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CASE REPORT

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Pseudogout attack induced during etidronate disodium therapy

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Abstract We report the first case of pseudogout attack in the distal interphalangeal (DIP) joints during etidronate disodium therapy. A 64-year-old woman had intermittent administration of etidronate disodium (Didronel; Sumitomo, Osaka, Japan) alone because of osteoporosis. Each cycle consisted of a daily dose of 200 mg for 2 weeks, repeating every 12 weeks. Two weeks after completing the third cycle, severe pain and swelling occurred in the DIP joints of the right middle, ring, and left ring finger; and skin ulcer formation was observed on the dorsal side of the DIP joints of the right middle and ring fingers as well as the left ring finger. Because monoclinic calcium pyrophosphate crystals were detected in the synovial fluid from the DIP joints of the right middle finger, we diagnosed these symptoms as induced by pseudogout attack. Oral loxoprofen sodium at a daily dose of 180 mg resulted in rapid symptom resolution. A decrease in function of calcium metabolism in elderly persons has been reported to be a cause of pseudogout attack. On the other hand, distal interphalangeal joint arthritis presenting as Heberden's nodes is a common condition in elderly patients. Therefore, pseudogout attack should be considered as an adverse drug reaction when administering bisphosphonate in elderly patients with Heberden's nodes.

Key words Distal interphalangeal (DIP) joint · Etidronate disodium · Pseudogout attack

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Introduction

Pseudogout is an arthritic condition that causes pain, stiffness, and swelling. It commonly affects only one joint at a time. The disease most often affects the knee or wrist, although it may involve the hips, shoulders, elbows, knuckles, toes, or ankles. Three cases of bisphosphonate-induced pseudogout have been reported in the literature, in association with cyclical oral etidronate,[1] weekly oral alendronate,[2] and intravenous pamidronate.[3] All three pseudogout cases included knee joints. We report a case of pseudogout attack involving the distal interphalangeal joints in an elderly patient during treatment with etidronate disodium.

Case report

A 64-year-old woman suffering from low back pain visited our hospital. Plain X-ray of the lumbar spine revealed osteoporotic change. Assessment of bone mineral density by dual-energy X-ray absorptiometry (DTX-2000; Toyo Medic, Tokyo, Japan) showed reduced bone mineral density of 0.25 g/cm^2 [52% of young adult mean (YAM)] at the metaphysis of the right radius. Urinary deoxypyridinoline (DPD) was elevated to 13.9 nmol/mmol creatinine (normal range: 2.8–7.6),[4] showing enhanced bone resorption. Therefore, intermittent administration of etidronate disodium (Didronel; Sumitomo, Osaka, Japan) alone was started, each cycle consisting of a daily dose of 200 mg for 2 weeks, repeating every 12 weeks. Immediately after the second cycle, swelling was observed in the distal interphalangeal (DIP) joints of the right middle and ring fingers and the left ring finger. The patient did not seek treatment and the swelling disappeared spontaneously within 1 week. Two weeks after completing the third cycle, severe pain and swelling recurred in the same joints, and skin ulcer formation was observed on the dorsal side of the DIP joints of the right middle and ring fingers as well as the left ring finger. She revisited our hospital.

Her past medical history and family history were not remarkable, but she had suffered from Heberden's nodes for several years. Hematologic and biochemical tests during the attack showed lowered calcium level of 7.9 mg/dl (normal range: 8.4–10.2), normal phosphate level of 3.7 mg/dl (normal range: 2.4–4.3) and normal albumin level of 4.2 (normal range: 3.8–5.3). Alkaline phosphatase, parathyroid hormone, C-reactive protein, and erythrocyte sedimentation rate were all within normal ranges. X-ray findings showed osteoarthritic changes associated with calcification in the DIP joints of the right middle and ring fingers as well as the left ring finger (Fig. 1).

Synovial fluid was aspirated from the DIP joints of the right middle finger for culture and crystal examination. Since monoclinic calcium pyrophosphate crystals were detected in the synovial fluid, we diagnosed these symptoms as being induced by pseudogout attack (Fig. 2). Cultures yielded no causative microorganisms. Oral loxoprofen sodium at a daily dose of 180 mg was initiated, resulting in rapid symptom resolution.

