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RESEARCH ARTICLE

Bullous Pemphigoid and Cognitive Impairment in Elderly Patients: A Case Report of Two Patients Highlighting the Possible Link with Neurodegeneration

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Background

Bullous pemphigoid (BP) is an autoimmune blistering disorder, predominantly affecting elderly patients, often in conjunction with neurodegenerative diseases such as dementia. Emerging research suggests a complex and bidirectional relationship between BP and cognitive decline, highlighting the need for deeper exploration into their shared pathophysiology.

Case Report

. Female, 78 years old, diagnosed with Lewy body dementia, presented with pruritic erythematous-bullous lesions that began on the limbs and later spread to the trunk. Diagnostic tests confirmed BP180-type BP. Treatment with topical steroids and systemic methylprednisolone led to significant improvement, though a flare-up occurred when steroid dosage was reduced.

. Male, 81 years old, diagnosed with mild neurocognitive disorder and Meniere's syndrome, developed pruritic bullous lesions on both lower limbs, accompanied by fever. Diagnostic process confirmed BP180-BP230-type BP. His condition improved rapidly with betamethasone and methylprednisolone, with no flare-ups upon treatment completion.

Conclusion

These cases highlight the complex relationship between BP and neurodegenerative diseases in elderly growing population. The mechanisms remain unclear, but potential factors include shared risk factors, autoantibody cross-reactivity, and BP as a marker of neurodegeneration. Preliminary evidence suggests that cognitive impairment may influence BP's clinical presentation, with different autoantibodies patterns linked to dementia severity. Continued research is crucial to elucidate these links.

The relationship between the nervous system and the skin is well-documented in the literature, with an increasing body of clinical evidence supporting an association between neurologic disease and distinct inflammatory skin conditions. This relationship is especially pronounced in the elderly population.[1] Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease, primarily affecting elderly patients with multiple co-morbidities. It is significantly associated with neurological disorders, which also represent a major prognostic factor. Risk factors for BP include old age, neurologic diseases (dementia, Parkinson's disease, cerebrovascular disease), and some particular drugs, including loop diuretics, spironolactone and neuroleptics. BP is immunologically characterized by tissue-bound and circulating autoantibodies directed against either the BP antigen 180 (BP180, or BPAG2) or the BP antigen 230 (BP230, or BPAG1e), or even both, which are components of hemidesmosomes involved in dermal–epidermal cohesion. The effect of these autoantibodies manifest clinically as urticarial plaques that often develop into large, tense blistering in the skin; the diagnosis of BP relies on immunopathologic examinations, particulary direct and indirect immunofluorescence microscopy, as well as anti-BP180/BP230 enzyme-linked immunosorbent assay.[2]

Over the past two decades, the high prevalence of neurological disorders (NDs) in elderly patients with BP has raised scientific concerns, particularly regarding the association between BP and dementia, with some studies suggesting a bidirectional relationship.[3,4]

We describe two cases of BP in elderly patients, both hospitalized at the "Augusto Murri" University Internal Medicine Unit of the Policlinico of Bari: one diagnosed with Lewy body dementia and the other with mild cognitive impairment (MCI), each presenting distinct autoimmune patterns.

In case 1, a 78 years old female, diagnosed with Lewy body dementia 2 years ago. She reported the onset of pruritic erythematous-bullous lesions, initially on the upper and lower limbs and later on the trunk, for approximately 2 weeks. She was on home treatment with quetiapine, trazodone, and citalopram.

Physical examination revealed erythematopapular lesions evolving into vesicles and bullae with erosive-crusty evolution, accompanied by intense pruritus, widespread over the entire body. Direct immunofluorescence (DIF) studies revealed deposition of IgG and C3 at the basement membrane zone (BMZ). IgG autoantibodies to full-length BP180, measured by enzyme-linked immunosorbent assay (ELISA), were positive (index value 171.6 UA/ml; normal <9). BP230 ELISA was negative. Based on these findings, the case was diagnosed as BP180-type bullous pemphigoid.

Histological examination of the incisional skin biopsy showed partial dermo-hypodermic detachment associated with deposition of fibrino-leucocytic material and mild chronic inflammatory infiltration, lympho-monocytic, and focally eosinophilic granulocytic. Treatment with topical betamethasone and gentamicin, along with systemic methylprednisolone and oxatomide, improved the skin lesions. However, a flare-up occurred upon tapering of methylprednisolone, necessitating a slower reduction.

