Pemphigus foliaceus

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Pemphigus Vulgaris

8

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Introduction and AIMS

Short Definition in Layman Terms

Pemphigus vulgaris (PV) is a chronic autoimmune blistering disease that affects the mucous membranes only (mucosal dominant PV) or both the mucous membranes and the skin (mucocutaneous PV) (Fig. 8.1; Table 8.1).

Learning Objectives
After reading this chapter you know how to recognize a patient with pemphigus vulgaris, which specific tests and diagnostics should be done to confirm your diagnosis en how to treat a patient with pemphigus vulgaris.

Case Study: Part 1
A 67-year-old female was referred to our clinic with an 18-month history of crusted erosions on the lip, which was previously treated as lichen planus. Later, she developed multiple itchy erosions located on the scalp, neck, breasts, groin and umbilicus. Dermatological examination revealed painful erosions on the oral and nasal mucosa in addition to the skin lesions. Nikolsky's sign was positive on the skin. The past medical history reported a TIA and she received various cardiovascular medication for several years.

Didactical Questions: Cross Section of Questions to Prime the Readers Interest

Why do some patients with pemphigus vulgaris have only mucous membranes affected, while others have both skin and mucous membranes affected? What is the histopathology of PV? How do autoantibodies cause acantholysis in skin and mucous membranes?

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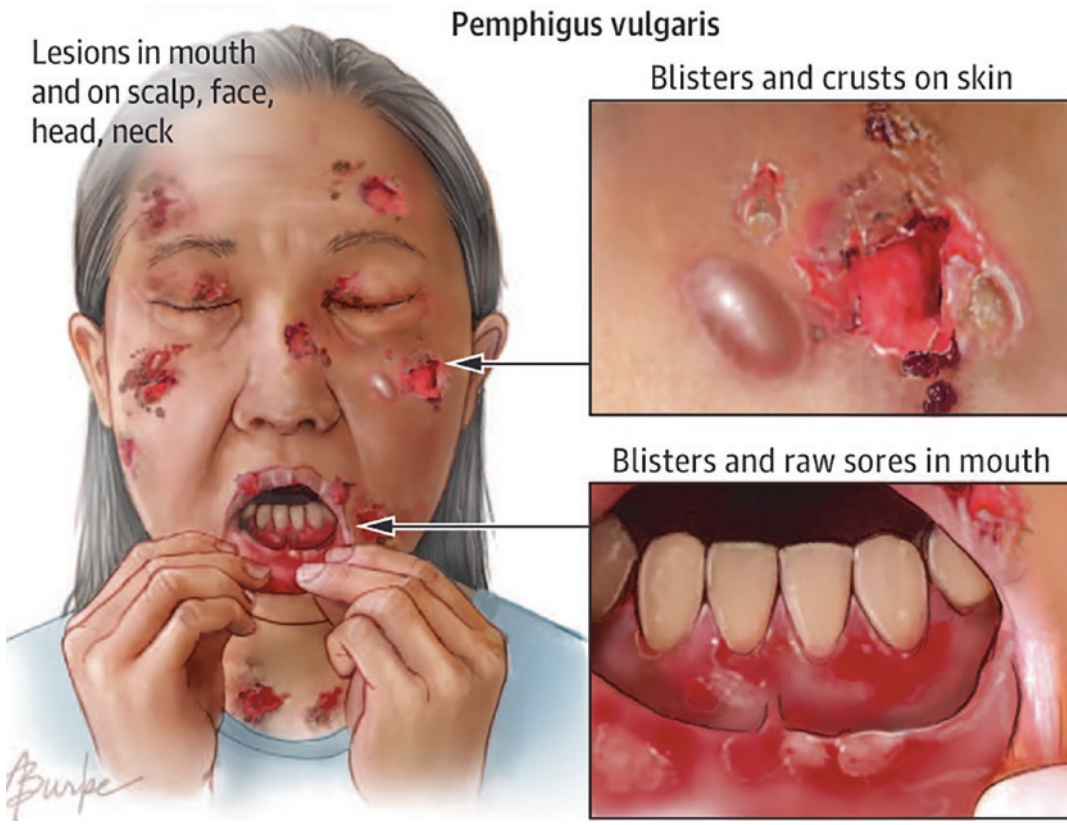

Fig. 8.1 Typical features of patient with pemphigus vulgaris. Drawings by Alison E. Burke adapted from [1]

Table 8.1 IF findings and clinical symptoms of subtypes of pemphigus

	Target antigens	DIF	Clinical symptoms
Pemphigus vulgaris, mucosal-dominant	Dsg3	ECS IgG, IgA ± C3c	Painful erosions of the oral mucosa
Pemphigus vulgaris, mucocutaneous	Dsg1, Dsg3	ECS IgG, IgA ± C3c	Painful blisters and erosions of the oral mucosa and skin
Pemphigus vegetans, Hallopeau type	Dsg3	ECS IgG, IgA ± C3c	Pustules accumulate in body folds and around orifices, easily secondarily infected
Pemphigus vegetans, Neumann type	Dsg3	ECS IgG ± C3c	Papillomas accumulate in body and around orifices, easily secondarily infected
Pemphigus foliaceus Chapter 9	Dsg1	ECS IgG ± C3c	Crusted plaques with multiple layers of scaling, which easily erodes at the scalp, temples, periorbicular area, neck, upper chest and back
Endemic pemphigus Chapter 9	Dsg1	ECS IgG ± C3c	Localized form (form fruste) and generalized form (bullous invasion, keratotic, hyperpigmented, pemphigus herpetiformis and exfoliative erythroderma)

