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Pemphigus: Subtypes, Clinical Features, Diagnosis, and Treatment

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Abstract

Pemphigus is a group of autoimmune blistering disorders associated with autoantibodies against the keratinocyte cell surface. Pemphigus has three major variants: pemphigus vulgaris (PV), pemphigus foliaceus (PF), and paraneoplastic pemphigus (PNP) which all have further subtypes. The variants of pemphigus are classified depending upon the clinical and histological features, immunofluorescence staining pattern, and autoantibody profile of the disease. The onset and course of pemphigus appear on the basis of interaction between genetic predisposition and various triggering factors. Pemphigus vulgaris is the most commonly seen and representative clinical form of pemphigus. Together with clinical manifestations, the histopathological and immunopathological data support the diagnosis. As though some pemphigus variants, particularly pemphigus vulgaris and paraneoplastic pemphigus, have a mortality risk, early diagnosis is necessary and onset of treatment should be promptly initiated. In this chapter, firstly, classification of pemphigus is described. After then, clinical features, histopathological and immunopathological findings, target antigens, etiopathogenesis and comorbidities of each pemphigus variant are discussed briefly.

Keywords: pemphigus, pemphigus variants, clinical manifestations, pathogenesis, histopathology, immunopathology

1. Introduction

Pemphigus is a distinct organ-specific autoimmune blistering disorder involving skin and mucous membranes associated with autoantibodies directed against desmosomes-intercellular adhesive molecule complex localized on the keratinocyte cell surface [1–4].

Pemphigus has three major variants, which are classified depending on the basis of the clinical, histological features, immunofluorescence staining pattern and autoantibody profile of the disease including **pemphigus vulgaris (PV)**, **pemphigus foliaceus (PF)**, and **paraneoplastic pemphigus (PNP)**, which all have further subtypes. Less frequently seen and newer variants of pemphigus include **IgA pemphigus (IGAP)** and **pemphigus herpetiformis (PH)** [1–6].

The term “pemphigus” originates from the Greek word “pemphix”, which has a meaning of “blister” [1]. It is a chronic potentially life-threatening bullous disorder if not treated on time [4, 7, 8]. The phenotypes of pemphigus represent a complex spectrum with multiple genetic and environmental factors playing a role in disease pathogenesis [9, 10].

Together with clinical manifestations, the histopathological and immunopathological data support the diagnosis of the disease. The best site for the cutaneous biopsy for the appropriate histopathological examination is a fresh (< 24 h) small vesicle or 1/3 of the peripheral portion of the blister including the perilesional normal appearing skin. For direct immunofluorescence microscopic (DIF) examination, a perilesional normal appearing skin area up to 1 cm from a fresh vesicle should be taken and should be transformed in saline or in a cylinder of liquid nitrogen in a period lesser than 36 h [11–13].

As though some pemphigus variants, particularly PV and PNP, are potentially life-threatening diseases, early diagnosis is necessary and early onset of immunosuppressive treatment should be promptly initiated [14]. Moreover, some variants of pemphigus may indicate the presence of an underlying malignancy [15].

In this chapter, after the classification of pemphigus, firstly, pathogenetic properties and mechanism of acantholysis are discussed. After then, the review of pemphigus including the epidemiology, clinical features, histopathological and immunopathological findings, target antigens, and comorbidities of each pemphigus variant is discussed briefly.

2. The classification of pemphigus

Pemphigus is classified into two major types according to the level of intraepidermal separation by the most authors: PV and PF [2, 16, 17]. In the last decades, rarer and newer variants of pemphigus have taken part in classification [1, 4, 6], which is described in the following sections.

3. Pathomechanism of pemphigus

The evidence outlines that pemphigus is mediated by pathogenic circulating anti-Desmoglein 1/3 (Dsg) antibodies, which mediate blister formation [1–6, 16–21]. Previously, it was accepted that the presence of anti-Dsg antibodies alone is sufficient for the development of pemphigus [22]. According to the compensation hypothesis, the development of pemphigus is based on the normal epidermal distribution of Dsg1 and 3 molecules and Dsg1 and 3 antibody profiles [2, 16]. However, several reports have been reported pointing the discrepancy between clinical phenotype and autoantibody profile that contradicts with this theory [22–26].

