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Case Report

A case of pseudogout attack after zoledronic acid treatment in primary hyperparathyroidism

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ABSTRACT

Pseudogout (PG) is an inflammatory arthropathy that develops due to the accumulation of calcium pyrophosphate dihydrate crystals in synovial structures. Herein, we present a 59-year-old male patient with PG developed as a result of zoledronic acid (ZA) infusion, which was administered due to primary hyperparathyroidism. The patient with parathyroid adenoma was given ZA since the calcium level did not decrease despite intravenous saline and loop diuretic. One day after ZA administration, the patient had severe pain, fever, and swelling in joints. The radiograph showed chondrocalcinosis. Calcium pyrophosphate deposition were observed in the arthrocentesis fluid under polarized light. The patient's symptoms regressed after anakinra and colchicine treatment. To the best of our knowledge, this is the first case report of a PG attack after ZA treatment for primary hyperparathyroidism. Additionally, there have been few cases of PG after bisphosphonate treatment for osteoporosis in the literature, signifying that more care should be taken when administering bisphosphonate therapy in patients with risk factors.

Keywords: Hypercalcemia, hyperparathyroidism, pseudogout, zoledronic acid.

Pseudogout (PG) is an inflammatory arthropathy that develops due to the accumulation of calcium pyrophosphate deposition (CPPD) in synovial structures.[1] It can occur as both acute and chronic arthritis. Patients are usually over the age of 60, and advanced age is a risk factor. Metabolic disorders such as hyperparathyroidism, hemochromatosis, hypophosphatasia, and hypomagnesemia may cause CPPD disease. Although it is most common in the knee, it can also involve the elbow, wrist, hip, symphysis pubis, metacarpophalangeal joints, and other joints.[2] In the literature, PG formation due to bisphosphonate (BP) infusion performed to treat osteoporosis has been described in only one case.[3] In this report, we present a case of PG that developed when zoledronic acid (ZA) infusion was administered to treat refractory hypercalcemia due to primary hyperparathyroidism (PHP).

CASE REPORT

A 59-year-old male patient presented with nausea and vomiting that had persisted for one month. No pathology was detected in the patient's physical examination, whose history was unremarkable. Calcium, creatinine, albumin, phosphorus, and parathormone levels were 16 mg/dL, 0.91 mg/dL, 4.1 g/dL, 1.5 mg/dL, and 642 pg/mL in the laboratory

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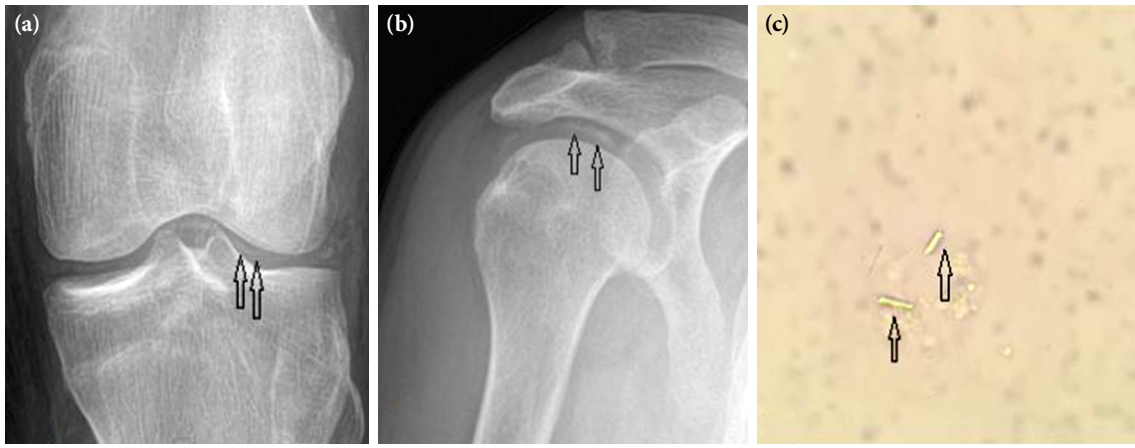

Figure 1. Chondrocalcinosis appearance in the **(a)** left knee and **(b)** right shoulder on a direct radiograph, and **(c)** calcium pyrophosphate deposition.

tests, respectively. Parathyroid ultrasonography of the patient revealed a 70×40×50 mm hypoechoic mass with polar vessels on color Doppler, extending to the mediastinum in the lower right was detected, which was thought to be a parathyroid adenoma. The patient was hospitalized for the treatment of hypercalcemia before the parathyroidectomy. Due to the high serum calcium level, the patient was hydrated with intravenous (IV) saline for four days, followed by loop diuretic therapy. Since the calcium level did not decrease despite the treatment, 4 mg of IV ZA was administered.

