Skeletal Radiol (2018) 47:191–194
DOI 10.1007/s00256-017-2764-9

SCIENTIFIC ARTICLE

Voriconazole-induced periostitis deformans: serial imaging in a patient with ANCA vasculitis

S. Cormican[1] · N. Adams[2] · P. O'Connell[2] · A. McErlean[2] · D. de Freitas[3]

Received: 24 April 2017 / Revised: 25 July 2017 / Accepted: 17 August 2017 / Published online: 2 September 2017
© ISS 2017

Abstract
Objectives A 61-year-old with acute granulomatosis and polyangiitis developed *Aspergillus fumigatus* pneumonia after admission to the intensive care unit with a small bowel perforation. This occurred after immunosuppression (intravenous methylprednisolone, intravenous cyclophosphamide, and plasmapheresis) for his initial presentation with stage 3 acute kidney injury.
Materials and methods The mycologist recommended long-term treatment with voriconazole after initial recovery.
Results After 7 months of treatment, the patient complained of joint pain and swelling in his hands. Radiographs, computed tomography, and single-photon emission computed tomography appearances were consistent with periostitis. A diagnosis of Voriconazole-induced periostitis deformans was made and the voriconazole was stopped. Plasma fluoride level was 278 μg/L (normal range < 50 μg/L). Discontinuation of voriconazole led to clinical improvement.
Conclusions Periostitis deformans due to fluorosis is a rare complication of voriconazole treatment. The imaging in our case is unusually dramatic. We were able to track the evolution of periosteal reactions over serial imaging.

Keywords Voriconazole · Periostitis deformans · Fluoride · Vasculitis · ANCA · Serial imaging · Bone · Skeletal · SPECT-CT · Fluorosis

✉ S. Cormican
cormicansarah@gmail.com

[1] Nephrology Department, Beaumont Hospital, Royal Oak, MI, USA

[2] Radiology Department, Beaumont Hospital, Royal Oak, MI, USA

[3] Rheumatology Department, Beaumont Hospital, Royal Oak, MI, USA

Introduction

Voriconazole is an anti-fungal agent used for the treatment and prophylaxis of fungal infections. We encountered a rare complication of treatment in a patient who developed ventilator-associated fungal pneumonia after immunosuppression for anti-neutrophil-cytoplasmic-antibody (ANCA)-positive vasculitis. Dramatic changes due to periostitis deformans were seen on plain films, computed tomography (CT), and single-photon emission computed tomography (SPECT). We were able to track the evolution of periosteal reactions over serial CTs before symptom onset.

Voriconazole-induced periostitis has been frequently described in the immunosuppressed transplant population, who receive anti-fungal treatment for intercurrent fungal infection [1, 2]. It has been uncommonly described in patients with immunosuppression for autoimmune disorders [3, 4]. Awareness of this complication in patients with autoimmune disease is of particular importance because of the potential for symptoms to be mistaken for disease recurrence. We present this case to highlight voriconazole-induced periostitis deformans as a differential diagnosis for joint pain and deformity in patients with autoimmune diseases.

Case report

A 61-year-old man without a significant past medical history was referred to our hospital with acute kidney injury requiring hemodialysis. Immunological investigations demonstrated a positive ANCA with proteinase-3 (PR-3) antibodies. Renal biopsy confirmed a diagnosis of crescentic glomerulonephritis with fibrinoid necrosis without fibrosis. These findings were consistent with a diagnosis of polyangiitis with granulomatosis (previously Wegner's granulomatosis). He received three doses of intravenous (IV) methylprednisolone and underwent

three sessions of plasmapheresis (4.5 l of double-cascade filtration each time). He received one dose of IV cyclophosphamide after the first session of plasmapheresis.

