Neutrophilic Dermatosis After Azathioprine Exposure

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Importance:
Azathioprine hypersensitivity syndrome can present clinically and histopathologically like Sweet syndrome. Shared clinical features include fever, constitutional symptoms, prompt response to systemic corticosteroid therapy, neutrophilia, and abrupt onset of erythematous cutaneous lesions. Histologically, both azathioprine hypersensitivity syndrome and Sweet syndrome are rich in neutrophils.

Observations:
An 81-year-old woman with Crohn disease presented with fever and an acute eruption of plaques on her extremities within 2 weeks of starting treatment with azathioprine. Laboratory evaluation was notable for leukocytosis and neutrophilia. Skin biopsy of an erythematous plaque on the thigh demonstrated a suppurative folliculitis. Azathioprine treatment was discontinued resulting in resolution of the clinical lesions within 5 days. Our case was compared with 18 cases with similar clinical features.

Conclusions and Relevance:
We report a case of azathioprine hypersensitivity syndrome and review the literature on azathioprine-induced eruptions with features of Sweet syndrome. Our patient’s distribution of lesions on the extremities and the finding of suppurative folliculitis on histopathology were not classical for Sweet syndrome. Azathioprine hypersensitivity syndrome seems to be a neutrophil-driven dermatosis; therefore, many overlapping features with Sweet syndrome are not surprising. Due to the potential for anaphylaxis with azathioprine rechallenge, a better term for a Sweet-like presentation in the setting of azathioprine administration is azathioprine hypersensitivity syndrome.


AZATHIOPRINE TREATS A VARIETY OF AUTOIMMUNE CONDITIONS, INCLUDING INFLAMMATORY BOWEL DISEASE, LUPUS ERYTHEMATOSUS, AND PEMPHIGUS VULGARIS, THROUGH INHIBITION OF DNA AND RNA SYNTHESIS. Azathioprine hypersensitivity syndrome is a rare adverse event occurring within weeks of azathioprine initiation and is characterized by the acute onset of fever, arthralgias, abdominal pain, nausea, and associated cutaneous eruptions. A diagnosis of azathioprine hypersensitivity syndrome may be delayed as the constellation of findings can mimic infection or a flare of the underlying autoimmune condition, such as inflammatory bowel disease, for which the immunosuppressant was initiated. Although the hypersensitivity syndrome is typically reversible on azathioprine cessation, subsequent azathioprine avoidance is crucial as rechallenge can lead to anaphylaxis.

In a recent literature review, 67 cases of azathioprine hypersensitivity syndrome have been reported. Sweet syndrome is one of several recognized clinical patterns of azathioprine hypersensitivity syndrome; other patterns include erythema nodosum, small-vessel vasculitis, acute generalized exanthematous pustulosis, and nonspecific dermatitis. Classical Sweet syndrome, originally described by Robert Sweet, MD, as “acute febrile neutrophilic dermatosis” in 1964, is characterized by fever, constitutional symptoms, peripheral blood neutrophilia, and abrupt onset of tender, erythematous papules, plaques, or nodules. Sweet syndrome has several well-known associations, including hematologic malignant neoplasms, solid tumors, infection, inflammatory bowel disease, pregnancy, and medications. Systemic corticosteroids are the gold standard of treatment and rapid clinical response is typical.

We describe a patient treated with azathioprine for Crohn disease, who developed azathioprine hypersensitivity syndrome within 2 weeks of treatment initiation. Although the patient had many clinical features of Sweet syndrome—fever, peripheral neutrophilia, and abrupt onset of skin lesions—these features are not specific to Sweet syndrome and over-
lap with those seen in azathioprine hypersensitivity syndrome. A comprehensive literature review was performed to further evaluate cases of Sweet syndrome attributed to azathioprine administration and cases of azathioprine hypersensitivity with features of Sweet syndrome. Characteristics examined included the timing of symptom onset, azathioprine dose, timing of symptom resolution, clinical manifestations, histopathologic features, and proposed mechanism(s).

REPORT OF A CASE

An 81-year-old woman with a history of Crohn disease and cecal cancer, status post hemicolectomy, was admitted to our hospital with 3 days of altered mental status, fever (temperature to 39.7°C), myalgias, and an acute, nontender eruption located primarily on the upper and lower extremities. Two weeks prior to her hospitalization, oral azathioprine therapy (75 mg/d) was added to a long-term corticosteroid regimen (budesonide, 9 mg/d) for management of Crohn disease. The patient had no known previous azathioprine exposure. She had been in her usual state of health until 1 week before admission, when she developed nausea, vomiting, diffuse myalgias, and arthralgias.

