

that systemic contact dermatitis is a delayed, cell-mediated hypersensitivity reaction; some reports have demonstrated the usefulness of a positive patch test in its diagnosis (6). In the present case, this pathogenic mechanism is suggested by clinical findings, delayed skin tests, patch test and challenge positivity with ofloxacin.

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Gabapentin-induced Bullous Pemphigoid

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Sir,

Gabapentin is a new antiepileptic drug that is being used increasingly in the treatment of chronic pain of different origins. It is generally considered a safe agent for patients with a history of allergic reactions (1). In more than 2000 patient exposures, only 2 cases of mild rash developed during preclinical trials in the USA (2). Since approval, only a few cases of rash associated with gabapentin have been reported, among them two cases of gabapentin-induced Stevens-Johnson syndrome (3, 4). We present a case of bullous pemphigoid presumably triggered by gabapentin.

CASE REPORT

A 61-year-old woman suffering from epilepsy for 11 years, treated with oxcarbazepine 900 mg twice a day, developed an exanthema and slight hair loss during treatment with lamotrigine. The patient had previously had a rash following rofecoxib. She was given gabapentin because of neurogenic pain in the legs. After 2 weeks of increasing doses she developed an itching maculopapular rash on the abdomen with further spreading to the upper legs and arms. She was treated with betamethasone dipropionate supplemented with oral loratadine with moderate effect. After a month, the elements became more nummular and gabapentin was discontinued.

A punch biopsy showed distinct acanthosis and hyperkeratosis along with hydrophic basal cell degeneration within the epidermis, and a perivascular oedema and interstitial cellular infiltration with eosinophils within the papillary dermis.

The patient was then referred to a dermatological department. Treatment with gabapentin was reinstated

in incremental doses of 300 mg as a result of the good clinical response to the neurogenic pains in the legs. After 1 week, an itching erosive bullous eruption developed on the trunk (Fig. 1). Treatment with gabapentin was stopped.

A new punch biopsy showed a subepidermal blister and a perivascular inflammation dominated by eosinophils and a few lymphocytes. Direct immunofluorescence of a perilesional biopsy displayed a distinct deposit of C-3 along the basement-membrane zone. Circulating IgG autoantibodies against the epidermal basement-membrane zone in a dilution of 1:100 were demonstrated by indirect immunofluorescence. Guinea-pig lower lip was used as antigen. The white blood cell count was 15.500 (90% neutrophils). No other abnormalities were found. The patient was treated with prednisolone 15 mg per day in combination with azathioprine



Fig. 1. Bullous eruption on the upper extremity of a 61-year-old woman.

50 mg once a day. After 2 months, no new blister formation was found and the medication decreased.

DISCUSSION

Several drugs have been associated with provoking the onset of or aggravating a pre-existing bullous pemphigoid. The list, which has recently been reviewed, consists of at least 30 different drugs (5) belonging to different pharmacological groups, although thiol compounds and sulphonamide derivatives are those most often associated. They include d-penicillamine, thiobutairit, gold-sodium thiosulphate, captopril, flupenthixol, thiopronin, sulphonamide, furosemide, tolbutamide and sulfasalazine (4, 6–8). The number and spectrum of medications in patients with bullous pemphigoid have been analysed in two multicentre case-controlled studies (5), but no statistically significant associations were found.

Whether or not the different drugs act through a direct mechanism on the immune system is not known. It is well known, however, that local irritation and damage to the skin can induce blister formation in bullous pemphigoid, as exemplified by the induction of disease by UV light, PUVA, physical agents including thermal burns, wounds, localized trauma, skin grafts and radiotherapy (9–12). Whether the induction of bullous pemphigoid in our patient took place through a similar mechanism can only be speculated, as the infiltrate in the dermis mainly consisted of eosinophils and the rash was initially characterized as an allergic reaction. The eosinophils might play a role, as they produce a protease that cleaves BP 180, one of the two major bullous pemphigoid antigens, also known as BPAG2 and collagen type XVII, with a molecular weight of 180 kDa (13). It is a transmembrane molecule with collagenous domains and a long extracellular portion that interacts with the anchoring filaments. The extracellular region adjacent to the transmembrane portion is the immunodominant epitope (14). These adhesion complex proteins may either be changed by these processes or exposed such that a host immunological response is triggered.

The inducing drug may also act as a hapten, altering the antigenicity of the lamina lucida or attaching to a cell site and eliciting the formation of autoantibodies (15). The overall understanding of the mechanism behind the blister formation is that autoantibodies bind to the bullous pemphigoid antigens and activate complement. Complement components start a series of inflammatory events with a cascade of attracting leukocytes, degranulating mast cells and releasing inflammatory mediators. The activated inflammatory cells release lysosomal enzymes and proteases, cleaving the target

antigens and disrupting the hemidesmosomes, resulting in blister formation.

In this case, as well in one of the other cases (3), the patient had adverse skin reactions to other drugs prior to the bullous eruption. So even though gabapentin is considered to have a low potential of adverse skin reactions, this report, along with previously published reports, suggests that gabapentin in patients with a strong history of skin reactions may provoke a repeated drug reaction.

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