CASE REPORT

Voriconazole-induced periostitis in a patient with overlap syndromes

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SUMMARY

A 52-year-old woman with overlap syndrome and interstitial pneumonia underwent immunosuppressive therapy and she was suspected to suffer from pulmonary aspergillosis. Oral voriconazole was initiated, and a rapid elevation of alkaline phosphatase (ALP) occurred after 4 weeks. After 2 months, the patient presented diffuse pain in bilateral skeletal regions, and bone scintigraphy revealed bilateral multiple areas of increased radiotracer uptake. We suspected the skeletal involvement as voriconazole-induced periostitis. Actually, the plasma fluoride level was increased. Voriconazole was replaced with itraconazole, and after 3 weeks, the patient stopped complaining of bone pain concomitant with the decrease in ALP. Voriconazole-induced periostitis is a rare condition but had previously been reported in solid organ or patients with bone marrow transplant who received a long-term voriconazole therapy. Our present case is distinctive of previous ones, because it occurred in a patient with connective tissue disease which had its rapid progression.

BACKGROUND

Voriconazole is a triazole agent that contains three fluoride atoms.¹ Although voriconazole is efficacious for the treatment of invasive aspergillosis and is recommended by most international guidelines,^{2–4} it is recently reported to cause fluorosis that develops diffuse painful periostitis.^{5–12} We report a case of voriconazole-induced periostitis in a patient with undifferentiated rheumatic diseases, or overlap syndrome. Voriconazole-induced periostitis was previously reported in solid organ or patients with bone marrow transplant who received a long-term voriconazole therapy. Recently, Gladue *et al*¹³ reported a case of voriconazole-induced periostitis in a patient with granulomatosis with polyangiitis. Our present report would be the next case of voriconazole-induced periostitis that occurred in the course of connective tissue disease. Furthermore, our patient presented the earliest onset of the findings, to the best of our knowledge.

CASE PRESENTATION

We report a case of a 52-year-old woman with a history of overlap syndrome, including systemic lupus erythematosus, systemic sclerosis, and dermatomyositis and interstitial pneumonia. She underwent immunosuppressive therapy including cyclosporine and β -methasone. She was admitted to our hospital for exacerbation of interstitial pneumonia, and was treated with cyclophosphamide pulse therapy. In the course of the treatment, CT scan of the chest showed a cavity in the upper right lung.

Although aspergillus antigen and β -D-glucan tests were negative, clinical history and imaging findings were compatible with pulmonary aspergillosis. Oral voriconazole was initiated at the dose of 600 mg/day, which persisted to maintain serum levels at about 3 μ g/mL. Approximately 4 weeks after the initiation of the voriconazole therapy, a rapid elevation of alkaline phosphatase (ALP) occurred. After the 2-month therapy, the patient presented diffuse pain in bilateral shoulders, humeri, scapulae and hypochondriac and femoral regions. After 4 months of the initiation of the therapy, bone scintigraphy was performed, which revealed multiple areas of increased radiotracer uptake in bilateral scapulae, ribs and cortex of femurs (figure 1). The bone metabolic markers were elevated; ALP, bone alkaline phosphatase (BAP), tartrate-resistant acid phosphatase (TRACP)-5b and pyridinoline cross-linked carboxyterminal telopeptide of type 1 collagen (1CTP) were 1060 IU/L (normal 115–359 IU/L), 89.3 μ g/L (normal 3.8–22.6 μ g/L), 857 mU/dL (120–420 mU/dL) and 14.0 ng/mL (normal <5.5 ng/mL), respectively, but serum levels of calcium (9.4 mg/dL adjusted by serum albumin levels, normal 8.7–10.1 mg/dL), phosphorus (3.5 mg/dL, normal 2.6–4.5 mg/dL), intact parathyroid hormone (46 pg/mL, normal 10–65 pg/mL), parathyroid hormone-related protein (<1.1 pmol/L, within normal range) and 1,25-dehydroxy vitamin D3 (20–60 pg/mL) were within normal ranges. CT scan revealed periosteal reactions in some sites and exostoses in the right scapula and left iliac bone (figure 2). MRI revealed high-intensity areas on T2-weighted imaging in cortex regions, and were compatible with periostitis. Bone biopsy was performed from exostosis of the left iliac bone, and the pathological examination revealed an increase of bone tissue with osteosclerosis. This was compatible with periostitis, but was not a specific finding of a distinct disease.