Before the fourth session of plasmapheresis, the patient developed abdominal pain with peritonism and was found to have a small bowel obstruction with perforation. Following surgery, he required circulatory support and mechanical ventilation. He developed ventilator-associated pneumonia. He was initially treated with IV Tazocin and fluconazole. This was changed to IV meropenem, linezolid, and caspofungin after further deterioration. Respiratory secretions from tracheal aspirates and a bronchoalveolar lavage grew *Aspergillus fumigatus* and caspofungin was switched to IV voriconazole (450 mg twice daily for two doses, then 300 mg twice daily). Serum β-D-glucan was elevated. Switch to oral treatment was made after 12 days.

After respiratory recovery and extubation, the patient remained on long-term treatment with 300 mg voriconazole twice daily. Of not, he also recovered normal function. Voriconazole levels were within the range of 3–5 mg/L (optimal trough levels are 2–6 mg/L). After 8 months in hospital, he was discharged for rehabilitation. He received no further immunosuppression for his ANCA disease in view of his life-threatening fungal infection.

Three months following discharge, the patient was re-admitted with a plateau in his rehabilitation and complained of polyarthralgia and swelling in the small joints of his hands. These were tender and swollen on examination. He had received 10 months of voriconazole treatment by this time.

The differential diagnosis at this point included autoimmune arthropathy related to ANCA-vasculitis, viral infection with reactive arthropathy, multifocal septic arthritis or metabolic disorder, e.g. hyperparathyroidism. Hypertrophic pulmonary osteoarthropathy was considered, but was thought to be less likely given multiple joint involvement throughout the body and an absence of clubbing.

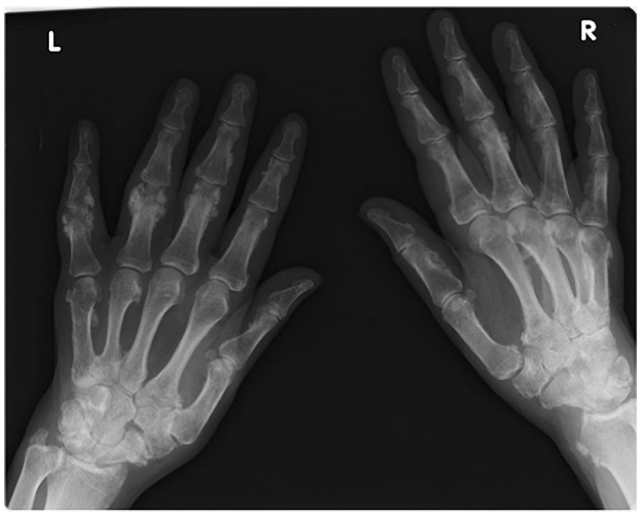

Fig. 1 Bilateral dorsopalmar views of the hands demonstrate florid bilateral periosteal reaction, which was most marked in the proximal phalanges bilaterally, with some involvement of the distal radius and ulna, carpal bones, metacarpals, and mid-phalanges

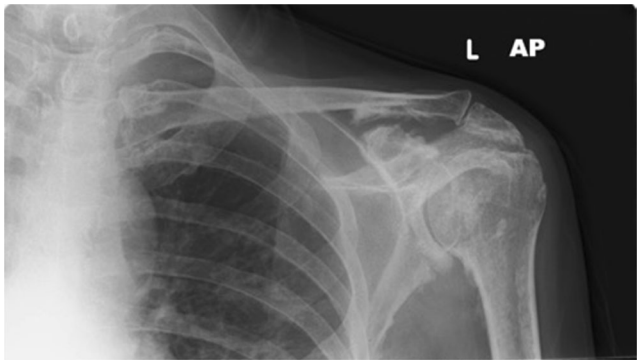

Fig. 2 Left shoulder radiograph demonstrates exuberant periosteal reaction in the lateral third of the clavicle, coracoid process, and acromion process of the scapula, lateral border of the scapula, proximal humerus, and humeral head

On laboratory work-up, inflammatory markers, renal function, and all electrolytes were within the normal ranges. Bilateral hand (Fig. 1), elbow, shoulder (Fig. 2), chest, pelvic, and knee (Fig. 3) radiographs were performed. These demonstrated bilateral exuberant, slightly asymmetrical periosteal reaction involving almost all bones of the appendicular skeleton and was most prominent in the hands and shoulders. No cortical destruction or focal lytic lesions were seen.

