WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 6, 431-440. Review Article ISSN 2277–7105

PEMPHIGUS VULGARIS: AN OVERVIEW

Neha Rangwar[1]*, Harshitha Kasavarjala[1], Pushpendra Kumar[2], Rewak Tyagi[3], Ruchi Priya[3] and Shaikh Mohmed Adnan Mohmed Javid[4]

[1]Malla Reddy College of Pharmacy, Maisammaguda, Hyderabad, Telangana, India- 500100.

[2]Pharm D, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India- 302017.

[3]Pharm D, Nims Institute of Pharmacy, Jaipur, Rajasthan, India- 3031214.

[4]Pharm D, Shree Dhanvantary Pharmacy College, Kim, Surat, Gujarat, India- 394110.

Article Received on
29 Jan. 2024,

Revised on 19 Feb. 2024,
Accepted on 10 March 2024

DOI: 10.20959/wjpr20246-31701

***Corresponding Author**
Neha Rangwar
Malla Reddy College of Pharmacy, Maisammaguda, Hyderabad, Telangana, India- 500100.

ABSTRACT

Rare autoimmune illnesses affecting the skin and mucous membranes are known as pemphigus. The skin and mucous membrane epithelium can develop vesicles and erosions due to these intraepidermal bullous diseases. Pemphigus vulgaris accounts for up to 70% of all cases, as is widely recognised. One of the first symptoms that patients may experience is the development of highly painful erosions on their mucosal membranes. The epidemiology of pemphigus varies substantially across the world. The prognosis, mortality rate, and clinical outcomes for pemphigus patients have evolved significantly. Erosion of the oral mucosa and subsequent skin involvement are common symptoms in patients with PV. It takes a long time for aphthous ulceration and other cutaneous symptoms of the illness to manifest since they usually show up after mucosal erosions have already happened. Osteoporosis is one of the infamous side effects of systemic corticosteroids, which are used in the treatment of pemphigus vulgaris. Systemic corticosteroids continue to play a pivotal role in treating pemphigus vulgaris (PV) due to their significant impact on PV management.

KEYWORDS: Immunoglobulin G, Paraneoplastic pemphigus, Corticosteroids, and Pemphigus vulgaris.

INTRODUCTION

Rare autoimmune illnesses affecting the skin and mucous membranes are known as pemphigus. The skin and mucous membrane epithelium can develop vesicles and erosions due to these intraepidermal bullous diseases. Because of these issues, people may have a much lower quality of life and a much lower chance of being sick or dying. In pemphigus etiopathogenesis, the production of autoantibodies targeting certain desmosome proteins is a characteristic. The rupture of intraepidermal adhesion, which happens when these autoantibodies bind to desmosomal components, causes acantholysis and the production of intraepithelial blisters. The histologic and clinical features of pemphigus, the circulating autoantibodies' targets and the specific antigens they target, have allowed for the recognition of subtypes of the disease. While nonclassical pemphigus variants such as paraneoplastic pemphigus (PNP), pemphigus herpetiformis (PH), and IgA pemphigus have been documented in the last few decades, the two most prevalent types are pemphigus vulgaris (PV) and pemphigus foliaceous (PF). Conventional wisdom is that, regardless of subtype, the initial step in the pathophysiology of pemphigus is the production of autoantibodies that target desmosomal components.[1] It is well-known that around 70% of all pemphigus cases are PV, and that humoral immunity plays a crucial role in disease pathogenesis, although T-cell-associated responses also play a substantial role in autoantibody promotion. One of the first symptoms that patients may experience is the development of highly painful erosions on their mucosal membranes. Infections affecting the oral mucosa cause dysphagia and a decrease in body weight more often than infections affecting any other mucosal surface. Mucosae of the pharyngolaryngeal, anal, vaginal, and conjunctival varieties have also been involved. Skin involvement is characterised by the appearance of flaccid vesicles.[2] These vesicles are most commonly observed in the flexural regions, face, head, and extremities. Skin involvement usually follows nasal involvement. In PV, the immune system assaults the transmembrane desmosomal glycoprotein desmoglein 3, and, in rare cases, desmoglein 1, causing acanthosis and intraepidermal blisters to form.[3] It is possible to create distinctive suprabasal epidermal blisters in passive transfer mouse models using anti-desmoglein 3 IgG antibodies. One clinically important disorder that often goes undiagnosed is pemphigus vulgaris (PV), an immunobullous disease that, if left untreated, can cause severe morbidity and even death. Because of the autoimmune mechanism that causes their pathogenesis, autoantibodies serve as the basis for diagnostic investigations and therapeutic attempts. Desmoglein (Dsg)1 and Dsg3 are the main antigens that aim to bind keratinocytes in epithelia the 'rivets' that hold the cells securely together. When keratinocytes divide and desmosomes

