

PEMPHIGUS VULGARIS – PATHOPHYSIOLOGY AND RECENT CONCEPTS FOR PULSE THERAPY - A SYSTEMATIC REVIEW.

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Abstract

Background: Vesiculo-bullous diseases are a group of chronic cutaneous disorders characterised by mucocutaneous blistering or erosions as a result of development of autoimmunity.

Aims: To understand the pathophysiology of pemphigus vulgaris and the recent concepts of Pulse therapy with different modalities and their various actions on different tissue levels. **Results & Conclusion-** Pulse therapy can be a boon to stomatologists if understood with clarity and applied with precision. It can definitely create miracles in saving lives and help in the outcome of the prognosis of most of the autoimmune disorders.

Keywords: Autoimmune Disorders, Pemphigus Vulgaris, Pulse Therapy.

INTRODUCTION

Autoimmune bullous diseases are a group of cutaneous disorders characterised by skin blistering or erosions as a result of development of autoimmunity. It can be classified according to the anatomical sites of blister into two types: intraepithelial and subepidermal. The term "pemphigus" refers to intraepithelial blistering skin disease. The term "pemphigoid" refers to blistering diseases occurring at the dermo-epidermal junction in general, although not every subepidermal bullous disease bears the term "pemphigoid" in the nomenclature¹. This article emphasizes on the most common intraepithelial bullous lesion, its pathophysiology and recent concepts with a clarity to the practicing stomatologists on administration of

pulse therapy with their controversies, precautions, modifications, outcome and toxicity.

PEMPHIGUS

The term pemphigus derives from the Greek (pemphix) which means *bubble or blister*. Pemphigus describes a group of chronic autoimmune bullous diseases, originally named by *Wichman* in 1791. This represents a group of potentially life threatening autoimmune mucocutaneous diseases characterized by epithelial blistering affecting cutaneous and or mucosal surfaces. The main damage resides into desmosomes due to antibodies directed against the extracellular domains of the cadherin type epithelial cell adhesion molecules: the desmogleins with intraepithelially immune deposits, and loss of cellular contact².

There are various types of pemphigus namely pemphigus vulgaris, pemphigus foliaceus, pemphigus erythematosus, drug induced pemphigus, pemphigus vegetans, IgA pemphigus, paraneoplastic pemphigus³.

PEMPHIGUS VULGARIS

Pemphigus vulgaris (PV) is the most common chronic autoimmune blistering disease of skin and mucous membranes, most cases occur in adults but cases in children though rare has been reported by Baratta et al⁴ characterized by intraepithelial blister formation that results from break down of cellular adhesion between epithelial cells. In 1964 autoantibodies against keratinocyte surfaces were described in patients with pemphigus. Clinical and experimental observations indicate the circulating autoantibodies are pathogenic. Blisters in PV are associated with binding of IgG autoantibodies to keratinocyte cell surface molecules. These intercellular or PV antibodies bind to keratinocyte desmosome free areas of keratinocyte cell membrane. PV is rare, with a reported incidence of 0.1-0.5 cases per 100000 individual's world wide. It is mostly seen in women and primarily manifest in adults during the 5th and 6th decade of life⁵.

PATHOPHYSIOLOGY

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.

In 1964, autoantibodies against keratinocyte surfaces were described in patients with pemphigus. Clinical and experimental observations indicate that the circulating autoantibodies are pathogenic. An immunogenetic predisposition was well established⁶.

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 cells⁶.

ANTIBODIES

Patients with the mucocutaneous form of pemphigus vulgaris have pathogenic anti-desmoglein 1 and anti-desmoglein3 autoantibodies. Patients with the mucosal form of pemphigus vulgaris have only anti desmoglein3 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. Disease activity correlates with antibody titers in most patients. 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 autoantibodies. Lack of in vivo antibody binding (reversion to a negative result on direct immunofluorescence) is the best indicator of remission and can help predict a lack of flaring when therapy is tapered⁶.

TREATMENT CONCEPTS

There are several recommended and accepted modalities are available for the treatment of Pemphigus with variable outcomes. The treatment of pemphigus associated with or without dermatological involvement has been a real challenge for practicing stomatologists as well as for the dermatologists. Even till date, the disease when appeared in the oral cavity, are managed with topical or systemic corticosteroids (prednisolone or methylprednisolone) of different duration and doses which results severe side effects and great dissatisfaction at the both end.

Though pulse therapy for the treatment of pemphigus of dermatological along with mucosal involvement has been in vogue by the several dermatologists⁴ across the world since few decades, but the practice has not been popular among oral clinicians. Even though there are enough evidences for the efficacy and outcome of the pulse therapy, but there continue to be doubts and queries behind the rationale of use of high doses of intravenous steroids and immunosuppressants in isolated refractory mucosal involvement of different degree.

