Voriconazole induced periostitis

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Summary
Poort S, van Rheenen R, Noordzij W. Voriconazole induced priostitis
A 62-year-old man, post liver transplantation, was seen with bone pains and swellings e.c.i. He was under long term treatment for an Aspergillus pneumonia with voriconazole. Evidence of multifocal periostitis was observed in the bone scintigraphy. Discontinuation of voriconazole resulted in improvement of symptoms

Introduction

We report the case of a 62-year-old man with diffuse and severe musculoskeletal pain. He underwent liver transplantation 16 weeks earlier, because of liver failure with hepatic encephalopathy, caused by cirrhosis based on hemochromatosis and alfa-1-antitrypsine deficiency. After initial liver transplantation, the patient suffered from acute rejection, for which he underwent re-transplantation two days later. As immunosuppressant to prevent rejection, tacrolimus two times a day 0,5 mg was prescribed. Four days post-surgery he developed pneumonia based on Aspergillus fumigatus and Aspergillus flavus infection, for which he was treated with voriconazole, 400 mg, twice daily.

Immediately after the surgery the patient suffered from pain in the shoulders. Initially, the pain was interpreted as a consequence of supine position during surgery. However, the pain worsened and extended multifocally throughout the body in the following weeks. Eventually the patient had to be hospitalized, four months after the re-transplantation. At that time he had lost 4 kg body weight. He was admitted to our department of gastroenterology, to analyze his general discomfort, nausea, diarrhea and painful joints. Physical examination revealed several sites of painful hard swellings on both arms and legs, firmly attached to the bone. Biochemical results showed hyperpotassaemia (5.3 mmol/L; normal values 3.5-5.0 mmol/L) and elevated C - reactive protein (11 mg/L; normal values <5 mg/L).

The patient was referred for three-phase technetium-99m labelled hydroxymethylene diphosphonate (HDP) bone scintigraphy to further analyze the painful bones and joints. Flow images showed slightly asymmetric hyperperfusion of the right lower leg. The blood pool phase, acquired 5 minutes post injection, showed high tracer accumulation in the right lower leg, indicating inflammation, due to capillary dilatation and increased blood flow (figure 1). Total body planar image, acquired three hours after injection, revealed multifocal intense accumulations, in peripheral and axial skeleton (figure 2). For more detailed localization of these ^{99m}Tc-HDP accumulations, single photon emission computed tomography combined with low dose computed tomography (SPECT/LDCT) was performed of the lower legs and thorax . The intense ^{99m}Tc-HDP accumulations were projected along the cortex, at the site of periosteal thickening (figure 3).

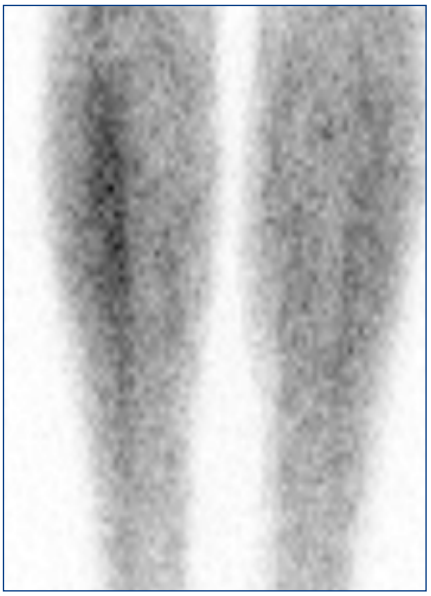

Figure 1. Anterior projections of the blood pool phase, showed increased tracer accumulation in the right tibia.

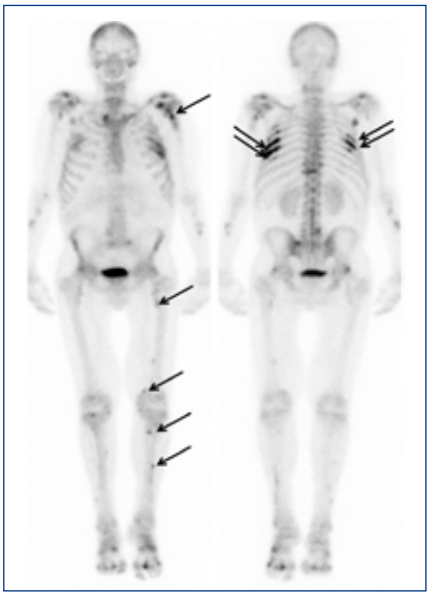

Figure 2. Anterior and posterior image of total body bone scintigraphy, showing pathological uptake in peripheral and axial skeleton. Arrows indicated the left humerus, several costae, left proximal and distal femur and the left tibia.

