

Case report

Erythema multiforme due to pyrazinamide

Perdu D, Lavaud F, Prévost A, Deschamps F, Cambie MP, Bongrain E, Barhoum K, Kalis B. Erythema multiforme due to pyrazinamide. *Allergy* 1996; 51: 340–342. © Munksgaard 1996.

Drug-induced erythema multiforme is reported with many antimicrobial and antipyretic medications. We present one patient who experienced erythema multiforme and urticaria after administration of pyrazinamide for treatment of cutaneous tuberculosis. The side-effects of pyrazinamide include hepatic or dermatologic disorders, but erythema multiforme has not yet, to our knowledge, been described. Clinical features and discontinuation and reintroduction of the drug led us to consider pyrazinamide the cause of the erythema multiforme, but allergologic studies remained negative, except for the presence of circulating immune complexes. The mechanism of this eruption remains obscure, and definite withdrawal of pyrazinamide seems to be the best therapeutic choice.

**D. Perdu¹, F. Lavaud¹, A. Prévost¹,
F. Deschamps¹, M.-P. Cambie²,
E. Bongrain¹, K. Barhoum³, B. Kalis²**

¹Department of Respiratory Diseases and Allergology, ²Department of Dermatology, and ³Pol Bouin Laboratory, University Hospital of Reims, Reims, France

Key words: adverse reactions; drugs; erythema multiforme; pyrazinamide.

Dominique Perdu, MD
Département des Maladies Respiratoires et Allergiques
CHR de Reims
45 rue Cognacq-Jay
51092 Reims Cedex
France

Accepted for publication 9 January 1996

Since 1952, pyrazinamide has been successfully used against human tuberculosis (1, 2). The most common side-effect is hepatitis, which occurs in 1–5% of patients (2–5); other adverse reactions include hyperuricemia and skin reactions (1–13%) (4, 5). Serious cutaneous symptoms have rarely been reported (3, 5–7). We present a case of erythema multiforme after pyrazinamide administration in a patient with cutaneous tuberculosis related to a pleural fistula.

Case report

A 75-year-old white man was admitted to the hospital for a thoracic tuberculosis cold abscess. The pleura was the origin of the infection, and a fistula explained the relation with the skin. Carcinoma of the right upper lobe of the lung was also associated with the cutaneous tuberculosis. The patient's pulmonary function did not allow surgery resection, and palliative treatment of the cancer was decided upon.

Antituberculosis treatment was started with isoniazid (200 mg/day), rifampin (600 mg/day), ethambutol (1200 mg/day), and pyrazinamide (1500 mg/day). After 26 days, thoracoabdominal and back circinate erythematous maculopapular lesions appeared without bullous lesion, mucous

membrane involvement, or systemic symptoms. Cutaneous lesions suggested erythema multiforme (Fig. 1). Biopsy confirmed the diagnosis (Fig. 2), but did not show deposition by immunofluorescence (IgA, IgG, IgM, and C3). Erythema multiforme disappeared with discontinuation of all drugs. Five days later, rifampin and pyrazinamide were reintroduced: a back maculopapular urticarial eruption occurred, regressing again after the withdrawal of the two drugs. A few days later, urticaria was again observed immediately after a single dose of pyrazinamide, leading to the definite discontinuation of the drug. No other skin reactions appeared after admin-



Fig. 1. Erythema multiforme of back caused by pyrazinamide.