Table 8.1 (continued)

	Target antigens	DIF	Clinical symptoms
Pemphigus erythematosus Chapter 9	Dsg1	ECS/ BMZ IgG ± C3c	Lupus-like butterfly rash and seborrheic distribution. Evoked by UV-light
Pemphigus herpetiformis Chapter 9	Dsg1, Dsg3	ECS IgG, IgA ± C3c	Grouped (herpetiform) distribution of itching erythematous vesicular/bullous/papular lesions, often in an annular-shaped pattern. Nikolsky's sign is negative
IgA pemphigus, subcorneal pustular dermatosis type Chapter 11	Dsc1	ECS IgA ± C3c	Erythematous skin lesions with tiny superficial circinate pustules, desquamation from the edges surfacing the entire body, particularly in the intertriginous areas
IgA pemphigus, intraepidermal neutrophilic IgA dermatosis type Chapter 11	Unknown	ECS IgA ± C3c	Annular erythematous plaques with circinate pustules and crusts that spread outwards and heal inwards in a sunflower-like appearance
Drug-induced pemphigus Chapter 12	Dsg1, Dsg3	ECS IgG, IgA ± C3c	Prodromal stage with pruritis and nonspecific lesions preceding the genuine pemphigus lesions, mimicking all variants of pemphigus
Paraneoplastic pemphigus Chapter 10	Envoplakin, periplakin, desmoplakin, BP230, A2ML1, Dsg1, Dsg3	ECS/ BMZ IgG, IgA ± C3c	Painful severe oral stomatitis, with hemorrhagic crusts. Flaccid to tense blisters at the face, trunk and extremities. Generalised lichenoid erythema. Sporadically shortness of breath. Underlying neoplasm

Dsg1 desmoglein 1, *Dsg3* desmoglein 3, *ECS* epithelial cell surface pattern

Facts and Figures

Definitions and Classification

The term pemphigus is derived from the Greek word *pemphix*, which means blister. Pemphigus is a group of heterogenic chronic mucocutaneous blistering diseases caused by autoantibodies directed against the desmosomal cadherins desmoglein 1 (Dsg1) and/or desmoglein 3 (Dsg3) (Table 8.1) [2]. Pemphigus can be divided into two major forms, based on the level of the blister in the epidermis. The superficial forms of pemphigus are grouped under pemphigus foliaceus, the deep forms under pemphigus vulgaris (mucosal-dominant pemphigus vulgaris and mucocutaneous pemphigus vulgaris) and its variant pemphigus vegetans.

Blistering in pemphigus is caused by autoantibodies directed against desmoglein 1 and/or 3.

Epidemiology

Pemphigus is rare and its incidence has been estimated to about of 0.2 cases per 100,000 per year in Central Europe. The incidence of the different subtypes of pemphigus varies from 0.076 in Finland to 0.67 in Tunisia. Countries with high incidence of pemphigus are Bulgaria, Greece and the Mediterranean region of Turkey. Pemphigus vulgaris (PV) is the most common subtype comprising 83.1% of all cases in Southern Turkey [3]. The mean age of onset of the disease is approximately 40–50 years of age. There is a slight female predominance.

Pathogenesis

In 1964 Beutner and Jordan observed circulating antibodies directed against the cell surface of keratinocytes in the sera of patients with PV [4]. Later it was demonstrated that autoantibodies in pemphigus are pathogenic and induce blister formation in skin organ culture systems and in neonatal mice. In 1982 Stanley et al characterized the PV antigen at the molecular level by immunoprecipitation using cultured keratinocytes extracts as a substrate. All the PV sera identified a glycosylated 130 kDa glycoprotein [5]. In 1991 Amagai et al isolated a cDNA clone for the PV antigen by immunoscreening a human keratinocytes expression library with autoantibodies prepared from the sera of patients with PV [6]. Analysis of the deduced amino acid sequences of the cDNA clones revealed the nature of pemphigus antigens being desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3). Both antigens are member of the cadherin family of calcium-dependant homodimeric 'adherins' that are located in epithelial cell-cell contacts such as adherens junctions and desmosomes.

Desmoglein Compensation Hypothesis

The desmoglein compensation hypothesis explains why skin or mucous membranes are affected in various forms of pemphigus. This theory states that Dsg1 and Dsg3 can compensate for each other and prevent acantholysis when autoantibodies bind to either molecule (Fig. 8.2) [7]. In skin, Dsg1 is expressed throughout the whole epidermis, but more intense in the superficial layers, whereas Dsg3 is confined to the basal and suprabasal layers. Antibodies to Dsg1 therefore cause blisters in the superficial epidermis since in this area Dsg3 is not present to compensate for the loss of Dsg1. The result is PF, which clinically only affects skin.

