Intraepithelial autoimmune blistering dermatoses: Clinical features and diagnosis

Carmen M. Montagnon, MD,[a] Stanislav N. Tolkachjov, MD,[b] Dedee F. Murrell, MA, BMBCh, MD,[c] Michael J. Camilleri, MD,[a,d] and Julia S. Lehman, MD[a,d]
Rochester, Minnesota; Dallas, Texas; and Sydney, Australia

Learning objectives
After completing this learning activity, participants should be able to describe the clinical features and diagnostic criteria for intraepithelial autoimmune bullous dermatoses including pemphigus (superficial, suprabasilar, drug-induced), paraneoplastic pemphigus/PAMS, and clinical and microscopic mimics.

Disclosures
Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors
The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Intraepithelial autoimmune blistering dermatoses are a rare group of skin disorders characterized by the intraepithelial disruption of intercellular connections through the action of autoantibodies. The first article in this continuing medical education series explores the background, epidemiology, clinical features, and diagnostic criteria of each of the major intraepithelial autoimmune blistering dermatoses, including pemphigus foliaceus, pemphigus erythematosus, pemphigus herpetiformis, fogo selvagem, pemphigus vulgaris, pemphigus vegetans, drug-induced pemphigus, IgA pemphigus, IgG/IgA pemphigus, and paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome. (J Am Acad Dermatol 2021;84:1507-19.)

Key words: drug-induced pemphigus; fogo selvagem; IgA pemphigus; IgA/IgG pemphigus; paraneoplastic autoimmune multiorgan syndrome; paraneoplastic pemphigus; pemphigus erythematosus; pemphigus foliaceus; pemphigus herpetiformis; pemphigus vegetans; pemphigus vulgaris.

INTRODUCTION

Pemphigus should be considered in patients who present with a persistent erosive and scaly cutaneous eruption or recurrent mouth ulcerations and who lack an alternative diagnostic explanation. Biopsy for routine microscopy and direct immunofluorescence (DIF) evaluation represents the gold standard for diagnostic confirmation of suspected pemphigus.

From the Department of Dermatology,[a] Mayo Clinic; Epiphany Dermatology, Dallas[b]; Department of Dermatology, St. George Hospital, University of New South Wales[c]; and Department of Laboratory Medicine and Pathology, Mayo Clinic.[d]
Funding sources: None.
IRB approval status: Not applicable.
Accepted for publication November 2, 2020.
Reprints not available from the authors.
Correspondence to: Stanislav N. Tolkachjov, MD, Epiphany Dermatology, 1640 FM 544, Suite 100, The Colony, TX 75056. E-mail: Stan.tolkachjov@gmail.com.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.11.075

Date of release: June 2021.
Expiration date: June 2024.

Scanning this QR code will direct you to the CME quiz in the American Academy of Dermatology's (AAD) online learning center where after taking the quiz and successfully passing it, you may claim *1 AMA PRA Category 1 credit*. NOTE: You must have an AAD account and be signed in on your device in order to be directed to the CME quiz. If you do not have an AAD account, you will need to create one. To create an AAD account: go to the AAD's website: www.aad.org.

Abbreviations used:

DIF:	direct immunofluorescence
DSG:	desmoglein
ELISA:	enzyme-linked immunosorbent assay
FS:	fogo selvagem
HLA:	human leukocyte antigen
IIF:	indirect immunofluorescence
PAMS:	paraneoplastic autoimmune multiorgan syndrome
PE:	pemphigus erythematosus
PF:	pemphigus foliaceus
PH:	pemphigus herpetiformis
PNP:	paraneoplastic pemphigus
PV:	pemphigus vulgaris
PVe:	Pemphigus vegetans
SPD:	subcorneal pustular dermatosis

Care must be taken to biopsy clinically intact epithelium, because sampling eroded skin or mucosa could yield inaccurate results. Serologic studies, including indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA) for desmogleins (DSG) 1 and 3, can support diagnosis and help in the subclassification of the various types of pemphigus. In rare cases in which it is not feasible to obtain biopsy for both, serologic studies may serve as a diagnostic proxy because of the high level of specificity of these tests. Fig 1 illustrates a diagnostic algorithm for patients with a suspected autoimmune mucocutaneous blistering disorder.

SUPERFICIAL IgG PEMPHIGUS: PEMPHIGUS FOLIACEUS

Key points

- Characterized by superficial skin acantholysis in a seborrheic distribution
- The autoantibody target is DSG-1

Clinical features

Pemphigus foliaceus (PF) commonly presents as an erosive dermatitis with crusted plaques, "puff pastry-" or "cornflake-" like scaling, erosions, and superficial, flaccid vesiculobullae in a seborrheic distribution involving the scalp, face, trunk, and upper extremities.[1,2] The lesions may coalesce to become a more generalized, erythrodermic exfoliative dermatitis covering the entire skin surface.[3,4] Exposure to sunlight and certain drugs are known triggering factors.[1] PF has also been reported in the setting of pathergic wounds, mimicking skin cancer.[5]

Diagnosis

Histopathology reveals acantholysis at the granular layer, a change that may be focal or subtle, depending on the area selected for biopsy (Fig 2).[6] In some cases, the granular layer should be carefully scrutinized, as changes can be subtle or focal. Care also must be taken to ensure that there is no substantial dyskeratosis, which might instead suggest Grover disease, or that there is no acantholysis throughout the epidermis, which might instead suggest Hailey-Hailey disease.

DIF reveals IgG with or without complement 3 (C3) antibody deposition within intercellular spaces between keratinocytes in a chicken-wire-like distribution.[4] Intercellular deposition of IgG can be seen nonspecifically, likely due to the presence of circulating ABO antibodies. Thus, the finding of a low-positive intercellular substance pattern on IIF, particularly in the setting of negative ELISA studies for DSG1 and DSG3, should be interpreted with caution.[7] Serologic studies with IIF demonstrate positive intercellular deposition of IgG on monkey esophagus. The autoantibody target is DSG-1, which, when detected via ELISA, has a sensitivity of 92% and specificity of 98% or greater.[4,8]

SUPERFICIAL IgG PEMPHIGUS: PEMPHIGUS ERYTHEMATOSUS

Key point

- Characterized by overlapping features of PF and systemic lupus erythematosus

Clinical features

Pemphigus erythematosus (PE) most commonly involves photodistributed areas, including the face, scalp, upper chest, and upper back.[2,9,10] When on the face, the lesions are usually found in a malar "butterfly" distribution, similar to that seen in systemic lupus erythematosus.[9-12] Characteristically, PE is exacerbated by ultraviolet exposure.[13,14] Lesions begin as flaccid bullae and evolve into erosions with scale and crust. Associated conditions include thymoma, myasthenia gravis, other autoimmune disorders, and bronchogenic carcinoma.[10,12,15,16]

Diagnosis

ELISA studies usually reveal circulating autoantibodies to DSG-1, although those directed against DSG-3 also may develop.[13] Other laboratory findings may include positive serologic antinuclear antibodies (detected in 30% to 83% of patients), lymphopenia, anemia, thrombocytopenia, proteinuria, elevated erythrocyte sedimentation rate, or rheumatoid factor.[9,10] Anti-double-stranded DNA, anti-Smith, anti-Ro, and antiribonucleoprotein antibodies are rarely present.[17] Patients occasionally meet the American College of Rheumatology criteria for systemic lupus erythematosus.[9]

