Azathioprine Hypersensitivity: a Sweet-like Syndrome

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Abstract

**Introduction:** Azathioprine is a purine analog used to treat autoimmune diseases and steroid refractory chronic diseases. Azathioprine hypersensitivity can present occasionally within weeks of initial therapy as Sweet-like Syndrome.

**Case Summary:** A 35 year old woman with Systemic Lupus Erythematosus (SLE) presented to the emergency department with complaints of generalized maculopapular rash, facial swelling and bilateral lower extremity edema of 4 days duration and two day history of constitutional symptoms like fever and nausea within two weeks of beginning of Azathioprine therapy to treat existing Lupus Nephritis.

**Reason for the Report:** Extensive skin signs include Erythema nodosum, small vessel vasculitis, acute widespread exanthematous pustulosis, sweet syndrome, and nonspecific dermatosis can be seen in patients with azathioprine hypersensitivity syndrome. It is known that the drug’s imidazole component interacts with particular proteins to produce haptons, which further trigger Type 3 hypersensitivity reactions.

**Outcome:** Our case demonstrates the very fast onset of Azathioprine-induced Sweet-like Syndrome that happens after taking the offending medication. After ruling out viral and autoimmune reasons, this diagnosis can be made using routine laboratory tests and the results of a skin biopsy. The use of corticosteroids coupled with the discontinuation of azathioprine led to the complete disappearance of symptoms.

**Introduction**

Azathioprine is a purine analogue that inhibits RNA and DNA synthesis. First used in 1961 as an immunosuppressant for kidney transplantation, and has become an effective corticosteroid-sparing agent in a variety of autoimmune inflammatory diseases. It has dose-dependent toxic side effects (myelosuppression, hepatotoxicity, among others) well recognised, with an overall incidence of side effects ranging from 10-5%, with cases of true hypersensitivity syndrome in approximately 2% of patients taking the drug. These hypersensitivity reactions are dose-independent and tend to occur during the first 4 weeks of therapy [1,2].

Sweet syndrome was first described by Dr. Robert Douglas Sweet in 1964 and referred to as febrile neutrophilic dermatosis (a group of heterogeneous inflammatory skin disorders that included Sweet’s syndrome, pyoderma gangrenosum, and sub-conjunctival pustular dermatosis). The syndrome is subdivided into three clinical types: Classical (or idiopathic), Malignancy-associated or drug-induced, and diagnosed by criteria proposed by Su and Liu and modified by von den Driesch. It is necessary to complete the 5 criteria diagnosis for drug-induced: 1) Abrupt onset of painful erythematous plaques or nodules. 2) Histopathological findings of dense neutrophilic infiltrate without evidence of leukoclastic vasculitis. 3) Fever >38°C 4) Temporal relation between use of medication and clinical presentation or relapse with re
administration. 5) Disappearance of lesions after drug discontinuation or treatment with systemic corticosteroids [2,3,4].

The association of this syndrome with infection, autoimmune diseases, neoplasm, and drug suggest an unusual hypersensitivity that may be mediated by cytokines, infiltration of neutrophils probably activated by interleukin (II)-1. This syndrome is more common in middle age women with a 4:1 female-to-male ratio and has a constellation of clinical symptoms, physical features, and pathological findings that include fever, neutrophilia, hypotension, or even shock, and can affect other organs such as bones, brain, eyes, kidneys, liver, and others. Histology will reveal neutrophils typically located in the upper dermis. One of the most commonly reported drugs causing Sweet’s syndrome is azathioprine [3,4].

**Reason for Report:**

Extensive skin signs include Erythema nodosum, small vessel vasculitis, acute widespread exanthematous pustulosis, sweet syndrome, and nonspecific dermatosis can be seen in patients with azathioprine hypersensitivity syndrome. It is known that the drug’s imidazole component interacts with particular proteins to produce haptens, which further trigger Type 3 hypersensitivity reactions.

**Case Presentation**

A 35-year-old woman with a medical history of Systemic lupus erythematosus (SLE) on treatment presented to the emergency services with generalised maculopapular rash, facial swelling and bilateral lower extremity oedema of 4 days duration and two-day history of fever and nausea. There was no associated pruritus or pain, and systemic examination was otherwise normal. The patient had been started on azathioprine (50mg OD) two weeks prior to this presentation for lupus nephritis (class 2/3). Her other medications included prednisolone, hydroxychloroquine and aspirin. The patient had exposure to sunlight while she went on a temple visit. But no significant dietary changes. Physical examination revealed diffuse reddish palpable tender non-blanching violaceous coalescent papules and macules on both upper and lower limbs with pustules interspersed between them (Figures 1A-C).

The involvement was generalised and there was facial swelling with prominent periorbital puffiness and lip swelling. Complete blood count, including eosinophil count, comprehensive metabolic panel, urinalysis, erythrocyte sedimentation rate and serum complement levels are within normal limits except for an elevated total leukocyte count of 13,000 cells/cu.mm and Neutrophils-89% (Peripheral smear shows Neutrophilic leukocytosis). Infectious work-up including HIV, hepatitis C antibody, hepatitis B surface antigen, was negative with a sterile blood and urine culture. Punch biopsy of a representative skin lesion from the back was performed on day 5 of symptom onset which showed patchy suppurative infiltrate composed primarily of neutrophils. In some areas the infiltrate was angiocentric. No papillary dermal edema was observed. There were occasional budding forms of candida (Figures 2 A-F).