While the production of pathogenic autoantibodies (Abs) is the key for the development of the disease, today it is obvious that many immunological steps are also required prior to the antibody induction [3, 22, 27]. Recent studies investigating the role of lymphocytes have demonstrated the role of T cells and B cells in mouse models of pemphigus and patients, revealing insights into the mechanisms of autoimmunity [28].

Today, it is obvious that some HLA class II alleles are involved in the activation of Dsg3-specific CD4⁺ T cells, which drives the pathogenetic pathways. The epidermal loss of adhesion is induced by pathogenic IgG Abs, which are produced by B cells. HLA-DRB1*04:02 is highly prevalent in PV, which provides the recognition of Dsg3 by CD4⁺ T cells. T cell-dependent B cell activation is critical for the induction of pathogenic IgG Abs [28–31].

Recent studies have also emphasized the important role of T regulatory (reg) cells in the development of pemphigus, and it has been concluded that a balance between self-reactive lymphocytes and T reg cells may be a key element in determining whether individuals produce pathogenic Abs and develop pemphigus or not [9, 32, 33].

4. Pemphigus vulgaris

PV is the most commonly seen and representative clinical form of pemphigus with an incidence of 0.1–0.5/100,000 population [1, 2, 7, 13]. The average age at onset is usually at fourth and fifth decades, but may occur in the elderly or children. The incidence rate is higher among patients with Jewish and Mediterranean ancestry [1, 2, 5, 7, 13]. Various environmental factors such as drugs (captopril, penicillamine), infections (herpes simplex virus, Epstein–Barr virus, etc.), pesticides, ultraviolet radiation (UVR), ionizing radiation, thermal burns, stress and food containing an allium, phenol, thiol, or urushiol have been reported to trigger PV [10, 13, 34].

4.1. Clinical features

Patients with PV may present with only mucosal involvement and some with both mucosal and skin involvement [2, 4, 5]. In majority of the patients, oral mucosa is the site of onset, while cutaneous involvement usually occurs subsequently. It is most commonly characterized by painful erosions, erosions with whitish exudate and erythematous patches usually localized on gingiva and buccal mucosa [1, 2, 4, 5, 13] (**Figures 1 and 2**). The other mucosal areas, nasal cavity, larynx (epiglottis, vocal cords), oropharynx, esophagus, vagina, vulva, penis, and anus may also be affected [1, 13]. Epistaxis and hoarseness are present owing to the involvement of the nose, pharynx, and larynx [1, 13, 35–37]. Genital mucosa is one of the frequent sites involved in PV after the oral mucosa [37].

Cutaneous involvement usually follows mucosal lesions by 3 or 4 months [1, 4, 5]. The skin lesions cause burning and painful sensation. Cutaneous lesions are characterized by flaccid bullae evolving into painful extensive erosive areas (**Figure 3**). These blisters appear on the normal or erythematous skin, which are fragile, break rapidly, and it is hard to find an unruptured bullae. The Nikolsky sign is present. The bullae in PV can be localized or generalized, and any area



Figure 1. The eroded lesions are seen on the palate, right and left sides of the lower lip.

of the skin may be involved. The most frequent areas affected are: face, axilla, and scalp, and this may be due to the fact that Dsg3 has its highest expression in these areas [1, 2]. Umbilicus and/or nail involvement are the other sites that may be affected [2, 4, 5, 13, 38–40]. The presence of the nail lesions may be the sign of relapse or recurrence of the disease [40]. Apart from these, cases of PV with the involvement of only cutaneous lesions have also been reported [41–43].

4.2. Histopathology

Intraepidermal suprabasal acantholysis and infiltration with predominantly neutrophils and eosinophils are observed (tombstone pattern) [2, 5, 13].

