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Invited Article

PEMPHIGUS VULGARIS – A SHORT REVEIW

Subash Vijayakumar*[1], Alkehya P[1], M. Sasikala[1], Ramchandra Dharak[2]

[1]Department of Pharmacy Practice, Vaagdevi College of Pharmacy, MGM Hospital, Warangal, A.P, India
[2]Professor & Head, Department of Dermatology, MGM Hosptial, Warangal, India.

ABSTRACT

Pemphigus is an autoimmune blistering disease of skin & mucosa characterized by circulating antibodies directed to the keratinocytes cell surface. The aim of this study was to review the pathophysiology, classification, diagnosis & treatment of the disease. We develop a search strategy to find any publication about PV & its management. So we search Science Directory, Google Search, Dove press & Pubmed bibliography database using the key phrase causes of pemphigus, diagnosis, clinical features & its treatment. Our review enlighted the treatment allow a better prognosis with lower mortality rates. This review resulted, on the basis of relevant literature its suggested that future strategies have to be developed for innovation of newer molecules for treating pemphigus & minimizing the complications associated with PV. This review may provide clear information to health care providers to pay more attention to alternative drug therapy.

Keywords: Pemphigus, Drug, Mortality and Morbidity.

INTRODUCTION

Pemphigus refers to a group of autoimmune blistering skin diseases termed pemphigus vulgaris (PV) and pemphigus foliaceus (PF) . Both are characterized by the presence of autoantibodies against keratinocyte adhesion molecules leading to the loss of cell–cell adhesion with consequent acantholysis and formation of blisters. Pemphigus vulgaris is characterized by the presence of autoantibodies directed against desmoglein3 (dsg3), whereas in pemphigus foliaceus an autoantibody to desmoglein1 (dsg1) is present. However, autoantibodies to additional keratinocyte antigens were also described . In most patients the etiology of the disease is unknown but diet or specific drugs have been implicated as causative or triggering agents. [1]

EPIDEMIOLOGY

Pemphigus is an uncommon disease with an incidence rate ranging 0.5–3.2/100,000/year. Although PV is usually considered a disease of adults, it has been reported in neonates and infants. Genetic predisposition linked to human leukocyte antigen (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 at an increased risk. [2] The mean age of the disease onset is 40–60 years. [3]. Most cases of pemphigus vulgaris associated with anthrax vaccine administration have not been reported. Considering the recent deliberate outbreaks of anthrax and continued threats of bioterrorism, the potential exists for widespread administration of the anthraxvaccine. Erythematous area involving the head and all over body shown in fig 1.

BIOLOGY OF PEMPHIGUS

Pemphigus are characterized by the production of autoantibodies directed against desmogleins (Dsg), Dsg3 in PV and Dsg1 in PF, that are keratinocyte transmembrane proteins localized in the desmosome and members of Ca-dependent adhesion molecules, the cadherins . The pathogenic property of antidesmoglein autoantibodies can be directly demonstrated by passive transfer experiments: immunoglobulins G (IgG) purified from patient sera during the active phase of the disease induce keratinocyte-cell membrane Ig deposit and blister formation when injected intraperitoneally into normal