stop functioning, blisters form.[4] It takes five doctors an average of ten months to diagnose PV. This holdup happened because nobody knew the symptoms were there nobody could identify them, and nobody confirmed the diagnosis. Since mucosal ulceration is usually the first sign of PV, it usually takes a while for the skin to go into engagement. Patients are now limited to seeing specialists in mucosal pathologies, including gynaecologists, oral surgeons, genitourinary medicine, ENT surgeons, and dentists, due to the rarity of immunobullous disorders. In their search for intact blisters, even doctors familiar with PV and PF run the risk of misleading them.[5]

Epidemiology

The epidemiology of pemphigus varies substantially across the world. The prognosis, mortality rate, and clinical outcomes for pemphigus patients have evolved significantly. Additional medical conditions that patients with pemphigus may be suffering from go unnoticed. Because of the limited number and varied results of earlier observational research, they have been proven. Annual incidence rates of PV range from 0.76 in Finland to 16.1 per 100,000 in Israel, demonstrating the disease's ethnic and geographical heterogeneity. Pemphigus is more common in some racial and ethnic groups than in others. This is especially true among Ashkenazi Jews and Mediterranean peoples. Recent population-based research found that the rate of PV was 3.6 times higher among Israeli Jews compared to Arabs.[6] North America had an annual incidence of PV of 32 per 100,000 Jewish people and 4.2 per 100,000 non-Jewish people. Patients with pemphigus who are of Ashkenazi Jewish descent are more likely to carry specific HLA class II genes, such as HLA-DRB104 and HLA-A10. These genes are directly related to this discovery. Among Jewish and Egyptian cohorts, a polymorphism mutation in ST18 was significantly associated with PV, according to a recent study. However, no such association was found in a German group. ST18 encodes a proapoptotic chemical.[6,7]

Pathophysiology

Autoantibodies cause pemphigus vulgaris by targeting keratinocyte proteins (desmogleins). When circulating immunoglobulin G (IgG) autoantibodies bind to intercellular adhesion molecules, keratinocytes lose their capacity to attach, and a process known as acantholysis ensues. Cantholysis happens when autoantibodies harm intracellular connections, making bullae easily burst. The "super-compensation hypothesis" was proposed very recently.[8] Implies the possibility of other variables contributing to PV. Several mechanisms exist within

antibody-induced acantholysis that can initiate cell separation. An example of such a mechanism is the activation of signal transduction.[9] Steric hindrance is another one; it stops sticky molecules from working as intended. Autoantibodies against desmoglein 1 (Dsg 1) and desmoglein 3 (Dsg 3) help to fill in the gaps in our understanding of PV aetiology. The desmosome complex, which includes the transmembrane glycoprotein desmogleins, is an essential component for cell-cell adhesion. In particular, Didona et al. investigated desmoglein binding by IgG.[10] Immunising desmoglein with IgG antibodies that target its extracellular cadherin domains often leads to a loss of its sticky properties, the direct suppression of Dsg 3 trans-interactions, and the activation of signalling pathways that promote endocytosis and depletion. The enzymatic inactivation of Dsg 1 and the gene deletion of Dsg 3 both produce disease in animals that is comparable to PV, according to research.[9,10] Injecting mice with IgG from patients suffering from PV results in mice with diseases similar to PV. Results demonstrated a dose-dependent effect, suggesting that reducing blood IgG levels against Dsg 1 and Dsg 3 can benefit patients. Autoantibodies against both Dsg 1 and Dsg 3 were found in patients with mucocutaneous disease, but only in cases where the disease had progressed to the mucous membranes. Desmoglein compensation theory explains this discovery by stating that the cutaneous epidermis includes both Dsg 1 and Dsg 3, and therefore disease cannot be caused by autoantibodies against either desmoglein alone. Because mucous membranes typically lack Dsg 1, which suppresses Dsg 3, autoantibodies focusing on Dsg 3 alone will lead to illness. Based on epitope mapping, antibodies bind to desmogleins, suggesting that they affect steric hindrance and hence obstruct desmoglein binding. Along with the previously mentioned explanation, the desmoglein non-assembly depletion theory offers an additional potential pathophysiology of PV. This theory proposes that autoantibodies bind desmoglein and each other, leading to crosslinking and rendering desmosomes incapable of maintaining cell-cell contact.[11] Although PV cases in families are uncommon, studies have shown that the disease has a genetic component. Compared to healthy controls, first-degree relatives of asymptomatic PV patients have a higher prevalence of blood plasma PV-IgG antibodies. Additionally, it was found that first-degree relatives were more likely to suffer from autoimmune diseases. The DRB10402 and DQB10503 alleles are among the most common ones associated with PV. So far, DRB10402 has shown promise in protecting RA. PV can be caused by medications such as captopril and penicillamine.[12] Such an event can be set off by regulating keratinocyte aggregation by enzymes, by affecting the creation of neoantigens, or by taking part in the binding of cell adhesion molecules. Cephalosporins, penicillin, and nonsteroidal anti-