In mucosa, Dsg3 is expressed throughout the whole epithelium, whereas Dsg 1 is confined to the superficial layers. Antibodies to Dsg3 therefore cause blisters deep in the mucosa, since in this area Dsg1 is not present to compensate for the loss of Dsg3. The skin remains unaffected, because Dsg1 is present throughout the epidermis and compensates for loss of Dsg3. The result is mucosal dominant PV.

If both Dsg1 and Dsg3 are targeted by antibodies, no compensation is possible. The level of blistering is suprabasal, since 'melting' of desmosomes starts in both skin and mucosa in the lower epithelium at entry point of IgG. The result is mucocutaneous PV.

The desmoglein compensation hypothesis explains the localization and the level of the blister in pemphigus

The exact cellular mechanism by which pemphigus IgG induces acantholysis has been a subject of debate since the discovery of pemphigus autoantibodies by Beutner and Jordan. Since then acantholysis has been explained by several theories: (1) steric hindrance, (2) deranged cell signalling, (3) impairment of desmosome assembly and increased desmosome disassembly

Steric Hindrance

Steric hindrance theory is based on the idea that there is direct interference of pemphigus IgG with the amino-terminal extracellular domain of desmogleins, which form the trans-adhesive interface between keratinocytes. This would lead to a lengthwise splitting of the desmosomes which has indeed been observed by electron microscopy in pemphigus patients and mouse models.

Cell Signalling

Signalling pathways that play a role in the pathogenesis of pemphigus involve complicated interactions between p38-mitogen activated protein kinase (p38MAPK), RhoA, protein kinase C (PKC), epidermal growth factor receptor (EGFR), plakoglobin and c-Myc [8].

Assembly and Disassembly

PV IgG leads to depletion of non-junctional Dsg3 by endocytosis. Eventually, assembly of desmosome fails due to shortage of non-junctional Dsg3 building blocks. Besides binding of PV IgG to non-junctional Dsg3, it might also be possible that PV IgG binds to junctional Dsg3 in the core domain of desmosomes. This leads to disassem-

