

REVIEW

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 10.1016/j.jaad.2010.04.041.)

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 under-recognized but important entity.

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 ($4.3\text{--}10.0 \times 10^3$) 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 leukocytoclasia. 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

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.



Fig 1. Patient 1. Firm, indurated, erythematous papules and nodules, 5 to 10 mm, with central pustules and vesicles.



Fig 2. Patient 2. Erythematous pustules on right side of face.



Fig 3. Patient 2. Indurated papules on palm of left hand.

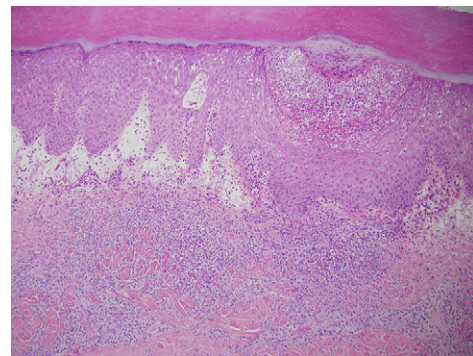


Fig 4. Photomicrograph shows papillary dermal edema with dense infiltrate of neutrophils without evidence of vasculitis. (Hematoxylin-eosin stain; original magnification: $\times 20$.)

range. On his second day of hospitalization, he developed an indurated papulopustular eruption on his face, neck, elbows, and hands (Figs 2 and 3). A biopsy specimen showed marked papillary dermal edema with a dense infiltrate of neutrophils but no evidence of vasculitis (Fig 4). Four days after admission, the patient's systemic symptoms improved and his rash resolved. His work-up for sepsis was negative. Other laboratory findings, including complement levels and dsDNA, were unchanged compared with baseline. On hospital discharge, his serum creatinine remained elevated at 2.1 mg/dL. He was not re-challenged with AZA as the initial presentation was consistent with AZA hypersensitivity syndrome.

Review of the literature

Including the present case series of two, 67 cases of AZA hypersensitivity from 1986 through 2009 were reviewed (Table I).¹⁻³⁶ Of these cases, 49%

(33/67) had cutaneous manifestations. Of those presenting with cutaneous findings, 76% (25/33) had biopsy or clinical features consistent with a neutrophilic dermatosis, whereas the other 24% (8/33) were reported as a non-specific cutaneous eruption. Most of the cases reported as neutrophilic dermatoses were from recent case reports in which a biopsy had been performed.^{1-6,9,14} Several earlier case reports had more detailed descriptions of skin findings suggestive of neutrophilic dermatoses, but were not biopsy confirmed.¹⁵⁻¹⁷ If the clinical cases suggestive of neutrophilic dermatoses were included with confirmed cases, then 88% (29/33) of patients presenting with cutaneous findings would have a neutrophilic dermatosis. Several patients in these case reports have skin findings very similar in description to the papulopustular lesions seen in our patients.^{16,17}

Of the patients with a biopsy-proven neutrophilic dermatosis, 64% (16/25) had IBD (Crohn's disease, ulcerative colitis). Many of these cases met the diagnostic criteria for drug-induced Sweet's syndrome, as described by Walker and Cohen.³⁷

Other features of AZA hypersensitivity with respect to onset, systemic symptoms, TPMT activity,

Table I. Reported cases of azathioprine hypersensitivity reactions

Cutaneous findings	No. of patients	Reference Nos.	Time of onset after starting AZA (days)	Underlying disease	Recurrence of side effects with rechallenge	TPMT level	Concurrent use of steroids	Elevated WBC	Sex (# of patients) average age
Sweet's syndrome	12	1-8	5-28	Crohn's disease UC SLE Myasthenia gravis	7/12	5/12 — N 7/12 — NR	10/12	10/12	M(9)/F(3) 46
Erythema nodosum	3	9	8-14	Crohn's disease	2/3	3/3 — N	3/3	3/3	M(1)/F(2) 47
Small-vessel vasculitis	7	1-13	8-46	RA Crohn's disease Wegener's Renal transplant	4/7	1/7 — N 6/7 — NR	1/7	3/7	M(2)/F(5) 56
Acute generalized exanthematous pustulosis	3	9, 14	16-18	Crohn's disease Urticaria Pemphigus foliaceus	1/3	2/3 — N 1/3 — NR	3/3	3/3	M(2)/F(1) 37
Nonspecific	8	10, 15-21	5-20	MCTD Demyelinating disease Psoriatic arthritis RA Vasculitis Wegener's MS	5/8	1/8 — N 7/8 — NR	4/8	3/8	M(4)/F(4) 47
None	34	21-36	3-25	MS Organ transplant Crohn's disease Vasculitis* Urticaria Other [†]	15/34	1/34 — N 33/34 — NR	5/34	7/34	M(16)/F(5) NR (18) 47
Total	67		3-46	IBD (18) Neurologic (15) Connective tissue (14) Transplant (6) Vasculitis (5) Other (9)	34/67	13/67 — N 54/67 — NR	26/67	29/67	M(34)/F(20) NR (13) 47

