Levetiracetam-induced bullous pemphigoid in a young adult woman

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INTRODUCTION

Bullous pemphigoid (BP), the most common autoimmune subepidermal blistering disorder, is characterized by the presence of tense bullae caused by circulating autoantibodies against the hemidesmosomal components BP antigen 1 (BP230) and/or BP antigen 2 (BP180).[1] Preferentially affecting elderly people, BP can infrequently occur in young adults and children.[1] Old age, chronic neurologic diseases (dementia, Parkinson disease, stroke, and epilepsy), and certain drugs may contribute to the development of BP.[1-3]

Levetiracetam is an antiepileptic drug that binds to the synaptic vesicle protein SV2A and regulates intraneuronal calcium and synaptic exocytosis.[4] One case report documents a 70-year−old woman with a past history of Alzheimer disease and stroke, who developed BP after starting levetiracetam for seizure prophylaxis.[4] We present, to our knowledge, the second reported case of levetiracetam-induced BP, this time occurring in a young adult.

Abbreviations used:

BP: bullous pemphigoid
DIBP: drug-induced bullous pemphigoid

CASE REPORT

A 31-year−old woman with a history of epilepsy presented to our clinics with a 3-week evolution of a pruritic skin eruption on her face, trunk, and extremities, 2 months after initiation of levetiracetam for seizure control. The patient denied the concomitant use of other medications and the presence of systemic symptoms, including fever, fatigue, and malaise. Physical examination demonstrated erythematous papules and plaques, confluent vesicles, and large tense bullae affecting the face, neck, trunk, and distal parts of the extremities, including the palmoplantar areas (Fig 1). There were no palpable cervical, axillary, or inguinal lymph nodes. A hemogram revealed leukocytosis (12,900 cells/μL) with associated peripheral eosinophilia (21%). Comprehensive metabolic panel, urinalysis, and ova and parasite test were unremarkable. A punch biopsy specimen of an erythematous papule on the right hand revealed a superficial and deep perivascular and interstitial lymphocytic infiltrate with abundant eosinophils. Serum enzyme-linked immunosorbent assay analysis for BP180 and BP230 antibodies was strongly positive, and a direct immunofluorescence test demonstrated linear deposition of IgG and C3 at the dermoepidermal junction (Fig 2), confirming the diagnosis of BP. Levetiracetam was immediately discontinued, and the patient was started on divalproex sodium. Prednisone 30 mg (0.5 mg/kg/day) and mycophenolate mofetil 2 g daily were started. Skin lesions resolved by 4 months of therapy, and then, the tapering down and discontinuation of treatment were completed in 3 months. No recurrence has occurred after 12 months of treatment cessation.

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Fig 1. Levetiracetam-induced bullous pemphigoid. Erythematous papules, vesicles, and bullae in the back, face, and palmoplantar areas.

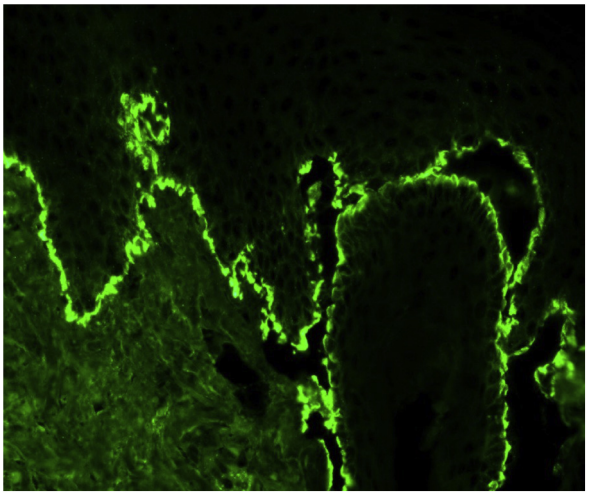

Fig 2. Direct immunofluorescence. Linear deposits of IgG and C3 at the dermoepidermal junction.

DISCUSSION

Although epilepsy, dementia, Parkinson disease, and stroke have been associated with BP, the average age of BP onset in patients with these neurologic disorders is 58.8, 80.7, 80.6, and 76.0 years, respectively.[2] Young age, the timing of onset of cutaneous lesions relative to levetiracetam introduction, the distribution of lesions, and the prompt improvement of the condition after levetiracetam discontinuation implicate levetiracetam as the culprit of drug-induced BP (DIBP) in our patient.

The clinical picture and histologic findings in both DIBP and idiopathic BP may exhibit subtle differences.[3] DIBP is characterized by a younger age of onset. Lesions usually present within 3 months after starting the culprit medication. Skin lesions of DIBP, although morphologically similar to idiopathic BP, tend to affect the trunk, limbs, palms, soles, and face and generally respond faster to treatment, once the offending drug is discontinued.[3] Facial involvement is unique to DIBP.[3] The remainder of the pattern of distribution is similar to that of idiopathic BP; and thus, it is more difficult to discern differences between them. DIBP is more likely to develop on normal-appearing skin, unlike the erythematous,

urticarial base commonly seen in idiopathic cases; it is also more likely to develop in mucous membranes.[3] Some cases of DIBP follow a more chronic and persistent course, despite the discontinuation of the culprit medication. Meanwhile, skin lesions of idiopathic BP have a predilection to occur in the lower abdomen and on the flexor surfaces of limbs, groins, and axillae, typically sparing the head and neck.[1,3,5] Both DIBP and idiopathic BP may show blood eosinophilia, although typically more exuberant in the drug-induced counterpart.[1,3] Histologically, both entities show subepidermal bullae and a dermal inflammatory infiltrate of lymphocytes, histiocytes, eosinophils, and, occasionally, neutrophils.[1,3] Serum enzyme-linked immunosorbent assay detects the presence of circulating IgG autoantibodies against BP180 and/or BP230 in both idiopathic and DIBP cases.[1,6] Direct immunofluorescence and indirect immunofluorescence findings are also similar.[1,3]

Karadag et al[4] reported a 70-year–old woman with Alzheimer disease and stroke who developed levetiracetam-induced BP after using the drug for 2 months. As observed in our case, the patient responded promptly without recurrence upon levetiracetam discontinuation and treatment with tetracycline and nicotinamide.[4] Several mechanisms of action have been postulated to explain the occurrence of DIBP.[3,7,8] Eosinophils, which are highly prevalent in the blood and tissue of patients with DIBP, secrete gelatinase B and matrix metalloproteinase 9, which may cleave the extracellular collagenous domain of BP180, thereby contributing to BP.[3,8,9] Some drugs may decrease the number of suppressor T cells, leading to increased production of autoantibodies against basement membrane antigens.[3,4,7] Some drugs may also act as haptens that bind to proteins in the lamina lucida, changing their antigenic properties and uncovering hidden epitopes that stimulate an autoimmune response.[1,3,4] Meanwhile, sulfhydryl-containing drugs may cause dermoepidermal splitting, with or without antibody formation.[1,3,4,7]

In conclusion, we presented a case of a young adult woman who developed DIBP secondary to levetiracetam. The prompt recognition of this adverse event, rapid discontinuation of the culprit medication, and establishment of adequate treatment are important to prevent further complications. To our knowledge, this is only the second reported case of levetiracetam-induced BP and the first such event reported to occur in a young adult patient.

Conflicts of interest

None disclosed.

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