Voriconazole-Associated Periostitis in a Heart Transplant Patient

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Introduction

Voriconazole is commonly used for the treatment and prophylaxis of invasive fungal infections in both immunocompetent and immunocompromised patients. Established adverse effects include visual disturbances, hepatic toxicity, and photosensitivity [1]. Recent reports have described painful periostitis in heart and lung transplant patients receiving voriconazole for treatment or prophylaxis of invasive fungal infections.

Case Report

A 60 year-old female with a history of a heart transplant was treated with voriconazole for presumed pulmonary aspergillosis. After approximately three months, she began to experience right arm pain. One month later, she was in a motor vehicle collision, and she attributed subsequent pain to that event. Her pain progressively worsened, spreading to her upper arms, thighs, hips, knees, and hands. Erythrocyte sedimentation rate and C-reactive protein were elevated, but other inflammatory markers including antinuclear antibodies, anti-double-stranded DNA antibody, and anti-histone antibody were negative.

Voriconazole was discontinued after approximately five months, and the patient was hospitalized for pain control and further work-up. Rheumatology was consulted for possible voriconazole-associated periostitis. Physical exam demonstrated tenderness to palpation at the shoulders and thighs without synovitis of the hands or digital clubbing. Laboratory results were notable for alkaline phosphatase of 304 units/liter at the time of admission (normal range: 31-95 units/liter). A technetium-99m Methylene Diphosphonate (MDP) bone scan acquired just after voriconazole was discontinued demonstrated marked improvement of periostitis. Diffuse MDP activity in the sternum is secondary to median sternotomy. A pacemaker generator shadow is present at the right upper chest. (B) Follow-up bone scan approximately five months after voriconazole was discontinued demonstrates marked improvement of periostitis.

Discussion

Periostitis associated with voriconazole therapy has been reported in patients with lung transplant [2,3], heart transplant [4,5], and other conditions [6]. These patients present with bone pain and elevated alkaline phosphatase. The lack of digital clubbing may help distinguish voriconazole-associated periostitis from secondary hyperparathyroid osteoarthropathy. Symptoms improve after voriconazole is discontinued, and radiographic and scintigraphic improvement is seen in the subsequent months.

There are two possible theories to explain the development of

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periostitis in patients treated with voriconazole. One is based on the fact that fluorine is organically bound in voriconazole and 5% of it is metabolized to free fluoride. It is therefore possible that voriconazole, via hepatic oxidative metabolism, results in unbound fluoride metabolites that cause variably elevated fluoride levels after extended use in predisposed patients via pharmacogenomic variations in drug metabolism. A second possibility is that renal insufficiency predisposes individuals to fluoride accumulation, because its renal clearance is directly related to glomerular filtration rate.

Differently from other reported cases, symptoms can develop shortly after voriconazole initiation. Recognition of this condition is important since discontinuation typically leads to prompt resolution of often disabling pain related to periostitis.

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Figure 2: (A) CT chest demonstrating periostitis in a left posterior rib. Frog-leg views of the right (B) and left (C) femur from a radiograph bone survey demonstrate multiple foci of periostitis.