Physical examination results were notable for marked erythema along the inferior eyelids (Figure 1A) and multiple pink 1- to 4-mm macules on the bilateral palms (Figures 1B). There were 20 to 30 violaceous to pink, indurated 3-mm to 1-cm papules and plaques on the bilateral upper and lower extremities, particularly on the bilateral knees and lateral thighs (Figure 1C and D). The face, chest, abdomen, and back were spared. The patient had leukocytosis (white blood cells, 13 100/µL) and neutrophilia (90%-94%), without eosinophilia. Otherwise, the complete blood cell count, creatinine level, and transaminase level were unremarkable. Thiopurine methyltransferase levels were not obtained. The results of a comprehensive systemic infectious disease workup were negative. Cerebrospinal fluid showed no microorganisms. A biopsy specimen from a representative pink plaque on the thigh demonstrated a patchy suppurative and granulomatous dermal infiltrate (Figure 2). The inflammatory infiltrate was composed primarily of neu-

![Figure 1. Clinical presentation of our patient's eruption after azathioprine initiation. A, Erythema along inferior eyelids. B, Pink macules on the left palm. C, Pink-violaceous papules and plaques on right lateral thigh. D, Pink-violaceous papules and plaques on bilateral knees.](image-url)
trophils and some histiocytes. In some areas, the infiltrate was perifollicular, and collections of neutrophils were noted within the follicular epithelium. Rare multinucleated giant cells were present. No papillary dermal edema was observed. No eosinophils were identified. Periodic acid–Schiff and Gram stains of the tissue were negative for organisms.

A diagnosis of azathioprine hypersensitivity syndrome was favored over azathioprine-induced Sweet syndrome for several reasons. (1) The clinical presentation of lesions on the extremities would be unusual for Sweet syndrome in which tender, edematous plaques typically occur on the head, neck, and trunk. (2) The biopsy specimen lacked the hallmark dense dermal neutrophilic infiltrate and massive papillary dermal edema of Sweet syndrome. (3) The systemic symptoms could all be attributed to a hypersensitivity reaction—with discontinuation of azathioprine alone (no other therapeutic intervention), the patient’s fever subsided within 2 days, and all skin lesions resolved completely within 5 days.

**DISCUSSION**

We completed a literature review of cases of azathioprine hypersensitivity syndrome with features of Sweet syndrome by entering the following search terms into PubMed: **azathioprine AND Sweet’s Syndrome, azathioprine-induced sweet’s syndrome, azathioprine AND neutrophilic dermatosis, azathioprine AND acute febrile neutrophilic dermatosis, and azathioprine hypersensitivity syndrome.** Our search revealed 18 cases that were reviewed and compiled (Table 1 and Table 2). Most affected patients (76.5%, n = 13) had inflammatory bowel disease, similar to our patient. Treatment with azathioprine was started for 12 of 19 patients within 2 weeks of presentation (Table 1). The mean time to symptom resolution was 5 days. In cases of rechallenge with azathioprine, the mean time to onset of reaction was 20 hours. In up to 50% of cases, as seen in our patient, azathioprine hypersensitivity syndrome has systemic symptoms that overlap with Sweet syndrome; nevertheless, cases reported in the literature as “azathioprine-induced Sweet’s syndrome” may be better labeled as azathioprine hypersensitivity syndrome—a sentiment previously expressed by others.

Established criteria for drug-induced Sweet syndrome include the following: (1) abrupt onset of painful erythematous plaques, (2) histopathologic evidence of dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis, (3) temperature higher than 39.7°C (fever), (4) temporal relationship between drug ingestion and clinical presentation, and (5) temporal resolution of lesions after drug withdrawal. Although our patient’s presentation met at least 3 of these 5 criteria for
Drug-induced Sweet syndrome (criteria 3 through 5), both clinical (criterion 1) and histological features (criterion 2) were nonclassical for Sweet syndrome. In short, lesions of Sweet syndrome are typically plaques on the upper body with microscopic dense dermal infiltrates and massive papillary edema, while our patient’s lesions were pink papules and plaques on the extremities with corresponding suppurative folliculitis.

