

# CASE REPORT

## Mercaptopurine-Induced Fever: Hypersensitivity Reaction in a Patient with Acute Lymphoblastic Leukemia

Lei Jia Chen, M.D., Ginah Nightingale, Pharm.D., and Maria R. Baer, M.D.

The antimetabolite mercaptopurine is commonly used as part of treatment regimens for acute lymphoblastic leukemia and as treatment for inflammatory bowel diseases. Adverse effects associated with mercaptopurine include myelosuppression, hepatotoxicity, and hyperpigmentation. We describe a 36-year-old man with Philadelphia chromosome-negative pre-B-cell acute lymphoblastic leukemia who experienced a serious mercaptopurine-induced hypersensitivity reaction requiring prolonged hospitalization and extensive laboratory testing and imaging. He was treated with a multiagent chemotherapy regimen. Mercaptopurine 60 mg/m<sup>2</sup>/day orally was started as part of his third course of chemotherapy. On day 9 of mercaptopurine therapy, the patient developed persistent fevers, shaking chills, and rigors that persisted in the absence of documented infection, consistent with drug fever. All symptoms and signs resolved after discontinuation of mercaptopurine. Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship between the patient's development of fever and mercaptopurine therapy. Mercaptopurine-induced fever has been reported in patients with inflammatory bowel diseases, but this case report is the first, to our knowledge, in a patient with acute lymphoblastic leukemia. Health care professionals should be aware of the possible development of fever as a hypersensitivity reaction in patients with acute lymphoblastic leukemia treated with mercaptopurine.

**Key Words:** mercaptopurine, hypersensitivity, drug fever, acute lymphoblastic leukemia.

(*Pharmacotherapy* 2010;30(1):65e-67e)

Mercaptopurine, an antimetabolite, is commonly used as part of treatment regimens for acute lymphoblastic leukemia and as treatment for inflammatory bowel diseases. Adverse effects associated with mercaptopurine include myelosuppression, hepatotoxicity, and hyperpigmentation. Hypersensitivity reactions to mercap-

purine have also been reported, with fever as the most common manifestation, as well as shaking chills, rash, arthralgias, sinusitis, and sepsis-like syndrome,<sup>1</sup> and mercaptopurine-associated hypersensitivity has been confirmed by drug rechallenge.<sup>2</sup> However, all cases occurred in patients with inflammatory bowel diseases. We describe a patient with acute lymphoblastic leukemia who was treated with mercaptopurine and developed fever, chills, and rigors.

### Case Report

A 36-year-old Hispanic man with a history of diabetes mellitus, hypothyroidism, hypertension, and peripheral neuropathy was diagnosed with Philadelphia chromosome-negative pre-B-cell

---

From the Department of Medicine, School of Medicine (Drs. Chen and Baer), and the Greenebaum Cancer Center (Dr. Baer), University of Maryland, Baltimore, Maryland; and the Department of Pharmacy, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania (Dr. Nightingale).

For reprints, visit <http://www.atypon-link.com/PPI/loi/phco>. For questions or comments, contact Maria R. Baer, M.D., University of Maryland Greenebaum Cancer Center, 22 South Greene Street, Baltimore, MD 21201; e-mail: mbaer@umm.edu.

acute lymphoblastic leukemia. He was treated with a chemotherapy regimen derived from the Cancer and Leukemia Group B protocol 19802.<sup>3</sup> His induction therapy included cyclophosphamide, daunorubicin, dexamethasone, vincristine and L-asparaginase, and his first consolidation course included cyclophosphamide, cytarabine, dexamethasone, and intrathecal methotrexate. During his third cycle of chemotherapy, which was his second consolidation course, in addition to receiving intravenous and intrathecal methotrexate on day 1 and oral methotrexate on days 1 and 2, followed by leucovorin rescue, mercaptopurine 60 mg/m<sup>2</sup>/day orally was started on day 1. Vincristine was withheld because of peripheral neuropathy.

On day 9 of mercaptopurine therapy, the patient developed a fever, peaking at 102.4°F, accompanied by shaking chills, rigors, malaise, generalized body aches, nausea, vomiting, occasional shortness of breath, and rash. He was admitted to the hospital for evaluation. The patient's home drug therapy consisted of NPH insulin, levothyroxine, acyclovir, trimethoprim-sulfamethoxazole (TMP-SMX) for *Pneumocystis carinii* pneumonia prophylaxis, senna, docusate, calcium acetate, immediate- and extended-release oxycodone, gabapentin, ondansetron as needed for nausea, and lactulose as needed for constipation. He had no known drug allergies.

Physical examination was remarkable for multiple nonpruritic, nontender petechial lesions on both forearms, mostly located around hair follicles. Laboratory results revealed a white blood cell count of  $11.5 \times 10^3/\text{mm}^3$  (normal range  $4.5\text{--}11.0 \times 10^3/\text{mm}^3$ ) with an absolute neutrophil count of 9660 cells/mm<sup>3</sup> and platelet count of  $33 \times 10^3/\text{mm}^3$  ( $153\text{--}367 \times 10^3/\text{mm}^3$ ). His serum methotrexate level was less than 0.02 μmol/L. Blood and urine cultures were sterile. Computerized tomography of the chest, abdomen, and pelvis revealed no foci of infection. He was treated empirically with intravenous antimicrobial agents (piperacillin-tazobactam, vancomycin, and micafungin); however, he continued to experience fevers as high as 103°F and rigors. Influenza was unlikely since this event occurred during September.