Corresponding Author: **Subash Vijaya Kumar** Email: vijayvijay66@yahoo.co.in

mice; newborns to mothers with PV may develop a transient form of the disease due to the maternal IgG autoantibodies that cross the placenta. The interaction of anti-Dsg antibodies (Ab) with their target antigens (Ag) is responsible for the loss of cell adhesion (acantholysis) and the formation of intra-epithelial blisters of the skin and mucous membranes. Immunochemical analysis of autoantibodies directed against desmogleins indicates that they predominantly but not exclusively bind to the extracellular domains of the proteins and exert their pathogenic effect through the inhibition of their adhesive properties. Anti-Dsg antibodies belong to IgG1 k, l and IgG4 k, l subclasses. Interestingly, IgG4 are produced during active phase of the disease, are absent in patients in remission, and are considered to display most of pathogenic properties. In contrast, no data are available about the structural characteristics of anti-Dsg Ab. The difficulty to derive pathogenic anti-Dsg Ab producing hybridomas or EBV-cell lines from peripheral blood lymphocytes (PBL) of pemphigus patients, likely due to technical limitation and/or the small number of specific B-cell precursors in PBL, did not allow to study anti-Dsg1 or Dsg3 autoantibodies at the clonal level and, in particular, to analyze the repertoire of VH and VL genes they utilize. Therefore, it is still questionable whether anti-Dsg Ab use recurrent VH and VL gene segments are encoded by germline or somatically- mutated genes, all questions that are directly relevant to the mechanisms of autoantibody production and B-cell activation. Results from such analysis might also incite to study the contribution of Ig polymorphism, in particular of IgG heavy chain (IGHV) and light chain variable (IGLV) loci, to disease susceptibility if, for example, VH and/or VL genes of a given family or a particular V gene were shown to be used recurrently to construct an anti-Dsg Ab response. T-cells intervene in the generation of the lesional mechanisms indirectly. Indeed, the production of IgG4 autoantibodies during active phase of pemphigus suggests the participation of mechanisms operating at not only the B- (switch of Ig classes and subclasses) but also the T-cell level such as the production of interleukins 4 (IL-4) and 13 (IL-13) which promote and are secreted by Th2-type T-cells. In addition, as in all organ-specific autoimmune diseases, the tolerance breakage to target autoantigens are thought, although not exclusively, to take place at the T-cell level, i.e., at the immunological synapse involving human leucocyte antigens (HLA) class II molecules, the initiating autoantigenic peptide(s) and T-cell receptors (TCR). Characterization of autoreactive T-cells and, more particularly, dissection of T-cell epitopes of Dsg3 and Dsg1 are underway in several laboratories [10e17] as well as the identification of HLA class II alleles that restrict Dsg-specific T-cell responses. Recent studies have identified immunodominant T-cell epitopes and started characterizing the repertoire of Dsg3- or Dsg1- specific T-cells at the clonal level. Therefore, the genes coding for the 3 major molecules of the immunological synapse i.e., TCR, major histocompatibility complex (MHC) and autoantigen should also be considered as candidate genes conferring susceptibility [4]. whereas classification of pemphigus of schematic diagram

PARANEOPLASTIC PEMPHIGUS

Paraneoplastic pemphigus is not a new disease. Cases have been reported with a diagnosis of lichen planus, erythema multiforme, or pemphigus vulgaris with atypical characteristics in association with a neoplastic process (frequently lymphoid). These were deemed to be paraneoplastic processes [4-6]. While most have not been documented, in some cases it has been possible to demonstrate retrospectively that they were paraneoplastic pemphigus. Approximately 80% of cases are associated with non- Hodgkin's lymphoma, chronic lymphocytic leukemia, and Castleman's tumor. An association with sarcomas, thymomas, and Waldenström's disease occurs less often, and only in exceptional cases is it found in conjunction with more common tumors, such as lung or breast cancer [8-10]. It is rare in childhood, when it is always associated with Castleman's disease. Anhalt et al defined criteria for the diagnosis of paraneoplastic pemphigus:

1. Clinical: The constant presence of painful mucosal erosions unresponsive to conventional treatments. When the skin is affected, this can take diverse forms. The existence of an occult or confirmed neoplasm.

2. Histology: Intraepithelial acantholysis (less obvious than in the classical forms of pemphigus), isolated keratinocyte necrosis, and basal vacuolization.

3. DIF of the perilesional tissue: Presence of IgG deposits in the intercellular spaces similar to those observed in pemphigus, although weaker and more focal. The combination of C3 in the basement membrane and intercellular IgG is quite characteristic.

4. IIF: Antibodies that bind to the intercellular spaces not only when stratified monkey esophagus epithelium or human skin is used as a substrate, which occurs with pemphigus, but also when other epithelial tissues and nonepithelial tissues are used, such as skeletal muscle and myocardial plaque. The most intense and characteristic IIF reactions are observed with the transitional epithelium of the urinary tract.

5. Immunoprecipitation: when extracts of human keratinocytes are used, the serum of these patients immunoprecipitates a complex of 4 polypeptides with molecular weights of 250, 230, 210, and 190 kd. They are all plakins, a group of proteins found in the intracellular

plaque of desmosomes and hemidesmosomes. Occasionally, an additional immunoprecipitation band of 170 kd has been identified.

PREDISPOSING FACTORS [13-17]

Most cases of pemphigus are idiopathic, but are triggered by:

1. Drugs
• Captopril
• Penicillamine (immunogenicity is caused by sulfahydryl groups, which resembles molecular structure of DSG 3; cross-reactivity)
• Rifampicin
• Phenyl butazone
2. Radiation
3. Surgery
4. Diet, particularly garlic
5. Emotional stress
6. Viruses—Human Herpes Virus 8 (HHV 8)
7. Emotional stress
8. Pesticide exposure
9. Pregnant females

DIAGNOSIS

Clinical Examination

In patients with PV and active blistering, firm sliding pressure with a finger separates normal-looking epithelium (Nikolsky's sign), but this is neither completely sensitive nor specific.

