Clinical, Cosmetic and Investigational Dermatology Dovepress

Open Access Full Text Article

CASE REPORT

Coexistence of Pemphigus Foliaceus and Bullous Pemphigoid: A Case Report

Jinxiang Yuan[1], Xinyi Yao[1], Lvye Liu[1], Junling Zhang[2]

[1]Graduate School, Tianjin University of Traditional Chinese Medicine, Tianjin, People's Republic of China; [2]Department of Dermatology, Tianjin Academy of Traditional Chinese Medicine Affiliated Hospital, Tianjin, People's Republic of China

Correspondence: Junling Zhang, Department of Dermatology, Tianjin Academy of Traditional Chinese Medicine Affiliated Hospital, Tianjin, People's Republic of China, Tel +86 13920301679, Email zhangjunlingtj@126.com

Abstract: Pemphigus foliaceus (PF) and bullous pemphigoid (BP) are distinct autoimmune bullous skin diseases mediated by autoantibodies targeting adhesion molecules in desmosomes and hemidesmosomes structural proteins in the epidermal-basement membrane zone, respectively. The coexistence of PF and BP is rare. We present the case of a 72-year-old male with clinical and histological features of both PF and BP. Treatment with immunoglobulin (10 g/day for 3 days), intravenous dexamethasone sodium phosphate (5 mg/day for 10 days), oral triamcinolone (30 mg/day for 10 days), and minocycline hydrochloride (20 mg/day for 10 days) resulted in significant improvement. This rare case highlights the importance of accurate diagnosis and effective treatment strategies for the coexistence of PF and BP.

Keywords: autoimmune blistering diseases, pemphigus foliaceus, bullous pemphigoid, comorbidity, epitope spreading, direct immunofluorescence

Introduction

Autoimmune blistering diseases (AIBDs) are a diverse group of diseases primarily caused by autoantibodies that lead to blisters and erosions on the skin and mucous membranes.[1] Depending on the location of the lesion, AIBDs can be classified into pemphigus and pemphigoid-like diseases. Pemphigus foliaceus (PF) is a subtype of pemphigus, which characterized by intraepidermal blistering and acantholysis due to autoantibodies targeting desmosomes.[2] Conversely, bullous pemphigoid (BP), the most prevalent subepidermal autoimmune blistering disease caused by targeting hemidesmosomal proteins in the epidermal-basement membrane zone, primarily bullous pemphigoid antigen 180 (BP180), bullous pemphigoid antigen 230 (BP230) resulting in the separation between the epidermis and dermis.[3] BP incidences range from 13 to 42 patients per million in Western countries.[4–7] PF incidences between 0.5 and 1.0 per million in Western Europe to 6.7 per million in Tunisia.[8–10]

PF is mediated by IgG4 autoantibodies targeting desmoglein 1 (Dsg1), a desmosomal core glycoprotein located within the granular and spinous layers of the epidermis. This immune attack disrupts keratinocyte adhesion, resulting in superficial skin blistering. Dsg1 is essential for maintaining cell–cell adhesion within the upper epidermis, and the disruption induced by these autoantibodies leads to keratinocyte detachment, subsequently forming blisters. Clinically, PF presents as superficial erosions or scaly lesions. The blisters are typically very superficial and fragile, leading to erosion upon rupture. Lesions are often distributed on the scalp, face, trunk, and upper limbs, appearing in a scattered pattern, often accompanied by pruritus or a burning sensation. Mucosal involvement is rare. Histopathological examination reveals superficial acantholysis with clefting and blistering in the granular and upper spinous layers, with an intact basal layer. In the superficial and mid-dermis, there is perivascular infiltration by lymphocytes and neutrophils. Direct immunofluorescence (DIF) shows intercellular IgG deposition in keratinocytes, predominantly in a "net-like" pattern. Indirect immunofluorescence (IIF) may detect Dsg1-targeting antibodies in the patient's serum, typically using monkey esophagus or human epidermis as substrates, displaying a reticular IgG pattern between keratinocytes. On the other hand,

