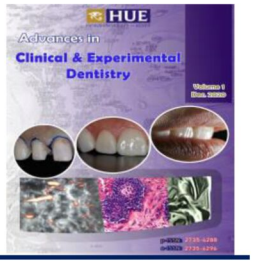
Advances in Clinical and Experimental Dentistry



State of the art management of oral pemphigus vulgaris

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Abstract

Background Pemphigus, which is one of vesiculobullous diseases that affect the oral mucosa and skin, is caused by antibody-mediated autoimmune reaction to desmogleins desmosomal transmembrane glycoproteins and leads to acantholysis.

Objective Because early diagnosis and effective treatment minimize the morbidity of pemphigus vulgaris (PV), this review highlights the recent advances and management of oral lesions of PV disease.

Results Recent therapeutic modalities include combining anti-CD20 with corticosteroids. Adjunctive therapies that have proven effective in reducing the indicated dosage of corticosteroids include rituximab intravenous immunoglobulin and cyclosporin.

Advances in Knowledge A computational bootstrapping of the clinicopathological picture of PV was conducted to provide a state-of-the-art view on the validity of following each treatment modality. Although all profiles are deficient in providing data for many items, corticosteroid therapy is the most investigated modality before and after receiving a treatment course.

Keywords

Autoimmune Vesiculobullous Disease, Oral Ulcers, Pemphigus Vulgaris, Rituximab

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1. Introduction

Pemphigus, which etymologically means blister, is potentially life-threatening autoimmune mucocutaneous diseases that erode the epithelium of the mucosa, skin, or both. IgG autoantibodies attack keratinocyte cell surfaces of intercellular junctions and cause destruction of epithelial cell-to-cell adhesion (acantholysis) [1-3]. Pemphigus affects 0.1%-5.5% of the population each year. Pemphigus vulgaris (PV) and pemphigus foliaceus occur more frequently than erythematosus pemphigus, vegetans pemphigus, IgA pemphigus, drug-induced pemphigus and paraneoplastic pemphigus. PV is the most common type of pemphigus and accounts for more than 80% of cases. PV tends to affect Ashkenazi Jews, Mediterranean and South Asian ethnic groups [4-8]. Because oral manifestations of pemphigus vulgaris appear at an early stage of the disease, their diagnostic value cannot be overemphasized. However, challenges are always observed when oral pemphigus vulgaris is concomitant with desquamative gingivitis [9-11]. This article views the contemporary understanding of PV, the effectiveness of its novel therapeutic modalities and recommendations for managing PV and its oral manifestation.

2. Pathophysiology

Key players of causing PV are desmoglein 3 (Dsg 3) and desmoglein 1(Dsg 1), which are part of the cadherin family of cell–cell adhesion molecules that are found in desmosomes. Dsg 1 and Dsg 3 are transmembrane adhesion molecules of desmosomes where they are specialized in facilitating epidermal keratinocyte cohesion and bind to intercellular molecules of the desmosomal plaque. In patients with PV, blisters are found superior to the basal cell layer and either erode the cutaneous membrane or oral mucosa with flaccid blisters [12-14].

Although Dsg 3 is found throughout the oral mucosa, it can be only detected in basal and immediate suprabasal layers of the epidermis. In contrast, Dsg 1 is found throughout the epidermis but more intensely detected in the superficial oral mucosa and weakly detected in the deep layers [17]. Therefore, antibodies against Dsg 3 are elevated in oral pemphigus vulgaris, but antibodies against Dsg 1 are higher in cutaneous PV [18]. Immune complex deposits (often IgGs) bind to desmosomal transmembrane proteins of keratinocytes in PV, which are two major autoantigens [19-20]. Moreover, desmoglein 4 and other non-desmoglein antigens, like the human α-9-acetylcholine receptor that regulates keratinocyte adhesion and keratinocyte annexin-like molecules binding acetylcholine (pemphaxin and catenin), may influence its etiopathogenesis [21-24]. Antigen presenting cells (APCs), via the action of their human leukocyte antigen (HLA) class II molecules, activate autoreactive T cells and B cells and pathogenic B cells and T cells and also induce antibody production [25].