Biopsy

This is best done on intact vesicle or bullae <24 hour old. Specimens are taken from the advancing edge of the lesion where the areas of characteristic suprabasilar acantholysis are seen. In PV, intercellular oedema develops in epithelial cells, dissolution of intercellular bridges occurs, and the widening of intercellular spaces occurs, which causes separation between the cells and formation of blister above the basal cell layer (suprabasilar split).[18] The present case showed typical histological features of intra-epithelial blistering disorder with supra-epithelial split and acantholytic cells.

Tzanzk Smear

The base of blister is scrapped and examined for acantholytic cells. The free-floating, rounded or ovoid acantholytic cells have an enlarged, hyperchromatic, centrally or eccentrically situated nucleus. Basal cells are tightly attached to basal lamina, but their attachment to one another is lost, producing a tomb-stone appearance.[19] Relatively fewer inflammatory cells are seen in PV compared with other bullous diseases.

Compressed-air Test

Application of a stream of compressed air to the oral mucus membrane of gingival tissues may cause a shimmering of the outer tissues followed by the formation of a bleb or a blister.

Immunofluoresence Studies

The clinical diagnosis is always confirmed by direct and indirect immunofl uorescence. [20]

Direct Immunofluoresence: Florescence-labeled antihuman immunoglobulins are placed over the patient's tissue specimen. Circulating antibodies of IgG type bound to the intercellular cement region of the oral mucosa can be detected. In case of PV, the technique will detect antibodies, usually IgG and compliment bound to the surface of keratinocytes. Indirect Immunofluoresence: Serum from a patient is placed over a prepared slide of an epidermal structure (usually monkey esophagus). The slide is then overlaid with fluorescein- tagged antihuman γ-globulin. Patients with PV have antikeratinocyte antibodies against intercellular substance that show up under a fluorescent microscope. The titer of antibody has been directly related to the level of clinical disease. The test distinguishes pemphigus from pemphigoid and other chronic oral lesions.[14]

Upper Gastrointestinal Endoscopy

It may be useful in identifying esophageal involvement [21]

Enzyme-linked Immunosorbent Assay (ELISA)

It can detect DSG 1 and DSG 3 in serum samples [18]

Immunoprecipitation and Immunoelectron Microscopy

The targeted antigen recognized by autoantibodies is a 130-KDa glycoprotein identical to DSG.

IMMUNOADSORPTION

In several autoimmune disorders, the therapeutic removal of immunoglobulins (Ig) from plasma by Immunoadsorption (IA), has been shown to be a useful alternative treatment [5]. While plasmapheresis nonspecifically removes plasma proteins, IA represents a more specific approach by selectively eliminating Ig and circulating immune complexes (CIC) [6]. IA has been successfully used in autoantibody mediated autoimmune disorders with elevated autoantibody titres, such as systemic lupus erythematosus (SLE), myasthenia gravis (MG), Guillian-Barre-syndrome (GBS), dermato myositis and autoimmune bullous disorders [7]. Nowadays many different IA columns are utilized to reduce the antibody levels in pemphigus patients. IA columns approved by the FDA include the protein A silica column (Prosorba, Fresenius Medical Care, Redmont, CA, USA) and the protein A sepharose column (Immunosorba, Fresenius Medical Care, St Wendel, Saarland, Germany). Other plasmaperfusion columns used in the treatment of pemphigus consist of crosslinked polyvinyl alcohol gel beads such as tryptophan as ligands (Immusorba TR 350®, Asahi Medical, Tokyo, Japan). The Therasorb® adsorber systen is based on coupling polyclonal sheep antibodies to a

sepharose matrix which selectively bind to plasma components as human Ig (Ig-Therasorb®, Miltenyi Biotech, Bergisch Gladbach, Germany). More recently developed adsorber systems contain synthetic peptides covalently bound to a sepharose matrix as which selectively bind to plasma components as human Ig (Ig-Therasorb®, Miltenyi Biotech, Bergisch Gladbach, Germany). More recently developed adsorber systems contain synthetic peptides covalently bound to a sepharose matrix as ligands for human Ig (Globaffin®, Fresenius Medical Care).