AZA, Azathioprine; BP, bullous pemphigoid; F, female; IBD, inflammatory bowel disease; LCV, leukocytoclastic vasculitis; M, male; MCTD, mixed connective tissue disease; MS, multiple sclerosis; N, normal; NR, not reported; PAN, polyarteritis nodosa; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TPMT, thiopurine methyltransferase; UC, ulcerative colitis; WBC, white blood cell count.

*Vasculitis includes Wegener granulomatosis, LCV, and PAN.

[†]Other includes myasthenia gravis, systemic lupus erythematosus, cryoglobulinemia, rheumatoid arthritis, bullous pemphigoid, kidney disease, and arthritis.

laboratory findings, and concurrent steroid use were similar to those described in other case reports and reviews.^{10,15,22} The age and sex of patients did not affect the presentation or risk for AZA hypersensitivity. The majority of patients developed AZA hypersensitivity within the first 4 weeks of therapy. Patients with certain diagnoses (IBD and neurologic disorders) comprised 49% (33/67) of patients. There were only 3 patients (4%) in our series who had dermatologic diagnoses (psoriasis, bullous pemphigoid, and pemphigus). Concurrent use of corticosteroids at presentation was common, occurring in 39% of patients (26/67).

DISCUSSION

AZA is an effective and well-tolerated immunosuppressive agent. While approved by the Food and Drug Administration in the United States for severe rheumatoid arthritis and prevention of rejection in renal transplantation, it has numerous off-label uses. AZA continues to be a useful steroid-sparing medication in the treatment of many systemic autoimmune conditions such as IBD, systemic lupus erythematosus, myasthenia gravis, and others.³⁸ The most common dermatologic conditions treated with AZA are pemphigoid and pemphigus and, less commonly, atopic dermatitis, psoriasis, and chronic actinic dermatitis.³⁸

AZA is a purine analog that inhibits both RNA and DNA synthesis. It was originally synthesized from 6-MP by the addition of an imidazole ring. This imidazole ring improved efficacy and reduced the rapid catabolism of 6-MP. The initial metabolism of AZA results in two products: 6-MP and the imidazole derivative (methylnitroimidazole moiety).³⁸ The metabolism of 6-MP by hypoxanthine phosphoribosyl transferase results in 6-thioguanine nucleotides, which are responsible for drug action and dose-dependent side effects.³⁸ Further metabolism of 6-MP by TPMT and xanthine oxidase yields inactive metabolites.

The overall incidence of side effects from use of AZA necessitating drug withdrawal ranges from 10% to 15%.²³ Cases of a true hypersensitivity syndrome to AZA have been reported in approximately 2% of patients taking the drug.²⁴ Dose-dependent side effects of AZA, such as myelosuppression, infection, nausea, vomiting, and hepatotoxicity, are well characterized and can occur at any time during drug-therapy. The incidence of dose-dependent side effects ranges from 4% to 27%.¹⁰ These side effects are not allergic in nature, but are the result of direct toxicity from 6-thioguanine nucleotides and can be related to low TPMT activity or inhibition of xanthine oxidase.³⁹

AZA hypersensitivity reactions may be more common than is generally accepted. In 2001, Craner and Zajicek²⁵ reported AZA hypersensitivity in 14 of 21 patients with multiple sclerosis (MS). Bajaj et al⁴⁰ reported early adverse events in 42 of 143 patients with Crohn's disease. While AZA hypersensitivity was not specifically mentioned in this series, 8 of 42 of patients (19%) had symptoms suggestive of AZA hypersensitivity. Patients with IBD or neurological disease comprised 49% of patients in our literature review (see Table I). This evidence suggests that patients with IBD or MS may be at higher risk for AZA hypersensitivity.^{25,40} The reasons for this are unclear but possibly involve a genetic polymorphism that predisposes persons to AZA hypersensitivity.⁴¹ This may also be due to the fact that more IBD and MS patients are treated with AZA, under-recognition of the disease, or reporting bias by certain specialties.