T cell subsets, including CD4+ and CD8+ T cells, show some sort of abnormalities in PV, which is evidenced by dysregulated T-helper cells. Th2 cells and IL-4 boost an autoimmune response, antibody production, and immunoglobulin class-switching. T regulatory (Treg) cells repress autoreactive CD4+ T cell activation and help in the control of inflammation. Treg cells deficiency causes spontaneous activation of autoreactive CD4+ T cells, which leads to the progression of PV. In PV, T helper cells increase and facilitate production of autoantibody by B cells.

Environmental and genetic factors, and the collapse of immune tolerance, may initiate the progression of autoimmune pemphigus. An intake of thiol-containing drugs, the overconsumption of garlic, and exposure to physical or viral agents can all predispose PV [26]. Immunologically speaking, several HLA alleles, such as HLA-DRB1*0402 and HLA-DQB1*0503, have been suggested as risk factors for PV. This explains the predominance of PV in particular populations such as Jews, Iraqis, Egyptians, Iranians and Indians. [28].

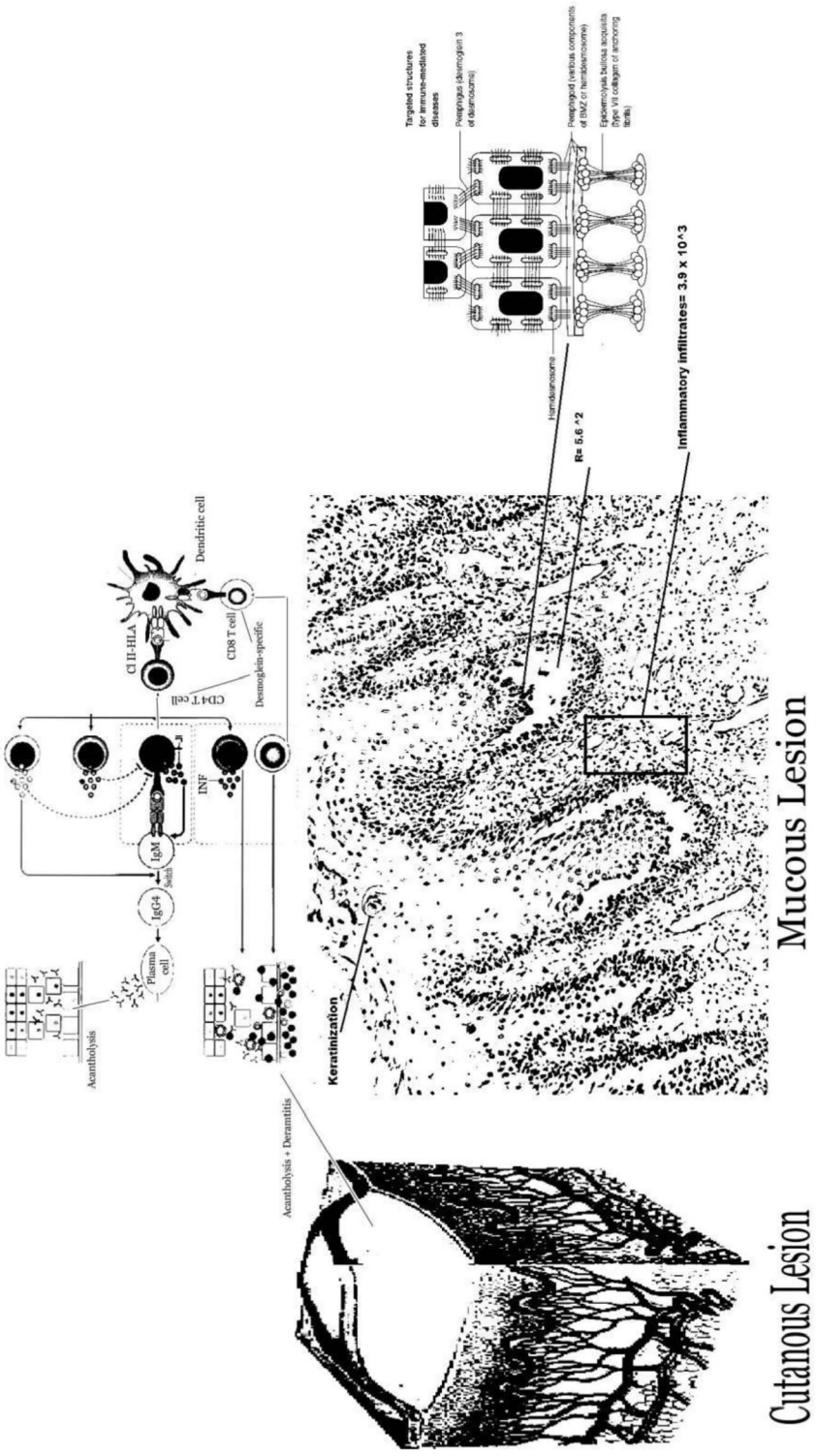

Figure 1. Location of Dsg 1 and Dsg 3 in the PV. APC deliver desmoglein (DSG) antigens that activates CD4+ and CD8+ T cells. These autoreactive T cells and B cells start the autoimmune activity causing acantholysis, and dermatitis in cutaneous PV.

The antigen presentation by dendritic cells (DCs) and the activation of the immune response require appropriate functioning of costimulatory markers such as CD40 and CD80. Furthermore, DCs release a group of cytokines (IL-6, IL-23, IL-10, IL-12, and IFN-α), which change the activation and proliferation of the innate and the effector lymphocytes such as helper T cells. Both inhibitory and stimulatory markers of DCs are needed for any immune response generated by these cells.

The DCs concentration often correlates with the serum autoantibody titre and disease severity, which has been observed in pemphigus foliaceus, but the detailed function of DCs is not clearly known as well as an explanation for the immunopathogenesis of PV [29].