However, biochemical studies focused on DSG3 turn-over in normal and pathologic conditions are still lacking. To date, it is not yet clear whether PV IgG are able to bind desmosome-assembled Dsg3 or block its extracellular domain before Dsg3 engages contacts with apposed cells and, however, it remains to address whether these interactions can cause desmosome splitting or prevent formation of new desmosomes, respectively. With regard to this, it is worth of note that detachment of keratinocytes from each other seems to occur first in the interdesmosomal areas, while desmosomes appear to separate only in the late acantholysis .Cell–cell dissociation by calcium depletion has been demonstrated in several cell types, including primary keratinocytes and various cell lines derived from stratified epithelia, such as HaCaT . In low calcium conditions, desmosomes are unstable and desmogleins rapidly become internalized after reaching the surface with subsequent accumulation of cytoplasmic vesicles. Similar structures are endocytotically formed after the disruption of desmosomes by proteases (Lanza and Cirillo, unpublished data; and PV IgG , suggesting that DSG 3 cross-linking could become unstable after binding to PV autoantibodies Serum from pemphigus vulgaris reduces desmoglein 3 half-life and perturbs its de novo assembly to desmosomal sites in cultured keratinocytes [23].

TREATMENT

Treatment of pemphigus based on modulation of cell adhesion Patients with pemphigus respond rapidly to corticosteroid treatment. Several lines of evidence suggest that the therapeutic effects of corticosteroids are not due to direct immunosuppression alone, since clinical improvement often occurs within 48 hours of dosing despite no change in titers of anti-desmoglein antibodies, and synthetic corticosteroids have been shown to directly inhibit pemphigus- sera-induced acantholysis in organ culture models . Methylprednisolone has recently been shown to abrogate phosphorylation of DSG3 in response to PV IgG, with an associated increase in cell-surface staining of Ecadherin, Dsg1 and Dsg3 on keratinocytes , suggesting a direct role for corticosteroids in modulating epidermal adhesion. Future studies dissecting the immunosuppressive and anti-acantholytic roles of corticosteroids may lead to the development of novel nonsteroidal therapeutic agents. Agonists of acetylcholine receptors have been suggested to be such agents, although this is highly speculative. Smoking has been observed to improve PV, possibly through nicotine. Furthermore, acetylcholinesterase inhibitors have been associated with some decrease in blistering in PV in mice and one patient . These clinical findings lend support to recent experiments showing that nicotinic and muscarinic forms of the acetylcholine receptor can modulate cell adhesion in cultured keratinocytes, perhaps via increased cadherin and catenin expression and signalling [22].

Figure 1. Erythematous area involving all over body

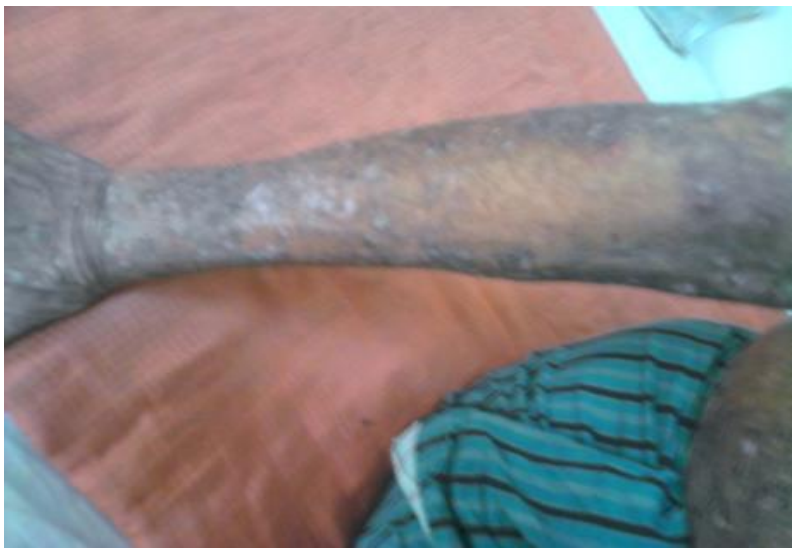


Figure 2. Pemphigus vulgaris is an autoimmune disorder in which there is deposition of mainly IgG-class antibodies intracellularly, as well as damage to desmosomes by antibodies directed against the extracellular domains of cadherin-type epithelial cell adhesion molecules, particularly DSG 3. Since oral epithelium largely expresses DSG 3, but skin expresses DSG 1 as well as DSG 3, damage to DSG 3 by antibodies results in oral lesions at an early stage, but skin integrity is maintained by DSG.