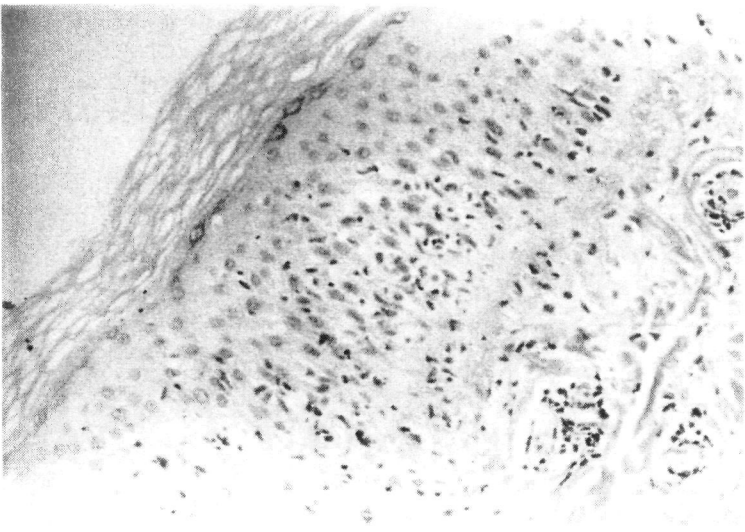


Fig. 2. Skin biopsy specimen from erythema multiforme lesion. Spongiosis with lymphocyte exocytosis and perivascular mononuclear infiltrate (hematoxylin-eosin stain $\times 100$).

istration of the three other antituberculosis drugs during the last 9 months of the treatment. However, the patient died after neoplastic progression of the lung cancer.

Allergologic studies

Skin prick tests were negative with a battery of common aeroallergens. Patch tests with the European Standard Series were negative. Control tests with histamine hydrochloride (10 mg/ml) and codeine (9%) were positive, causing wheals of 8.5 and 10 mm, respectively. Skin prick tests with isoniazid (5 mg/ml), rifampin (30 mg/ml), ethambutol (25 mg/ml), and pyrazinamide (50 mg/ml) were negative. Intradermal injection of pyrazinamide with a native product (1 mg/ml) and specific patch tests (pyrazinamide 1% and 10% aqueous; pyrazinamide 1% and 10% ethanol) (8) showed negative results. Moreover, the diameter of the intracutaneous tuberculin skin reaction was 12 mm.

Human basophil degranulation tests with the four antituberculosis drugs (dilution 1/10 000 to 1/10) and a lymphoblastic transformation test with pyrazinamide (native product) gave no specific results.

Total serum IgE (Prist-Pharmacia) and eosinophil count showed normal values. Immunologically abnormal results were discovered, as positive anti-nuclear antibody (1/200), presence of circulating immune complexes (IgG and IgM), IgG cryoglobulinemia to 80 mg/l, lymphopenia (relative decrease of CD8), and hypocomplementemia with CH 50 < 20 U (N: 60–150 U) and C4: 0.004 g/l (N: 0.2–0.5 g/l).

Discussion

Pyrazinamide, a synthetic pyrazine analog of nicotinamide (1, 2, 8), has been recently reintroduced in antituberculosis treatment, but at a lower dose to

reduce hepatotoxicity (2, 5). Adverse reactions are described but are often benign: small rises in liver excretion of uric acid by the metabolite pyrazinoic acid, arthralgias, gastrointestinal disturbances, malaise, and fever (2–8). Among the various skin reactions that occur (2, 3, 5, 7, 8) are rash (2, 5, 8), urticaria (9), flushing (3), burning sensation of the skin (7, 8), development of reddish-brown discoloration of the skin on sun-exposed areas (7, 8), pellagra (6), photosensitivity (3), and exfoliative dermatitis (5), but such adverse skin reactions are uncommon.

Targetlike lesions with a circinate or concentric macular eruption suggest erythema multiforme (10). Infections, carcinoma, and drugs explain most of this eruption, which can be severe if the mucous membrane is involved (10, 11). Rifampin (10) and isoniazid (7) have been described as possible causes. We present a case of pyrazinamide-induced erythema multiforme in which the causal relationship was proved by the reappearance of eruption after administration of this drug. To our knowledge, no similar case has been published. Medical research has often proved the drug origin of eruption which disappears when drugs are withdrawn. Moreover, biologic results and skin and serologic tests are often negative (12), even if hypersensitivity is possible. In our observation, immunodepression due to cancer and tuberculosis could explain the negativity of allergologic tests. This negativity could also be caused by the metabolites of pyrazinamide (10, 12, 13), such as pyrazinoic acid (2), which were not tested by allergologic methods.