Table 2 summarizes the aggregate clinical and histopathologic characteristics of all reported cases of azathioprine-induced Sweet syndrome as well as other cases reported as azathioprine hypersensitivity syndrome with features of Sweet syndrome (n = 18). The most common dermatologic findings included erythematous papules, plaques, and pustules, followed by nodules and vesicles. The lesions were painful in most cases. Although the lower extremities are rarely involved in classical Sweet syndrome, which favors the head and neck, they were frequently involved in the reviewed cases (Table 2). Neutrophilia was the most common finding, and there was no report of eosinophilia. IgE levels were not reported in any of the cases.

A dermal neutrophilic infiltrate and mild to significant dermal edema were the most common histopathologic findings (Table 2). No evidence of leukocytoclastic vasculitis was found in any of the cases. The patchy and suppurative granulomatous infiltrate observed in our case was not noted in the cases reviewed. Two cases reported neutrophilic infiltration into hair follicles similar to the histopathology of our case. In a review of 67 cases of azathioprine hypersensitivity, among patients with cutaneous findings, 76% (25 of 33) had biopsy or clinical features consistent with neutrophilic dermatoses. Among cases in which cutaneous histopathology showed a neutrophilic dermatosis, most patients (16 of 25) had inflammatory bowel disease. Given the association between inflammatory bowel disease and several neutrophilic dermatoses, it is possible that patients with inflammatory bowel disease have a neutrophilic diathesis, and neutrophils may be overrepresented in an inflammatory response, such as a drug eruption. Similar to patients in our review, many patients with inflammatory bowel disease are treated long-term with corticosteroids at the time of azathioprine initiation. Given that corticosteroids increase the rate of neutrophil margination, clinical expression of a neutrophilic diathesis may be more likely in these patients. Of the 4 cases reviewed in which patients were not receiving concurrent corticosteroids, a neutrophilic infiltrate was also described on histopathology.

Our case and review of the literature suggest that azathioprine hypersensitivity syndrome is primarily neutrophil mediated. The precise mechanism of azathioprine hypersensitivity syndrome remains unknown but some potential mechanisms include a type III or IV hypersensitivity reaction and neutrophil activation. The timing of the eruption, on the order of weeks, supports a delayed hypersensitivity reaction. The mechanism of anaphylactic shock, in a subset of patients, could be secondary to type 1 IgE-mediated anaphylaxis or non-IgE-mediated anaphylactoid reaction. Other cutaneous eruptions associated with azathioprine, such as acute generalized exanthematous pustulosis, erythema nodosum, and leukocytoclastic vasculitis, are possible hypersensitivity reactions that are characterized by neutrophilic infiltrates. Acute generalized exanthematous pustu-

<table>
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<tr>
<th>Patient No./Sex/Age, y</th>
<th>Condition</th>
<th>Azathioprine Dose</th>
<th>Onset After Azathioprine Initiation</th>
<th>Resolution After Azathioprine Discontinuation</th>
<th>Prednisone Dose</th>
<th>Time After Rechallenge to Symptoms</th>
<th>Reference</th>
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<tr>
<td>1/F/39</td>
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<td>5 d</td>
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<td>4 d</td>
<td>35</td>
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<td>10 d</td>
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<td>2 wk</td>
<td>60</td>
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<td>1 d</td>
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<td>Yes, within 6 h</td>
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<td>5 d</td>
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<td>18 d</td>
<td>1 wk</td>
<td>15</td>
<td>-</td>
<td>24</td>
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Abbreviation: NR, data not reported in reference.

*Given as milligrams per day unless otherwise indicated.
llosis is a neutrophilic cell-mediated hypersensitivity reaction (type IVd), characterized by presentation of soluble antigens and activation of neutrophils through granulocyte-macrophage colony-stimulating factor and chemokine (C-X-C motif) ligand 8 (formerly interleukin 8) production. A similar mechanism of hypersensitivity and neutrophil activation through cytokine dysregulation may underlie the cases reviewed.

