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REVIEW
PEMPHIGUS

Clinicians' pearls and myths in pemphigus

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ABSTRACT

Pemphigus comprises a heterogeneous group of autoimmune blistering diseases, which can affect both skin and mucous membranes, especially oral mucosa. This group of diseases shows usually a chronic-relapsing course. Since pemphigus is a rare disease, the diagnosis is often delayed, because it is based upon the recognition of consistent clinical, histologic, and direct immunofluorescence findings, as well as indirect immunofluorescence, and/or enzyme-linked immunosorbent assay. Usually the patients are treated for multiple other conditions before starting the correct therapy, leading to a critical reduction of the patients' quality of life. This review is a succinct compilation of pearls gathered from clinical experience in pemphigus and the myths that may have influenced everyday practice but have been proven false. This review provided a selection of such dilemmas and controversies, focusing on myths and pearls that can help young dermatologist in the clinic, while also dispelling them.

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KEY WORDS: Pemphigus, Review; Dermatology.

Pemphigus diseases are group of rare, chronic, potentially life-threatening autoimmune blistering disorders characterized by intraepithelial acantholysis, induced by the binding of circulating autoantibodies (immunoglobulin G [IgG] or less common immunoglobulin A [IgA]) against desmosomal adhesion molecules. According to the auto-antibody profile, patients develop cutaneous and/or mucosal erosions flaccid bullae, or pustules.^{1,2} Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are the two most frequent clinical forms among the various subtypes. Nevertheless, rarer subtypes such as IgA pemphigus, paraneoplastic pemphigus (PNP), should also be considered in the differential diagnosis.^{3,4} The different forms of pemphigus are distinguished by their clinical features, associated autoantigens, laboratory findings and co-morbidities. The clinical myths and pearls presented here highlight some of the commonly held assumptions regarding pemphigus diseases to illuminate subtleties of managing patients with this condition (Table I).

Myths and pearls

Myth: diagnosis can be made clinically

The diagnosis of pemphigus is often delayed⁵ because even in cases in which the clinical findings strongly suggest pemphigus, failure to recognize the clinical features and to confirm the diagnosis by immune serological measures is common. The diagnosis of pemphigus is based upon the recognition of characteristic clinical, histologic, and direct immunofluorescence (DIF) findings, as well as indirect immunofluorescence (IIF), and/or enzyme-linked immunosorbent assay (ELISA). Detection and binding of autoantibodies against desmosomal adhesion molecules are the basis of diagnostic investigations. Nevertheless, clinical assessment should include clinical history, a complete examination of cutaneous and mucosal surfaces and a review of the patient's medications. The standard laboratory work-up for patients with clinical findings suggestive of pemphigus includes a lesioned skin or mucosal biopsy

TABLE I.—*Pemphigus: clinician myths and pearls.*

Myths
Diagnosis can be made clinically
Pemphigus may affect only the elderly
Neonatal pemphigus is not a curable disease
Pemphigus is a curable disease
Pearls
Pemphigus group has two major entities
Pemphigus herpetiformis shows a clinical phenotype resembling dermatitis herpetiformis
IgA pemphigus may be associated with internal diseases
Paraneoplastic pemphigus: lesions in the oral cavity and the lips may be a hint for underlying malignancy
Paraneoplastic pemphigus: cutaneous lesions may resemble other skin diseases leading to diagnostic delay

for routine hematoxylin and eosin (H&E) staining and perilesional skin or mucosal biopsy for DIF. Furthermore, serum collection for detection of autoantibodies by enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence (IIF) are very relevant and complementary.

Pearls: pemphigus group has two major entities

The pemphigus group include two major entities; pemphigus vulgaris (PV) and pemphigus foliaceus (PF) that are characterized by different autoantibody profiles, distinct clinical presentation and encounter about 90–95% of cases in clinical practice. Based on the autoantibody repertoire, PF is characterized by IgG autoantibodies directed against desmoglein-1 (DSG-1) leading to subcorneal loss of epidermal adhesion with cutaneous involvement only. In PV, two phenotypes may arise. In mucosal PV, IgG autoantibodies are detected against desmoglein-3 (DSG-3) responsible for blistering and erosions of the mucosal surfaces. In mucocutaneous PV, both anti-DSG-1 and anti-DSG-3 IgG autoantibodies are present and may cause extensive mucocutaneous blistering and erosions. Moreover, PF shows an endemic form, which is called fogo selvagem (wildfire) and occurs in rural areas of South America and Tunisia.⁶⁻⁹

Myth: pemphigus may preferentially affect the elderly

The age at initial presentation of pemphigus has a peak incidence in most populations between the 4th and 6th decade.^{4, 10} The relative frequencies of pemphigus vary greatly depending on the ethnicity and geographical area.^{11, 12} Newborns, children, and young adults may be affected, but less often than adults. 1-4% sporadic form of PV has been described in children.^{13, 14} Furthermore, the endemic variant of PF, fogo selvagem, frequently affects children and individuals less than 20 years old.^{9, 15}

