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CASE REPORT

Bullous pemphigoid with neurofibroma-like histopathological change in two patients without neurofibromatosis type 1: Coincidence or association?

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Abstract

The author reports two cases of Bullous pemphigoid (BP) with neurofibroma (NF)-like histopathological change. The two patients without neurofibromatosis type 1 (NF1) presented with several bullae on their trunk. Based on the results of positivity for anti-BP180 antibody, direct immunofluorescence, and histopathological findings, they were diagnosed with BP. Histologically, another lesion in the dermis, which was composed of spindle cells with wavy nuclei, collagen fibers, and mast cells, was located close to the bulla. Immunohistochemically, the spindle cells were diffusely positive for S-100 protein and CD34, and weakly positive for epithelial membrane antigen in certain foci. These findings were considered to be "NF-like" histopathological change. This is the first two cases of BP with NF-like histopathological change in patients without NF1.

Keywords: Dermatology, bullous pemphigoid, neurofibroma, neurofibromatosis type 1, mast cell

INTRODUCTION

Bullous pemphigoid (BP) is a subepidermal blistering disease, which is caused by an autoimmune response to two hemidesmosome structural proteins (BP180 and BP230) in the epidermal basement membranes. BP is the most common autoimmune blistering disease and the elderly are more commonly affected.[1] Clinically, tense blisters, erosions and crusts accompanied by edematous erythema appear on the trunk and the extremities in this disease. Direct immunofluorescence analysis of lesional skin shows linear deposition of immunoglobulin (Ig) G and complement (C) 3 along the dermoepidermal junction. Autoantibodies against BP180 and BP230 are detected in BP patients by enzyme-linked immunosorbent assay (ELISA). A histological examination of a skin biopsy specimen reveals subepidermal blisters with inflammatory cells including eosinophils, neutrophils, mast cells, and lymphocytes in the dermis.[2] BP is sometimes accompanied by other disorders, such as collagen vascular diseases, diabetes mellitus, pernicious anemia, and vitiligo.[3] This is the first two cases of BP with neurofibroma (NF)-like histopathological change in patients without neurofibromatosis type 1 (NF1).

CASE REPORT

The patients included one woman (age: 95 years) and one man (age: 80 years), with similar clinical presentations. None of the patients had any clinical or family history of NF1 (gene analysis was not performed). Each of the patients presented with several bullae, erosions, and erythematous lesions on their trunk (FIG. 1). The laboratory test results for these patients showed similarities, such as positivity for anti-BP180 antibody, negativity for anti-desmoglein-1 antibody, and negativity for anti-desmoglein-3 antibody. Direct immunofluorescence in both cases revealed linear deposition of IgG and C3 along the dermoepidermal junction. The patients were diagnosed with BP on the basis of these results.

Pathology findings

Each patient's biopsy specimen was taken from a bulla. Both patients presented with

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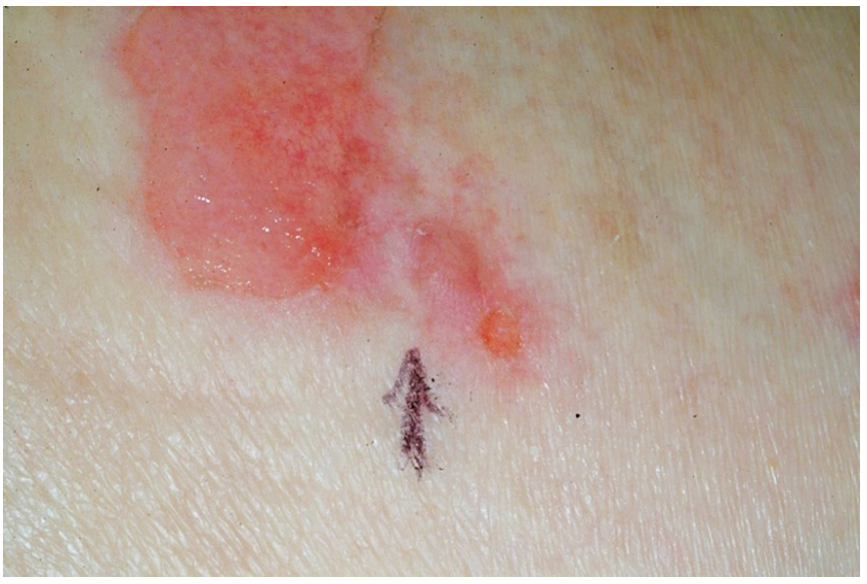

FIG. 1: Clinical appearance of several bullae and erosions on the trunk of a 95-year-old woman.

common histopathological findings, including a subepidermal bulla that was infiltrated with eosinophils and mast cells, which was consistent with BP (FIG. 2A, B). Additionally, another lesion in the dermis, which was composed of spindle cells with wavy nuclei, collagen fibers, and mast cells, was located close to the bulla (FIG. 2A, C). Immunohistochemically, mast cells were highlighted by c-Kit (FIG. 2D). The spindle cells were diffusely positive for S-100 protein (FIG. 2E) and CD34, and weakly positive for epithelial membrane antigen (EMA) in certain foci. These findings were considered to be "NF-like" histopathological change.

