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Pemphigus And Its Variants – A Brief Review

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ABSTRACT:

Pemphigus is a rare autoimmune disease characterized by blistering of the skin and mucous membranes, with an incidence of 0.1–0.5 per 100,000 individuals worldwide. The disease is most prevalent in Ashkenazi Jews due to specific HLA class II gene associations. Pemphigus encompasses several subtypes, including pemphigus vulgaris, pemphigus foliaceus, pemphigus vegetans, paraneoplastic pemphigus, bullous pemphigoid, and mucous membrane pemphigoid, each with distinct clinical and histological features. The pathogenesis typically involves autoantibodies targeting desmosomal proteins, leading to acantholysis and blister formation. Clinical manifestations often begin with oral lesions, progressing to skin blistering, and may involve significant morbidity and mortality if not diagnosed and treated promptly. Current treatments primarily focus on immunosuppressive therapies, including corticosteroids and monoclonal antibodies, tailored to individual patient needs and disease severity. Understanding the pathogenesis, clinical presentation, and evolving therapeutic strategies is essential for effective management of pemphigus and its variants.

Keywords: vesiculobullous, pemphigus, autoimmune disease

INTRODUCTION:

Pemphigus, a term derived from the Greek word *pemphix*, meaning blister, is a rare autoimmune disease affecting the skin and mucous membranes[1]. It has an estimated worldwide annual incidence of 0.1–0.5 per 100,000 individuals, reflecting its rarity on a global scale[2]. This disease occurs across all racial and ethnic groups; however, its highest incidence is observed in Ashkenazi Jews, a trend attributed to the increased presence of specific HLA class II genes, particularly HLA-DRB1*04 and HLA-A*10[3, 4]. The disease

predominantly manifests during the fifth and sixth decades of life, though a small number of cases have been documented in children, highlighting its potential to affect younger populations[5, 6]. Pemphigus encompasses a group of acantholytic autoimmune dermatoses that target mucocutaneous membranes, with acantholysis—loss of cell-to-cell adhesion—resulting in potentially life-threatening bullae and erosions. The disease is classified into multiple subtypes, including pemphigus vulgaris (PV), pemphigus foliaceus (PF), IgA pemphigus, and paraneoplastic pemphigus (PNP), each presenting distinct clinical and pathological features. Given the considerable morbidity and mortality associated with these disorders, it is essential to review their pathogenesis, clinical manifestations, and diagnostic processes, alongside evaluating both standard and emerging therapies for effective management. Although rare, pediatric cases of pemphigus have been reported, including instances in patients as young as six, indicating that the disease can affect children, albeit infrequently. Globally, the male-to-female ratio of pemphigus patients is nearly equal, yet adolescent girls show a slightly higher susceptibility compared to boys[7, 8].

VARIANTS

I. PEMPHIGUS VULGARIS

Pathogenesis:

The pathogenesis of pemphigus involves the presence of circulating and tissue-bound autoantibodies to the keratinocyte cell surface desmosomal molecules desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1). Dsg3 and Dsg1 belong to the cadherin superfamily involved in cell–cell adhesion. These autoantibodies cause loss of cell–cell adhesion between epithelial cells, which results in suprabasilar intraepithelial vesicle formation [9].

Etiology:

The etiology of PV involves a combination of genetic predisposition, immunologic factors, and environmental triggers[10]. Genetically, there is a strong association with certain HLA alleles, particularly HLA-DR4 and HLA-DR14, suggesting a hereditary susceptibility to dysregulated immune responses[11]. Immunologically, pathogenic IgG autoantibodies, primarily of the IgG4 subclass, target Dsg1 and Dsg3, leading to the loss of cell adhesion and blister formation. Environmental factors, such as certain medications (e.g., penicillamine, captopril, and non-steroidal anti-inflammatory drugs), physical or emotional stress, infections, or trauma, can act as triggers in genetically predisposed individuals. Additionally, viral infections, particularly herpesviruses, and hormonal influences may play a role, as PV often presents during middle age[12].

Clinical features:

The clinical presentation typically begins with painful blisters in the mouth, making eating and swallowing difficult. As the disease progresses, flaccid blisters appear on the skin, particularly on the scalp, face, chest, and back. These blisters are fragile and rupture easily, leading to painful erosions that can become infected[13]. Other mucosal surfaces, such as the nose, throat, eyes, and genitals, may also be affected. A positive Nikolsky sign, where slight pressure on the skin causes it to shear off, is indicative of PV. Early diagnosis and treatment are crucial to prevent complications and improve outcomes[14].

