

## Azathioprine Hypersensitivity Presenting as Sweet Syndrome in a Child with Ulcerative Colitis

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Sweet syndrome is a cutaneous lesion characterized by tender, red inflammatory nodules or papules. We describe a pediatric case of Sweet syndrome presenting 10 days after treatment with azathioprine. As azathioprine is widely used in children with inflammatory bowel disease, clinicians should be aware of this unusual adverse reaction.

**Key words:** Azathioprine, Children, Hypersensitivity, Sweet syndrome.

**S**weet syndrome, or acute febrile neutrophilic dermatosis, is a cutaneous lesion characterized by tender, red inflammatory nodules or papules, usually affecting the upper limbs, face and neck. It can become generalized, and patients often are ill with associated signs and symptoms, including malaise, high fever, neutrophilia, elevated erythrocyte sedimentation rate and C-reactive protein levels, which mimic an infectious process. It has rarely been seen as a manifestation of azathioprine hypersensitivity in adults [1-4].

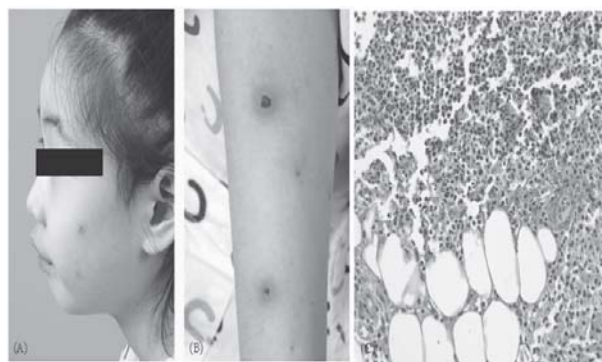
### CASE REPORT

A nine-year-old girl was referred for management of refractory ulcerative Colitis (UC) that had been diagnosed one year previously. She had no history of reported drug allergies and had been prednisolone-dependent (2 mg/kg/day) for much of the preceding year, with her disease flaring after attempts to reduce the prednisolone dosage. During the hospitalization, she received mesalazine treatment (48 mg/kg/day) without prednisolone, but it was ineffective. She underwent azathioprine therapy (1 mg/kg/day) and 10 days later was hospitalized for fever (temperature of 39.2°C), skin rash and hematochezia.

Physical examination was significant for numerous erythematous, painful, 1-3 mm vesicular lesions with central pustules on her face and both arms (**Fig. 1**). Laboratory results showed an elevated white blood cell count (13,470/ $\mu$ L) with neutrophilia, microcytic

hypochromic anemia (hemoglobin 9.2 g/dL, MCV 80.9 fL, MCH 24.8 pg), hyponatremia (132 mmol/L), and a markedly raised erythrocyte sedimentation rate (89 mm/hr) and C-reactive protein level (3.13mg/dL). Anti-nuclear antibody was negative, but c-type anti-neutrophil cytoplasmic antibody (c-ANCA) was positive. Her thiopurine methyltransferase (TPMT) activity was normal (18.2 U/ml RBC, reference range: 15.1-26.4 U/ml RBC). Blood cultures and urinalysis were obtained and the patient was started on cefotaxime (100 mg/kg/day) for a possible infectious etiology.

Two days after the cefotaxime treatment, the patient still had a fever. The patient then received metronidazole (30 mg/kg/day) for a week and prednisone (1.7 mg/kg/day). However, she was febrile with shaking chills and nausea. Cultures taken from blood and urine prior to antibiotic therapy were sterile. Biopsy specimens and tissue cultures were taken from the pustular lesions. Pathologic evaluation of skin biopsy showed massive neutrophilic infiltrate in the entire dermis (**Fig. 1**). Tissue culture results were negative for bacterial or fungal infection. Based on the clinical course, a diagnosis of sweet syndrome was made. As the patient's fever had not subsided in spite of the administration of antibiotics and steroid, we presumed that the sweet syndrome was caused by the azathioprine and was not due to inflammatory bowel disease. The azathioprine therapy was discontinued. Within 48 hours, the patient's fever abated and her skin lesions improved. Following this improvement, the



**Fig. 1** Pustular and crust lesions surrounded by erythema appeared on face (a) and arm (b) 10 days after administration of azathioprine. (c) Skin biopsy of pustular lesion shows massive neutrophilic infiltration in entire dermis (H&E, x400).

prednisolone dose was reduced to 0.4 mg/kg per day without a recurrence of her symptoms.

At follow-up after two weeks, there had been no recurrences of her symptoms, and her UC was comparatively well controlled by prednisolone and mesalazine treatment.

## DISCUSSION

The criteria for drug-induced SS have been reviewed by many authors [3,5] and include abrupt onset of painful erythematous plaques or nodules, histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis, pyrexia (temperature  $>38^{\circ}\text{C}$ ), and a temporal relationship between drug ingestion and clinical presentation, as well as resolution after withdrawal. Our patient meets most of these criteria.

ANCA have been described in some cases, and may be pathogenically relevant through the activation of neutrophils [6]. In our case, c-ANCA was positive. Kemmett, *et al.* [7] reported the presence of c-ANCA in six of the seven patients with sweet syndrome and speculated whether ANCA may be helpful in establishing the diagnosis of sweet syndrome.

Azathioprine is a widely used immunosuppressive agent that has been used increasingly as a steroid-sparing agent for the treatment of Crohn's disease and UC. Azathioprine rarely causes a hypersensitivity syndrome which is characterized by fever, headache, arthralgias, and rash, with possible cardiovascular, renal, lung, and hepatic involvement [8]. Skin lesions include erythematous or maculopapular eruptions, vesicles or pustules, urticaria,

purpuric lesions, erythema multiforme, or erythema nodosum. A case of acute generalized exantematous pustules induced by azathioprine like our case also has been reported [9]. Diagnosis is often missed or delayed, as the clinical features are often misinterpreted as either sepsis or an exacerbation of the underlying disease state. According to previous studies [10], TPMT activity was not predictive of this type of adverse effect.