Fig. 1. **a** Ulcer formation (*arrow*) is observed on the dorsal side of the distal interphalangeal (DIP) joint of the left ring finger. **b** On plain X-ray, osteoarthritic changes and amorphous calcification shadow (*arrow*) are found in the DIP joint

Discussion

In 1991, Gallacher et al.[1] reported the first case of pseudogout attack in a 68-year-old patient treated intermittently with etidronate disodium 400 mg/day for 2 weeks every 12 weeks. The patient developed pyrexia together with pain and swelling in the left knee, right ankle, left elbow, both wrists, and small joints of the hands 4 weeks after the second course. Detection of calcium pyrophosphate crystals in the synovial fluid of the right wrist led to a diagnosis of pseudogout attack, and prompt recovery was achieved by rest and naproxen administration. Weekly alendronate also induced acute pseudogout in a 47-year-old nursery nurse.[2] She was diagnosed with osteoporosis and commenced on weekly alendronate 70 mg. A few hours after the first dose, she noticed pain and swelling in her right knee. After the second dose of alendronate, the pain intensified and her left knee also began to swell. Both knees were then aspirated and a yellow, turbid fluid was drawn from each knee. Polarizing light microscopy revealed intracellular, rhomboid-shaped crystals with weakly positive birefringence; findings typical of calcium pyrophosphate dehydrate (CPPD) crystals. Each knee was injected with intra-articular steroid and the symptoms resolved rapidly. Malnick et al. described a patient with primary hyperparathyroidism who was treated with intravenous pamidronate disodium 45 mg for acute hypercalcemia (12.5 mg/dl). Following treatment, serum calcium decreased to normal values (9.2 mg/dl) and concomitantly the patient developed acute pseudogout arthritis of both knees. Treatment with indomethacin resulted in uneventful recovery.[3]

In our case, skin ulcer formation was observed on the dorsal side of the DIP joints of the right middle and ring fingers as well as the left ring finger. Sometimes skin ulcer formation occurs due to perforation of the mucus cyst associated with Heberden's nodes. We suspect that the skin ulcer formation in our case was also caused by perforation of mucus cyst as a result of severe pseudogout attack.

As a mechanism of pseudogout attack, etidronate disodium is known to induce deposition of calcium pyrophosphate in joints through inhibiting urinary excretion of phosphate, thereby elevating the blood phosphate concentration.[5] However, other mechanisms may also be involved.

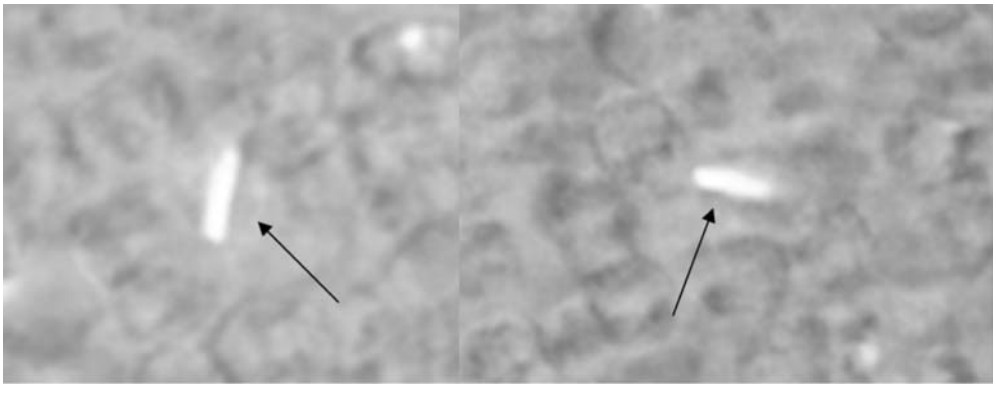

Fig. 2. Polarizing microscopic examination of the right middle finger DIP joint fluid obtained by arthrocentesis. Monoclinic crystals phagocytosed by white blood cells are observed (*arrow*) (×400)

Since bisphosphonate is a hydrolysis-resistant pyrophosphate analog, catabolism of pyrophosphate in the articular cartilage or competitive inhibition of dissolution of calcium pyrophosphate crystal (catalyzed by alkaline phosphatase) may induce an increase or alteration in intra-articular pyrophosphate concentration, leading to deposition of calcium pyrophosphate crystals.[6,7]

As a cause of pseudogout attack, Geelhoed and Kelly have reported that acute change of serum calcium concentration stimulates the precipitation of calcium crystals in the joint fluid and induces acute attack of pseudogout.[8] Although we did not have baseline data prior to the onset of the pseudogout attack, intermittent therapy of a normal oral dose of etidronate disodium appeared to be associated with subnormal blood calcium concentration in our case. In elderly persons, a decrease in function of calcium metabolism has been reported.[9] Therefore, pseudogout attack should be considered as an adverse drug reaction when administering bisphosphonate to the elderly.

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