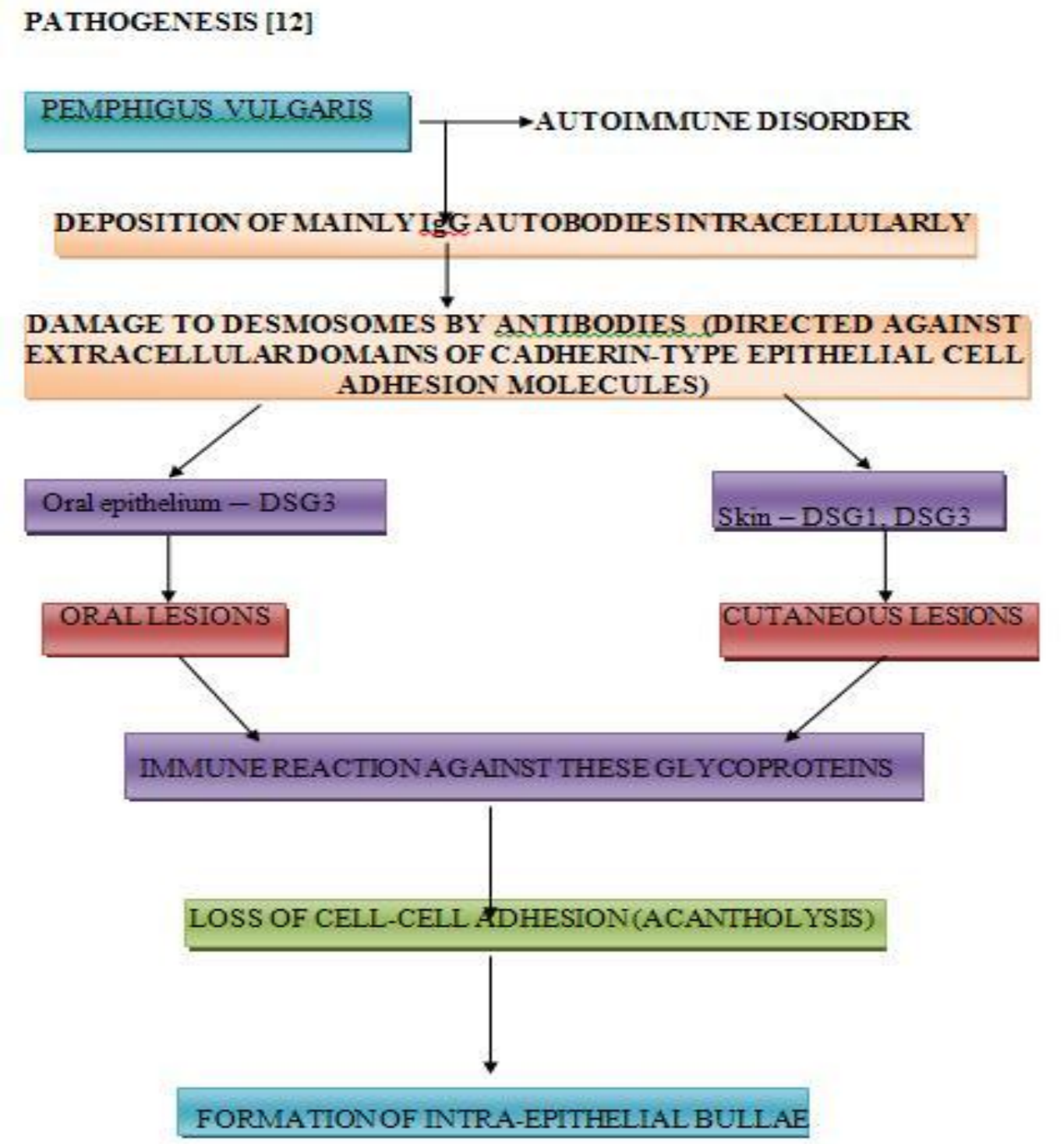


Figure 3. Desquamative erythematous