4.3. Immunopathology and target antigens

DIF examination shows lace-like IgG deposition with or without C3 on the surface of the keratinocytes in the mid-lower or entire epidermis [2, 5, 12, 13, 16]. Indirect immunofluorescence



Figure 2. The erosions with whitish exudates are seen on the left posterior side of the buccal mucosa.

(IIF) examination, using a substrate of normal human skin or monkey esophagus, shows circulating antiepithelial IgG and lace-like deposition [2, 4, 5, 12]. Enzyme-linked immunosorbent assay (ELISA) is also available in detecting antigens of PV and serves as a tool for assessing the disease severity [44, 45]. Target antigens identified in PV are Dsg1 (with a molecular weight (MW) of 165 kD) and Dsg3 (MW-130 kD) [2–5, 9]. Desmocollin (Dcs) is another antigen that is thought to be responsible in some pemphigus patients [46, 47].

4.4. Associated diseases

Myasthenia gravis (MG) and abnormalities of thymus including benign or malignant thymoma and thymic hyperplasia have been reported to be associated with PV [2, 5, 48, 49]. Thymic abnormalities may precede or follow the onset of pemphigus. The other common disorders that have been reported to be associated with PV are systemic lupus erythematosus (SLE), bullous pemphigoid (BP), and PF [48].



Figure 3. The extensive erosions localized on the back of the patient.

5. Pemphigus vegetans

Pemphigus vegetans (P veg) is accepted as the rarest variety of PV comprising of only 1–2% of all pemphigus patients. P veg has been reported to occur in all age groups, affecting primarily middle-aged females (sex ratio: F/M = 14/3) [50].

5.1. Clinical features

P veg is characterized by vegetative lesions preferentially affecting intertriginous (axillary, inframammary areas) and periorificial regions [2, 5, 50–52]. The initial course of the disease is similar to PV. In the later stages, tumid vegetating, hypertrophic and verrucous lesions occur specifically between skin folds [5, 50, 53]. Two subtypes of P veg are recognized. The first one is Neumann P veg, which usually begins like PV with easily rupturing vesicles and bullae that evolve to form hypertrophic granulating erosions and then vegetating exuding masses. The second type is Hallopeau P veg, which is initially characterized by pustular lesions that break and gradually evolve into vegetating erosions [5, 50]. Mucosal involvement may not always be seen. Involvement of the vermillion border of the lips is the clinical hallmark of oral involvement [54]. Nail involvement is rarely described [50]. In P veg, the course of the disease is long, with remission and recurrence periods. Hallopeau P veg has a relatively benign course, while the Neumann type is often refractory to therapy. One of the frequent complications is the development of secondary bacterial infections, and also malnutrition and cachexia may coexist to the condition [5, 50].

5.2. Histopathology

Suprabasal acantholysis is present in the earlier stages of P veg similar to PV. In the following periods, irregular epidermal hyperplasia, papillomatosis, microabscess composed of eosinophils and neutrophils are also seen [2, 5, 50].

5.3. Immunopathology and target antigens

DIF and IIF examination results are indistinguishable from the findings of PV. As P veg is a subtype of PV, it is expected to react with the same antigens, Dsg1 and Dsg3 [2, 5, 50]. The presence of auto-Abs targeting additional desmosomal proteins including Dsc1, Dsc2, Dsc3 and periplakin have also been reported [51, 55].

5.4. Associated diseases

There are a few reports of P veg associated with internal malignancies and HIV infection [48, 50, 56, 57].

6. Pemphigus foliaceus

PF (foliaceus originates from the Latin word folium with a meaning of “leaf”) is the superficial form of pemphigus [1, 2, 4, 5]. PF has a universal occurrence and occurs sporadically, while the endemic form of PF, called as fogo selvagem (FS) or wild fire (WF), is predominantly seen in the rural and tropical regions of Brazil [5, 7, 16, 58, 59]. Another variant of PF, a localized form, is called as pemphigus erythematosus (PE) [16, 59]. Sporadic form of PF is most common in Europe and USA [16]. The average age of PF ranges between 40 and 60 years, while FS is very often in children, adolescents and young adults. It is usually seen equally in both

females and males with a female preponderancy [59, 60]. FS occurs in genetically related family members. It has been reported that black fly (*Simulium nigrimanum*) bites were more frequent in patients with FS than in control patients [61, 62]. The authors suggested this vector or other infectious agents carry a molecule-triggering anti-Dsg1 response through antigen mimicry or cross-reactivity [58, 61].

