

Topical mesalazine as a cause of Stevens-Johnson syndrome

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ABSTRACT

Mesalazine is a drug routinely used in ulcerative colitis and usually has few side effects. There have been reports of uncommon cases of severe mucocutaneous damage, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), induced by salicylates. It is important to diagnose these promptly due to the high morbidity and mortality rates. We describe the case of a 46-year-old female with ulcerative proctitis, who developed SJS following topical mesalazine use. The lesions responded well to intravenous corticosteroids after discontinuation of the drug.

Key words: Mesalazine. Stevens-Johnson syndrome. Toxic epidermal necrolysis.

INTRODUCTION

Mesalazine has proved to be an effective treatment in ulcerative colitis. It is routinely used both orally and topically and side effects are uncommon (1). There are some reports of the development of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with mesalazine use (1,2). Although very uncommon, these dermatological conditions are serious and affect multiple systems. They need to be recognized early due to the associated high morbidity and mortality rates (3). This article describes the case of a female patient with ulcerative proctitis, who developed SJS after topical administration in the form of mesalazine suppositories.

CASE REPORT

A 46-year-old female diagnosed in 2008 with ulcerative proctitis was initially treated with oral mesalazine of 3 g/day and subsequently switched to rectal suppositories of 1 g/day. She discontinued follow-up and treatment due to clinical improvement. In October 2016, she attended the clinic after the onset of rectal tenesmus with mucus and blood. A colonoscopy confirmed moderate rectal involvement, with no other lesions in the rest of the colon or the terminal ileum. Subsequently, she resumed mesalazine suppositories at a dose of 1 g/day.

Two weeks later, she developed bullous lesions in the oral region. These failed to improve with nystatin treatment and more blisters appeared on the trunk, upper and lower limbs, palms of the hands and soles of the feet, with an associated fever of 38 °C (Figs. 1 and 2). She had no associated genital lesions and was in general good health. Nikolsky's sign was negative and the laboratory tests showed C-reactive protein (CRP) levels of 129.3 mg/l, mild leucocytosis with neutrophilia and anemia of 100 g/l, with no other abnormalities.

Intravenous aciclovir was started due to a suspicion of a disseminated herpes infection. This was discontinued when the polymerase chain reaction (PCR) assay proved negative for *herpes virus* and *varicella-zoster virus*. Intravenous corticosteroids were also initiated and the patient underwent a dermatological assessment. This included a skin biopsy, which yielded findings consistent with SJS.

The patient made good progress and the lesions disappeared. Her clinical features were attributed to topical mesalazine following direct questioning and having ruled out the concomitant use of other drugs. She was treated with budesonide enemas for management of her rectal disease in order to avoid the use of salicylates.

DISCUSSION

Mesalazine is a drug with a proven efficacy for the induction and long-term maintenance of the remission of ulcerative colitis. It has an excellent safety profile and its side effects are rare. However, they include serious dermatological reactions such as SJS or TEN (1,2). SJS and TEN are two variants of the same entity, almost exclusively drug-induced, in which the dermoepidermal junction is disrupted. It has a low incidence of approximately 1-2 cases per million people per year (3). It is an immune-mediated condition in

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Fig. 1. Erythema, erosions and crusting on the lips.



Fig. 2. Bullous and eroded lesions on the back and the posterior side of the arm.

which CD8⁺T lymphocytes activated by drugs induce apoptosis and necrosis of epidermal keratinocytes (3,4).

Normally, the onset of skin lesions tends to be preceded by an influenza-like illness consisting of fever, general malaise and upper respiratory tract symptoms (3-5). The skin lesions are macules with blisters or flat atypical targets. At first they appear predominantly on the face, trunk and proximal limbs. Subsequently, they tend to spread to the rest of the trunk and the distal limbs. There is often palmoplantar involvement (3). Skin fragility is characteristic, with a separation of the epidermis when pressure is applied to the lesion (Nikolsky's sign). Mucosal involvement is common, and erosive and hemorrhagic mucositis can affect the eyes, mouth, nose and genitals (3,4).

SJS and TEN are distinguished by the percentage of body surface area involved, < 10% SJS, 10-30% overlap syndrome and > 30% TEN (3). Although it is rare, SJS/TEN can be a

devastating disease. In severe cases, the acute phase may be accompanied by a range of systemic complications due to respiratory and gastrointestinal involvement, triggering multi-organ failure (3,4).

Diagnosis is based on clinical and histological criteria (3,5). The morphology and extent of the lesions, in the context of drug exposure or disease, should raise suspicions (6). Even though a suspected diagnosis is reached on clinical grounds, histopathological examination of a skin biopsy is required to confirm or rule out other blistering diseases. However, the histology is not pathognomonic (3,5).

Any drug can cause this condition, although the most common are allopurinol, beta-lactam antibiotics, antiepileptic drugs, sulfonamides and non-steroidal anti-inflammatory drugs (NSAIDs). The lesions tend to appear within the first eight weeks after the start of treatment. Infections or infections combined with drug use have been suggested as causative agents (7,8). There have been case reports of SJS induced by *Mycoplasma pneumoniae* infection, mainly in children (3,7).

Sulfasalazine is a drug often implicated in the development of SJS/TEN (3,6,9). In the case of 5-aminosalicylic acid (5-ASA) formulations, there are only two published case reports. Lemoli et al. (1) published the first case of TEN related to oral balsalazide in 2006. This patient had started taking it after discontinuing sulfasalazine due to the development of a skin rash and had previously shown good tolerance to topical mesalazine use. A second case was subsequently published in 2007 by Fukunaga et al. (2). In this case, the onset of TEN could arguably have been induced by one of the components of the mesalazine preparation, rather than mesalazine itself. The case we report here is the first to be described following topical mesalazine use.

It is essential to identify the culprit drugs and withdraw them promptly. The patient should also be admitted to a burns unit or intensive care unit if skin involvement is very extensive. The most important prognostic factor is early discontinuation of all suspect treatments (7,9). The use of corticosteroids is controversial. Some studies suggest using them due to their anti-inflammatory effect, whereas an increased risk of morbidity and mortality has been observed in other studies, mainly related to the development of sepsis. The use of intravenous gamma globulin, cyclophosphamide or ciclosporin has also been suggested (3,7).

The mortality rate ranges from below 10% for SJS to over 30% for TEN. Sequelae occur in approximately 24% of patients and tend to be related to scarring from the lesions. Mucosal involvement can lead to synechia and stenosis and eye involvement can result in blindness (7).

Recurrence is extremely rare, unless the drug responsible for the initial episode is re-administered, or the patient is given another related drug capable of causing a cross-reaction. This has the potential to produce a fatal reaction (7). Thus, voluntary exposure to the drug is formally contraindicated, as is the use of other formulations of the same drug. Therefore, other treatment options have to be used, as in our case.

In summary, mesalazine is a safe drug with a low rate of side effects, which include case reports of serious dermatological conditions such as SJS and TEN. These lesions can occur with oral and topical formulations, as in our case, and must be recognized promptly due to the high associated morbidity and mortality rates.

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