

Nifedipine-Induced Erythema Multiforme

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INTRODUCTION

Nifedipine is widely used for the treatment of cardiovascular disease. Approximately 30% of its users experience side effects related to its vasodilating action such as headache, flushing, and dizziness.¹ Severe skin rash is infrequently cited as a complication of nifedipine.^{2,3} We report a patient who developed erythema multiforme (EM) after starting nifedipine.

CASE

A 47 year-old female presented to a community hospital with a three-day history of fever, malaise, headache, and a maculopapular rash. Over the next twenty-four hours in hospital, the rash progressed to a generalized rash with vesicles. At this point, she was transferred to a tertiary, health care centre.

Her only pre-existing medical condition was hypertension for which she had been receiving hydrochlorothiazide/triamterene for several years. Four to six weeks prior to her admission, her antihypertensive therapy was changed to nifedipine XL 30 mg daily. She had no recent contact history with any infectious illness and no recent history of a cough or sore throat.

Review of systems was remarkable only for the painful, non-itchy rash, in addition to swollen ankles and sore joints. On examination, the patient's blood pressure was 130/80 mmHg, temperature 39.7°C, heart rate 100 beats/minute, and respiratory rate 15/minute. Examination of her mouth revealed a redness of the palate and a rash on the tongue. The skin rash itself was of the maculopapular type covering approximately 85% of her body surface with red patches of variable size and shape that blanched with pressure. There were vesicles on the lower limbs with sore, broken, and peeling skin. The patches were generally coalescent around the trunk and back and more discrete on the extremities. There was a denuded area over her back, buttocks, and thighs in addition to several non-tense, bullous lesions around her toes on both feet. Abdominal exam also revealed a palpable, painful lymph node approximately 3 cm in diameter in the right groin.

Serum chemistries were remarkable for slightly decreased concentrations of calcium (1.98 mmol/L; N=2.1-2.6), potassium (3.3 mmol/L; N=3.5-5.5), and magnesium (0.54 mmol/L; N=0.65-1.25). White blood cell count was $4.2 \times 10^9/L$ (N=4.5-12.5), with a moderate left shift. The fluid from the blisters was sterile and immunologic tests for complement were normal.

On admission to the community hospital (day three of reaction), nifedipine was discontinued and the patient was treated with IV hydrocortisone followed by oral prednisone 20 mg tid in addition to hydroxyzine 25 mg tid, and acetaminophen prn. The next day, following transfer to the tertiary care centre, cloxacillin 1g IV q6h was initiated on the recommendation of the infectious disease service.

The dermatology service considered the rash to be of moderate severity, possibly Stevens-Johnson and most likely drug-related. There was also a possibility of the rash progressing to toxic epidermal necrolysis (TEN) with a remote chance of pemphigus. However, the results of a punch biopsy from the edge of the blisters on her leg supported a diagnosis of EM. Histology showed sections with extensive epidermal necrosis and formation of a blister that was intraepidermal. There was no evidence of acantholysis or eosinophilia but examination of the underlying dermis also revealed a mild to moderate degree of lymphoid cellular infiltrate. Direct immunofluorescence and fibrinogen staining ruled out primary bullous disease (pemphigus or pemphigoid).

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The blistered areas of the rash were treated with saline-soaked compresses followed by mupirocin ointment three times daily, while the non-blistered areas were treated with clobetasol applied twice daily. On the day following transfer to the tertiary centre, the patient began to complain of mouth pain for which she received acetaminophen with codeine and hydrogen peroxide. An extemporaneous formulation of sucralfate and benzydamine was subsequently added.

Over the next few days her skin continued to denude. At the suggestion of plastic surgery, the patient was treated as a burn patient. The cloxacillin was discontinued, daily tub baths were started, bacitracin dressings were applied to the open areas twice daily, and clobetasol cream was applied to the non-blistered areas.

Over the next week the rash improved although her skin continued to peel and one week following her transfer to the tertiary care centre she was discharged.

