

REVIEW ARTICLE

A Review on – Pemphigus Vulgaris: Unnecessary Immunity.

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Received 7 April 2010; Accepted 3 May 2010

ABSTRACT

Pemphigus is derived from the Greek word *pemphix* meaning bubble or blister. Pemphigus describes a group of chronic bullous diseases, originally named by Wichman in 1791. Pemphigus vulgaris is an autoimmune, intraepithelial, blistering disease affecting the skin and mucous membranes and is mediated by circulating autoantibodies directed against keratinocyte cell surfaces. Blisters in pemphigus vulgaris are associated with the binding of IgG autoantibodies to keratinocyte cell surface molecules. These intercellular or pemphigus vulgaris antibodies bind to keratinocyte desmosomes and to desmosome-free areas of the keratinocyte cell membrane. The binding of autoantibodies results in a loss of cell-to-cell adhesion, a process termed acantholysis. The antibody alone is capable of causing blistering without complement or inflammatory cells. pemphigus vulgaris is estimated at 1.6 cases per 100,000 population. Pemphigus vulgaris is a potentially life-threatening autoimmune mucocutaneous disease with a mortality rate of approximately 5-15%. The aim of treatment in pemphigus vulgaris is the same as in other autoimmune bullous diseases which is to decrease blister formation, promote healing of blisters and erosions. Corticosteroids have improved overall mortality, but now much of the mortality and morbidity in these patients relates to the adverse effects of therapy. Immunosuppressive drugs are steroid sparing and should be considered early in the course of the disease

Key Words: Pemphigus Vulgaris, Keratinocyte, Autoantibodies.

INTRODUCTION

Pemphigus is derived from the Greek word *pemphix* meaning bubble or blister. Pemphigus describes a group of chronic bullous diseases, originally named by Wichman in 1791. The term pemphigus refers to a group of autoimmune blistering diseases of the skin and mucous membranes characterized histologically by intraepidermal blister and immunopathologically by the finding of in vivo bound and circulating immunoglobulin G (IgG) antibody directed against the cell surface of keratinocytes. The 3 primary subsets of pemphigus include pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus. Each type of pemphigus has distinct clinical and immunopathologic features. Pemphigus vulgaris accounts for approximately 70% of pemphigus cases. [1]

Pathophysiology

Blisters in pemphigus vulgaris are associated with the binding of IgG autoantibodies to keratinocyte cell surface molecules. These intercellular or pemphigus vulgaris antibodies

bind to keratinocyte desmosomes and to desmosome-free areas of the keratinocyte cell membrane. The binding of autoantibodies results in a loss of cell-to-cell adhesion, a process termed acantholysis. The antibody alone is capable of causing blistering without complement or inflammatory cells. [5]

Pemphigus vulgaris antigen

- Intercellular adhesion in the epidermis involves several keratinocyte cell surface molecules.
- Pemphigus antibody binds to keratinocyte cell surface the molecules desmoglein 1 and desmoglein 3.
- The binding of antibody to desmoglein may have a direct effect on desmosomal adherens or may trigger a cellular process that results in acantholysis. [3]

Antibodies

Patients with the mucocutaneous form of pemphigus vulgaris have pathogenic antidesmoglein 1 and antidesmoglein 3

autoantibodies. Patients with the mucosal form of pemphigus vulgaris have only antidesmoglein 3 autoantibodies. Patients with active disease have circulating and tissue-bound autoantibodies of both the immunoglobulin G1 (IgG1) and immunoglobulin G4 (IgG4) subclasses. More than 80% of the patients with active disease produce autoantibodies to the desmosomal protein desmoglein. In patients with pemphigus vulgaris, the presence of antidesmoglein 1 autoantibodies, as determined by enzyme-linked immunosorbent assay (ELISA), is more closely correlated with the course of the disease compared with antidesmoglein 3 auto antibodies.^[4]

Complement

Pemphigus antibody fixes components of complement to the surface of epidermal cells. Antibody binding may activate complement with the release of inflammatory mediators and recruitment of activated T cells. T cells are clearly required for the production of the autoantibodies, but their role in the pathogenesis of pemphigus vulgaris remains poorly understood. Interleukin 2 is the main activator of T lymphocytes, and increased soluble receptors have been detected in patients with active pemphigus vulgaris.^[1]

Mortality.