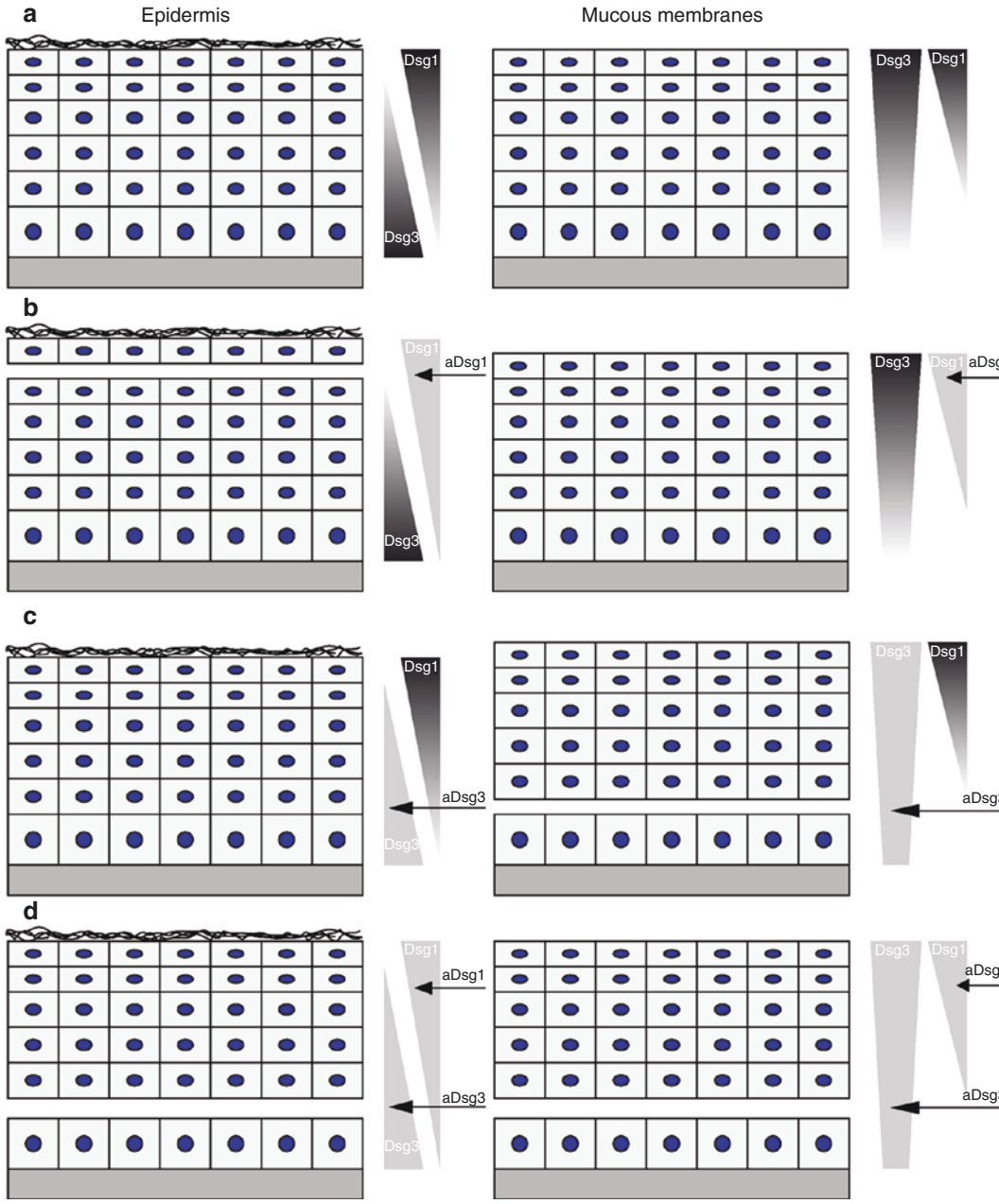

Fig. 8.2 Desmoglein compensation hypothesis. (**a**) Normal distribution of desmoglein (Dsg)1 and Dsg3 in the epidermis and mucous membrane. (**b**) In pemphigus foliaceus, IgG directed against Dsg1 causes subcorneal blistering in skin because in the lower layers Dsg3 compensates for the loss of function of Dsg1. In mucosa however anti-Dsg1 antibodies do not cause blistering, because there is sufficient Dsg3 present throughout all the layers to compensate for Dsg1. (**c**) In mucosal-dominant pemphigus vulgaris (PV), IgG directed against Dsg3 does not cause blistering of the skin because Dsg1 compensates for the loss of function of Dsg3. However there is suprabasal blistering of the mucous membranes because there is not sufficient Dsg1 present to compensate for Dsg3. (**d**) In mucocutaneous PV antibodies directed against both Dsg1 and Dsg3 cause blistering of the skin and the mucous membranes

bly of Dsg3 from the desmosomes, and possible internalization into endosomes.

Diagnosis Paths

History and Physical Examination

Almost all patients with pemphigus vulgaris have painful erosions of the oral mucosa. More than half of the patients also develop blisters and erosions on the skin (mucocutaneous PV). In mucosal dominant PV, there are only oral lesions present (Fig. 8.3).

The disease often starts on the mucous membranes in the oral cavity leading to erosions. The most common sites are the gingiva, buccal mucosa, and tongue. The erosions extend peripherally and may spread to involve the pharynx and larynx with difficulty in eating and drinking and hoarseness of the voice. The lesions do not scar, and therefore are benign. Blood crusts may be present on the nasal septum. Other mucosal surfaces include conjunctiva, oesophagus, vagina, urethra and rectum.

After weeks to months, the disease progresses with lesions appearing on the skin (Fig. 8.4). The predeliction site on the skin are facial temples, scalp, and upper chest. The first lesion of the skin is a blister that is filled with a clear fluid, on a normal or erythematous skin, which breaks easily resulting in painful erosion. The fluid within the blisters may become hemorrhagic, turbid or even seropurulent. The erosions enlarge to form large denuded areas, which become crusted. Crusts are piled up into vegetating plaques due to reblistering of regenerated epithelium underneath. The cutaneous barrier loss may lead to complication as infections or metabolic disturbances. Before systemic corticosteroids became available, about 75% of patients who developed PV died within a year.

A characteristic feature of all forms of active and severe pemphigus is the Nikolsky sign, pro-

