

## CASE REPORT

## Azathioprine hypersensitivity presenting as a neutrophilic dermatosis in a man with ulcerative colitis

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## SUMMARY

We report a case of a 46-year-old man with ulcerative colitis being treated with oral prednisolone and azathioprine. Two weeks after the initiation of azathioprine he presented with fever, fatigue, myalgias and arthralgias and a painful cutaneous eruption that was most marked in a sun-exposed distribution. This was accompanied by loose, non-bloody diarrhoea. Histopathological assessment of a skin biopsy supported a diagnosis of a neutrophilic dermatosis. The azathioprine was temporarily withheld and oral prednisolone was increased as it was thought that the neutrophilic dermatosis was associated with the underlying ulcerative colitis. The patient's symptoms and cutaneous eruption resolved quickly and azathioprine was re-introduced. Within 24 h, systemic symptoms returned along with a florid recrudescence of his cutaneous eruption. This rapidly improved upon withdrawal of azathioprine.

**Key words:** adverse drug reaction, inflammatory bowel disease, Sweet's syndrome.

## INTRODUCTION

Azathioprine is widely used as a corticosteroid-sparing agent in the maintenance of inflammatory bowel disease.<sup>1</sup> Azathioprine hypersensitivity syndrome is a well-documented adverse effect presenting with fever, a variable cutaneous eruption and inflammation of one or more internal organs including the liver, kidneys, lungs and/or heart.<sup>2,3</sup> We describe a patient who presented with a neutrophilic dermatosis resembling Sweet's syndrome, which was initially suspected to be associated with the underlying ulcerative colitis, but which was subsequently thought to be due to azathioprine-induced hypersensitivity.

## CASE REPORT

The patient, a 46-year-old man, had a background history of ulcerative colitis that had been diagnosed 2 years previously. Disease activity was limited to the rectum and distal colon, and there was no history of extra-intestinal manifestations. He had been prednisolone-dependent for much of the preceding 2 years, with his ulcerative colitis flaring upon attempts to reduce the prednisolone dosage below 15 mg daily. Oral sulfasalazine had been ineffective, and 5-aminosalicylate enemas had been poorly tolerated.

Approximately 8 weeks prior to presentation, he experienced a flare of his ulcerative colitis, with inflammatory diarrhoea occurring up to six times per day. This was managed with an increase in his prednisolone to 50 mg daily. At 2 weeks prior to presentation, azathioprine was introduced at a dosage of 50 mg twice daily, and the prednisolone dosage was gradually tapered. At the time of his presentation, his prednisolone dosage was 15 mg daily.

The patient's current illness began while he was working in a rural mining town, and led to his transfer to a major city teaching hospital via the Royal Flying Doctor Service. The illness began approximately 5 days prior to his transfer. He initially developed a high fever, accompanied by sweating, fatigue, and widespread myalgias and arthralgias. Two days later, he developed a painful cutaneous eruption that was most marked over the upper back, shoulders, neck, face and ears. This was accompanied by loose, non-bloody diarrhoea two times per day. There were no relevant symptoms pertaining to other organ systems. Prior to transfer, he was noted to be febrile (38.6°C) and hypotensive (blood pressure 86/61 mm Hg). He was treated en route to the major city teaching hospital with intravenous fluid resuscitation and broad-spectrum intravenous antibiotics (ceftriaxone and flucloxacillin), on suspicion of sepsis.

Upon arrival, he was relatively well looking, and his blood pressure improved to 100/70 mm Hg. Examination of his skin revealed a florid eruption consisting of scattered erythematous papules and plaques, some of which were

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## Abbreviations:

|       |                                       |
|-------|---------------------------------------|
| G-CSF | granulocyte colony stimulating factor |
| IBD   | inflammatory bowel disease            |



**Figure 1** Clinical presentation of azathioprine-induced hypersensitivity presenting as a neutrophilic dermatosis. A florid eruption of erythematous papules and plaques appeared over a sun-exposed distribution in this 46-year-old man with ulcerative colitis after 2 weeks of azathioprine administration.



**Figure 2** A large pustule surrounded by erythema and purpura appeared on the base of the left index finger after 2 weeks administration of azathioprine.

highly oedematous with incipient vesiculation (Fig. 1). There were small pustules atop some of the plaques. The rash was mostly confined to the upper torso, face, neck and ears. On the anterior upper chest, there was a clearly demarcated rash in a V-shaped distribution, corresponding with a sun-exposed pattern. A large pustule surrounded by erythema and purpura was present on the base of the left index finger (Fig. 2). There were also a few scattered purpuric plaques on his thighs. Despite the patient's complaints of arthralgias, there was no evidence of synovitis, and no other relevant positive findings on systemic examination.

