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Pemphigus Vulgaris: A Review On Etiopathogenesis, Clinical Features and Challenges In The Management

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ABSTRACT

Pemphigus vulgaris is a chronic autoimmune intraepithelial disease that forms flaccid blisters and erosions of skin and mucous membranes. Pemphigus vulgaris is a rare disease resulting from an autoimmune process in which IgG serum antibodies are produced against normal desmosomal adhesion molecules (desmoglein 3 and to lesser extent desmoglein 1) on the cell membrane of keratinocytes causing loss of cell adhesion, with separation of epithelial layers (acantholysis) and also appearance of blisters on skin or mucosa. Patients have ill-defined, irregularly shaped, gingival, buccal, or palatine erosions, which are painful and slow to heal. Pemphigus vulgaris shows have an approximately equal prevalence among men and women. PV Causes genetics like HLA DR4 and HLA DR14. The mucous membranes often affected are those of oral cavity other surfaces involved including conjunctiva, oesophagus labia, vagina, cervix, vulva, penis, urethra, nasal mucosa, and anus. The diagnosis is based on set of criteria: clinical features, histology and immunological tests. Laboratory examinations include: Tzanck smear to detect acantolytic cells, direct and indirect immunofluorescence, ELISA test and when diagnosis remain uncertain, immunoprecipitation and immunoblotting techniques are helpful. The main objective of therapeutic management is to control the disease, heal the bullous skin and mucous lesions and to minimize the associated functional impairment. The standard treatment for pemphigus vulgaris is use of systemic corticosteroids. Azathioprine and mycophenolate mofetil are used in case of nonsteroidal treatment. In case of recalcitrant pemphigus, Rituximab is extremely effective when other treatments fail to control the disease. The present review emphasized the etiopathogenesis, clinical characteristics, diagnosis and treatment strategies for Pemphigus vulgaris and challenges in the management of this uncommon disease.

Key words: Pemphigus vulgaris (PV), Acantholysis, keratinocytes, Oral lesions, Nikolsky sign, prednisolone, immunosuppressive agent,

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INTRODUCTION

Pemphigus is a group of potentially life-threatening autoimmune diseases characterized by cutaneous and/or mucosal blistering. Pemphigus can be classified into six types: Pemphigus vulgaris, pemphigus vegetans, pemphigus erythematous, pemphigus foliaceus, paraneoplastic pemphigus, and IgA pemphigus. Pemphigus vulgaris, which has multiple clinical variants, is an autoimmune blistering disorder of skin and mucous membranes, usually affecting the elderly, with a strong immunogenetic link and showing oral lesions as an initial manifestation in 50% of cases.[(1)] Pemphigus vulgaris is one of the most severe presentations that very often leads to serious patient conditions that are difficult to handle on an outpatient basis, and repeatedly requires intensive care. It is a rare autoimmune skin disease and affects around 3 cases per 100,000 populations. Females aged 40-60 years are mostly affected.[(2)] The morbidity and mortality of PV is related to the extent of the disease, the drug dose required to eradicate lesions, the age of the patient, the antibody titer,and the presence of comorbidities. [(5,6)] The Pemphigus vulgaris is frequent disaster with death rate ranging from 65 % to 90 %,while the use of systemic corticosteroids and other advanced therapeutic methods have reduced approximately 10 % of the mortality rate.[(3, 4)]

Etiopathogenesis:

PV results from an autoimmune process in which IgG serum antibodies are produced against normal desmosomal adhesion molecules on the cell membrane of keratinocytes. The serum antibodies responsible for PV are always IgG type, and IgG4 has been associated with the active phase of the disease and IgG1 with the remission phase. [(7)] However, although the antibodies found in intercellular spaces of the epithelial tissue are usually IgG type, they can also be IgM or Ig A types, and complement protein C3 can even be observed. The normal epithelial adhesion molecules implicated are desmoglein 3 and, to a lesser extent, desmoglein 1 (Dsg3 and Dsg1).