Received: 22 August 2024
Accepted: 15 November 2024
Published: 28 November 2024

BP is mediated by autoantibodies—primarily IgG1 and IgG4—targeting the basement membrane zone (BMZ) proteins BP180 and BP230, components of hemidesmosomes. Anti-BP180 antibodies impair the dermal-epidermal junction, leading to subepidermal blistering. Additionally, BP patients exhibit complement activation, triggering inflammatory cell infiltration that further disrupts the dermal-epidermal junction and causes blister formation. Clinically, BP is characterized by tense blisters and pruritic, erythematous plaques. The blisters are mainly subepidermal, robust, and less prone to rupture. Lesions often appear on the limbs and trunk, and they can be widespread. BP patients may experience intense pruritus and a burning sensation, and the disease course is usually prolonged and prone to recurrence; some cases involve mucosal lesions. Histologically, BP is characterized by subepidermal blisters. The dermal papillae often show significant infiltration of eosinophils, along with neutrophils and monocytes. Fissures and inflammatory cell infiltration are typically seen at the basement membrane zone. DIF in BP reveals linear IgG and C3 deposition along the BMZ. IIF may detect BP180 and BP230 autoantibodies in serum, with linear IgG and C3 deposition at the BMZ when testing for BMZ antibodies.

In clinical practice, oral prednisone or prednisolone is the mainstay treatment for PF, starting with a relatively high initial dose that is gradually tapered down. Topical corticosteroids are suitable for mild localized lesions to reduce the systemic side effects of oral medications. When corticosteroids alone are insufficient or cause significant side effects, immunosuppressants like methotrexate are often combined to enhance efficacy and reduce steroid dosage. Other options for more severe cases include cyclosporine and mycophenolate mofetil. Rituximab, a biologic, has been reported as effective for patients with corticosteroid-refractory or corticosteroid-dependent PF; as a B-cell depleting agent, it targets CD20-positive B cells to reduce autoantibody production. Intravenous immunoglobulin (IVIG) can serve as an adjunctive therapy for refractory cases, temporarily increasing immunoglobulin levels to neutralize pathogenic antibodies. BP clinically manifests as tense bullae, which are deeper than those in pemphigus foliaceus and more commonly seen in elderly patients. Corticosteroids are crucial in BP management, with oral prednisone typically prescribed for severe cases, following a similar protocol to that for PF. For localized or mild BP, topical corticosteroids alone. If monotherapy with steroids is suboptimal, immunosuppressants like methotrexate or mycophenolate mofetil can be added to enhance therapeutic effects and reduce steroid use. Rituximab has also been employed in recent years for BP treatment, mainly for refractory cases unresponsive to steroids and immunosuppressants. Omalizumab, an anti-IgE monoclonal antibody, has shown some efficacy in refractory BP, particularly for patients with high IgE levels. In severe cases, IVIG serves as adjunctive therapy, often combined with other treatments to help achieve rapid symptom relief. Treatment for both pemphigus foliaceus and bullous pemphigoid primarily depends on corticosteroids and immunosuppressants, while biologics play an essential role in managing refractory cases. Due to the unique characteristics of each disease and patient-specific factors, medication choice and dosage may vary in clinical practice.

The primary distinction between PF and BP lies in the targeted antigens of the respective autoantibodies. In rare cases, these two diseases can coexist, suggesting potential shared pathogenic mechanisms, such as similar environmental triggers or genetic susceptibility. Some researchers propose that the coexistence of these autoimmune blistering diseases in the same patient may be linked to inter-molecular epitope spreading. This phenomenon occurs when tissue damage from a primary autoimmune or inflammatory skin disease exposes protein components that are usually undetectable by the immune system, leading to secondary autoimmune skin disease through epitope spreading and autoantibody production.[11,12] Accurately diagnosing the coexistence of these two diseases poses a challenge, as PF lesions typically present as superficial blisters or erosions confined to the skin surface, whereas BP manifests as deeper, tense blisters. When both conditions coexist, the patient's lesions may exhibit features of both superficial and deep blisters, complicating the diagnostic process.