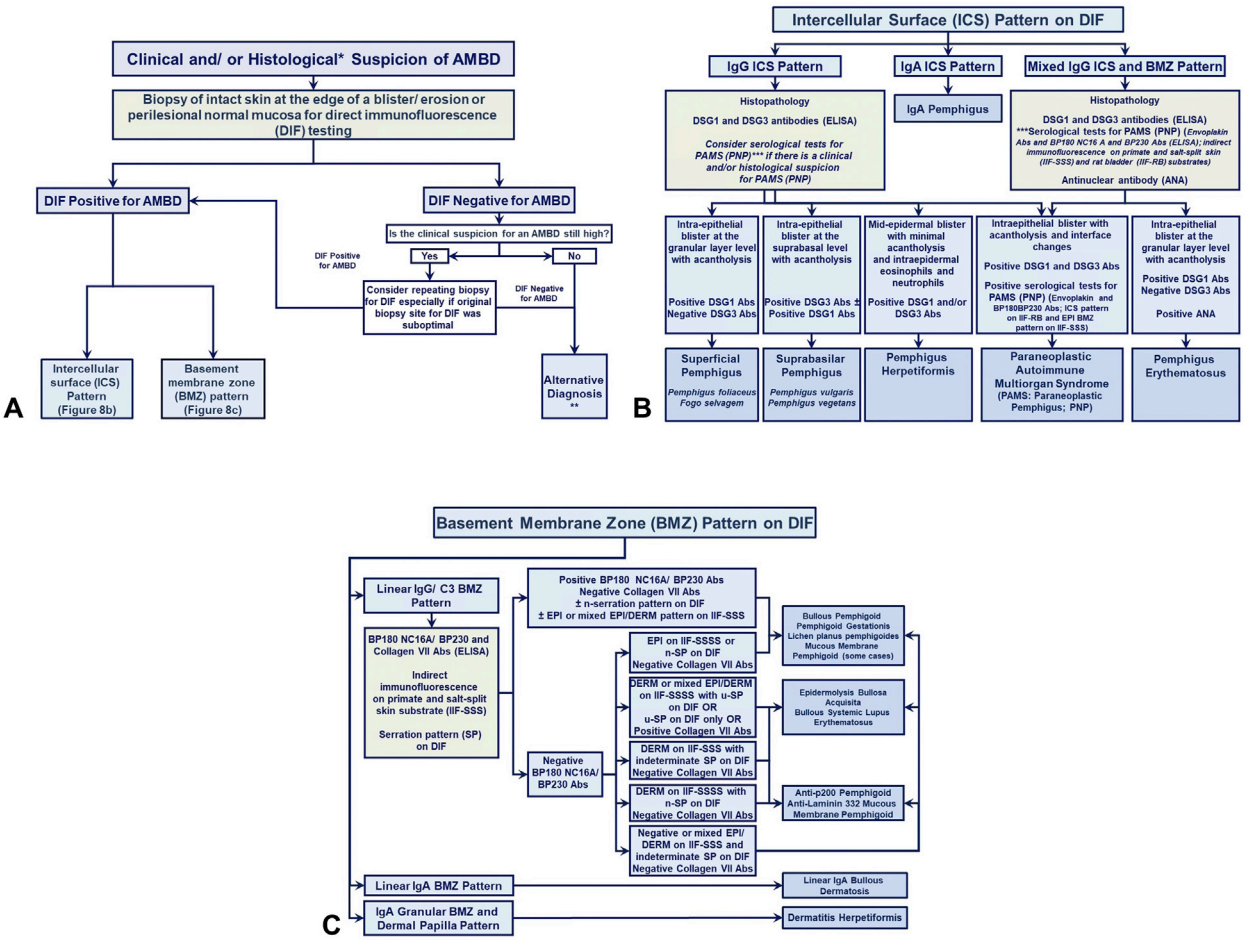

Fig 1. Diagnostic approach to a patient with a suspected AMBD. **A**, In general, for all AMBDs, biopsy for histopathology should be obtained from a new blister and biopsy for DIF should be obtained from perilesional skin ≤ 1 cm from the blister.[97] DIF testing on a skin biopsy from an appropriate site is the initial test to diagnose an AMBD. A negative test is usually sufficient to exclude a diagnosis of AMBD; however, if clinical suspicion is high and there is no other obvious alternative diagnosis, repeat biopsy for DIF testing should be considered, especially if the original biopsy was from a suboptimal site. **B**, Diagnostic algorithm for an ICS pattern on DIF testing of a skin biopsy. **C**, Diagnostic algorithm for a BMZ pattern on DIF testing of a skin biopsy. *AMBD*, Autoimmune mucocutaneous blistering disorder; *BMZ*, basement membrane zone; *DERM*, dermal pattern; *DIF*, direct immunofluorescence; *DSG*, desmoglein; *EPI*, epidermal pattern; *ICS*, intercellular; *IIF-SSSS*, indirect immunofluorescence on salt-split skin; *SP*, serration pattern. *see Table I; **see Table II; ***Other rare autoimmune subepidermal AMBD include anti-collagen IV pemphigoid and anti-p105 pemphigoid.

Like PF, PE shows subcorneal acantholysis on histopathology.[12,18] DIF demonstrates the combined pattern of cell-surface IgG with or without C3 deposition and granular deposits of 1 (most commonly, IgM) or multiple conjugates along the dermoepidermal junction.[9,13,14] IIF reveals cell-surface deposition on monkey esophagus substrate in the majority of patients with PE.[11] An antinuclear antibody may be observed within keratinocyte nuclei, which have been found to be present nonspecifically and in patients with connective tissue disorders.[19,20]

SUPERFICIAL IgG PEMPHIGUS: FOGO SELVAGEM

Key point

- Endemic form of PF that occurs in certain areas of Brazil, Colombia, and Tunisia

Background

Fogo selvagem (FS), which translates to "wildfire" in Portuguese, is also known as Brazilian pemphigus or endemic PF.[21,22] FS occurs in certain subtropical areas of Brazil, most commonly in inhabitants of poor, rural housing conditions near rivers and

Table I. Characteristic findings of intraepithelial autoimmune blistering disorders

Disorder	Clinical features	Histopathology	DIF	Autoantibody target
PF	Crusted plaques, puff pastry- or corn flake-like scaling; erosions; superficial, flaccid vesiculobullae in a seborrheic distribution	Subcorneal acantholysis	IgG with or without C3 antibody deposition within intercellular spaces between keratinocytes	DSG-1
PE	Flaccid bullae that erode with scale and crust, forming well-marginated erythematous hyperkeratotic plaques in photodistributed areas	Subcorneal acantholysis	Combined pattern of IgG and C3 deposition both intercellularly between keratinocytes and as granular deposits along the DEJ forming a ''lupus band''	DSG-1 with or without- 3
PH	Severe pruritus and erythematous urticarial plaques or a vesiculobullous eruption	Eosinophilic spongiosis; neutrophilic spongiosis, subcorneal, or suprabasal acantholysis may also be seen	Superficial intraepithelial deposits of IgG and C3; deposits in the lower epidermis may also be seen	DSG-1, DSG-3, desmocollin 1, desmocollin 3, and an unknown 178 kDa protein
FS	Generalized exfoliating dermatitis	Subcorneal acantholysis	IgG and C3 antibody deposition within intercellular spaces between keratinocytes	DSG-1
PV	Fragile, flaccid bullae on normal or erythematous skin that break to reveal denuded skin with or without overlying crust; lesions commonly begin in the oral cavity and subsequently spread to the skin	Suprabasilar acantholysis	Intercellular deposition with IgG with or without C3	DSG-3, DSG-1
PVe	Vegetative plaques in intertriginous areas and oral mucosa	Acanthosis, papillomatosis, and acantholysis that is typically suprabasilar	Deposition of IgG and C3 in the epidermal intracellular spaces	DSG-3 with or without-1; autoantibodies against desmocollins 1 and 2 and periplakin also may be seen
Drug-induced pemphigus	Variable, may present with features similar to PF, PV, or PE	Histopathology depends on the clinical presentation	Intercellular staining in most cases	DSG-1 with or without-3

Continued

Table I. Cont'd

Disorder	Clinical features	Histopathology	DIF	Autoantibody target
IgA Pemphigus	Vesicles and pustules overlying well-demarcated areas of erythematous skin	SPD subtype: subcorneal pustules; IEN subtype: pustules throughout the whole epidermis; PVe variant: epidermal acanthosis with subcorneal and/or intraepidermal neutrophils	Intercellular IgA deposition	SPD subtype: IgA autoantibodies to desmocollin 1
PNP/PAMS	Severe hemorrhagic stomatitis, along with varied clinical morphologies, including targetoid or lichenoid lesions or vesiculobullous lesions	Varied; may show suprabasilar acantholysis, subepithelial separation, and lichenoid interface dermatitis with prominent keratinocyte necrosis	May reveal IgG with or without C3 deposited on keratinocytes; concomitant linear deposition along the BMZ may be seen; lichenoid tissue reaction is frequently seen	Plectin, desmoplakins I and II, envoplakin, periplakin, BP-230, and DSG-1 and 3

