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Review Article

PEMPHIGUS VULGARIS: AN INSIGHT ON CONVENTIONAL AND EMERGING TREATMENT MODALITIES

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ABSTRACT
According to Sir William Osler, Mouth is the mirror of the body which reflects systemic diseases. The oral mucosa may be affected by a variety of muco-cutaneous diseases and oral lesions may occur first or very early in several muco-cutaneous disorders. Pemphigus is a group of potentially life threatening, chronic auto immune disorder characterized by epithelial blistering affecting muco-cutaneous surfaces. Autoantibodies in pemphigus vulgaris are directed against desmoglein in epithelial desmosomes, and the immune deposits result in intra-epithelial splitting (acantholysis). Oral lesions in the form of blisters and erosions are the first to manifest, and diagnosis is made by positive nikolsky's sign, coupled with characterstic histopathology and immunofluorescent features. Corticosteroids form the mainline of treatment, but adjuvant and newer therapies are also been used at an increasing rates. This article deals about the etio-pathogenesis, clinical characterstics, diagnosis and treatment strategies for pemphigus vulgaris.
Keywords: muco-cutaneous disorders, pemphigus vulgaris, corticosteroids, adjuvants.

INTRODUCTION

The term "Pemphigus", is derived from the greek word *pemphix* (bubble or blister)[1] and vulgaris is derived from latin word (common).[2] Pemphigus is a potentially life threatening disease that causes blisters and erosions of the skin and mucous membranes.[3] Pemphigus vulgaris (PV) is a rare, chronic, intra-epidermal bullous disease with a potentially fatal outcome[4] and originally named by Wickman in 1791.[1]

Epidemiology

Pemphigus is an uncommon disease with an incidence rate ranging from 0.5 to 3.2 per 100,000 per year.[4] Men and women are equally affected. The mean age of onset is 50–60 years. Pemphigus vulgaris has been observed in children and in the elderly.[5]

Etio-pathogenesis

The etiology of pemphigus vulgaris is uncertain. Genetic predisposition linked to HLA class II alleles may occur, as it is more frequently seen in certain ethnic groups and within families. Ashkenazi jews and people of Mediterranean origin are affected at an increased risk.[6] Other initiating factors include-

1. Drugs:[7]
- Captopril
- Penicillamine (immunogenicity is caused by Sulphydryl groups which resembles molecular structure of desmoglein 3; crossreactivity)
- Rifampicin
- Phenyl butazone
2. Radiation
3. Surgery
4. Diet particularly garlic[8]
5. Emotional stress
6. Viruses – HHV 8 [9]
7. Emotional stress
8. Pesticide exposure
9. Pregnant females[10]

The demonstration by Beutner and Jordan of serum antibodies directed against the intercellular substance of stratified squamous epithelium was the first in a series of findings that suggested that PV may be an auto immune disease.[11] Pemphigus vulgaris is an autoimmune disorder in which there is deposition of mainly IgG class antibodies intracellularly, as well as damage to desmosomes by antibodies directed against the extracellular domains of cadherin-type epithelial cell adhesion molecules, particularly desmoglein 3. Since oral epithelium largely expresses DS 3 ; but skin expresses DSG 1 as well as DSG 3,damage to DSG 3 by antibodies results in oral lesions at an early stages but skin integrity maintained by DSG .However, if damage to DSG 1 antibodies appear, cutanous lesions appear and the disease tends to be more severe.[12] The antigen-antibody reaction activates the complement system resulting in acantholysis and fluid accumulation and characterstic vesiculobullous lesions.[13] The current theory argues that acantholysis in PV occurs as an active process resulting from intracellular signaling triggered as a result of immunoglobulins (IgG) binding to the keratinocyte membrane antigen in a receptor ligand fashion.[13] Recently, nondesmoglein autoantibodies to cholinergic receptors (human alpha 9 acetylcholine receptor) have also been found capable of inducing clinical features of PV. Also, there has been the mention of the role of TNF-α and IL-2 as mediators in the blistering process of PV.[13]

