

Bullous Drug Eruption Secondary to Nicotinic Acid/Laropiprant

Dear Editor,

Nicotinamide with tetracycline or doxycycline is used in the treatment of bullous pemphigoid. Nicotinamide is used in doses of 1500 to 2000 mg/day in divided doses in these cases. Nicotinic acid/laropiprant (Tredaptive®) is a lipid lowering agent which contains 1000 mg of nicotinic acid (niacin) and 20 mg of laropiprant which is a selective antagonist of prostaglandin D2 receptor. Laropiprant does not have any lipid lowering effect but works to suppress the flushing caused by nicotinic acid which is due to the prostaglandin D2 mediated cutaneous vasodilation.¹ Nicotinamide is the biologically active amide metabolite of nicotinic acid. We report a case of bullous drug eruption to a drug that contains nicotinic acid, the premetabolite of a treatment compound of bullous pemphigoid.

Case Report

A 62-year-old Chinese gentleman with a past history of hypertension, hypertriglyceridemia and chronic renal impairment was started on 1 tablet of nicotinic acid/laropiprant (containing 1000 mg of nicotinic acid) daily for lipid lowering as there was inadequate control on rosuvastatin and fenofibrate. He then developed a pruritic erythematous rash associated with tense blisters 2 days later on the trunk, upper and lower limbs. Other than nicotinic acid/laropiprant, he had not taken any new medications, health supplements, over-the-counter medications, topical treatment or traditional medications. He had never experienced this rash.

On examination, there were erythematous urticated plaques on the limbs with tense blisters noted over the left upper limb, left thigh and a deblistered bullae on the back of his right knee (Fig. 1). There was no mucosal, genital or conjunctival involvement. His skin was non-tender. There was no evidence of scarring. In view of the temporal sequence, a diagnosis of bullous drug eruption secondary to nicotinic acid/laropiprant versus bullous pemphigoid was made.

His blood results were unremarkable with a normal eosinophil differential count of $0.39 \times 10^9/L$ and normal liver function tests. There was no change in his baseline renal function test. A skin biopsy done on a newly formed blister showed subepidermal blister formation with perivascular and interstitial infiltrate of eosinophils and

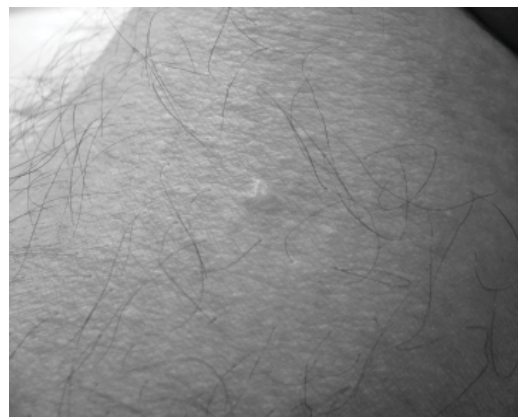


Fig.1. Tense blister on the right thigh on a background of urticated plaques.

lymphocytes. Direct immunofluorescence on perilesional tissue was negative for C3, C1q, IgA, IgG and IgM along the dermoepidermal junction.

Nicotinic acid/laropiprant was stopped and he was started on a course of prednisolone at 0.5 mg/kg/day. The lesions rapidly resolved. Upon follow-up 2 weeks later, the patient had discontinued prednisolone on his own with no recurrence of the cutaneous reaction. He has not had any recurrence of the rash 6 months after that as well. His lipid lowering medication was changed to fenofibrate and ezetimibe/simvastatin (Vytorin).

Discussion

Nicotinamide, which is an amide derivative of nicotinic acid, used in combination with tetracycline or doxycycline, has been used as an effective alternative to prednisolone for treatment of bullous pemphigoid. This case is interesting as the medication containing the compound used in treatment of bullous pemphigoid also triggered a bullous drug eruption. In our patient, the impression was that of a bullous drug eruption secondary to nicotinic acid/laropiprant in view of the temporal sequence in combination with the negative direct immunofluorescence findings in a fresh perilesional lesion and a rapid resolution of the cutaneous reaction upon stopping the offending agent while being off prednisolone. This is the third case report of a bullous drug eruption associated with nicotinic acid and its derivatives. The previous 2 case reports were related to the administration of xantinol nicotinate for treatment of vascular disorders.^{2,3}

A drug challenge to either compounds on its own would be useful to elicit the culprit drug.

Bullous drug eruptions may be classified into: spongiotic or eczematous, acute generalised exanthematous pustulosis, fixed drug eruption, Stevens-Johnson syndrome and toxic epidermal necrolysis, drug-induced pemphigus, drug-induced bullous pemphigoid, and linear IgA bullous dermatosis. There are various pathophysiological processes behind these such as spongiosis, subcorneal pustule formation, keratinocyte necrosis, anti-epidermal antibody mediated and basement membrane zone immunoglobulin deposition. A study has shown in blistering diseases including bullous drug eruption of both intraepidermal and subepidermal type, there was increased lymphocytes with a predominance of T-lymphocytes (CD3+) supporting a cell-mediated allergic reaction.⁴ There were also increased neutrophils or eosinophils in these lesions reflecting ongoing activation of Th1 and Th2 activity. Drug-induced bullous pemphigoid was a differential, however, the direct immunofluorescence was negative. Other laboratory findings such as the Bullous Pemphigoid Antigen 180 (BP 180) and Bullous Pemphigoid Antigen 230 (BP 230) would have been helpful. Medication known to cause drug-induced bullous pemphigoid include frusemide, amoxicillin, ampicillin, penicillin, penicillamine, psoralen and ultraviolet A light (PUVA), and beta-blockers.⁵

The most reported adverse reaction of nicotinic acid/laropiprant is cutaneous flushing.¹ Other cutaneous adverse reactions reported include paresthesia, erythema, pruritus, urticaria and angioedema.⁶

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