inflammatory medications are among the other substances that have been associated with drug-induced PV. Finally, there is no concrete evidence to support the assertions that certain foods like peppers, garlic, red wine, and leeks cause PV, although some case reports have linked the two.[13]

Clinical presentation

The formation of intraepidermal splits is a defining feature of pemphigus variants. There are five distinct kinds of pemphigus, and it's crucial to take each one into account: foliaceous, erythematosus, drug-induced, and paraneoplastic. In this context, PV is the only subject under consideration. Erosion of the oral mucosa and subsequent skin involvement are common symptoms in patients with PV. It takes a long time for aphthous ulceration and other cutaneous symptoms of the illness to manifest since they usually show up after mucosal erosions have already happened. A mouth ulcer may be the sole external sign of the condition in some cases. It is possible to injure multiple mucosal locations, such as the oropharynx, oesophagus, conjunctiva, nasal passages, larynx, urethra, vulva, and cervix.[14,15] The skin can become involved, either locally or extensively. Lacerations typically manifest on pressure points, the scalp, the face, the groyne, and the axillae. Flaccid blisters, which could eventually enlarge, could appear in these regions. These blisters will produce irritating erosions when they pop. Although PV can affect any area of the body and typically develops in adults, the buccal and labial mucosa are common sites for it. A blister can spread to nearby skin with just a little pressure in direct Nikolsky, and shearing can be induced by pushing on clinically normal skin in indirect Nikolsky; both signs characterise this condition. Although these signs should be considered diagnostic of PV, they are not diagnostic of PV on their own. Nail degeneration, paronychia, subungual hematomas, and neonatal pemphigus vulgaris are rare extra symptoms.[16]

Differential diagnosis

Diagnostic techniques, including skin or mucosal biopsy for DIF, are required for a conclusive diagnosis of pemphigus vulgaris because patients frequently have therapy for other blistering disorders before this one. Mucosal lesions can have a variety of causes, including aphthous ulcers, lichen planus, paraneoplastic pemphigus, stomatitis caused by the herpes simplex virus, or an inflammatory illness such as lupus erythematosus or dermatitis herpetiformis.[17] Other autoimmune blistering skin disorders that could be at play here include pemphigus vegetans, pemphigus foliaceous, paraneoplastic pemphigus, bullous

pemphigoid, linear IgA disease, erythema multiforme, Grover disease, or Hailey-Hailey illness. Several additional blistering disorders must be ruled out before pemphigus vulgaris can be considered. Blisters typically develop as a result of inflammatory, viral, or autoimmune processes.[18]

Evolution and Complications

Systemic corticosteroids, the gold standard treatment for pemphigus vulgaris, are infamous for their side effects, one of which is osteoporosis. Osteonecrosis affects 9–40% of patients taking corticosteroids for an extended length of time, and fractures affect 30–50%. The Fracture probability Assessment (FRAX) can further stratify the chance of osteoporotic fracture in individuals who do not have osteoporosis based on a T score. This information is useful for the use of medicines in the prevention of bone loss.[19] Corticosteroids can cause several adverse effects, including but not limited to increased hunger, sleeplessness, high blood pressure, oedema, adrenal suppression, cataracts, and slower wound healing. Infections, abnormalities in liver and renal function, changes in electrolytes, osteoporosis, hypertension, diabetes, anaemia, and gastrointestinal bleeding should be constantly monitored in patients with early-stage untreated PV when most fatalities occur.[20]