Clinical Features

Of the four main types of pemphigus, pemphigus vulgaris is the most common ; pemphigus foliaceus, pemphigus vegetans, and pemphigus erythematosus are less common. There may indeed be only two main forms of pemphigus because pemphigus vegetans may be a variant of pemphigus vulgaris and pemphigus erythematosus may be a localized variant of pemphigus foliaceus.[14] Pemphigus vulgaris presents as flaccid, thin walled vesicles and/or bullae, that usually rupture to leave an area of erosion and ulceration.[15] Various mucosal surfaces such as oral, ocular, nasal, pharyngeal, laryngeal, upper respiratory and anogenital

mucous membranes can be involved. 80-90% of patients with pemphigus vulgaris develop oral lesions sometime during the course of disease, and, in 60% of cases, the oral lesions are the first sign.[3] Oral lesions usually begins as a vesicle or bulla . Early oral lesions may consist of a single hemorrhagic bulla or shallow ill defined irregular ulcers. However a whitish superficial covering which is the collapsed roof of a bulla is consistent and characteristic finding. Blisters, which rapidly lead to chronic erosions and ulcers[16], are seen mainly in the buccal mucosa, palate, ventral surface of tongue and lips[17,18]. Pemphigus should be considered whenever there are multiple persistent oral erosions, but in the early stages, the erosions may be recurrent[19]. Advanced signs usually consist of severe desquamative or erosive gingivitis[20], but gingival lesions are uncommon at the onset or may appear as isolated blister or erosions, or both, mainly on free gingiva, and may be difficult to recognize as bullous lesions[21]. Lips may be covered by thick hemorrhagic crusts. In advanced cases , the lesions may resemble erythema multiforme. The disease shows positive Nikolsky's sign but is not specific for PV.[15] During active stage of the lesion, when lateral pressure is applied on the blister or perilesional skin or normal appearing skin, it results in removal of upper layer of epidermis known as Nikolsky's sign.

Asboe-hansen : When finger is applied directly over an intact blister it produces lateral spread of lesion.

Diagnostic Criteria

The diagnosis of pemphigus vulgaris is based on 3 independent sets of criteria: clinical features, histology and immunological tests.[22] This chronic autoimmune cutaneous mucosal disease is often diagnosed late when it is presented only in the oral cavity and the diagnosis is confirmed using pathological examination and direct immunofluorescence (DIF) testing of the healthy perilesional mucosa of patient with pemphigus vulgaris.[23]

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.

Corticosteroids

-Corticosteroids form the mainstay of treatment in Pemphigus cases. In patients with P. vulgaris there is pronounced imbalance of helper T – T supressor ratio, which is restored by corticosteroid therapy.[24] Oral lesions of Pemphigus Vulgaris may respond partially to topical or intralesional corticosteroids. Systemic corticosteroids. (1-2 mg/kg/day) remain the mainstay of therapy of patients with oral lesions. Corticosteroids with less adverse effects are preffered. eg .Deflazacort.[25] In cases of severe disease 80mg daily Prednisolone may be used.

Systemic corticosteroids are the most useful drugs for the treatment of PV, first used for this purpose by thorn et al and popularized by Costello et al and lever and white.[26] Since their introduction, the mortality associated with PV has declined, and is now estimated to be 5-15%. However, several patients develop severe adverse effects from prolonged administration of high doses of systemic corticosteroids. These adverse effects include hypertension, osteoporosis, atherosclerosis, peptic ulcer disease, aseptic necrosis, diabetes mellitus/glucose intolerance, susceptibility to infections, and septicemia, amongst others.[27]

The next group of agents that were introduced in the treatment of pemphigus vulgaris was a group of anti-inflammatory and immunosuppressant agents. These medications are used to provide potential corticosteroid-sparing effect,[28] and included drugs such as dapsone, gold, and systemic antibacterials. They are often used in combination with other immunosuppressant agents such as azathioprine, methotrexate, and cyclophosphamide. Recently, several new therapeutic agents and treatment modalities have been reported in the treatment of patients with pemphigus vulgaris. These newer therapies include mycophenolate mofetil, chlorambucil, dexaamethasone-cyclophosphamide pulse therapy, immunoablative therapy with cyclophosphamide, plasmapheresis, extracorporeal photochemotherapy, intravenous immunoglobulin (IVIg) therapy, and, most recently, anti-CD20 chimeric monoclonal antibody (rituximab) therapy.