Oral manifestation:

Mucous membranes are typically the first to be affected in pemphigus vulgaris (PV), with mucosal lesions often appearing months before cutaneous lesions. These lesions are seen in 50-70% of patients and are more commonly irregular, poorly defined erosions on the gingiva, buccal, or palatal surfaces, which are painful and slow to heal. Intact bullae are rare in the mouth. The erosions spread peripherally, causing the epithelium to shed. They can occur throughout the oral cavity and may be widespread and extensive. In some cases, the erosions may extend to the larynx, leading to hoarseness. Due to the pain, patients often find it difficult to eat or drink. Other mucosal areas, including the conjunctiva, esophagus, labia, vagina, cervix, penis, urethra, and anus, can also be affected. The oral lesions resemble those found on the skin[14].

Histologic feaures:

Pemphigus is microscopically characterized by the formation of a vesicle or bulla entirely within the epithelium, just above the basal layer, resulting in a distinctive suprabasal "split". Prevesicular edema weakens epithelial junctions, causing acantholysis, the loss of cell cohesion, resulting in free-floating epithelial clumps known as "Tzanck cells." These cells, identified by swollen nuclei and hyperchromatic staining, are detectable via the rapid "Tzanck test" on cytologic smears [14]. Vesicular fluid, especially in older lesions, contains polymorphonuclear leukocytes and lymphocytes but shows minimal inflammation, a characteristic feature of pemphigus. Secondary infections may obscure this low inflammatory profile[15].

Treatment:

Systemic corticosteroids like prednisone are the mainstay of treatment but pose significant long-term risks. To mitigate these, steroid-sparing agents (e.g., azathioprine, mycophenolate mofetil, and methotrexate) and rituximab, an anti-CD20 monoclonal antibody often used as first-line therapy, are effective option [16, 17]. Adjunctive therapies like intravenous immunoglobulin (IVIG) are useful for refractory cases. Management involves achieving disease control with corticosteroids, followed by tapering to reduce relapse risk. Supportive

care, such as wound management and pain control, is crucial, and treatment should be tailored to disease severity and patient needs under expert dermatological care[18, 19, 20].

II. PEMPHIGUS VEGETANS

Pemphigus vegetans is a rare clinical variant of pemphigus vulgaris accounting for 1–2% of all pemphigus. It is characterized by vegetating plaques primarily localized to the flexural areas. Historically, two subtypes with different clinical features and course are described: Neumann P Veg and Hallopeau P Veg[21, 22].

Etiology:

Pemphigus vegetans is an autoimmune disease caused by autoantibodies against desmogleins 1 and 3, disrupting keratinocyte adhesion and leading to erosive lesions[22]. Genetic predisposition (e.g., HLA-DR4, HLA-DR14), medications such as penicillamine, captopril, infections (Viral or bacterial), and immune dysregulation contribute to its onset. External factors like stress and UV exposure may exacerbate the condition[23, 24].

Clinical features:

Pemphigus vegetans is characterized by the development of pustules that evolve into moist, thickened, verrucous plaques, primarily affecting intertriginous areas such as the axillae, groin, and perineum. These vegetative plaques often have a foul odor and are associated with pruritus, which distinguishes this condition from pemphigus vulgaris. The disease may involve the mucous membranes, particularly the oral cavity, where painful erosions and plaques can impair eating and speaking. Two subtypes exist: the Neumann type, which is more aggressive and resembles pemphigus vulgaris with mucosal involvement, and the Hallopeau type, which is milder and presents with pustules that evolve slowly. Systemic symptoms like fever and malaise can occur in severe cases, often due to secondary infections[24].

Histologic features:

Histologically, pemphigus vegetans is characterized by acantholysis, which causes loss of adhesion between keratinocytes and results in intraepidermal clefting and blister formation. The epidermis exhibits hyperplasia with papillomatous and verrucous projections, giving the lesions their vegetative appearance[25]. Dense eosinophilic infiltration is a prominent feature, often forming eosinophilic microabscesses within the epidermis. Additional findings include hyperkeratosis and parakeratosis, with thickening of the stratum corneum and retention of nuclei. Suprabasal clefting, where separation occurs above the basal layer, is a hallmark finding. Diagnosis is confirmed by direct immunofluorescence, which shows intercellular deposition of IgG and C3 in a characteristic "chicken wire" pattern[26].