The binding of antibodies to desmoglein at mucosal or cutaneous level gives rise to the loss of cell adhesion, with separation of epithelial layers (acantholysis) and the consequent appearance of blisters on skin or mucosae.[(8)]

Antigens other than desmoglein:

Pemphigus autoimmunity may not be limited to anti-desmoglein antibodies. Nondesmoglein antibodies induce pemphigus-like lesions in neonatal mice. Non-Dsg PV IgGs also cause gross skin blisters with PV-like suprabasal acantholysis and staining perilesional epithelium in a fishnet-like pattern, indicating that the PV phenotype can be induced without anti-Dsg 3 or anti-Dsg 1

antibody. Acantholytic autoantibodies target a novel human alpha 9 acetylcholine receptor regulating keratinocyte adhesion, a novel keratinocyte annexin-like molecule binding acetyl-choline and termed pemphaxin.[9]

Possible Etiological Factors:

Although PV is considered an idiopathic disease, a series of environmental factors that trigger the disease have been identified.

Diet:

The role of diet in the aetiology of pemphigus is reviewed elsewhere, but garlic in particular may cause occasional cases of pemphigus.[10]

Drugs:

Traditionally, drugs that are capable of inducing pemphigus are divided into two main groups according to their chemical structure:

1) Drugs containing a sulfhydryl radical (thiol drugs or SH drugs), such as penicillamine and captopril.

2) Non thiol or other drugs, the latter often sharing an active amide group in their molecule. Phenol drugs, rifampicin, diclofenac, captopril and other ACE are occasionally implicated.

3) Cosmetics have been implicated in the high prevalence of PV.

Viruses:

The initiating factor in PV remains enigmatic but particularly in view of the apparently transmissible nature of some pemphigus variants, the role of viruses has been suggested. Most recently, attention has been directed toward the herpesviruses. Very occasionally, the onset of PV has been reported concurrently with or following, herpesvirus infections, and the possibility of epitope spreading or molecular mimickry has been suggested as the pathogenesis.

Association with other disorders: Pemphigus

Vulgaris may occasionally be associated with other autoimmune disorders, such as rheumatoid arthritis, myasthenia gravis, lupus erythematous or pernicious anaemia. [11]

CLINICAL FEATURES:

Oral lesions are the first manifestation of the disease in 50-90% of cases. However, they are the first manifestation in only 18% of outpatients at dermatology clinics. [12] In patients with early onset of oral lesions, these remain the sole symptoms of the disease for a period of 2-6 months until the appearance of cutaneous lesions, accounting for the importance of oral manifestations for dermatologists. Blisters can appear at any localization of the oral mucosa, although the most frequent sites are those subject to friction, such as the soft palate, buccal mucosa, ventral tongue,

gingiva, and lower lip. PV can involve other mucosae besides the oral mucosa, including conjunctive, nasal, pharyngeal, laryngeal, oesophageal, genital, and anal mucosae. [12, 13]

DIAGNOSIS:

Many disorders damaging epithelial adhesion molecules are of autoimmune aetiology, may have systemic manifestations and can be difficult to differentiate clinically.[14] Therefore, without further investigation, it can be difficult if not impossible to determine the molecular basis of vesiculobullous, erosive, or ulcerative disorders affecting the oral mucosa or gingivae. Clinical features such as a positive Nikolsky sign are not specific. Therefore, in addition to a full history and examination, biopsy examination and appropriate histopathological and immunological investigations are frequently indicated.

Laboratory examinations include:

Tzanck smear to detect acantholytic cells, useful in lesions of the oral mucosa; direct immunofluorescence to detect intercellular deposits of immunoglobulin G, M, A and C3 protein on epidermis and perilesional skin, offering 100% sensitivity; indirect immunofluorescence to detect pemphigus antibodies in serum; ELISA test using recombinant Dsg1 and Dsg3 to measure anti-Dsg1 and anti-Dsg3 antibodies in serum and when the diagnosis remains uncertain, immunoprecipitation and immunoblotting techniques. [14, 15]

MANAGEMENT:

Treatment Measures:

Periodontal therapy is an essential part of overall treatment of pemphigus. Optimal oral hygiene is important because the gingival involvement may present an exaggerated response to bacterial plaque. Oral lesions are difficult to treat because of trauma to the surface epithelium whenever the patient eats.

