

Severe distributive shock, neutrophilic dermatosis, and Kounis syndrome in the setting of azathioprine hypersensitivity syndrome

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Case Report

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Abstract

Background: Azathioprine is a purine synthesis inhibitor used as an immunosuppressive therapy for many immune-mediated diseases. Azathioprine hypersensitivity reaction is a rare, life-threatening adverse reaction characterized by a range of multisystem manifestations including fever, abdominal pain, arthralgias, erythematous cutaneous eruption, acute renal failure, neutrophilia, and more rarely, distributive shock. Furthermore, allergic coronary vasospasm (Kounis syndrome) has been described as a reaction to several allergens, but has previously never been associated with azathioprine or its hypersensitivity syndrome.

Case Presentation: We describe a case of a 59-year-old male with Crohn's disease who developed severe azathioprine hypersensitivity syndrome that included distributive shock, cutaneous eruption of neutrophilic dermatosis, and ST-elevation acute coronary syndrome consistent with Kounis syndrome. Clinical improvement was seen after cessation of azathioprine and administration of glucocorticoid therapy. This case report is the first of its kind to describe such a severe reaction to azathioprine, especially with the occurrence of Kounis syndrome.

Conclusion: In patients receiving azathioprine, hypersensitivity syndrome, distributive shock, neutrophilic dermatosis, and Kounis syndrome should be recognized as potential adverse events.

BACKGROUND

Azathioprine hypersensitivity syndrome (AHS) is a rare, life-threatening adverse reaction characterized by a range of adverse effects including fever, hypotension, abdominal pain, arthralgias, erythematous cutaneous eruption, acute renal failure, and neutrophilia.(1) It is thought to be mediated by a type III or IV hypersensitivity reaction, and/or from increased production of inflammatory cytokines.(2–4) Of the relatively few cases of AHS reported in the literature,(1–6) none have described concurrent allergic coronary vasospasm (Kounis syndrome). We describe a case of a 59-year-old male with fibrostenotic Crohn's disease who developed severe AHS with therapy initiation and subsequently Kounis syndrome upon a re-challenge with azathioprine.

CASE PRESENTATION

A 59-year-old man with longstanding fibrostenotic Crohn's disease presented with a one-day history of fever and abdominal pain. One week prior to his hospital admission, he had a surveillance colonoscopy demonstrating progression of his Crohn's disease, and therefore started on azathioprine 125 mg daily alongside budesonide. The patient was admitted to hospital with a working diagnosis of sepsis and was started on empiric parenteral ceftriaxone. Investigations including chest radiograph, blood and urine cultures, and computed tomography of the abdomen and pelvis revealed no source of infection. Azathioprine was held on admission due to concern of immunosuppression exacerbating an underlying infectious process.

Two days after admission, he continued to have persistent tachycardia and fever which progressed to septic shock and acute renal failure. The patient received broad spectrum antimicrobial therapy with piperacillin-tazobactam and vancomycin, stress-dose methylprednisolone, and vasopressor support with norepinephrine for refractory shock. During his course in the ICU, he developed an acute rash, predominantly on his extremities and torso (Fig. 1A-C). The rash was treated with topical steroid cream and a punch biopsy from the dorsal right hand was sent for pathological assessment.

With clinical improvement, and the decreasing concern for immunosuppression, the patient's azathioprine was re-started on day 7 of his ICU admission. After receiving a single re-challenge dose of azathioprine, the patient developed recurrent vasodilatory shock and decline in level of consciousness, requiring endotracheal intubation, fluid resuscitation, and re-initiation of vasoactive medications. His electrocardiogram demonstrated transient ST elevation in the inferior and septal leads with an elevated serum high-sensitivity troponin T of 1290 ng/L. Urgent cardiac catheterization revealed no evidence of obstructive coronary artery disease.

At this point, AHS was suspected to be the cause of the patient's distributive shock given the timeline of recent initiation of azathioprine prior to presentation, improvement with cessation of the medication, and immediate clinical decline with a re-challenging dose. The results of the skin biopsy from the dorsum of the right hand (Fig. 2A-D) revealed a variable perivascular and diffuse mixed inflammatory infiltrate composed of neutrophils with mononuclear inflammatory cells and eosinophils present in the upper dermis, with upper dermal extravasation of red cells, and a neutrophilic infiltrate with microabscess formation present in the superficial subcutis. Based on clinicopathologic correlation, a diagnosis of neutrophilic dermatosis, consistent with AHS was rendered, alongside acute coronary syndrome related to this drug reaction (Kounis syndrome).

After identification of AHS as the most likely cause of the patient's clinical syndrome, azathioprine was discontinued indefinitely, and immunosuppression was provided with systemic corticosteroids. The dermatologic abnormalities resolved completely over the following two weeks.