Treatment:

Treatment regimen consisted of prednisone for all patients except for one who had localized scalp Hallopeau P Veg which has been treated effectively in 6 weeks without relapses by local infiltrations of corticosteroids (triamcinolone) [26.] The treatment of pemphigus vulgaris centers on immunosuppressive therapy to control the autoimmune response. First-line treatment involves systemic corticosteroids like prednisone, often combined with steroid-sparing agents (e.g., azathioprine, mycophenolate mofetil, or cyclophosphamide) to minimize side effects. Rituximab, targeting CD20-positive B cells, is effective for refractory cases and increasingly used earlier. Adjunct therapies, such as dapsone and topical corticosteroids, help manage localized lesions. IVIG and plasmapheresis are options for severe or resistant cases[27]. Supportive care, including pain management, infection prevention, wound care, and monitoring for treatment-related adverse effects, is vital. Tailored treatment plans based on disease severity and patient health optimize outcomes.

III. PEMPHIGUS FOLIACEOUS

Pemphigus foliaceus is an autoimmune blistering disorder that primarily affects the superficial layers of the epidermis. It is caused by autoantibodies targeting **desmoglein 1**, a desmosomal protein critical for cell adhesion in the upper epidermis. Unlike pemphigus vulgaris, it typically does not involve mucous membranes due to the restricted expression of desmoglein 1 to the skin[28].

Etiology:

Genetic predisposition, particularly associated with specific HLA alleles, plays a significant role in its development. Environmental factors, such as ultraviolet (UV) radiation and endemic exposures like black fly bites in certain regions (e.g., Brazil's Fogo Selvagem), can act as triggers. Additionally, some drugs, including penicillamine and captopril, may induce or exacerbate the condition. Infections and systemic factors, such as stress, can also contribute to disease onset or exacerbation[28].

Clinical Features:

Pemphigus foliaceus primarily affects the skin, presenting as superficial, fragile blisters that rupture easily, leaving behind crusted erosions. Unlike other forms of pemphigus, mucosal involvement is rare[29]. Lesions typically begin on the seborrheic areas, such as the scalp, face, chest, and upper back, and may gradually spread to other parts of the body. Pruritus is common, and the condition can cause significant discomfort. Nikolsky's sign, where gentle pressure on the skin induces detachment of the epidermis, is often positive. Chronic cases may lead to extensive skin involvement, resulting in secondary infections, fluid loss, and systemic complications[30].

Histological Features:

Pemphigus foliaceus is characterized histologically by acantholysis in the upper epidermis, particularly within the granular and upper spinous layers, leading to the formation of subcorneal blisters. The basal layer remains intact, distinguishing it from other pemphigus variants. The inflammatory infiltrate in the dermis is typically sparse, consisting of lymphocytes and occasional eosinophils[31]. On direct immunofluorescence (DIF), there is a characteristic intercellular deposition of IgG and/or C3 in a "fishnet" pattern, most prominent in the superficial layers of the epidermis. The disease is mediated by autoantibodies targeting desmoglein 1, a desmosomal protein crucial for keratinocyte adhesion in the upper epidermis. These features collectively help in differentiating pemphigus foliaceus from other autoimmune blistering disorders[32].

Treatment:

Treatment involves systemic corticosteroids and immunosuppressive agents like azathioprine or mycophenolate mofetil. Rituximab, intravenous immunoglobulin (IVIG), or plasmapheresis may be considered in severe or refractory cases. Topical corticosteroids and supportive skin care are also important for localized disease or mild cases[32].

IV. PARANEOPLASTIC PEMPHIGUS

Etiology:

PNP is associated with underlying neoplastic diseases. The most common associated neoplasms include: Non-Hodgkin lymphoma, chronic lymphocytic leukemia, Castleman disease, Thymoma, Retroperitoneal sarcomas, Waldenström macroglobulinemia[33].

Pathogenesis:

The pathogenesis of paraneoplastic pemphigus (PNP) involves a complex interplay of autoimmune mechanisms and external factors. Autoantibodies targeting plakin family proteins and other desmosomal and hemidesmosomal antigens disrupt epithelial integrity, leading to detachment of cells (acantholysis) and chronic erosive mucositis, the diagnostic hallmark of PNP[33]. IgG deposits in the bronchial epithelium contribute to pulmonary complications like bronchiolitis obliterans[34]. The associated malignancy drives autoantibody production through immune dysregulation or antigenic cross-reactivity. Additional factors, such as chemotherapy-induced toxicity, infections from immunosuppression, and malignancy-related effects, exacerbate epithelial and pulmonary damage. Together, these processes result in the severe mucocutaneous and respiratory manifestations characteristic of PNP.