6.1. Clinical features

PF is considered as a more benign form of the disease generally presenting with only cutaneous involvement [2, 5, 16, 59]. However, transition from PV to PF or vice versa may be observed [63–65]. More rarely, transition to BP has been reported [65]. The primary clinical feature of PF is fragile, superficial bullae evolving rapidly to erosive lesions. Nikolsky sign is positive. PF usually begins on the trunk, but may also be localized on the face and scalp. Sometimes yellowish crusted and scaly erythematous plaques on face and trunk predominate the clinical findings resembling the clinical picture of seborrheic dermatitis [2, 5, 16, 59, 66]. In FS, the disease usually begins on the head, neck, and seborrheic regions of the skin. The oral mucosa, palms of the hands, and plant of the feet are usually spared [59, 66]. In both PF and FS, lesions may become confluent and can transform to exfoliative erythroderma [67]. These patients should be hospitalized due to the risk of metabolic instability and mortality [1, 16, 59]. Pain and/or burning sensation may be noted. Unlike PV, there is no oral or other mucosal involvement [2, 5, 16, 59]. Mildest form of PF may be misdiagnosed for years [61].

6.2. Histopathology

Histological separation is more superficial than PV and exists along the granular layer. Eosinophilic spongiosis may also be seen in very early forms of PF [2, 5, 16, 59].

6.3. Immunopathology and target antigens

DIF and IIF examination findings are identical to the findings of PV [1, 5, 16, 59]. The intensity of the fluorescent stain is greater in the upper epidermis. Dsg1 is the specific target antigen [59].

6.4. Associated diseases

PF may be associated with MG and thymoma [2, 5, 16, 48]. A few cases of coexistence of PF with psoriasis [68, 69], malignancy [70, 71] and Graves' disease [72] have been reported. There also a few reports regarding cases of UVR and radiotherapy-induced PF [59, 73, 74].

7. Pemphigus erythematosus

PE, also known as Senear-Usher syndrome, is a localized form of PF [2, 5, 16, 59]. It affects most frequently elderly population. Clinical and immunological features of PE resemble both PF and cutaneous lupus erythematosus (LE) [16, 75]. Clinically erythematous plaques, scaly

to crusted lesions, occur across the malar areas of the face in a butterfly distribution mimicking the clinical appearance of LE [16]. The lesions are usually induced by UVR [75]. In 80% of the patients, antinuclear antibodies (ANA) without the presence of anti-ds-DNA antibodies may be detected [1, 2, 5, 16, 59]. DIF examination of the lesions may show both intercellular (IC) deposition IgG/C3 and granular deposition of IgG and C3 at the dermoepidermal junction (lupus band test) [5, 16, 59, 75].

8. Paraneoplastic pemphigus

PNP is a rare disease that manifests with clinically distinct painful mucosal erosions and polymorphic cutaneous lesions [1, 4, 15, 76]. The incidence of PNP is thought to be less common than PV or PF. PNP presents most often in older patients aged between 45 and 70 years [77, 78]. In almost all cases, PNP is associated with neoplasms mostly with lymphoproliferative diseases [4, 15, 66, 76–78].