Pulse therapy has been defined as intermittent/discontinuous infusion of very high doses of corticosteroids along with other

immunosuppressants, like Cyclophosphamide, Azathiopine or Methotrexate either in bolus form or orally over a short period of time to achieve maximum benefits of steroid with minimum side effects^{6,7}. This modality not only enable us to reach the goal very fast but also will decrease the need of long duration of systemic steroid dependency. Though *Pulse* was first introduced by Pasricha and Ramji in 1984 but the first successful reported Pulse was in 1973 by Kouwz and Cohn, in a renal graft case for the prevention of rejection.

Drugs commonly and broadly used for the Pulse therapy are⁷-

- (a) Corticosteroids
- (b) Immunosuppressive

Different combinations of Pulse,-

The existing modifications are as follows and are indicated with their specific indications with all expected result and side effects^{7,8}.

(a) Dexamethasone and Cyclophosphamide Pulse

On first day, 100-200 mg of Dexamethasone (4-6 mg/kg body weight) is mixed with 500 ml of 5% Dextrose solution and is infused for 2 hours.

On the second day, 100-200 mg of Dexamethasone and 500 mg of Cyclophosphamide is mixed with 5 % Dextrose solution and is infused for 2 hours.

On the third day, only 100 mg of Dexamthasone is mixed with 5 % Dextrose and infused for 2 hours.

The same cycle is being repeated on every 28 days for a period of 9 months and in between the two Pulsed day 50 mg of Cyclophosphamide once a day is prescribed orally.

(b) Methylprednisolone and cyclophosphamide Pulse

This is also another variant of Pulse where instead of Dexamethasone, the recommended combination is Methylprednisolone 500-1000mg (20-30 mg /kg body weight) along with cyclophosphamide or Azathiopine or Methotrexate(7.5 mg)

Azathiopine (DAP) and Methotrexate (DMP) are not infused, rather they are reserved for oral route. Rituximab, the recently introduced well known immunosuppressive, though basically reserved for rheumatoid arthritis cases can also be successfully be used for skin pemphigus, as per lymphoma protocol. DMP is not generally practiced routinely; it is reserved for those cases, where patients are not responding with DCP/DAP, even after 12 Pulsed therapy in phase 1.

Effect of glucocorticoids

Glucocorticoids (GC) are broadly used to achieve immunosuppressive and anti-inflammatory effect^{7,8}. Various studies have shown the genomic and nongenomic effects of steroids on the cells depending upon the available concentrations of the drug in plasma,-

Effects of low plasma concentration of steroids-steroids forms a complex with cytosolic GC receptors (GCR) to activate the MAPK signaling pathway⁸. As a result of activated GCR complex moves into the nucleus which stimulate the GC-responsive element to bring about the much needed anti-inflammatory and immunosuppressive effects.

Effect of high plasma concentrations of steroids- GC in high concentrations intercalates with the cell membrane to form GCR which brings about the apoptosis and inductions of lipomodulin, thus the immunosuppression is achieved⁸.

COMPLICATIONS OF PULSE THERAPY

Inspite of so many advantages over the conventional therapy⁹, Pulse are not routinely practiced in mild form of oral mucosal pemphigus cases where patient may or may not be presented with skin lesions, because of it reserved toxicity.

(a) Some immediate side effects are penned down as follows⁹,- mood alteration, hyperactivity, psychosis, disorientation, sleep disturbances, which are found nearly 10% of all the cases.

Patient become more susceptible to secondary infections and turned out with hyperglycemia and hypokalemia.

Hiccups, fascial flushings, diarrhoea, weakness, generalized swelling, arthro-mayalgia and shock also noted in cases.

(c) Some late side effects are also noted like; shift or suppression of hypothalamus pituitary adrenal (HPA)

(d) Axis, avascular necrosis, osteoporosis of long bones specially the weight bearing one, cataracts, coronary artery diseases, strokes, hypertension, peptic ulcer diseases, hemorrhagic cystitis, diffuse hyper-pigmentations, obesity and squamous cell carcinoma of urinary bladder, alopecia,, blurring of vision, menstrual disorders, amenorrhoea, azospermia and dysphagia etc.

To avoid these complications a numbers of modification have been proposed by different

researchers in their studies for the treatment of pemphigus with pulse like^{7,8,9}.

(a) Antibiotics and antifungals are advised to control superadded infections

(b) Thorough cleaning and scrubbing of skin and scalp and maintenance of very good oral hygiene

(c) Intermittent Pulse can be administered at shorter intervals if disease is severe.

(d) Rather a total duration of pulse for 18 month in phase 2 & 3, the duration may be reduced based on clinical severity, IF/DIF study, and on response to ongoing therapy

(e) Additional daily oral steroids with progressive tapering doses may be added in cases of severe ulcerations in phase one therapy till the lesion shows features of healing, before stepping into phase 2 therapy

(f) Cyclophosphamide-induced haemorrhagic cystitis can be very well prevented by infusion of 500ml 5% Dextrose and frequent emptying the bladder during the infusion of the drug. The toxicity can also be well controlled by IV infusion of mesna during the therapy with cyclophosphamide in 5 divided doses

(g) Steroid induced severe osteoporosis can be prevented by intake of calcium supplement, vitamin D, and bisphosphonate.

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