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CASE REPORT | LIVER

Azathioprine-Induced Hypersensitivity Vasculitis

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ABSTRACT

Vasculitic skin rash is a rare but known manifestation of azathioprine hypersensitivity reactions, with several published case reports. In this report, we describe the case of a 63-year-old man on azathioprine for autoimmune hepatitis, who developed a delayed systemic hypersensitivity reaction with biopsy-proven vasculitis, approximately 10 months into his treatment. This resolved after azathioprine discontinuation and has not recurred to date after subsequent administration of 6-mercaptopurine. This case highlights the need for continued monitoring for delayed hypersensitivity reactions to azathioprine after initiation of therapy.

KEYWORDS: azathioprine; hypersensitivity; vasculitis; autoimmune hepatitis

CASE REPORT

A 63-year-old man was diagnosed with biopsy-proven autoimmune hepatitis in September 2020 in the context of raised liver chemistries and elevated autoimmune markers with an elevated immunoglobulin G of 29.2 g/L, positive anti-smooth muscle antibody (titer 1:80), and positive antinuclear antibody (titer 1:160). His liver biopsy demonstrated moderate-to-marked interface hepatitis, moderate periportal fibrosis, and an inflammatory infiltrate of eosinophils and a small number of plasma cells.

His other medical history included hypertension, dyslipidemia, and a basal cell carcinoma removal. His other prescription medication was a combination tablet of amlodipine/perindopril 10 mg/5 mg daily. He had no known drug or other allergies.

At diagnosis, liver transaminases were markedly elevated, with an alanine aminotransferase (ALT) of >2,500 IU/L and an aspartate aminotransferase (AST) of >1,500 IU/L. Alkaline phosphatase (ALP) was 170–200 IU/L, gamma glutamyl transferase (GGT) 900–1,500 IU/L, and bilirubin 70–150 μmol/L.

He was commenced on azathioprine 225 mg daily (patient weight 224 lb, body mass index 34 kg/m^2) and a gradually tapering dose of prednisolone in December 2020. He responded well to this treatment, with a progressive improvement in his liver chemistries. By early January 2021, ALT had reduced to 147 IU/L and AST to 98 IU/L and bilirubin to 13 μmol/L; ALP was at the upper limit of normal (109 IU/L); and GGT remained raised (1,077 IU/L) but gradually improved over the next few months. His prednisolone was discontinued in April 2021 and his liver chemistries remained stable thereafter, with an ALT and AST both of <50 IU/L and a slightly elevated ALP (130–140 IU/L) and GGT (220–280 IU/L).

He was compliant with azathioprine, with no reported adverse effects initially, and his dose remained stable. Approximately 3 months after starting azathioprine, he reported a transient viral-like illness, with fatigue, cough, and rash over his chest and torso; this resolved spontaneously after several days with no treatment. Approximately 10 months into azathioprine treatment (October 2021), he developed an illness with progressive fatigue, myalgias, fevers, and polyarthralgia (affecting metacarpophalangeal joints, elbows, ankles, and knees) with significant functional impairment (difficulty walking and using hands for functional tasks, eg, turning a door knob). The polyarthralgia was bilateral and roughly symmetrical. He also developed a bilateral lower limb rash with several pustular target-shaped lesions on both lower limbs; the rash was not painful or pruritic (Figure 1). He did not describe gastrointestinal or other system symptoms.

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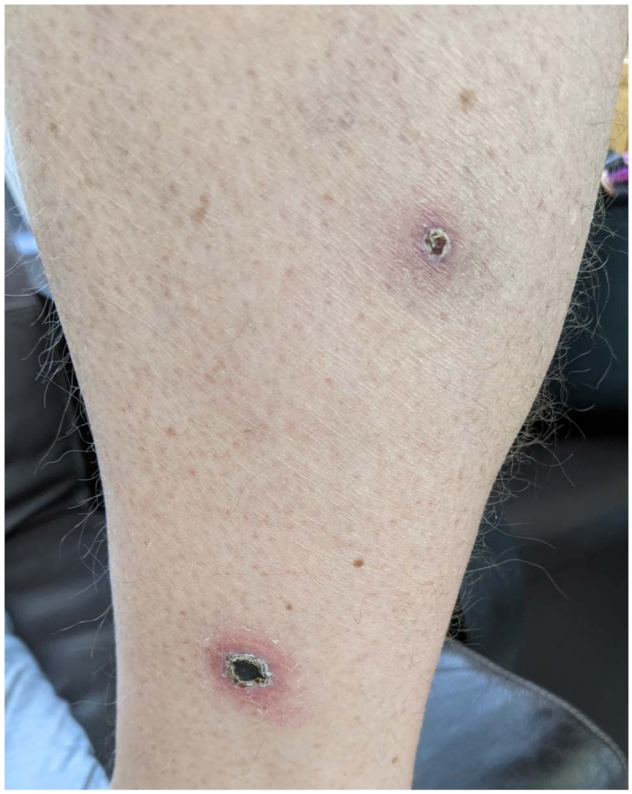

Figure 1. Cutaneous manifestation of hypersensitivity reaction, with pustular target shaped lesions on lower limb.

Blood tests revealed raised inflammatory markers with an erythrocyte sedimentation rate of 72 mm/h and a C-reactive protein of 43 mg/L and slightly raised neutrophils (7.8×10^9/L). Liver function was stable; ALP was 143 IU/L, ALT 23 IU/L, AST 25 IU/L, GGT 232 IU/L, and bilirubin 10 μmol/L. The 6-thioguanine level was 127 mol/8 $\times$ 10^8 red blood cells (below the therapeutic threshold) and the 6-methylmercaptopurine level 2,907/8 $\times$ 10^8 red blood cells (below the liver toxicity threshold).

