Acute Pseudogout Following Intravenous Neridronate for Osteoporosis

To the Editor:

An 84-year-old woman with a history of surgical menopause at the age of 37 years, gastroesophageal reflux disease, and prolonged corticosteroid use (prescribed by her general pratictioner for osteoarthritis-related pain), sustained a low-trauma vertebral fracture at L3 level. Radiographs showed previous L2 fracture. Other investigations were unremarkable, except for low 25-OH vitamin D levels (22.1 ng/ml) and elevated plasma parathyroid hormone (144 pg/ml). She was then diagnosed with osteoporosis, supplemented with 300,000 IU of oral cholecalciferol, and started therapy with neridronic acid (NA), 100 mg intravenously[1]. Corticosteroids had been tapered before starting NA. The day after her first NA dose, she noticed polyarthralgia, myalgia, and fever (to 38˚C). Over the subsequent 5 days, symptoms eased, but she experienced progressive pain and swelling of her left shoulder. Pain was severe and she was unable to lift her left arm for activities of daily living. She came to observation 13 days after the infusion of NA. Her shoulder was still swollen, tender, and warm, and movements were still restricted.

She was systemically well, and standard laboratory investigations revealed slightly high C-reactive protein (2.57 mg/dl) and erythrocyte sedimentation rate (48 mm/h). 25-OH vitamin D was improved to normal levels (30.4 ng/ml) and parathyroid hormone decreased, although it was still higher than reference values (92.5 pg/ml). Plasma uric acid level was within the normal range (4.5 mg/dl).

Her left shoulder was then aspirated, and a yellow, turbid fluid was drawn. It was biochemically analyzed and sent for culture. Polarizing light optical microscopy revealed intracellular, rhomboid-shaped crystals, with slight birefringence, suggestive for calcium pyrophosphate dihydrate (CPPD) crystals. Synovial fluid examination revealed white blood cells 16,770/mm^3 (89% neutrophils), uric acid 4.6 mg/dl, protein 4.9 g/dl, glucose 114 mg/dl, lactate dehydrogenase 972 U/l (normal value 208–450). Synovial fluid culture was negative. She underwent radiographs of knees and shoulders, which were negative for chondrocalcinosis.

We stopped therapy with bisphosphonates, and started parathyroid hormone receptor agonist therapy, vitamin D, calcium supplement, and 25 mg indomethacin 3 times daily. After a week of treatment she was well. The pain, stiffness, and swelling of the shoulder disappeared, as did the systemic symptoms.

In this patient, a systemic inflammatory reaction, followed by acute CPPD arthritis, was associated with her first NA infusion. Synovial fluid analysis and clinical findings were consistent with the diagnosis of pseudogout. Even if calcium hydrogen phosphate crystal deposition had been considered in the differential diagnosis, early detection of birefringent crystals with optical microscopy suggested CPPD crystals, since brushite crystals are birefringent but rarely small and rhomboidal. Prompt antiinflammatory therapy resolved the pseudogout attack.

There are few reports of pseudogout following bisphosphonate treatment for osteoporosis and complex regional pain syndrome. Only 4 cases were reported: 1 with weekly alendronate[2], 1 with etidronate[3], and 2 with pamidronate[4,5].

Aminobisphosphonates, such as NA, have been related to a systemic inflammatory response (which comprises fever, generalized illness, joint pain, and myalgia), probably because of accumulation of isopentenyl-pyrophosphate and subsequent activation of Vγ9/Vδ2 T cells by T cell receptor, which in turn promotes copious production of tumor necrosis factor-α and interleukin 6[6].

In contrast, the mechanism by which bisphosphonates can produce a pseudogout attack is unclear. We suggest that the NA could inhibit the resorption or breakdown of pyrophosphate in the articular space and indirectly support the persistence of these crystals in synovial fluid, contributing to the onset of pseudogout attack[7]. Another possible explanation is that NA can inhibit alkaline phosphatase activity and so could promote CPPD crystal formation, inhibiting dissolution and promoting acute pseudogut. However, both these interpretations remain speculative.

This is the first report of pseudogout after NA treatment. Although uncommon, physicians need to know about this side effect. Its diagnosis is based on a synovial fluid analysis.

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