

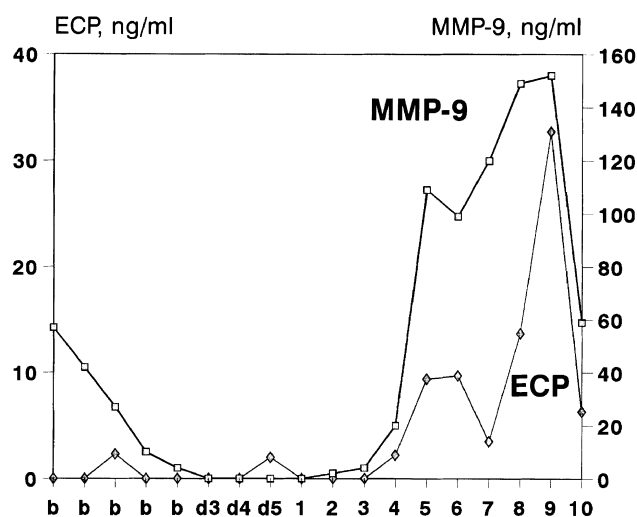


Figure 1. ECP and MMP-9 in nasal lavage fluid after nasal challenge with house-dust-mite extract. b) Lavage before challenge; d3, d4, d5) Lavage after challenge with *D. pteronyssinus* extract (10^3 , 10^4 , and 10^5 SQU/ml, ALK, Denmark). 1–10) Hours after last allergen challenge.

the study was approved by the medical ethical committee of the University Hospital Rotterdam-Dijkzigt (5).

Before nasal challenge with allergen extract, nasal lavage was performed four times to obtain baseline mediator levels. Nasal lavage was performed as described by Naclerio et al. (1).

Both nostrils were washed with 5 ml saline, prewarmed to 37°C.

To prevent nasal congestion, 0.125 ml 0.1% oxymetazoline was sprayed into each nostril 5 min before the first allergen challenge. For allergen challenge, 0.125 ml allergen extract was sprayed into each nostril, and 10 min later nasal lavage was performed. Lavage fluid was collected in plastic tubes and kept on ice. Within 1 h after collection, the lavage fluid was centrifuged; the supernatant was stored at -20°C.

MMP-9 was determined by ELISA (Biotrak, Amersham, Buckinghamshire, UK) according to the manufacturer's instructions. This ELISA primarily detects proMMP-9 (MMP-9 proenzyme) and proMMP-9 bound to tissue inhibitors of metalloproteinases (TIMPs-1 and -2). ECP was estimated by RIA, according to the manufacturer's instructions (Pharmacia, Uppsala, Sweden).

In four patients, maximum MMP-9 levels were observed 9 or 10 h after nasal provocation with allergen. In Fig. 1, the results of nasal lavage are shown for one of these four patients. In the fifth patient, a maximum MMP-9 level (340 ng MMP-9/ml lavage fluid) was already observed 3 h after allergen provocation. As

shown before (5), a maximum ECP level in lavage samples from this patient was also seen as early as 3 h after nasal provocation.

Matrix metalloproteinases, a family of zinc-dependent proteases, have been implicated in pathologic tissue degradation in diseases such as rheumatoid arthritis, osteoarthritis tumor invasion, and, recently, asthma (4). Our results further extend these observations into the field of allergic rhinitis.

The ELISA we used primarily recognizes enzymatically inactive proMMP-9; active MMP-9 has only 2.7% cross-reactivity with proMMP-9 in this ELISA (information supplied with the MMP-9 ELISA, Amersham). The relative amounts of active MMP-9 and proMMP-9 in lavage samples should be the subject of a future study. In summary, our study indicates that nasal allergen provocation induces MMP-9 release as part of the late-phase inflammatory response.

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Accepted for publication 12 January 1999
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ISSN 0105-4538

References

1. Naclerio RM, Proud D, Peters SP, et al. Inflammatory mediators in nasal secretions during induced rhinitis. *Clin Allergy* 1986;16:101–110.

2. de Monchy JGR, Kauffman HF, Venge P, et al. Bronchoalveolar eosinophilia during allergen-induced late asthmatic reactions. *Am Rev Respir Dis* 1985;131:373–376.
3. Okada S, Kita H, George TJ, Gleich GJ, Leiferman KM. Migration of eosinophils through basement membrane components *in vitro*: role of matrix metalloproteinase-9. *Am J Respir Cell Mol Biol* 1997;17:519–528.
4. Mautino G, Oliver N, Chanez P, Bousquet J, Capony F. Increased release of matrix metalloproteinase-9 in bronchoalveolar lavage fluid and by alveolar macrophages of asthmatics. *Am J Respir Cell Mol Biol* 1997;17:583–591.
5. van Toorenenbergen AW, Gerth van Wijk R, Vermeulen AM, Zijlstra FJ. Increase of albumin, eosinophil cationic protein, histamine, leukotrienes and mast cell tryptase in nasal lavage fluid after challenge with inhalant allergen extract. *Agents Actions* 1992;36 Suppl C:C421–C424.

Isoniazid-induced bullous skin reaction

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Key words: epidermal necrolysis; isoniazid; pemphigoid; tuberculosis.

● CUTANEOUS eruptions, the most frequent adverse reaction to isoniazid (2% of patients), include acneiform eruption, urticaria, purpura, lupus erythematosus-like syndrome, pellagra-like syndrome, exfoliative dermatitis, toxic



Figure 1. Bullous lesions of left leg, at admission to our department (second eruption).

epidermal necrolysis, and Stevens-Johnson syndrome (1). We report an exceptional case of bullous eruption caused by isoniazid that clinically mimicked pemphigoid eruption.