Hypersensitivity reactions to AZA are dose independent and tend to occur during the first 4 weeks of therapy. Unlike dose-dependent side effects, these reactions occur regardless of TPMT levels. Abnormal metabolism of AZA does not appear to predict erythema nodosum,⁹ Sweet's syndrome,⁶ or other manifestations of disease. All cases reviewed showed either a normal TPMT level, as in our cases, or did not report the TPMT level (see Table I). While the 6-MP moiety of AZA and its metabolites are thought to be responsible for most side effects, the imidazole component could be responsible for hypersensitivity reactions. This process may involve the generation of a hapten when the imidazole binds certain proteins.⁴² Supporting this theory are several case reports of patients with AZA hypersensitivity who were able to tolerate subsequent administration of 6-MP.^{26,43} However, there are also case reports of similar reactions to 6-MP following both initial administration and rechallenge with 6-MP after AZA hypersensitivity.^{9,27} Therefore, the exact mechanism is still unclear. Genetic polymorphisms in the inositol triphosphate pyrophosphatase gene may also be associated with AZA hypersensitivity.⁴⁴

Hypersensitivity reactions are thought to represent a type III or IV hypersensitivity response, whereas a true drug allergy reaction is a type I, IgE-mediated response. Although uncommon, AZA has been associated with a shock syndrome manifested by profound hypotension.^{14,15,17,18,22,28,45} For this reason, once hypersensitivity to the drug has been identified, re-challenge is contraindicated. Our first patient was re-challenged before the diagnosis was appreciated.

The systemic symptoms of AZA hypersensitivity most commonly include fever, malaise, arthralgias,

Table II. Systemic manifestations of AZA hypersensitivity

Onset 1-4 weeks after initiation of therapy
Fever, chills
Nausea, vomiting, diarrhea
Arthralgias, myalgias
Cutaneous eruption (neutrophilic dermatosis)
Leukocytosis
Other organ involvement (liver/renal dysfunction)
Shock (rare)

myalgias, nausea, vomiting, diarrhea, and rash (Table II). Occasionally, liver or kidney dysfunction, hypotension, and shock may be present. The skin findings have not been well categorized until this literature review.

Skin manifestations have historically been described as macular-papular, vesicular, or pustular.^{2,15-17,19} In addition, there are reports of purpura, urticaria, and erythema nodosum.^{11,12,22} More recently, there are several reports of Sweet's syndrome (SS) associated with AZA hypersensitivity.¹⁻⁷ Our first patient similarly displayed Sweet's syndrome—like lesions, while our second patient met the diagnostic criteria for drug-induced SS. In the past, cases lacked cutaneous findings or included descriptions of nonspecific cutaneous eruptions without a biopsy. More recently, as in our cases, there seems to be a predominance of cutaneous eruptions with features of neutrophilic dermatoses (Tables I and III). Furthermore, a hypersensitivity reaction with cutaneous findings may be more likely in patients with underlying IBD, as 48% of patients with skin manifestations carried the diagnosis of IBD. Despite the wide use of AZA in dermatology, there are very few case reports of hypersensitivity in patients treated for dermatologic conditions (eg, immunobullous disease, atopic dermatitis, psoriasis, photodermatoses).³⁸

Of particular interest are patients who present with apparent drug-induced SS and the dilemma of whether to diagnose drug-induced SS or AZA hypersensitivity presenting as SS in these patients. SS associated with autoimmune conditions has been reported.⁴⁶ SS associated with IBD does not occur commonly and classically occurs during a disease flare.^{3,5,13} On the basis of our experience and patients described in the literature, we believe that SS in the presence of AZA initiation is best classified as AZA hypersensitivity rather than drug-induced SS. In several case reports, AZA hypersensitivity was completely dismissed as an etiologic factor, and SS was attributed to other causes.^{5,7,8}

Table III. Cutaneous findings in AZA hypersensitivity

Erythema nodosum
Sweet's syndrome
Small-vessel vasculitis (LCV)
Acute generalized exanthematous pustulosis
Nonspecific rash
Urticaria
Pustules
Purpura
Macular-papular

LCV, Leukocytoclastic vasculitis.