Research shows that pemphigus group of diseases contain autoantibodies to desmosomal and non-desmosomal adhesion molecules other than Dsgs, including c-catenin, E-cadherin, desmoplakin, tight junction proteins, and collagen XVII/BP180 [30].

It is not suggested that anti 9α acetylcholine receptor (AChR) antibodies on the surface of keratinocytes, which show nicotinic-like and muscarinic-like effects, are responsible for acantholytic changes in PV by altering the normal regulation of keratinocyte adhesion via the cholinergic signalling pathway [31-32]. However, the pathophysiologic activity in oral PV differs much more than in cutaneous PV [9-11].

3. Clinical Oral Presentation

Oral symptoms of PV range from mild discomfort to painful erosions or ulcers. The buccal mucosa, palate, gingiva, tongue, floor of the mouth and lips, are most commonly affected. Desquamative gingivitis is a relatively common manifestation of PV. Gingiva showed positive Nikolsky's sign in more than 90% of cases that were diagnosed as PV based on oral lesions. Oropharyngeal involvement leads to dysphagia, odynophagia, and hoarseness. Oral manifestations of PV may remain the sole symptoms of the disease 2-6 months before the eruption of cutaneous lesions [9, 33-36]. Other oral manifestations include halitosis, sialorrhea, and formation of brown or blackish crusts at the vermillion border [37].

PV is a chronic disease and shows a progressive increase in severity. PV is life-threatening disease if left untreated because patients suffer from dehydration, protein loss, and opportunistic infections [38]. A definitive diagnosis of PV can be established with evident Nikolsky's phenomenon, microscopically through the presence of acantholysis, and by detecting antibody deposition between epithelial cells using a direct immunofluorescence test.

In cases of persistent gingivostomatitis, persistent multiple oral erosions, or severe desquamative or erosive gingivitis, PV should be suspected [39].

Juvenile PV is extremely rare and shows preferential involvement of the oral mucosa similar to adulthood [40].

According to Akman et al. [41], in PV patients the periodontal health is worse. PV might contribute to the development and progression of periodontitis. PV patients should adhere to a periodic periodontal follow-up schedule.

