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Pemphigus: A Review on Recent Treatment Advancments

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ABSTRACT
Pemphigus is considered to be a chronic mucocutaneous autoimmune disease with the clinical features of blisters that initially appear in the oral cavity and later in the skin. Early diagnosis and treatment helps to determine the course and prognosis of the disease. There are various variants of pemphigus and if not treated on time can become fatal. Systemic corticosteroids are considered to be the standard therapy for pemphigus vulgaris (PV). Management of PV is along term process and involves the prolonged use of steroids to control the disease and prevent relapses, but associated adverse events constantly remain a great challenge. Regular clinical evaluation of patients with pemphigus on steroids is mandatory. Various latest treatment modalities have been started to treat the disease and reduce its relapse which include the use of drugs in the form of AZA, MMF and RTX.
KEYWORDS: Cutaneous, autoimmune, corticostereiods, Azathioprine, Mycophenolate mofetil, Rituximab

I. INTRODUCTION

The term pemphigus is derived from a Greek word 'pemphix', which means blister or bubble, and it is a group of chronic blistering epithelial diseases in which there is production of IgG autoantibodies against extracellular domains of cell membrane proteins of keratinocytes which results in acantholysis which means the loss of cell-cell adhesion between keratinocytes. In pemphigus, there are IgG autoantibodies which are specifically directed against desmogleins (desmoglein 1 and desmoglein 3), which are part of the cadherin family of cell–cell adhesion molecules which are found in desmosomes, and these are the structures mainly responsible for maintaining intercellular adhesion in stratified squamous epithelia, such as the skin and oral mucosa.

Pemphigus can be broadly classified into three major forms namely pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus. Pemphigus vulgaris and pemphigus foliaceus are the classic forms of pemphigus. Histological analysis reveals that pemphigus vulgaris blisters lie deep in the epidermis or oral epithelium above the basal layer, whereas pemphigus foliaceus blisters occur in the superficial layers of the epidermis, mainly in the granular layer. Paraneoplastic pemphigus is characterized by the presence of an associated neoplasm, usually of lymphoid tissue.

Phemphigus diseases are a group of rare autoimmune bullous diseases that affects the skin and mucous membranes. They have a significant morbidity and mortality, as well cause an important impairment in quality of life.

Classification of pemphigus subtypes

Pemphigus vulgaris: It is associated with humoral autoimmune response and has three subtypes:

Mucosal-dominant type (limited cutaneous involvement): it has blisters in the deep layers of the oral mucosa owing to anti-desmoglein 3 IgG autoantibodies

Mucocutaneous type (both mucosal and cutaneous involvement): it has blisters in the deep layers of the oral mucosa and epidermis, owing to anti-desmoglein 3 and anti-desmoglein 1 IgG autoantibodies, respectively

Cutaneous type (cutaneous involvement alone): it has blisters in the deep layers of the epidermis owing to anti-desmoglein 1 and pathogenically weak anti-desmoglein 3 autoantibodies

Pemphigus foliaceus: it is associated with humoral autoimmune response and has no mucosal involvement, blisters in the superficial layers of the epidermis owing to anti-desmoglein 1 IgG autoantibodies

Paraneoplastic pemphigus: it is caused by both humoral and cellular autoimmune responses; mucosal and cutaneous blisters owing to anti-desmoglein 3 and/or anti-desmoglein 1 IgG autoantibodies in combination with interface dermatitis and has inflammation at the dermal–epidermal junction or has severe oral lichenoid reaction (chronic inflammation of the oral mucosa) owing to self-reacting T cells.

Other Pemphigus variants:

Pemphigus vegetans

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Pemphigus erythematosus
Herpetiform pemphigus
Drug-induced pemphigus

CLINICAL MANIFESTATIONS

The clinical manifestations are either mucosal or mucocutaneous involvement. Almost all patients present have mucosal lesions, mainly in the oral mucosa, with or without cutaneous lesions.

Oral lesions are present initially in 50%-70% of cases and occur in 90% of patients during the course of the disease. They are mainly characterized by painful erosions, blisters are not much intact, mostly hey are fragile and break easily. The most commonly affected areas are the buccal and palatine mucosa, lips, and gingiva. The erosions are mostly multiple and are present in different sizes and irregular shapes. Gingival involvement causes desquamative gingivitis. The lesions may extend up to the vermilion border of the lips, forming a fissured hemorrhagic crust. Oral lesions hence make eating difficult. Other mucous membranes can also be involved, including the conjunctiva, nasal mucosa, pharynx, larynx, esophagus, vagina, penis, and anus. Oral involvement continues for months before progressing to involvement of the skin or other mucous membranes and at times it may also be the only manifestation of the disease.