ANA, Antinuclear antibodies; *C3*, complement 3; *DIF*, direct immunofluorescence; *DEJ*, dermoepidermal junction; *DSG*, desmoglein; *ELISA*, enzyme-linked immunosorbent assay; *FS*, fogo selvage; *IEN*, intraepidermal neutrophilic; *IgG*, imunoglobulin G; *PAMS*, paraneoplastic autoimmune multiorgan syndrome; *PE*, pemphigus erythematosus; *PF*, pemphigus foliaceus; *PH*, pemphigus herpetiformis; *PV*, pemphigus vulgaris; *PVe*, pemphigus vegetans; *PNP*, paraneoplastic pemphigus; *SPD*, subcorneal pustular dermatosis.

streams.[21,23,24] Of this population, 3% to 5% are affected by FS. An association with risk of FS and the expression of the human leukocyte antigen (HLA)-DRB1*0404 and HLA-DRB1*1406 alleles has been noted.[21,22] There also appears to be an association between FS and the black fly, *Simulium nigrimanum*, bite, which is hypothesized to induce antigenic stimulation and production of IgG4 autoantibodies to DSG-1 via molecular mimicry.[21,23,25] Other forms of endemic FS have been reported to occur in Colombia and Tunisia.[21,26]

Clinical features

FS most commonly presents with erosions or as generalized exfoliative dermatitis.[21]

Diagnosis

DIF studies of perilesional biopsies reveal deposition of IgG with or without C3 in the epidermal intercellular spaces, identical to findings in PF.[22] Histopathology reveals subcorneal acantholysis as well as the presence of a mixed inflammatory infiltrate, including eosinophils and neutrophils in the epidermis and superficial dermis.[22] Serologic studies demonstrate positive intercellular deposition on monkey esophagus substrate with IIF testing. Autoantibodies against DSG-1 can be detected using ELISA, with a level of sensitivity greater than 90%.[22] Sera from patients with PF and FS would show indistinguishable findings with IIF and ELISA testing.

SUPRABASILAR IgG PEMPHIGUS: PEMPHIGUS VULGARIS

- The most common pemphigus variant
- DSG-3 is the autoantibody target

Background

Pemphigus vulgaris (PV) is the most common variant of pemphigus, comprising approximately 70% of pemphigus cases.[24] PV is strongly associated with HLA-DR4 and HLA-DR6 genotypes.[27,28] PV is also known to be associated with viral infections, including herpes simplex, cytomegalovirus, Epstein-Barr virus, and human herpesvirus-8.[29,30] Associated comorbidities include autoimmune thyroid disease, rheumatoid arthritis, thymoma, and diabetes mellitus type 1.[31,32]

Clinical features

The oral mucosa is the first site of involvement in most cases, commonly involving the buccal, palatine, or gingival mucosa (Fig 3).[33-37] The mucosal surfaces of the larynx, esophagus, conjunctiva, nasal cavity, urethra, vulva, and cervix also may be involved.[28,38-43] Lesions may remain in the oral cavity or spread to the skin, with an average lag time of 4 months.[33,35] When involving the skin, lesions

Table II. Differential diagnosis of autoimmune mucocutaneous blistering disorder

Diagnostic category	Differential diagnosis
Genetic Disorders	Hereditary epidermolysis bullosa, incontinentia pigmenti, porphyria, Darier disease, Hailey-Hailey disease
Infections/arthropod bite	Herpes zoster, herpes simplex, hand-foot-and-mouth disease, bullous impetigo, staphylococcal scalded skin syndrome, blistering dactylitis, bullous erysipelas, bullous cellulitis, bullous tinea pedis, and bullous arthropod bite reaction
Medication reactions	Fixed drug eruption, SJS/TEN, drug-induced pseudoporphyria, AGEP, toxic erythema of chemotherapy, phototoxic drug reaction, and bromoderma/iododerma (DDX of pemphigus vegetans)
Eczematous dermatitis	Acute allergic contact dermatitis (eg, poison ivy dermatitis), phytophotodermatitis, dyshidrotic dermatitis (pompholyx), and prurigo nodularis
Urticarial reactions	Chronic idiopathic urticaria
Interface reactions	Bullous lichen planus, bullous lesions of systemic lupus (TEN-like due to severe interface reaction), erythema multiforme, and graft-versus-host disease
Pustular reactions (DDX of IgA pemphigus)	Subcorneal pustular dermatosis, AGEP, pustular psoriasis, and amicrobial pustulosis
Vasculopathic reactions	Bullous vasculitis, urticarial vasculitis, and occlusive vasculopathy
Deposition disorders/Metabolic disorders/Disorders of connective tissue fibers	Bullous amyloidosis, bullosis diabeticorum, bullous solar elastosis, and bullous lichen sclerosus
Trauma	Friction blister, coma blister, fracture blister, delayed postburn or post skin graft blisters, and bullous dermatitis artefacta
Neoplasms	Lymphangioma circumscriptum, bullous mycosis fungoides, and bullous melanoma
Other	Edema blisters, eosinophilic dermatosis associated with hematologic malignancy, and Grover disease

AGEP, Acute generalized exanthematous pustulosis; *C3*, complement 3; *DDX*, differential diagnosis; *SJS/TEN*, Stevens Johnson syndrome/toxic epidermal necrolysis.

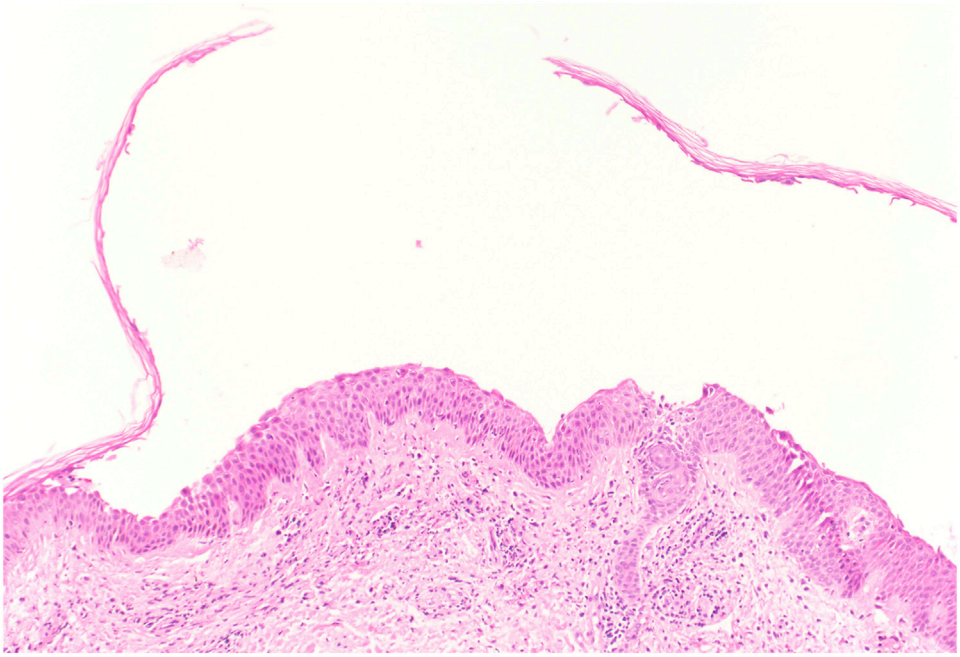

Fig 2. Pemphigus foliaceus histopathology (Hematoxylin-eosin stain; original magnification: ×20), showing superficial acantholysis.

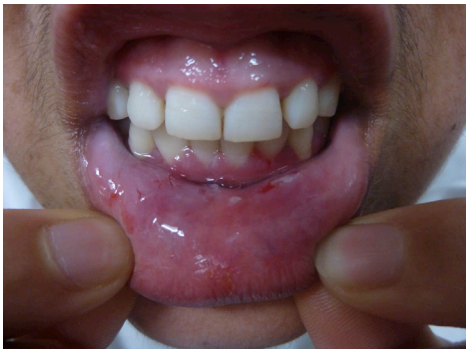

Fig 3. Oral pemphigus vulgaris in a young female with hirsutism.