In addition, the use of an implant-supported prosthesis is preferable to the use of a removable prosthesis in these patients. The main treatments for pemphigus are the administration of systemic corticosteroids and immunosuppressive drugs. However,

effectiveness of these treatment modalities is case-sensitive and frequent clinical relapses have been reported [41-45]. This necessitates a search for new or adjunctive therapeutic modalities.

4. Therapeutic Modalities

Before the emergence of corticosteroids, PV had a poor prognosis because of water imbalance and secondary systemic infections. However, today it is the most common type of pemphigus. In more than 50% of cases, the disease begins with oral lesions, which may precede cutaneous lesions by several months or may be the only manifestations in some patients [46].

The goal of pemphigus treatment is to maintain complete remission, which is defined as the absence of new or established lesions [31]. Ideally, all systemic therapy should be stopped; however, remission achieved by minimal therapy, prednisone (≤10 mg/day), or minimal adjuvant therapy (or a combination of these) may be a more realistic goal for the management of PV [47].

Because of the rarity of pemphigus, published guidelines for its management mostly rely on expert consensus, except for a few evidence-based controlled studies. Treatments recommended by European and Japanese guidelines include corticosteroids and immunosuppressive reagents such as azathioprine and cyclophosphamide, plasmapheresis, intravenous immunoglobulin (IVIG), and rituximab. The goal of most therapies is to improve symptoms by reducing serum autoantibodies, either directly or through generalized immune suppression [33,34]. The advantages of rituximab, a monoclonal anti-CD20 antibody that targets CD20+B cells, in managing PV have been previously highlighted [7].

4.1 Corticosteroids for treating PV

On diagnosing PV, the standard treatment of PV is with systemic corticosteroids to control the aggressiveness of the disease and then consolidate management with other immunosuppressive agents. The steroid dosage varied among each medical institution according to the severity and recalcitrance of PV. To standardize the optimal dosage, the recommended steroid treatment is initiated at 1 mg/kg daily (60 mg daily on average).

Generally, oral lesions of PV are usually refractory lesions that resist treatment more than cutaneous lesions [10]. Lesions of the oral mucosa in patients with low titers of circulating antibodies may be temporarily controlled with topical creams that contain corticosteroids. Also, an intralesional injection of triamcinolone acetonide (20 µg/L) or paramethasone every 7-15 days can be applied to treat recalcitrant cases [7, 48-52].

Sun exposure, radiographs, stress, and traumas exacerbate the severity of PV [51]. Because oral traumas can trigger or worsen PV, Bystryn et al. [16] recommended the prophylactic administration of 20 mg prednisone/day in addition to the patient's normal requirement for 5-7 days before any dental procedure associated with trauma to the gingiva [52].

In most cases, mycophenolate mofetil, rituximab, or IVIG are indicated. Azathioprine, methotrexate, cyclophosphamide, plasmapheresis, and more recently, protein A immunoadsorption are acceptable second-line agents [7]. 120 pemphigus vulgaris patients were given prednisolone monotherapy (prednisolone 2 mg/kg per day at a maximum dose of 200 mg/day) or prednisolone and azathioprine concomitant therapy (azathioprine 2.5 mg/kg per day for 2 months and then minimized to 50 mg/day) to reduce the steroid dose without compromising the efficiency of the treatment [53].

However, some patients with severe PV remain recalcitrant to both steroids and azathioprine and present with uncontrolled oral and cutaneous ulceration clinically.