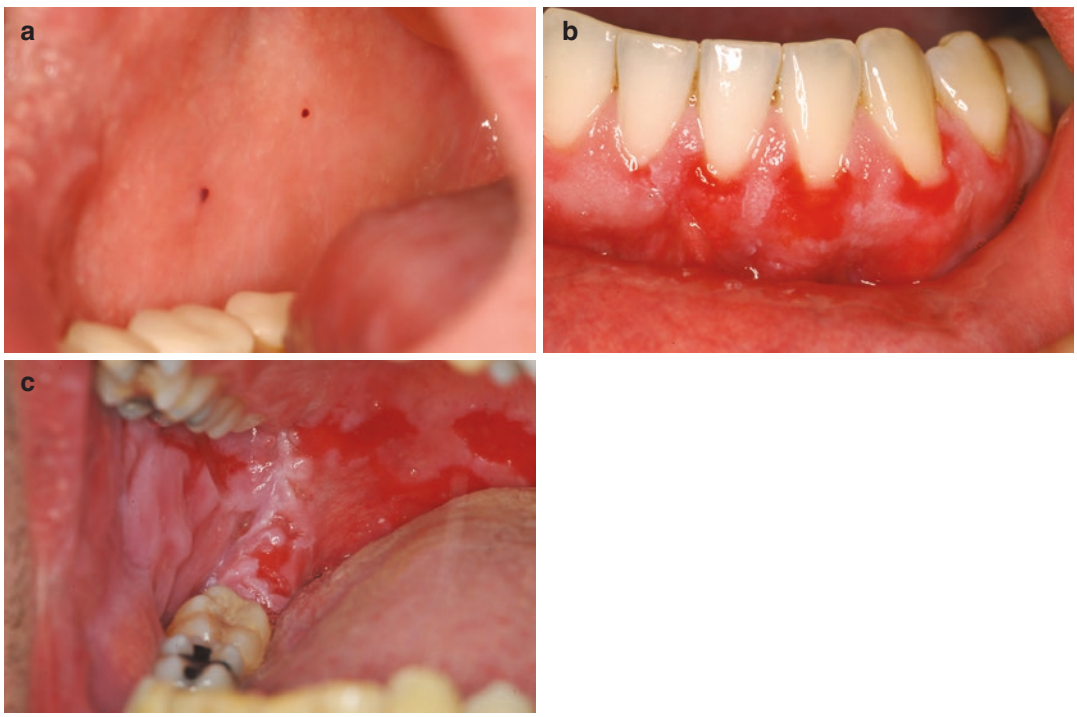

Fig. 8.3 Mucosal-dominant pemphigus vulgaris. Early phase shows (**a**) hemorrhagic vesicles on buccal mucosa, and (**b**) desquamative gingivitis. Late phase shows (**c**) whitish blister roofs (like bacon) and erosions on buccal mucosa and soft palate

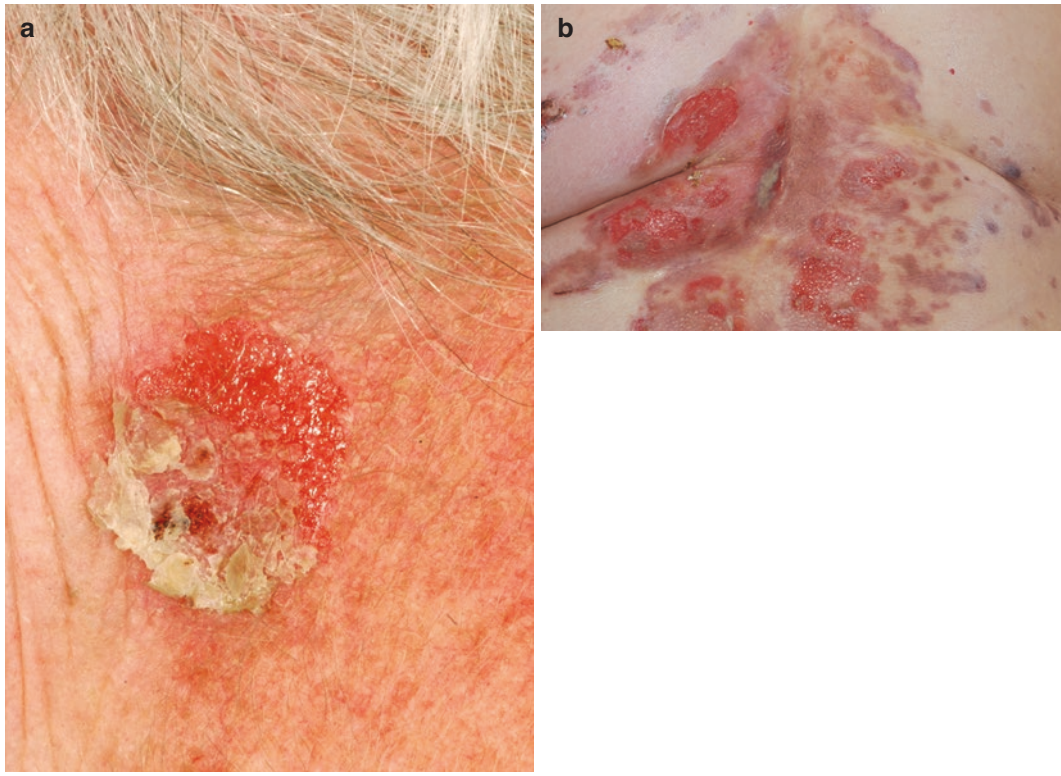

Fig. 8.4 Mucocutaneous pemphigus vulgaris. (**a**) Positive Nikolsky's sign type II on a crust of the temple. (**b**) Symmetrical erosions in dusky erythema on the back

duced when lateral pressure is applied adjacent to a lesion leading to separation of the epidermis.

Lesions of PV generally heal with crusts followed by re-epithelialisation. There is no scarring, although postinflammatory hyperpigmentation may persist for months in patients with Fitzpatrick skin types IV and V. Mild forms of the disease may regress spontaneously. Most patients with pemphigus vulgaris eventually enter a phase of complete remission in which they can be maintained lesion-free with minimum doses of corticosteroids (i.e. prednisolone <10 mg) or without therapy. As medications are tapered, flares in disease activity with development of new lesions and itching are not uncommon.

