

Azathioprine Hypersensitivity Presenting as Neutrophilic Dermatositis and Erythema Nodosum

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PRACTICE POINTS

- Azathioprine is a well-known immunosuppressant for renal transplant recipients and inflammatory bowel disease with several off-label uses in dermatology including immunobullous dermatoses, neutrophilic dermatoses, and autoimmune connective tissue diseases.
- Azathioprine hypersensitivity is rare and can present with systemic symptoms of fever and a neutrophilic dermatosis, which is usually self-limited but can progress to an anaphylactoid reaction with multiorgan failure.
- If a more mild hypersensitivity reaction is appreciated, then a rechallenge is not recommended and should be avoided.

To the Editor:

Azathioprine (AZA) hypersensitivity is an immunologically mediated reaction that presents within 1 to 4 weeks of drug initiation.¹ Its cutaneous manifestations include Sweet syndrome, erythema nodosum (EN), and acute generalized exanthematous pustulosis, with 88% of cases presenting as neutrophilic dermatoses.² Confirmation with cutaneous biopsy and cessation of medication is essential to prevent life-threatening anaphylactoid reactions.

A 58-year-old man with a history of Crohn disease was admitted with high fevers ($>38.9^{\circ}\text{C}$); abdominal pain; diarrhea; and a nonpruritic “pimple-like” rash on the face, chest, and back with a tender nodule on the right leg of 5 days’ duration. Eight days prior to admission, he had started AZA for treatment

of Crohn disease. In the hospital he received intravenous metronidazole for a presumed bowel infection; however, the lesions and symptoms did not resolve. Other medical history included psoriatic arthritis for which he was taking oral prednisone 50 mg daily; prednisone was continued during hospitalization.

Physical examination showed that the patient was alert and well appearing. On the face, upper chest and back (Figure 1), shoulders, and knees



Figure 1. Pustule on the back.

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were fewer than 20 sparsely distributed, nontender, 3- to 4-mm pustules. The patient's scalp, lower back, abdomen, arms, and feet were spared. There also was a solitary 3.5-cm, tender, erythematous nodule on the right lower leg (Figure 2). Blood tests revealed leukocytosis ($15,000/\text{mm}^3$ [reference range, $4300\text{--}10,300/\text{mm}^3$]) with neutrophilia (90%) and an elevated C-reactive protein level of 173 mg/L (reference range, $<10\text{ mg/L}$). Liver function tests were normal. Thiopurine methyltransferase (TPMT) was on the low end of the reference range. Tissue culture of a shoulder pustule grew only *Staphylococcus non-aureus*. Blood cultures were negative. A 4-mm punch biopsy specimen from the right leg nodule revealed septal panniculitis with neutrophilic and granulomatous infiltrate consistent with EN.

A clinical diagnosis of AZA hypersensitivity was made. Antibiotics and AZA were discontinued and the patient's lesions resolved within 6 days. Medication rechallenge was not attempted and the patient is now managed with infliximab.

Azathioprine is a well-known and commonly used drug for inflammatory bowel diseases, rheumatoid arthritis, and prevention of transplant rejection.



Figure 2. Erythematous nodule on the right lower leg.

Hypersensitivity is a lesser-known complication of AZA therapy, with most reactions occurring within 4 weeks of treatment initiation. A PubMed search of articles indexed for MEDLINE using the search terms *azathioprine* and *hypersensitivity* found only 67 documented cases of AZA hypersensitivity between 1986 and 2009.² Common findings include fever, malaise, arthralgia, nausea, vomiting, diarrhea, headache, and neutrophilic dermatoses.

Previously reported cases of AZA hypersensitivity with cutaneous manifestations include Sweet syndrome (17.9%), small vessel vasculitis (10.4%), EN (4.4%), acute generalized exanthematous pustulosis (4.4%), and nonspecific cutaneous findings (11.9%).² One other case reported AZA hypersensitivity presenting as EN with a neutrophilic pustular dermatosis.³ Although Sweet syndrome-like lesions, EN, and acute generalized exanthematous pustulosis have been reported in the context of inflammatory bowel disease, in this case the appearance of these symptoms within 1 week of AZA initiation and resolution after AZA discontinuation is highly suggestive of AZA hypersensitivity. Also, several reports have documented rapid (within a few hours) recurrence of symptoms on rechallenge with AZA.⁴⁻⁶ Moreover, cases of cutaneous AZA hypersensitivity reactions in patients with no history of inflammatory bowel diseases have been reported.⁶⁻⁸

As in this case, cutaneous AZA hypersensitivity can occur even in the setting of normal TPMT levels, suggesting that this phenomenon is a dose-independent reaction.² Abnormal metabolism of AZA does not appear to be related to previously reported neutrophilic pustular dermatosis^{3,4} or EN.⁴ Although the mechanism of hypersensitivity is unclear, there is a report of a patient who developed AZA hypersensitivity but was able to tolerate 6-mercaptopurine, a metabolite of AZA. The authors suggested that the imidazole component of AZA might be responsible for hypersensitivity reactions.⁹

The differential diagnosis of a patient with these findings includes infectious, rheumatologic, neurologic, or autoimmune diseases, as well as septic shock. Hence, negative cultures and a failure to respond to antibiotics make infection less likely. An appropriate time course of AZA initiation, the development of rash, and a cutaneous biopsy can lead to prompt diagnosis and cessation of AZA.

Once AZA hypersensitivity is suspected, the drug should be discontinued and the reaction should resolve within 2 to 3 days² and the skin lesions within 5 to 6 days.^{2,10} Medication rechallenge is contraindicated because AZA rarely has been associated with shock syndrome and hypotension.¹¹⁻¹⁹

Azathioprine hypersensitivity is a serious yet still underrecognized condition in the dermatologic community. In our case, symptoms appeared rapidly and resolved quickly after AZA was discontinued. Azathioprine-induced neutrophilic dermatosis presenting with EN should be recognized as a potential dermatologic manifestation of AZA hypersensitivity, which is a dose-dependent reaction even with normal TPMT levels. Rechallenge with AZA is not recommended due to the risk of a life-threatening anaphylactoid reaction.

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