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LETTER

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Consecutive pseudogout attacks after repetitive granulocyte colony-stimulating factor administration for neutropenia

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Several risk factors account for pseudogout development including hemochromatosis, hypothyroidism, primary hyperparathyroidism, and hypomagnesemia.[1–4] Intra-articular injection of hyaluronic acid[5] and parenteral administration of granulocyte colony-stimulating factor (G-CSF) have precipitated acute attacks in two cases.[6,7] We report another case of G-CSF related pseudogout that re-presented at a lesser intensity every time G-CSF was administered to the patient in question.

A 74-year-old man developed marked swelling of left foot, ankle, and leg 5 days after receiving three doses of 300 µg of G-CSF subcutaneously for neutropenia ensued after his 4th course of chemotherapy (CEOP: cyclophosphamide, etoposide, vincristine, and prednisolone) for anaplastic large T-cell lymphoma stage IVB. On examination his left foot, ankle, and leg were red, swollen, and tender. He had had low-grade pyrexia at 37.5°C for 2 days. Deep vein thrombosis, early cellulites, and sepsis were excluded by Doppler ultrasound and skin and blood cultures. C-reactive protein was elevated at 50 mg/dl. Aspiration of the 1st metatarsophalangeal (MTP) joint did not yield fluid. X-rays of feet, ankles, knees, and wrists revealed minor osteoarthritic changes at the 1st MTP of the left foot but no chondrocalcinosis. Health checks before the diagnosis of lymphoma had revealed normal serum urate levels and the patient had never suffered episodes of gout/pseudogout in the past. At the time of lymphoma diagnosis a 24-h urinary urate excretion was normal as well as thyroid function and serum magnesium levels. The patient received allopurinol the day before starting each chemotherapy course and for 2 weeks thereafter. This episode was considered pseudogout and treated with colchicine 500 µg four times daily for 5 days, with remission of pain and swelling.

Four weeks after the 5th course of CEOP the patient was again neutropenic and to avoid treatment delay G-CSF was given as above. Pain and swelling developed at the 1st left MTP joint and ankle but to a lesser extent from the previous time, and required only 2 days of colchicine 500 µg four times a day to bring symptoms under control.

Polarizing microscopy of a drop of fluid aspirated from the left 1st MTP revealed birefringent calcium pyrophosphate dihydrate (CPPD) crystals, some free, some within neutrophils, but no urate crystals. Five weeks after the 6th course of CEOP the patient was again neutropenic, developed sepsis, and received i.v. antibiotics and G-CSF at the usual dosage to hasten improvement. Minor pain and swelling developed at the 1st left MTP and settled with naproxen 250 mg 6-hourly for 2 days.

Granulocyte colony-stimulating factor improves neutrophil production and function,[8] prevents neutropenia and febrile neutropenia in patients with lymphoma, and allows dose intensity of chemotherapy.[9] Accordingly, G-CSF was given repetitively in this patient despite the severe attack after the first administration but we did not use prophylactic colchicine as we were not foreseeing further attacks. So far, pseudogout following G-CSF has occurred in an 83-year-old woman with chronic renal failure and neutropenia unrelated to chemotherapy. In her case neutrophils were markedly increased in the synovial fluid from the affected knees.[6] In addition pseudogout reactivated in a 70-year-old woman who received G-CSF after chemotherapy for ovarian cancer.[7] As cells containing pyrophosphate crystals are present in uninflamed joints of patients with CPPD-related arthropathy indicating a balanced low-grade phagocytosis,[10] a phase of neutropenia followed by an influx of young and more active neutrophils in the joint may alter the balance precipitating an acute attack. A similar reasoning may apply to the case of gout developing after G-CSF in a stem cell donor.[11]

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Rheumatological side effects of G-CSF include arthralgia,[12] in one case repetitive,[13] flares of psoriatic arthritis,[14] systemic lupus erythematosus,[15] rheumatoid arthritis,[16] and worsening of back pain in ankylosing spondylitis.[17] As further cases of G-CSF-induced arthralgia/arthritis accrue in the medical literature, pseudogout should enter the differential of acute joint pain of elderly patients receiving G-CSF for whatever reason.[18] On the other hand our case shows that G-CSF need not be discontinued if clinically indicated.

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