One day after ZA treatment, sudden severe pain, fever, swelling, and redness were detected in the right shoulder, right wrist, and left knee. Joint movements were severely limited and painful. The blood count was normal, and C-reactive protein increased by 158 mg/dL. Radiographs revealed chondrocalcinosis in the joint space of the right shoulder and left knee, as shown in Figures 1a and 1b. Joint fluid was examined microscopically by performing arthrocentesis on the left knee. Although few polymorphonuclear leukocytes and lymphocytes were observed, no microorganisms were found. Calcium pyrophosphate dihydrate crystals were detected in the sample, which was examined under polarized light as demonstrated in Figure 1c, and a diagnosis of PG was made. The patient was administered IV anakinra, an interleukin (IL)-1 antagonist, 2×100 mg for one day and colchicine 2×0.5 mg/day.Joint swelling and redness regressed beginning from the second day of treatment. After ZA treatment, the patient, whose calcium regressed to 10.2 mg/dL, was safely scheduled for parathyroidectomy. Pathological examination of a sample taken during parathyroidectomy revealed parathyroid adenoma. The calcium level decreased to 8.5 mg/dL after the operation. In the postoperative period, the patient's colchicine treatment was continued, the joint symptoms did not recur in the three-month follow-up.

DISCUSSION

To the best of our knowledge, this is the first case report of a PG attack after ZA treatment administered for PHP. The causes of acute PG attacks are not well understood; however, elderliness, osteoarthritis, PHP, and hemochromatosis are established as the main risk factors. In cases with PHP, PG has been defined in the postoperative period following a decrease in serum calcium levels.[4] Dissolution of CPPD by the inhibition of alkaline BP, rapid decrease in serum calcium, crystal formation in joints, and release of cytokines that cause a flu-like syndrome after IV BP infusion are the causes of PG development.[5] There are limited cases of PG triggered by BP treatment given for osteoporosis in the literature,[5] and three of such cases developed after ZA.[3,5] Influenza-like symptoms, such as fatigue, fever, arthralgia, and myalgia, have been frequently described after the administration of IV ZA. However, if there are significant signs of arthritis such as redness, warmth, swelling, as in our case, PG should be considered.[3] In PG, the wrist, ankle, knee, shoulder, and hip joints can be affected. In suspected cases, radiological imaging of the joint and microscopic examination of the joint fluid is diagnostic. Intracellular CPPD crystals with no or weak positive birefringence are observed in the joint

fluid. Calcium pyrophosphate dihydrate crystals lead to the stimulation of proinflammatory cytokines, particularly IL-1. Treatment is usually symptomatic as crystal formation cannot be prevented.[1,6] The most commonly used agents are nonsteroidal anti-inflammatory drugs, colchicine, and systemic corticosteroids, and there are no detailed studies for a treatment method. In a retrospective study, it has been determined that colchicine reduces the exacerbation of chronic PG.[7] Interleukin-1 plays an essential role in PG, both in the inflammatory response to crystals and the pathogenesis of articular cartilage damage.[8] In case-based studies evaluating the IL-1 antagonist anakinra, it is an effective treatment in acute attack.[9] Anakinra, which is used to treat PG, is regarded as a safe treatment in terms of side effects.[8] In our case, severe arthritis after ZA infusion was relieved after a single-day anakinra treatment, and the PG attack did not recur, with the colchicine treatment continuing in the postoperative period.

In conclusion, the patient's PHP, age, the significant increase in the calcium at admission, and the rapid decrease in the calcium level after ZA treatment are the conditions that predisposed the PG attack. Caution should be exercised when administering BP in patients with risk factors whose calcium level cannot be controlled by IV fluid and furosemide therapy, and PG, which rarely develops in cases with intense joint symptoms, should be considered.

Patient Consent for Publication: A written informed consent was obtained from the patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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