Pemphigus vulgaris is a potentially life-threatening autoimmune mucocutaneous disease with a mortality rate of approximately 5-15%. Mortality in patients with pemphigus vulgaris is 3 times higher than the general population. Complications secondary to the use of high-dose corticosteroids contribute to the mortality rate. Morbidity and mortality are related to the extent of disease, the maximum dose of systemic steroids required to induce remission, and the presence of other diseases. Prognosis is worse in patients with extensive pemphigus vulgaris and in older patients.^[3]

Sex

The male-to-female ratio is approximately equal. In adolescence, girls are more likely to be affected than boys.^[2]

Age

The mean age of onset is approximately 50-60 years; however, the range is broad, and disease onset in older individuals and in children has been described. Patients are younger at presentation in India than in Western countries.^[2]

History

Mucous membranes: Pemphigus vulgaris presents with oral lesions in 50-70% of patients, and almost all patients have mucosal lesions at some point in the course of their disease. The diagnosis of pemphigus vulgaris should be considered in any patient with persistent oral erosive lesions.

Skin: Most patients with pemphigus vulgaris develop cutaneous lesions. The primary lesion of pemphigus vulgaris is a flaccid blister, which usually arises on healthy-appearing skin but may be found on erythematous skin. New blisters usually are flaccid or become flaccid quickly. Affected skin often is painful but rarely pruritic. **Drug induced pemphigus vulgaris :** Drugs reported most significantly in association with pemphigus vulgaris include penicillamine, captopril, cephalosporin, pyrazolones, nonsteroidal anti-inflammatory drugs (NSAIDs), and other thiol-containing compounds. Rifampin, emotional stress, thermal burns, ultraviolet rays, and infections (eg, coxsackievirus, Herpesviridae family) have also been reported as triggers for pemphigus vulgaris.^[5]

Physical

Mucous membranes typically are affected first in pemphigus vulgaris. Mucosal lesions may precede cutaneous lesions by weeks or months. Patients with mucosal lesions may present to dentists, oral surgeons, or gynecologists.

Mucous membranes

Intact bullae are rare in the mouth. More commonly, patients have ill-defined, irregularly shaped, gingival, buccal, or palatine erosions, which are painful and slow to heal. The erosions extend peripherally with shedding of the epithelium.

The mucous membranes most often affected in pemphigus vulgaris are those of the oral cavity, which is involved in almost all patients with pemphigus vulgaris and sometimes is the only area involved. Erosions may be seen on any part of the oral cavity. Erosions can be scattered and often are extensive. Erosions may spread to involve the larynx, with subsequent hoarseness. The patient often is unable to eat or drink adequately because the erosions are so uncomfortable. In juvenile pemphigus vulgaris, stomatitis is the presenting complaint in more than 50% of the cases. Other mucosal surfaces may be involved, including the conjunctiva, esophagus

(causes odynophagia and/or dysphagia), labia, vagina, cervix, vulva, penis, urethra, nasal mucosa, and anus. [4]



Skin

The primary lesion of pemphigus vulgaris is a flaccid blister filled with clear fluid that arises on healthy skin or on an erythematous base, as shown in the images below.



Early, small blister filled with clear fluid arises on healthy skin.

The blisters are fragile; therefore, intact blisters may be sparse. The contents soon become turbid, or the blisters rupture, producing painful erosions, which is the most common skin presentation and is shown in the image below.

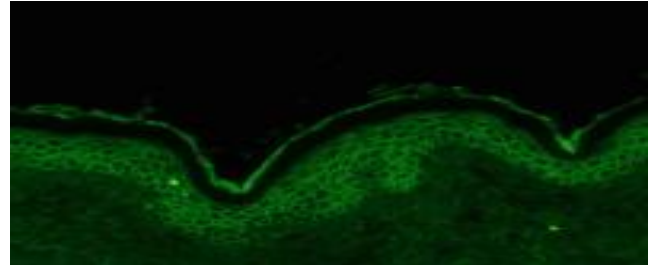


Flaccid blister filled with clear fluid arises on healthy skin

Erosions often are large because of their tendency to extend peripherally with the shedding of the epithelium.