DISCUSSION

AHS is relatively rare, seen in only about 2% of patients initiating this immunosuppressive therapy.(1–4) Adverse effects have been reported to occur between two and fourteen days after initiation of the medication.(1–6) Once a patient is sensitized, a re-challenge of the drug will typically have a rapid onset of the reaction, with previous case reports in the literature documenting onset within hours of re-exposure.(1–6) As supported by our case, the hypersensitivity reaction from re-exposure to azathioprine is often more severe, with hypotension and shock reported in up to one-third of cases.(1–6) The mainstay of treatment is supportive measures with fluid resuscitation and vasopressor/inotropic support if necessary. The hypersensitivity reaction typically resolves within days to weeks of cessation of the drug.

Various rashes have been associated with AHS including erythema nodosum, small-vessel vasculitis, acute generalized exanthematous pustulosis, nonspecific dermatitis, and Sweet syndrome. In the present case, we observed a cutaneous eruption of neutrophilic dermatosis (similar to Sweet's syndrome) which in a literature review of 67 azathioprine hypersensitivity cases was the most common dermatologic pattern with 12 cases (18%) as compared to other rashes.(1, 5)

While the rash of neutrophilic dermatosis and distributive shock has been previously described in the setting of AHS, there have been no reports of azathioprine hypersensitivity and concurrent acute coronary syndromes related to allergic reaction or Kounis syndrome. The clinical presentation of Kounis syndrome can consist of anginal chest pain, palpitations, acute pulmonary edema, and allergic reactions in the context of a known history of allergy exposure.(7, 8) Three variants have been described in the literature. The type I variant (most common, 73% of cases) consists of coronary artery spasm with or without elevation in cardiac biomarkers. The type II variant (22% of cases) consists of both coronary artery spasm and plaque erosion or rupture and manifests as an acute myocardial infarction. The type III variant is characterized by stent thrombosis from an allergic reaction (5% of cases). Treatment for each variant consists of standard antithrombotic treatment for acute coronary syndromes as well as immunosuppression with corticosteroids (in type I, II, III) and antihistamines (in type II, III).(7, 8) The prognosis of Kounis syndrome is generally favorable.(7, 8) The only known predisposing factor to Kounis syndrome is exposure to a known allergen. We suspect the patient described in our case experienced a type II Kounis syndrome as part of a reaction to azathioprine.

CONCLUSIONS

Given the presentation of Kounis syndrome in the setting of severe AHS demonstrated in this case, azathioprine hypersensitivity should be considered in the differential diagnosis of patients recently started on the medication presenting with a distributive shock and acute coronary syndrome. Cessation of azathioprine appears to be effective in resolving both reactions. Avoidance of azathioprine should be strongly recommended in patients who develop this severe reaction, especially given the availability of alternate immune-mediating therapies.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The authors confirm that informed consent was obtained from the patient regarding preparation of this case report, and was obtained by the primary author, Dr. Samuel Su.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SS, YW, KZ, SH, DJ, and MB contributed to the writing and approval of the final manuscript.

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Figures

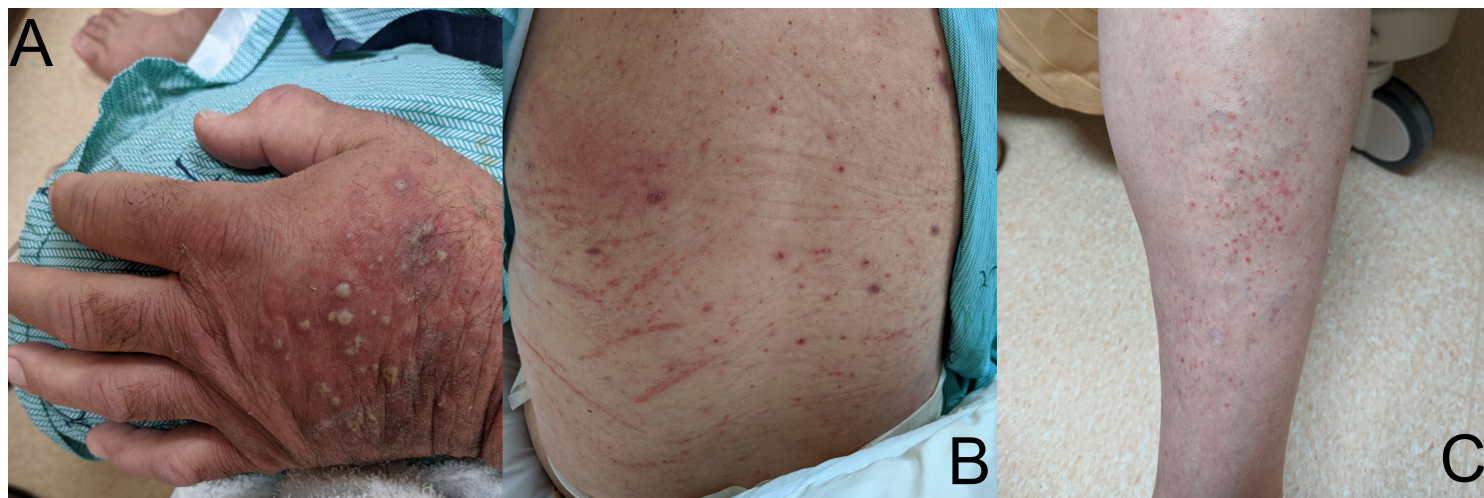


Figure 1

Cutaneous eruptions that developed in our reported case of AHS. A) Dorsal aspect of left hand: Erythematous plaque with pustules, some papules, and patchy crusting. B) Back: Patchy poorly demarcated erythema, irregularly distributed variably excoriated macules and papules, and linear scratch marks. C) Left leg: multiple small erythematous non-blanching petechiae.

