Pamidronate Results in Symptom Control of Hypertrophic Pulmonary Osteoarthropathy in Cystic Fibrosis*

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Hypertrophic pulmonary osteoarthropathy (HPOA) may complicate the advanced lung disease that is associated with cystic fibrosis, resulting in severe joint pain and early-morning stiffness. Symptoms are usually controlled with the administration of nonsteroidal anti-inflammatory drugs, physiotherapy, and, on occasions, oral corticosteroids. This report describes a case of refractory HPOA with complete remission following the administration of IV pamidronate, which is a potent inhibitor of osteoclastic bone resorption. Symptom relief resulted for up to 3 months, but repeated courses of pamidronate have been required to maintain symptom control.

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Key words: biphosphonates; cystic fibrosis; hypertrophic pulmonary osteoarthropathy; pamidronate

Abbreviations: CF = cystic fibrosis; HPOA = hypertrophic pulmonary osteoarthropathy; NSAID = nonsteroidal anti-inflammatory drug

Hypertrophic pulmonary osteoarthropathy (HPOA) is a well-recognized complication of cystic fibrosis (CF) and occurs more frequently in patients with advanced lung disease. Joint pain, stiffness, mastalgia, and gynecomastia may complicate HPOA in patients with CF and are usually controlled by therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), physical therapy, and occasionally therapy with systemic corticosteroids.

CASE REPORT

We report the case of a 27-year-old woman with CF who presented with severe diffuse bone pain and HPOA, which responded to therapy with IV pamidronate. The patient had moderate bronchiectasis (FEV₁, 65% of predicted), and chronic Pseudomonas aeruginosa infection. The treatment of pulmonary disease included physiotherapy, therapy with aerosolized bronchodilators, therapy with intermittent nebulized aminoglycosides, and two previous hospital admissions for therapy with IV antibiotics. The patient was well-nourished (body mass index, 24.6 kg/m²), but a liver biopsy had confirmed the presence of biliary cirrhosis, which was complicated by portal hypertension (ie, splenomegaly, thrombocytopenia, and esophageal varices, which had been controlled with sclerotherapy).

In June 1999, the patient presented with an 8-week history of severe bilateral ankle and knee pain, and right elbow and right wrist pain. The pain was being poorly controlled with simple analgesia and was impairing the patient’s sleep at night. The pain was associated with severe early-morning stiffness and required leave from full-time employment as a clerical officer. A clinical examination revealed bony tenderness proximal to both ankles, which was associated with minimal ankle edema. There was no clinical evidence of synovitis or of an inflammatory arthritis. The findings of chest and abdominal examinations were unchanged from those of earlier examinations, and the results of spirometry testing were consistent with earlier values. Rheumatoid factor was negative, and antinuclear antibody level was weakly positive (nucleolar titer 160; the normal reference is <40 titre). How-

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ever, the results of tests for double-stranded DNA, extractible nuclear antigen, and antineutrophil cytoplasmic antibodies were negative. A radiograph demonstrated bilateral periosteal reaction and eccentric calcification of the distal radius, fibula, and tibia, which were consistent with the presence of HPOA (Fig 1). An isotopic bone scan confirmed increased activity at the margins of the distal radius and tibia.

In view of the complications of portal hypertension, varices, and thrombocytopenia, therapy with NSAIDs was avoided. Rapid relief of bone pain and joint stiffness was obtained with oral prednisolone (50 mg/d) therapy, but the symptoms recurred as before when the dose was reduced to < 7.5 mg/d. Therefore, 5 months after presentation, IV pamidronate (30 mg) was administered following a 48-h increase in the prednisolone dose to 40 mg/d. Pamidronate was not complicated by increased bone pain, and all symptoms resolved completely within 72 h of the infusion, allowing a rapid reduction in the prednisolone dose. No other side effects were seen following administration of pamidronate. Four subsequent infusions of pamidronate have been administered following the recurrence of severe bone pain, at intervals of 10 to 16 weeks after the previous infusions, with complete relief of symptoms, which allowed the patient to return to full-time employment. The patient has continued to receive low dose, alternate-day prednisolone therapy and is currently receiving 5 mg on alternate days, with the aim of weaning the dose to zero.

The patient’s pulmonary status has been complicated by one episode of bilateral pneumonia and by a parapneumonic effusion, which required inpatient IV antibiotic therapy for 3 weeks in May 2000. Subsequently, the results of spirometry testing returned to normal values.

**DISCUSSION**

HPOA is a relatively uncommon but potentially disabling complication of CF. It occurs in 2 to 7% of patients with CF, usually in older patients with advanced lung disease.1 Symptoms associated with HPOA may be controlled by therapy with NSAIDs or corticosteroids. In view of coexisting hepatic disease and concerns about the morbidity associated with long-term therapy with high-dose corticosteroids, further options were considered. The recently released cyclooxygenase-2 inhibitor drugs (eg, celecoxib) were not available at the time of the initiation of bisphosphonate therapy, and no data are available regarding the safety or efficacy of its administration in patients with HPOA.

We report for the first time the use of bisphosphonate therapy in a case of refractory HPOA in a patient with CF. Disodium pamidronate is a potent inhibitor of osteoclastic bone resorption, which is thought to be responsible for its therapeutic effect. Pamidronate has been used to treat conditions with increased osteoclastic activity, including lytic bony metastatic malignancy, advanced multiple myeloma, tumor-induced hypercalcemia, and symptomatic Paget disease of the bone. The activation of endothelial cells and platelets occurring with neovascular proliferation appears to be a key feature of HPOA that may contribute to increased osteoclastic activity.2 Bisphosphonate therapy has been demonstrated to be effective in achieving symptom control in patients with HPOA complicating advanced lung cancer.3

IV pamidronate therapy has been effective in controlling bone pain in patients with HPOA complicating CF without significant morbidity. The lack of severe bone pain following pamidronate infusion in our patient, who was receiving corticosteroids, parallels information from other reports.4,5 While response to IV bisphosphonates has been encouraging, repeated courses of pamidronate may be required to maintain symptom control.

**REFERENCES**