Erosion.



Direct immunofluorescence showing intercellular immunoglobulin G throughout the epidermis of a patient with pemphigus vulgaris.

Skin biopsy specimens placed in transport media may yield false-negative results; therefore, fresh tissue is the preferred substrate for DIF studies. [3]

TREATMENT

Medical Care

The aim of treatment in pemphigus vulgaris is the same as in other autoimmune bullous diseases, which is to decrease blister formation, promote healing of blisters and erosions, and determine the minimal dose of medication necessary to control the disease process.

Corticosteroids have improved overall mortality, but now much of the mortality and morbidity in these patients relates to the adverse effects of therapy. Whether massive doses of steroids have any advantage over doses of 1 mg/kg/d is unclear. Immunosuppressive drugs are steroid sparing and should be considered early in the course of the disease. Epidermal growth factor may speed healing of localized lesions. Many authorities now use rituximab as first- or second-line therapy. The antitumor necrosis factor drugs sulfasalazine and pentoxifylline have been reported as effective adjunctive treatments, reducing the serum level of tumor necrosis factor and resulting in rapid clinical improvement. Dapsone has been suggested as a steroid-sparing agent in the maintenance phase of pemphigus vulgaris treatment; dapsone has also been suggested as a first-line agent.

Intravenous immunoglobulin therapy has been suggested as efficacious in pemphigus vulgaris treatment. Amagai et al reported on the successful use of intravenous immunoglobulin in pemphigus patients who did not fully respond to systemic steroids, and Asarch et al reported its use in pediatric patients.

Photodynamic therapy has been suggested as a possible adjunctive treatment for recalcitrant ulceration.^[6]

Consultations

Management of patients with pemphigus vulgaris requires coordination of care between the dermatologist and the patient's primary care physician.

An ophthalmologist should evaluate patients with suspected ocular involvement and those requiring prolonged high-dose steroids. Patients with oral disease may require a dentist and/or an otolaryngologist for evaluation and care. Patients on systemic steroids should maintain adequate vitamin D and calcium intake through diet and supplements. Patients with a history of renal calculi should not receive calcium carbonate. Patients receiving long-term systemic corticosteroids should be evaluated by a rheumatologist within the first 30 days of treatment for osteoporosis risk assessment and consideration of a bisphosphonate for prophylaxis against osteoporosis.^[2]

Diet

No dietary restrictions are needed, but patients with oral disease may benefit from avoiding certain foods (eg, spicy foods, tomatoes, orange juice) and hard foods that may traumatize the oral epithelium mechanically (eg, nuts, chips, hard vegetables and fruit).^[2]

Activity

Advise patients to minimize activities that traumatize the skin and that may precipitate blistering, such as contact sports. Nontraumatic exercises, such as swimming, may be helpful. Additionally, Dental plates, dental bridges, or contact lenses may precipitate or exacerbate mucosal disease.^[2]

Medication

The aim of treatment is to reduce the inflammatory response and autoantibody production. While target-specific therapy is not available, non-target-specific treatments currently are used. The most commonly used medications are corticosteroids. The introduction of corticosteroids has reduced mortality greatly, but significant morbidity remains.