areas involving breast and lumbar region

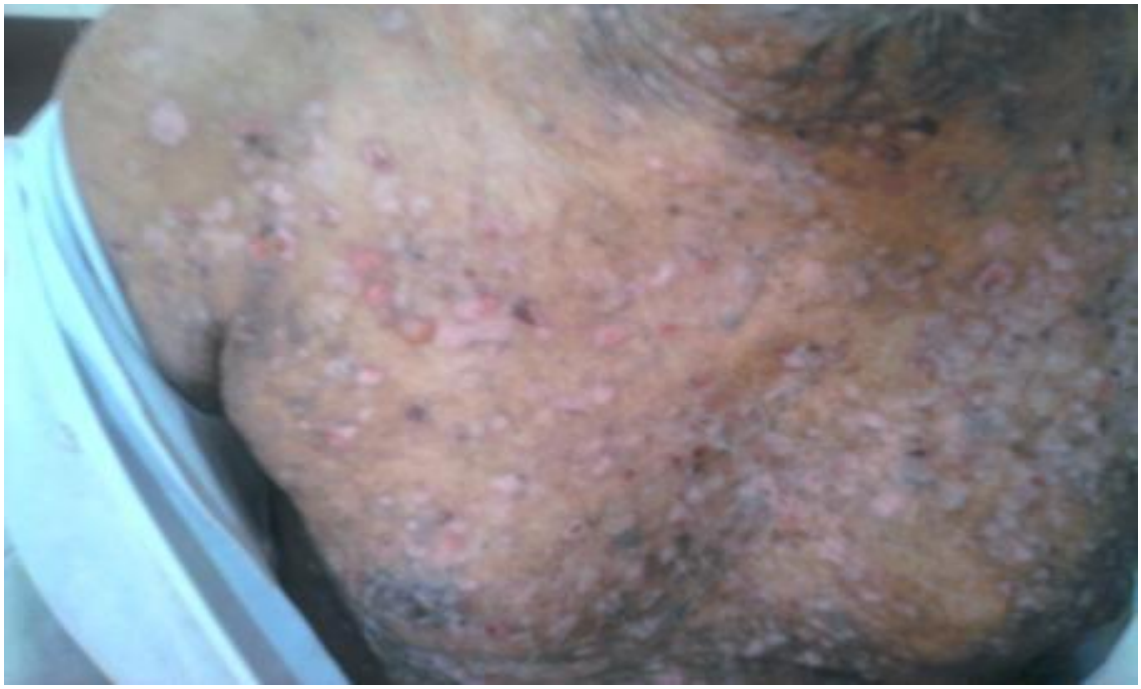