Diet Considerations:

Patients on steroid therapy are monitored for weight gain and advised low salt, low fat, low calorie diet. Also advised increased consumption of potassium and protein rich meals. [16]

TREATMENT CHALLENGES:

The primary objective of the therapeutic management of PV is initially to control the disease, heal the bullous skin and mucous lesions, and minimize the associated functional impairment. Subsequently, the real challenge is to prevent relapses and to avoid adverse events associated with the prolonged use of steroids and immunosuppressive agents. Such intent management requires close clinical monitoring of efficacy and safety of treatment. PV is characterized by diversity that makes every patient a unique challenge. [17] Patients might present with lesions solely on mucous

membranes and have limited cutaneous or extensive mucocutaneous involvement. Comorbidities such as diabetes mellitus, hypertension, previous or existent malignancies, chronic infections, and associated complications might limit available treatment options. The aim should be to achieve as rapid a remission as possible, as few flare-ups as possible, and minimal morbidity associated with treatment agents. The challenge is to minimize hospitalization and improve patients' quality of life. (18)

Treatment Agents:

The aim of pharmacologic therapy for PV is to reduce inflammatory response and autoantibody production.

Steroids:

Oral lesions of Pemphigus Vulgaris may respond partially to topical or intralesional corticosteroids. Systemic corticosteroids remain the mainstay of therapy of patients with oral lesions. The guidelines by EDF and European Academy of Dermatology and Venereology recommend initial prednisolone dose at 0.5 mg–1.5 mg/kg/d and if control of the disease is not reached within 2 weeks, a higher prednisolone dose (up to 2 mg/kg) could be administered. (19) If doses of prednisolone above 100 mg/d are required, pulse treatment with either oral or intravenous (IV) steroids may be considered. A common pulse regimen used is 100 mg/d of IV dexamethasone for 3 days every 2–3 weeks. (20) Once remission is induced and maintained with healing of the majority of lesions, the dose can be tapered by 25%. Reduction may be performed biweekly with slower decreases when doses below 20 mg/d are reached. CSs can be combined with an immunosuppressive agent, particularly when complications due to expected prolonged use (≥4 months) such as hypertension, diabetes mellitus, and osteoporosis are expected. A recent systematic review that evaluated RCTs with adjuvant therapy with azathioprine, mycophenolate mofetil (MMF), cyclophosphamide, cyclosporine, intravenous immunoglobulin (IVIG), plasma exchange, and infliximab in PV patients concluded that adjuvants were not beneficial for achieving remission, but were found to collectively decrease the risk of relapse by 29%.Second-line treatment in the case of contraindications to glucocorticoids or complications due to expected prolonged use (≥4 months) consists in the combined or single use of immunosuppressant such as azathioprine, MMF, dapsone, methotrexate, cyclophosphamide, and cyclosporine. In recent years, the use of IVIG and biologics such as infliximab, and especially rituximab, has been reported to produce excellent results in refractory cases. (19)

Azathioprine:

It is considered a first-line adjuvant immunosuppressant according to the EDF guidelines. Dose varies between 1 and 3 mg/kg/d, based on the activity of the thiopurine methyltransferase (TPMT) enzyme, involved in the metabolism of the drug. When TPMT levels are high, normal doses of azathioprine (up to 2.5 mg/kg/d) are administered, while adults with PV and intermediate or low TPMT levels should receive a maintenance dose (up to 0.5–1.5 mg/kg/d). A dose of 50 mg/d could initially be administered, and if no idiosyncratic reactions occur, it could be increased after a week. Azathioprine should not be used in patients with no TPMT activity. [21]

