CASE REPORT

Azathioprine-induced bullous Sweet's syndrome: a rare association

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SUMMARY

A 52-year-old man presented with high-grade fever, headache and painful vesicular skin rash involving the upper trunk and upper extremities, 8 days after initiation of chemotherapy with azathioprine (50 mg/day), which had been prescribed for acral vitiligo. There was neither any history of preceding respiratory or gastrointestinal tract infection, nor was the patient known to have malignancy, drug hypersensitivity, inflammatory bowel disease, vasculitis or other autoimmune disease. Laboratory results revealed leucocytosis with neutrophilia and markedly elevated acute phase reactants. Antinuclear antibody, perinuclear and cytoplasmic antineutrophil cytoplasmic antibody were found negative. Punch biopsy from skin of the upper trunk revealed dense neutrophilic infiltration of dermis without signs of vasculitis, suggestive of Sweet's syndrome. In view of the temporal association with azathioprine and absence of an obvious alternative aetiology, provisional diagnosis of drug-induced bullous Sweet's syndrome was made. Azathioprine was discontinued and high-dose oral prednisolone initiated. The response was dramatic with resolution of skin lesions within 72 h without further recurrence at fourth week of follow-up.

BACKGROUND

Bullous Sweet's syndrome is rarely encountered in clinical practice. The pseudovesicular appearance of cutaneous lesions is often misleading. Azathioprine is a commonly prescribed drug. Azathioprine-induced bullous Sweet's syndrome has been rarely reported.

CASE PRESENTATION

A 52-year-old man had been prescribed azathioprine 50 mg/day for treatment of acral vitiligo. Eight days later, he presented to us with high-grade fever, headache and painful skin rash involving the upper trunk and upper extremities. Physical examination revealed numerous painful, vesicular, papulonodular cutaneous lesions over the neck, upper trunk and upper extremities (figures 1–3). The patient was febrile (39°C) and toxic. There was neither history of preceding respiratory or gastrointestinal tract infection, nor was he known to have malignancy, drug hypersensitivity, inflammatory bowel disease, vasculitis or other autoimmune disease. Laboratory results revealed leucocytosis (14 200 cells/mm³) with neutrophilia (polymorphonuclear cells 80%), markedly elevated erythrocytic sedimentation rate (92 mm in first hour) and C reactive protein (CRP) (141 mg/L). Antinuclear antibody

Figure 1 Erythematous, vesicular lesions with a few tense bullae over anterior aspect of neck and upper trunk.

(by immunofluorescence), perinuclear and cytoplasmic antineutrophil cytoplasmic antibody (ANCA) (by immunofluorescence) were negative. A complete haemogram showed haemoglobin 14 gm/dL, red blood cell (RBC) count of 4.5 million/mm³, haematocrit 46%, mean corpuscular volume (MCV) 91 fL, mean corpuscular haemoglobin (MCH) 31 pg/cell, MCH concentration (MCHC) of 35 g/dL, platelet count 210 000/mm³ and normochromic normocytes. No abnormal cells were present in the peripheral blood smear. Blood

Figure 2 Erythematous, vesicular lesions with a few tense bullae over posterior aspect of neck and upper trunk.

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Figure 3 Erythematous, vesicular lesions with a few tense bullae over lateral aspect of neck and upper trunk.

culture, liver function tests, renal function tests, urinalysis, fasting plasma glucose, postprandial plasma glucose levels, glycosylated haemoglobin, ultrasound of the abdomen, gastrointestinal endoscopy and X-ray of the chest were unremarkable. Three millimetre punch biopsy from skin of the upper trunk revealed dense neutrophilic infiltration of dermis without signs of vasculitis (figures 4 and 5), suggestive of Sweet's syndrome. Thiopurine methyl transferase (TPMT) activity was within normal limits (20.4 U/mL RBC, reference range: 15.1–26.4 U/mL RBC). In view of the temporal association with initiation of azathioprine, and absence of an obvious alternative aetiology, a provisional diagnosis of drug-induced Sweet's syndrome was made. Azathioprine was discontinued and high-dose systemic corticosteroid (prednisolone) initiated. The response was

Figure 4 Skin biopsy (10x) showing dense neutrophilic infiltrate of dermis without evidence of vasculitis.

Figure 5 Skin biopsy (40x) showing dense neutrophilic infiltrate of dermis without evidence of vasculitis.

dramatic with resolution of the skin lesions within 72 h (figure 6) without further recurrence at fourth week of follow-up.

INVESTIGATIONS

Laboratory results revealed leucocytosis (14 200 cells/mm³) with neutrophilia (polymorphonuclear cells 80%), markedly elevated erythrocytic sedimentation rate (92 mm in first hour) and CRP (141 mg/L). Antinuclear antibody (by immunofluorescence), perinuclear and cytoplasmic ANCA (by immunofluorescence) were negative. A complete haemogram showed haemoglobin 14 g/dL, RBC count of 4.5 million/mm³, haematocrit 46%, MCV 91 fL, MCH 31 pg/cell, MCHC of 35 g/dL, platelet count 210 000/mm³ and normochromic normocytes. No abnormal cells were present in the peripheral blood smear. Three millimetre punch biopsy from skin of the upper trunk revealed dense neutrophilic infiltration of dermis without signs of vasculitis suggestive of Sweet's syndrome.

DIFFERENTIAL DIAGNOSIS

- ▶ Herpes simplex virus infection.
- ▶ Herpes zoster virus infection.
- ▶ Bullous systemic lupus erythaematosus.
- ▶ Pyoderma gangrenosum.
- ▶ Erythaema multiforme.
- ▶ Erythaema nodosum.
- ▶ Cellulitis.
- ▶ Other vesicobullous disorders (bullous pemphigoid, pemphigus, etc).