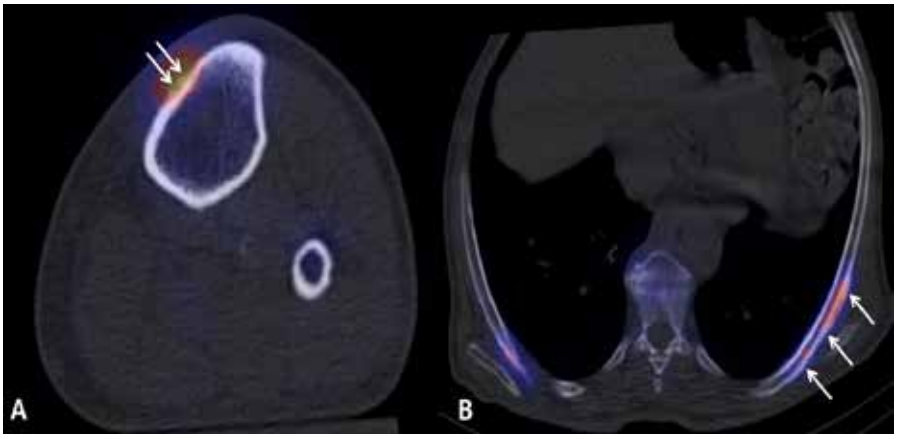

Figure 3A. Axial projection of the SPECT/LDCT of the left tibia. The arrow directs towards a focal high uptake, corresponding to a local calcification of the periost.

Figure 3B. Axial projection of the SPECT/LDCT of the thorax. The arrows point at HDP foci, corresponding to local periost calcifications.

These images were interpreted as voriconazole induced periostitis, upon which treatment with voriconazole was discontinued. Within 3 days potassium and CRP levels were normalized, the pain in bones and joints dissolved completely. In addition, the patient steadily started gaining weight again.

Discussion

Voriconazole is a triazolderivative with broad spectrum antifungal activity, widely used in transplant recipients with opportunistic fungal infections. It is registered in the Netherlands for treatment of invasive aspergilloses, candidaemia in non-neutropenic patients, fluconazol-resistent severe invasive candida-infections and severe fungal infections caused by scedosporium and fusarium species.

Common side effects, affecting over 10% of the voriconazole users, are dyspnoea, fever, mild transient visual disturbance, headache, gastro-intestinal complaints, skin rash and elevated liver enzyme levels. Although several case reports have mentioned voriconazole induced periostitis (1-12), periostitis is listed to appear less than seldom (<0.1%) (13).

Drug clearance is primarily dependent on metabolism by cytochrome P450 enzymes in the liver. Antifungal agents are known to inhibit cytochrome P450 3A4/5 (CYP3A4/5) enzymes, which are involved in the metabolism of tacrolimus (5, 6). Therefore co-administration of voriconazole and tacrolimus results in a significant increase of tacrolimus blood levels (6). A frequent side effect of tacrolimus use is hyperpotassaemia, which in our case can be explained by co-administration of voriconazole.
Voriconazole enhances osteoblasts to proliferate, osteogenic differentiation and to express vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) (8). The biological mechanisms contributing to voriconazole-induced periostitis are unknown.
Voriconazole induced periostitis is characterized by multiple areas of periosteal ossification of bones in axial and peripheral skeleton (14). In our case, the radiographic features are nodular periostitis involving the appendicular and axial skeleton, this are consistent with other cases (1, 2). Early non-ossified periosteal reactions could be visualized with magnetic resonance imaging (MRI). Findings include irregular and thick periosteal oedema characterized by T2/STIR hyperintensity along the outer cortical surfaces, as shown previously in another voriconazole-induced periostitis (12). Ossified periosteal reactions can be demonstrated on plain radiography, ultrasound, computed tomography (CT), MRI and bone scintigraphy. Bone scintigraphy has high sensitivity for detection of periosteal reaction, but low specificity, due to false positives caused by oedema or hyperaemia (15). Also, a whole-body bone scintigraphy is useful for a global assessment of all involved sites. Therefore bone scintigraphy is a serviceable imaging technique for visualization of periostitis.

A patchy pattern of intense HDP accumulation along the bones is a characteristic finding in periostitis (1, 2, 11). The differential diagnosis for diffuse periostitis includes hypertrophic osteoarthropathy (Bamberger-Marie syndrome); pachydermoperiostosis, chronic venous insufficiency, thyroid acropachy and hypervitaminosis A (11, 14, 16-18). Voriconazole induced periostitis is often nodular, dense and irregular in appearance, in contrast to the smooth periosteal reaction seen in hypertrophic osteoarthropathy and thyroid acropachy (16, 18). Another distinction is that voriconazole induced periostitis also often involves flat bones, whereas pachydermoperiostosis and hypertrophic osteoarthropathy have a predilection for tubular portion of long bones (14, 16). Thyroid acropachy is characterized by prominent smooth flowing periosteal reaction of tubular bones usually in hands and feet with soft tissue (14, 16, 17). Hypervitaminosis A, located commonly in the flat bones, is characterized in the acute phase by periostitis either single-layered or lamellated, in addition to physeal and metaphyseal abnormalities (14, 18).

Serologically, elevation in both alkaline phosphatase and serum fluoride levels is characteristic in cases of voriconazole induced periostitis (1, 7, 19). Unfortunately this was not determined in our case.