Emerging therapies in pemphigus vulgaris

Systemic corticosteroids continue to play a pivotal role in treating pemphigus vulgaris (PV) due to their significant impact on PV management. As an initial line of defence against mild PV, systemic corticosteroids require several weeks to start working. When your symptoms begin to improve, you can gradually decrease the dosage. To induce remission, you should enhance the dosage again if more than three lesions return.[4,9] An extra layer of protection can be provided by supplementing your corticosteroid treatment with azathioprine or mycophenolate mofetil (MMF). As a purine homolog, azathioprine inhibits purine biosynthesis. Oral and intravenous infusion are the two ways it can be given. You should discontinue azathioprine use if you do not feel better after three months of treatment. It is important to take renal function into account when making dosage adjustments. Thorough observation is required to reduce the likelihood of negative outcomes. Nausea and vomiting are common side effects of azathioprine. Bone marrow suppression is one mechanism by which azathioprine causes pancytopenia, thrombocytopenia, and leukopenia. One way that MMF suppresses the immune system is by blocking the synthesis of purines. Oral and intravenous infusion are the two ways it can be given. It is common for MMF to be effective

within two months of beginning therapy. Many people experience unpleasant side effects, the most prevalent of which are gastrointestinal distress, sickness, vomiting, and diarrhoea. Intravenous injections can cause thrombosis and superficial thrombophlebitis. When treating moderate to severe pemphigus, corticosteroids and anti-CD20 monoclonal antibodies like rituximab and ofatumumab were the first lines of defence.[20] The monoclonal antibody rituximab stops B lymphocytes from becoming plasma cells, which can make autoantibodies, by targeting CD20. Most people say they start to feel better after three months of taking the medication intravenously. It is not uncommon for infusions to cause side symptoms such as nausea, vomiting, headache, and fever. A rare but serious side effect of rituximab, like other monoclonal antibodies, is progressive multifocal leukoencephalopathy (PML). Among the third-line treatments for PV, which are mentioned in references.[10,20] you can find immunoadsorption, methotrexate, cyclophosphamide, dapsone, and IVIG. Most of the new, potential treatments for PV, which are monoclonal antibodies, have not been investigated due to the high cost of conducting large-scale research. Rituximab is an alternative to the anti-CD20 monoclonal antibodies obinutuzumab, ofatumumab, and veltuzumab. Treatments that target B-cell derived B-cell activation factor (BAFF), a proliferation-inducing ligand (APRIL), CD19, Bruton kinase (BTK), and interleukin (IL-4) are also showing promise in PV. To produce better therapies, future PV research should concentrate on identifying the specific harmful compounds and cytokines.[18,20]

General management

If you take good care of your blisters and erosions, they should heal faster. To avoid inflicting more erosions and blisters, handle the skin delicately. Analgesics may be necessary, particularly when changing bandages, so wear surgical gloves and adhere to aseptic procedures. Use a mild antiseptic solution or a bleach bath for a gentle cleanse. Remove any blisters that are still intact, but don't remove the blister roof. Use a mixture of half-liquid paraffin and half-white soft paraffin, or another mild emollient ointment, and apply it either directly to the skin or onto a dressing. Apply dressings that do not cling (such as silicone mesh or gauze soaked in petroleum). One of these could be an antiseptic. To stop erosions from seeping, apply a second, absorbent dressing over the first. Take extra precautions to identify and cure any infection.[12,20]

REFERENCES

1. Hodak, E., Kremer, I., David, M., Hazaz, B., Rothem, A., Feuerman, P., & Sandbank, M. Conjunctival involvement in pemphigus vulgaris: a clinical, histopathological and immunofluorescence study. *The British Journal of Dermatology*, 1990; *123*(5): 615–620. https://doi.org/10.1111/j.1365-2133.1990.tb01478.x
2. Sagher, F., Bercovici, B., & Romem, R. Nikolsky sign on cervix uteri in pemphigus. *The British Journal of Dermatology*, 2006; *90*(4): 407–411. https://doi.org/10.1111/j.1365-2133.1974.tb06425.x
3. Hertl, M. T cell control in autoimmune bullous skin disorders. *The Journal of Clinical Investigation*, 2006; *116*(5): 1159–1166. https://doi.org/10.1172/jci28547
4. Kappius, R. H., Ufkes, N. A., & Thiers, B. H. *Thiers BH*, 2023.
5. Bilgic, A., & Murrell, D. F. What is novel in the clinical management of pemphigus? *Expert Rev Clin Pharmacol*, 2019; *12*(10): 973–980.
6. Papara, C., Danescu, S., Rogojan, L., Leucuta, D. C., Candrea, E., Zillikens, D., & Baican, A. Lymphocyte-predominant lesional inflammatory infiltrates of the skin are associated with mucosal-dominant phenotype in pemphigus. *Journal of Cutaneous Pathology*, 2023; *50*(8): 754–762. https://doi.org/10.1111/cup.14395
7. David, M., Katzenelson, V., & Mimouni, D. The distribution of pemphigus vulgarisIgG subclasses in patients with active disease. *J Eur Acad Dermatol Venereol*, 2006.
8. Hertl, M., Jedlickova, H., Karpati, S., Marinovic, B., Uzun, S., Yayli, S., Mimouni, D., Borradori, L., Feliciani, C., Ioannides, D., Joly, P., Kowalewski, C., Zambruno, G., Zillikens, D., & Jonkman, M. F. Pemphigus. S2 Guideline for diagnosis and treatment – guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). *Journal of the European Academy of Dermatology and Venereology: JEADV*, 2015; *29*(3): 405–414. https://doi.org/10.1111/jdv.12772
9. Rodríguez-Santiago, M. A., García-Marín, J., Lamela-Domenech, A., & Vega-Martínez, M. Pemphigus Vulgaris in a black patient: Early recognition of disease saves lives. *Journal of Dermatology and Skin Science*, 2021; *3*(2): 5–8. https://doi.org/10.29245/2767-5092/2021/2.1137
10. Bystryn, J. C. The adjuvant therapy of pemphigus. An update. *Archives of Dermatology*, 1996; *132*(2): 203–212. https://doi.org/10.1001/archderm.132
11. Joly, P., Horvath, B., Patsatsi, A., Uzun, S., Bech, R., Beissert, S., Bergman, R., Bernard, P., Borradori, L., Caproni, M., Caux, F., Cianchini, G., Daneshpazhooh, M., De, D.,