DISCUSSION

In the patients, there were no clinically identifiable nodules around the bullae. The skin lesions improved with oral administration of prednisolone, which is considered the main treatment for BP. The clinical aspect did not appear to be different between common BP and the condition in the current two cases, although the dermal lesions were consistent with NF histologically and immunohistochemically. Therefore, the author considered that the term "NF-like" histopathological change, rather than NF, was appropriate for the dermal histological findings in the patients. Other spindle cell lesions, such as dermatofibroma and neurotized melanocytic nevus, were considered in the differential diagnosis of the patients. However, these lesions were ruled out because of the positive immunohistochemical results for S-100 protein, CD34, and EMA.

Autoantibodies against BP180 and/or BP230 play a major role in pathogenesis of BP.[4] The binding of autoantibodies to these hemidesmosome structural proteins causes inflammatory responses including complement activation and mast cells degranulation. Subsequently, activated eosinophils and neutrophils release different proteolytic enzymes. The inflammatory process injures tissue with a disruption of dermoepidermal adhesion, resulting in subepidermal blisters.[4] Regarding NF, it is a benign soft tissue tumour, which is composed of Schwann cells, fibroblasts, perineurial cells, endothelial cells, lymphocytes, and mast cells.[5] Mast cells are usually prominent in NF and can be helpful to diagnose histologically. Most cases of NF present with solitary, localised, cutaneous lesions. The aetiology and pathogenesis of solitary NF are not well known.[6] Meanwhile, multiple NFs are the cardinal feature of NF1. NF1 results from inherited or *de novo* germline mutations in the NF1 tumour suppressor gene that encodes the protein neurofibromin and normally down-regulates RAS signaling.[7] The microenvironment of NF1, especially infiltration of mast cells induced by chemoattractant stem cell factors or local trauma, contributes to formation of NFs.[5] In the presence of the mutation, secretion of various cytokines from mast cells causes proliferation of Schwann cells, fibroblasts, perineurial cells, and endothelial cells, leading to NF formation.[8]