Dapsone

Dapsone is an anti-inflammatory agent that was initially used to treat leprosy. Dapsone was suggested to be an effective adjuvant to corticosteroids in PV.[29] However, the exact mechanism of action of dapsone in pemphigus vulgaris remains unknown. Dapsone exhibits antibiotic effect, interferes with neutrophil chemotactic migration, reduces the release of prostaglandins and leukotrienes, inhibits neutrophil adherence to basement membranes, inhibits the generation of toxic radicals and protect cells from neutrophil- and eosinophil-mediated injuries. It does not stop the initial pathogenesis process but exhibits anti-inflammatory effects.[30] The mean maintenance dose of dapsone required to sustain a clinical response has been reported to be approximately 100mg daily.[31]One of the most common and almost invariable adverse effects of dapsone is hemolytic anemia. This usually occurs in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Prior to initiating dapsone therapy, serum levels of G-6-PD should be measured. However, there are some patients who still develop anemia despite normal levels of G-6-PD. Another short-term adverse effect of dapsone that can be potentially fatal is the 'sulfone syndrome'.[31] This syndrome is a hypersensitivity reaction to dapsone, characterized by drug-induced hepatitis, fever, and rash occurring within 2 months of starting the drug. Other adverse effects such as methemoglobinemia, agranulocytosis, and neuropathies can also occur.[31]

Gold

Gold was first described in the treatment of PV since 1973. Intramuscular gold injections were given to 26 patients over a 10-year period as steroid-sparing agent.[32] Gold 50 mg was given weekly after test dose, and was reduced to monthly when prednisolone was taken off. Its use appeared to be lessened recently due to concerns of its efficacy and safety. Side effects of gold are dermatitis, pigmentation, diarrhoea, oral ulcers, proteinuria, blood disorders, alopecia, peripheral neuritis, pulmonary fibrosis, cholestatic jaundice and rarely colitis.

Tetracyclines / Nicotanamide

Variable combinations of tetracyclines with or without nicotinamide have been described in PV. Sixteen patients were given nicotinamide 1.5 g and tetracycline 2 g daily. In 12, no systemic steroids were given and of these only three cleared and three improved.[33] Of the four patients given additional prednisolone, there was clearance in one, partial improvement in two and no response in another.[33] Tetracyclines with or without nicotinamide could be considered as adjuvant treatment, perhaps in milder cases of PV.

Azathioprine

Azathioprine is metabolized to 6-thioguanine, which produces DNA strand breaks and blocks DNA synthesis.[34] It is probably the most commonly used immunosuppressive agent.[29] Azathioprine also allowed reduction in the dose of the steroid used and hence its side effects.[29]The side effects of azathioprine include bone marrow suppression, liver dysfunction and increased incidence of malignancy. Azathioprine is metabolized by thiopurine methyltransferase (TPMT). Low enzyme activity leads to accumulation of cytotoxic thiopurine metabolites which increase the risk of toxicity.[34]

Methotrexate

Successful use of methotrexate in the treatment of pemphigus vulgaris was initially reported by Peck and Osserman[35] in 1969. Dosage ranges between 10–30 mg/wk. Baseline assessment should be done prior to initiating the therapy and includes include a CBC with differential and platelet counts, hepatic enzymes, renal function tests, and a chest x- ray. Hematology should be carried out at least monthly, renal function and liver function every 1–2 months. The adverse effects included nausea, vomiting, lassitude, gastrointestinal pain, leukopenia, and systemic infections. Fetal death and/or congenital anomalies, bone marrow suppression, hepatotoxicity, ulcerative stomatitis, lymphomas may also occur. Patients may develop megaloblastic anemia secondary to use of methotrexate. This is because methotrexate acts as a folic acid antagonist by inhibiting the enzyme folic acid reductase. Hence, it is recommended that patients taking methotrexate should also be taking up to 1mg of folic acid per day to prevent the development of anemia.[36]