More than 50% of the time, hypersensitivity reactions to AZA occur with systemic symptoms identical to those of SS (fever, leukocytosis, malaise, arthralgias), but no cutaneous manifestations or cutaneous findings other than SS are described. There are cases of cutaneous eruptions that may resemble SS, as in our case, but are not characteristic or do not meet the diagnostic criteria outlined by Walker and Cohen.³⁷ For example, our first patient had lesions that looked like SS and demonstrated pathergy, yet they were non-tender and lacked histologic features classic for the diagnosis. While there was a neutrophilic infiltrate, there were also abundant lymphocytes, histiocytes, and eosinophils as well as minimal dermal edema.

Additionally, AZA hypersensitivity appears to occur independent of corticosteroid use. Similar to our findings (see Table I), Fields et al¹⁵ found that 39% of patients (19/49) who were diagnosed with AZA hypersensitivity were taking corticosteroids at presentation. This is atypical for SS since corticosteroids are the treatment of choice.

Other atypical features include the location of lesions and preponderance of gastrointestinal symptoms. While lesions of SS occur most commonly on the head, neck, and trunk, the lesions tend to favor the lower extremities in patients with AZA hypersensitivity. In our study, 58% (7/12) of patients presented with gastrointestinal symptoms (nausea, vomiting, diarrhea), which is uncommon for SS. The more accurate characterization of this disease process may improve future recognition and understanding of the mechanisms behind AZA hypersensitivity.

The pathophysiology of drug-induced SS has not been completely elucidated. It may involve an underlying hypersensitivity reaction.⁴⁶ The same may be true of non-drug-induced SS representing a hypersensitivity to an infection or malignancy. This may, in part, explain the increased frequency of AZA hypersensitivity presenting as SS. Another etiologic factor in drug-induced SS is a quick spike in

leukocyte number and activity as is seen with granulocyte colony-stimulating factor. The relative neutrophilia caused by corticosteroids may contribute to the development of SS caused by AZA hypersensitivity in a similar fashion.

On initial presentation, most cases of AZA hypersensitivity are confused with infection or exacerbation of an underlying condition, as was the case in our patients. The concern for infection is a priority, especially with fever and leukocytosis in a patient receiving immunosuppressive therapy. However, work-up for infection generally yields negative findings and screening serologies for disease activity, such as complement levels or double-stranded DNA (dsDNA) antibodies, in SLE tend to be normal.^{10,29,30} Additionally, in our patient dsDNA, C3, and C4 remained negative. Under these circumstances, the diagnosis of AZA hypersensitivity syndrome is implicated rather than a flare of the underlying disease.

AZA hypersensitivity is often recognized upon resuming or re-challenge with AZA where symptoms recur within hours of the first dose. The presence of new skin findings in the absence of infection or disease flare should alert the clinician to the possibility of AZA hypersensitivity. Most cases of AZA hypersensitivity resolve within 2 to 3 days after withdrawal of the medication and may not necessitate an increase in corticosteroid dose.

Limitations of this study are indicated by a small case series and a retrospective review of the literature. Despite a thorough review of the literature, it is possible that not all cases of AZA hypersensitivity are included in this review. In previous case reports, some data were not reported, such as concurrent use of steroids, TPMT level, or even age and sex of patients. In addition, earlier case reports included only descriptions of cutaneous findings that were often nonspecific or not supported by skin biopsy findings. Underreporting or lack of recognition of this entity may also bias results.

In conclusion, we report two cases of AZA hypersensitivity with cutaneous manifestations of neutrophilic dermatoses. Our review of the literature indicated that the most common cutaneous manifestation of AZA hypersensitivity is a neutrophilic dermatosis. Biopsy findings were consistent with SS, erythema nodosum, small-vessel vasculitis, and acute generalized exanthematous pustulosis. AZA hypersensitivity syndrome tends to occur within 4 weeks after initiation of therapy and is unrelated to the gender or age of the patient or TPMT levels, but may be related to the underlying disease. Recognizing AZA hypersensitivity syndrome will lead to early discontinuation of the drug, simplify

the medical evaluation, and avoid unnecessary morbidity for patients.

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