Cutaneous involvement can be either localized or generalized. Most patients develop flaccid blisters of clear content on normal or erythematous skin. The blisters break easily, resulting in painful erosions that bleed easily and profusely. Skin lesions can be observed in any location, but mostly occur on trunk, groin, armpits, scalp, and face and very rarely on the palms and soles. These erosions become covered by crusts, with no tendency to heal. Healing is usually without a scar, but pigmented changes can be seen. Nikolsky's sign, which is caused by the epidermal detachment of the mechanical pressure at the edge of a blister or normal skin, is usually present in PV. Blisters can also be extended by vertical pressure over an intact blister, called the Asboe-Hansen sign or Nikolsky II sign. PV is a chronic disease and has high chances of remission and exacerbation. Without proper treatment, PV can be fatal, skin can lose its epidermal barrier function, leading to loss of body fluids, malnutrition, and secondary infections. Secondary bacterial infection is one of the most common complications and can progress to septic shock.

DIAGNOSIS

Histopathological examination: It helps to identify the level of blister cleavage in order to diagnose pemphigus, and to differentiate with other subepidermal bullous lesions, such as acantholytic keratinocytes which can be observed in various vesiculobullous diseases. For the biopsy, it is always best to choose a recent blister (less than 24 hours of appearance) that fits inside a 4 mm punch or a small fusiform excision, because PV blisters usually rupture easily. If this cannot be done than a perilesional area should be biopsied, so that the blister roof is attached to the adjacent skin and does not detach during histological processing.

Direct immunofluorescence examination: This examination is mostly based on the in vitro antigen-antibody reaction, which is revealed by ultraviolet-excited fluorochromes (fluorescein isothiocyanate). When tissue deposition of the searched product occurs, the fluorochrome will shine (apple green color).

Indirect immunofluorescence examination: This test assists in the diagnosis of PV and hence causes the detection of circulating autoantibodies. The normal skin of another individual (originating from the foreskin, breast, or eyelid, which are easy to obtain and are present with good antigenicity) or a specimen of monkey esophagus are used as substrate.

Immunohistochemical examination: It consists of a combination of immunological and histological methods for the detection of specific antigens in tissues or cells (immunocytochemistry), which are based on the identification of the antigen-antibody complex.

Serological diagnosis: ELISA is a very sensitive and specific method that allows detection of IgG antibodies in over 90% of patients using recombinant Dsg1 and Dsg3. It is considered to be a quantitative method and has a good correlation with clinical severity, and may be useful for patient follow-up. Immunoblotting and immunoprecipitation are other available serological test but due to their complexity and cost, they are not very useful in clinical practice and are mostly used in research.

TREATMENT

The treatment involves the use of systemic medications (oral or intravenous). Treatment should be started as early as possible, aiming to achieve and maintain disease remission. Generally the treatment is quite prolonged, and can last many years. Since the advent of targeted therapies, the management of pemphigus has gradually changed over the time. Till now only systemic

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corticosteroids (CS) and immunosuppressants had been the main drugs of choice. Among conventional adjuvant immunosuppressants, both EADV and BAD guidelines have suggested that azathioprine (AZA) and mycophenolate mofetil (MMF) are first line steroid-sparing agents. A recent study by Joly et al now supports using Rituximab (RTX) as a first line adjuvant therapy for pemphigus, as it has shown an increased fficacy compared to CS alone and also has reduced incidence of CS-related serious adverse events and overall mortality.

Corticosteroids and Immunosuppressants

Corticosteroids: Prednisolone is recommended as a first-line therapy in combination with an immunosuppressive agent, such as azathioprine (AZA) and mycophenolate mofetil (MMF), or RTX. In addition, prednisolone alone at a dose of 1–1.5 mg/kg/day is still recommended as first line therapy in patients who are not eligible for treatment with RTX or other immunosuppressive adjuvants. Various adverse effects are seen in patients undergoing long-time CS therapy, including increased overall reaction to infections and infestations, secondary adrenal insufficiency, osteoporosis, transient hyperglycaemia, hypertension, and posterior subcapsular cataract along with cutaneous effects like purpura, telangiectasias, atrophy, striae rubrae, acneiform or rosacea-like eruptions, infections, stern obesity and facial oedema.

Immunosuppressive Adjuvants

Azathioprine: AZA is considered as a safe CS-sparing agent, recommended as a first-line adjuvant immunosuppressant. A dose of 50 mg AZA per day is recommended as initial therapy; the dose can be increased to the optimal dose based on TPMT activity. Adverse effects are seen in 15–30% of patients. Severe adverse effects include myelosuppression, pancytopenia, and hepatotoxicity. Other adverse effects include nausea, pancreatitis, diarrhea, aphthous stomatitis, maculopapular rashes, and anaphylaxis

Mycophenolate mofetil: MMF is a prodrug that converts to mycophenolic acid (MPA) upon oral administration MMF is also recommended as a first-line adjuvant immunosuppressant. The recommended dose of 2 g/day divided in two doses. In patients with a reduced renal function a reduced dosage should be given. Severe adverse effects have been rarely reported. Mild symptoms like nausea, vomiting, and diarrhea are commonly seen.