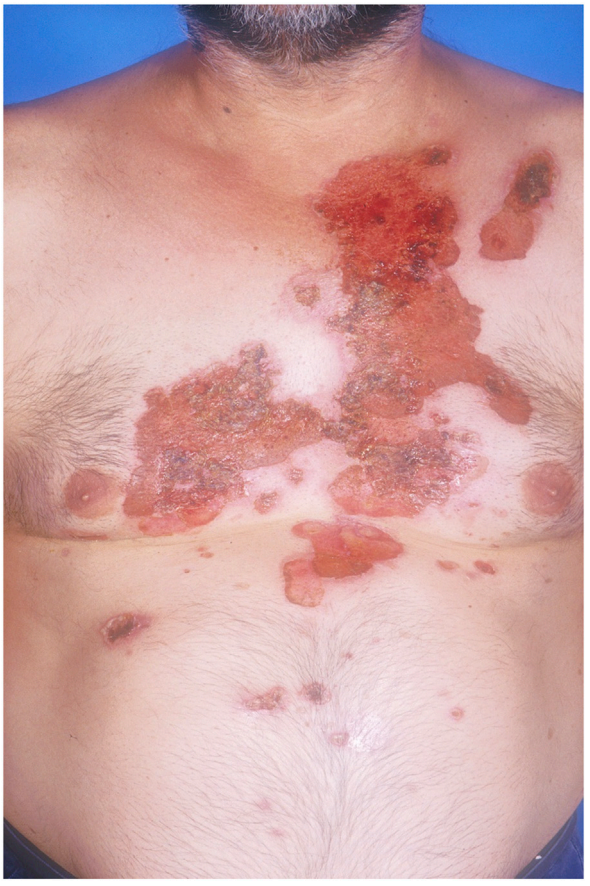

Fig 4. Pemphigus vulgaris involving the chest and abdomen.

may remain localized or become generalized, with most common sites being the trunk, groin, axilla, scalp, face, and pressure points (Fig 4).[28] The lesions generally present as fragile, flaccid, or ruptured bullae or denuded skin with the surrounding skin appearing either mildly erythematous or normal.[28,36]

Diagnosis

Diagnosis includes correlation of the clinical presentation, histopathology, DIF, and detection of

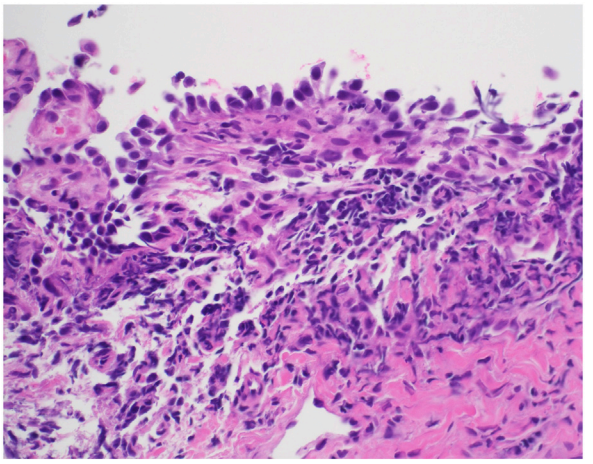

Fig 5. Pemphigus vulgaris histopathology, showing suprabasilar blister with tombstoning and acantholysis (Hematoxylin-eosin stain; original magnification: ×40)

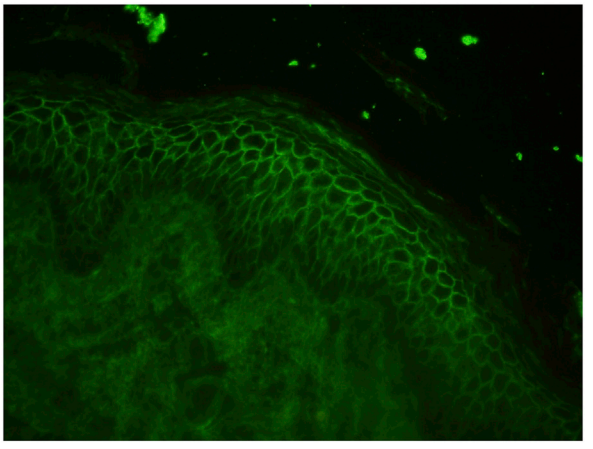

Fig 6. Pemphigus vulgaris direct immunofluorescence, showing intercellular deposition with IgG.

serum antibodies either via IIF or ELISA testing.[6] Intact skin at the edge of a blister should be biopsied for routine microscopy. Skin biopsied from this site should also suffice for DIF testing.[28] When obtaining punch biopsies for DIF of oral mucosa, samples of clinically unaffected buccal mucosa have been shown to be as sensitive as perilesional biopsies.[44] Histopathology typically reveals suprabasilar acantholysis (Fig 5).[6] DIF shows intercellular deposition with IgG with or without C3 (Fig 6). If DIF is not interpretable due to damaged epidermis, searching for characteristic cell-surface deposits on the epithelial cells of any adnexal structures on DIF specimens may be useful for diagnosis.[45] As with PF, intercellular deposition of IgG can be seen nonspecifically, which is thought to be an artifact from circulating ABO antibodies. Thus, the finding of a low-positive intercellular substance pattern on IIF, particularly in

the setting of negative ELISA studies for DSG1 and DSG3, should be interpreted cautiously.[7] Serum studies demonstrate the presence of cell-surface deposition on monkey esophagus IIF and positive DSG-3 (with or without DSG-1) autoantibodies by ELISA. Specifically, mucosal PV is characterized by the presence of serum autoantibodies to DSG-3, although autoantibodies to DSG-1 may also develop, usually when skin involvement develops.[24,46] Detection of DSG-3 via enzyme-linked immunosorbent assay (ELISA) has a sensitivity of 95% and specificity of 98% or greater.[8] Peripheral blood eosinophilia may be seen in 45% of patients.[36]

For the diagnosis of pemphigus, the gold standard remains correlation of clinical features with compatible histopathology (showing acantholysis, though not required for diagnosis) and cell-surface deposition of IgG with or without C3 on DIF. Serologic studies, such as IIF and ELISA for DSG1 and DSG3, offer ancillary evidence for the diagnosis and may be used as a diagnostic proxy when a biopsy cannot be feasibly obtained.

SUPRABASILAR IgG PEMPHIGUS: PEMPHIGUS VEGETANS

Key point

- Characterized by the presence of vegetative plaques in the intertriginous areas and oral mucosa

Clinical features

Pemphigus vegetans (PVe) is associated with the development of vegetative plaques in intertriginous areas and oral mucosa.[21,47-49] The Hallopeau subtype generally begins as pustules, follows a more indolent course, and generally results in long-term remission.[47,48] The Neumann subtype generally presents with more generalized, erosive, vesiculobullous lesions and tends to follow the clinical course of classic PV, with relapses and remissions.[47,48]

Diagnosis

Histopathology shows epidermal acanthosis and intraepidermal abscesses with neutrophilic and eosinophilic infiltrates. Suprabasilar acantholysis may be present early in the disease course.[21,50,51] DIF studies show deposition of IgG and C3 in the epidermal intracellular spaces in a pattern indistinguishable from that of PV.[21,47] Serologic testing demonstrates cell-surface deposition on monkey esophagus substrate via IIF and circulating autoantibodies against DSG-1 or 3 by ELISA.[49,52] Additional autoantibodies reported to be present in affected patients include those directed against desmocollins 1 and 2 and periplakin.[51]

OTHER FORMS OF IgG PEMPHIGUS: PEMPHIGUS HERPETIFORMIS

Key point

- Resembles dermatitis herpetiformis clinically and pemphigus histopathologically

Clinical features

Pemphigus herpetiformis (PH) most commonly presents with the subacute onset of severely pruritic, erythematous, urticarial or vesiculobullous papules and plaques, often arranged in an annular configuration and resembling dermatitis herpetiformis.[46,53,54] Occasionally, PH may evolve into more typical PF or PV.[55]