Dmochowski, M., Drenovska, K., Ehrchen, J., Feliciani, C., Goebeler, M, Schmidt, E. Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the European Academy of dermatology and venereology (EADV). *Journal of the European Academy of Dermatology and Venereology: JEADV*, 2020; *34*(9): 1900–1913. https://doi.org/10.1111/jdv.16752

12. Sirois, D. A. Diagnostic patterns and delays in Pemphigus vulgaris: Experience with 99 patients. *Archives of Dermatology*, 2000; *136*(12): 1569–1570. https://doi.org/10.1001/archderm.136.12.1569
13. Huilgol, S. C., & Black., M. M. Management of the immunobullous disorders. II. Pemphigus. *Clinical and Experimental Dermatology*, 1995; *20*(4): 283–293. https://doi.org/10.1111/j.1365-2230.1995.tb01327.x
14. Mihai, S., & Sitaru, C. Immunopathology and molecular diagnosis of autoimmune bullous diseases. *Journal of Cellular and Molecular Medicine*, 2007; *11*(3): 462–481. https://doi.org/10.1111/j.1582-4934.2007.00033.x
15. Hietanen, J., & Salo, O. P. Pemphigus: an epidemiological study of patients treated in Finnish hospitals between 1969 and 1978. *Acta Dermato-Venereologica*, 1982; *62*(6): 491–496.
16. Kridin, K., Zelber-Sagi, S., & Bergman, R. Pemphigus Vulgaris and Pemphigus Foliaceus: Differences in Epidemiology and Mortality. *Acta Dermato-Venereologica*, 2017; *97*(9): 1095–1099. https://doi.org/10.2340/00015555-2706
17. Vu, T. N., Lee, T. X., & Ndoye, A. The pathophysiological significance of non-desmoglein targets of pemphigus autoimmunity. Development of antibodies against keratinocyte cholinergic receptors in patients with pemphigus vulgaris and pemphigus foliaceus. *Arch Dermatol*, 1998; *134*(8): 971–980.
18. Szafer, F., Brautbar, C., Tzfoni, E., Frankel, G., Sherman, L., Cohen, I., Hacham-Zadeh, S., Aberer, W., Tappeiner, G., & Holubar, K. Detection of disease-specific restriction fragment length polymorphisms in pemphigus vulgaris linked to the DQw1 and DQw3 alleles of the HLA-D region. *Proceedings of the National Academy of Sciences of the United States of America*, 1987; *84*(18): 6542–6545. https://doi.org/10.1073/pnas.84.18.6542
19. Berkowitz, P., Chua, M., Liu, Z., Diaz, L. A., & Rubenstein, D. S. Autoantibodies in the autoimmune disease pemphigus foliaceus induce blistering via p38 mitogen-activated protein kinase-dependent signaling in the skin. *The American Journal of Pathology*, 2008; *173*(6): 1628–1636. https://doi.org/10.2353/ajpath.2008.080391

20. Lee, E., Lendas, K. A., & Chow, S. Disease-relevant HLA class II alleles isolated by genotypic, haplotypic, and sequence analysis in North American Caucasians with pemphigus vulgaris. *Hum Immunol*, 2006; *67*(1–2): 125–139.