

A Rare Case of Hallopeau-Type Pemphigus Vegetans with Premalatha Sign: A Case Report and Literature Review

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ABSTRACT:

Pemphigus vegetans (PVeg) is the rarest clinical variant in the pemphigus group of vesiculobullous autoimmune diseases, accounting for less than 2% of all pemphigus cases.¹ It is classified into two subtypes: Hallopeau and Neumann, which differ in severity and prognosis. PVeg presents with flaccid bullae or pustules that break down into thickened, papillated plaques, mainly involving the skin folds, scalp, face, and mucous membranes. In some cases, oral lesions may resemble the surface of the brain, a distinctive feature known as the Premalatha sign. The diagnosis of PVeg relies on a combination of clinical presentations, histopathological findings, and laboratory investigations.

We reported a case of PVeg characterized by involvement of skin folds, oral ulcers, and a cerebriiform tongue (Premalatha sign). A tissue sample taken from a lesion in the right groin revealed papillomatous hyperplasia of the epidermis, suprabasal separation with acantholytic cells, and intraepidermal abscesses, consistent with a classic presentation of PVeg. Direct immunofluorescence revealed IgG deposits in the intercellular spaces of the epidermis, while indirect immunofluorescence detected a high titer of pemphigus IgG autoantibodies. Additionally, the anti-desmoglein 3 antibody test was positive. The patient received a three-month regimen of prednisolone and azathioprine, leading to successful treatment without relapse. This outcome confirmed the diagnosis of Hallopeau-type PVeg, which is linked to a more favorable prognosis.

Key words: Cerebriiform tongue, Premalatha Sign, Pemphigus vegetans, Hallopeau and Neumann type, rituximab

Case report

A 74-year-old male visited the Institute of Dermatology with a primary concern of recurring vegetative plaques in the intertriginous regions and painful oral erosions persisting for the past 7 months. The lesions initially appeared as small vesiculopustules on his face, scalp, left axilla, and inguinal region. These lesions subsequently ruptured to form erosions, which gradually progressed into jagged masses. He was previously treated with oral antibiotics and antifungal medications for

a presumed infectious disease, but there was no improvement.

On examination, large, well-defined papillomatous, vegetating erythematous plaques were observed in the perianal and axillary regions, with hypertrophic granulation tissue at the periphery of the lesions (Figure 1). Multiple ill-defined erythematous patches with crusting were observed on the face (Figure 2A). Additionally, painful oral ulcers and a cerebriiform tongue (Premalatha sign) were

also noted (Figure 2B). A provisional diagnosis of Pemphigus vegetans (PVeg) was established. He denied fatigue, shortness of breath, numbness, tingling, or pain in the extremities, there was no drooling, stridor, oral or genital chancres, and no lymphadenopathy.



Figure 1 Bilateral, well-defined, papillomatous vegetating erythematous plaques on the perianal: A and axillary regions: B

An incisional biopsy specimen was obtained from the vegetative lesion on the right groin. Histopathologic sections revealed pseudoepitheliomatous hyperplasia of the epidermis, with suprabasal separation, acantholytic cells, and intraepidermal abscess composed of neutrophils mixed with eosinophils (Figure 3, 4). The dermis showed superficial perivascular infiltration by lymphocytes, eosinophils, and neutrophils. Direct immunofluorescence demonstrated

positive IgG in the intercellular space of the epidermis. Blood testing for indirect immunofluorescence revealed a high titer (1:1280) of pemphigus IgG autoantibody. The anti-desmoglein 3 antibody was positive at a level of >200 RU/ml. Investigations for complete blood count, liver function, creatinine, and metabolic panels were all within the normal range. An extensive evaluation for hidden neoplasms or other infection like koh preparation and associated autoimmune conditions was conducted, but no such findings were identified.



Figure 2 A) Multiple ill-defined erythematous patches with crusting were observed on the face. B) Oral ulceration with a cerebriform tongue (Premalatha sign)