TREATMENT

Azathioprine was discontinued and high-dose systemic corticosteroid (prednisolone at 1 mg/kg) prescribed. The dose of prednisolone was tapered gradually in the subsequent weeks. Following gradual dose tapering, since Sweet's syndrome did not recur up to the fourth week of follow-up, it was discontinued eventually at completion of 6 weeks of therapy.

OUTCOME AND FOLLOW-UP

The response was dramatic with resolution of the skin lesions within 72 h without further recurrence at fourth week of follow-up.

Figure 6 Complete resolution of skin lesions over anterior and posterior aspects of neck and upper trunk.

DISCUSSION

Sweet's syndrome, or acute febrile neutrophilic dermatosis, is a clinical condition characterised by abrupt onset of tender, erythematous papules, nodules and plaques occurring usually on the face, neck and upper extremities, characteristically associated with fever and peripheral neutrophilia. It was first described by Robert Sweet, in 1964, and occurs in various clinical settings. The classical form is observed in young females typically with a history of preceding respiratory or gastrointestinal tract infection, inflammatory bowel diseases or pregnancy.^{1 2} It may also occur in association with malignancies or use of certain drugs.³ The diagnosis is made on the basis of clinical and histopathological findings. Revised diagnostic criteria by von den Driesch⁴ for diagnosing the idiopathic/classical form requires presence of two major and two minor clinical findings as follows: Major criteria

- ▶ Abrupt onset of tender or painful erythematous plaques or nodules, occasionally with vesicles, pustules or bullae
- ▶ Predominantly neutrophilic infiltration in the dermis, without leukocytoclastic vasculitis

Minor criteria

- ▶ Preceding non-specific respiratory or gastrointestinal tract infection or vaccination, or association with inflammatory disease, haemoproliferative disorders, solid malignant tumours or pregnancy
- ▶ Periods of general malaise and fever ($>38^{\circ}\text{C}$)
- ▶ Laboratory values during onset showing an erythrocyte sedimentation rate >20 mm, positive CRP, segmented nuclear neutrophils, bands $>70\%$ in peripheral blood smears and leucocytosis ($>8000/\mu\text{L}$) (meeting 3 of 4 of these values is required)
- ▶ Excellent response to treatment with systemic corticosteroids or potassium iodide.

Dense neutrophilic infiltrate in reticular dermis, interstitial leukocytoclastic nuclear debris, extensive papillary dermal oedema, sparing of the epidermis and absence of vasculitis are histopathological hallmarks.⁵ The lesions respond dramatically to systemic corticosteroids and usually resolve without scarring. In persistent cases, the underlying cause needs to be evaluated and treated. Treatment with several drugs including potassium iodide, indomethacin, dapsone, colchicine, cyclosporine,

etretinate, clofazimine, pentoxifylline, metronidazole, doxycycline, methotrexate, cyclophosphamide, chlorambucil, infliximab, interferon α and intravenous immunoglobulin have been tried with variable success rates.

Sweet's syndrome can present in the following clinical scenarios: classical or idiopathic, drug-induced and malignancy-associated. Classical Sweet's syndrome is common in women and occurs in the setting of a preceding upper respiratory or gastrointestinal tract infection, inflammatory bowel disorders or pregnancy.^{1 2} Malignancy-associated Sweet's syndrome has been reported to occur with underlying solid tumours and haematogenous malignancies, of which acute myelogenous leukaemia is most frequent.³ Several drugs have been implicated, however, incidence with granulocyte colony stimulating factor is commonest. Following initiation of an offending drug, it takes an average of 7.5 days for clinical symptoms to appear.¹ The Walker and Cohen criteria¹ require the presence of all of the following five features for diagnosing drug-induced Sweet's syndrome:

1. Abrupt onset of painful, erythematous plaques or nodules.
2. Histopathological evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis.
3. Fever $>38^{\circ}\text{C}$
4. Temporal relationship between drug ingestion and clinical presentation or temporally related recurrence after oral challenge
5. Temporally related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids.

The classical skin lesions are painful erythematous papules, nodules or plaques, frequently involving the face, neck and upper extremities.⁵ Often, significant oedema of upper dermis gives a pseudovesicular or bullous appearance to the skin lesions,⁶ as noted in this case. Lesions may be photodistributed, which occurs on sun-exposed areas of the arms, hands and upper chest,^{1 7 8} as was observed in our case. Azathioprine, infrequently, has been known to cause Sweet's syndrome, but the occurrence of the bullous variant is indeed a rarity.⁹ It is important for the treating physician to be aware of this rare association for prompt withdrawal of the offending drug is required as a first step to definitive treatment.

Learning points

- ▶ While evaluating a febrile patient presenting with abrupt onset of painful, erythematous plaques or nodules, diagnosis of Sweet's syndrome should be borne in mind.
- ▶ Sweet's syndrome is common in women with preceding upper respiratory or gastrointestinal tract infections, history of inflammatory bowel disease or pregnancy. Sweet's syndrome may also occur secondary to drugs or malignancy.
- ▶ Physicians prescribing azathioprine should be aware of its rare association with Sweet's syndrome. Azathioprine-induced bullous variants of Sweet's syndrome have been rarely reported.
- ▶ Extensive subepidermal oedema may produce a deceptively vesicular or bullous appearance of the cutaneous lesions and may preclude the diagnosis.

Contributors SNB, PPC, KG and CB were involved in diagnosis and management of the patient. SNB, PPC and KG performed the literature search and wrote the manuscript. CB provided intellectual input.

Competing interests None declared.

Patient consent Obtained.

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