Mycophenolate Mofetil:

MMF is a safe steroid-sparing agent. [22]The optimal dose is weight dependent with a dose of 2 g/d recommended for the average patient of 75 kg. Progressive dose increase by 500 mg/wk until the final dose of 2 g/d has been proposed to avoid gastrointestinal adverse events. [23]

Dapsone:

Dapsone is recommended in a dose of 100 mg/d or up to ≤1.5 mg/kg/d as a steroid-sparing agent. However, dapsone did not exhibit any benefit on remission of the disease. Before initiating therapy with dapsone, serum G6PD activity should be tested. [19]

Methotrexate:

Methotrexate could be used as a steroid-sparing agent in a dose of 10–20 mg/wk. [19]

Rituximab:

Rituximab is an anti-CD20 monoclonal humanized antibody with the potential to reduce desmoglein autoantibodies and selectively deplete B cells and is indicated in patients who remain dependent on more than 10 mg prednisolone combined with an immunosuppressive adjuvant according to the EDF. [24] Administration schedule in literature is either 1,000 mg IV every 2 weeks or 375 mg/m2 every week. The same dosage can be administered again in case of clinical relapses. [25]

Intravenous immunoglobulins:

Treatment with IVIG can be used in refractory disease or in case of contraindications to immunosuppressive adjuvants. The usual dose is 2 g/kg/cycle IV administered over 2–5 consecutive days, monthly. [19]

Dexamethasone-Cyclophosphamide Pulse Therapy:

Dexamethasone-cyclophosphamide pulse is a combination of an anti-inflammatory and a chemotherapeutic agent. [26] This refers to the intermittent administration of high doses of intravenous CS and cyclophosphamide, usually three daily doses of dexamethasone (100 mg) or

methylprednisolone (500–1000 mg) and a single dose of cyclophosphamide (500 mg) given monthly.

Other Therapeutic Strategies:

Immunoadsorption, Therapeutic plasma exchange- plasmapheresis Immunoablative therapy, extracorporeal photochemotherapy (ECP) are some of the other strategies used in management of PV.

Step-by-step therapy after control of the disease:

The EDF proposed a useful treatment algorithm for use after the consolidation phase. The patients usually require 1–3 months for complete healing of the lesions.

- Start tapering steroids as soon as disease control is reached.
- Taper prednisolone by 25% every 2 weeks. When the patient reaches a dose, 20 mg, taper more slowly. A 5 mg reduction every 4 weeks could be suitable for most of the patients.
- If less than 3 lesions reappear during tapering of oral CS therapy, raise dose to the last effective dose for the patient.
- If the patient presents with a relapse (.3 lesions), reincrease oral CS therapy, going two steps back in the previous dose until control of the lesions is achieved. Subsequently, restart tapering of systemic steroids. If you cannot obtain disease control, go back to the initial dose.
- If oral CSs are given as monotherapy, add an immunosuppressant. If oral CSs are already combined with an immunosuppressant, consider replacing a first-line immunosuppressant by another or the use of a second-line immunosuppressant including immunoadsorption, IVIG, or rituximab.
- Monitor the patient for adverse events, and remember that prolonged immunosuppressive therapy increases the risk of side effects.

CONCLUSION:

Pemphigus vulgaris is a rare cause of chronic ulceration of the oral mucosa. It is a potentially fatal disease with most cases showing early oral manifestations, requires early diagnosis and early treatment to prevent future complications. The treatment of choice is steroidal therapy via the oral or intravenous route, which offers an adequate response and can be favourably modified after prognosis. Pulse therapy appears to be novel path breaking therapy for treating PV. Conventional immunosuppressive and anti-inflammatory agents such as azathioprine, mycophenolate mofetil and cyclosporine are associated with severe adverse events. However, as more studies incorporate

the common definitions and guidelines, the level of evidence and strength of therapy recommendation will improve, resulting in shorter treatment and better quality of life for the patients.

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