The morphology of these skin lesions can mimic that of several other mucocutaneous and systemic conditions. The differential diagnosis includes infectious and inflammatory disorders, neoplastic conditions, reactive erythemas, vasculitis. Skin lesions and negative cultures help in the diagnosis. In addition, negative test results for autoimmune diseases are important for diagnosis. In our case, an infection focus or signs of an autoimmune disease could not be detected. Clinical and histopathologic findings supported the drug-induced sweet syndrome and cessation of the drug caused a rapid regression in symptoms. In patients without prior exposure to azathioprine, signs and symptoms usually begin approximately two weeks from the initial azathioprine exposure [1], which began after 10 days in this child.

We believe that azathioprine-induced sweet syndrome may be under-diagnosed because it can easily be misinterpreted as inflammatory bowel disease-related skin changes.

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## REFERENCES

1. Garey KW, Streetman DS, Rainish MC. Azathioprine hypersensitivity reaction in a patient with ulcerative colitis. *Ann Pharmacother.* 1998;32:425-8.
2. Paoluzi OA, Crispino P, Amantea A, Pica R, Iacopini F, Consolazio A, *et al.* Diffuse febrile dermatosis in a patient with active ulcerative colitis under treatment with steroids and azathioprine: a case of Sweet's syndrome. Case report and review of literature. *Dig Liver Dis.* 2004;36:361-6.
3. El-Azhary RA, Brunner KL, Gibson LE. Sweet syndrome as a manifestation of azathioprine hypersensitivity. *Mayo Clin Proc.* 2008;83:1026-30.
4. Yiasemides E, Thom G. Azathioprine hypersensitivity presenting as a neutrophilic dermatosis in a man with ulcerative colitis. *Australas J Dermatol.* 2009;50:48-51.
5. Su WP, Liu HN. Diagnostic criteria for Sweet's syndrome. *Cutis.* 1986;37:167-74.
6. 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.
7. Kemmett D, Harrison DJ, Hunter JA. Antibodies to

- neutrophil cytoplasmic antigens: serologic marker for Sweet's syndrome. *J Am Acad Dermatol.* 1991;24: 967-9.
8. El-Azhary RA. Azathioprine: current status and future considerations. *Int J Dermatol.* 2003;42:335-41.
  9. Elston GE, Johnston GA, Mortimer NJ, Harman KE. Acute generalized exanthematous pustulosis associated with azathioprine hypersensitivity. *Clin Exp Dermatol.* 2007;32:52-3.
  10. McGovern DP, Travis SP, Duley J, Shobowale-Bakre el M, Dalton HR. Azathioprine intolerance in patients with IBD may be imidazole-related and is independent of TPMT activity. *Gastroenterology.* 2002;122:838-9.

## H1N1 Infection in children with Hematological Malignancies

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In the recent pandemic of H1N1 infection, pediatric patients with haematological malignancies were considered high risk for severe illness. There is paucity of data regarding course of H1N1 infection in this subgroup. We describe H1N1 infection in 3 children with acute leukemia. All three patients presented with neutropenic fever; 2 had probable fungal pneumonia based on chest imaging and galactomanan estimation. Diagnosis of H1N1 infection was delayed in all 3 patients as it was not suspected initially. One patient died despite treatment. H1N1 infection may coexist with other infections in febrile neutropenia.

**Key words :** H1N1 infection, Hematological malignancies, Pneumonia.

**R**isk factors for severe illness and death due to H1N1 infection include young children, obesity, chronic lung disease, pregnancy, heart disease, neurocognitive disorders and immunosuppression [1]. In India, till now there have been 31866 confirmed cases and 1517 deaths of lab confirmed cases [2]. We describe the diagnostic challenges, course and outcome of H1N1 infection in three children with different hematological malignancies.

### CASE REPORT

We had three patients with different haematological malignancies in varied phases of treatment who were found to have H1N1 infection between December 2009 and March 2010. The clinical details are shown in **Table I**. Diagnosis of H1N1 infection was based on quantitative polymerase chain reaction from nasopharyngeal swabs. Chest radiological findings mimicked invasive aspergillosis in two patients. Galactomanan assay was also supporting fungal infection in these patients thereby suggesting a diagnosis of probable invasive aspergillosis. Bronchoalveolar lavage could be performed in only one patient (patient 3) who grew *Pseudomonas* species in the lavage fluid. All children were neutropenic at the onset of symptoms. One patient (patient 1) died due to respiratory

failure and shock. In this patient, there was a delay of more than 10 days to initiate treatment with oseltamivir, H1N1 infection was not suspected initially. The diagnosis and treatment of H1N1 infection was delayed in patient 3 also, but he improved with treatment as his disease was in remission and total leucocyte counts and neutrophil counts were showing on improving trend.

### DISCUSSION

It is interesting to study the course of this infection during the recent pandemic in this subgroup of patients as pediatric age group and malignancies both are considered to be risk factors for severe illness due to this infection. Patients with hematological malignancies are expected to have more morbidity and mortality due to the already compromised immunity, associated neutropenia, and coexistent bacterial and fungal infections. Usually a diagnosis of bacterial infection is considered in the setting of neutropenic fever and thereafter a fungal infection is considered if fever persists. It is for this reason that the diagnosis of H1N1 infection was not considered initially in our patients. The diagnosis was further delayed due to the radiological features being suggestive of invasive fungal infection in two patients. It is possible that H1N1 could have been a coexistent infection with other usual infections