Cyclosporin

Initial small case series reported that cyclosporin was a useful adjuvant with steroid-sparing effects in PV.[37] Cyclosporine inhibits production of interleukin-2 and interferon-gamma by lymphocytes.[34] Side effects of cyclosporine include renal function impairment (dose dependent increase in urea and creatinine in the first week), hypertension, hypertrichosis, gingival hypertrophy, tremor, gastrointestinal symptoms, hepatic dysfunction, hyperkalemia and hyperuricaemia.

Mycophenolate Mofetil

Mycophenolate mofetil is a newer chemotherapeutic agent that has been reported to be effective in the treatment of pemphigus vulgaris.[38] Mycophenolate mofetil is an inhibitor of lymphocyte proliferation and acts by selectively inhibiting the *de novo* pathway of purine synthesis.[39] Total daily doses of 2-2.5 g are typically given in two divided doses with prednisolone.[38] The adverse effect profile of mycophenolate mofetil is well known. The most common adverse effects in patients taking mycophenolate mofetil are leukopenia, anemia, gastrointestinal distress including nausea and diarrhea, and elevation of transaminases .[40]

Chlorambucil

Chlorambucil is another alternative agent that can be used in the treatment of refractory pemphigus vulgaris.[41] The mechanism of action of chlorambucil involves the inhibition of DNA synthesis through alkylation of nucleic acids. Chlorambucil has primarily an immunosuppressant effect on B cells. Patients treated with chlorambucil have been observed to have adverse effects, such as leukopenia and thrombocytopenia. Other adverse effects reported to be associated with chlorambucil include acute myeloblastic leukemia, azospermia, anovulation, gastrointestinal toxicity, drug fever, seizures, pulmonary fibrosis, and interstitial pneumonitis.[41]

Dexamethasone-Cyclophosphamide Pulse Therapy

Dexamethasone-cyclophosphamide pulse is a combination of an anti-inflammatory and a chemotherapeutic agent.[42,43] Cyclophosphamide is a potent alkylating agent with cytostatic properties that cross-links DNA and other macromolecules, such as RNA and proteins, causing failure of cell division. This chemotherapeutic agent was used since it would act upon both B cells and T cells and suppress autoantibody production. It was combined with dexamethasone for two major reasons. The first was to provide an immediate immunosuppressant effect, since cyclophosphamide can take 4 weeks to produce an effective clinical response. The second reason for adding cyclophosphamide was that it eliminated the need for use of high doses of oral systemic corticosteroids.[44] The adverse effects profile from IV systemic corticosteroids and cyclophosphamide was less severe than that of oral systemic corticosteroids and oral cyclophosphamide.[45,46] 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. Pasricha and Ramji first described this therapy for PV.[47] Doses and frequency are arbitrary. The most common adverse effect are multiple infections as a result of receiving high doses of immunosuppressant drugs. These infections included viral and fungal infections, pulmonary tuberculosis, and Gram-negative septicemia, resulting in a mortality rate ranging between 4 and 6%. Other adverse effects included diabetes mellitus, cardiac complications, alopecia, amenorrhea, and sterility.[42,43] Haemorrhagic cystitis and pituitary adrenal suppression has also been reported.