Clinical features:

The clinical features of paraneoplastic pemphigus (PNP) are diverse, with mucosal lesions being the hallmark, characterized by chronic, erosive, and painful mucositis[34]. Cutaneous lesions show variable morphology, mimicking conditions like bullous pemphigoid, pemphigus, erythema multiforme, lichen planus, graft-versus-host disease, or toxic epidermal necrolysis-like desquamation. Pulmonary involvement, seen in about 93% of cases, often presents as bronchiolitis obliterans, a progressive and life-threatening condition leading to respiratory failure. Typically, severe mucosal disease precedes skin manifestations, necessitating high clinical suspicion due to the variability in presentation. These features underscore the complexity and severity of PNP, requiring prompt recognition and management[35].

Histologic features:

The histologic features of paraneoplastic pemphigus (PNP) include acantholysis, characterized by the detachment of epithelial cells in lesional skin or mucosa, which disrupts tissue integrity[35]. Lichenoid interface dermatitis, marked by inflammation and damage at the dermoepidermal junction, is another common finding. Direct immunofluorescence typically reveals intercellular staining or basement membrane zone staining, consistent with the autoimmune nature of the disease. Additionally, serologic evidence of anti-plakin antibodies supports the diagnosis, highlighting the autoimmune attack on structural proteins critical for epithelial cohesion. These histologic features are essential for confirming PNP in the context of clinical suspicion[36].

Treatment:

The treatment of paraneoplastic pemphigus (PNP) primarily focuses on the early diagnosis and management of the underlying malignancy, as this is crucial for improving outcomes. Standard therapy involves corticosteroids, often combined with other immunosuppressive agents like rituximab, though responses to treatment are variable[36]. Refractory cases may benefit from monoclonal antibodies such as alemtuzumab, while daclizumab was previously used but is no longer available. Symptom management, including antiseptic mouthwashes for mucosal lesions and narcotic pain medications, is essential for patient comfort. Despite these approaches, PNP remains highly resistant to treatment, with a mortality rate of 75–90%, primarily due to sepsis, malignancy, or respiratory failure, and most treatment data are limited to case reports[37].

V. BULLOUS PEMPHIGOID:

Etiology:

Genetic predisposition plays a significant role in the development of BP, with certain genetic factors increasing susceptibility to the disease. Environmental factors, particularly drug triggers, can also provoke BP in genetically susceptible individuals. Drugs containing sulfhydryl groups (e.g., penicillamine, captopril) or other chemical structures (e.g., aspirin, certain cephalosporins) can alter the antigenic properties of BMZ proteins or act as haptens, leading to the formation of autoantibodies. Inflammatory pathways, including complement activation and neutrophil chemotaxis, contribute to the disruption of the BMZ and the formation of blisters, further exacerbating the condition[38].

Pathogenesis:

Drugs can trigger bullous pemphigoid (BP) in genetically predisposed individuals by either modifying the immune response or altering the antigenic properties of the epidermal basement membrane[38]. They may act as haptens, binding to proteins in the lamina lucida and changing their antigenic structure, or they might provoke an autoimmune response by uncovering hidden epitopes. Both systemic and topical drugs have been implicated, often grouped by their chemical structure. Many systemic drugs contain sulfhydryl groups (thiols), such as penicillamine, captopril, penicillin, furosemide, and some cephalosporins. These drugs may interact with proteins in the lamina lucida, acting as haptens and triggering autoantibody production[39, 40]. Furosemide is historically significant among sulfa drugs, with free sulfhydryl groups thought to be central to drug-induced BP (DIBP). Some sulfa drugs, like penicillamine, may also reduce suppressor cell activity, leading to an overproduction of autoantibodies. Other drugs, including certain cephalosporins, aspirin, and non-thiol/non-phenol drugs like ACE inhibitors and NSAIDs, may also contribute to BP. Aspirin, in particular, is suggested to alter the antigenicity of the lamina lucida or attach to cell surfaces, promoting autoantibody formation and BP onset.

Clinical features:

Bullous pemphigoid primarily affects elderly individuals, with approximately 80% of patients being over 60 years old, although it can occur in younger individuals as well[41]. There is no clear gender preference. The skin lesions often begin as a nonspecific rash, typically on the limbs, appearing urticarial or eczematous. This rash can persist for weeks or even months before vesiculobullous lesions emerge. These vesicles and bullae develop in both the prodromal rash areas and in normal skin, with the abdomen often being affected. The lesions are usually thick-walled and may remain intact for several days. If rupture occurs, it leads to a raw, eroded area that heals quickly[41].

Oral manifestation:

Oral lesions in bullous pemphigoid occur less frequently than in cicatricial pemphigoid, with prevalence ranging from 10% to 45% in various studies. These lesions, as reviewed by Shklar and colleagues, typically present as vesicles, erosions, and ulcers. A notable characteristic of oral involvement is the similarity of gingival lesions to those seen in cicatricial pemphigoid. Gingival involvement often affects much or all of the gingival mucosa and is extremely painful. The gingival tissues appear highly erythematous and may desquamate with minimal frictional trauma. The vesicles and subsequent erosions can develop not only on the gingiva but also on other areas of the oral cavity, such as the buccal mucosa, palate, floor of the mouth, and tongue[, 41].