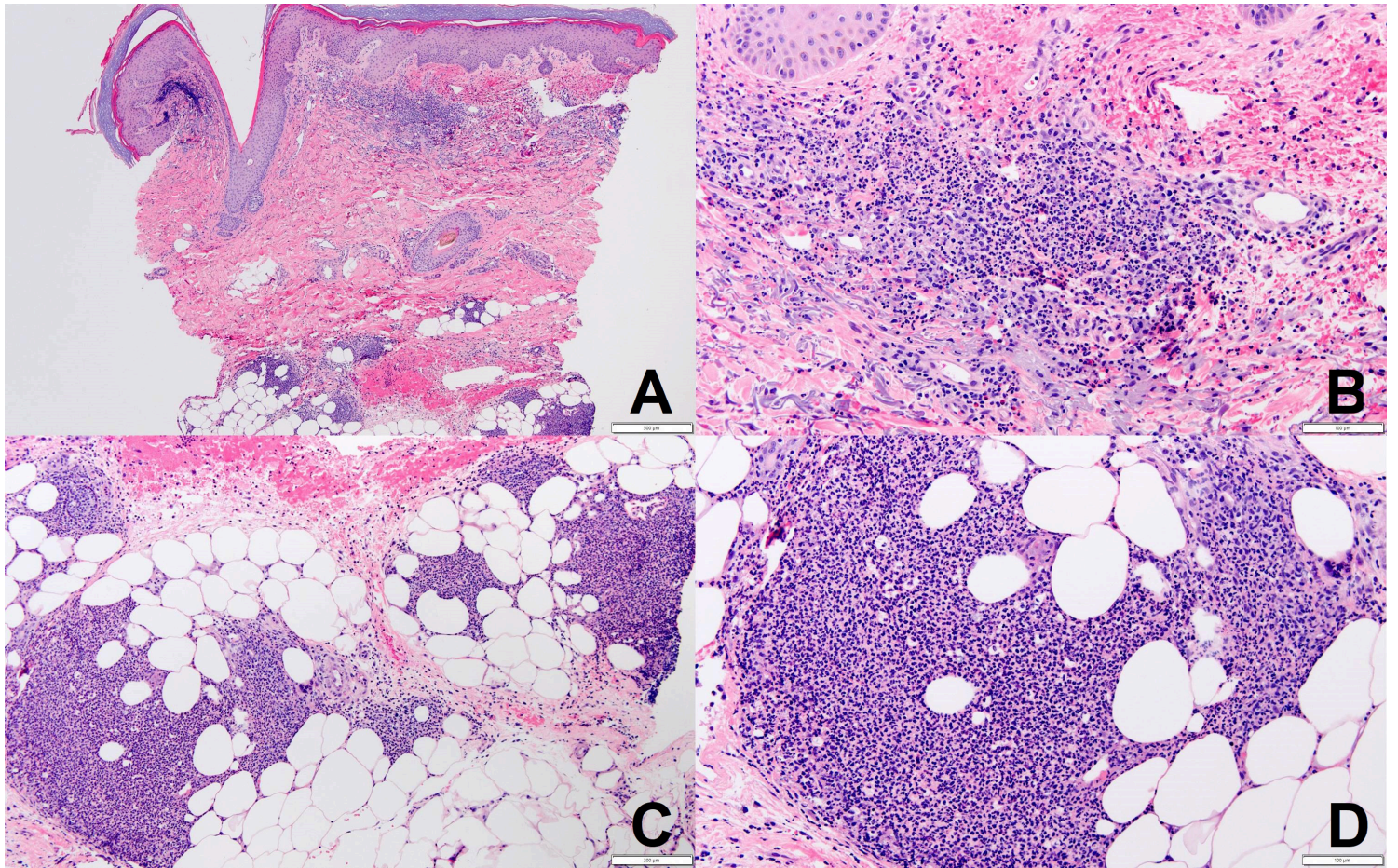


Figure 2

Skin punch biopsy from right hand dorsum demonstrating a patchy upper dermal and superficial subcutaneous inflammatory infiltrate composed of neutrophils. Extravasated red cells are also seen in the upper dermis (A, B). Note the karyorrhexis in the dermal infiltrate (B) and the microabscess formation in the subcutis (C, D) [Hematoxylin and Eosin. Original magnification X40 (A), X200 (B), X100 (C) and X200 (D)]