ABSTRACT

This review article describes the Pemphigus. Pemphigus is a group of rare autoimmune diseases that cause blistering of the skin and mucous membranes (mouth, nose, throat, eyes, and genitals). Some forms of the disease, including the most common form, may be fatal if left untreated.

KEYWORDS: Pemphigus, Autoimmune disease, Skin lesion.

PEMPHIGUS

Pemphigus comes from the Greek word “pemphix,” meaning “bubble” in reference to the blisters that are characteristic of the disease. Pemphigus describes a group of chronic bullous diseases, originally named by Wichman in 1791. Pemphigus refers to a group of chronic blistering diseases which develop as a consequence of auto-antibodies.
directed against a variety of desmosomal proteins. Pemphigus is a blistering disorder caused by auto-antibodies that result in the dissolution of intracellular attachments within the epidermis and mucosal epithelium. The term pemphigus once included most bullous eruptions of the skin, but diagnostic tests have improved, and bullous diseases have been reclassified. The term pemphigus refers to a group of autoimmune blistering diseases of the skin and mucous membranes. Characterized histologically by intra-epidermal blister and immune-pathologically by the finding of circulating immunoglobulin (IgG) antibody directed against the cell surface of keratinocytes.[6-11]

The primary subsets of pemphigus include.

- Pemphigus vulgaris
- Pemphigus vegetance
- Pemphigus foliaceus
- Fogo selvagem
- Pemphigus herpetiformis
- Paraneoplastic pemphigus
- Ig A pemphigus
- Drug induced pemphigus
- Contact pemphigus

The majority of individuals who develop pemphigus are in fourth to sixth decades of life. The condition as a whole is rare, with an annual incidence ranging from 0.1-0.5/1,00,000. It is commoner in Jewish population The clinical features and, therefore, classification of these disorders depends upon the level of separation within epidermis.[2,4,6]

**Pemphigus vulgaris**[1,2,3,6,8]

Pemphigus vulgaris is by far the most common variant, accounting for 80% of cases. In addition to affecting humans, pemphigus has been described in a variety of animals including dogs, cats, goats and horses. Involves the mucosa and skin, especially on the scalp, face, axilla, groin, trunk, and points of pressure. It may present as oral ulcers that may persist for months before skin involvement. Self-limiting neonatal disease through trans-placental transfer of maternal auto-antibodies has also rarely been documented. Pemphigus vulgaris is a B cell-mediated diseases in which auto-antibodies
develop to antigens within the desmosome-tonofilament junction of the intracellular bridges. Such auto-antibodies fix complement and initiate inflammation, which causes a supra-basilar split (intraepithelial blister) as the primary pathogenesis. Pemphigus vulgaris usually presents with painful skin and/or oral ulcers. The lesions actually begin as short-lived vesicles that rupture because of their supra-basilar position. Many patients will develop oral pemphigus lesions and no skin lesions. Such “oral-pemphigus” represents a distinctive clinical form of pemphigus vulgaris. In this form, blacks are affected more frequently.

**CLINICAL FEATURES**

The disease begins in the mouth in 50-70% of patients. With painful erosion or bullae and, after a period of weeks or months, the blisters spread to involve the skin. Oral lesions most commonly affect the buccal, palatine, and gingival mucosae. The typical skin lesion is a fragile, flaccid blister, which develops on normal or erythematous skin, and readily ruptures, leaving a painful crusted, raw, bloody erosion. Blisters can be induced by rubbing the adjacent, apparently normal skin with a finger - the Nikolsky sign. Direct pressure applied to the center of the blister is also followed by lateral extension - the Asboe-Hansen sign.

Healing is often accompanied by post-inflammatory hyper-pigmentation but **scarring is not feature**. The individual will often present with irritability from the pain, fever, from secondary infection and dehydration, and cervical lymphadenitis from secondary infections of numerous oral ulcers. The individual may not be eating because of the pain and may appear listless from dehydration, hypoglycemia, and analgesic use. Rarely, nail involvement in the form of hemorrhagic paronychia, trachyonychia, is encountered in patients. Occasional modes of presentation include linear lesion, postsurgical, post-burn and post-irradiation pemphigus. In addition to oral and cutaneous involvement, lesions have been described at a wide variety of sites including the pharynx, larynx, esophagus, eye, external-genitalia, urethra and anal mucosa. The development of pemphigus may be associated with a variety of disorders including other auto-immune bullous dermatoses, particularly bullous pemphigoid, lupus erythematosus, thymoma and myasthenia gravis. As in the many other diseases with immunological pathogenesis, pemphigus is accompanied by an increased incidence of internal malignancy including thyoma, lymphoma and kaposi’s sarcoma.