Laboratory results showed an elevated white cell count with neutrophilia, and a markedly raised C-reactive protein (Table 1). Electrolytes, urea and creatinine as well as liver function tests were normal. Complement (C3 and C4) levels were normal. Rheumatoid factor, anti-nuclear antibody, anti-DNA, extractable nuclear antibody and anti-neutrophil

**Table 1** Summary of laboratory investigation findings

| Test                                 | Result | Normal range |
|--------------------------------------|--------|--------------|
| Haemoglobin (g/L)                    | 134    | 135–180      |
| White cell count ( $\times 10^9/L$ ) | 11     | 4–11         |
| Platelets ( $\times 10^9/L$ )        | 230    | 150–400      |
| Sodium (mmol/L)                      | 137    | 134–146      |
| Potassium (mmol/L)                   | 3.8    | 3.4–5.0      |
| Urea (mmol/L)                        | 3.9    | 3.0–8.0      |
| Creatinine ( $\mu\text{mol/L}$ )     | 50     | 60–110       |
| Albumin (g/L)                        | 28     | 35–50        |
| C-reactive protein (mg/L)            | 260    | <5           |

cytoplasmic antibody studies were negative. A chest radiograph revealed a very small right-sided pleural effusion. Swabs were collected from the pustular skin lesions for microscopy and culture, and two sets of blood cultures were collected. An incisional skin biopsy was taken from a pustular plaque on the right arm, for histopathology.

Pending the results of the above investigations, a provisional diagnosis of a neutrophilic dermatosis (most closely resembling Sweet's syndrome) was made, and the patient's prednisolone dosage was increased to 75 mg daily. The condition was considered to be likely associated with the patient's underlying ulcerative colitis, as azathioprine-induced Sweet's syndrome has not been previously described. Nevertheless, the azathioprine was temporarily withheld.

The patient responded dramatically to prednisolone 75 mg daily orally, with definite flattening of his skin lesions and resolution of most of his systemic symptoms within 48 h. Histopathology on the skin biopsy (Fig. 3) showed marked superficial oedema with florid neutrophilic infiltration in the absence of vasculitis, consistent with Sweet's syndrome. The biopsy also showed an acute folliculitis. Cultures taken prior to antibiotic therapy from blood and skin swabs were sterile.

Following the patient's improvement, azathioprine was re-introduced while the patient was still taking prednisolone 75 mg daily. Within 24 h, his systemic symptoms returned and there was a florid recrudescence of his cutaneous eruption. This rapidly improved again on withdrawal of azathioprine. Following this improvement, the prednisolone dose was reduced to 50 mg per day without a recurrence of his symptoms. A final diagnosis of azathioprine-induced hypersensitivity presenting as a neutrophilic dermatosis was made.

At a 6-month telephone follow up, there were no recurrences of his symptoms, and his ulcerative colitis was well controlled on other therapy. A follow-up chest radiograph showed resolution of his pleural effusion.

## DISCUSSION

The phenotype of this patient's presentation, proven by histopathology, was that of a neutrophilic dermatosis. The presentation of a febrile illness with painful oedematous and pustulating plaques, distributed mostly on the upper body,

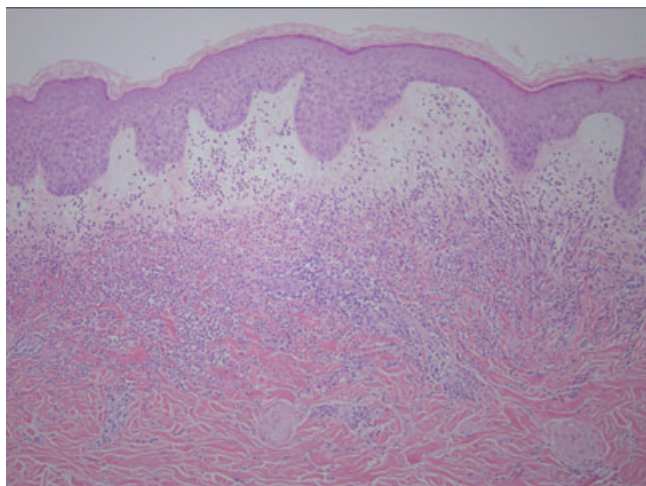


**Figure 5** Histopathology of skin specimen taken from a representative plaque on the right upper arm was consistent with a neutrophilic dermatosis. There is marked superficial dermal oedema with a florid neutrophilic infiltration in the dermis. There is no vasculitis (H&E;  $\times 40$ ).