Cyclophosphamide: CYP is an alkylating prodrug with antineoplastic and immunosuppressive properties. It is converted in the liver into two active metabolites, phosphoramide mustard and aldophosphamide, which deregulate DNA replication and induce cell death. The recommended oral dose is 2 mg/kg/day. Because of its rather unfavorable safety profile, CYP is not recommended as a first-line CS-sparing agent but rather as a rescue drug as it has various adverse effects like nausea, vomiting, diarrhea, hyperpigmentation of the skin/nails, and alopecia. Leukopenia, anemia, and thrombocytopenia may also occur.

Dapsone: Dapsone can be used alone or in combination with topical clobetasol as first-line therapy in mild PF.

Methotrexate: Methotrexate (MTX) (10–20 mg/week) is also considered a third-line CS-sparing drug in PV.

Cyclosporine: very less data is found regarding the adjuvant use of cyclosporine in PV. Chrysomallis et al had reported an inconclusive effect of adjuvant cyclosporine and a higher incidence of toxicities in combination treatment with prednisolone.

Rituximab

Rituximab is a type of monoclonal anti-CD20 antibody which targets $CD20^{+}$ B cells. Rituximab therapy when given in an early stage in the disease results in better clinical response. Relapse rates after rituximab therapy range vary between 40% and 81%and generally increase with the length of the follow-up. During long-term follow-up of the disease, 35–45% of patients with pemphigus who are treated with rituximab remain in complete clinical disease remission when systemic therapy is done. There is a lot of controversy about the maximum RTX dose in pemphigus. Two main protocols are used: the rheumatoid arthritis protocol, which consists of two 1,000 mg infusions 2 weeks apart, and the lymphoma protocol, which consists of four 500 mg infusions once a week. On the other hand, high dose regimens should be preferred instead of low-dose regimens, due to longer disease response.

Maintenance Therapy with Rituximab in Pemphigus

Relapse can be seen in about 40–80% of the patients, within a mean time ranging from 6 to 24 months. Other cycles of RTX were shown to be effective in relapsed patients, suggesting that patients may benefit from maintenance with RTX, but the exact timing of RTX re-treatment to prevent

relapse is uncertain. Relapse following RTX can be due to persistence of autoreactive B-cells, because of incomplete B-cell depletion, or re-appearance of Dsg-specific B-cell clones during B-cell repopulation. Thus, its important to monitor the activation of B-cell which appears to be a suitable tool to predict the risk of relapse following RTX.

Intravenous Immunoglobulin

IVIg consist of human plasma-derived IgG, sugars, salts and solvents. It is derived from large plasma pools. These have the tendency to cause various anti-inflammatory effects, including Fc receptor blockade, stimulation of antibodies production against different subclasses of T lymphocytes, inhibition of different T-cell functions, complement hindrance via inactivating C3 precursors, dendritic cell downregulation, B-lymphocyte apoptosis, inhibition of phagocytosis, and increment of response to steroids. However, the main mode of action is an increased catabolism of immunoglobulins via binding to the neonatal Fc receptor (FcRn) .

Immunoadsorption

IA is considered to be an ideal treatment for pemphigus patients with severe and extensive disease at baseline. Combining IA with immunosuppressive therapies results in faster clinical responses as compared to the immunosuppressive therapy alone, since IA allows immediate removal of pathogenic antibodies, whose serum concentration reflects both disease activity and severity. Current guidelines suggest IA as a first-line treatment in pemphigus patients, in whom lesions cover (1) > 30% of the body surface or (2) > 25% of oral or genital mucous membranes or involve (3) the conjunctiva or (4) the esophagus and can also be recommended in refractory patients with more than 3 months of active disease despite at least two immunosuppressive therapies.

II. CONCLUSION:

No doubt these are considered as rare diseases, but the incidence of autoimmune bullous dermatoses is continously increasing and are being associated with a high degree of fatality and occasional mortality. These cutaneous damages which include blister formation, pain, itch, and associated functional limitations have a psychological as well as emotional impact on patients and can severely affect the patient's quality of life. Pemphigus is a life-threatening disorder and early detection is very important to achieve the favorable prognosis. Systemic corticosteroids are considered as the first-line of treatment, even though their optimal dosing regimen remains unknown. Various recent advancements with these corticosteroids have ben achieved along with many therapeutic alternatives, but treatment needs to be specific to each patient depending upon its need and efficiency. However, we can hope that the future can be more specific to antigen-specific immune suppression because continous efforts are being made by researchers to develop novel targeted therapies for the treatment of PV.

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