Diagnosis

Histopathology is generally nonspecific, revealing eosinophilic spongiosis in virtually all cases, neutrophilic spongiosis in 50% of cases, and subcorneal or suprabasal acantholysis in 50% of cases.[46,53] Intraepidermal neutrophilic or eosinophilic collections also may be observed. DIF most commonly shows superficial intraepithelial deposits of IgG and C3, similar to those seen in PF; however, deposits in the lower epidermis also may be seen.[56] The characteristic pattern of stippled IgA deposition within dermal papillae and along the basement membrane zone seen in DH is not present. Serum eosinophilia is observed in approximately 40% of affected patients.[53] Serum samples of patients with PH have been reported to contain autoantibodies to DSG-1, DSG-3, desmocollin 1, desmocollin 3, and an unknown 178 kDa protein.[54,57-61] As is seen with other pemphigus variants, autoantibodies to DSG-1 are associated with subcorneal acantholysis, and autoantibodies to DSG-3 are associated with suprabasilar acantholysis.[53] Because DIF findings of PH are essentially identical to those of PF or PV, diagnosis of PH requires careful correlation of pathology with clinical features. Correct diagnosis of PH is important, because the treatment regimen is unique and often includes dapsone alone in combination with systemic corticosteroids.[46]

OTHER FORMS OF IgG PEMPHIGUS: DRUG-INDUCED PEMPHIGUS

Key point

- PF is the most common clinical presentation of drug-induced pemphigus

Clinical features

Some of the mostly commonly reported causative drugs include angiotensin-converting enzyme inhibitors, penicillins and other antibiotics, and nonsteroidal anti-inflammatory drugs.[62-64] The most

common presentation of drug-induced pemphigus resembles that of PF (46%), followed by PV (33%) and PE (20%).[37,65]

Diagnosis

Histopathology mirrors the clinical presentation, with intraepidermal acantholysis seen in the PF variant and suprabasilar acantholysis seen in the PV variant.[65] Dermal infiltrates containing neutrophils, eosinophils, or lymphocytes may be seen in a perivascular or diffuse pattern.[65] DIF shows intercellular deposition of IgG and C3 in most cases.[65] Patients typically have circulating autoantibodies to DSG-1 or 3, as can be demonstrated by ELISA. IIF with monkey esophagus substrate shows intercellular deposition with IgG.[66] The *in vitro* interferon-gamma release from lymphocytes test has been used to support a diagnosis of drug-induced pemphigus, but this test is not widely available outside of a research setting.[67] Therefore, an accurate diagnosis of drug-induced pemphigus requires a high clinical index of suspicion and careful history taking.

OTHER FORMS OF IgG PEMPHIGUS: PARANEOPLASTIC PEMPHIGUS/ PARANEOPLASTIC AUTOIMMUNE MULTIORGAN SYNDROME

Key points

- Most commonly associated with an underlying hematologic malignancy in adults
- May affect respiratory epithelium, leading to bronchiolitis obliterans in some cases

Background

Alternative names for paraneoplastic pemphigus (PNP) include neoplasia-induced pemphigus and paraneoplastic autoimmune multiorgan syndrome (PAMS), with the latter term being preferred due to the recognition that this entity may have multiorgan involvement.[46,58] PNP/PAMS is a rare and aggressive disease that represents 3% to 5% of pemphigus cases.[37,68] It is associated generally with an underlying malignancy, most commonly hematologic (84% of cases in adults), although cases in which no malignancy was ever detected have been reported.[68-71] Associated neoplasms include non-Hodgkin lymphoma, Castleman disease, thymoma, Waldenstrom macroglobinemia, Hodgkin lymphoma, monoclonal gammopathy, epithelial carcinomas, and sarcomas, among others.[68] The diagnosis of a malignancy generally precedes the development of PNP/PAMS, although in approximately one third of patients, mucocutaneous lesions precede or herald the diagnosis of malignancy.[72] The etiology is thought to be related to autoantibodies generated against tumor antigens, which then cross-react with antigens in the epidermis.[24] Identified autoantibody targets include plectin, desmoplakins I and II, envoplakin, periplakin, BP-230, and DSG-1 and 3.[24,73,74]

Clinical features

PNP/PAMS often begins with severe hemorrhagic stomatitis, which is notoriously resistant to therapy.[37,46,68,72] Other mucosal regions that may be affected include the nasopharynx, ano-genital region, esophagus, and conjunctiva.[68] Skin involvement usually follows mucous membrane involvement, may involve the palms and soles, and is typically widespread.[68] The morphology of skin lesions is diverse and can include diffuse erythema, targetoid lesions resembling those of erythema multiforme/Stevens Johnson syndrome, vesicles or bullae, lichenoid papules, scaly plaques, exfoliative erythroderma, erosions, or ulcerations.[68] This polymorphous skin eruption may mimic the clinical presentation of PV, erythema multiforme, or lichen planus.[24,72] Patients treated with rituximab and therefore with depletion of B-cell lineage may be more likely to demonstrate a T-cell pattern of skin disease, such as that seen with lichenoid skin reactions.[75] The morphology of a patient's mucocutaneous lesions may evolve over time, reflecting different stages of the disease.[72] PNP/PAMS affects the respiratory epithelium in up to 93% of cases, conferring a high risk for bronchiolitis obliterans.[68] The leading cause of death in affected patients is infection, with complications from bronchiolitis obliterans, the underlying malignancy, or therapy also listed as causes.[76]

Diagnosis

As in other forms of pemphigus, biopsy for routine histopathology should be performed on early lesions when possible, and biopsy for DIF should be performed on noneroded perilesional skin or mucosa.[72] Histopathologic features may be varied but can show suprabasilar acantholysis, subepithelial separation, and lichenoid interface dermatitis with prominent keratinocyte necrosis (Fig 7).[25,73] Because only a lichenoid interface infiltrate without definite acantholysis can be seen in some cases, it is essential to have a high index of suspicion for this disease, particularly in patients with severe mucositis or other clinically suggestive features. DIF may reveal IgG with or without C3 deposited on keratinocyte surfaces, although concomitant linear deposition along the basement membrane zone also may be seen.[74] In addition, a lichenoid tissue reaction, characterized by clustered cytoid bodies with immunoglobulin and complement, as well as shaggy

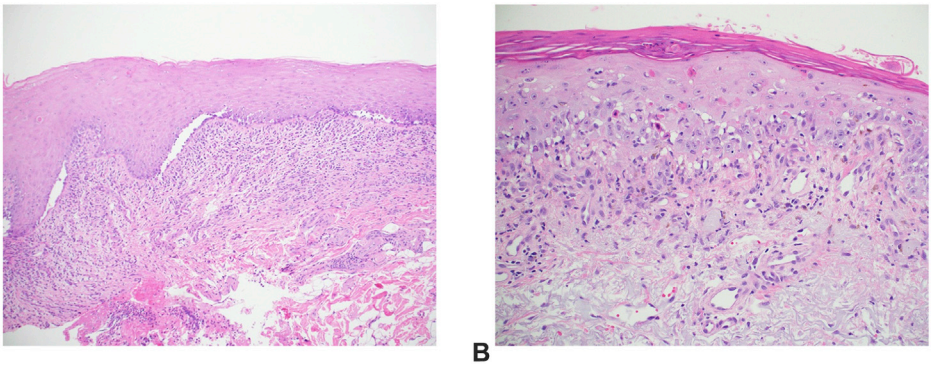

Fig 7. Paraneoplastic pemphigus histopathology. **A**, Lichenoid inflammation and suprabasilar acantholysis. **B**, Lichenoid inflammation only, without appreciable acantholysis. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: A, ×20; B, ×40.)