Immunosuppressants should be considered early in the course of disease, as steroid-sparing agents. Mycophenolate mofetil and azathioprine are the usual first-line agents. Rituximab and intravenous immunoglobulin have also proven useful alone or in combination, and some authorities are now using rituximab as first-line therapy for severe disease. If not treated, pemphigus can be fatal due to overwhelming infection of the sores. The most common treatment is the administration of oral steroids, especially prednisone, and often in high doses. The side effects of cortico-steroids may require the use of so-called steroid-sparing or adjuvant drugs. The immuno-suppressant CellCept (Mycophenolic acid) is among those being used.^[10]

Intravenous gamma globulin (IVIG) may be useful in severe cases, especially paraneoplastic pemphigus. Mild cases sometimes respond to the application of topical steroids. Recently, Rituximab, an anti-CD20 antibody, was found to improve otherwise untreatable severe cases of Pemphigus vulgaris.^[11-12]

All of these drugs may cause severe side effects, so the patient should be closely monitored by doctors. Once the outbreaks are under control, dosage is often reduced, to lessen side effects. If paraneoplastic pemphigus is diagnosed with pulmonary disease, a powerful cocktail of immune suppressant drugs is sometimes used in an attempt to halt the rapid progression of bronchiolitis obliterans, including methylprednisolone, ciclosporin, azathioprine and thalidomide. Plasmapheresis may also be useful. If skin lesions do become infected, antibiotic may be prescribed. Tetracycline antibiotics have a mildly beneficial effect on the disease, and are sometimes enough for Pemphigus Foliaceus. In addition, talcum powder is helpful to prevent oozing sores from adhering to bedsheets and clothes.^[5]

Pulse therapy

It is first used dexamethasone-cyclophosphamide pulse (DCP) therapy for pemphigus in 1982. DCP therapy regimen has revealed that pemphigus can now be considered to be a completely curable disease. In this therapy dexamethasone 100 to 140 mg (according to body weight) is given in combination with immunosuppressant drugs (cyclophosphamide) for three consecutive days in 250 ml 5% dextrose intravenous in two and half hour. During this therapy patient are examined for blood pressure sodium and potassium level in blood. This therapy is repeated on patient in every three to four weeks

according to new blister formation and its continued until formation of new lesion are stopped.^[4]

REFERENCE

1. Williams DM. Vesiculobullous mucocutaneous disease: pemphigus vulgaris. *J Oral Pathol Med* 1989; 18:544-553.
2. Anhalt GJ, Kim S-C, Stanley JR, et al. Paraneoplastic pemphigus: an autoimmune mucocutaneous disease associated with neoplasia. *N Engl J med* 1990; 323:1729-1735.
3. Calvanico NJ, Robledo MA, Diaz LA. Immunopathology of pemphigus. *J Autoimmun* 1991; 4:3-16.
4. Horn TD, Anhalt GJ. Histologic features of paraneoplastic pemphigus. *Arch Dermatol* 2009; 128:1091-1095.
5. Lamey P-J, Rees TD, Binnie WH, et al. Oral presentation of pemphigus vulgaris and its response to systemic steroid treatment. *Oral Surg Oral Med Oral Pathol* 2002; 74:54-557.
6. Becker BA, Gaspari AA. Pemphigus vulgaris and vegetans. *Dermatol Clin* 2001; 11:429-452.
7. Helm TN, Camisa C, Valenzuela R, Allen CM. Paraneoplastic pemphigus: a distinct autoimmune vesiculobullous disorder associated with neoplasia. *Oral Surg Oral Med Oral Pathol* 1993; 75:209-213.
8. Mutasim DF, Pelc NJ, Anhalt GJ. Paraneoplastic pemphigus. *Dermatol Clin* 1993; 11:473-481.
9. Paterson AJ, et al. Pemphigus vulgaris precipitated by glibenclamide therapy. *J Oral Pathol Med* 1993; 22:92-95.
10. Stanley JR. Cell adhesion molecules as targets of autoantibodies in pemphigus and pemphigoid, bullous diseases due to defective epidermal cell adhesion. *Adv Immunol* 1993; 53:291-325.
11. Mignogna MD, et al. Oral pemphigus: clinical significance of esophageal involvement: report of eight cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 84:179-184.
12. Robinson JC, et al. Oral pemphigus vulgaris: a review of the literature and a report on the management of 12 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 84:349-355.
13. Sirois D, Leigh JE, Sollecito TP. Oral pemphigus vulgaris preceding cutaneous lesions: recognition and diagnosis. *J Amer Dent Assoc* 2000; 131:1156-1160.