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Case Report **OPEN ACCESS**

Intravenous immunoglobulin as an effective treatment for refractory pemphigus vegetans: A case report

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ABSTRACT

Pemphigus vegetans (PVeg), which affects < 2% of pemphigus cases, presents a therapeutic challenge when refractory to conventional treatments. Herein, we describe the case of a 58-year-old woman diagnosed with Hallopeau-type PVeg who demonstrated a complete response to intravenous immunoglobulin (IVIG) after failing multiple conventional therapies. The patient exhibited vegetative plaques at multiple sites, with notable nail involvement. Her disease remained poorly controlled despite a 7-year course of systemic corticosteroids, immunosuppressants, and rituximab. Two courses of IVIG (5% concentration, 2 g/kg) resulted in the complete resolution of the disease. This case highlights IVIG's therapeutic potential in refractory PVeg and emphasizes the importance of recognizing atypical manifestations, including nail involvement. While this single case yielded promising results, future studies must validate the role of IVIG in the management of treatment-resistant PVeg.

Keywords: pemphigus vegetans, intravenous immunoglobulin therapy, nail dystrophy, immunosuppressive therapy, autoimmune bullous disease

INTRODUCTION

Pemphigus encompasses a group of rare autoimmune bullous diseases characterized by autoantibodies that target desmosomal adhesion proteins, particularly desmoglein 1 and desmoglein 3 [1]. These autoantibodies induce acantholysis, disrupting intercellular adhesion and resulting in mucocutaneous blistering and erosions [1]. Pemphigus vulgaris (PV) represents the predominant subtype of pemphigus, accounting in approximately 80% of cases [2]. Pemphigus vegetans (PVeg), a rare variant comprising < 2% of pemphigus cases [3], produces pustules and vegetative plaques in the intertriginous areas and mucosal membranes [4]. The therapeutic management of PVeg begins with systemic corticosteroids as the mainstay of treatment. However, the chronic nature of the disease often necessitates the addition of steroid-sparing agents [5]. For refractory cases, alternative therapeutic strategies are required. We present a case where intravenous immunoglobulin (IVIG) successfully treated PVeg, a therapeutic approach that has demonstrated efficacy in PV [6, 7] but has limited evidence in PVeg cases.

MATERIALS AND METHODS

Case Presentation

A 58-year-old woman with type 2 diabetes mellitus presented to our clinic in 2017 with a 2-month history of a painful, discharging rash affecting multiple sites. The initial examination revealed fissured hyperkeratotic plaques with erythema, oozing, and pustules involving the genital area, axillae (part A in **Figure 1**), neck, perioral region, and scalp (part B in **Figure 1**). The notable findings included bilateral boggy masses of the thumbnails with associated nail dystrophy affecting the left middle finger (part C in **Figure 1**).

At presentation, laboratory investigations revealed low zinc levels (9.02 mcmol/L; normal range: 10.09-16.83 mcmol/L). Other routine laboratory studies, including chest radiography, borrelia antibodies, KOH examination, HIV serology, and RPR tests were normal or non-reactive. Gram staining of the lesional material revealed polymorphonuclear cells (neutrophils and eosinophils) and gram-positive cocci.

Histopathological examination of the initial skin biopsy revealed features consistent with PVeg, including pronounced acanthosis, elongated rete ridges, dense inflammatory infiltrates, and eosinophil transmigration within the epidermis (parts A, B, C, and D in **Figure 2**). Although direct immunofluorescence is typically valuable for confirming a diagnosis of PVeg, this test was not available in our setting. The diagnosis of Hallopeau-type PVegs were diagnosed based on clinical and histopathological findings.

Treatment Course

The patient initially responded partially to topical fluticasone propionate 0.05% cream twice daily and oral zinc sulfate 50 mg/day. In July 2017, an acute disease flare prompted an escalation to systemic therapy with prednisolone