Given the similarities between cases reported as azathioprine-induced Sweet syndrome and azathioprine hypersensitivity syndrome with Sweet syndrome features, it is likely that these entities represent the same process in which susceptible patients develop fever, leukocytosis with neutophilia, and an acute cutaneous eruption often within 2 weeks of azathioprine initiation. Although in some cases, the neutrophilic infiltrate may histopathologically mimic Sweet syndrome, more commonly, as with our patient, a nonspecific neutrophilic process is observed. Also, unlike classical Sweet syndrome, this eruption has a proclivity for lower extremity involvement. Use of the diagnosis azathioprine hypersensitivity syndrome—inclusive of azathioprine-induced Sweet syndrome—is effective in conveying that the lesions are induced by azathioprine, have a reproducible clinical presentation with variable histopathology (not always Sweetlike), and resolve with discontinuation of the medication.

In several of the cases we reviewed, patients were rechallenged with azathioprine resulting in reproduction of symptoms in every case. This high rate of rechallenge suggests that the role of azathioprine in this reaction pattern may not be clearly understood or recognized by many physicians. Azathioprine hypersensitivity syndrome can lead to life-threatening shock, as reported in multiple cases. The most common presentation is shock and circulatory collapse, which is even more severe on rechallenge with azathioprine. Based on a literature review of azathioprine hypersensitivity syndrome, hypertensive shock occurred in 4 of 49 cases of azathioprine hypersensitivity syndrome. Azathioprine-induced shock can result in multiorgan failure, which is the most likely cause of death from this hypersensitivity syndrome. Clear terminology is necessary for proper communication with nondermatologists and essential for accurate documentation of the allergic reaction, as azathioprine rechallenge may lead to a more severe hypersensitivity reaction and potentially death.

Accepted for Publication: January 6, 2013.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Cyrus, Stavert, and Choi. Acquisition of data: All authors. Analysis and interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Study supervision: Choi.

Conflict of Interest Disclosures: None reported.

REFERENCES


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### President Kennedy’s White House Tan

This year marks the 50th anniversary of the Kennedy assasination. Many of us will never forget that Friday, November 22, 1963, when we heard the tragic news that President John F. Kennedy (1917-1963) had been shot in Dallas, Texas.

President Kennedy was a charismatic leader, full of wit and humor. He seemed to be the image of youth and vigor, always tanned and seemingly ready to pass a football.

The truth was quite different. Kennedy suffered from Addison disease, a fact kept concealed from the public during his political career. During September 1947, while overseas, he developed weakness, nausea, vomiting, and hypotension. He was diagnosed as having Addison disease at the London Clinic. Kennedy’s Addison disease probably resulted from autoimmune adrenal destruction, as do most cases today in adults. Kennedy also had a striking yellow skin discoloration that was noticed months earlier and mentioned in *Time* magazine: “...young John Kennedy, still atabrine-yellow from PT-boat service in the Pacific.”

Atabrine (quinacrine hydrochloride), an antiimalarial agent used during World War II, can cause a transient yellow skin discoloration. Perhaps Kennedy’s yellow-brown discoloration reflected both the increased melanin of Addison disease and residual atabrine dermatitis. Thomas Addison, in 1855, was the first to describe such hyperpigmentation in his classic treatise on adrenal disease. The hyperpigmentation is the result of the excessive stimulation of melanogenesis by adrenocorticotropic hormone (ACTH) and α-melanocyted-stimulating hormone (α-MSH), whose production is increased because of a lack of negative pituitary feedback from corticosteroids.

Addison disease was often fatal until desoxycorticosterone, the first synthetic corticosteroid, became available in the late 1930s. Although weak in effect, the drug was lifesaving but had to be given parentally. Kennedy was treated with desoxycorticosterone acetate drug pellets implanted subcutaneously in his thigh every 3 months. Oral cortisone became available in the early 1950s and was added to his regimen. He improved clinically, and his discoloration subsided.

With proper hormone replacement, Addisonian hyperpigmentation lightens considerably over time but may not disappear. This skin lightening results from the corticosteroid feedback suppression of the elevated levels of ACTH and α-MSH, which lead to the increased melanogenesis. Thus, President Kennedy may have been left with residual Addisonian pigmentation that contributed to his famous White House tan. In addition, his full checks may have indicated mild Cushionoid features, suggesting that there were difficulties in optimally adjusting his maintenance corticosteroid therapy.

John F. Kennedy faced the challenges of his life, including his medical illnesses, with great courage. Fifty years after that sad day in Dallas, we continue to reflect on the life of this popular president, who inspired us to become better Americans, dedicated to serving our country and the world.

Leonard J. Hoenig, MD

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