Managing coexisting PF and BP poses significant treatment challenges. Both PF and bullous pemphigoid BP require systemic immunosuppressive therapy, but each condition exhibits differing responses to immunosuppression. When they coexist, a combination of immunosuppressive agents and biologics is often necessary. However, designing a treatment regimen is complex, with precise dosing control being critical, as even slight miscalculations can lead to excessive immunosuppression or inadequate treatment. Due to the rarity of coexisting PF and BP cases, standardized treatment guidelines for such cases are currently lacking. Management largely relies on individualized approaches and physician experience, posing challenges for long-term care.

Case Presentation

A 72-year-old man presented with a 2-week history of erythema and papules with pruritus on his limbs. Two weeks prior, new blisters the size of a soybean appeared on the lower limbs, which were easy to burst, positive for Nikolsky's sign, and self-itching. Following scratching, the blister eroded and spread to the upper limbs, increasing erythema and erosion without oral or joint involvement. Three days before his visit, without apparent cause, he experienced diffuse erythema, new tense blisters, and severe itching, prompting his hospital visit. The patient's past medical history was unremarkable, with no similar family history or special medication history.

Dermatological examination revealed generalized erythema and edema on the limbs, with dark red to purplish red color and scabby desquamation. Scattered blisters, some tense and others broken, superficial erosions, dark brown scabs, and lichenized rashes were observed. There was no mucous membrane involvement (Figure 1a–c).

Histopathological examination of an erythematous-vesicular lesion on the right upper arm showed cracks and blisters can be seen in the granular layer and the upper part of the spinous layer, lymphocytic and neutrophils infiltration in the superficial dermis (Figure 1d). Subepidermal clefts were found with eosinophils and lymphocytes within blisters and the superficial dermis (Figure 1e). DIF revealed reticular linear deposition of IgG deposition along the intercellular space (ICS) in PF (Figure 1f) and linear deposition of IgG and C3 along the BMZ in BP (Figure 1g). Laboratory tests showed elevated Dsg1 at 136.3 U/mL (reference range: 0–14 U/mL), elevated Immunoglobulin E(IgE) >2500 u/mL, and normal levels of desmoglein-3 (Dsg3), bullous pemphigoid antigen 180 (BP180), bullous pemphigoid antigen 230 (BP230) and type VII collagen, laminin gamma 1, laminin 332 are negative, excluding acquired epidermolysis bullosa and laminin gamma 1 type pemphigoid. Based on these findings, he was diagnosed PF associated with BP.

Treatment included intravenous immunoglobulin (10 g/day) for 3 days, followed by intravenous dexamethasone sodium phosphate (5 mg/day), oral triamcinolone (30 mg/day), and minocycline hydrochloride (20 mg/day). After 10 days, the redness and swelling subsided, most blisters dried and scabbed, and no new blisters formed. At one, three, and six months post-discharge, no new erythema or blisters were noted. Three months post-treatment, antibody levels and IgE normalized, with no significant abnormalities in blood, urine, liver, kidney function, and electrolytes. Maintenance therapy included oral triamcinolone (4 mg/day).

Discussion

The coexistence of PF and BP was first reported in 1979, with seven cases documented internationally, involving patients aged 62–88 years.[13–19] In three cases, the disease transitioned from BP or PF to the coexistence of both, while four cases showed simultaneous occurrence at initial diagnosis (Table 1).

In our case, the patient exhibited clinical features of erosion, tense blisters, and erythema. Histopathology revealed intraepidermal clefting, subepidermal blisters, eosinophilic and lymphocytic infiltration, and DIF showed IgG and Complement 3(C3) deposition along the ICS and BMZ. ELISA indicated positive Dsg1 antibodies, while Dsg3, BP180, BP230, type VII collagen, laminin gamma 1, and laminin 332 were negative. These findings excluded diseases like acquired epidermolysis bullosa, confirming the diagnosis of coexisting BP and PF.