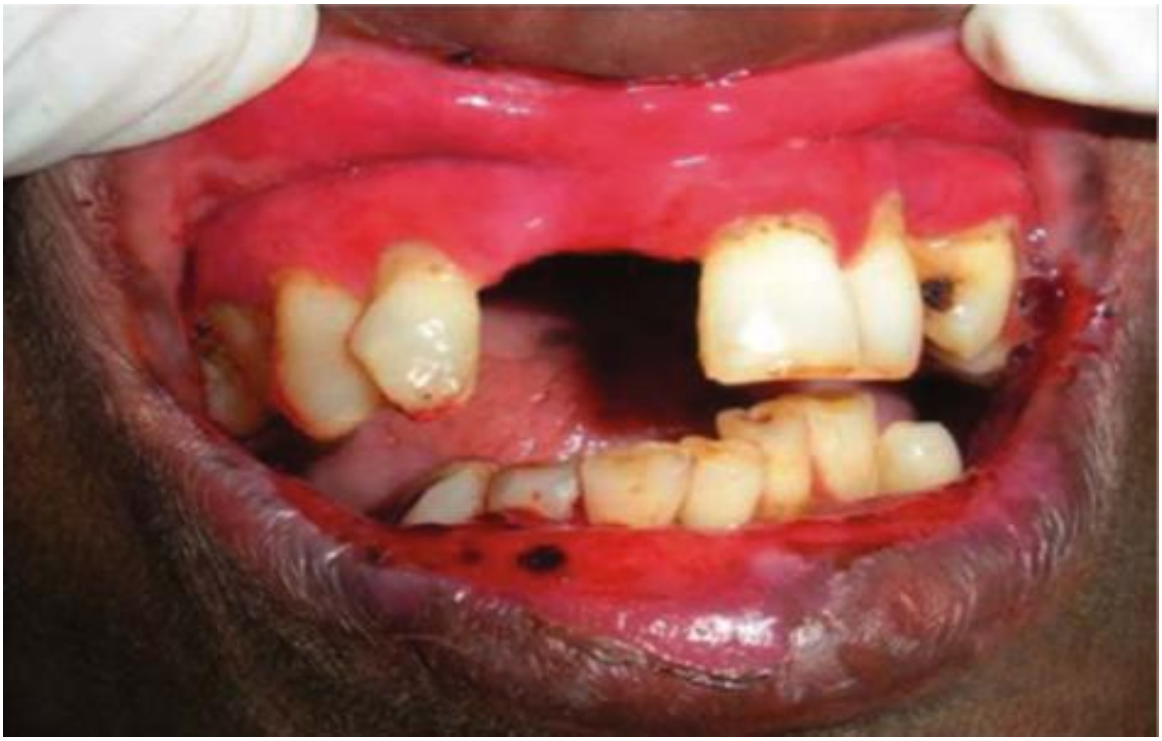
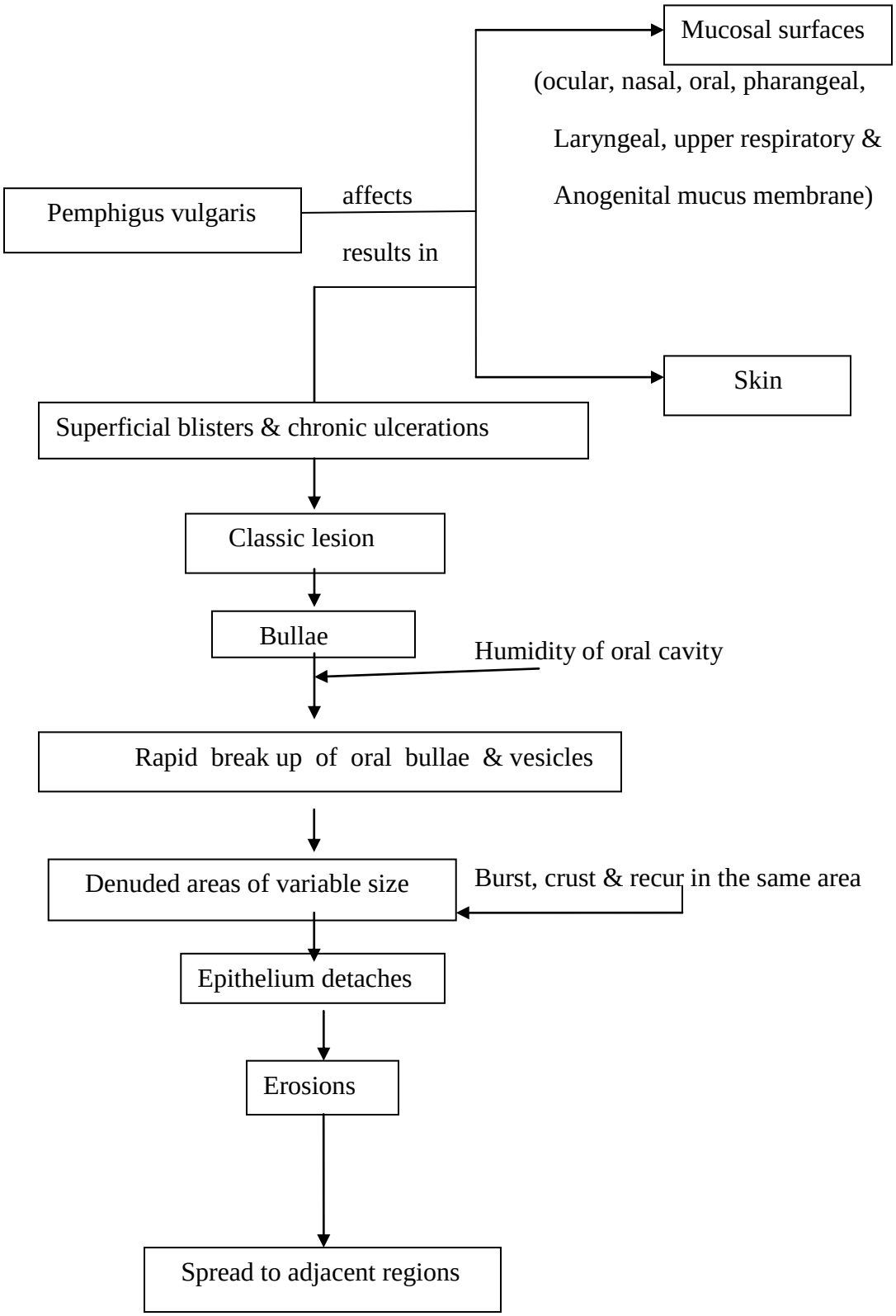