**TREATMENT**
Only "Oral - pemphigus vulgaris" responds well to systemic corticosteroid regimen. Approximately 70% of pemphigus vulgaris with both oral and skin lesions also respond to systemic corticosteroid regimen. The remaining 30% of cases of this type of pemphigus vulgaris respond incompletely to prednisone and require the addition of either.

Cyclophosphamide 50 to 100 mg by mouth twice daily, or Azathioprine 50 to 100 mg by mouth twice daily In cases that remain refractory to this regimen, methotrexate, 25 mg per week, may be substituted for azathioprine, or plasmapheresis combined with azathioprine may be used as a method for reducing the corticosteroid dosage.

In resistant or progressive cases or in cases in which the effects of long-term corticosteroids accumulate,

Dapsone, 100 mg per day, combined with either Gold sodium thiomalate or Azathioprine or Plasmapheresis, has also been used as a corticosteroid-sparing regimen. Because patients will present with a recent history of a decreased oral intake and frequently secondary infection, it is often necessary first to provide hydration with intravenous fluids and to begin antibiotic therapy and pain control measures while the biopsy specimen is being processed.

**Emerging Therapies**

Over the years, advances have been made to expand therapeutic armamentarium for pemphigus.

**Emerging therapies include**

- Intravenous immunoglobulin (IVIg),
- Plasmapheresis,
- Immunoadsorption (IA),
- Extracorporeal photochemotherapy (ECP),
- Rituximab,
- Tumor necrosis factor-alpha (TNF-α)
- Antagonists (infliximab and etanercept),
- Cholinergic agonists,
and other experimental therapies such as desmoglein 3 peptides and KC706 Pemphigus vegetation\(^{2,8,10}\)

Pemphigus vegetance a chronic variant of p. vulgaris, has a somewhat better prognosis than p. vulgaris with occasional cases associated with spontaneous remission. It accounts for 1-2% of all the cases of pemphigus. As the vulgaris variant p. vegetation typically presents in adult. There have been a small number of cases described in childhood including a dapsone-responsive IgA-mediated variant. The lesions, which present as blisters and erosion, are particularly prolific in the flexure, especially the axillae, the groin, the infra-mammary region, the umbilicus and at margins of the lips.\(^{12-14}\) The scalp is also said to be the site of predilection. Soon thereafter, patients characteristically develop hypertrophic vegetation and pustules at the blistered edges. The oral cavity is commonly affected and a cerebriform or “scrotal” tongue is said to be a diagnostic clue in cases of early involvement. Esophageal involvement presenting as erosion and white plaques has been described in a number of patients and the nasal mucosa, larynx, vulva, vagina and anus may also be affected.\(^{15,16}\) Nail involvement including onycholysis and pustules is sometimes seen. Peripheral blood eosinophilia is commonly present.

**Two clinical subtypes are recognized**

- In the Neumann variant (the more serious form), lesions usually begin as described in p.vulgaris, but the ensuing erosions develop vegetation. The course of this variant is similar to that of p.vulgaris.

- In the Hallopeau variant (pyodermite vegetation) the eruption begins as pustular lesions that rapidly evolve into verrucous vegetating plaques. Bullae are usually not seen. This is a milder variant in which spontaneous remission is common.

**Pemphigus foliaceus**\(^{17-20}\)

**Clinical features**

Pemphigus foliaceus(p. foliaceus) affects the middle aged and elderly. It has a very variable age of onset, sometimes affecting young adults and even, occasionally, children. The superficial blisters of p. foliaceus are exceedingly fragile and therefore much less obvious; erosions and large leafy scales or crusts are often predominant. The lesions may remain localized to the scalp, face and trunk for many months or years, leading to a mistaken diagnosis of seborrheic dermatitis, seborrheic keratosis or even lupus erythematosus.
Sometimes the eruption involves the entire surface of the body or produce a clinical resemblance to exfoliative dermatitis. The mucous membrane involvement is rare. Exceptionally, patients may present with localized disease, typically restricted to the face. *p. foliaceus* often has a much more benign course than *p. vulgaris*. Very occasionally, patients may develop *p. foliaceus* during or after a previous episode of *p. vulgaris* and vice versa. This is accompanied by an antigen shift. Very exceptionally, maternal antibodies have been known to cross the placenta resulting in neonatal disease. In addition to idiopathic *p. foliaceus*, drug-induced variants, notably due to penicillamine, is also reported.