Furthermore, the antibody titer became negative in three patients, and researchers concluded that this regimen was useful for treating recurrent pemphigus.
However, certain studies have also shown complications in the prednisolone + cyclosporin group and concluded that concomitant therapy offered no advantages.
Many clinical studies have confirmed the effectiveness of a single cycle of high-dose IVIG therapy (400 mg/kg per day for 5 days) in patients with steroid-resistant pemphigus, which was effective in treating all patients with minimal adverse drug reactions [54].
Clinically, the combined use of plasma exchange with oral steroids can reduce the dose of steroids. However, a recent case report emphasized the importance of plasmapheresis as a useful intervention in patients with PV who do not respond to conventional therapy.
Another PV treatment is a combination of oral steroids and cyclophosphamide in patients who are resistant to treatment with immunosuppressants, such as azathioprine and cyclosporine, but the possibility of adverse drug reactions requires careful monitoring. Cyclophosphamide pulse therapy may be effective in cases of pemphigus vulgaris that are resistant to several therapeutic modalities [13]. However, once monthly cyclophosphamide (15 mg/kg) with concomitant daily prednisolone at 60 mg was initiated, all patients improved one month after treatment. Relapse, which was primarily mucosal, occurred after 3 weeks to 8 months in nine patients. Thus, cyclophosphamide pulse therapy, combined with prednisolone, can be efficient in treating refractory PV, but close monitoring for adverse drug reactions is crucial.
The use of mycophenolate mofetil on refractory pemphigus resulted in a viable reduction in steroid dose and induction of remission without adverse drug reactions. Low-dose methotrexate was administered concomitantly with oral steroids in relapsing pemphigus patients. This led to the conclusion that concomitant therapy with methotrexate can be useful in the treatment of cases that have been otherwise resistant to steroid tapering and in the treatment of relapsed cases. Overall, adverse drug reactions were few and mild.
Topical agents likely have a role in the management of oral disease, although this depends upon the severity of the disease. Topical agents that have been previously employed are largely composed of different corticosteroids, and there have been some reports of efficacy with topical ciclosporin or tacrolimus for corticosteroid recalcitrant oral disease. Systemic corticosteroids are a first-line therapy for severe oral or cutaneous PV and a spectrum of corticosteroid sparing agents have been proposed as adjuvant therapies.
The latter include azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, ciclosporin and perhaps systemic tacrolimus. It is suggested that IVIG is effective for rapidly progressing, severe, and treatment-resistant PV. There is some evidence that anti-TNF-a biological agents or rituximab are beneficial treatments for PV that involve the oral mucosa. Again, topical delivery systems that could efficiently deliver antibody-based biological agents to oral lesions could avoid the necessity for systemic administration and its attendant side effects. Of relevance for the local application of drugs, adjuvant perilesional or intralesional triamcinolone acetonide injections may lessen or cause a resolution of signs and symptoms of oral PV [57].

4.2 Rituximab for treating PV

B cell-specific biologics have been increasingly used in the past decade to treat autoimmune diseases. When considering the treatment of refractory PV, there is increasing evidence for the successful use of the monoclonal anti-CD20 antibody, rituximab [58].

Rituximab is an anti-CD20 chimeric antibody that selectively targets pre-B lymphocytes and mature B lymphocytes, resulting in depletion of autoantibody-secreting plasma cells and improved clinical response. Additionally, rituximab significantly decreases the Dsg3-

specific, autoreactive CD4 T helper (Th) cells that may contribute to the observed fast and long-term clinical responses in PV3 [59].

Craythorne et al. have used a novel dosing regime in an attempt to reduce other adjuvant immunosuppression and corticosteroids to zero, so that the patient remains treatment free following completion of rituximab infusions.

Rituximab was administered in 8 weekly infusions at a dosage of 375 mg /m2, with a premedication of oral paracetamol 500 mg, and chlorphenamine 10 mg. Monthly infusions were then administered for at least 4 months, while concurrent immunosuppression was gradually withdrawn. The rate of serious adverse events in PV treated with rituximab has decreased over time [58].

4.3 New Anti-CD20 Monoclonal Antibodies

Other new anti-CD-20 biologicssuch as veltuzumab, ofatumumab, ocrelizumab, and obinutuzumab, are possible treatments for autoimmune blistering diseases. Anti-CD20 antibodies are diverse and possess different pharmacologic properties, and possibly, different clinical responses. Type I anti-CD20 monoclonal antibodies (rituximab, ofatumumab, ocrelizumab) have a more potent CDC response and increased B cell binding than Type II (obinutuzumab), while Type II monoclonal antibodies exhibit stronger induction of apoptosis [67]. Subcutaneous injection is a suitable alternative to infusion in the administration of biologics, preventing infusion reactions and potentially decreasing the cost of administration. Subcutaneous veltuzumab has been shown to be effective in one PV patient, with complete remission after two administrations [7].