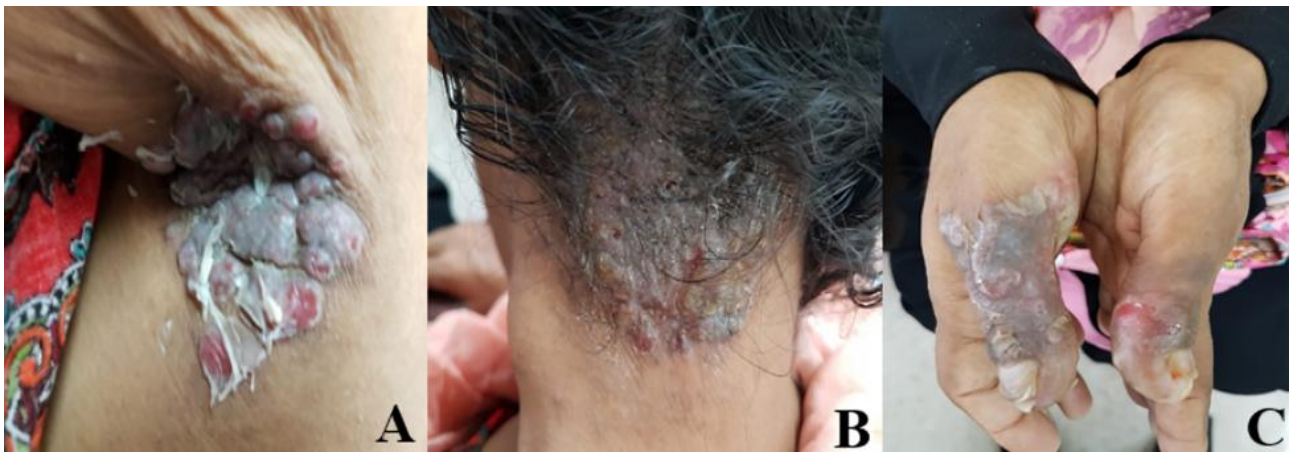

Figure 1. Clinical presentation of PVeg: (A) verrucous hypertrophic vegetative plaques with erosions in the axillary region; (B) vegetative changes with erythema and scaling on the scalp; & (C) boggy inflammatory masses affecting the thumbnail bed with associated nail dystrophy (Clinical photographs obtained during routine clinical evaluation at our institution with the patient's written informed consent for publication)

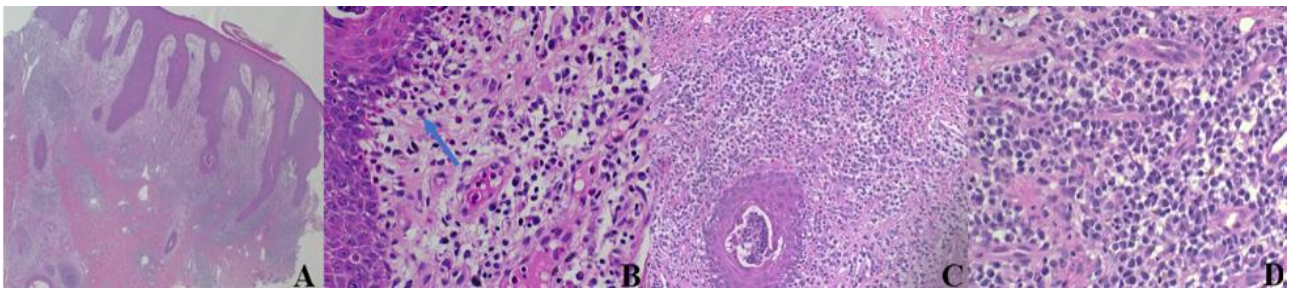

Figure 2. Histopathologic features of PVeg: (A) epidermal acanthosis with elongated rete edges and dense epidermal inflammatory infiltrate (H&E, ×40); (B) epidermal transmigration of eosinophils (arrow) with focal spongiosis (H&E, ×200); (C) dermal prominent plasmocytic infiltration with scattered eosinophils (H&E, ×100); & (D) higher magnification showing details of dermal inflammatory infiltrate (H&E, ×400) (Histopathological micrographs obtained from tissue specimens processed at our institution's Pathology Department with appropriate permissions for publication)

20 mg daily on a tapering schedule, accompanied by an increased zinc sulfate dose of 200 mg daily, which achieved initial disease control.

Over the subsequent 6 years (2017-2023), she developed recurrent disease exacerbations that required management with mycophenolate mofetil 500 mg twice daily and varying prednisolone doses (5-30 mg). Rituximab therapy (two doses of 1,000 mg) was unsuccessful because of adverse effects. Disease recurrence in July 2023 necessitated therapeutic intensification with increased prednisolone (15-25 mg), reinstitution of mycophenolate mofetil, and addition of clobetasol 0.05% shampoo.

Despite escalation to high-dose prednisolone (40 mg) in January 2024, the disease remained active, prompting initiation of IVIG therapy. The first course of IVIG (5% concentration, 2 g/kg) administered over 3 consecutive days in May 2024 with concurrent prednisolone (25 mg) yielded an initial improvement. Following a mild disease flare, the administration of a second IVIG course in July 2024 combined with prednisolone 20 mg on a tapering schedule achieved complete disease resolution (part A and part B in **Figure 3**).

