Erythema nodosum as azathioprine hypersensitivity reaction in a patient with bullous pemphigoid

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Abstract

A 65-year-old woman with bullous pemphigoid presented with fever and several red-purple nodular subcutaneous lesions on both lower legs 1 week after starting treatment with azathioprine (AZA). Biopsy of a skin nodule was compatible with erythema nodosum (EN) and hypersensitivity reaction to AZA was suspected. AZA was subsequently discontinued, observing complete remission of fever and EN within 2 weeks. This case highlights the importance of recognizing EN as a possible manifestation of hypersensitivity reaction to AZA.

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Full Text

Introduction

Azathioprine (AZA) is an immunosuppressive agent, whose most common adverse effects comprise gastrointestinal symptoms; granulocytopenia; hepatitis; and less frequently, nephritis, pancreatitis, and skin lesions. [1] erythema nodosum (EN) is a rare but documented manifestation associated with AZA treatment. [2] We herein report for the first time the occurrence of this side effect in a patient with bullous pemphigoid (BP).

Case Report
A 65-year-old woman had been recently diagnosed as having BP on the basis of a generalized pruriginous bullous eruption affecting predominantly the trunk and the limbs, and a compatible biopsy. Treatment with prednisone (60 mg Q.D.) was started and the skin lesions progressively improved within 3 weeks. After checking that thiopurine methyltransferase (TPMT) activity was normal, AZA (50 mg Q.D.) was introduced as a corticosteroid-sparing agent. One week later, well-tolerated fever along with several tender, dusky red-purple nodular subcutaneous lesions appeared on both lower legs [Figure 1]. There was no evidence of any other symptoms or clinical findings. Complete blood count, laboratory tests, and chest radiograph showed no abnormalities. Mantoux test was negative. Biopsy of a skin nodule was performed and histological examination revealed septal panniculitis with lymphocytic infiltration of the hypodermis [Figure 2], findings highly suggestive of EN. Aside from prednisone and AZA, no other medications were administered at that time. Hypersensitivity reaction to AZA was suspected and the drug was discontinued, observing complete remission of the fever and EN within 2 weeks. {Figure 1} {Figure 2}

Discussion

AZA is a thiopurine-derived immunosuppressive drug that is commonly used in several dermatological and rheumatic diseases as a corticosteroid-sparing agent, so recognizing AZA hypersensitivity reactions are important in daily clinical practice. Similar prevalence in men and women, a wide range of age of presentation (16-76 years), and a broad variation in the initial dose of AZA (100 ± 48 mg) have been described previously. [1] De Fonclare et al. [2] reported three cases of EN associated with AZA in patients with inflammatory bowel disease. Similarities and differences between those cases and ours can be noted. The time interval between AZA initiation and EN appearance varied from 1 to 2 weeks (a mean of 12 days), similar to our case. However, those patients had fever, rash, and arthralgias in addition to EN. Interestingly, TPMT activity was normal both in de Fonclare’s cases and ours. On the other hand, complete remission of all clinical and biochemical abnormalities after discontinuing AZA was noted in all cases, as in our case. Finally, unlike de Fonclaire et al., we did not re-administer the patient AZA to confirm the diagnosis since life-threatening complications, even with using small doses of AZA or 6-mercaptopurine, have been reported previously. [2],[3] However, the suspicion of AZA hypersensitivity remained very high because of the following: The chronology of the patient’s illness in relation to the initiation of AZA (only 1 week of time between the cause and the suspected effect); the presence of features of hypersensitivity to AZA described previously: Fever and EN; the absence of other causes that could justify the development of fever and EN; and the fast improvement and remission of EN after AZA withdrawal.

The mechanisms involved in AZA hypersensitivity reaction remain unclear. The side effects associated with AZA use have been classified as early or late events. Late adverse reactions are usually dose-dependent and they can be anticipated in part by evaluation of TPMT activity. By contrast, early adverse effects (which normally occur 4 weeks following treatment initiation) are usually idiosyncratic, non-dose-dependent reactions due to hypersensitivity mechanisms and therefore, difficult to predict. [4] Nevertheless, it has not been yet elucidated whether the drug itself (via its imidazole component) or one of its metabolites (6-mercaptopurine mainly) acts as a hapten that binds to a protein molecule and lastly a type-1 hypersensitivity reaction is elicited. [2],[3] Finally, genetic polymorphisms in the inositol triphosphate pyrophosphatase gene may also be involved in developing AZA hypersensitivity. [5]

To continue, we want to highlight the interest of this report. On the one hand, this is the first case of EN as a consequence of AZA treatment described in the medical literature in a patient with BP. On the other hand, we want to emphasize that EN may be a clinical sign of hypersensitivity to AZA in patients who have recently started to take this drug. Since hypersensitivity to AZA includes a wide variety of manifestations shared by many rheumatic diseases, this condition should be considered as an alternative diagnosis to the onset or worsening of symptoms secondary to the underlying disease.
References