This patient's presentation aligns with Sárdy's findings, suggesting ES due to prolonged desmosome antigen exposure and lack of immunosuppressive therapy.[20] Persistent immune stimulation by desmosomal/hemidesmosomal antigens might not have been fully controlled by immunosuppressive agents, leading to the activation and expansion of antigen-specific responses, and thus the coexistence of both diseases. Similarly, studies have found that in patients with progressive neurodegeneration and neuroinflammation, neuronal subtypes of BP180 become exposed, leading to a cross-immune reaction between neural and cutaneous antigens and a breakdown in self-tolerance. In patients with neurodegenerative diseases without concurrent BP, serum IgG positivity for BP180 and BP230 has been observed. Similarly, positive reactions for BP230 IgG have been detected in brain extracts from the sera of patients without neurodegenerative diseases.

Typically, BP patients show a positive reaction for anti-BP180 and/or anti-BP230 antibodies. The negative result in this case may be due to the patient not having produced sufficient levels of BP180/230 antibodies, with antibody levels below the detection limit. Additionally, in some patients, anti-BP180 and anti-BP230 antibodies may form immune complexes with

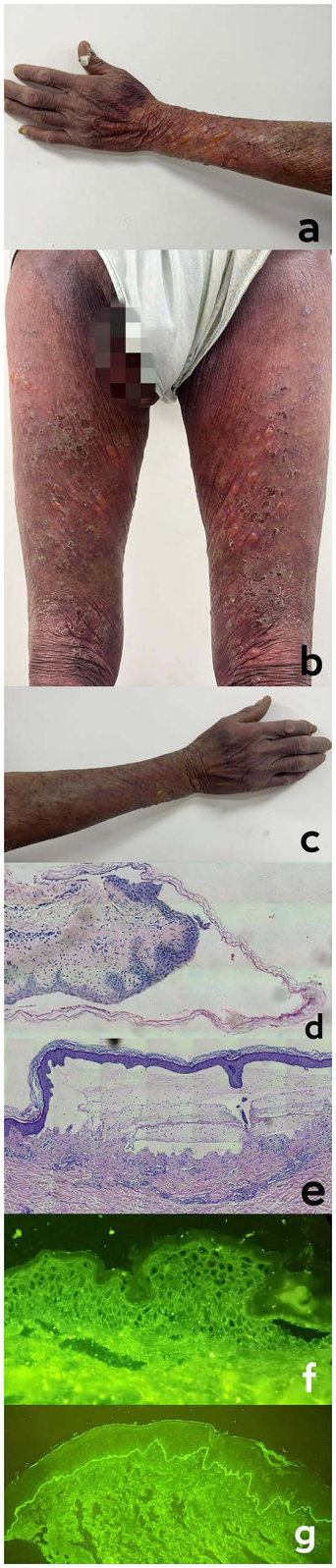

Figure 1 Clinical features, histopathology, and DIF findings. (**a–c**) Erythema, blisters, erosions, and crusts on limbs, erythematous blisters on both thighs. Nikolsky's sign was negative. (**d**) cracks and blisters can be seen in the granular layer and the upper part of the spinous layer, lymphocytic and neutrophils infiltration in the superficial dermis (HE, Original magnification×100). (**e**) Subepidermal clefts were found with eosinophils and lymphocytes within blisters and the superficial dermis (HE, Original magnification×100). (**f**) DIF revealed reticular linear deposition of IgG along the ICS in PF (Original magnification×100). (**g**) DIF revealed linear deposition of IgG and C3 along the BMZ in BP (Original magnification×100).

Table 1 Reported Cases of Pemphigus Foliaceus with Bullous Pemphigoid

Case	Sex	Age	Order	Progress Time	Histological Characteristics
Rantanen[13]	Male	62	BP progresses to PF	5 years	Intraepidermal fissure, intercellular IgG (+); Subdermal bulla, IgG(+) and C3 deposition in basement membrane
Harrington[14]	Male	75	PF progresses to BP	28 mouths	Subdermal eosinophil aggregation, IgG(+) and IgA(+) between epidermis and basement membrane zone
Kraigher[15]	Female	82	At the same time found	At the same time found	Epidermal acantholysis, subcutaneous blister, IgG(+) in epidermis and basement membrane, C3 basement membrane deposition
Ishiko[16]	Male	63	PF progresses to BP	6 years	Intraepidermal and subepidermal blisters, the dense layer can be seen at the bottom of subdermal fissure, and IgG(+) and C3 are deposited in the epidermis and basement membrane
Lin[17]	Male	71	At the same time found	At the same time found	Epidermal granular layer acantholysis, dermal edema, lymphocyte and eosinophil aggregation, dermal-epidermal junction and IgG(+) in epidermis
Ando[18]	Female	88	At the same time found	At the same time found	Epidermal acantholysis, subcutaneous blister, IgG(+) in epidermis and basement membrane
Tsujiwaki[19]	Male	88	At the same time found	At the same time found	Subepidermal blister, eosinophil aggregation in the upper dermis, IgG(+) between the epidermis and basement membrane zone