The patient underwent a whole-body planar bone scan, which demonstrated diffuse abnormalities in the upper limbs, thorax, and lower limbs (Fig. 4). A technetium-99 m SPECT was performed that demonstrated avid tracer uptake in the areas of periosteal reaction (Fig. 5).

On review of previous imaging he had undergone a CT thorax 8 months before presentation that showed normal proximal humeri and scapulae (Fig. 6a). A CT thorax carried out 4 months before presentation showed subtle early periosteal

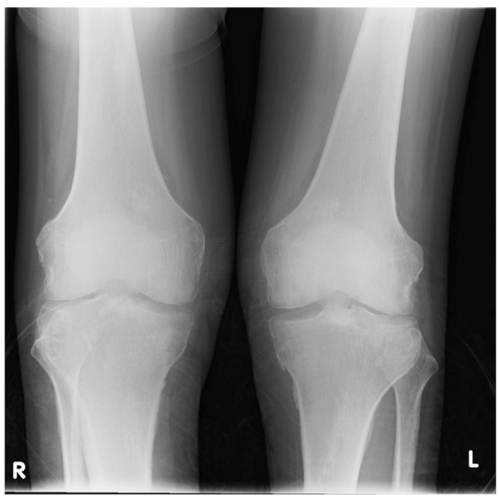

Fig. 3 Radiograph of both knees showing periosteal reactions affecting the tibial metaphyses

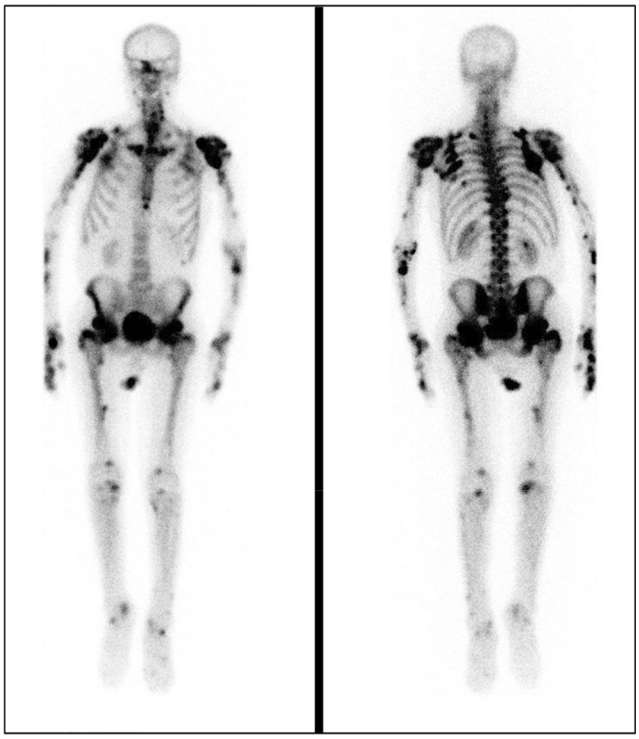

Fig. 4 Whole-body planar bone scan demonstrating multifocal increased tracer uptake. In the upper limbs, there is significantly increased uptake in the proximal humeri, scapulae, around the elbow joint, carpals, metacarpals, and phalanges. There is parallel linear uptake along the outline of the diaphysis of the humeri, which was most obvious on the left side in a distribution consistent with uptake within the periosteal reaction. There is uptake in a number of the posterior ribs. In the lower limbs, there is increased tracer uptake in the inferior iliac bone, proximal femora, and to a lesser degree along the femur and tibia

reaction in the proximal humeri (Fig. 6b). CT thorax at the time of symptom onset showed florid periosteal reactions (Fig. 6c). A diagnosis of voriconazole-induced periostitis deformans was made after discussion with the radiology and rheumatology teams.