was most in keeping with Sweet's syndrome. There were a number of atypical features, namely the apparent sun-exposed distribution of the cutaneous eruption, the presence of the large purpuric pustule on the hand, and the prominent follicular involvement on histopathology. However, the neutrophilic dermatoses represent a spectrum of disease, and overlapping forms exist that cannot always be neatly categorized. This case would be best considered as Sweet's syndrome.

Sun-exposed distribution of Sweet's syndrome lesions has previously been described in two case reports, but appears to be rare.<sup>4</sup> In our patient, we considered that the apparent sun-exposed distribution represented a Köbner phenomenon in sun-damaged skin. However, in the two previously reported cases, the lesions occurred in the absence of any actinic erythema.<sup>4</sup> Photo-aggravation by UVA1 has been formally documented in one patient by phototesting.<sup>4</sup>

Sweet's syndrome is associated with a variety of underlying diseases. IBD is a well-documented but relatively uncommon association. A review in 2005 identified only 36 cases of Sweet's syndrome occurring in association with ulcerative colitis,<sup>5</sup> and it is possibly even less commonly associated with Crohn's disease.<sup>6</sup> A variety of other neutrophilic dermatoses are also described in IBD, including pyoderma gangrenosum, erythema nodosum, bowel associated dermatosis-arthritis syndrome, pustular eruption of ulcerative colitis, and pyodermitis-pyostomatitis vegetans.<sup>7-9</sup> Many of these conditions represent variations of the same disease spectrum, and overlapping forms exist. Interestingly, follicular involvement has been well described as a histological feature in some IBD-associated neutrophilic dermatoses.<sup>8-10</sup>

Although the initial clinical suspicion was of Sweet's syndrome associated with the patient's underlying ulcerative colitis, withdrawal and (inadvertent) rechallenge of his aza-

thioprine indicated that the condition was drug-induced. Criteria for drug-induced Sweet's syndrome have been defined as: (i) abrupt onset of painful erythematous plaques or nodules; (ii) histopathological evidence of dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis; (iii) pyrexia (temperature  $> 38^{\circ}\text{C}$ ); (iv) temporal relationship between drug ingestion and clinical presentation, or temporal-related recurrence after oral challenge; and (v) temporal-related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids.<sup>11</sup> Our patient certainly meets these criteria for drug-induced Sweet's syndrome. The subject is detailed in a recent review.<sup>12</sup> A considerable number of drugs have been implicated, but those showing the most definite associations include G-CSF, all-transretinoic acid, minocycline and vaccines.<sup>12</sup> Several of these drugs (e.g. G-CSF) have effects on neutrophils as their key mode of action. Anti-neutrophil cytoplasmic antibodies have been described in some cases, and may be pathogenically relevant through the activation of neutrophils.<sup>10</sup>

Azathioprine hypersensitivity syndrome is an uncommon but well-described syndrome that typically occurs within the first 4 weeks of initiation of azathioprine therapy.<sup>2</sup> It is an idiosyncratic, non-IgE mediated reaction that appears to be unrelated to thiopurine methyltransferase levels.<sup>13</sup> The clinical presentation varies but commonly includes fever, hypotension, myalgia, arthralgia, respiratory symptoms, gastrointestinal upset, abnormal liver function tests, and rash.<sup>1</sup> Diagnosis is often missed or delayed, as the clinical features are often misinterpreted as either sepsis or an exacerbation of the underlying disease state being treated.<sup>1,14</sup> The cutaneous manifestations are variable and may not be prominent. They may include maculopapular eruptions, urticaria, and purpuric eruptions.<sup>14</sup> A few case reports exist of disorders in the neutrophilic dermatosis spectrum, including erythema nodosum-like eruptions<sup>1</sup> and acute disseminated exanthematous pustulosis induced by azathioprine.<sup>15</sup>

