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Voriconazole-induced periostitis

D.C. Fernández-Ávila[1], M. Diehl[2], A.M. Degrave[2], M. Buttazzoni[2], T. Pereira[2], M.A. Aguirre[3], A.L. Basquiera[4], M. Scolnik[1]

[1]Rheumatology Section, Internal Medicine Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [2]Metabolic bone disease Section, Endocrinology Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [3]Internal Medicine Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [4]Hematology Section, Internal Medicine Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

SUMMARY

Voriconazole is a fluorinated drug from the triazole group that is widely used in the prophylaxis and treatment of fungal infections in immunosuppressed patients.

Chronic use of this medication can generate, as an adverse effect, a multifocal, asymmetric, diffuse and nodular periosteal reaction, associated with severe and disabling skeletal pain and elevated alkaline phosphatase and serum fluoride.

Radiography is the imaging technique of choice for periostitis diagnosis. In general, clinical manifestations and radiographic findings disappear, when the drug is discontinued.

We report the clinical case of a 44 year-old woman diagnosed with acute myeloid leukemia, who developed an invasive fungal infection treated with voriconazole after a stem cell transplant. Nine months after starting antifungal treatment, she manifested symptoms and radiological signs compatible with periostitis.

Due to clinical suspicion, we decided to suspend voriconazole, with consequent resolution of clinical manifestations and radiological findings.

Key words: *Periostitis, voriconazole, bone pain, case report.*

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INTRODUCTION

Voriconazole is a highly fluorinated antifungal agent, from the triazole group, which acts by blocking a fundamental enzyme in the fungus cytoplasmic membrane, thus increasing its permeability. It is widely used in the prophylaxis and treatment of fungal infections in immunosuppressed patients.

Multiple adverse events associated with this drug have been described, the most important being a cutaneous malignancy, which is associated with treatment duration and shows an aggressive and multifocal behavior. Alteration of liver enzymes, other types of skin changes, central and peripheral nervous system involvement, and bone changes have also been reported. Some toxic effects, such as neuropsychiatric and gastrointestinal manifestations, are related to voriconazole blood supratherapeutic concentrations, which should be closely monitored (1).

Although the pathogenesis is not fully understood, chronic use of voriconazole can induce a diffuse periosteal reaction, generally asymmetric, with nodular morphology which mainly affects the bones of hands, clavicles, ribs, acetabulum and scapula (2). Symptoms are nonspecific, and in most cases there is severe and disabling pain, myalgia and in some cases, palpable bony overgrowths.

Images can show multifocal periostitis with new bone formation that can be nodular or fluffy, associated with elevated serum levels of alkaline phosphatase and fluoride. In general, periostitis resolves after withdrawal of voriconazole, a feature that may be useful for diagnostic confirmation (3).

CASE REPORT

We present the case of a 44 year-old woman treated at our hospital, diagnosed with acute myeloid leukemia in June 2017, who underwent allogeneic hematopoietic stem

Corresponding author:
Diana Carolina Fernández Ávila
Rheumatology Section,
Internal Medicine Department,
Hospital Italiano de Buenos Aires,
Postal C1181ACH, Buenos Aires, Argentina
E-mail: diana.fernandez@hospitalitaliano.org.ar

cell transplantation in December of the same year. The patient was admitted from May to October 2018 for severe graft-versus-host disease with intestinal and liver involvement, and was treated with high-dose glucocorticoids and infliximab.

During hospitalization, she presented a disseminated infection caused by *Scedosporium apiospermum* that was interpreted as an invasive fungal infection with cutaneous, cerebral and pulmonary involvement, for which intravenous voriconazole was started. Previous to her discharge, the patient was switched to oral voriconazole at a dose of 300 mg twice daily to maintain therapeutic levels. Nine months after starting the antifungal therapy, the patient complained of severe and disabling generalized bone pain, arthralgias, swelling of hands and fingers with predominantly proximal, nodular lesions on extensor surfaces and limitation of flexion-extension of the carpus. No clubbing was detected.