antigens, making them difficult to detect through conventional serological testing. Research has shown that BP may involve additional antigen components, such as the C-terminal domain of BP180 and the 120-kDa BP180 fragment, including LAD-1 (a cleavage product of BP180), resulting in negative anti-BP180 and anti-BP230 antibody tests. There may be hidden or atypical antibodies targeting other antigens.[21,22] In some patients, IgE antibodies target specific fragments of BP180, potentially directly triggering mast cells and basophils to release inflammatory mediators, which subsequently leads to skin inflammation and pruritus.[23] Furthermore, BP patients often exhibit an enhanced Th2-type immune response, which promotes IgE production. Th2 cytokines stimulate B cells to secrete IgE, resulting in elevated serum IgE levels.[24]

Conclusion

PF combined with BP is rare and prone to misdiagnosis. This case report aims to improve clinical understanding and diagnosis of this condition. Clinicians should consider the possibility of coexisting PF and BP when encountering different tension blisters, edematous erythema with erosion, epidermal acantholysis, subcutaneous blisters, reticular linear deposition of IgG along the ICS and linear deposition of IgG and C3 along the BMZ.

Ethics Statement

Institutional approval was not required to publish the case details.

The publications of images were included with the patient's consent.

Consent Statement

Informed consent was provided by the patient for publication of the case.

Acknowledgments

The authors would like to thank the patients recruited for participation in this study and all the colleagues in the department who contributed to this case study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Tianjin Natural Science Foundation (NO.23JCYBJC00680).

Disclosure

The author(s) report no conflicts of interest in this work.