Plasmapheresis

The goal of plasmapheresis was to acutely reduce the pathogenic autoantibody in the plasma through a filtration process.[48] Plasmapheresis was administered in cycles. One cycle of plasmapheresis involved the removal of 400–4000mL of blood plasma and subsequent replacement by an equal volume of isotonic albumin (5%) solution. The number of cycles used to achieve clinical control ranged from 3 to 48 (mean of 12.2 cycles) over a period between 2 weeks and 10 months. The interval between plasmapheresis cycles varied from three to four times a week to one cycle every 4 weeks. Plasmapheresis has been used in patients who are refractory to therapy with steroids in doses of 2mg/kg/day. The low levels of antibodies resulting from plasmapheresis cause a rebound effect where new antibodies are produced in excess

of the original levels. However, this rebound effect can be controlled by administration of an immunosuppressive agent[49]. The agents most commonly used to suppress the rebound phenomenon include azathioprine, cyclophosphamide and prednisone.[49] However, the use of high-dose immunosuppressant treatments has also resulted in an increased risk of developing adverse effects such as systemic infections. Some of these infections have been fatal. The most common infections that patients have developed are pneumonia, herpes zoster, urinary tract infections, and skin infections.

Rituximab

Rituximab is a chimeric monoclonal antibody that targets the B cell differentiation antigen CD20, an integral membrane protein that participates in B cell activation and proliferation. It is found on pre-B cells, immature B cells, mature B cells, and immature plasma cells. By eliminating CD20+ B cells from the peripheral blood with rituximab while suppressing T-cell function, both the humoral and cell mediated components of pemphigus vulgaris can be blocked. The goal of treatment with rituximab was to acutely reduce the presence of the pathogenic autoantibody in the plasma by targeting pemphigus-specific CD20-positive B cells. Treatment was administered intravenously at a dosage of 375 mg/m2. The number of doses necessary to provide clinical control ranged from four to eight (mean of five doses) over a period of 1–12 months. Occasionally, adverse effects such as infusion-related symptom complex of fever, chill, nausea, pruritus, bronchospasm, and dyspnea could occur . A major adverse effect of rituximab is systemic infection, septicemia, and death.[50,51]

Immunoablative Therapy

Immunoablative therapy is a new method of treatment that has been recently used in the treatment of autoimmune diseases. There is one case report which describes the use of immunoablative high dose cyclophosphamide without stem-cell rescue in a patient with pemphigus vulgaris.[52] Immunoablative therapy with high-dose cyclophosphamide without stem-cell rescue can be used in patients whose disease is progressive and unresponsive to conventional oral agents. The use of this treatment modality is limited.

Extracorporeal Photochemotherapy

Extracorporeal photochemotherapy (ECP), also known as photopheresis, is a novel form of immunotherapy that was initially used in the treatment of the Sezary form of cutaneous T-cell lymphoma. It has also been used in other T-cell mediated disorders, including graft-versus-host disease, scleroderma, and systemic lupus erythematosus.[53] The exact mechanism of action of ECP is unknown. It is proposed that the mechanism of action could involve inhibition of pathogenic antibody production by B lymphocytes.[54] The treatment consists of exposure of white blood cells to 8 methoxypsoralen and irradiation with UVA light. The procedure was conducted over a period of 4 hours on two consecutive days. Adverse effects from ECP were usually mild and transitory. These included psoralen-induced nausea, vomiting, diaphoresis, hypotension, and low-grade fever.[55] ECP has not been associated with the significant immunosuppression that accompanies many other therapies used in the treatment of pemphigus vulgaris.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) is being increasingly used in immune-mediated diseases. Postulated mechanisms include: functional blockade of Fc receptor, elimination of immune complexes, antiidiotypic suppression of autoantibodies, inhibition of complement-mediated damage, modulatory effects on cytokines release and cellular response, and blockade of cell surface death receptor Fas and its ligand.[56] IVIG is usually well tolerated. Side effects include vasomotor symptoms such as headache, myalgia, flushing, nausea, tachycardia, usually in the first hour after infusion. Anaphylactic reactions may occur in patients with IgA deficiency. Uncommonly, acute renal failure and haemolysis had been reported.[56]

CONCLUSION

In conclusion, the treatment of pemphigus vulgaris has been a challenge for decades and continues to be so. However, the mortality of patients with pemphigus vulgaris has been significantly reduced with the advent of new therapies and treatment modalities. The optimistic view is that during the next few decades, multicenter trials will be conducted to establish a consensus on the approach to the multi-step algorithmic treatment of pemphigus vulgaris.

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