Myth: neonatal pemphigus is not a curable disease

Newborn babies may develop blisters at the time of delivery which is a demanding situation for both, parents and physicians. Of note, not every blistering disorder in newborns is genetic; autoimmune disorders may also cause blistering in newborns. Neonatal pemphigus is a rare transient condition due to transplacental transmission of IgG autoantibodies from a mother with pemphigus. The clinical features, laboratory findings and associated autoantigens of neonatal pemphigus are consistent with pemphigus. Neonatal PF occurs less frequently than neonatal PV.^{16, 17} Cutaneous blisters usually resolve spontaneously within 30 days. Mild topical corticosteroids may help speed up healing. Prematurity and fetal death seem to be associated with particularly severe disease in pregnant mothers with pemphigus. Therefore, careful management of pregnant women with PV requires close collaboration between dermatologist and neonatologist.

Myth: pemphigus is a curable disease

There is currently no cure for pemphigus, but several treatment strategies can help keep the symptoms under control or in complete remission. The main aim of treatment is to stop blistering and prevent new ones forming. However, relapses occur in up to 50% of patients, and severe adverse events related to immunosuppressants in up to 65% of patients. Only 50% of patients may stop taking corticosteroids within 3 years.¹⁸⁻²⁰

The introduction of the anti-CD20 monoclonal antibody, rituximab, has revolutionized the treatment of both, PV and PF with regard to high therapeutic efficacy and limited side effects.²⁰ Treatment of pemphigus with 2 x 1 g rituximab given 2 weeks apart has demonstrated efficacy when given in combination with moderate or low doses of corticosteroids.²⁰ About 70-90% of patients achieve complete clinical remission off-corticosteroids within 6-24 months.²⁰

Pearl: pemphigus herpetiformis shows a clinical phenotype resembling dermatitis herpetiformis

Pemphigus herpetiformis or herpetiform pemphigus is a rare clinical variant of PV, pruritus is quite common. Cutaneous findings include annular and arcuate erythematous plaques, which are arranged in a herpetiform or annular pattern. Mucosal involvement is uncommon despite the common presence of anti-DSG-3 IgG antibodies. Given the clinical similarities, dermatitis herpetiformis (also known as Duhring's disease) should be considered as a

differential diagnosis. In addition to IgG autoantibodies mainly against DSG-3, anti-desmocollin-1 (DSC-1) or anti-DSC-3 IgG reactivity may be recorded.²¹ Gluten sensitivity is not detectable in pemphigus herpetiformis. Pemphigus herpetiformis and IgA pemphigus together account for <5% of pemphigus cases.²²

Pearl: IgA pemphigus may be associated with internal diseases

IgA pemphigus (IGAP) is divided into two phenotypes; the subcorneal pustular dermatosis-type (SPD-type) which is characterized by IgA autoantibodies against Dsc-1 and the intraepidermal neutrophilic dermatosis-type (IEN-type) where the autoantigen is largely unknown. The SPD-type IGAP is clinically undistinguishable from classic subcorneal pustular dermatosis (Sneddon-Wilkinson disease) with tiny pustules in the flexural surfaces. DIF is needed for the making the proper diagnosis. The IEN-type IGAP is characterized by blisters, pustules and crusts that tend to coalesce in a herpetiform or circinate pattern surrounded by erythematous plaques with prominent peripheral collar-ette-like scaling giving the so cold 'sunflower' appearance for the lesions. Mucosal involvement is uncommon. The trunk and proximal extremities are common sites for involvement. Pruritus may or may not be present. Diagnosis is made by direct immunofluorescence and histopathology. IgA pemphigus has been reported to be associated with monoclonal IgA gammopathy, inflammatory bowel disease, and rheumatic autoimmune disorders.²³

Pearls: lesions in the oral cavity and on the lip may be a hint for underlying malignancy in paraneoplastic pemphigus

Despite the fact that pemphigus is a rare disease, awareness of any atypical presentation, must alert the clinicians to consider paraneoplastic pemphigus (PNP). PNP is an extreme rare variant of pemphigus and is caused by an underlying malignancy, mainly associated with hematologic neoplasms,²⁴ non-Hodgkin lymphoma, chronic lymphocytic leukemia, Castleman's disease and thymoma.^{25, 26} Less common is the association with other malignancies such as carcinomas of epithelial origin (e.g. adenocarcinoma of pancreas, colon, breast and prostate).^{26, 27} Sarcomas²⁸ and malignant melanoma²⁹ have also been reported. Several reports reveal that more than half of patients diagnosed with PNP have an occult underlying malignancy at the time of initial presentation.³⁰ PNP is a heterogenous disease, diagnosis is highly challenging. The earliest

and most common clinical presentation is severe erosive stomatitis with the characteristic hemorrhagic cheilitis; bloody crusts on the vermillion border of the lip with blisters, vesicles, erosions.³¹

