitis.1

Voriconazole-induced periostitis should be considered in the differential diagnosis in elderly immunosuppressed patients with diffuse bone pain on antifungal treatment. Periostitis is a benign condition, and usually, discontinuation of the drug leads to clinical improvement. Early recognition of voriconazole-induced periostitis results in both improved patient clinical outcomes and avoidance of unnecessary diagnostic testing.

Disclosure
The authors have no multiplicity of interest to disclose.

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