Pemphigus vegetans is a subtype of PV in which lesions accumulate in body folds (axillae, submammary, and groin) and around orifices (lips, anus). The lesions consist of pustules (Hallopeau type) (Fig. 8.5a) or papillomas (Neumann type) (Fig. 8.5b) or a combination of both (Fig. 8.5c). The affected skin is easily secondarily infected, which explains the foul smelling. As mentioned before, vegetating plaques are common in PV (Fig. 8.6), but the presence of sterile pustules or papillomas in the forementioned regions make it pemphigus vegetans.

General Diagnostics

The initial histopathological finding in pemphigus is intercellular widening between keratinocytes in the epidermis, accompanied by invasion of eosinophilic granulocytes (*eosinophylic spongiosis*). Characteristic for PV is an intraepidermal blister usually just above the basal layer due to loss of cell-cell contact (*suprabasilar acantholysis*) (Fig. 8.7). A few rounded-up acantholytic keratinocytes (*acanthocytes*) as well as clusters of detached epidermal cells float in the blister cavity. The basal cells loose lateral desmosomal

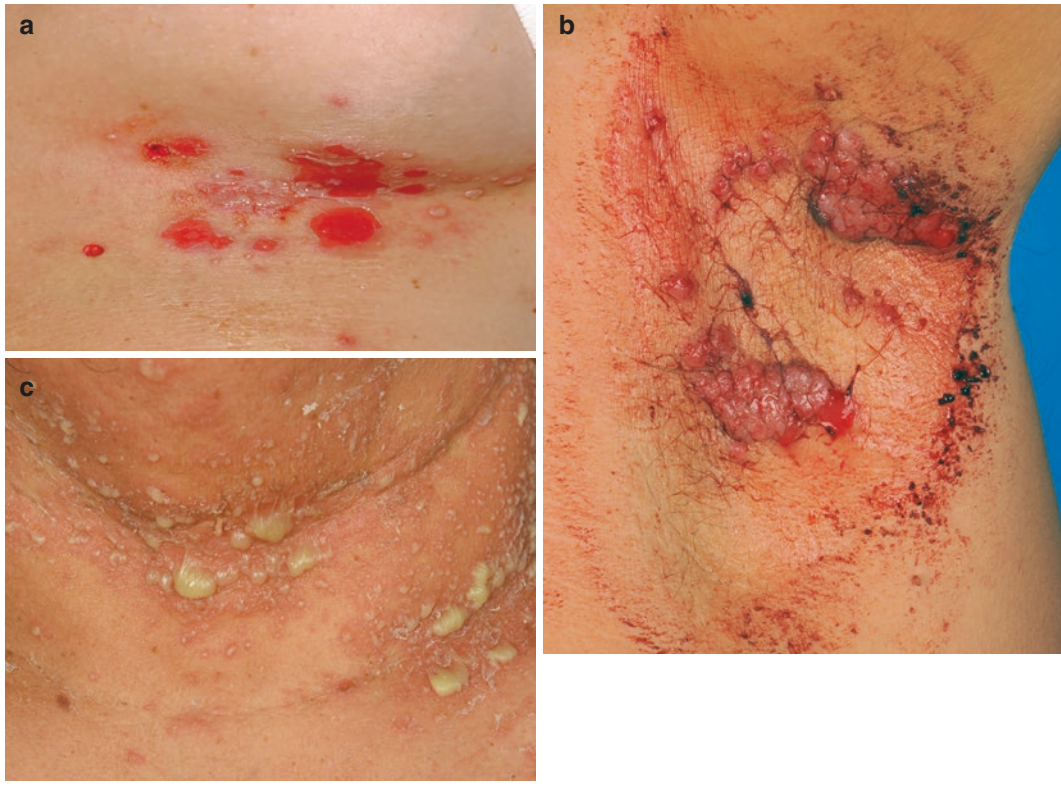

Fig. 8.5 Pemphigus vegetans. (**a**) Hallopeau type with pustules in the body folds. (**b**) Neumann type with papillomas in the axilla (**c**) Hallopeau type with pustules in the body folds

