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RESEARCH LETTER

Severe dermatitis caused by diltiazem

To the Editor,

Skin rash which caused by drugs shows a high polymorphism, which is determined, on the one hand, by the large amount of drugs used, and on the other hand, by the presence of polymedication, particularly in seriously-ill elderly patients, that increases the possibility for interaction among them, with the attendant risk of morphological expression of medicinal rash.

The spectrum of these reactions ranges from mild rash to the most severe forms, which are Stevens-Johnson's syndrome and epidermal toxic necrolysis. The term epidermal necrolysis is a neologism proposed by Lyell[1] to indicate necrosis and separation of epidermis. Blisters are merely exudates accumulating under the necrotic epidermis. The necrolysis phenomenon results from massive apoptosis of the epidermal cells, together with the degradation of the adhesion molecules between the basal cells and the basal membrane of the epidermis.[2] Stevens-Johnson's syndrome and epidermal toxic necrolysis are considered to be variants of the same disease, based on their similar condition (epidermal necrolysis), similar risk factors, causes and frequent progression from Stevens-Johnson's syndrome to toxic epidermal necrolysis. The main difference between these two conditions resides in the extension of the skin lesions: classified as Stevens-Johnson's syndrome when necrolysis affects less than 10% of the body surface; as superposition of both when it affects from 10 to 30%; and as toxic epidermal necrolysis when it affects over 30% of the body surface.[3]

We here present the case of a 66-year-old woman, with a history of depressive syndrome treated with mirtazapine and previous cholecystectomy, who in the past year reported dyspnoea on moderate effort. Fifteen days before admission, she started to suffer cough and expectoration, and subsequently fever of 39 °C and increased dyspnoea. She also reported palpitations starting a few days before admission.

On admission the patient had a temperature of 39 °C, 140 beats per minute, arrhythmia, BP 120/60, 88% oxygen saturation, normal cardiac auscultation and pulmonary auscultation with hypoventilation and bilateral wheezing. The rest of the physical examination was normal.

The chest X-ray carried out was normal and the ECG showed atrial fibrillation at 140 beats per minute. Blood count showed 14200 WBCs with normal formula, normal RBCs and platelets. Biochemistry showed glucose 125, GPT 44, with other normal parameters.

Figure 1 Skin rash with some pustular lesions and areas of skin detachment.

The admission treatment was levofloxacin, furosemide, diltiazem, digoxin, sintrom (coumarin), cloperastine, N-acetyl cysteine, and bromazepam, continuing treatment with mirtazapine. Twelve days later, the patient started to suffer from a maculopapular rash, first erythematous and then purple in colour, which started on her head, neck, and upper chest and then descended to affect all of her skin. Despite discontinuing all of the drugs, some pustular lesions (on her back), large blister lesions and areas of skin detachment appeared, affecting the trunk, the arms and the legs (Figs. 1 and 2). Pathological studies can be observed in Fig. 3. The patient also had ulcer lesions in the oral mucosa. The day after the condition started, imipenem had been added to the treatment.

Treatment was instituted with chlorphenamine and methylprednisolone intravenously at doses of 120 mg/day, despite which progressive evolution of the skin lesions continued. After the blister lesions and skin detachment occurred, and for fear of an evolution to a highly severe

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Figure 2 Areas of skin detachment in the arm.

condition such as Stevens-Johnson's syndrome or toxic epidermal necrolysis, it was decided to add cyclosporine 300 mg/day, intravenously for the first three days and orally from then on. Twenty-four hours after starting treatment with cyclosporine, the progression of the skin rash stopped, with progressive improvement of the lesions and complete healing in about two weeks. The doses of both the cyclosporine and the steroids were decreased to discontinuation in two weeks.

One week after the skin condition had disappeared, concomitantly with a febrile condition, the patient had a new generalised, mild macular rash, while she has being treated with ampicillin, mirtazapine, fraxiparine, digoxin, spironolactone, verapamil, ranitidine, acetaminophen, nistatin, risperidone and lorazepam, which subsided after drug discontinuation and adding antihistamines to the treatment.