In case 2, a 81 years old male, diagnosed with mild neurocognitive disorder for approximately one year, with rapidly worsening symptoms and loss of function in activities of daily living (ADLs), and Meniere's syndrome with objective vertigo and severe balance disturbances. He reported edema and pruritic bullous lesions on both lower limbs, associated with fever spikes. Currently on home treatment with lorazepam. Physical examination revealed hyperchromic sequelae and slightly raised erythematous patches on the trunk and limbs, with two tense serous bullous lesions on the left flank. Plantar erosions resembling suspected bullae were noted. Direct immunofluorescence (DIF) studies were unavailable. IgG autoantibodies to full-length BP180 were positive (index value 80.7 UA/ml; normal <9). BP230 ELISA was also positive (index value 28.7 UA/ml; normal <8). Based on these findings, the case was diagnosed as BP180-BP230 type bullous pemphigoid.

Histological examination showed a subepidermal blister containing eosinophilic granulocytes and fibrinous material, with diffuse eosinophilic granulocytic inflammatory infiltration in an interstitial dermal distribution, as well as perivascular and periappendageal involvement. At first glance, this pattern may suggest pemphigus, due to the presence of an intraepidermal or near-epidermal blister and the prominent eosinophilic inflammatory component, features that can occasionally overlap with those seen in pemphigus variants. However, immunopathological analysis revealed positivity for BP180 and BP230 autoantibodies, which are specific markers for bullous pemphigoid, thus redirecting the diagnosis. Bullous pemphigoid is defined by subepidermal blistering and immune reactivity against hemidesmosomal proteins at the dermo-epidermal junction,

unlike pemphigus, which is characterized by suprabasal acantholysis and anti-desmoglein autoantibodies. The combination of histological features, eosinophil-rich infiltrate, and serological findings, along with the clinical context, confirms the diagnosis of bullous pemphigoid. Despite initial histological resemblance to pemphigus, the overall findings are more consistent with bullous pemphigoid. Topical betamethasone and gentamicin, along with systemic methylprednisolone and oxatomide, improved the skin lesions. No flare-ups occurred, and the healing process was faster compared to the previous case. Additionally, antibiotic therapy was started with ceftriaxone and later switched to teicoplanin, resolving the febrile condition and reducing inflammatory markers.

We report two cases of elderly patients with prior diagnoses of neurodegenerative disease associated with cognitive disturbances, presenting with bullous dermatosis suggestive of pemphigoid. Both cases exhibited distinct autoimmune patterns and divergent clinical manifestations. The first patient was hospitalized for 17 days, and the second for 11 days. In both cases, first-line treatment with systemic corticosteroids was sufficient to achieve disease control, without the need for escalation to immunosuppressive or immunoregulatory therapies.

BP is not a rare disease, with global prevalence estimates ranging from 2.4 to 42.7 per 100,000 population, with higher rates in Europe and North America than in Asia and Africa.[5] The mechanism underlying the association between bullous pemphigoid (BP) and neuropsychiatric disorders remains incompletely understood, although an increasing body of research is clarifying the mechanisms and correlations responsible for the onset of this disease.

Several hypotheses have been proposed to explain the potential link between BP and neurodegenerative diseases. One possibility is that BP and dementia share common risk factors, such as aging, genetic susceptibility, inflammation, oxidative stress, and vascular damage.[6,7] Another theory suggests that BP, given that both skin and nervous tissue derive from the same ectoderm, may act as a marker of neurodegeneration. In this context, BP autoantibodies might cross-react with neuronal antigens, leading to neuronal damage.[8] Furthermore, BP autoantibodies against BP180/BP230 brain isoforms could cross-react with their skin isoforms, contributing to the disease process. Finally, BP could be a consequence of dementia, as cognitive impairment may compromise the skin's barrier function, increasing susceptibility to infections and trauma.[3] Most of the existing literature suggests that bullous pemphigoid tends to develop after the onset of a neurological disorder, with one study reporting a mean interval of approximately 6.7 years between the two conditions. Although some inconsistencies exist regarding the sequence of neurological disease and bullous pemphigoid diagnosis, there is general agreement on an increased risk of neurological comorbidities in patients diagnosed with bullous pemphigoid.[1]

Further research is needed, but existing evidence suggests that neuropsychiatric diseases may influence the immunological phenotype of BP. A retrospective study found that BP patients with co-morbid neuropsychiatric disease had higher seropositivity rates for anti-BP230 autoantibodies compared to those without. These patients also exhibited higher eosinophil levels, which may exert neurotoxic effects. Additionally, another study found an inverse association between BP180 autoantibodies and cognitive function, suggesting that BP180 autoantibodies are linked to more severe dementia.[9]

This report presents two cases of bullous pemphigoid (BP) in elderly patients with coexisting cognitive impairment, suggesting a possible interplay between cutaneous autoimmunity and neurodegeneration. However, several limitations should be acknowledged.