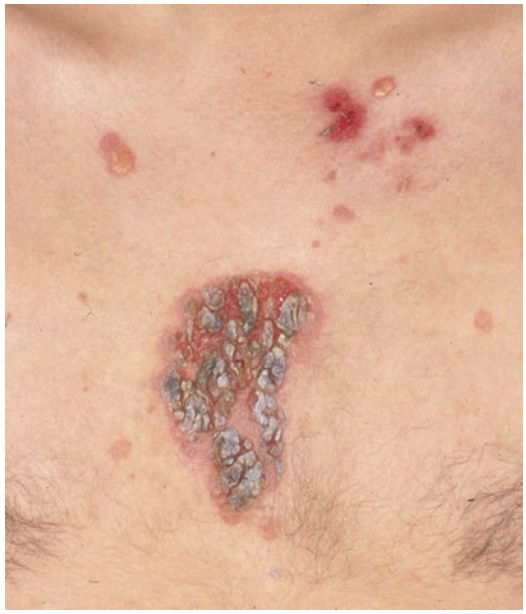

Fig. 8.6 Pemphigus vulgaris: a common vegetating plaque

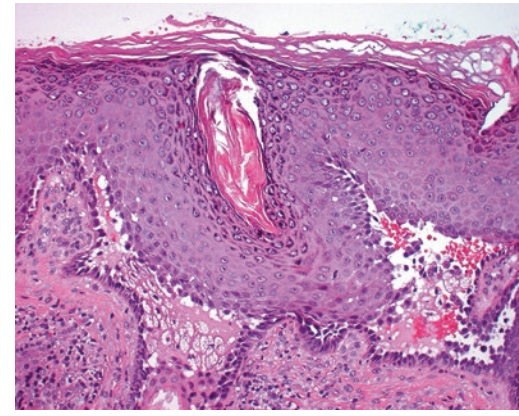

Fig. 8.7 Histopathology of pemphigus vulgaris. Suprabasal acantholysis with basal cells lining the blister floor like 'tombstones' (H&E)

contact with adjacent keratinocytes, but remain attached to the basement membrane via hemidesmosomes, thus giving the appearance of a row of tombstones. The acantholytic process may also involve the hair follicles.

Pemphigus is microscopically characterized by acantholysis

Specific Diagnostics

Immunological Tests

All forms of pemphigus are associated with the presence of skin-bound and circulating antibodies against epithelial cell surface antigens.

Direct Immunofluorescence

Tissue-bound intercellular antibodies are present in lesions and adjacent healthy skin in virtually all patients with pemphigus as detected by direct immunofluorescence microscopy (IF). They are usually IgG, but IgM and IgA with or without complement may also be deposited. See Chap. 4 for more on direct IF in pemphigus.

Indirect Immunofluorescence

Circulating epithelial cell surface (ECS) antibodies in the serum are detectable in up to 89% of patients by ELISA and/or indirect IF.

ELISA

Enzyme-linked immunosorbent assays (ELISA) are available to detect antibodies directed against Dsg1 and Dsg3 (See Chap. 6). The presence of antibodies directed against Dsg3 is associated with mucosal PV, whereas antibodies directed against Dsg1 are associated with PF. Both types of antibodies are present in mucocutaneous PV. ELISA kits are available with the ectodomain of desmoglein produced in insect cells (company) or in human cells (company). The latter has the advantage of containing the mature protein only and not the propeptide as well. It is thought that pathogenic antibodies are directed against conformational epitopes only and these epitopes are present in the mature desmogleins, while non-pathogenic antibodies recognize both mature and propeptide isoforms, correlating with binding of nonconformational epitopes.

There is a correlation between the titre of desmoglein 1 antibodies and skin activity of the disease. Serum monitoring of antibody titres may be useful in guiding therapy, since a rise in their titre usually precedes a recurrence in disease activity, while they usually decrease with successful treatment and disappear in patients in remission.

Case Study: Part 2

Histopathology of lesional skin sampled from the edge of a blister showed suprabasal acantholysis. Direct immunofluorescence microscopy staining of lesional peribullous skin and healthy skin revealed deposition of IgG and C3c along the ECS. Indirect immunofluorescence microscopy on monkey esophagus was positive for ECS IgG antibodies. ELISA identified positive values of anti-Dsg1 and anti-Dsg3 titers (>150). A diagnose was made of mucocutaneous pemphigus vulgaris.

Treatment Tricks

Initial Treatment and Escalator

Systemic Corticosteroids

The treatment of pemphigus was symptomatic until the introduction of corticosteroids in the 1950s. The majority of patients in the pre-steroid era usually died from overwhelming sepsis within 1 year after disease onset. The use of systemic corticosteroids has transformed an almost invariably fatal disease into a chronic disease whose mortality is less than 6%. However the side effects of systemic steroids; including infection, diabetes, osteoporosis, myopathy, gastrointestinal bleeding, cataracts or central nervous system toxicity result in substantial morbidity and also mortality in pemphigus vulgaris. Therefore later other immunosuppressive agents were introduced to reduce side effects of systemic corticosteroids (see below)

Systemic corticosteroids have an important role at the initial treatment to achieve disease control as their effect is quick and pronounced.

Rituximab

Rituximab has revolutionized the treatment of pemphigus turning the chronic disease to an almost curable disease, where patients can experience a long-term complete remission without any medication. Rituximab is recently registered for pemphigus vulgaris, based on the large randomized controlled trial showing superiority in efficacy and safety above systemic prednisolone alone [9]. According to the S2K European guideline, rituximab is the first line treatment for pemphigus vulgaris, in the initial phase in combination with prednisolone [10].