Given the large number of drugs involved, some of which could be necessary for the patient in a later date, it was decided to perform drug allergy tests. It was considered that levofloxacin and furosemide were the drugs most likely to have caused the skin condition, and so it was decided to exclude these two drugs from the study.

Prick and intradermal test were performed with PPL (penicilloyl-polylysine), MMD (mixture of minor determinants) (Diater, Valencia, Spain), penicillin, imipenem and ampicillin with a negative result. Patch tests were carried out with the other drugs with negative results.

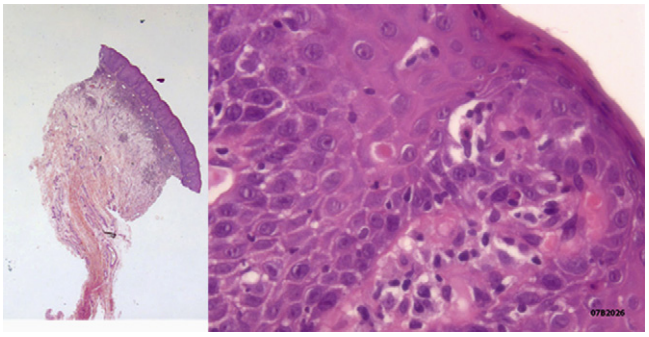

Figure 3 (Left) An epidermis with hyperkeratosis and acanthosis, with a widening of the interpapillary crests and fusion, associated with dense inflammatory infiltrate in a superficial band is seen. H&E 50×. (Right) A detailed image of the above lesion which shows the dermis-epidermis junction with the presence of multiple apoptotic Civatte bodies. H&E 200×.

Oral challenges were performed with ampicillin, mirtazapine, digoxin, spironolactone, verapamil, ranitidine, acetaminophen, nistatin, risperidone, lorazepam, sintrom, cloperastine, N-acetyl cysteine, and bromazepam, with negative results. Intramuscular challenge was performed with imipenem and subcutaneous challenge with fraxiparine with negative results.

One day after the oral challenge with 30 mg of diltiazem, the patient started to suffer from a generalised maculopapular rash (of the same characteristics as that leading to the initial severe condition), and therefore it was decided to start treatment with methylprednisolone 60 mg/day and cyclosporine 200 mg/day, which were maintained for seven days with steadily decreasing doses. The skin rash subsided completely, with no other more severe lesions occurring.

Subsequently, given that the challenge with diltiazem was positive, oral challenges were then performed with levofloxacin and furosemide, with negative results.

The first drug challenges performed were with those that the patient was taking when she had the second mild macular rash, that, as she tolerated all the drugs possibly involved, was attributed to a rash associated to the febrile condition that the patient then had.

Subsequently, thinking that the severe skin disease could be secondary to levofloxacin or furosemide, it was decided to perform challenges with the other drugs taken by the patient at the start of the condition, although retrospectively, diltiazem should have also been included in this group, and thus prohibited as well.

Given that when the patient had the skin disease, treatment with methylprednisolone at doses of 120 mg/day could not reverse the condition, and it was required to add cyclosporine, when the patient started with the maculopapular rash the day after oral challenge with 30 mg of diltiazem[4] (of the same characteristics as that leading to the initial severe condition), it was decided to add treatment with steroids and cyclosporine, which were maintained for one week, and the skin condition disappeared completely, with no more severe lesions occurring.

This case could illustrate the value of adding cyclosporine in patients with a severe skin allergy, results consistent with those of other authors.[5,6] Although there are no large series of cases published on the treatment with cyclosporine in severe cases of skin allergy, such as Lyell syndrome, the results are generally favourable to treatment with this drug.[7]

In our case the drug could reverse the skin disease, which had not been achieved with steroids at doses of 120 mg/day of methylprednisolone. In addition, it must be noted that after the oral challenge with diltiazem, treatment with cyclosporine and steroids could prevent the development of a new severe skin disease in the patient, who only had a maculopapular skin rash, and this subsequently subsided without progressing to a more severe form.

Although this is only one isolated case, and more studies are necessary, we consider that it could be beneficial to add cyclosporine[8] at an early stage of treatment in the case of severe skin reactions to drugs.

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