References

1. Beek NV, Zillikens D, Schmidt E. Bullous autoimmune dermatoses-clinical features, diagnostic evaluation, and treatment options. *Dtsch Arztebl Int*. 2021;118:413–420. doi:10.3238/aerztebl.m.2021.0136
2. Schmidt E, Kasperkiewicz M, Joly P. Pemphigus. *Lancet*. 2019;394:882–894. doi:10.1016/S0140-6736(19)31778-7
3. Schmidt E, Zillikens D. Pemphigoid diseases. *Lancet*. 2013;381:320–332. doi:10.1016/S0140-6736(12)61140-4
4. Bertram F, Brocker EB, Zillikens D, et al. Prospective analysis of the incidence of autoimmune bullous disorders in Lower Franconia, Germany. *J Dtsch Dermatol Ges*. 2009;7:434–440. doi:10.1111/j.1610-0387.2008.06976.x
5. Langan SM, Smeeth L, Hubbard R, et al. Bullous pemphigoid and pemphigus vulgaris–incidence and mortality in the UK: population based cohort study. *BMJ*. 2008;337:a180. doi:10.1136/bmj.a180
6. 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;161:861–868. doi:10.1111/bjd.2009.161.issue-4
7. Joly P, Baricault S, Sparsa A, et al. Incidence and mortality of bullous pemphigoid in France. *J Invest Dermatol*. 2012;132:1998–2004. doi:10.1038/jid.2012.35
8. Pisanti S, Sharav Y, Kaufman E, et al. Pemphigus vulgaris: incidence in Jews of different ethnic groups, according to age, sex, and initial lesion. *Oral Surg Oral Med Oral Pathol*. 1974;38:382e7. doi:10.1016/0030-4220(74)90365-x
9. Stanley JR, Amagai M. Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. *N Engl J Med*. 2006;355(17):1800–1810. doi:10.1056/NEJMra061111
10. Bastuji-Garin S, Souissi R, Blum L, et al. Comparative epidemiology of pemphigus in Tuni sia and France: unusual incidence of pemphigus foliaceus in young Tunisian women. *J Invest Dermatol*. 1995;104:302–305. doi:10.1111/1523-1747.ep12612836
11. Cornaby C, Gibbons L, Mayhew V, et al. B cell epitope spreading: mechanisms and contribution to autoimmune diseases. *Immunol Lett*. 2015;163:56–68. doi:10.1016/j.imlet.2014.11.001
12. Matsuda H, Oiso N, Ishii N, et al. Bullous pemphigoid in infancy showing epitope - spreading phenomenon: recovery with topical therapy. *Acta Derm Venereol*. 2015;95:610–611. doi:10.2340/00015555.2026
13. Rantanen T, Niemi KM. A further case of coexisting bullous pemphigoid and pemphigus foliaceus. *Br J Dermatol*. 1979;101:611–612. doi:10.1111/j.1365-2133.1979.tb15109.x
14. Harrington CI, Sneddon IB. Coexistence of bullous pemphigoid and pemphigus foliaceus. *Br J Dermatol*. 1979;100:441–445. doi:10.1111/j.1365-2133.1979.tb01647.x
15. Kraigher O, Wohl Y, A GAT, et al. A mixed immunoblistering disorder exhibiting features of bullous pemphigoid and pemphigus foliaceus associated with Spirulina algae intake. *Int J Dermatol*. 2008;47:61–63. doi:10.1111/j.1365-4632.2007.03388.x
16. Ishiko A, Hashimoto T, Shimizu H, et al. Combined features of pemphigus foliaceus and bullous pemphigoid: immunoblot and immunoelectron microscopic studies. *Arch Dermatol*. 1995;131:732–734. PMID: 7778933. doi:10.1001/archderm.1995.01690180112024
17. Lin SS, Wang KH, Yeh SW, et al. Simultaneous occurrence of pemphigus foliaceus and bullous pemphigoid with concomitant herpesvirus infection. *Clin Exp Dermatol*. 2009;34:537–539. doi:10.1111/j.1365-2230.2008.02989.x
18. Ando S, Sato-Matsumura KC, Kasai M, et al. Desmoglein1 and BP 180 ELISA indexes correlating with disease activity in a patient with coexisting pemphigus foliaceus and bullous pemphigoid. *Clin Exp Dermatol*. 2009;34:e995–996. doi:10.1111/j.1365-2230.2009.03656.x
19. Tsujiwaki M, R A, Nomura Y, et al. Coexistence case of bullous pemphigoid and pemphigus foliaceus. *Eur J Dermatol*. 2013;23:552–553. doi:10.1684/ejd.2013.2084
20. Sárdy M, Borovaya A, Horváth ON, et al. Successful rituximab treatment of juvenile bullous pemphigoid with esophageal scarring due to epitope spreading. *J Dtsch Dermatol Ges*. 2016;14:618–621. doi:10.1111/ddg.12902
21. Seppänen A. Collagen: a shared antigen in neurodermatolog ical interactions? *Clin Dev Immunol*. 2013;2013:240570. doi:10.1155/2013/240570
22. Messingham KA, Aust S, Helfenberger J, et al. Autoantibodies to collagen are present in Parkinson's disease and localize to tyrosine-hydroxylase positive neurons. *J Invest Dermatol*. 2016;136:721–723. doi:10.1016/j.jid.2015.12.005
23. Yayli S, Pelivani N, Beltraminelli H, et al. Detection of linear IgE deposits in bullous pemphigoid and mucous membrane pemphigoid: a useful clue for diagnosis. *Br J Dermatol*. 2011;165:1133–1137. doi:10.1111/j.1365-2133.2011.10481.x
24. Chen F, Wang Y, Chen X, et al. Targeting interleukin 4 and interleukin 13: a novel therapeutic approach in bullous pemphigoid. *Ann Med*. 2023;55:1156–1170. doi:10.1080/07853890.2023.2188487