

Case Report

AZATHIOPRINE HYPERSENSITIVITY SYNDROME: A CASE REPORT

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ABSTRACT

We report here the case of a 51-year-old man presenting to the Emergency Department with a febrile cutaneous eruption with diffuse arthralgia 10 days after the onset of azathioprine therapy. The clinical examination did not reveal any inflammatory syndrome and the results of all bacteriological tests were negative. A skin biopsy was performed, which revealed a granulocytary pustula with superficial dermal oedema and a neutrophil infiltration without sign of vasculitis. A side effect of azathioprine was suspected, and treatment was discontinued. Fortunately, the patient recovered within a few days.

Azathioprine hypersensitivity syndrome is a rare side effect of azathioprine. Hypersensitivity syndrome is an idiosyncratic, non-IgE-mediated reaction that appears to be unrelated to thiopurine methyltransferase levels. Diagnosis is mainly clinical and requires an exclusion of other processes. The only treatment option available is to stop azathioprine intake.

Key words: Azathioprine; side effect; hypersensitivity; cutaneous eruption; neutrophil infiltration

INTRODUCTION

Drug hypersensitivity syndrome (DHS) was first reported in the 1930s in patients treated with aromatic antiepileptic drugs, such as phenytoin (PHT), carbamazepine (CBZ), phenobarbital (PB), lamotrigine, etc. (1).

Azathioprine is an immunosuppressive drug widely administered to patients undergoing renal transplantation or suffering from an inflammatory disease, such as inflammatory bowel disease (IBD), but also from rheumatoid arthritis, vasculitis, chronic hepatitis, a number of dermatological diseases, or to prevent solid-organ transplant rejection. It is well known

that azathioprine is associated with many side effects, which can appear immediately or weeks to months after treatment. The overall incidence of side effects is 10% to 15% (2). Azathioprine hypersensitivity has been reported in 2% of patients (2). Early side effects include fever, hepatitis, nephritis, pneumonia, hypotension, arthralgia, pancreatitis, digestive symptoms and cutaneous manifestations.

We present here a case of DHS and discuss its differential diagnosis.

CASE REPORT

A 51-year-old patient presented to the Department of Gastroenterology of our institution with an exacerbation of Crohn's disease. Azathioprine therapy was started. In addition to 25 mg of azathioprine, the patient was also instructed to take Entocort 3 mg twice a day.

Ten days later, the patient presented to the Emergency Department with a fever of 38°C with chills, cough and dyspnoea. The next day, he developed back pain and arthralgia. A pustular rash first appeared on the joints, and then extended to the whole body (Figure 1). This eruption was not pruritic.

Laboratory tests revealed an inflammatory syndrome with increased C reactive protein (27.8 mg/dL). There was no neutrophilia. Electrolyte balance, kidney function and liver enzyme levels were normal.

The results of urine culture and haemocultures were negative. Serology for *Mycoplasma pneumoniae*, Chlamydia, Legionella, Lyme, Brucella, anti-streptolysin O and Yersinia were negative.

Three days after admission, the patient complained of diarrhoea. A cutaneous biopsy was performed, which revealed a granulocytary pustula with superficial dermal oedema. A neutrophil infiltration was also noted, without any sign of vasculitis.

The results of the biopsy were consistent with Sweet's Syndrome. The bacteriological culture of the pustules was negative.



Figure 1: Cutaneous eruption.

Thiopurine S-methyltransferase (TPMT) activity was normal; therefore, a genetic predisposition to toxicity due to drug metabolism by TPMT was ruled out.

Azathioprine therapy was discontinued. The patient remained afebrile and free of symptoms for five days. The cutaneous eruption resolved over the next few days.

DISCUSSION

Azathioprine is an imidazolyl derivative of 6-mercaptopurine. It has both cytotoxic and immunosuppressive effects (3), and inhibits RNA and DNA synthesis. One of the main enzymes involved in thiopurine metabolism is TPMT, which induces the formation of inactive metabolites. Because it differs among individuals, measurement of TPMT activity is encouraged prior to starting azathioprine therapy.

Hypersensitivity syndrome is not well known and is often confused with an infectious disease, although bacteriological tests show negative results. A recent review revealed that 67 cases of azathioprine hypersensitivity syndrome have been reported between 1986 and 2009 (2).

Hypersensitivity syndrome is an idiosyncratic, non-IgE-mediated reaction that appears to be unrelated to thiopurine methyltransferase levels (4). The resulting clinical manifestations correspond to a type III or IV allergic reaction (2). This early side effect of azathioprine is not dose-dependent, contrary to the long-term ones. It is due to direct toxicity of a catabolic product of azathioprine, i.e., 6-thioguanine nucleotide. The incidence of this effect ranges from 4% to 27% (2).

There is no test to diagnose hypersensitivity syndrome. A characteristic of this syndrome is the onset of symptoms during the first four weeks after initiation of azathioprine therapy, and their remission within five days after the drug intake has been stopped. Upon reintroduction of the drug, recurrence of symptoms can be noted (2). Furthermore, drug reintroduction can cause anaphylaxis (5).

The various clinical manifestations of azathioprine hypersensitivity include fever, musculoskeletal symptoms (arthralgia, myalgia, etc.), cutaneous eruptions, neurological symptoms and other organ involvement, such as cardiovascular, renal, gastrointestinal and respiratory symptoms. The most common symptoms are fever, malaise, arthralgia, myalgia, nausea, vomiting, diarrhoea and cutaneous rash (2).

Hypersensitivity syndrome can manifest as an erythema nodosum, Sweet's syndrome, small vessel vasculitis, acute generalised exanthematous pustulosis or a non-specific rash (urticaria, pustules, purpura, macula, and papules) (2).

All skin manifestations include a neutrophil infiltration with superficial dermal oedema without vasculitis.

Sweet's syndrome is characterised by acute onset of painful, erythematous plaques with histological findings of a neutrophil infiltrate, fever and neutrophilia (2). The cutaneous eruption in Sweet's syndrome develops primarily on the head, neck and upper torso. Sweet's syndrome is frequently associated with an underlying disease, such as IBD.

A few studies have shown that Sweet's syndrome can be due to the disease itself, as opposed to the eventually administered azathioprine.

In the present case, Sweet's syndrome was not considered in the differential diagnosis because there was no neutrophilia.

CONFLICT OF INTEREST: None.

REFERENCES

1. Kumari R, Tinshina DK, Thappa DM. Drug hypersensitivity syndrome. *Indian J Dermatol Venereol Leprol.* 2011; 77(1): 7-15.
2. Bidinger JJ, Sky K, Battafarano DF, Henning JS. The cutaneous and systemic manifestation of Azathioprine hypersensitivity syndrome. *J Am Acad Dermatol* 2011; 65(1): 184-191.
3. Park D, Fergusson A, Ford L, Berg J, Adel H. Mansur Side effects from Azathioprine in a patient with thiopurine S-methyl transferase deficiency. *Respiratory Medicine CME.* 2009; 2: 102-105.
4. Yiasemides E, Thom G. Azathioprine hypersensitivity presenting as a neutrophilic dermatosis in a man with ulcerative colitis. *Australas J Dermatol* 2009; 50(1): 48-51.
5. Olaiwan O, Wendling J, Pouzoulet J, Gaulier A, Ingen-Housz-Oro S, Sigal M. Cutaneous manifestation of hypersensitivity to Azathioprine in a Crohn's disease patient. *Gastroenterol Clin Biol.* 2008; 32(12): 1075-1076.

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