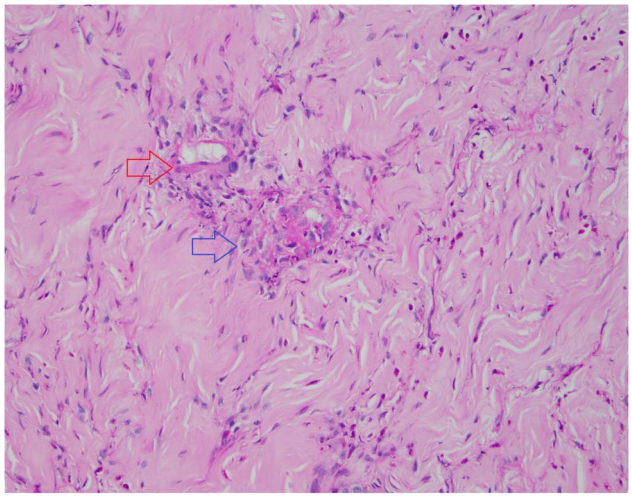

Figure 2. Histology of skin biopsy, showing fibrinoid change within small vessels (red arrow) associated with perivascular inflammatory debris (blue arrow), consistent with a hypersensitivity vasculitis.

Table 1. Naranjo adverse drug reaction probability scale

Question	Answer	Score
1. Are there previous conclusive reports on this reaction?	Yes	+1
2. Did the adverse event appear after the suspected drug was administered?	Yes	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	Yes	+1
4. Did the adverse event reappear when the drug was readministered?	Unknown	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	No	+2
6. Did the reaction reappear when a placebo was given?	Unknown	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	No	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	Unknown	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	No	0
10. Was the adverse event confirmed by any objective evidence?	Yes	+1
Total[a]		7

a Score ≥9 indicates a definite drug reaction, 5–8 indicates a probable drug reaction, 1–4 indicates a possible drug reaction, and ≤0 indicates a doubtful drug reaction.[1]
Table modified from Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981; 30:239–245.

He was started on prednisolone at 50 mg with a gradual taper and a course of oral flucloxacillin for a possible staphylococcal skin infection. A punch biopsy of the skin lesions was obtained, with the histology showing hypersensitivity vasculitis (Figure 2). With initiation of steroid therapy, his polyarthralgia improved within days. His course of prednisolone was discontinued after 4 weeks. After consultation with his gastroenterologist, azathioprine was discontinued in December 2021.

His rash and constitutional symptoms resolved over the next several weeks, with a corresponding reduction in his inflammatory markers. All symptoms relating to his hypersensitivity reaction completely resolved after discontinuation of azathioprine.

The Naranjo adverse drug reaction probability scale is used to standardize the assessment of causality for all adverse drug reactions.[1] In our case, the score was 7, which indicates a probable adverse drug reaction to azathioprine (Table 1).

He was initiated on 6-mercaptopurine (6-MP) in February 2022. To date, he has tolerated this therapy well, with stable liver chemistries and no clinical features of a hypersensitivity reaction.

DISCUSSION

Azathioprine hypersensitivity reactions have been described in the literature, occurring in approximately 2% of patients.[2] Systemic symptoms include fever, malaise, arthralgias, myalgias, gastrointestinal symptoms, and cutaneous manifestations; a shock-like syndrome has also been described. These reactions are dose-independent and do not have a relationship with thiopurine methyltransferase levels.[2]

Among cases of azathioprine hypersensitivity, cutaneous manifestations are common. In one literature review, of 67 cases of azathioprine hypersensitivity, 33 (49%) had cutaneous manifestations.[2] A variety of cutaneous manifestations have been described; however, only a few cases of hypersensitivity vasculitis have been reported.[3]

In most case reports, azathioprine therapy was discontinued after the development of the hypersensitivity reaction. However, in one report, therapy was continued given the lack of alternative treatments, albeit at a lower dose.[4] Readministration of azathioprine is generally contraindicated, given the potential for a severe shock-like syndrome.[2]

Variable evidence exists on whether administration of 6-mercaptopurine (an azathioprine metabolite) is advised in patients who develop azathioprine hypersensitivity. Some case reports have found an absence of hypersensitivity after administration of 6-MP.[5] However, others have noted similar reactions to 6-MP.[6]

Azathioprine hypersensitivity reactions tend to occur early in the course of treatment, within 4 weeks after initiation in most patients.[2] However, delayed reactions have also been reported. One case report described the development of pruritus and cutaneous small vessel vasculitis, supported by histology and intradermal tests, in a 56-year-old woman with Crohn's disease who had been using azathioprine for 2 years; symptoms began on doubling of her daily dose.[4]

One unusual feature of the hypersensitivity reaction in our patient was its extremely delayed onset at 10 months, with no dose changes and no identifiable triggers for the development of the reaction at this stage of therapy. Our patient's transient illness 3 months into treatment may have been an earlier manifestation of hypersensitivity, although if this was the case, such symptoms would not be expected to resolve with continuing treatment.

This case illustrates the challenges associated with identification of azathioprine hypersensitivity reactions, which may occur at a variable time in the treatment course, and for clinicians to maintain vigilance in monitoring patients on azathioprine therapy.

DISCLOSURES

Author contributions: M. Sangiorgio is the primary author, contributed to drafting of the manuscript and subsequent revisions, and is the article guarantor. A. Bhagwat is the secondary author and reviewed initial and subsequent drafts and provided. A. Davies is the secondary author and contributed to data collection and images.

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