As to the laboratory workup, creatinine (0.94 mg/dL [normal 0.5-1.2]), calcium (9.5 mg/dL [normal 8.5-10.5]), and phosphate (4.2 mg/dL [normal 2.5-4.5]), parathyroid hormone/PTH (44 pg/mL [normal 8.5-77.1]) and 25 OH vitamin D (31 ng/mL) levels were within the normal range, but we found an increase in alkaline phosphatase (1097 U/L [normal 31-100]) and gamma-glutamyl transferase (953 IU/L [normal 9-38]), and of several markers of bone remodeling, such as bone alkaline phosphatase (191.8 ug/L [normal 3.8-22.6]), osteocalcin (152 ng/ml [normal 11-46]) and beta cross laps (4.86 ng/mL [normal <0.573]), as well as high levels of fluoride in urine (31 mg/L [normal <3 mg/L]). PTH and 25 OH vitamin D were determined by chemiluminescence. Beta cross laps was performed by Electrochemiluminescence Immunoassay, bone alkaline phosphatase by chemiluminescence, osteocalcin by electrochemiluminescence and finally 24 h urine fluoride was measured by fluoride specific ion electrode.

Initial radiographs revealed a bilateral, irregular, nodular periosteal reaction in metacarpal bones and phalanges (Figure 1), as well as in the bilateral acetabular region. A positron emission tomography with fluorodeoxy-glucose computed tomography (FDG-PET/CT) was performed in which multiple hypermetabolic periosteal lesions with exophytic growth towards soft tissues were observed in scapulae, humerus, ulna, radii, ribs, hips and femurs (Figure 2).

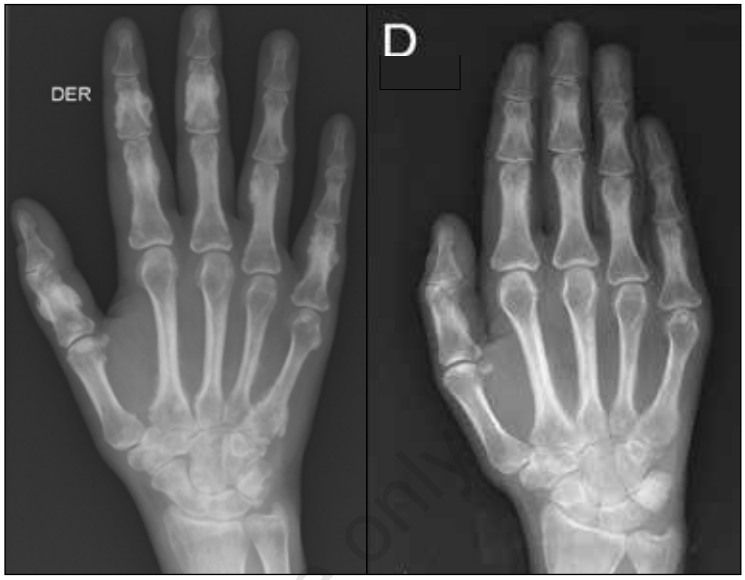

Figure 1 - Right hand X-ray performed 9 months after starting voriconazole (left radiograph) and 3 months after its interruption (right radiograph).

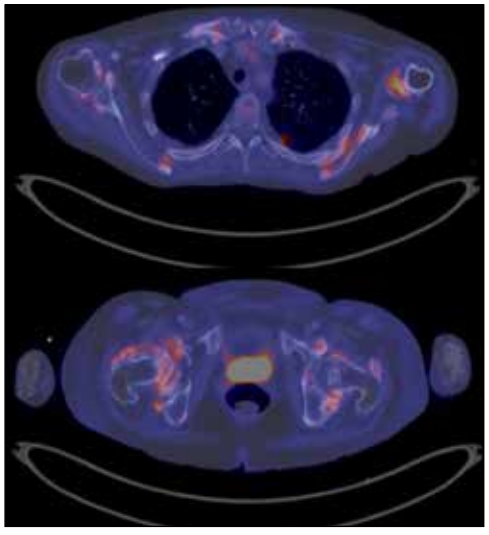

Figure 2 - Positron emission tomography with fluorodeoxy-glucose computed tomography (FDG-PET/CT) performed 9 months after starting voriconazole showing bone changes in the shoulder and pelvic girdles.

The clinical picture was interpreted as periostitis secondary to the chronic use of voriconazole, a fact that prompted the switch to isavuconazole. Symptoms resolved a few weeks later and hand X-rays performed 3 months later showed an almost complete resolution of the periostitis.