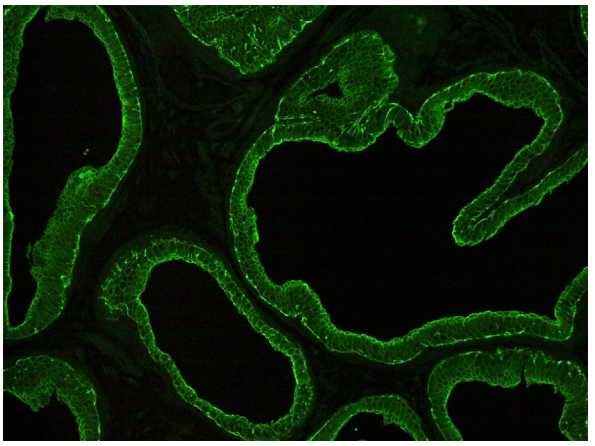

Fig 8. Paraneoplastic pemphigus indirect immunofluorescence on rat bladder epithelium substrate, showing cell-surface deposition of IgG.

fibrinogen deposition along the basement membrane zone, is often present and may be the only DIF feature.[76] Diagnosis is confirmed with positive cell-surface deposition with IIF on rat bladder epithelium substrate (Fig 8) or the presence of autoantibodies to envoplakin, desmoplakin, or periplakin on ELISA or immunoblotting.[73] Other investigations should include work up for underlying malignancy, as well as testing of pulmonary function, examination of the lymph nodes, and imaging of the chest, abdomen, and pelvis. Positron emission tomography/computed tomography scanning is a preferred method of imaging given its additional role in staging of hematologic malignancies, the most commonly associated disease category in adults.[72,77]

OTHER FORMS OF PEMPHIGUS: IgA PEMPHIGUS

Key point

- DIF reveals epidermal intercellular IgA deposition

Background

IgA pemphigus is distinguished from other types of pemphigus by the deposition of IgA and not IgG in the intercellular spaces on DIF.[78] IgA pemphigus exists as 4 subtypes: subcorneal pustular dermatosis (SPD)-type, intraepidermal neutrophilic-type, IgA PF, and PVe-like subtype.[79-82] Pyodermatitis-pyostomatitis vegetans, a mucocutaneous disorder associated with inflammatory bowel disease, is thought to represent a PVe-like subtype when cell-surface deposition of IgA on DIF is present, and there may be overlap between these 2 diseases.[81,83] Monoclonal gammopathy (IgA isoform) is seen in about 20% of patients with the SPD subtype.[84,85] Other reported associated malignancies include multiple myeloma, B-cell lymphoma, inflammatory bowel disease (particularly in the PVe-like subtype involving the mucosa), and lung cancer.[86]

Clinical features

Most patients present with vesicles and pustules overlying well-demarcated areas of erythematous skin, regardless of histopathologic subtype.[78] The IEN subtype is sometimes described as having a flower-like appearance, due to lesions with peripheral extensions and central crusting.[87] IgA pemphigus most commonly involves the trunk and proximal extremities but also may be seen on the scalp, in the postauricular area, or in intertriginous areas.[79]

Diagnosis

Histopathology may show any combination of subcorneal pustules, intraepidermal neutrophils, superficial dermal perivascular neutrophils, and acantholysis, although all of these features may be subtle.[79] The SPD subtype is characterized by the

presence of subcorneal pustules that sometimes are accompanied by focal acantholysis, while the IEN subtype is characterized by pustule formation.[78,85] The PVe-like subtype shows epidermal acanthosis with subcorneal or intraepidermal neutrophils.[81,82] DIF shows intercellular IgA deposition.[84] IIF testing with IgA shows intercellular deposition on monkey esophagus substrate. Serum of patients with the SPD subtypes typically contain IgA autoantibodies to desmocollin 1, although this test is not widely available commercially. Autoantibody targets for the 3 remaining subtypes remain unknown. However, results from ELISA testing have inconsistently reported autoantibodies to DSG-1 and -3, as well as autoantibodies to desmocollins 1, 2, and 3.[78,79,81,88-91]

OTHER FORMS OF PEMPHIGUS: IgG/IgA PEMPHIGUS

IgG/IgA pemphigus is a rare subtype of pemphigus characterized by the presence of both IgG and IgA autoantibodies directed against the intercellular desmosomes.[92] Clinically, IgG/IgA pemphigus is a heterogeneous disease that may resemble IgA pemphigus or IgG pemphigus (e.g., PV, PF).[80,93] Almost half of affected patients have an associated underlying systemic disease at the time of diagnosis, such as a malignancy.[93] IgG and IgA autoantibodies against DSG-1, DSG-3, and desmocollins have been reported.[92,94-96]

Conflicts of interest

None disclosed.

REFERENCES

1. Metry DW, Hebert AA, Jordon RE. Nonendemic pemphigus foliaceus in children. *J Am Acad Dermatol*. 2002;46(3):419-422.
2. Schmidt E, Kasperkiewicz M, Joly P. Pemphigus. *Lancet*. 2019;394(10201):882-894.
3. Awdeh F, Gilhooley E, Grady CO, Connolly M. Refractory pemphigus foliaceous treated with rituximab. *BMJ Case Rep*. 2019;12(5):e229026.
4. Dasher D, Rubenstein D, Diaz LA. Pemphigus foliaceus. *Curr Dir Autoimmun*. 2008;10:182-194.
5. Tolkachjov SN, Frith M, Cooper LD, Harmon CB. Pemphigus foliaceus demonstrating pathergy after Mohs micrographic surgery. *Dermatol Surg*. 2018;44(10):1352-1353.
6. Murrell DF, Pena S, Joly P, et al. Diagnosis and management of pemphigus: recommendations by an international panel of experts. *J Am Acad Dermatol*. 2020;82(3):575-585.e1.
7. Lee FJ, Silvestrini R, Fulcher DA. False-positive intercellular cement substance antibodies due to group A/B red cell antibodies: frequency and approach. *Pathology*. 2010;42(6):574-577.
8. Harman KE, Gratian MJ, Seed PT, Bhogal BS, Challacombe SJ, Black MM. Diagnosis of pemphigus by ELISA: a critical evaluation of two ELISAs for the detection of antibodies to the major pemphigus antigens, desmoglein 1 and 3. *Clin Exp Dermatol*. 2000;25(3):236-240.
9. Pritchett EN, Hejazi E, Cusack CA. Pruritic, pink scaling plaques on the face and trunk. Pemphigus erythematosus. *JAMA Dermatol*. 2015;151(10):1123-1124.
10. Vassileva S, Drenovska K, Manuelyan K. Autoimmune blistering dermatoses as systemic diseases. *Clin Dermatol*. 2014;32(3):364-375.
11. Amerian ML, Ahmed AR. Pemphigus erythematosus. Presentation of four cases and review of literature. *J Am Acad Dermatol*. 1984;10(2 Pt 1):215-222.
12. Malik M, Ahmed AR. Concurrence of systemic lupus erythematosus and pemphigus: coincidence or correlation? *Dermatology*. 2007;214(3):231-239.
13. Chandan N, Lake EP, Chan LS. Unusually extensive scalp ulcerations manifested in pemphigus erythematosus. *Dermatol Online J*. 2018;24(1):13030/qt1vd4j2t2.
14. Oktarina DA, Poot AM, Kramer D, Diercks GF, Jonkman MF, Pas HH. The IgG "lupus-band" deposition pattern of pemphigus erythematosus: association with the desmoglein 1 ectodomain as revealed by 3 cases. *Arch Dermatol*. 2012;148(10):1173-1178.
15. Cruz PD Jr, Coldiron BM, Sontheimer RD. Concurrent features of cutaneous lupus erythematosus and pemphigus erythematosus following myasthenia gravis and thymoma. *J Am Acad Dermatol*. 1987;16(2 Pt 2):472-480.
16. Amerian ML, Ahmed AR. Pemphigus erythematosus. Senear-Usher syndrome. *Int J Dermatol*. 1985;24(1):16-25.
17. Scheinfeld NS, Howe KL, DiCostanzo DP, Craig E, Cohen SR. Pemphigus erythematosus associated with anti-DNA antibodies and multiple anti-ENA antibodies: a case report. *Cutis*. 2003;71(4):303-306.
18. Lyde CB, Cox SE, Cruz PD Jr. Pemphigus erythematosus in a five-year-old child. *J Am Acad Dermatol*. 1994;31(5 Pt 2):906-909.
19. Sousa JX Jr, Miyamoto D, Zimbres JM, Costa DV, Aoki V. Clinicopathological evaluation of in vivo epidermal nuclear fluorescence. *Clin Exp Dermatol*. 2009;34(3):314-318.
20. Shu S, Provost T, Croxdale MB, Reichlin M, Beutner EH. Nuclear deposits of immunoglobulins in skin of patients with systemic lupus erythematosus. *Clin Exp Immunol*. 1977;27(2):238-244.
21. Joly P, Litrowski N. Pemphigus group (vulgaris, vegetans, foliaceus, herpetiformis, brasiliensis). *Clin Dermatol*. 2011;29(4):432-436.
22. Hans-Filho G, Aoki V, Bittner NRH, Bittner GC. Fogo selvagem: endemic pemphigus foliaceus. *An Bras Dermatol*. 2018;93(5):638-650.
23. Friedman H, Campbell I, Rocha-Alvarez R, et al. Endemic pemphigus foliaceus (fogo selvagem) in Native Americans from Brazil. *J Am Acad Dermatol*. 1995;32(6):949-956.
24. Kridin K. Pemphigus group: overview, epidemiology, mortality, and comorbidities. *Immunol Res*. 2018;66(2):255-270.
25. Thivolet J. Pemphigus: past, present and future. *Dermatology*. 1994;189(suppl 2):26-29.
26. Hans-Filho G, Aoki V, Rivitti E, et al. Endemic pemphigus foliaceus (fogo selvagem)—1998. The Cooperative Group on Fogo Selvagem Research. *Clin Dermatol*. 1999;17(2):225-235. discussion 105-226.
27. Kayani M, Aslam AM. Bullous pemphigoid and pemphigus vulgaris. *BMJ*. 2017;357:j2169.
28. Venugopal SS, Murrell DF. Diagnosis and clinical features of pemphigus vulgaris. *Immunol Allergy Clin North Am*. 2012;32(2):233-243. v-vi.
29. Mashiah J, Brenner S. Medical pearl: first step in managing pemphigus—addressing the etiology. *J Am Acad Dermatol*. 2005;53(4):706-707.