First, the primary limitation is the small sample size, which inherently restricts the generalizability of our findings. Although case reports and small case series can provide preliminary insights or raise new hypotheses, they are not designed to establish causal relationships. The co-occurrence of BP and neurocognitive disorders in our patients may reflect coincidental comorbidity rather than a definitive pathogenic link.

Second, the descriptive and retrospective nature of the report lacks standardized neurocognitive assessments and does not allow for temporal evaluation of disease progression. In case 2, direct immunofluorescence (DIF) studies were not available, potentially limiting the diagnostic robustness.

Third, the presence of potential confounding factors, including polypharmacy, age-related immunosenescence, and other comorbidities—particularly cardiovascular and metabolic conditions—was not systematically controlled. Notably, both patients were receiving medications, such as neuroleptics and benzodiazepines, that have been implicated as possible triggers or risk factors for BP.

Additionally, BP is not a rare condition among the elderly, and its occurrence in patients with neurodegenerative disorders may also reflect overlapping epidemiological trends related to aging, rather than specific pathogenic mechanisms. Finally, although immunopathological findings support a differential autoimmune profile in the two cases, the limited sample prevents any firm conclusions regarding correlations between specific antibody patterns (e.g., BP180 vs. BP230)

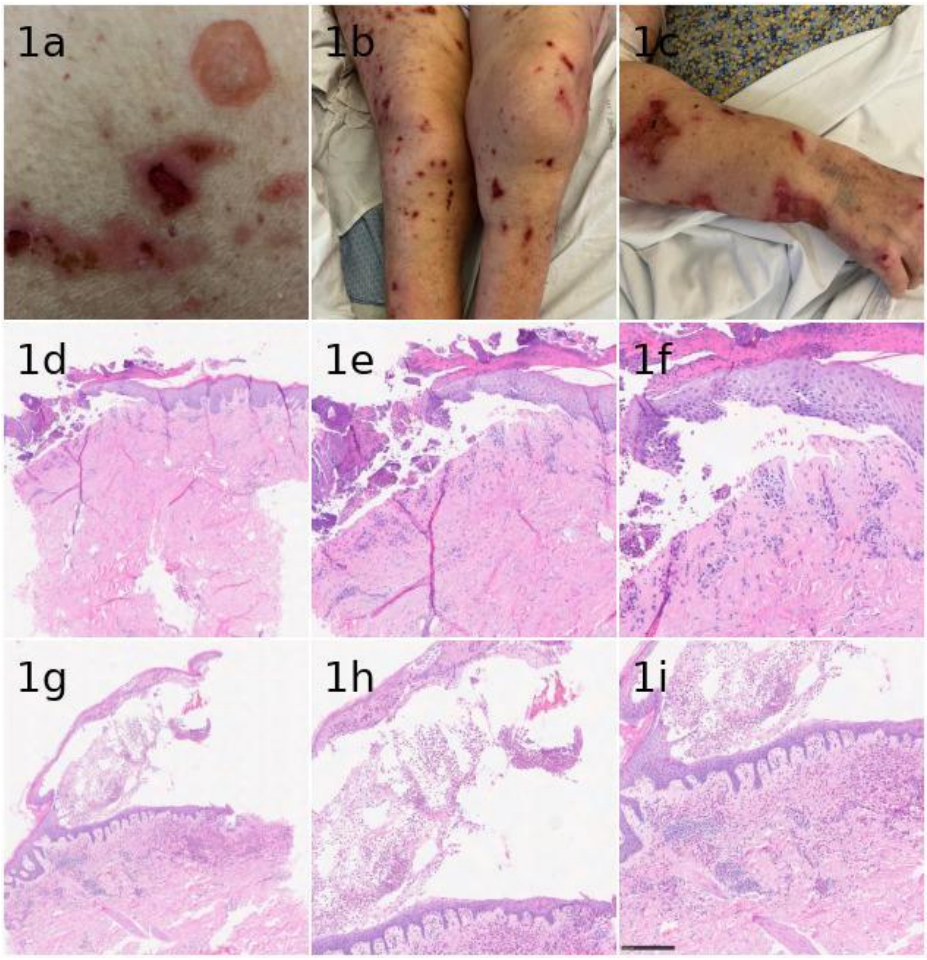

Figure 1. Clinical and histopathological findings in two elderly patients with bullous pemphigoid.