DISCUSSION AND CONCLUSIONS

Voriconazole-induced periostitis is an infrequent complication characterized by nonspecific pain and/or myalgias, in one or more skeletal areas, without digital clubbing, associated with bone growth or exostoses and elevated serum alkaline phosphatase and fluoride. Bone pain can be very severe and disabling, with only partial response to different analgesics and minimal response to steroids.

The main radiological finding is periosteal ossification in multiple areas, and the most frequently affected sites are the upper limbs, clavicle, and phalanges of the hands (4). In general, new bone formation is dense, irregular, nodular, and bilateral, although in some patients it may be milder. At FDG-PET/CT a greater metabolic activity can be observed in the foci of periostitis, even though this is not the initial suggested diagnostic method (5).

The main hypothesis that explains how voriconazole can generate or trigger this periostitis is subacute fluoride toxicity, secondary to the use of the antifungal agent. Voriconazole contains in its structure three fluorine atoms that represent 16.25% of its molecular weight. This means that a dose of 400 mg contains 65 mg of fluorine (6). In addition, 5% is metabolized into free fluorine. The risk of skeletal effects is elevated in patients with fluoride intakes greater than 6 mg/day (7). When present in large quantities, fluoride can be integrated into the extracellular matrix in the form of fluorapatite, increasing bone density and giving it more resistance to resorption, but increasing bone brittleness. Fluoroapatite may stimulate the activity of osteoblasts leading to exostosis and secondary periostitis (8).

A small retrospective study compared the use of voriconazole with other azoles, such as itraconazole and posaconazole, and found that only patients who received voriconazole showed more frequently periostitis. The authors found that the clinically relevant skeletal disease was associated with kidney failure and blood fluoride levels greater than 10 fold the normal value, regardless of the length of use of voriconazole. They also found that bone changes were rapidly reversible, when treatment was discontinued (9).

Another retrospective study that included 195 patients on long-term voriconazole treatment found that those who developed periostitis had higher levels of plasma fluoride and alkaline phosphatase and had higher daily and cumulative levels of the drug, compared to patients without periostitis (10).

Despite these findings, other studies suggest that voriconazole induces periostitis by a fluoride-independent pathway, which is not yet fully understood. It is also unclear why the vast majority of patients who use long-term voriconazole do not present skeletal manifestations and what are the factors that predispose to the development of this complication.

The estimated incidence of this entity varies between 15% and 50% according to different studies; the interval between the initiation of treatment and the appearance of symptoms ranges between 6 months and 3 years, although there are reports of onset of symptoms as early as 6 weeks after starting voriconazole. As to the dose, most of patients who developed periostitis received 400 mg per day of voriconazole, which is the most commonly used dose, but also cases with different doses were reported (8).

One differential diagnosis to consider is hypertrophic osteoarthropathy (HOA) or *Pierre-Marie-Bamberger syndrome*, a rare condition characterized by abnormal proliferation of the skin and periosteal tissue in the upper and lower limbs. This entity can be primary, with autosomal dominant inheritance, or secondary, related to a wide variety of clinical entities, mainly intrathoracic malignancies, chemotherapy or congenital heart disease. It is characterized by

the clinical triad of joint pain, periostitis and digital clubbing (11), as well as joint effusion with a predominance in large joints, without elevation of alkaline phosphatase. In general, the periostitis induced by this disease is usually symmetrical, milder and involves the diaphysis of the long bones (12).

The low frequency of symptomatic periostitis associated with voriconazole treatment and the difficulty in identifying risk factors, as well as the clinical characteristics of patients susceptible to developing this entity could suggest that it is an idiosyncratic effect and that there are factors both in the patient (environmental and genetic) and the drug (pharmacokinetics and pharmacodynamics) that could trigger this pharmacological complication (11).

This case highlights the importance of early recognition of this rare and potentially reversible side effect of voriconazole.

Contributions

DCF-Á, AMD, MD, MS participated in patient evaluation, analysis and interpretation of studies, literature review, draft the article and final approval of the version to be published; MB,TP participated in literature review and article draft; MAA, ALB participated in patient evaluation, analysis and interpretation of studies, and final approval of the version to be published.

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