Biopsy of a skin lesion on hospital day 2 demonstrated acute pustular folliculitis. Given the patient's persistent fevers despite sterile cultures and empiric antimicrobial therapies, the possibility of drug fever was considered. Thus his TMP-SMX was discontinued on day 3, but the fever persisted. Mercaptopurine was then

discontinued on day 5, and the patient's symptoms and fever resolved completely.

Three weeks later, TMP-SMX was restarted without incident, and methotrexate was again administered intravenously, intrathecally, and orally as part of subsequent chemotherapy courses, also without incident. Rechallenge with mercaptopurine was not attempted.

## Discussion

To our knowledge, fever attributed to mercaptopurine used in the management of acute lymphoblastic leukemia has not been documented in the literature. However, mercaptopurine-induced fever and other hypersensitivity reactions, including arthralgias, rash, and sinusitis, have been described in patients receiving the drug for the management of inflammatory bowel diseases, especially Crohn's disease.<sup>1</sup> The mechanism for mercaptopurine-induced fever has been postulated to be allergic in nature. In reports of mercaptopurine-induced fever in patients with inflammatory bowel diseases, the patients developed new-onset unexplained fevers, arthralgias, and malaise within the first month after initiation of therapy, and their symptoms disappeared within a week after drug discontinuation.<sup>1,2,4</sup>

Our patient's course appears typical of a hypersensitivity-type reaction to mercaptopurine treatment. His symptoms began 9 days after the start of therapy and were not attributable to an acute infectious process. He defervesced after discontinuation of the drug. He was not rechallenged to confirm this hypersensitivity reaction. However, attempted desensitization to mercaptopurine in patients with inflammatory bowel diseases has been reported in the literature.<sup>1,5</sup>

The probability that an adverse drug reaction is the cause of a problematic clinical event is usually hard to confirm. We assessed the relationship between our patient's fever and mercaptopurine using the Naranjo adverse drug reaction probability scale, a scoring system that assigns an adverse drug reaction to a probability category of definite, probable, possible, or doubtful.<sup>6</sup> Using this scale, our patient's mercaptopurine-induced fever represented a probable causal adverse reaction (score of 6).

Although mercaptopurine-induced fever has been well documented as a hypersensitivity reaction in patients with inflammatory bowel diseases, this case report is the first, to our knowledge, in a patient receiving

mercaptopurine as part of a treatment regimen for acute lymphoblastic leukemia. Compared with patients with inflammatory bowel diseases, patients with acute lymphoblastic leukemia are generally more immunocompromised from their disease and from the effects of chemotherapy. In addition, high-dose corticosteroids are used in many acute lymphoblastic leukemia protocols. Patients with acute lymphoblastic leukemia are therefore probably less likely to mount and manifest allergic reactions, providing an explanation for why treatment-related hypersensitivities are less commonly seen and/or reported in this patient population.

Patients with acute lymphoblastic leukemia often present with fevers and flu-like symptoms after undergoing a course of chemotherapy; however, these symptoms are usually caused by infection. Health care providers should also be aware of hypersensitivity-type adverse reactions related to mercaptopurine, and these should be included in the differential diagnosis of fever, chills, and rigors in patients with acute lymphoblastic leukemia receiving mercaptopurine as part of their treatment regimen.

### Conclusion

Mercaptopurine is commonly used as part of

treatment regimens for acute lymphoblastic leukemia. Our patient with acute lymphoblastic leukemia experienced a serious mercaptopurine-induced hypersensitivity reaction consisting of fever, shaking chills, and rigors. Health care professionals and patients should be aware of the possible development of hypersensitivity reactions in this patient population treated with mercaptopurine.

### References

1. Korelitz BI, Zlatanich J, Goel F, Fuller S. Allergic reactions to 6-mercaptopurine during treatment of inflammatory bowel disease. *J Clin Gastroenterol* 1999;28:341-4.
2. Lobel EZ, Korelitz BI, Vakher K, Panagopoulos G. Prolonged remission of severe Crohn's disease after fever and leucopenia caused by 6-mercaptopurine. *Dig Dis Sci* 2004;49:336-8.
3. Stock W, Johnson J, Yu D, et al. Daunorubicin dose intensification during treatment of adult acute lymphoblastic leukemia (ALL): final results from cancer and leukemia group B study 19802 [abstract]. *Blood* (American Society of Hematology annual meeting abstracts) 2005 106:1833.
4. Rehr EL, Swanson KA, Kern JA. Mercaptopurine-induced fever in a patient with Crohn's Disease. *Ann Pharmacother* 1992;26:907-9.
5. Mutinga M, Castells M, Horan R, Farraye F. Successful desensitization to 6-mercaptopurine in a patient with Crohn's disease. *Am J Gastroenterol* 2000;95:1383-4.
6. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45.