8.1. Clinical features

The onset of the lesions usually presents with initially limited cheilitis and/or ulcerative stomatitis, which then progresses to severe, intractable, hemorrhagic stomatitis with persistent painful mucosal ulcerations in the oropharynx and esophagus [4, 5, 15, 16, 77]. Oral lesions usually extend to the vermillion border of the lips [15, 77]. Eye involvement especially includes conjunctival erosions and occurs in 70% of patients [79–82]. Cutaneous lesions are usually seen after the onset of mucosal involvement with a duration of days to months [77, 83, 84]. Cutaneous lesions are widespread and are usually polymorphic including lichenoid lesions, erythema multiforme-like lesions, vesiculobullous and erosive lesions. The palmar involvement is usually observed [4]. Lichen planus-like lesions localized on skin, nails and/or mucosa resemble lichen planus, target-like lesions resemble erythema multiforme, and bullous lesions and erosive lesions resemble PV and bullous pemphigoid [4, 15, 66, 76, 77, 83–87]. Cutaneous lesions mimicking graft versus host disease or Stevens-Johnson syndrome may also be observed [86, 87].

As though most of the patients with PNP are associated with malignancies, the prognosis of PNP is severe with a high mortality rate [15, 77, 83, 84, 88, 89]. Internal organ involvement including lungs (Bronchiolitis obliterans), thyroid, kidney and gastrointestinal system has been documented [15, 88, 89]. Most authors have reported that the term “paraneoplastic pemphigus” is too restrictive to describe the developing multiorgan syndrome involvement and have suggested a new nomenclature named as paraneoplastic autoimmune multiorgan syndrome (PAMS) [15, 88].

8.2. Histopathology

Several biopsies are often required to achieve the diagnosis [77, 81]. The histopathological features of PNP reveal variability according to the type of the morphology of the cutaneous

lesion [15, 77, 84, 90]. Intraepidermal suprabasal acantholysis (resembling PV), keratinocyte necrosis and vacuolar interface changes (resembling erythema multiforme/lichen planus) may be observed [77, 90].

8.3. Immunopathology and target antigens

DIF examination is characterized by the deposition of immunoreactants (IgG deposits with or without compleman) in IC region of epidermis and deposition of IgG/IgM and/or C3 along the basal zone membrane (BZM) [15, 17, 77, 84]. IIF using rat bladder epithelium as substrate shows an IC pattern that appears to be highly specific but less sensitive for PNP/PAMPS (including monkey esophagus (86% sensitivity) and murine tongue (100% sensitivity)). A variety of antigens including Dsg1, Dsg3, envoplakin, periplakin, bullous pemphigoid antigen1 (BPAG1), plectin, desmoplakin 1, and desmoplakin 2 can be detected by immunoprecipitation [15, 17, 77, 84].

8.4. Associated diseases

PNP usually precedes the diagnosis of the underlying malignancy. In 1/3 of the cases, the underlying malignancy has not been diagnosed at the time of diagnosis. Therefore, when a diagnosis of PNP is made, a comprehensive workup for an underlying malignancy is mandatory [4, 15, 76, 77]. Hematological malignancies are associated with 84% of the patients of PNP. The most common reported hematological malignancies are non-Hodgkin lymphoma (38.6%), chronic lymphocytic leukemia (18.4%), Castleman disease (18.4%), and thymoma (5.5%) [15, 48, 77, 84].

9. Pemphigus herpetiformis

PH is a rare and distinct entity of pemphigus [6, 11]. It has been first described in patients who had clinical features that resemble dermatitis herpetiformis, but showed the features of pemphigus histopathologically and immunologically [6, 11, 91, 92]. It usually accounts 6–7% of cases and affects females and males equally [11, 92].

9.1. Clinical features

Patients usually have erythematous, gyrate, annular and polycyclic lesions with clusters of pustules, vesicles, in herpetiform pattern. The clinical presentation of PH may be atypical and may mimic various other bullous diseases [6, 92]. Pruritus is usually present [6, 11, 92, 93]. Mucous involvement is not a usual finding [6, 11]. PH usually has a good psis, although some cases may progress into classic pemphigus [11, 94].

9.2. Histopathology

The histopathological examination shows eosinophilic or neutrophilic spongiosis and micro-abscesses (neutrophils and/or eosinophils) in the mid or subcorneal epidermis mostly without acantholysis. Acantholysis may be seen in the later stages of the disease process and may be minimal [6, 11, 92, 93].