The pathogenicity of erythema multiforme, when drugs are suspected, has often remained obscure, and the association of toxicity and hypersensitivity cannot be excluded (12, 13). IgE-mediated reactions may cause multiformelike reactions (14), but late-phase reaction or immune complex-mediated inflammation may also induce erythema multiforme (14). Deposits of immune complexes in the walls of vessels in the superficial cutaneous microvasculature have been found in erythema multiforme lesions (11). Elevated levels of immune complexes and reduced levels of complement components in blister fluids have also been detected (15). In our observation, the presence of circulating immune complexes suggests an immune mechanism, but the results of immunofluorescence in cutaneous biopsy were negative, and immune complexes may also be increasingly involved in the pathogenesis of numerous disease states, particularly infectious and neoplastic diseases (11). Cell-mediated (delayed) hypersensitivity might also be suspected, but the patch test results remained negative.

In some cases, a reintroduction test can be useful when antituberculosis drugs are absolutely neces-

sary (3). However, serious adverse effects can appear, such as the Stevens-Johnson syndrome or Lyell's syndrome (10, 13, 14), and we suggest that a reintroduction test be avoided in cases of erythema multiforme.

Definite discontinuation of the drug is the logical treatment, but it is not always possible (7, 12). Hyposensitization has been described with pyrazinamide after urticaria (9). Indeed, hyposensitization in hospitalization with antihistamine treatment may reduce the risk of a severe adverse reaction (12), but, in cases of erythema multiforme, hyposensitization entails an unknown and therefore unacceptable risk. In fact, pyrazinamide is not unavoidable in tuberculosis treatment, and, for our patient, tritherapy treatment for 9 months has been successful without adverse reactions.

References

1. Kushner S, Dalalian H, Sanjurjo JL, et al. Experimental chemotherapy of tuberculosis. II. The synthesis of pyrazinamide and related compounds. *J Am Chem Soc* 1952;74:3617-21.
2. Davidson AT, Le HQ. Drug treatment of tuberculosis – 1992. *Drugs* 1992;43:651-73.
3. Girling DJ. Adverse effects of antituberculosis drugs. *Drugs* 1982;23:56-74.
4. Van Scoy RE, Wilkowske CJ. Antituberculous agents. *Mayo Clin Proc* 1992;67:179-87.
5. Pretet S, Perdrizet S. La toxicité du pyrazinamide dans les traitements antituberculeux. *Rev Fr Mal Respir* 1980;8:307-20.
6. Jorgensen J. Pellagra probably due to pyrazinamide: development during combined chemotherapy of tuberculosis. *Int J Dermatol* 1983;22:44-5.
7. Høldiness MR. Adverse cutaneous reactions to antituberculosis drugs. *Int J Dermatol* 1985;24:280-5.
8. Goday J, Aguirre A, Diaz-Perez JM. A positive patch test in a pyrazinamide drug eruption. *Contact Dermatitis* 1990;22:182-3.
9. Soye F, Surpras P, Vestri R, Philip-Joet F, Arnaud A. Reaction inhabituelle au Pirilène. *Rev Fr Allergol* 1988;28:1.
10. Vanarsdel PP. Adverse drug reactions. In: Middleton EJ, Reed CE, Ellis EF, editors. *Allergy: principles and practice*. St Louis, MO: CV Mosby, 1983;1389-1414.
11. Kazmierowski JA, Wuepper KD. Erythema multiforme: immune complex vasculitis of the superficial cutaneous microvasculature. *J Invest Dermatol* 1978;71:366-9.
12. Anderson JA, Adkinson NF. Allergic reactions to drugs and biologic agents. *JAMA* 1987;258:2891-9.
13. Mathews KP. Clinical spectrum of allergic and pseudoallergic drug reactions. *J Allergy Clin Immunol* 1984;74:558-66.
14. Kaplan AP. Drug-induced skin disease. *J Allergy Clin Immunol* 1984;74:573-9.
15. Safai B, Good RA, Day NK. Erythema multiforme: report of two cases and speculation on immune mechanism involved in the pathogenesis. *Clin Immunol Immunopathol* 1977;7:379-85.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.