DISCUSSION

EM can be categorized as iatrogenic, infectious, or idiopathic and many etiologic factors have been identified in its pathogenesis.⁴ While a specific trigger is identified in only about half the cases, medications are frequently implicated. Of those in which a trigger is identified, 50 to 60% of cases of EM are felt to be secondary to drugs and almost any drug can be implicated.^{5,7} The hypothetical mechanism of this reaction involves antigen-antibody complex formation with the resulting hypersensitivity reaction and inflammation causing epidermal death and separation.

The product monograph for Adalat XL[®] describes an incidence of 2.3% for rashes, a rate similar to that of the placebo group in some studies.¹ However, a number of cases of serious skin and appendage disorders have been described following nifedipine administration. True urticaria and urticaria exanthema are among the most common reactions noted, while bullous eruption, exfoliative dermatitis, and EM are less common.⁸ Stern et al³ estimated the relative rates of cutaneous reactions with three calcium channel blockers, nifedipine, diltiazem, and verapamil based on reports provided to the FDA's Division of Epidemiology and Drug Surveillance, and the American Academy of Dermatology's Adverse Drug Reaction Reporting System between 1976 and 1985. Of the total of 379 case reports of cutaneous adverse drug reactions (serious and nonserious) associated with calcium channel blockers, 146 cases were associated with nifedipine. Some of the more serious reactions requiring hospitalization or treatment included four cases of Stevens-Johnson Syndrome (SJS), two cases of EM, and 11 cases of exfoliative dermatitis. Severe cutaneous reactions to nifedipine, including: lichenoid drug eruption,⁹

generalized bullous fixed drug eruption,² drug-induced urticarial allergic eruption,⁸ pemphigus foliaceus,¹⁰ exfoliative dermatitis,¹¹ and morbilliform rash¹² have also been reported.

The time course and presentation of our case is similar to that of other severe dermatologic reactions to nifedipine. In most reports there has been a lag between the initiation of nifedipine and onset of rash ranging from two weeks to several months. A prodrome consisting of fever, malaise, and myalgias is often evident and the rash is usually progressive. Similarly, biopsy results of other case reports have included epidermal necrosis, perivascular mononuclear cell infiltrates of the dermis, and intra-epidermal bullae. In all reported cases, rashes have improved upon nifedipine withdrawal and in many cases positive rechallenges have confirmed nifedipine as the causative agent.^{2,8-12}

Nearly one-third of patients report prodromal symptoms occurring one to 14 days prior to the onset of the mucocutaneous diseases. Symptoms, if present, are variable and nonspecific and may include flu-like symptoms such as those experienced by this patient of malaise, fever, and myalgias in addition to headache, sore throat, cough, chest pain, nausea, vomiting, and diarrhea.⁵⁻⁷ Skin lesions develop over a two- to seven-day period and, as the word "multiforme" suggests, have variable manifestations. They usually appear first as erythematous macules and become edematous and papular with distinctive target lesions.⁴ The centre of these lesions may be beefy red, vesicular or a typically depressed pale area of epidermal necrosis.⁵ The earliest rash is often a symmetric eruption of red macules and edematous papules and plaques.⁶ The erythematous papular skin lesions enlarge by peripheral expansion to cover the body and, as described in our case, can progress to form bullae and vesicles.^{4,7} When vesicles and bullae occur, separation from the epidermis and attached basement membrane from the dermis is the rule.⁵ More severe forms resemble a second degree burn and can result in extensive sloughing of the epidermis.^{4,13}

In the minor variant of EM, mucous membrane involvement is mild and, if present, usually limited to the mouth.⁵ SJS or EM major is characterized by additional and more severe mucous membrane involvement. This patient's cutaneous symptoms did extend to her oral mucosa causing severe pain but no additional mucous membrane involvement was detected.

Toxic epidermal necrolysis, another variant of EM major similar to SJS is considered by some to be a continuation or progression of EM; however, it is more extensive with greater than 10% of the body surface area denuded and mortality ranging from 25 to 70%.⁹ Sloughing of skin did occur in the case presented here but was

relatively mild with no major fluid or electrolyte abnormalities.

In conclusion, a number of severe cutaneous reactions have been associated with nifedipine. Prompt recognition and withdrawal of the drug are important for a favourable response and outcome. ☒

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