9.3. Immunopathology and target antigens

DIF examination shows IC deposits of IgG and C3 in epidermis, while IIF examination shows circulating IgG auto-Abs. The target antigen is usually Dsg 1 (or less frequently Dsg3) [6, 11, 95]. Recent studies have demonstrated DSc1, Dsc3 and unknown protein 178-kDa protein [11, 92, 96] by immunoblotting.

9.4. Associated diseases

There is evidence of association of PH with some diseases such as SLE, autoimmune hemolytic anemia and psoriasis and with some malignancies (prostate, esophagus) in the literature [11, 97–101].

10. IgA pemphigus

IGAP is a rare entity of pemphigus [6, 11]. It has two clinical types: intraepidermal neutrophilic type (IEN) and subcorneal pustular dermatosis (SPD) [6, 11, 66]. It is usually observed in the middle-aged or the elderly with an average age at 48 years, but also has been reported in childhood [6, 11]. There is a slight predominance of females [6].

10.1. Clinical features

Patients with both types of IGAP present with flaccid vesicles or pustules on either erythematous or normal skin mostly localized on axillary and groin areas, but trunk, proximal extremities and abdominal regions are also involved. The pustules tend to coalesce to form annular or circinate pattern. SPD is clinically indistinguishable from the disease subcorneal pustular dermatosis. In IEN type, pustules coalesce to form a sunflower-like configuration [2, 6, 11, 102, 103]. Pruritus is severe and affects patients' daily activities. Mucosal involvement is rare [2, 6, 11].

10.2. Histopathology

There is slight acantholysis and neutrophilic infiltration in epidermis. In SPD type, neutrophilic infiltration is localized subcorneally in the upper epidermis, while in IEN type in lower epidermis or entire epidermis [5, 6, 11].

10.3. Immunopathology and target antigens

In DIF examination, deposition of IgA in IC space of epidermis is detected. IgG and/or C3 is sometimes deposited but is weaker than IgA. In the SPD type, deposition is limited to upper epidermis, while in IEN type, it is deposited in lower epidermis or in whole epidermis [6, 11]. Using healthy human skin and monkey esophagus, circulating IgA auto-Abs have been demonstrated in 50% of the patients [5, 11]. The antigens in IGAP are Dsg1, Dsg3, Dsc1, and Dsc3 [3, 4].

10.4. Associated diseases

In SPD type, the most frequently reported association is monoclonal IgA gammopathy [11, 48, 103]. **The skin symptoms may precede monoclonal IgA or may be detected during the disease course** [104]. **The other associated diseases are** multiple myeloma, lymphoma, Crohn disease, and ulcerative colitis [48, 103, 104].

11. Conclusion

Pemphigus, especially some types, is a life-threatening disease and has a mortality risk. Therefore, the diagnosis should be made as soon as possible, and the treatment should be started. Today, a better understanding of the role of immunological dysregulation in the pathogenesis will also cause offering newly targeted therapeutical agents in the treatment of pemphigus.

Abbreviations

Abs	Antibodies
ACE	Angiotensin-converting enzyme
ANA	Antinuclear antibody
Anti-ds DNA	Double-stranded DNA antibody
BO	Bronchiolitis obliterans
BZM	Bazal zone membrane
C3	Compleman 3
DIF	Direct immunofluorescence
Dsc	Desmocollin
Dsg	Desmoglein
ELISA	Enzyme-linked immunosorbent assay
FS	FogoSelvagem
HLA	Human leucocyte antigen
IC	Intercellular
IEN	Intraepidermal neutrophilic type
Ig	Immunoglobulin

IGAP	IgA Pemphigus
IIF	Indirect immunofluorescence
MG	Myasthenia gravis
MW	Molecular weight
P veg	Pemphigus vegetans
PAMPS	Paraneoplastic autoimmune multi-organ syndrome
PE	Pemphigus erythematosus
PF	Pemphigus foliaceus
PH	Pemphigus herpetiformis
PNP	Paraneoplastic pemphigus
PV	Pemphigus vulgaris
Reg	Regulatory
SLE	Systemic lupus erythematosus
UVR	Ultraviolet radiation
WF	Wild fire

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