Acute Gout Episodes During Treatment With Capecitabine: A Case Report

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CASE REPORT

A 56-year-old Caucasian man presented to the Emergency Room with rectal bleeding and was found by colonoscopy to have adenocarcinoma of the sigmoid colon. Comorbidities included mild hypertension (on propranolol), hyperlipidemia (on atorvastatin), and a 4-year history of well-controlled gout with only 3 past episodes of acute exacerbations (for which he was taking colchicine only during the acute flare-ups). A preoperative computed tomography (CT) scan showed a 3-cm segment of thickening within the sigmoid colon, but no evidence of metastatic disease (Figure 1). He underwent laparoscopic resection of the left colon, and the pathology confirmed a pT2a pN1 (1 of 5 lymph nodes positive) adenocarcinoma of the sigmoid colon with a normal mismatch repair profile. For adjuvant treatment, the patient declined intravenous chemotherapy and opted for 8 cycles of oral capecitabine at a dose of 1000 mg/m^2 of body surface, twice daily on days 1 through 14 every 21 days. The patient's laboratory parameters before starting capecitabine were within normal limits. Three days after the first cycle of capecitabine was initiated, the patient reported an acute episode of gouty arthritis in the right first metatarsophalangeal joint. He was treated with colchicine, which resulted in significant improvement in the erythema, swelling, and pain. He successfully completed the first cycle of capecitabine and subsequently proceeded to the second cycle. A couple of days later, he again developed acute arthritis in the right first metatarsophalangeal joint and required colchicine to relieve his symptoms. The patient denied any precipitating factors such as new medications or any dietary alterations, including meat, seafood, or alcohol intake. Serum uric acid levels were not obtained, as they may be difficult to interpret during an acute gout flare-up. Given the temporal relation to capecitabine, the gout episodes were attributed to its use. Despite the risk of further flare-ups with capecitabine, the patient decided to complete adjuvant chemotherapy, which at this writing is ongoing. Allopurinol was not initiated, because of concerns of decreased capecitabine activity.

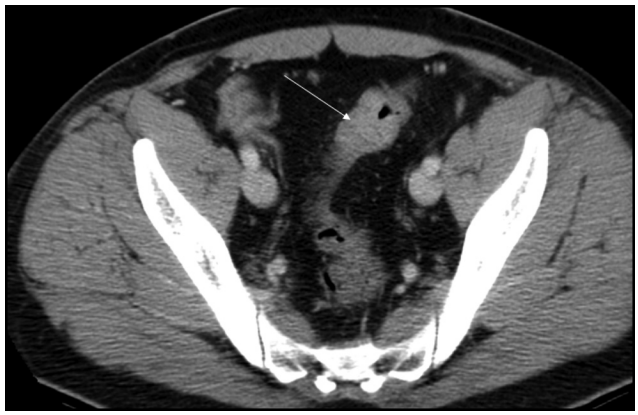

Figure 1. CT scan of the abdomen and pelvis showing a 3-cm segment of thickening within the sigmoid colon (arrow).

DISCUSSION

Capecitabine is an orally administered antimetabolite that is rapidly converted to 5-fluorouracil (5-FU) in tumor tissues. Like 5-FU, it acts by inhibiting thymidylate synthase as well as incorporating into RNA and DNA.[1] The FDA has approved its use in the treatment of adjuvant colorectal cancer (CRC), metastatic CRC, and metastatic breast cancer. Given its increased convenience for patients, capecitabine has largely replaced 5-FU in several other settings, including gastric, esophageal, pancreatic, and biliary cancers.

The toxicity profile of capecitabine is well known. The most common side effects (incidence >10%) include fatigue, diarrhea, abdominal pain, increased bilirubin, nausea, stomatitis, anorexia, bone marrow suppression, and hand–foot syndrome.[1–3] Less frequent adverse events (incidence, 5–10%) include chest pain, conjunctivitis, cough, rash, nail changes, and myalgia. The most recent product monograph for capecitabine was revised in 2011, and it does not describe gout flare-ups or increased uric acid production as sequelae of taking the drug.[1]

We report the case of a patient who began to have episodes of gout during the first and second cycles of adjuvant capecitabine for stage III colon cancer. Chemotherapy-induced gout has already been described in the context of other commonly used chemotherapeutic agents, such as paclitaxel and gemcitabine.[4,5] To the best of our knowledge, this is the first case report to describe an acute gout episode in association with capecitabine use in a patient with an underlying history of gout, but without any evidence of tumor lysis syndrome.

Gout (monosodium urate crystal deposition disease) is characterized by extracellular urate supersaturation and consequent precipitation in the articular cartilages, tendons, or surrounding tissues. Risk factors include hypertension, renal insufficiency, hypertriglyceridemia, hypercholesterolemia, hyperuricemia, diabetes, obesity, and dietary factors, including meat, seafood, sugar sweetened soft drinks, and consumption of foods high in fructose.[6] The prevalence of both gout and hyperuricemia has increased over the past 2 decades, which is most likely related to increasing frequencies of obesity and hypertension.[7]

Several pharmacologic agents can induce hyperuricemia, and sometimes gout, usually by interfering with the renal tubular excretion of urate, but also in some instances by increasing the formation

of uric acid. The most common agents that can promote flares of gout are diuretics (thiazide and loop diuretics), salicylates, pyrazinamide, ethambutol, nicotinic acid, cyclosporin, 2-ethylamino-1,3,4-thiadiazole, fructose, and some cytotoxic agents.[8] The present case suggests that capecitabine may also precipitate an episode in patients with well-controlled gout. Similar cases were recently reported with paclitaxel and gemcitabine.[4,5]

The mechanism for a gemcitabine-induced gout episode may be explained by the results of an in vitro study conducted in pancreatic cancer cell lines treated with gemcitabine. DNA damage induced by gemcitabine led to an increase in MICA/B expression, which correlated with a 3-fold increase in uric acid levels in the cell line lysates.[9] The authors concluded that DNA damage-induced MICA/B expression was mediated through increased uric acid production. However, further studies are needed to better characterize the role of chemotherapeutic agents in inducing episodes of gout.

Although chance alone may have led to the development of two episodes of gout (one in each of the first two cycles of capecitabine) in our patient, the present case illustrates a marked worsening that occurred in temporal association with capecitabine, indicating probable causation. No changes in dietary intake of purines or alcohol use were present during treatment with capecitabine, possibly implicating a direct effect of this chemotherapeutic agent on tissue crystal homoeostasis. In a patient with a long history of gout that was well controlled, it is unlikely that the patient would be intentionally exposed to other known precipitating factors of gout. No prophylactic treatment with allopurinol was offered to our patient because of concerns about interactions of allopurinol with 5-FU with possible decreased efficacy of 5-FU. The European Medicines Agency (EMA) suggests avoiding concomitant use of allopurinol with capecitabine.[10]

The current case is timely, as a recent study revealed a significantly higher overall incidence of cancer among patients with gout than in control subjects, even after adjustment for age and sex, indicating that gout may be associated with increased cancer risk.[11] If this relationship holds true, a growing number of patients with gout may develop a cancer that requires treatment with capecitabine. Considering that capecitabine may precipitate acute episodes of gout and that allopurinol should be avoided in these patients, management of gout in this setting can be challenging. Thus, health professionals should be aware of the possible association of these two disease entities.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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