Gabapentin-Induced Bullous Pemphigoid

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Bullous pemphigoid is an autoimmune blistering dermatosis with separation of the epidermis from the dermis. This disease process is common among elderly patients and manifests with subepidermal vesicles and tense bullae. Patients with bullous pemphigoid are more likely to have also received a previous diagnosis of a neurologic disorder. Gabapentin is an antiepileptic that is used to manage neuropathic pain. The authors describe, to their knowledge, the first report of gabapentin-induced bullous pemphigoid in an elderly man with no history of rashes or reactions to other medications.

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An autoimmune blistering dermatosis, bullous pemphigoid is caused by autoantibodies directed against BP230 and BP180 proteins of the dermoepidermal junction, leading to an inflammatory cascade that causes separation of the epidermis from the dermis.[1] Bullous pemphigoid is commonly seen in elderly patients and manifests with subepidermal vesicles and tense bullae. Bullous pemphigoid has been shown to be triggered by or associated with various drug therapies.[2,3] Gabapentin, an antiepileptic medication used to manage neuropathic pain, is reportedly associated with Stevens-Johnson syndrome, a condition that includes severe rash.[4,5] To our knowledge, one report has associated bullous pemphigoid with gabapentin,[2] and the patient in that case had a rash that developed as a reaction to other medications. Patients with bullous pemphigoid are more likely to have received a previous diagnosis of a neurologic disorder.[6,7] We present a case of gabapentin-induced bullous pemphigoid in a patient with a previously diagnosed seizure disorder.

Report of Case

An 87-year-old man with a history of type 2 diabetes mellitus, hyperlipidemia, hypertension, epilepsy, hypothyroidism, and neuropathic pain presented to the emergency department. The patient had a chief complaint of a persistent pruritic rash and blisters that started on his upper extremities and spread to his trunk and lower extremities that had been ongoing for 3 months. At the time of initial evaluation, the patient was taking amlodipine, glipizide, thyroxine, finasteride, simvastatin, omeprazole, aspirin, and enalapril for the past 2 years. He had been taking carbamazepine for seizure secondary to a neurocysticercosis infection for the past 4 years. Approximately 4 months previously, he started taking gabapentin for diabetic neuropathy. About 3 weeks after initiation of the gabapentin, pruritus and, subsequently, the rash and blisters developed.

On physical examination, the patient was afebrile, with multiple excoriated erythematous plaques on his arms, legs, and torso, with multiple tense bullae and erosions ranging in size from 0.5 cm to 1.2 cm (*Figure 1* and *Figure 2*). There was no involvement of face, oral mucosa, or interphalangeal web spaces.

A bedside punch biopsy was performed. Histopathologic evaluation showed a subepidermal bulla with a fibrinopurulent crust; the lesions were negative for acantholysis, epidermal necrosis, and fungal microorganisms. Direct immunofluorescence study of perilesional skin showed linear immunoglobulin G along the dermoepidermal junction, which indicated positive direct immunofluorescence. Indirect immunofluorescence on salt-split skin preparation revealed linear C3 and immunoglobulin G localized to the epidermal side of the artifactually induced vesicle in perilesional skin.

The findings were diagnostic for the pemphigoid group of diseases. The diagnosis of gabapentin-induced bullous pemphigoid was made clinically based on the proximity between initiation of gabapentin and cutaneous eruption and lack of previous skin reactions or rash to other medications. Gabapentin and carbamazepine were both discontinued, and the patient was discharged home with clobetasol cream and encouraged to return for follow-up as needed. The patient did not return for follow-up but was admitted to the emergency department for an unrelated illness 4 weeks after discharge, and it was noted that the pruritus and cutaneous findings had resolved.

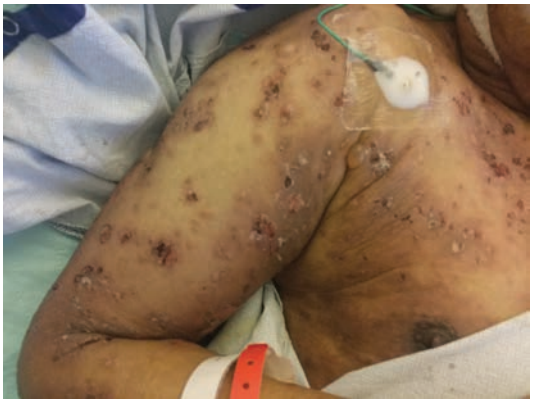

Figure 1.
Multiple tense bullae and erosions on the upper torso and extremities of an 87-year-old man with gabapentin-induced bullous pemphigoid.

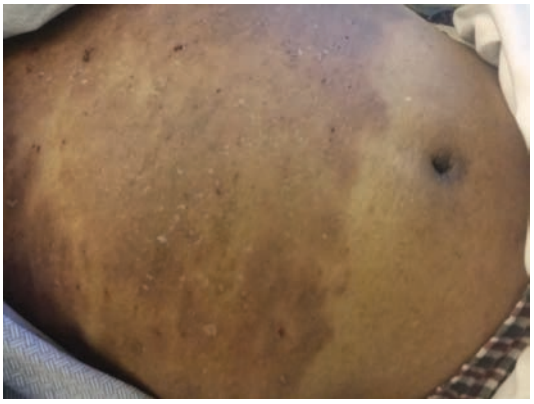

Figure 2.
Excoriated erythematous plaques on the torso of an 87-year-old man with gabapentin-induced bullous pemphigoid.

Discussion

Bullous pemphigoid is a blistering skin disease in which autoantibodies develop to hemidesmosomal components of the epidermal basement membrane zone, including 2 major antigenic proteins, the 230-kD antigen (BPAG1) and the 180-kD antigen (BPAG2).[1] Bullous pemphigoid has been reported to be medication induced in some cases.[3] Most notably, in a case-control study of the medication history of consecutive patients with bullous pemphigoid compared with that of control patients, a statistically significant OR was found in the association of previous loop diuretic use and bullous pemphigoid.[3] However, the mechanism through which the disease is induced is not well understood. A proposed mechanism suggests that the inducing drug may act as a hapten, altering the antigenicity of the lamina lucida or attaching to a cell site and eliciting the formation of autoantibodies.[8]

Additionally, eosinophils have been found to produce and release 92-kD gelatinase, which then cleaves the extracellular, collagenous domain of recombinant 180-kD bullous pemphigoid autoantigen, thereby contributing significantly to the tissue damage in bullous pemphigoid.[9] This process may also play a role in drug-induced bullous pemphigoid because eosinophils are a prominent part of many drug reactions. A few case-control studies have found that patients with bullous pemphigoid are more likely to have various neurologic diseases, schizophrenia, psoriasis, cerebrovascular disease, and dementia before the diagnosis of bullous pemphigoid is made.[6,7] The patient in the current case had a previous diagnosis of a seizure disorder, which is consistent with this finding.

Conclusion

To our knowledge, the present case is the first to report direct correlation between initiation of gabapentin and bullous pemphigoid with no previous rashes or reactions to other medications. Although the patient was also treated with carbamazepine, which has been associated with bullous pemphigoid,[3] carbamazepine is less likely to have caused the outbreak because the patient had been taking it for 4 years without any adverse reactions. Approximately 1 month after the initiation of gabapentin, bullous pemphigoid began developing, which strongly suggests that gabapentin was the offending drug. The patient's symptoms resolved within a month of discontinuing gabapentin, which also supports the correlation between gabapentin and bullous pemphigoid.

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