**Fogo selvagem**

Fogo selvagem (*Brazilian pemphigus foliaceus, “wild fire”, endemic pemphigus foliaceus*) The condition is associated with poverty and malnutrition and particularly affects children and young adults. There is striking familial incidence. The clinical presentation of fogo selvagem has been divided into a number of categories including localized and generalized forms. Localized disease presents in a variety of ways including small blisters and erosions or violaceous papules and plaques distributed mainly in the seborrheic areas. Such lesions may be clinically misdiagnosed as discoid lupus erythematosus. Generalized presentation includes bullous exfoliative, exfoliative erythrodermic and disseminated plaque and nodular variants.

**Clinical evaluation**

Presence of subcorneal acantholysis. Positive direct and indirect immunofluorescence and/or immunoprecipitation or ELISA assays. Confirm epidemiological data.

**Pemphigus herpetiformis**[^2,6,8]

Pemphigus herpetiformis (PH) was first introduced by Jablonska and colleagues. Pemphigus herpetiformis (herpetiformis pemphigus, acantholytic dermatitis herpetiformis) is a variant of pemphigus which shows clinical features resembling dermatitis herpetiformis with the histology and immunofluorescent findings of pemphigus. It is rare. 7.3% of cases of pemphigus. Equal gender distribution. Affects population of age 31-83 years.

**Clinical features**
Patient presents with intensely pruritic, grouped, erythematous papules and plaques, vesicles and blisters, sometimes associated with mucous-membrane involvement. Urticaria may also be a presenting feature. Nikolsky sign is variably present. The lesions are generalized, there is a tendency for the extensor surface of the extremities to be particularly involved. Exceptionally, herpetiform pemphigus may be associated with an underlying malignancy.

**Pemphigus erythematosus**[2,8]

(p. erythematosus Senear–Usher syndrome)

Is a mild localized form of superficial pemphigus with the histological and immunohistologic findings of p. foliaceus combined with features of lupus erythematosus. The condition shows worldwide distribution and slightly female predominance. Exceptionally, it has been described in children. Clinically, it is commonly confined to the head, neck and upper trunk, and typically resembles p. foliaceus. Lesions are erythematous, scaly and crusted, with or without superficial vesicles, blisters or erosions. Facial involvement often shows a butterfly distribution reminiscent of lupus erythematosus or seborrheic dermatitis.

**Mucous membrane involvement is exceedingly rare**

There are reports of p. erythematosus developing after treatment of drugs, notably D-penicillamine, and propranolol, captopril, pyritinol, thiopronine, ceftazidime. It has also been described as complication of heroin abuse. P. erythematosus may rarely be associated with thymoma. Typically, the thymoma precedes the onset of cutaneous lesions, which often manifests following thymectomy. P. erythematosus may also be a manifestation of paraneoplastic pemphigus.

**Paraneoplastic pemphigus**[8]

Paraneoplastic pemphigus (PNPP) was first reported in 1990 by Anhalt et al. as an autoimmune blistering disorder associated mostly with lymphoproliferative malignancies. Paraneoplastic pemphigus (PNPP) is a severe variant of pemphigus that is associated with an underlying neoplasm – most frequently non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, or thymoma. Castleman disease and Waldenstrom macroglobulinemia are also associated. The damage to the epithelium is due to both an autoimmune reaction with epithelial cells and cell-mediated cytotoxicity.

**Clinical features**
Patients develop severe blistering and erosions of the mucous membranes and the skin. The onset of the disease is often rapid and oral and conjunctival lesion are both common and often severe. The lesion may resemble the inflammatory lesions of a drug reaction, lichen planus, or EM, as well as the blisters seen in pemphigoid. In severe cases, the lesion may mimic TEN and often also involve the respiratory epithelium. Unlike EM or TEN, the lesion of paraneoplastic pemphigus continue to progress over weeks to months.

**Oral manifestations**

Oral lesions are the most common manifestation of paraneoplastic pemphigus (PNPP). It is often extensive and painful. Lesions are frequently inflamed and necrotic, with large erosion covering lips, tongue, and soft palate. Mucositis is a constant feature of PNPP. The stomatitis usually presents as extensive erosions and ulcerations affecting all surfaces of the oro-pharynx with preferential involvement of the lateral borders of the tongue.

The ulcers typically extend onto the vermilion of the lips, resulting in the characteristic hemorrhagic crusts. The mucositis of PNPP can extend to the pharynx, larynx and esophagus, causing soreness and dysphasia. The involvement of conjunctival mucosa is frequent with occasional progression to visual impairment.