30. Konda D, Chandrashekar L, Dhodapkar R, Ganesh RN, Thappa DM. Clinical markers of herpes simplex virus infection in patients with pemphigus vulgaris. *J Am Acad Dermatol*. 2019. https://doi.org/10.1016/j.jaad.2019.06.002.
31. Parameswaran A, Attwood K, Sato R, Seiffert-Sinha K, Sinha AA. Identification of a new disease cluster of pemphigus vulgaris with autoimmune thyroid disease, rheumatoid arthritis and type I diabetes. *Br J Dermatol*. 2015;172(3):729-738.
32. Gibson LE, Muller SA. Dermatologic disorders in patients with thymoma. *Acta dermato-venereol*. 1987;67(4):351-356.
33. Harman KE, Brown D, Exton LS, et al. British Association of Dermatologists' guidelines for the management of pemphigus vulgaris 2017. *Br J Dermatol*. 2017;177(5):1170-1201.
34. Sirois D, Leigh JE, Sollecito TP. Oral pemphigus vulgaris preceding cutaneous lesions: recognition and diagnosis. *J Am Dent Assoc*. 2000;131(8):1156-1160.
35. Ryan JG. Pemphigus. A 20-year survey of experience with 70 cases. *Arch Dermatol*. 1971;104(1):14-20.
36. Korman N. Pemphigus. *J Am Acad Dermatol*. 1988;18(6):1219-1238.
37. Kneisel A, Hertl M. Autoimmune bullous skin diseases. Part 1: clinical manifestations. *J Dtsch Dermatol Ges*. 2011;9(10):844-856;quiz 857.
38. Hodak E, Kremer I, David M, et al. Conjunctival involvement in pemphigus vulgaris: a clinical, histopathological and immunofluorescence study. *Br J Dermatol*. 1990;123(5):615-620.
39. Hale EK, Bystryn JC. Laryngeal and nasal involvement in pemphigus vulgaris. *J Am Acad Dermatol*. 2001;44(4):609-611.
40. Lurie R, Trattner A, David M, Sandbank M. Esophageal involvement in pemphigus vulgaris: report of two cases and review of the literature. *Dermatologica*. 1990;181(3):233-236.
41. Trattner A, Lurie R, Leiser A, et al. Esophageal involvement in pemphigus vulgaris: a clinical, histologic, and immunopathologic study. *J Am Acad Dermatol*. 1991;24(2 Pt 1):223-226.
42. Marren P, Wojnarowska F, Venning V, Wilson C, Nayar M. Vulvar involvement in autoimmune bullous diseases. *J Reprod Med*. 1993;38(2):101-107.
43. Sagher F, Bercovici B, Romem R. Nikolsky sign on cervix uteri in pemphigus. *Br J Dermatol*. 1974;90(4):407-411.
44. Carey B, Joshi S, Abdelghani A, Mee J, Andiappan M, Setterfield J. The optimal oral biopsy site for diagnosis of mucous membrane pemphigoid and pemphigus vulgaris. *Br J Dermatol*. 2020;182(3):747-753.
45. Lehman JS, Camilleri MJ. Diagnostic utility of direct immunofluorescence findings around hair follicles and sweat glands in immunobullous disease. *J Cutan Pathol*. 2013;40(2):230-235.
46. Robinson ND, Hashimoto T, Amagai M, Chan LS. The new pemphigus variants. *J Am Acad Dermatol*. 1999;40(5 Pt 1):649-671;quiz 672-643.
47. Ahmed AR, Blose DA. Pemphigus vegetans. Neumann type and Hallopeau type. *Int J Dermatol*. 1984;23(2):135-141.
48. Messersmith L, Krauland K. Pemphigus vegetans. StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2021. Accessed February 1, 2021. Available at: https://www.ncbi.nlm.nih.gov/books/NBK545229
49. Son YM, Kang HK, Yun JH, et al. The neumann type of pemphigus vegetans treated with combination of dapsone and steroid. *Ann Dermatol*. 2011;23(suppl 3):S310-S313.
50. Lakhmiri M, Maouni S, Znati K, et al. [Pemphigus vegetans]. *Ann Dermatol Venereol*. 2020;147(1):78-79.
51. Ruocco V, Ruocco E, Caccavale S, Gambardella A, Lo Schiavo A. Pemphigus vegetans of the folds (intertriginous areas). *Clin Dermatol*. 2015;33(4):471-476.
52. Mergler R, Kerstan A, Schmidt E, Goebeler M, Benoit S. Atypical clinical and serological manifestation of pemphigus vegetans: a case report and review of the literature. *Case Rep Dermatol*. 2017;9(1):121-130.
53. Laws PM, Heelan K, Al-Mohammedi F, Walsh S, Shear NH. Pemphigus herpetiformis: a case series and review of the literature. *Int J Dermatol*. 2015;54(9):1014-1022.
54. Prado R, Brice SL, Fukuda S, Hashimoto T, Fujita M. Paraneoplastic pemphigus herpetiformis with IgG antibodies to desmoglein 3 and without mucosal lesions. *Arch Dermatol*. 2011;147(1):67-71.
55. Maciejowska E, Jablonska S, Chorzelski T. Is pemphigus herpetiformis an entity? *Int J Dermatol*. 1987;26(9):571-577.
56. Kasperkiewicz M, Kowalewski C, Jablonska S. Pemphigus herpetiformis: from first description until now. *J Am Acad Dermatol*. 2014;70(4):780-787.
57. Ishii K, Amagai M, Komai A, et al. Desmoglein 1 and desmoglein 3 are the target autoantigens in herpetiform pemphigus. *Arch Dermatol*. 1999;135(8):943-947.
58. Porro AM, Caetano Lde V, Maehara Lde S, Enokihara MM. Non-classical forms of pemphigus: pemphigus herpetiformis, IgA pemphigus, paraneoplastic pemphigus and IgG/IgA pemphigus. *An Bras Dermatol*. 2014;89(1):96-106.
59. Kubo A, Amagai M, Hashimoto T, et al. Herpetiform pemphigus showing reactivity with pemphigus vulgaris antigen (desmoglein 3). *Br J Dermatol*. 1997;137(1):109-113.
60. Tateishi C, Tsuruta D, Nakanishi T, et al. Antidesmocollin-1 antibody-positive, antidesmoglein antibody-negative pemphigus herpetiformis. *J Am Acad Dermatol*. 2010;63(1):e8-e10.
61. Ohata C, Koga H, Teye K, et al. Concurrence of bullous pemphigoid and herpetiform pemphigus with IgG antibodies to desmogleins 1/3 and desmocollins 1-3. *Br J Dermatol*. 2013;168(4):879-881.
62. Fellner MJ, Mark AS. Penicillin- and ampicillin-induced pemphigus vulgaris. *Int J Dermatol*. 1980;19(7):392-393.
63. Kuechle MK, Hutton KP, Muller SA. Angiotensin-converting enzyme inhibitor-induced pemphigus: three case reports and literature review. *Mayo Clin Proc*. 1994;69(12):1166-1171.
64. Saito Y, Hayashi S, Yamauchi A, et al. Tracing the origins of active amide group-positive drug-induced pemphigus vulgaris along the Silk Road: a case report of candesartan-induced pemphigus vulgaris and review of nonthiol drug-induced pemphigus. *Int J Dermatol*. 2018;57(11):e131-e134.
65. Bialy-Golan A, Brenner S. Penicillamine-induced bullous dermatoses. *J Am Acad Dermatol*. 1996;35(5 Pt 1):732-742.
66. Pietkiewicz P, Gornowicz-Porowska J, Bowszyc-Dmochowska M, Dmochowski M. A retrospective study of antihypertensives in pemphigus: a still unchartered odyssey particularly between thiols, amides and phenols. *Arch Med Sci*. 2015;11(5):1021-1027.
67. Brenner S, Goldberg I. Drug-induced pemphigus. *Clin Dermatol*. 2011;29(4):455-457.
68. Paolino G, Didona D, Magliulo G, et al. Paraneoplastic pemphigus: insight into the autoimmune pathogenesis, clinical features and therapy. *Int J Mol Sci*. 2017;18(12):2532.
69. Ohzono A, Sogame R, Li X, et al. Clinical and immunological findings in 104 cases of paraneoplastic pemphigus. *Br J Dermatol*. 2015;173(6):1447-1452.
70. Verrini A, Cannata G, Cozzani E, Terracini M, Parodi A, Rebora A. A patient with immunological features of paraneoplastic pemphigus in the absence of a detectable malignancy. *Acta Derm Venereologica*. 2002;82(5):382-384.
71. Ostezan LB, Fabre VC, Caughman SW, Swerlick RA, Korman NJ, Callen JP. Paraneoplastic pemphigus in the absence of a known neoplasm. *J Am Acad Dermatol*. 1995;33(2 Pt 1):312-315.