Review of the literature reveals several case reports that resemble our case, but in which the authors attribute the syndrome to underlying IBD rather than azathioprine. One case report describes a 39-year-old woman with a severe flare of ulcerative colitis, who developed fever and a widespread, painful pustular skin eruption 4 weeks after the initiation of azathioprine.<sup>10</sup> Histopathology showed dense neutrophilic infiltration as well as follicular involvement. The cutaneous eruption and the patient's colitis both settled after azathioprine was changed to cyclophosphamide. The authors attribute the patient's eruption as an association with the underlying ulcerative colitis, without mention of azathioprine as a possible aetiological factor. Similarly, another case report describes a 47-year-old woman with an exacerbation of Crohn's disease who developed typical Sweet's syndrome lesions 5 days after the initiation of azathioprine.<sup>6</sup> Although the azathioprine was ceased due to some suspicion of its involvement, the authors still favoured the Sweet's syndrome to be associated with the underlying Crohn's disease.<sup>6</sup>

In our case, our initial assessment was identical, for the same reasons; however, rechallenge of the drug suggested

otherwise. Rechallenge with azathioprine is not recommended, as clinical manifestations may recur more quickly and more severely upon rechallenge.<sup>1,16</sup> Because azathioprine is an imidazole derivative of 6-mercaptopurine, it is recommended that patients should also avoid 6-mercaptopurine.

## REFERENCES

1. de Fonclare AL, Khosrotehrani K, Aractingi S, Duriez P, Cosnes J, Beaugerie L. Erythema nodosum-like eruption as a manifestation of azathioprine hypersensitivity in patients with inflammatory bowel disease. *Arch. Dermatol.* 2007; **143**: 744–8.
2. Knowles SR, Gupta AK, Shear NH, Sauder D. Azathioprine hypersensitivity-like reactions—a case report and a review of the literature. *Clin. Exp. Dermatol.* 1995; **20**: 355–6.
3. Garey KW, Streetman DS, Rainish MC. Azathioprine hypersensitivity reaction in a patient with ulcerative colitis. *Ann. Pharmacother.* 1998; **32**: 425–8.
4. Belhadjali H, Marguery MC, Lamant L, Giordano-Labadie F, Bazex J. Photosensitivity in Sweet's syndrome: two cases that were photoinduced and photoaggravated. *Br. J. Dermatol.* 2003; **149**: 675–7.
5. Ytting H, Vind I, Bang D, Munkholm P. Sweet's syndrome – an extraintestinal manifestation in inflammatory bowel disease. *Digestion* 2005; **72**: 195–200.
6. Burrows NP. Sweet's syndrome in association with Crohn's disease. *Clin. Exp. Dermatol.* 1995; **20**: 279–80.
7. Delaney TA, Clay CD, Randell PL. The bowel-associated dermatosis–arthritis syndrome. *Aust. J. Dermatol.* 1989; **30**: 25–7.
8. Salmon P, Rademaker M, Edwards L. A continuum of neutrophilic disease occurring in a patient with ulcerative colitis. *Aust. J. Dermatol.* 1998; **39**: 116–18.
9. Vazquez J, Almagro M, del Pozo J, Fonseca E. Neutrophilic pustulosis and ulcerative colitis. *J. Eur. Acad. Dermatol. Venereol.* 2003; **17**: 77–9.
10. Sarkany RP, Burrows NP, Grant JW, Pye RJ, Norris PG. The pustular eruption of ulcerative colitis: a variant of Sweet's syndrome? *Br. J. Dermatol.* 1998; **138**: 365–6.
11. Walker DC, Cohen PR. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug-induced Sweet's syndrome. *J. Am. Acad. Dermatol.* 1996; **34**: 918–25.
12. Thompson DF, Montarella KE. Drug-induced Sweet's syndrome. *Ann. Pharmacother.* 2007; **41**: 802–11.
13. Hinrichs R, Schneider LA, Ozdemir C, Staib G, Scharffetter-Kochanek K. Azathioprine hypersensitivity in a patient with peripheral demyelinating polyneuropathy. *Br. J. Dermatol.* 2003; **148**: 1076–7.
14. Corbett M, Schlup M. Azathioprine hypersensitivity mimicking underlying inflammatory bowel disease. *Intern. Med. J.* 2001; **51**: 366–7.
15. Elston GE, Johnston GA, Mortimer NJ, Harman KE. Acute generalized exanthematous pustulosis associated with azathioprine hypersensitivity. *Clin. Exp. Dermatol.* 2007; **32**: 52–5.
16. Knowles S, Shear NH. Azathioprine hypersensitivity reactions: caution upon rechallenge. *Muscle Nerve.* 1997; **20**: 1467–8.