RESULTS

The administration of IVIG therapy led to complete resolution of the patient's PVeg after a 7-year course of refractory disease. Following the second course of IVIG, there was complete clearance of the scalp lesions (part A in **Figure 3**) and resolution of the nail inflammation with improvement in the nail dystrophy (part B in **Figure 3**). The patient remained disease-free at the time of reporting, demonstrating the effectiveness of IVIG as a therapeutic option for this case of treatment-resistant PVeg.

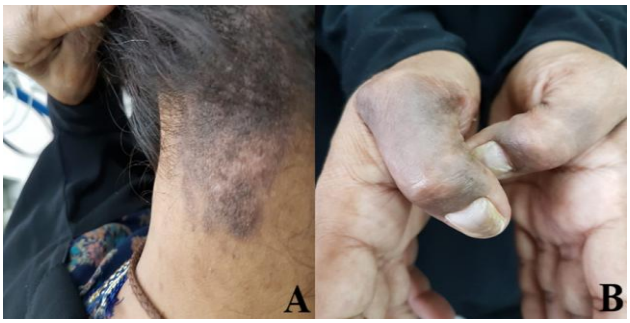

Figure 3. Treatment response to IVIG: (A) complete clearance of scalp lesions demonstrating successful response after two courses of IVIG therapy & (B) resolution of thumbnail inflammation and improvement in nail dystrophy following treatment (Clinical photographs documenting treatment response, acquired during follow-up evaluations with the patient's written informed consent for publication)

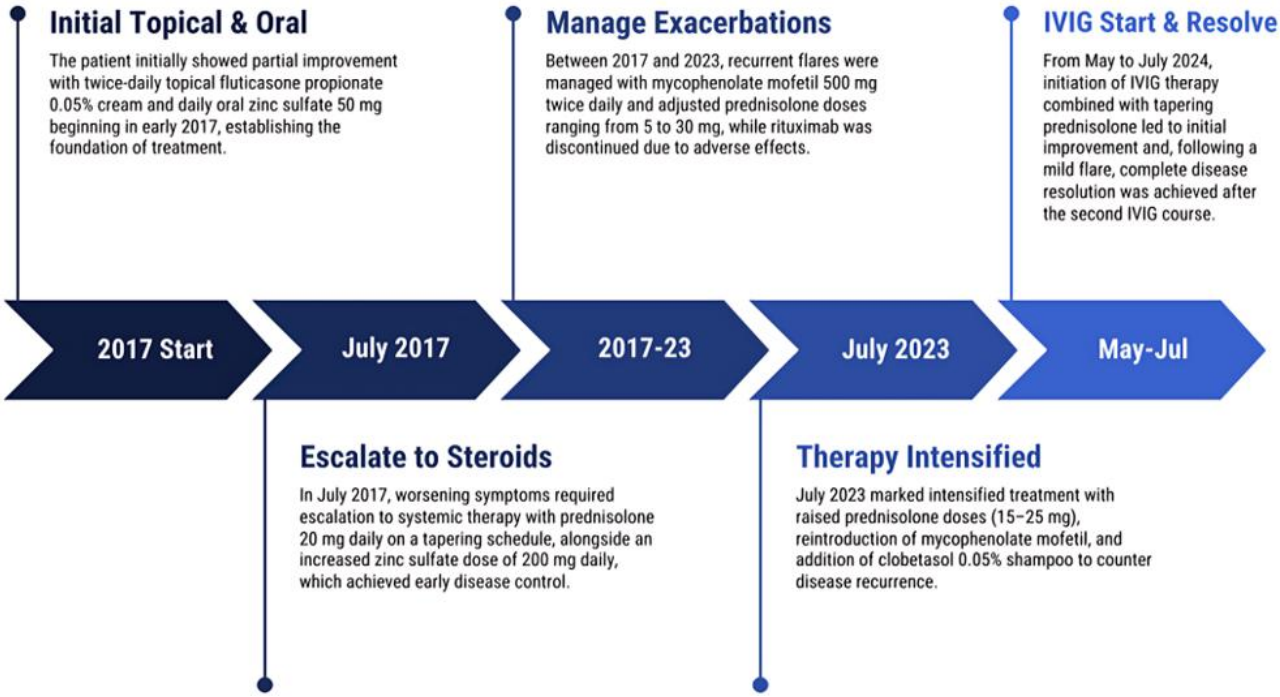

Figure 4. Therapeutic timeline of PVeg management over seven years (2017-2024): The timeline illustrates treatment progression from conventional therapy (prednisolone and mycophenolate mofetil) through therapeutic intensification (increased corticosteroid dosing and rituximab trial) to successful IVIG treatment (despite multiple therapeutic adjustments with systemic corticosteroids and immunosuppressants, disease control remained inadequate until complete resolution was achieved following the second IVIG course) (Original schematic illustration designed by the authors using digital graphic software specifically for this publication)

Following the second IVIG course, the patient underwent clinical monitoring with monthly evaluations of cutaneous and nail lesions for the initial three months, followed by quarterly assessments thereafter. Throughout this 8-month post-treatment period, we observed no disease recurrence, and the patient maintained complete clinical remission with clearance of vegetative plaques and significant improvement in nail dystrophy while requiring only a maintenance dose of prednisolone (5 mg daily). No significant adverse events were documented during either IVIG course. **Figure 4** illustrates the comprehensive therapeutic timeline and treatment progression throughout the seven-year disease course, highlighting the transition from conventional therapy to successful IVIG treatment.

