The cutaneous and systemic manifestations of azathioprine hypersensitivity syndrome

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Background: Azathioprine (AZA) hypersensitivity syndrome is a rare side effect that typically occurs early in the initiation of therapy and may include a cutaneous eruption. It is often under-recognized because it mimics infection or disease exacerbation. Until recently, the cutaneous findings associated with AZA hypersensitivity have been reported using nonspecific, descriptive terms without a supportive diagnostic biopsy.

Objective: To characterize the cutaneous and histologic findings associated with AZA hypersensitivity syndrome.

Methods: We conducted a retrospective analysis of two cases of AZA hypersensitivity syndrome and describe the cutaneous manifestations and histological findings of each case. A review of the English literature for cases of AZA hypersensitivity or allergic or adverse reactions associated with AZA was performed.

Results: Sixty-seven cases of AZA hypersensitivity were reviewed; 49% (33/67) had cutaneous manifestations. Of those cases presenting with cutaneous findings, 76% (25/33) had biopsy results or clinical features consistent with a neutrophilic dermatosis, whereas the other 24% (8/33) were reported as a nonspecific cutaneous eruption.

Limitations: Only case reports in which the skin findings could be classified were reviewed.

Conclusions: The predominant cutaneous reaction reported in the literature and observed in the present case series is a neutrophilic dermatosis. Hypersensitivity to AZA can manifest along a wide clinical spectrum from local neutrophilic disease to a systemic syndrome. Skin findings may be an important early clue to the diagnosis of AZA hypersensitivity and aid in prompt recognition and treatment of this potentially life-threatening adverse drug effect. (J Am Acad Dermatol 2011;65:184-91.)

Key words: adverse reaction; azathioprine; azathioprine hypersensitivity syndrome; side effects; Sweet's syndrome.

INTRODUCTION

Azathioprine (AZA) (Imuran, Azasan), the nitroimidazole of 6-mercaptopurine (6-MP), was first used in 1961 as an immunosuppressant for kidney transplantation. Since then it has become an effective corticosteroid-sparing agent in a variety of autoimmune inflammatory diseases to include rheumatoid arthritis, systemic lupus erythematosus, vasculitis, inflammatory bowel disease (IBD), bullous

Abbreviations used:

AZA:	azathioprine
IBD:	inflammatory bowel disease
6-MP:	6-mercaptopurine
MS:	multiple sclerosis
SS:	Sweet's syndrome
TPMT:	thiopurine methyltransferase

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pemphigoid, pemphigus, and others. Dose-dependent toxic side effects (myelosuppression, gastrointestinal side effects, hepatotoxicity) have been well recognized. Less well-characterized is AZA hypersensitivity syndrome and its cutaneous manifestations.

We present two cases of the skin manifestations of AZA hypersensitivity syndrome and review the literature to better characterize the skin findings in this underrecognized but important entity.

CAPSULE SUMMARY

- Azathioprine (AZA) hypersensitivity syndrome is a dose-independent allergic reaction that occurs during the first 4 weeks of therapy.
- Systemic symptoms most commonly include fever, malaise, arthralgias, myalgias, nausea, vomiting, diarrhea, and a cutaneous eruption.
- The most commonly reported cutaneous manifestations are Sweet's syndrome, erythema nodosum, acute generalized exanthematous pustulosis, leukocytoclastic vasculitis or non-specific eruption.
- Symptoms and cutaneous findings improve within 5 days of discontinuing AZA.
- Rechallenge is contraindicated because of the potential for life-threatening shock syndrome.

MATERIAL AND METHODS

From July 2007 through March 2009, the Department of Dermatology at Wilford Hall Medical Center (Lackland AFB, Texas) was consulted on two cases of a "rash" thought to be caused by AZA. The clinical records and photographs of these cases were reviewed. A thorough review of the English-language literature was performed comparing the results of previous case reports with our two patients. The PubMed database was searched using the following terms: azathioprine, hypersensitivity, allergic reaction, rash, Sweet's syndrome, and toxicity. Several additional sources were also obtained from the reference section of other articles. Specific features of each case were examined and compared to analyze for any common features with respect to underlying disease, presentation, treatment, and resolution of AZA hypersensitivity. Particular attention was focused on cutaneous findings at presentation.

RESULTS

Case 1

A 39-year-old Caucasian woman with Crohn's disease presented with vomiting, diarrhea, fever, and arthralgias 4 weeks after starting AZA therapy. Before she started AZA, her thiopurine methyltransferase (TPMT) levels were in the normal range. Her AZA dose at presentation was 100 mg daily. She was also taking prednisone, 30 mg daily. Her AZA was discontinued, and she was admitted to the hospital for work-up and treatment of sepsis and exacerbation of Crohn's disease. Her white blood cell count on admission was elevated at 14,000 (4.3-10.0 $\times 10^3$) with 84% neutrophils (36%-66%). Three days later a mildly pruritic, generalized papulopustular eruption developed, which was most prominent on her lower legs and flexor forearms (at sites of shaving and venipuncture). Individual lesions were 5- to 10-mm firm, indurated, erythematous papules and nodules with a central pustule or vesicle (Fig 1). Lesions demonstrated pathergy and spared only the palms and soles. The patient had several painless oral mucosal and conjunctival erosions but no genital involvement. A shave biopsy specimen taken from her upper back showed a dermal and perivascular diffuse infiltrate of neutrophils, lymphocytes, and histiocytes with focal leukocytoclasis. Her systemic symptoms and eruption resolved 5 days after the AZA had been discontinued. Her work-up for sepsis yielded negative findings and other laboratory findings were unremarkable. There was no evidence of eosinophilia or liver dysfunction.

Several weeks later the patient underwent rechallenge with a 25-mg dose of AZA. Within 24 hours, she developed arthralgias, malaise, and cutaneous lesions. The skin lesions again erupted on the forearms and distal legs with an appearance similar to that of the initial lesions. The AZA was discontinued, and the patient was diagnosed with AZA hypersensitivity syndrome.

Case 2

A 33-year-old obese Caucasian man with systemic lupus erythematosus complicated by a recurrence of proliferative glomerulonephritis was admitted to the hospital for fever, arthralgias, diarrhea, and dark urine 2 weeks after starting AZA. His TPMT level was in the normal range. On admission, he was taking AZA, 300 mg daily, and prednisone, 35 mg daily. The AZA was discontinued and a work-up for sepsis was initiated. His serum creatinine was elevated from a baseline of 1.4 to 2.7 mg/dL (normal range 0.7-1.5 mg/dL). He also had elevated alanine aminotransferase and aspartate aminotransferase at 89 U/L (normal range, 3-55 U/L) and 113 U/L (4-50 U/L), respectively. Although he had neutrophilia (83%), his WBC and eosinophils were within normal