Plasma fluoride level was 278 μg/L (normal range < 50 μg/L). Alkaline phosphatase was also elevated to >1,000 IU/L (normal range < 130 IU/L). Discontinuation of voriconazole led to rapid clinical improvement and normalization of alkaline phosphatase. Anti-fungal treatment was discontinued. Posaconazole treatment was trialed as an alternative, but the patient's liver function tests deteriorated on this treatment. Since discharge, he has been followed up in the nephrology outpatients' clinic. He has had no respiratory deterioration off anti-fungal treatment and there has been no evidence for vasculitis relapse.

Discussion

Periostitis due to fluorosis is a known but rare complication of voriconazole treatment. Voriconazole contains 16% fluoride by weight and long-term treatment may lead to fluoride toxicity. Periostitis is thought to occur because of fluorapatite formation and subsequent stimulation of osteoblastic activity and new bone formation [1]. Patients present with painful joints in both upper and lower limbs, with swollen, tender joints on examination. Appropriate imaging includes plain radiographs, planar bone scan, CT, and SPECT [5]. Plasma fluoride levels are elevated.

Most previous literature relates to solid-organ transplant recipients (especially lung transplant recipients) who are at a high risk for pulmonary aspergillosis and frequently require long-term antifungal treatment [6]. Cases among hematology patients, who are also at a high risk for invasive fungal disease following heavy immunosuppression, have also been reported [7]. In previous reports of voriconazole-induced periostitis deformans, time on treatment before the development of symptoms ranges from 6 months to 3 years [8, 9].

Immunosuppression is required for the treatment of vasculitis and connective tissue disorders. However, periostitis as a complication of anti-fungal treatment has been less commonly reported in this patient group. To our knowledge, there have been two previous case reports. One of these occurred in a patient with granulomatosis and polyangiitis, who presented with hip pain and was initially believed to have suffered a relapse of her autoimmune disease [3]. This differential was also considered in our case. The second case occurred in a patient with overlap syndrome and interstitial pneumonia complicated by pulmonary aspergillosis. This patient responded to a switch to itraconazole [4].

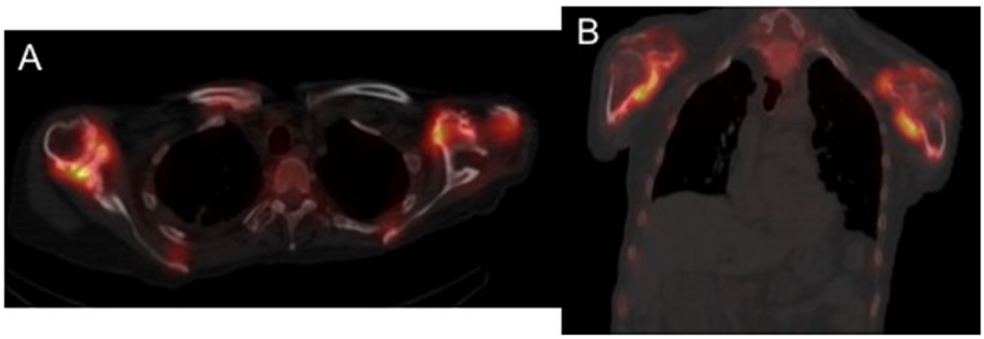

Fig. 5 Fused axial and coronal single-photon emission computed tomography images of the thorax show bilateral, symmetrical increased tracer uptake within the areas of periosteal reaction in the proximal humeri and scapulae