Pearls: paraneoplastic pemphigus cutaneous lesions may resemble other skin diseases causing diagnostic delay

In PNP, heterogenous cutaneous lesions may resemble other skin diseases such as erythema multiforme,³² toxic epidermal necrolysis,³³ linear IgA bullous dermatosis,³⁴ bullous pemphigoid³⁵ or lichen planus,³⁶ onychodystrophy,³⁷ alopecia^{38, 39} as well as ocular lesions^{35, 40} may occur and although rare, these may also present in the absence of any mucosal involvement.³⁹ Of note, the time interval between the onset of oral lesions and initial cutaneous manifestations may vary from days to months.

During clinical examination, oral lesions, the earliest manifestation of PNP, are often misdiagnosed as herpes simplex virus infection, Behçet's disease, oral candidiasis, recurrent aphthous stomatitis and or mucosal reaction to local irritants.²⁶ In such cases, characteristic resistance to therapy should alert the clinician to consider PNP as a differential diagnosis. Moreover, the cutaneous lesions of PNP are not only heterogeneous (varying from patient to patient) as they are polymorphous from multiform lesions to extensive toxic erythroderma. Also, during disease progression cutaneous manifestation may change, and one morphology may transform into another.^{33, 41-43} Flaccid blisters, which are not uncommon in PNP, may be initially diagnosed as PV or PF. In such cases, acral blisters as well as blisters in palms and soles, when present, may serve as a hint to exclude PV.^{44, 45} Diagnosis and management of PNP is challenging and requires a multidisciplinary evaluation and close collaboration between different clinical disciplines, but the prognosis is still very somber and mainly dependent on the course of the underlying malignancy (Table II).⁴⁶

Conclusions

Learning points

In conclusion, the learning points of this analysis showed that: 1) pemphigus is a rare autoimmune blistering disorder which may be easily missed by healthcare professionals other than dermatologists; 2) the pemphigus group include two major entities and several rare variants; 3) pemphigus may affect newborn babies, children, young adults and elderly individuals with a peak incidence be-

TABLE II.—*Synopsis of clinical and laboratory findings in pemphigus.*

	Auto-antigens	Clinical features		Immunofluorescence		Histopathology
		Mucosa	Cutaneous	Direct	Indirect	
PV	Dsg 1; Dsg 3	erosions	Flaccid bullae and erosions	Cell surface deposits of IgG and/or C3 on epidermal keratinocytes	Cell surface deposits of IgG on monkey esophagus epithelium	Suprabasal acantholysis of epidermis
PF	Dsg 1	absent	Fragile blisters, shallow erosions, erythematous patches, crusts	Cell surface deposits of IgG and/or C3 on epidermal keratinocytes	Cell surface deposits of IgG on monkey esophagus epithelium	Subcorneal or granular layer acantholysis of epidermis
PNP	Dsg 3 EVPL, PPL, A2ML1 and others	Severe stomatitis, conjunctivitis, involvement of all mucosal surfaces	Variable findings (blisters, erosions, lichenoid lesions). Other: bronchiolitis obliterans	Cell surface deposits of IgG and/or C3 on epidermal keratinocytes	Cell surface deposits of IgG on monkey esophagus and urinary bladder epithelium	Suprabasal acantholysis of epidermis. Suprabasal keratinocyte apoptosis, lichenoid interface dermatitis
IgA-Pemphigus	Dsc 1 and others	absent	vesicles, pustules, crusts in annular, circinate, or herpetiform morphology	Cell surface deposits of IgA on epidermal keratinocytes	Intercellular deposits of IgA on monkey esophagus	Subcorneal clefts and pustules, minimal acantholysis; mixed infiltrate in dermis. Intraepidermal pustules; minimal acantholysis; mixed dermal infiltrate

DSG: desmoglein, DSC: desmocollin, EVPL: envoplakin, PPL: periplakin, A2ML1: A2-macroglobulin-like.

tween the 4th and 6th decade; 4) neonatal pemphigus is a rare transient condition due to transplacental transmission of IgG autoantibodies from mothers with anti-desmoglein 3 IgG antibodies, which usually resolve spontaneously within 30 days; 5) despite considerable relapse rate of up to 40%, novel targeted therapies help keep the symptoms under control or in complete remission; 5) IgA pemphigus may be associated with monoclonal IgA gammopathy, inflammatory bowel disease, and rheumatic autoimmune disorders; 6) paraneoplastic pemphigus is mainly associated with hematologic neoplasms and disorders and may be the first sign for an underlying malignancy; and 7) oral lesions, as earliest manifestation of PNP, are often misdiagnosed as herpes simplex virus infection, Behçet's disease, oral candidosis, recurrent aphthous stomatitis and stomatitis to local irritants.

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