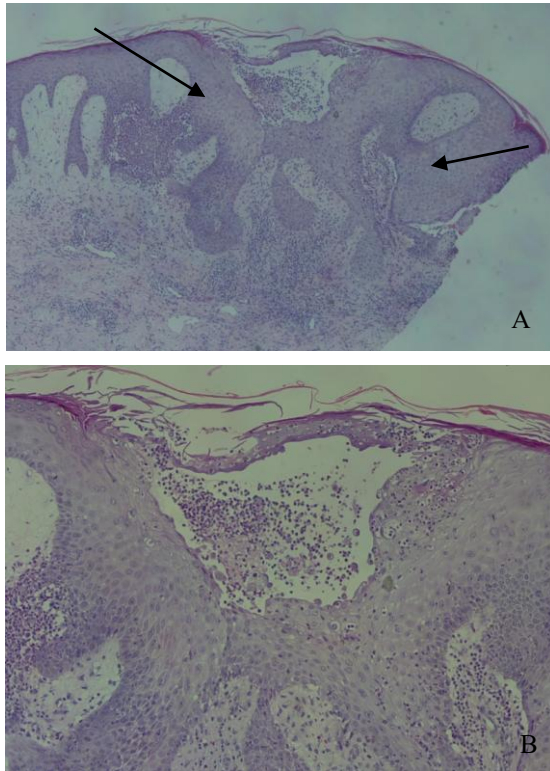


Figure 3 Skin biopsy specimen from the right groin revealed pseudoepitheliomatous hyperplasia of the epidermis, suprabasal separation (arrow sign), and acantholytic cells. (H&E; original magnification: A. X40, B. X100)

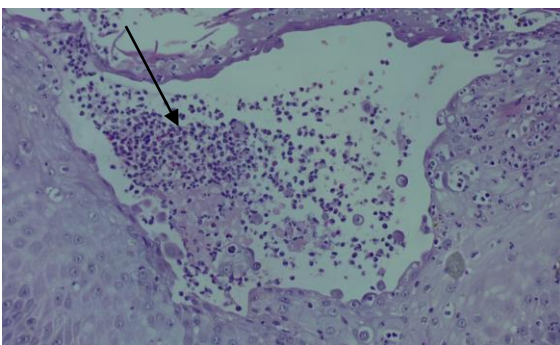


Figure 4 Intraepidermal abscess composed of neutrophils mixed with eosinophils. (H&E; original magnification: X 400)

Based on the overall findings, the definitive diagnosis for this patient was PVeg, Hallopeau type. The patient was initially treated with prednisolone 40 milligrams per day (0.6 mg/kg/day) and azathioprine 50 milligrams per day, along with moderate-potency topical corticosteroids. The patient's condition gradually improved, while tapering the dose of prednisolone. The lesions completely resolved over 3 months, with no recurrence of any new lesions (Figure 5).

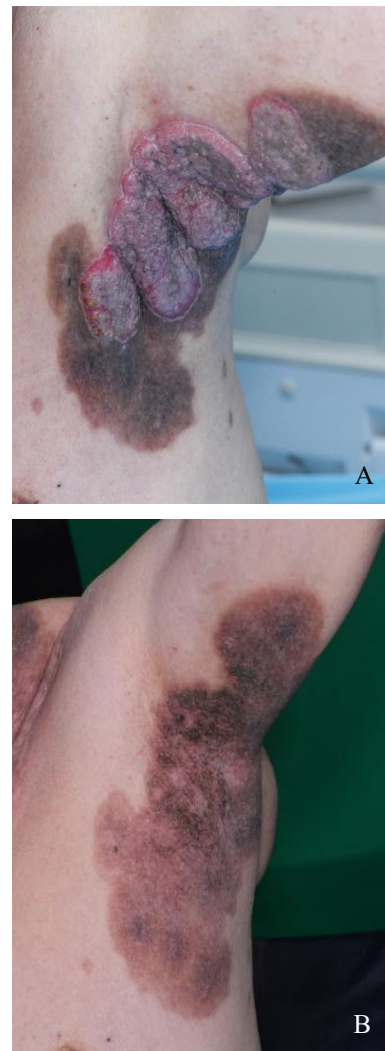


Figure 5 The lesion of pemphigus vegetans at the left axilla, before: A and after: B treatment

Discussion

Pemphigus refers to a rare and potentially life-threatening group of autoimmune blistering diseases, which include pemphigus vulgaris (PV), pemphigus foliaceus (PF), paraneoplastic pemphigus (PNP), and IgA pemphigus. In all forms, blisters and erosions develop as a result of autoantibodies attacking desmoglein 1 or 3, causing intraepidermal keratinocyte detachment and acantholysis².

PVeg is an uncommon subtype of pemphigus vulgaris, initially identified by Neumann in 1876. It presents with flaccid blisters or pustules that break down, leading to the formation of hypertrophic, vegetative plaques, primarily affecting intertriginous areas, as well as the scalp, face, and mucous membranes. Painful oral lesions are frequently observed (60-80%)³. In some cases, a cerebriform tongue (CT); sulci and gyri pattern resembling the brain's surface, known as the Premalatha sign, may appear. CT, also referred to as scrotal tongue or lingua plicata appears as grooves on the dorsal and lateral aspects of the tongue. It is relatively common condition, occurring in 10-20% of the population. Clinically, it is marked by fissures up to 6 mm. in depth extend along the tongue, differential diagnosis for scrotal tongue include amyloid infiltration, geographic tongue, macroglossia, syphilitic glossitis and vitamin deficiencies. The exact etiology is unknown, but it may be inherited and could follow a polygenic or autosomal dominant pattern with partial penetrance. It can precede, accompany, or follow the skin lesions of PVeg and is often resistant to treatment. Skin biopsy and histology of the cerebriform tongue reveal typical features of PVeg. This sign serves as a useful diagnostic clue for identifying PVeg^{4,5}.