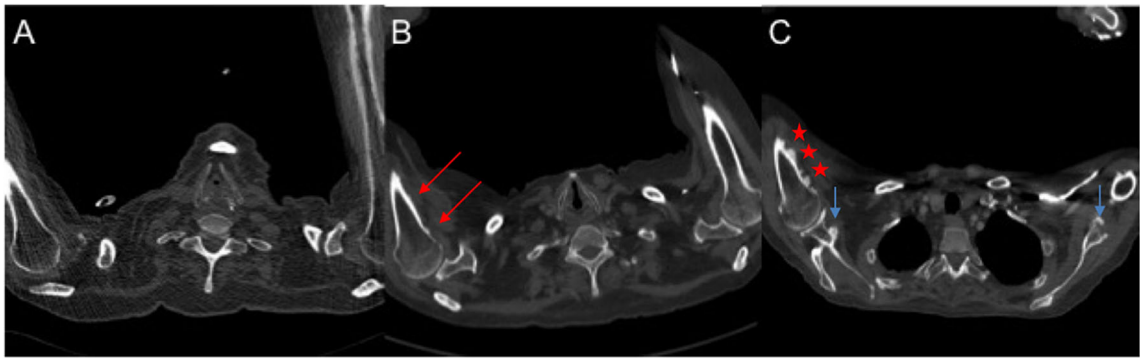

Fig. 6 **a** Axial cut from the CT thorax on admission to the intensive care unit and before initiation of voriconazole treatment shows normal bone and periosteum at the level of the upper humeri. **b** Axial cut from CT thorax after 5 months of voriconazole treatment (but before symptom onset) shows small focal areas of periosteal reaction (*red arrows*). **c** CT thorax at symptom onset (after 10 months of treatment with voriconazole) shows extensive periosteal reaction in the proximal humeri (*red stars*) and scapulae (*blue arrows*)

Of note, itraconazole, fluconazole, and posaconazole have not been associated with periostitis, despite posaconazole-containing fluoride [6]. Posaconazole has activity against *Aspergillus* and is an option for patients who cannot receive voriconazole.

One retrospective review suggested a 13% incidence of musculoskeletal pain related to fluoride toxicity among patients treated with long-term voriconazole [7]. Awareness of this adverse event is important to allow prompt discontinuation where appropriate. It is of particular relevance among patients with auto-immune disease, as the symptoms of periostitis may mimic a flare of rheumatic disease.

In summary, we present a patient who developed voriconazole-induced periostitis deformans after voriconazole treatment for pulmonary aspergillosis following immunosuppression for ANCA vasculitis. This has rarely been described in patients with underlying autoimmune disease and awareness is important to avoid misdiagnosis, for example, of disease recurrence.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

References

1. Wermers R, Cooper K, Razonable R, et al. Fluoride excess and periostitis in transplant patients receiving long-term voriconazole therapy. Clin Infect Dis. 2011;52(5):604–11.
2. Gladue H, Fox D. Voriconazole-induced periostitis causing arthralgias mimicking a flare of granulomatosis with polyangiitis. J Clin Rheumatol. 2013;19(8):444–5.
3. Hirota K, Yasoda A, Fujii T, Inagaki N. Voriconazole-induced periostitis in a patient with overlap syndromes. BMJ Case Reports. 2014. https://doi.org/10.1136/bcr-2013-203485.
4. Tailor T, Richardson M. Case 215: Voriconazole-induced periostitis. Radiology. 2015;274(3):930–5. https://doi.org/10.1148/radiol.14122800.
5. Gerber B, Guggenberger R, Fasler D, et al. Reversible skeletal disease and high fluoride serum levels in hematologic patients receiving voriconazole. Blood. 2012;120(12):2390–4.
6. Ostrem M, Merten J, Hogan W, et al. Incidence of fluoride toxicity in Allogeneic hematopoietic stem cell transplant (HSCT) patients taking Voriconazole. Biol Blood Marrow Transplant. 2013;19(2):S377–8.
7. Wang T, Wang T, Altman R, et al. Periostitis secondary to prolonged voriconazole therapy in lung transplant recipients. Am J Transplant. 2009;9(12):2845–50. https://doi.org/10.1111/j.1600-6143.2009.02837.x.
8. Chen L, Mulligan M. Medication-induced periostitis in lung transplant patients: periostitis deformans revisited. Skeletal Radiol. 2010;40(2):143–8. https://doi.org/10.1007/s00256-010-0997-y.
9. Bucknor M, Gross A, Link T. Voriconazole-induced periostitis in two post-transplant patients. J Radiol Case Rep. 2013;7(8):10–7