The patient did not have cutaneous candidial manifestations and KOH mount of skin scrapings had turned out to be negative. Direct immunofluorescence testing was performed within 4 hours of obtaining
the biopsy specimen and did not reveal any immune complex deposits. The patient scored between 5 and 7 as per the Naranjo algorithm, suggesting that it was a probable drug reaction. Given that the patient had been recently started on azathioprine, this reaction was attributed to azathioprine. The patient was diagnosed with azathioprine hypersensitivity syndrome after excluding other infectious, malignant and autoimmune causes of her presentation. Azathioprine was discontinued. The patient was already on prednisone (1mg/kg) daily, and it was continued and planned for tapering later. The lesions slowly subsided over two weeks with desquamation appearing over the extremities along with the resolution of the rash (Figures 1D-F) and completely resolved later. We didn’t rechallenge the drug as it has been shown that it causes life-threatening reactions (hypotension and shock) [7]. Hypersensitivity reactions to azathioprine are generally dose independent hence the serum levels were not measured.

Discussion

Azathioprine induced hypersensitivity syndrome present with a wide gamut of manifestations. Bidinger et al have performed the largest literature review on azathioprine hypersensitivity syndrome [1]. Usual clinical patterns with cutaneous findings include erythema nodosum, small vessel vasculitis, acute generalised exanthematous pustulosis, Sweet syndrome and nonspecific dermatosis. It occurs within the first four weeks of therapy initiation. Unlike dose-dependent side effects, these reactions occur independent of TPMT (Thiopurine Methyltransferase) levels and most AZA hypersensitivity syndrome patients had normal TPMT levels. The imidazole (methyl nitroimidazole moiety) component in azathioprine was thought to associate with certain proteins generating haptns and causing type 3 hypersensitivity reactions after immune complex deposition over the vessel walls [5]. Genetic polymorphisms in the inositol triphosphate pyrophosphatase gene may also be associated with AZA hypersensitivity [6]. Photosensitivity with azathioprine has also been studied previously. AZA is activated to thioguanine nucleotides which are the precursors for the incorporation of the base analog 6-thioguanine (6-TG) into DNA [1]. One important property of DNA 6-TG is its ability to absorb the ultraviolet A (UVA) radiation, leading to skin photosensitivity.

In a review of 17 cases of azathioprine-induced eruptions with features of Sweet syndrome, it was recognised that a “Sweet-like-syndrome” is seen more commonly rather than a classical Sweet syndrome [2]. 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 degree C, (4) temporal relationship between drug ingestion and clinical presentation, and (5) temporal resolution of lesions after drug withdrawal. Although our patient met 3 out of 5 criteria, both clinical (criterion 1) and histological features (criterion 2) were nonclassical for Sweet syndrome. This was in concordance with the same report and review described by Cyrus et al. [2] Cutaneous flare would also be possible but no immune complex/complement deposits in dermal basement membrane or peripheral hypocomplementemia were seen. Diagnosis is confirmed by skin biopsy and DIF. But in our case DIF turned out to be negative.
An isolated case of drug-induced hypersensitivity syndrome by a known trigger should be treated with discontinuation of the trigger. Most cases resolve within 2–3 days after medication discontinuation and may not require corticosteroids. Given the mortality with Azathioprine induced hypersensitivity, cutaneous and systemic manifestations respond well with stoppage of drug alone and conservative management with intravenous fluids in case of vascular collapse. Complete Resolution of manifestations noted within a week. Rechallenge with Azathioprine had previously resulted in increased risk of mortality and morbidity [8].

Outcome:

The index case we present had a good prognostic outcome and resolution of the symptoms she presented with, once the offending drug was discontinued. Our case demonstrates the very fast onset of Azathioprine-induced Sweet-like Syndrome that happens after taking the offending medication. After ruling out viral and autoimmune reasons, this diagnosis can be made using routine laboratory tests and the results of a skin biopsy. The use of corticosteroids coupled with the discontinuation of azathioprine led to the complete disappearance of symptoms.

Conclusion

Though the patient’s presentation resembled drug induced Sweet syndrome, clinically, lesions of Sweet syndrome are typically plaques on the upper body with microscopic dense dermal infiltrates and massive papillary dermal edema, while our patient’s lesions were pink papules and plaques with interspersed pustules predominantly on the extremities with corresponding neutrophil rich infiltrates histologically. Hence, the presentation can be said to be of an azathioprine hypersensitivity syndrome with a sweet-like manifestation.

Declarations

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Competing interests None declared.

Patient consent for publication Obtained.

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References


**Figures**

![Image 1A](image1a.jpg) ![Image 1B](image1b.jpg) ![Image 1C](image1c.jpg)  
![Image 1D](image1d.jpg) ![Image 1E](image1e.jpg) ![Image 1F](image1f.jpg)
Figure 1

A-C: Facial edema with coalescing maculopapular lesions over extremities on presentation

D-F: Resolution of the signs after stopping azathioprine.

Figure 2

A - Section shows acanthotic stratified squamous epithelium with moderate to dense perivascular (angiocentric) neutrophilic infiltration with endothelial swelling (endothelialitis) and no evidence of fibrinoid necrosis. There is evidence of neutrophilic exocytosis. (Haematoxylin and Eosin stain, x200)

B – Section shows dermal capillary packed with budding forms of candida species. (Periodic acid Schiff stain, x 200)

C – Section shows dermis highlighting neutrophilic endothelialitis and endothelial swelling with no evidence of fibrinoid necrosis. Occasional eosinophils are also seen. (Haematoxylin and Eosin stain, x400)

D - Section shows dermal capillary packed with budding forms of candida species. (Periodic acid Schiff stain, x 400)

E – Section shows budding forms of candida species in epidermis. (Periodic acid Schiff stain, x 400)
F - Section shows budding forms of candida species in the region of follicular plug. (Gomori methenamine silver stain, x 400)

Supplementary Files

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- GraphicalAbstract.jpg