Because the symptoms began after the initiation of voriconazole and the pattern of bilateral multiple periosteal involvements is compatible, we suspected the skeletal involvement as voriconazole-induced periostitis. As for the aetiology of voriconazole-induced periostitis, fluorosis caused by excess intake of fluorides contained in voriconazole is supposed. So we measured the plasma fluoride level and revealed it to be 24.9 μ mol/L (normal 1–4 μ mol/L, toxic level >15 μ mol/L).

TREATMENT

As the fluoride toxicity was suspected, voriconazole was discontinued and itraconazole was started at the dose of 200 mg/day.

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Figure 1 Bone scintigraphy representing multiple areas of increased radiotracer uptake in bilateral scapulae, ribs and cortex of the femurs after 4 months of the initiation of voriconazole.

OUTCOME AND FOLLOW-UP

After the discontinuance of voriconazole for 3 weeks, the patient stopped complaining of bone pain and ALP decreased to 458 IU/L. Nevertheless, the plasma fluoride level still remained to be 19 μ mol/L.

DISCUSSION

Prolonged ingestion or inhalation of high levels of fluoride ion causes skeletal fluorosis. Fluoride ion is reported to stimulate osteoblasts and lead to osteosclerosis.^{14 15} Chronic toxicity of fluoride ion contributes to increase the poor-quality bone and painful calcification or ossification of tendon and ligament.¹⁶ The chemical and structural characters of fluoride ion resemble those of hydroxide, and the alteration of hydroxyapatite to fluorapatite induces bone fragility.¹⁷ Voriconazole contains three fluoride atoms, which account for 16.3% by weight.² As oral bioavailability of fluoride was reported to be 96%, about 78 mg of fluoride was ingested each day in our case. The WHO states that there is a clear excess risk of skeletal fluorosis for a total fluoride intake of 14 mg/day and a suggestive evidence of an increased risk of bone effects at total intakes above 6 mg/day.¹⁸ Thus, our

patient had taken total daily fluoride 13 times more than the upper limit of the fluoride amount suggested by WHO. In addition, the plasma fluoride level still remained to be 19 μ mol/L 3 weeks after the discontinuance of voriconazole, which is higher than those of general population. Fluoride is excreted in urine or accumulated in bone, and the plasma level of fluoride drops to the value of that before intake of the drug, in 24 h.¹⁹ We think fluoride accumulation in bone caused extended release of fluoride from bone in our case.

Voriconazole-induced periostitis is suspected to be caused by the accumulation of fluoride.^{8 9 11} Patients with voriconazole-induced periostitis develop diffuse pain in extremity and exhibit an elevation of ALP. These symptoms are reported to appear from 6 weeks to 53 months after the initiation of voriconazole.^{5–12} Radiographic image reveals symmetric periosteal reaction, and skeletal lesions consist of periosteal thickening, periosteal calcification, calcification of ligaments and osteosclerosis predominantly in proximal long bones, ribs, scapulae and iliac bones. Bone scintigraphy exhibits multiple areas of increased radiotracer uptake corresponding to multifocal periosteal lesions.^{5–7 10 12} These symptoms are reversible and improve

Figure 2 CT images showing exostoses in the right scapula and left iliac bone (red arrows).

within a few weeks after discontinuation of voriconazole. In the past, all cases of voriconazole-induced periostitis were reported to be occurred in transplant recipients^{5–8 12} or in patients with haematological disorders.^{9 11} Recently, Gladue *et al*¹³ reported a case of voriconazole-induced periostitis in a patient with granulomatosis with polyangiitis. Our present report would be the next case of voriconazole-induced periostitis that occurred in the course of connective tissue disease. Furthermore, in our case, the elevation of ALP occurred 4 weeks after the initiation of voriconazole and the diffuse pain developed within 2 months. This is the finding ever reported in the earliest onset of the disease. Drug–drug interactions or inflammatory processes on periosteum might be the pathogenesis of this condition.¹¹

In conclusion, we report a case of voriconazole-induced periostitis developed in a patient with connective tissue disease. As the skeletal symptoms are reversible and ameliorated after the discontinuance of voriconazole, physicians should be aware of it when patients taking voriconazole suffer diffuse bone pains.

Learning points

- ▶ We must suspect voriconazole-induced periostitis for diffuse bone pain and increased alkaline phosphatase (ALP) in a patient who is taking voriconazole.
- ▶ Voriconazole-induced periostitis is a reversible condition and the discontinuance of voriconazole ameliorates the symptoms.
- ▶ Voriconazole-induced periostitis can occur in patients suffering from collagen diseases.

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