Histopathological:

The histopathological assessment of an early bulla shows a subepidermal blister containing a net of fibrin with a variable number of eosinophils and/or neutrophils accompanied by a dermal inflammatory infiltrate mainly consisting of eosinophils and neutrophils. In the nonbullous phase, histopathological findings may be nonspecific, since only subepidermal clefts and eosinophilic spongiosis may be observed[42].

Treatment:

The primary goal of treatment for bullous pemphigoid is to reduce blister formation and promote the healing of blisters and erosions. Treatment must be tailored to each patient, taking into account pre-existing conditions and other individual factors. Most patients require treatment for 6 to 60 months, after which many experience long-term remission. However, some individuals may have persistent disease that necessitates treatment for many years[42,43].

VI. MUCOUS MEMBRANE PEMPHIGOID:

Etiology:

Genetic factors, such as certain HLA types, may predispose individuals to the condition, but environmental triggers like infections or medications can also play a role. It is often associated with other autoimmune conditions, suggesting a shared immune pathway. The disorder involves a T-cell mediated immune response that contributes to the formation of blisters and tissue scarring[44].

Pathogenesis:

The pathogenesis of mucous membrane pemphigoid (MMP) involves autoantibodies targeting basement membrane zone (BMZ) components like BPAg2 (most common), BPAg1, α6/β4 integrins, laminin-332, and collagen type I. These autoantibodies trigger complement-mediated inflammation, recruiting immune cells (lymphocytes, eosinophils, neutrophils, mast cells) that release proteolytic enzymes, causing epithelial detachment. Anti-laminin 5 IgG and antibodies to α6 integrins also induce blistering, while TGF-β activates fibroblasts, promoting fibrosis and scarring[45].

Clinical features:

Mucous membrane pemphigoid (MMP) is a chronic, progressive condition affecting multiple mucosal sites and sometimes the skin. The oral mucosa is most commonly involved (85%), followed by the ocular conjunctiva (65%), nasal mucosa (20–40%), skin (25–30%), anogenital area/pharynx (20%), larynx (5–15%), and esophagus (5–15%). Lesions may heal with scarring, and disease severity varies widely. Patients with localized oral or skin disease and minimal scarring are classified as "low-risk," while those with high-risk sites (ocular, nasopharyngeal, esophageal, laryngeal, genital) face greater scarring and poorer outcomes. High-risk involvement can lead to blindness, asphyxiation, swallowing difficulties, or significant functional impairment. Scoring systems assess MMP activity and treatment outcomes, but no universal grading standard exists. A recent system by Reeves et al. found no correlation in severity between oral and ocular disease[46].

Histological features:

Histologically, mucous membrane pemphigoid (MMP) is characterized by subepithelial blister formation, where separation occurs at the basement membrane zone (BMZ). The underlying connective tissue exhibits a mixed inflammatory infiltrate, including lymphocytes, eosinophils, and neutrophils. The overlying epithelium remains intact but detaches from the connective tissue. Direct immunofluorescence (DIF) studies of perilesional tissue typically reveal linear deposits of immunoglobulins (IgG, IgA) and complement component C3 along the BMZ, indicating an autoimmune response. Notably, acantholysis is absent, distinguishing MMP from other blistering disorders like pemphigus[47].

Treatment plan:

Mucous membrane pemphigoid (MMP) management focuses on preventing scarring, preserving function, and improving quality of life. Low-risk cases benefit from topical corticosteroids or tacrolimus, while severe cases require systemic therapies like dapsone, immunosuppressants, or rituximab. Monitoring for side effects is essential. Nonpharmacologic options include surgery for complications and low-level laser therapy.

IVIG and rituximab show promise for refractory cases. A tailored, cautious approach ensures effective and safe care[48].

CONCLUSION:

Pemphigus and its variants are life-threatening autoimmune blistering disorders with complex pathogenesis and diverse presentations. Advances in understanding desmosomal proteins and autoantibodies have improved diagnostics and enabled targeted therapies like rituximab, alongside corticosteroids and immunosuppressants. Despite progress, challenges in optimizing care, reducing side effects, and enhancing quality of life persist. Emerging therapies show promise but need further validation. Future efforts should focus on disease triggers, personalized treatments, and preventive strategies, with a multidisciplinary approach key to improving patient outcomes.

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