DISCUSSION

PVeg presents with two distinct clinical patterns: the Hallopeau type, which is milder and begins with pustules that erode into vegetative erosions; and the Neumann type, which is more common and severe, starting with vesicles and bullae that progress to hypertrophic granulating erosions [8]. While lesions typically affect intertriginous areas and oral mucosa [4], some patients, including ours, may present without oral involvement, as documented in recent literature [9].

Although rare, digital manifestations of PVegs include changes in the nail apparatus, such as paronychia and nail dystrophy. Our patient's bilateral thumbnail masses and dystrophy exemplify these uncommon features, emphasizing the importance of recognizing atypical presentations.

The histopathological findings in our case were consistent with those reported in the literature, including epidermal hyperplasia with acanthosis and papillomatosis, spongiosis, suprabasal acantholysis, eosinophilic and neutrophilic microabscesses, and perivascular lymphocytic infiltrates [8]. Although direct immunofluorescence typically confirms the diagnosis by demonstrating intercellular IgG and C3 deposition with desmoglein autoantibodies [1], we established our diagnosis of Hallopeau-type PVeg through comprehensive clinicopathological correlation. This case illustrates that when direct immunofluorescence testing is unavailable, careful correlation of clinical presentation with characteristic histopathological features can support an accurate diagnosis.

Our patient's 7-year disease course remained refractory to conventional therapy, and rituximab was discontinued because of adverse effects. IVIG therapy resulted in a notably successful response. IVIG has demonstrated efficacy in refractory PV [6], protecting keratinocytes through multiple pathways: upregulation of anti-apoptotic proteins, inhibition of apoptotic enzymes, and blockade of cell death receptors [7]. The pathophysiological similarities between PV and PVeg suggest that IVIG is a viable therapeutic option for refractory PVeg. The report in [5] on a treatment-resistant case further emphasizes the need for effective therapeutic alternatives in challenging cases.

IVIG therapy demonstrated important clinical advantages in our case. Of particular significance was the substantial corticosteroid dose reduction it enabled (from 40 mg to 5 mg daily), potentially mitigating long-term steroid-associated morbidity [6]. The durability of IVIG's therapeutic effect was notable, especially given the previous failure of conventional immunosuppressants over a 7-year disease course. This

finding aligns with previous reports [6] regarding IVIG efficacy in refractory PV, suggesting potential parallels in treatment response mechanisms between PV and PVeg variants [7]. Extended observation periods are essential to definitively establish the long-term efficacy of IVIG therapy in refractory PVeg and to develop standardized protocols for maintenance therapy and relapse management. Based on our experience, we suggest that IVIG should be considered as a therapeutic option for cases of PVeg that prove refractory to conventional immunosuppressive therapy and rituximab [5].

However, further research with larger patient cohorts is necessary before formal treatment algorithms can be established, and cost-effectiveness analyses should be conducted, considering the resource implications of IVIG therapy compared to conventional treatments.

This study has important limitations that warrant consideration. Although promising, as a single case report with an 8-month follow-up period, our findings do not establish definitive treatment guidelines or long-term efficacy beyond this timeframe [10]. The unavailability of direct immunofluorescence testing, though mitigated through careful clinicopathological correlation and consistent clinical presentation typical of Hallopeau-type PVeg [8], highlights the diagnostic challenges in resource-limited settings.

CONCLUSION

This case demonstrates the potential efficacy of IVIG as a therapeutic option for refractory PVeg. Our experience highlights the importance of recognizing atypical presentations, including nail involvement, and supports a stepped therapeutic approach to therapy. Although our findings are promising, more extensive studies are needed to validate IVIG's role in the management of refractory PVeg.

Author contributions: SA: project leadership, literature review, data collection, writing of introduction and discussion sections, manuscript conceptualization, and finalization; **SAA:** data collection, case report writing, and final manuscript review; **MSA:** data collection and case report writing; & **AM:** clinical care of the patient, diagnostic workup, supervision of manuscript preparation, and critical revision of intellectual content. All authors have agreed with the results and conclusions.

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Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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