PVeg has two clinical subtypes that differ in phenotype and clinical course: Hallopeau and

Neumann. In the Hallopeau type, which accounts for 1% to 5% of all pemphigus cases, the initial lesions are pustules that later evolve into papillomatous plaques^{6,7}. It typically follows a benign course. In contrast, the Neumann type often presents with vesiculobullous lesions resembling pemphigus vulgaris. These lesions rupture and progressively transform into fungoid plaques. The Neumann type is associated with a more aggressive clinical course and poorer prognosis. Differentiating between the Hallopeau and Neumann types is crucial due to these differences in clinical behavior. Our patient's findings were consistent with the Hallopeau-type variant of PVeg, characterized by the development of vesiculopustules in the intertriginous areas that coalesced, eroded, and progressed to vegetative erythematous plaques. A summary of these differences is provided in Table 1^{6,8}.

The differential diagnoses for PVeg include condyloma acuminata, Hailey-Hailey disease, and pyodermitis-pyostomatitis vegetans, as they exhibit similar clinical and histological characteristics but yield negative immunofluorescence findings⁹.

The management of PVeg follows a similar approach to pemphigus vulgaris, usually requiring systemic corticosteroids at a dose of 1 mg/kg/day, along with immunosuppressive agents like azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, and methotrexate^{10,11}. The goal is complete remission off therapy. However, some patients may achieve only partial remission off treatment or complete remission with minimal therapy. Alternatives like dapsone, combined with systemic steroids, have shown successful outcomes in some reports¹².

Table 1 Summary of the clinical characteristics and differences between the Hallopeau and Neumann types of Pemphigus vegetans

	Hallopeau Type	Neumann Type
Clinical presentation		
Early lesion	- Pustules rather than vesicles	- Vesicles rupture to form hypertrophic, granulating erosions that are prone to bleeding.
Late lesion	- Vegetating plaques	- Vegetative growths secrete serum and pus - Margins are lined with small pustules - New vegetative tissues form at the periphery
Distribution	- Mainly flexural area - Cerebriform tongue	- Non intertriginous area may be seen
Histopathology	Similar findings - Suprabasal separation with acantholytic cells - Pseudoepitheliomatous hyperplasia - Intraepidermal collections of eosinophils and neutrophils form microabscesses, more pronounced in the Hallopeau-type variant.	
Direct immunofluorescence	Deposition of IgG and C3 in the intercellular space of the epidermis	
Indirect immunofluorescence	Positive for circulating pemphigus IgG autoantibodies	
Serum autoantibodies	Mainly desmoglein 3 (Dsg3)	
Treatment	- Response to lower doses of systemic corticosteroids - Often combined with immunosuppressants	- Requires higher doses of systemic corticosteroids - Often combined with immunosuppressants
Severity	- Less severe	- More severe
Prognosis	- Better prognosis - Prolonged remission and fewer relapses	- Poorer prognosis - Have periods of remission and relapse

According to the treatment guidelines published in 2020, rituximab either as monotherapy or in combination with corticosteroids is recommended as the first-line treatment for mild to moderate or severe pemphigus. In a recent study evaluating the efficacy of the anti-CD20 monoclonal antibody; rituximab in autoimmune blistering diseases (including PV, PVeg, PF, epidermolysis bullosa acquisita, and both bullous pemphigoid and graft versus host disease), 94% of patients showed complete or partial clinical improvement, while 6%

experienced disease progression (notably in cases of PVeg, PF and PNP)¹³.

Based on the clinical findings of vegetative plaques in the flexural areas, oral mucosal involvement, and cerebriform tongue (Premalatha's Sign), along with histopathological features showing suprabasal clefts with numerous eosinophils and acantholytic cells, a diagnosis of pemphigus vegetans was confirmed. Our patient improved dramatically over a 3-month course of systemic corticosteroids and azathioprine. After 9-month treatment, azathioprine was

administered 50 mg (0.8 mg/kg/day), and prednisolone tapering to 5 mg/day (0.1 mg/kg/day). The level of anti-desmoglein 3 antibody was decreased from more than 200 RU/ml to negative, supporting the diagnosis of pemphigus vegetans, Hallopeau type. Finally, considering pemphigus vegetans in the differential diagnosis can facilitate accurate management.

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