Rituximab is a chimeric murine-human monoclonal anti-CD20 antibody, originally developed for the treatment of B-cell malignancies. CD20 is an antigen expressed on the surface of pre-B and mature B cells. Rituximab binds to transmembrane CD20, reduces circulating B cells and prevents their maturation into all antibody-secreting plasma cells, not just those making pathogenic antibodies. It has shown efficacy in patients with refractory antibody-mediated autoimmune disorders. Rituximab is registered for pemphigus vulgaris. The recommended dosage regime by the European guideline is, a cycle of 2 × 1000 mg with a 2-week interval. The cycle is restarted after 6 months in case of absence of complete remission. In patients with complete remission, a maintenance infusion of 500 mg is advised at month 6, 12 and 18. When patients are treated with rituximab and use 2 or more immunosuppressive agents besides this, then treatment to prevent *Pneumocystis jirovice* pneumonia and herpes pneumonia should be started with cotrimoxazole 480–960 mg/day and valaciclovir 500 mg/day during the 3 months following the rituximab infusion.

Rituximab is the first line treatment for pemphigus vulgaris, at the initial phase eventually in combination with systemic corticostreoids

Immunosuppressive Agents

Immunosuppressive agents are commonly used in combination with systemic corticosteroids in order to increase efficacy and may have a steroid-sparing effect, thereby allowing reduced maintenance doses and less side effects of systemic corticosteroids. The most commonly used adjuvants are azathioprine (2–3 mg/kg), mycophenolate mofetil (2000 mg/day), mycophenolic acid (1440 mg/day), cyclophosphamide (≤2 mg/kg), methotrexate (10–15 mg/week) and dapsone.

High Dose Human Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) neutralizes autoantibodies by several mechanism including anti-idiotypic antibodies, interference with the cytokine network, modulation of B- and T-cell functions, inhibition of complement and cytokine production, and blocking activation and upregulation of inhibitory Fc receptors. A major advantage if IVIG compared with other treatment options is its excellent safety profile. Adverse events are generally mild and reported side effects include headache, fever, chills, myalgia, flushing, hypotension, tachycardia and gastrointestinal symptoms. The standard dose is 2 g/kg/month in 2–4 gifts. The costs of IVIG medication monthly are as high as $10 000 months. Low dose IVIG (0.2 mg/kg/month) may be effective in selected cases [11].

Plasmapheresis and Immunoadsorption

Rapid removal of circulating autoantibodies can be achieved by plasmapheresis (exchanging plasma by fresh-frozen plasma or human albumin) or by immunoadsorption (only removing immunoglobulin). In the past years immonoadsorption replaced plasmapheresis in the treatment of pemphigus. Immunoadsorption allows the

processing of the two- to threefold plasma volume per treatment session and is associated with a lower rate of adverse events like infections and allergic reactions [12].

Follow-Up and Tapering

Treatment should be started with rituximab in combination with high dose predniso(lo)ne in a dosage of 1.0–1.5 mg/kg per day. Taper by 25% reduction in biweekly steps (at <20 mg more slowly!). A rule of the thumb quick tapering schedule is 80–60–40–30–25–20–15–12.5–10–7.5–5–2.5–0 mg in steps of 2-weeks. Raise dose by two steps dose when new lesions occur, or continue dose if tapering is not possible.

When patients are treated with rituximab and use 2 or more immunosuppressive agents besides this, then treatment to prevent *Pneumocystis jirovice* pneumonia and herpes pneumonia should be started with cotrimoxazole 480–960 mg/day and valaciclovir 500 mg/day during the 3 months following the rituximab infusion.

Case Study: Part 3

First-line treatment consisted of prednisolone (1 mg/kg) in combination with two intravenous infusions of 1000 mg rituximab separated by 2 weeks, which was preceded by screening according to protocol. The dosage of prednisolone was tapered with 10 mg per 2 weeks until 30 mg per day and after that by 5 mg per 2 weeks. The erosions on the skin healed promptly whereas the oral mucosal erosions persisted and healed more slowly. Oral swabs for bacterial and fungal culture as well as Herpes simplex (HSV) PCR were frequently performed to rule out superinfection causing delayed healing of the mucosa. At month 6, the patient showed complete remission off-therapy and a maintenance infusion of 500 mg of rituximab was administered followed by 500 mg of rituximab at month 12. After 18 months, the patient was discharged from outpatient care and instructed to contact us in case of clinical signs of relapse.

Review Questions

1. What is the most common location of mucocutaneous pemphigus vulgaris is?
   (a) Temples
   (b) Feet
   (c) Genitals
2. The most important risk factor for pemphigus is
   (a) Hair colour
   (b) Country of birth
   (c) Profession
3. Patients with mucosal dominant PV have antibodies directed against
   (a) desmoglein 1
   (b) desmoglein 3
   (c) desmoglein 1 and 3
4. First line treatment of pemphigus is
   (a) superpotent topical corticosteroids
   (b) systemic corticosteroids
   (c) azathioprine
   (d) rituximab

Answers

1. (a)
2. (b)
3. (b)
4. (d)

On the Web

JAMA Dermatology Patient Page, Pemphigus http://archderm.jamanetwork.com/article.aspx?articleid=1879985

International Pemphigus & Pemphigoid Foundation http://www.pemphigus.org/

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