**Laboratory findings**

Histopathology of PNPP includes changes suggestive of EM, lichen planus, pemphigoid and pemphigus. There is inflammation at dermal-epidermal junction and keratinocyte necrosis in addition to the characteristic acantholysis seen in PV. DIF shows deposition of IgG and complement along the basement membrane as well as keratinocyte surface in an intercellular location. IIF demonstrates antibodies that not only bind to epithelium but to liver, heart, and bladder tissue.

**Management**

Patient with PNPP secondary to localized tumor such as Castleman disease improve with the surgical removal of the tumor. Patient with PNPP resulting from lymphoma, however, have a poor prognosis and usually die within 2 years from a combination of the underlying disease, respiratory failure, and extensive mucocutaneous involvement. Use of a combination of prednisone and immunosuppressive drug therapy may help
control severity of the skin lesion but oral, conjunctival, and pulmonary disease is frequently resistant to treatment.

**IgA pemphigus**[^2,8]

**Clinical features**

Is a rare dapsone – responsive variant of pemphigus that, is characterized by intracellular. IgA deposition and presents clinically with pustular rather than vesicular lesion. This disease has been described under a number of different names, such as intra-epidermal neutrophilic IgA dermatosis, IgA pemphigus foliaceus, IgA herpetiform pemphigus, intra-epidermal IgA pustulosis, intracellular, IgA dermatosis, intracellular IgA vesiculo cutaneous dermatosis. Middle aged most common or elderly but children are also affected. The sex incidence is equal. No racial or geographic predilection. Drug induced variants have occasionally been documented. IgA pemphigus is divided into two major subtypes.

- Subcorneal Pustular Dermatosis (SPD) variant IgA pemphigus foliaceus  
- And intra Epidermal Neutrophilic IgA dermatosis (IEN) variant IgA pemphigus vulgaris.

Patients with Subcorneal pustular dermatosis (SPD) IgA pemphigus presents with flaccid pustular lesion, often arising on an erythematous base and typically affecting the trunk and proximal limbs. Occasionally, there is generalized skin involvement. The lesions are crusted and progresses with peripheral extension to form ring like rosette pattern. Patients with intra-epidermal neutrophilic IgA dermatosis (IEN) IgA pemphigus presents with generalized pustules and crusts and erythematous macules with peripheral vesicles forming so-called sunflower - like configuration. Pruritus is common and is sometimes severe.

**Drug- induced pemphigus**[^1,2,8]

Drug-induced pemphigus is a well-established variant of pemphigus. Since the 1950s, evidence has grown that drugs may cause or exacerbate pemphigus. More than 200 cases of drug-induced pemphigus have been reported, with penicillamine accounting for almost 50. In patients who take penicillamine for longer than 6 months, it is estimated that7% develop pemphigus. A drug origin should be considered in every new patient with pemphigus. The most common variant of pemphigus associated with drug exposure is pemphigus foliaceus,
although vulgaris has also been described. In penicillamine-treated patients, pemphigus foliaceus is more common than pemphigus vulgaris, with an approximate ratio of 4:1.

**Contact pemphigus**[1,2,7,8]

**Clinical features**
Onset of pemphigus precedes contact with topical substances. The pathogenesis is not understood, but in some cases the exposure is thought to somehow trigger or induce pemphigus. Substances that have been implicated include nickel, pesticides, chromium sulfate, tincture of benzoin, phenol, diclofenac, dihydro diphenyl trichlor ethane, ketoprofen and feprazone. Further study is necessary to elucidate the relationship between exposure to topical agents and contact pemphigus.

**Pathogenesis and histological features**
Whether this phenomenon relates to systemic absorption, contact allergy or a direct “toxic” effect on epidermal antigen is yet unknown. Biopsy of contact pemphigus shows histological features similar to those of p.vulgaris. Immunofluorescent studies show intercellular IgG and sometimes C3 deposition.

**Differential diagnosis**
The main differential diagnosis is with classic pemphigus. Only clinical information will allow distinction of contact pemphigus from other members of the pemphigus family of disorder.

**CONCLUSION**
Though rare but pemphigus constitutes a group of subtypes that involve oral mucous membrane. Sometimes this finding has a diagnostic value. As the entity involves the oral mucous membrane and skin thorough knowledge of clinical feature, pathogenesis, differentiating features is of at most importance for identification and understanding the disease and treatment purpose. This presentation is attempt of the same.

**REFERENCES**
3. McKee P, Calonje E, Granter S.R., Pathology of the Skin; 3ed edition; Elsevier; Mosby
11. Lee S. E, Kim S.C., Paraneoplastic pemphigus; Dermatologica Sinica., 2010; 28; 1–14