A 63-year-old man presented to another institution with pulmonary tuberculosis characterized by cavitation of the right upper lobe and diffuse bilateral miliary tubercles due to *Mycobacterium tuberculosis*. Fifteen days after treatment began (streptomycin [1 g/d], isoniazid [500 mg/d], rifampicin [600 mg/d], and pyrazinamide [2 g/d]), he developed erythematous rash, with bullous lesions located on the trunk and the four members. In addition, cytolytic hepatitis concomitantly occurred (ASAT=208 U/l, ALAT=261 U/l) without any detectable viral infection. Normalization of skin aspect and of hepatic parameters occurred within 2 weeks after suspension of antituberculosis treatment. At that time, isoniazid (300 mg/d), pyrazinamide (1.5 g/d), and rifampicin (600 mg/d) were

prescribed again. Five days later, the patient presented several bullous cutaneous lesions involving both forearms and feet, and, more importantly, the back. He was then admitted for the first time to our department. These lesions were well limited, tense, and scattered over erythematous zones (Fig. 1). The extent of the blisters could not be enlarged by the application of external pressure (negative Nikolsky's sign). No mucous membrane lesion was noted. No biological sign of hepatitis was observed.

A skin biopsy showed a subepidermal blister with extensive necrosis of the epidermis and a mixed inflammatory cell infiltrate in the upper dermis containing lymphocytes and macrophages and hemosiderin deposits. These

The tuberculosis drug isoniazid caused a bullous skin reaction mimicking pemphigoid eruption.

deposits were probably related to previous purpuric vasculitis. No antibody directed against basement membranes, epidermis constituents, or complement deposits was found on the skin biopsy.

All skin tests (prick, patch, and intradermal injections) with antituberculosis drugs were negative. One year after onset, the same tests were still negative.

Then, because of

- 1) the absolute need for specific antituberculosis treatment
- 2) the likelihood of isoniazid's involvement in view of its more frequent implication in a skin adverse drug reaction than other drugs (2, 3),

ethambutol (1.2 g/d), rifampicin (600 mg/d), and pyrazinamide (2 g/d) were successively started (at 1-week intervals) without side-effects. After 9 months, the tuberculosis was cured without any other skin or liver reaction.

The chronology of this observation strongly suggests the responsibility of isoniazid, for the following reasons:

- 1) a new eruption occurred each time that isoniazid was taken by the patient
- 2) each time, cutaneous lesion resolution was observed when antituberculosis drugs were withdrawn
- 3) no cutaneous lesion occurred when a treatment for tuberculosis without isoniazid was prescribed.

The chronology, with a delay of about 2 weeks between the first intake of isoniazid and the skin side-effects, is consistent with previous reports of Stevens-Johnson syndrome related to isoniazid (4). Initially, cytolytic hepatitis was observed, but there was no relapse during the second treatment regimen including isoniazid, pyrazinamid, and rifampicin. The absence of clinical association between cutaneous and hepatic involvement at the second treatment suggests that the mechanisms of hepatic and cutaneous side-effects are different, and are not linked (5). All skin tests were carried out within 2 weeks of the acute skin lesion onset and 1 year after, and they were negative; thus, they did not make

any positive contribution to the diagnosis, as usual in this kind of skin adverse reaction.

The numerous cutaneous side-effects of isoniazid are of different type (cited above) and are usually benign. In contrast, if bullous eruptions are exceptional, and related to epidermal necrosis, they may lead to Lyell's syndrome or Stevens-Johnson syndrome. A few well-documented observations have already been published (2, 6). The specific interest of our observation is due to the fact that, while the histopathology was typical of epidermal necrosis, the clinical presentation strongly suggested dermal-epidermal décollement, as seen in bullous pemphigoid eruptions, and this clinical aspect has not previously been reported.

This particular bullous skin lesion mimicking pemphigoid eruption after the onset of an antituberculosis treatment must be considered a possible toxic side-effect of isoniazid.

Acknowledgments This work was supported in part by a grant from Comité Départemental de Meurthe-et-Moselle contre les Maladies Respiratoires et la Tuberculose. We thank Nathalie Thomas for typing the manuscript.

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Accepted for publication 12 January 1999
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ISSN 0105-4538

References

1. Holdiness MR. Adverse cutaneous reactions to antituberculosis drugs. *Int J Dermatol* 1985;**24**:280-285.
2. Bomb BS, Purohit SD, Bedi HK. Stevens-Johnson syndrome caused by isoniazid. *Tubercle* 1976;**57**:229-230.
3. Mital OP, Singh RP, Katiyar SK, Mehrotra RK. Toxic epidermal necrolysis due to isoniazid. *Indian J Tuberc* 1976;**23**:32-33.
4. Nanda A, Kaur S. Drug-induced toxic epidermal necrolysis in developing countries. *Arch Dermatol* 1990;**126**:125.
5. Thompson NP, Caplin ME, Hamilton MI, et al. Anti-tuberculosis medication and the liver: dangers and recommendations in management. *Eur Respir J* 1995;**8**: 1384-1388.
6. Kvasnicka J, Rezac J, Svejda J, et al. Disseminated intravascular coagulation associated with toxic epidermal necrolysis. *Br J Dermatol* 1979;**100**:551-553.