Of the next-generation therapeutic anti- CD20 antibodies, only ofatumumab is undergoing clinical trials for refractory PV [68-69].

Bruton tyrosine kinase (BTK) is a non-receptor cytoplasmic tyrosine kinase BTK is a key member of the B-cell receptor signaling pathway and is involved in all aspects of B-cell development, including proliferation, maturation, differentiation, apoptosis, and cell migration [70]. In the absence of BTK, B cells have a high rate of apoptosis. In humans, BTK mutations result in X-linked agammaglobulinemia, a severe primary immunodeficiency characterized by the absence of peripheral B lymphocytes, low concentrations of serum immunoglobulins, and recurrent bacterial infections [71]. The use of BTK inhibitors started with ibrutinib for the treatment of B-cell lymphomas. Recently, BTK emerged as an appealing target for the treatment of inflammatory and autoimmune disorders because it functions in multiple signaling pathways.

Tirabrutinib is an orally administered BTK inhibitor being developed by Ono Pharmaceuticals for the treatment of autoimmune disorders and hematologic malignancies. A study of tirabrutinib for refractory pemphigus in Japan is currently recruiting patients [72].

4.4 Photobiomodulation therapy for treating PV

Two of the early pioneers demonstrated contrasting applications of light treatments; Finsen noting its ability to destroy microbes that is now termed photodynamic therapy (PDT), while Mester observed stimulation (and later inhibition) of biological responses and is now termed photobiomodulation (PBM) therapy [73-79].

Photobiomodulation therapy has important implications in many oral diseases that have etiopathologic components of immune dysregulation, pain, and inflammation as it alleviates pain, modulates the inflammatory or immune responses, and promotes wound healing and tissue regeneration.

PBM therapy has also been noted to be effective in managing PV as well. Skin examination revealed blisters and ulcers on the trunk, abdomen, and limbs. PBM therapy was performed (660 nm diode laser, output power 100 mW, fluence 35 J/cm2, 3 J per point, time of 20 s per point) to alleviate oral pain and stimulate oral and cutaneous healing. The treatment was performed using a scanning motion, three to four points around and above each blister or erosion, about 6 mm above the lesion. Treatment was continued daily until diminution of skin lesions and oral healing. Patients were followed for up (7 months and 3 years, respectively) and demonstrated an immediate decrease in symptoms (70% after first therapy session) and complete alleviation after three sessions [80-89].

Cholinergic agonists showed promising results as they protect the keratinocyte monolayers against anti desmoglein antibody-induced acantholysis and reverse acantholysis produced by pemphigus vulgaris immunoglobulins. Plasmin inhibitors such as aprotinin can also prevent the development of acantholysis by inhibiting the conversion of plasminogen into plasmin [7, 15, 29].

Given the controversial results about the efficacy of each therapeutic modalities [90-102], all countries tend to apply their protocols. Countries that have reported the highest number of PV cases are contributing the most to this area of research. Table 2 shows the percentage of research articles and clinical trials retrieved over the past two decades on investigating various therapeutic modalities for PV.

***Table 1**. Research on investigating various therapeutic modalities sorted on the most contributing countries*

	Steroids	Rituximab	IVIG	Cyclosporin	Combination
United States	30%	27%	29%	32%	50%
Germany	9%	12%	11%	10%	15%
Italy	3%	8%	10%	8%	4%
UK	1%	7%	8%	6%	5%
Iran	1%	5%	7%	6%	5%
Japan	4%	5%	3%	5%	4%
France	3%	5%	3%	4%	4%
Australia	8%	4%	3%	3%	3%
India	6%	4%	3%	2%	2%
Israel	6%	3%	3%	3%	2%
Spain	5%	3%	3%	2%	2%
Canada	4%	2%	3%	2%	2%
Poland	3%	2%	2%	2%	1%
Turkey	3%	2%	2%	2%	1%
Brazil	3%	2%	2%	2%	1%
Greece	3%	2%	1%	1%	1%
Mexico	2%	2%	1%	1%	1%
Switzerland	2%	2%	1%	1%	1%
Netherlands	2%	1%	1%	1%	1%
Croatia	2%	1%	1%	1%	1%
China	1%	1%	1%	4%	2%