72. Anhalt GJ. Paraneoplastic pemphigus. *Adv Dermatol*. 1997;12:77-96. discussion 97.
73. Powell JG, Grover RK, Plunkett RW, Seiffert-Sinha K, Sinha AA. Evaluation of a newly available ELISA for envoplakin autoantibodies for the diagnosis of paraneoplastic pemphigus. *J Drugs Dermatol*. 2015;14(10):1103-1106.
74. Mahoney MG, Aho S, Uitto J, Stanley JR. The members of the plakin family of proteins recognized by paraneoplastic pemphigus antibodies include periplakin. *J Invest Dermatol*. 1998;111(2):308-313.
75. Cummins DL, Mimouni D, Tzu J, Owens N, Anhalt GJ, Meyerle JH. Lichenoid paraneoplastic pemphigus in the absence of detectable antibodies. *J Am Acad Dermatol*. 2007;56(1):153-159.
76. Leger S, Picard D, Ingen-Housz-Oro S, et al. Prognostic factors of paraneoplastic pemphigus. *Arch Dermatol*. 2012;148(10):1165-1172.
77. Lehman VT, Barrick BJ, Pittelkow MR, Peller PJ, Camilleri MJ, Lehman JS. Diagnostic imaging in paraneoplastic autoimmune multiorgan syndrome: retrospective single site study and literature review of 225 patients. *Int J Dermatol*. 2015;54(4):424-437.
78. Gruss C, Zillikens D, Hashimoto T, et al. Rapid response of IgA pemphigus of subcorneal pustular dermatosis type to treatment with isotretinoin. *J Am Acad Dermatol*. 2000;43(5 Pt 2):923-926.
79. Tsuruta D, Ishii N, Hamada T, et al. IgA pemphigus. *Clin Dermatol*. 2011;29(4):437-442.
80. Toosi S, Collins JW, Lohse CM, et al. Clinicopathologic features of IgG/IgA pemphigus in comparison with classic (IgG) and IgA pemphigus. *Int J Dermatol*. 2016;55(4):e184-e190.
81. Wolz MM, Camilleri MJ, McEvoy MT, Bruce AJ. Pemphigus vegetans variant of IgA pemphigus, a variant of IgA pemphigus and other autoimmune blistering disorders. *Am J Dermatopathol*. 2013;35(3):e53-e56.
82. Abellaneda C, Mascaro JM Jr, Vazquez MG, Pablo IM, Iranzo P. All that glitters is not pemphigus: pyodermatitis-pyostomatitis vegetans misdiagnosed as IgA pemphigus for 8 years. *Am J Dermatopathol*. 2011;33(1):e1-e6.
83. Clark LG, Tolkachjov SN, Bridges AG, Camilleri MJ. Pyostomatitis vegetans (PSV)-pyodermatitis vegetans (PDV): a clinicopathologic study of 7 cases at a tertiary referral center. *J Am Acad Dermatol*. 2016;75(3):578-584.
84. Aste N, Fumo G, Pinna AL, Biggio P. IgA pemphigus of the subcorneal pustular dermatosis type associated with monoclonal IgA gammopathy. *J Eur Acad Dermatol Venereol*. 2003;17(6):725-727.
85. Yasuda H, Kobayashi H, Hashimoto T, Itoh K, Yamane M, Nakamura J. Subcorneal pustular dermatosis type of IgA pemphigus: demonstration of autoantibodies to desmocollin-1 and clinical review. *Br J Dermatol*. 2000;143(1):144-148.
86. Petropoulou H, Politis G, Panagakis P, Hatziolou E, Aroni K, Kontochristopoulos G. Immunoglobulin A pemphigus associated with immunoglobulin A gammopathy and lung cancer. *J Dermatol*. 2008;35(6):341-345.
87. Kuan YZ, Chiou HT, Chang HC, Chan HL, Kuo TT. Intraepidermal neutrophilic IgA dermatosis. *J Am Acad Dermatol*. 1990;22(5 Pt 2):917-919.
88. Wang J, Kwon J, Ding X, Fairley JA, Woodley DT, Chan LS. Nonsecretory IgA1 autoantibodies targeting desmosomal component desmoglein 3 in intraepidermal neutrophilic IgA dermatosis. *Am J Pathol*. 1997;150(6):1901-1907.
89. Karpati S, Amagai M, Liu WL, Dmochowski M, Hashimoto T, Horvath A. Identification of desmoglein 1 as autoantigen in a patient with intraepidermal neutrophilic IgA dermatosis type of IgA pemphigus. *Exp Dermatol*. 2000;9(3):224-228.
90. Prost C, Intrator L, Wechsler J, et al. IgA autoantibodies bind to pemphigus vulgaris antigen in a case of intraepidermal neutrophilic IgA dermatosis. *J Am Acad Dermatol*. 1991;25(5 Pt 1):846-848.
91. Kridin K, Patel PM, Jones VA, Cordova A, Amber KT. IgA pemphigus: a systematic review. *J Am Acad Dermatol*. 2020;82(6):1386-1392.
92. Feng SY, Zhi L, Jin PY, Zhou WQ, Yin YP. A case of IgA/IgG pustular pemphigus. *Int J Dermatol*. 2012;51(3):321-324.
93. Criscito MC, Cohen JM, Toosi S, et al. A retrospective study on the clinicopathological features of IgG/IgA pemphigus. *J Am Acad Dermatol*. 2020. https://doi.org/10.1016/j.jaad.2020.07.126.
94. Bruckner AL, Fitzpatrick JE, Hashimoto T, Weston WL, Morelli JG. Atypical IgA/IgG pemphigus involving the skin, oral mucosa, and colon in a child: a novel variant of IgA pemphigus? *Pediatr Dermatol*. 2005;22(4):321-327.
95. Zaraa I, Kerkeni N, Sellami M, et al. IgG/IgA pemphigus with IgG and IgA antidesmoglein 3 antibodies and IgA antidesmoglein 1 antibodies detected by enzyme-linked immunosorbent assay: a case report and review of the literature. *Int J Dermatol*. 2010;49(3):298-302.
96. Chorzelski TP, Hashimoto T, Nishikawa T, et al. Unusual acantholytic bullous dermatosis associated with neoplasia and IgG and IgA antibodies against bovine desmocollins I and II. *J Am Acad Dermatol*. 1994;31(2 Pt 2):351-355.
97. Elston DM, Stratman EJ, Miller SJ. Skin biopsy: biopsy issues in specific diseases. *J Am Acad Dermatol*. 2016;74(1):1-16; quiz 17-18.