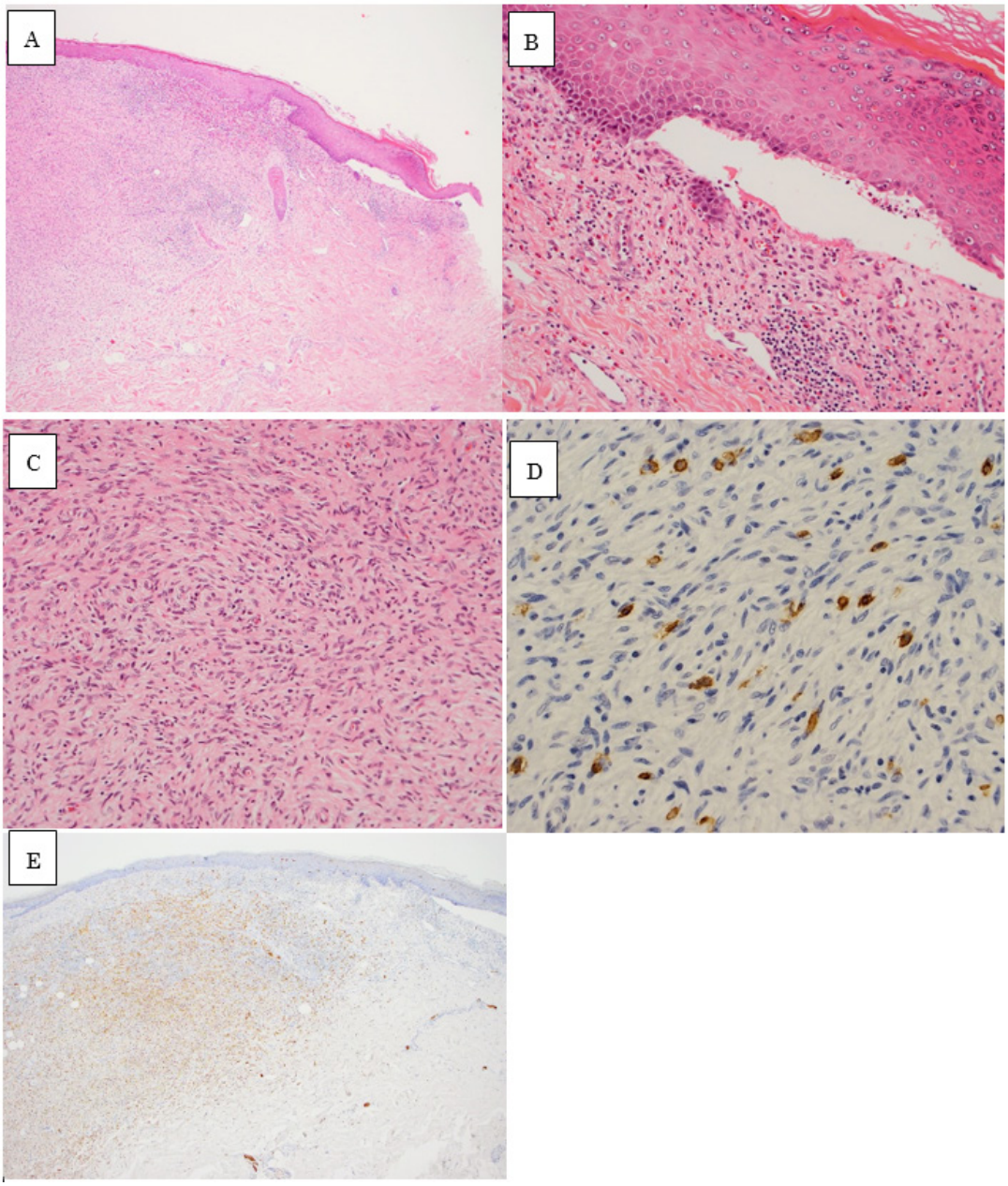

FIG. 2: (A) Histopathological features of a biopsy specimen taken from a bulla in an 80-year-old male patient. The bulla (right side) and a dermal lesion (left side) can be seen (H&E, x100). (B) High-power view of the bulla shows a subepidermal bulla with eosinophilic infiltration (H&E, x200). (C) High-power view of the dermal lesion shows proliferation of spindle cells with collagen fibers and infiltration of mast cells (H&E, x200). (D) Mast cells highlighted by c-Kit (x400). (E) Spindle cells diffusely positive for S-100 (x40).

Thus, mast cells are a common important factor in both BP and NF. Yesudian *et al*.[9] reported a case of BP accompanied by NFs in a patient with NF1 and considered that mast cells might play a key role in the genesis. Interestingly, infiltration of mast cells was observed in the current cases. Mast cells are basically derived from the bone marrow and are released into the blood. After leaving the vasculature, these mature cells are normally located in the endoneurial, perineurial, and epineurial spaces of peripheral nerves.[10] Nerve damage induces increased accumulation of mast cells.[10] Although the possibility that both BP and NF-like change coexisted incidentally could not be excluded, mast cells induced by

BP causing tissue injury could have been an essential histogenetic factor in NF-like change and it might be an incomplete form of NF in the absence of the NF mutation.

CONCLUSION

To the best of my knowledge, this is the first report of BP accompanied by NF-like histopathological change in patients without NF1. The author speculates the histopathological change could be related with BP in the current cases. However, only one biopsy could be evaluated in each current patient followed for a limited term. In order to clarify its exact genesis and clinicopathological significance, further investigation is necessary.

Conflict of interest: The author declared no conflict of interest.

REFERENCES

1. Marazza G, Pham HC, Scharer L, *et al*. Incidence of bullous pemphigoid and pemphigus in Switzerland: a 2-year prospective study. Br J Dermatol. 2009; 161: 861–8.
2. Ujiie H, Shibaki A, Nishie W, *et al*. What's new in bullous pemphigoid. J Dermatol. 2010; 37: 194-204.
3. Taylor G, Venning V, Wojnarowska F, *et al*. Bullous pemphigoid and autoimmunity. J Am Acad Dermatol. 1993; 29: 181-4.
4. Kasperkiewicz M, Zillikens D. The Pathophysiology of Bullous Pemphigoid. Clinic Rev Allerg Immunol. 2007; 33: 67–77.
5. Liao CP, Booker RC, Brosseau JP, *et al*. Contributions of inflammation and tumor microenvironment to neurofibroma tumorigenesis. J Clin Invest. 2018; 128: 2848-61.
6. Shi L, Liu FJ, Jia QH, *et al*. Solitary plexiform neurofibroma of the stomach: a case report. World J Gastroenterol. 2014; 20: 5153-6.
7. Allaway RJ, Gosline SJC, La Rosa S, *et al*. Cutaneous neurofibromas in the genomics era: current understanding and open questions. Br J Cancer. 2018; 118: 1539-48.
8. Riccardi VM. The potential role of trauma and mast cells in the pathogenesis of neurofibromas. In: Ishibashi y, Hori y, eds. Tuberous Sclerosis and Neurofibromatosis – Epidemiology, Pathophysiology, Biology and Management. 1st ed. Amsterdam: Elsevier publications, 1990; 167-90.
9. Yesudian PD, Wilson NJ, Parslew R. Bullous pemphigoid and neurofibromatosis – a chance association requiring special vigilance. Clin Exp Dermatol. 2000; 25: 658-9.
10. Tucker T, Riccardi VM, Sutcliffe M, *et al*. Different patterns of mast cells distinguish diffuse from encapsulated neurofibromas in patients with neurofibromatosis 1. J Histochem Cytochem. 2011; 59: 584-90.