5. Advances in Knowledge

We collated a corpus of all published articles that reported a treatment for PV. Running python codes and corpus analysis, we retrieved the concordance of each clinicopathological items that was assessed in order to provide the state-of-the-art view on the validity of following each treatment modality. As Table 2 shows, all profiles of steroids, rituximab, IVIG, cyclosporin and combination of two modalities are deficient in providing data for many items, corticosteroid therapy is the most investigated modality before and after receiving a treatment course.

Therefore, this article provides the proposed advances in treating PV although they lack unequivocal empirical evidence. The missing gaps are also shown and future directions can be inferred from the many missing data in Table 2.

Table 2. Clinicopathological correlation with various treatment modalities

	Efficiency of treatment modality				
	Steroids	Rituximab	IVIG	Cyclosporin	Combination
Clinical picture					
Age	+++	+	+++	NA	++
Gender	NA	NA	NA	NA	NA
Race	NA	NA	NA	NA	NA
Pain	+++	+	++	+	++
Oral involvement	++	++	++	++	++
Resistance to treatment	++	++	++	++	++
Serology					
anti-Dsg1 IgG	++++	++++	++++	NA	NA
anti-Dsg3 IgG	++	++	++	++	NA
anti-Dsg4 IgG	++	++	++	NA	NA
DSG-specific-B	++	++++	++	NA	NA
Interleukin-33	NA	NA	NA	NA	NA
Mean Platelet Volume	++	NA	++	++	NA
Histopathology					
Acantholysis	++	++	++	++	NA
Epidermal spinous cells	++	++	+	NA	NA
Keratinocytes expression	++	NA	++	++	NA
Lymphocytic infiltrate	+++	+	+	NA	NA
Mast cell	NA	NA	NA	NA	NA
Endothelial activity	++	+	+	NA	NA
Immunohistochemistry					
CD44 antibody	+	NA	NA	NA	++
CD117 antibody	NA	NA	NA	NA	NA
C3d antibody	+++	NA	+++	NA	+
Bax antibody	NA	++	++	++	++
anti-Dsg1,2,3 antibody	+	+	NA	+	++
P-cadherin	+	NA	NA	NA	NA
Vascular endothelial growth factor	NA	NA	NA	NA	NA
Endoglin	NA	NA	NA	NA	NA
Matrix metalloproteinase 9	++	NA	NA	NA	NA
Plakoglobin	NA	NA	NA	NA	NA
Epithelial acetylcholine receptors α9	NA	NA	NA	NA	NA
Pemphaxin	NA	NA	NA	NA	NA
PCR/ sequencing					
CK17 mRNA	NA	NA	NA	NA	NA
HLA-alleles	NA	NA	NA	NA	NA

6. Conclusion

PV, a potentially fatal disease with most cases showing initial oral manifestations, requires early diagnosis as well as early treatment to prevent future complications. The diagnosis of PV is based on 3 main factors, clinical features, histopathology, and immunofluorescence studies.

Take-home Messages

1. Increasing the knowledge and awareness of dental health care professionals of oral lesions of PV is critical as the oral lesions precede the skin lesions in 60% of the cases.

2. Long term regular follow-up is essential to identify the possible remissions of this disease.

3. Veltuzumab, ofatumumab, ocrelizumab, and obinutuzumab and immunosuppressants can be used with steroids to reduce its dosage without jeopardizing the efficacy of treatment.

4. Clinicopathologic studies are needed to provide implications on the efficacy of each treatment modality.

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