(a–c) Case 1 – Clinical presentation with tense bullae, erosions, and crusts on erythematous skin of the lower and upper limbs.

(d–f) Case 1 – Histopathological sections of skin and subcutaneous tissue (original magnification: d = 500 µm, e = 250 µm, f = 100 µm) showing partial dermo-hypodermal detachment with fibrino-leukocytic deposition and mild chronic inflammatory infiltrate, predominantly lympho-monocytic with focal eosinophilic granulocytes.

(g–i) Case 2 – Histopathological sections of skin and subcutaneous tissue (original magnification: g = 500 µm, h = 250 µm, i = 250 µm) demonstrating an infraspinous blister containing eosinophilic granulocytes and fibrinous material, with a diffuse eosinophilic inflammatory infiltrate in the dermis distributed interstitially, perivascularly, and around adnexal structures.

and the presence or severity of neurodegeneration. Further studies, including prospective cohorts with standardized neurological and dermatological evaluations, are needed to clarify the temporal and mechanistic relationship between bullous pemphigoid and cognitive decline.

Continued exploration of the etiology and mechanisms underlying BP and its association with neurodegenerative diseases, such as dementia, is highly warranted.[10]

At the time of admission to the ward and the signing of the medical record, as per standard protocol, authorization for the acquisition of images and data for educational and research purposes was granted by the patients' legal guardians, acting as their court-appointed support administrators.

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Conflicts of Interest

The author declares no conflict of interest.

References

1. John Tanaka, Christopher Henderson, Matilda W Nicholas. Skin Disease and Neurological Conditions of the Elderly. *Current Geriatrics Reports Springer*. 2018;7:238–242.
2. Philippe Bernard, Frank Antonicelli. Bullous Pemphigoid: A Review of its Diagnosis, Associations. *Am J Clin Dermatol*. 2017;18(4):513-528.
3. Qi Zhou ,Zhenrong Xiong,Dejiang Yang, et al. The association between bullous pemphigoid and cognitive outcomes in middle-aged and older adults: A systematic review and meta-analysis. *PLOSONE*. 2023; 1-2.
4. Anna-Kaisa Försti, Jari Jokelainen, Hanna Ansakorpi, et al.Psychiatric and neurological disorders are associated with bullous pemphigoid- a nationwide Finnish Care Register study. *Sci Rep*. 2016;6(1):37125.
5. Lingling Lu, Linjiao Chen, Yujuan Xu, et al. Global incidence and prevalence of bullous pemphigoid: a systematic review and meta-analysis. *Journal of Cosmetic Dermatology*. 2022;21(10):4818-4835,.
6. Paweł Pietkiewicz, Justyna Gornowicz-Porowska, Monika Bowszyc-Dmochowska. Bullous pemphigoid and neurodegenerative diseases: a study in a setting of a Central European university dermatology department. *Aging Clinical and Experimental Research*. 2016;28: 659–663.
7. Y C Lai, Y W Yew, W C Lambert. Bullous pemphigoid and its association with neurological diseases: a systematic review and meta-analysis. *Journal of the European Academy of Dermatology and Venereology*. 2016;30(12):2007–2015.
8. Michael Kasperkiewicz, Detlef Zillikens, Enno Schmidt. Pemphigoid diseases: pathogenesis, diagnosis, and treatment. *Autoimmunity*. 2012;45(1):55-70.
9. Sarah M Dyson, Priya U Patel, Laszlo Igali, et al. Bullous pemphigoid in a patient with a neuropsychological disorder and a possible novel drug trigger: A case report and review of the literature. Skin Health and Disease published by John Wiley & Sons Ltd on behalf of British Association of Dermatologists. 2022;2(4):176.
10. Zhen Xie, Yang Gao, Lidi Tian. Pemphigus and pemphigoid are associated with Alzheimer's disease in older adults: evidence from the US Nationwide inpatient sample 2016–2018. *BMC Geriatrics*. 2023;28:872.