Figure 4. Desquamative erythematous areas involving the marginal and attached gingiva in relation to upper anterior teeth.



CLINICAL FEATURES [11]



CLASSIFICATION OF PEMPHIGUS [5]

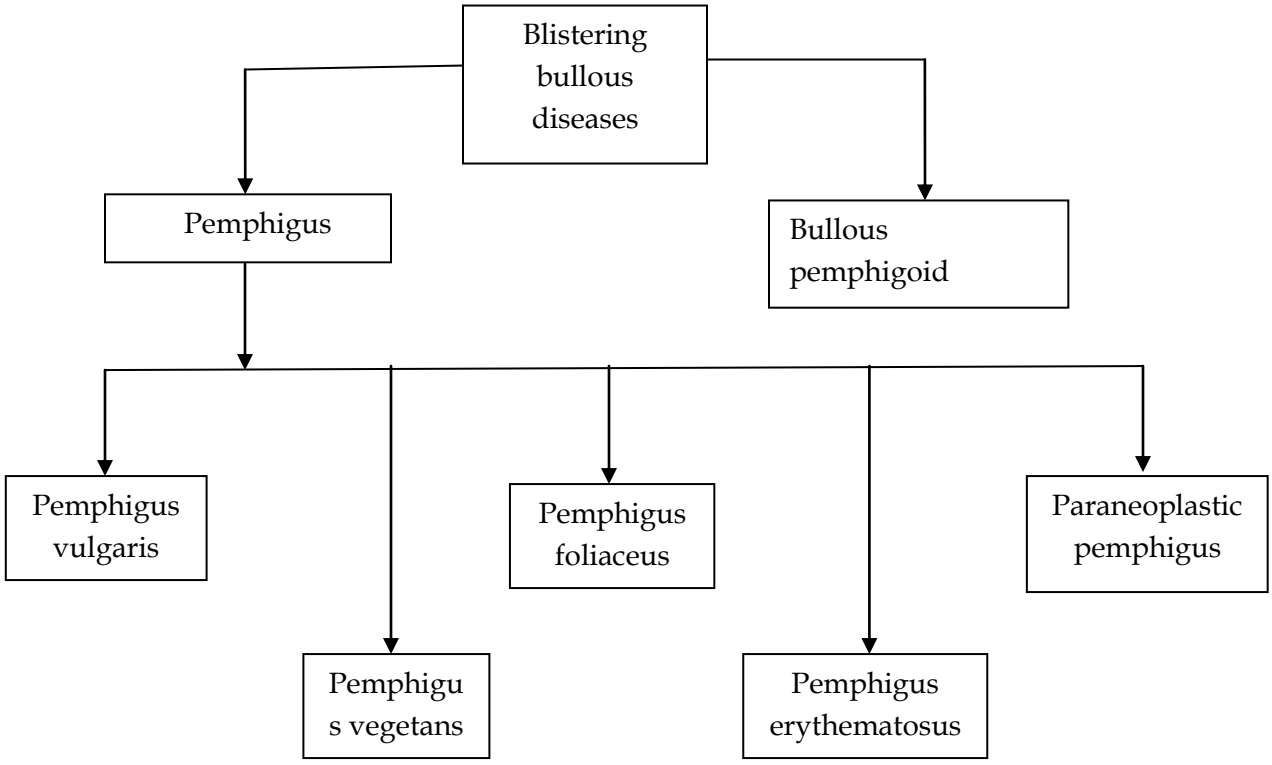


Table 1. Clinical Features and skin biopsy findings in immune-mediated blistering skinconditions [5]

Disease	Age	Site of blisters	Nature of blisters	Mucous membrane	Antigen	Circulating antibody (indirect IF)	Fixed antiboby (direct IF)	Treatment
Pem.vulgaris	40-60	Head, scalp, groin	Flaccid & fragile, many erosions	100%	Desmoglein-3	IgG	IgG, C3, intercelluar	Systemic corticosteroids, cyclophosphamide
Pem.foliaceus	20-60	Scalp, face, chest	Crusted scaly lesions, fluid filled blisters	70%	Desmoglein-1	IgG	IgG, C3, intercelluar	Systemic corticosteroids,
Bullous pemphigoid	60s & over	Trunk (especially flexures) & limbs	Tense	occasionally	BP-220 (part of hemidesmosome)	IgG (70%)	IgG,C3 at BMZ	Systemic corticosteroids, Azathioprine

CONCLUSION

Pemphigus vulgaris although a life threatening disease, today it can be successfully treated with a combination of immunosuppressive agents. The past medical history, severity & course of disease, early diagnosis, possible side effects of the therapy are taken into the considerations for treatment. The treatment allows a better prognosis with lower mortality rates. This review may provide clear information to health care providers to pay more attention to alternative drug therapy. In future, the development of the newer agents is further needed to improve the therapy.

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