Pemphigoid diseases affecting the skin

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14 Pemphigoid Diseases Affecting the Skin

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Bullous Pemphigoid

Introduction and Aims

Short Definition in Layman Terms

Bullous pemphigoid (BP) is the most common blistering disease of the skin and mucous membranes (Fig. 14.1). BP mainly affects elderly and is clinically characterized by severe itch with tense blisters, erythema or urticarial plaques. Not all patients have skin blistering, approximately 1 in 5 patients has nonbullous pemphigoid (NBP) with severe itch and eczematous skin lesions. BP and NBP are mediated by an immune response against two structural proteins in the hemidesmosomes that are important for maintaining the integrity of the skin. Dysfunction may lead to subepidermal blistering in BP. Treatment of BP and other subtypes of pemphigoid is based on suppression of the immune system, with corticosteroid creams applied to the skin or oral drugs.

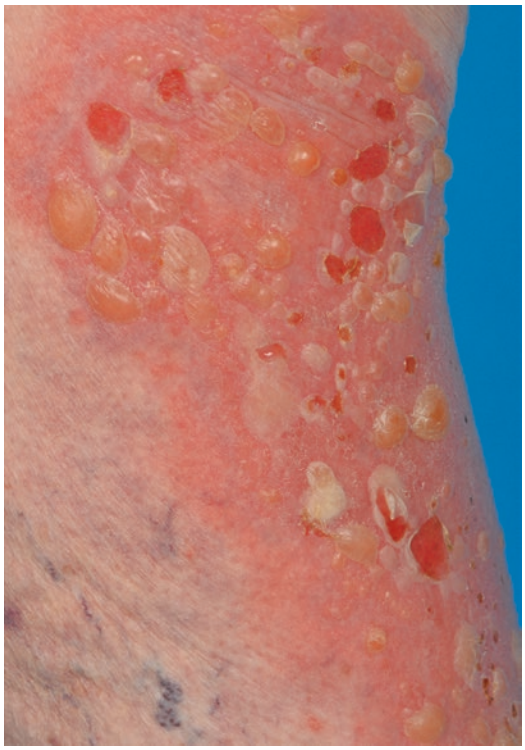

Fig. 14.1 Infiltrated urticarial plaques with tense blisters on predilection sites of BP: the flexural surfaces of the legs and the thighs. Multiple ruptured blisters leave eroded areas

BP is the most common autoimmune blistering disease mainly affecting elderly

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Learning Objectives

After reading this chapter, you should be able to recognize the typical clinical presentation of BP, but also be aware of non-bullous pemphigoid. Moreover, you are familiar with the target antigens, the hallmarks in histopathology and immunofluorescence microscopy and diagnostic criteria. You should also be aware of treatment options in BP.

Case Study: Part 1

A 83-year-old woman with severe itch for several months is treated by her general practitioner with several ointments. Later on, she also develops erythematous papules and urticarial plaques on her back and extremities, with also some vesicles. Diagnosed as urticaria, she was treated with topical corticosteroids and oral antihistamines, without improvement. The dermatologist noted multiple tense blisters on erythematous skin, and erosions on the flexor aspects of the extremities at physical examination. Nikolsky sign was negative, and mucous membranes were unaffected.

Didactical Questions: Cross Section of Questions to Prime the Reader's Interest

Which diagnostic steps are essential when a blistering disease is suspected? What are the similarities and differences between pemphigus and pemphigoid, can you make the differentiation on clinical symptoms alone? How do you make the diagnosis of BP and NBP and what is the first choice treatment?

Facts and Figures

Definitions and Classification

Pemphigoid: the etymology of the word pemphigoid is 'form of a blister' (*pemphix*, blister and *eidos*, form in Greek). Therefore, the adjective 'bullous' is not strictly necessary. In 1953, Walter F. Lever differentiated pemphigoid diseases from pemphigus, based on histopathology and clinical presentation. He described intraepidermal separation and loss of cell adherence between keratinocytes (acantholysis) in pemphigus, and introduced the term bullous pemphigoid (BP) for diseases with subepidermal splitting [1]. BP is defined by autoantibodies against two hemidesmosomal proteins: BP180 and BP230. The classification of pemphigoid diseases includes several subtypes, based on different clinical symptoms, target antigens and autoantibody isotypes (Table 14.1). BP is the most common pemphigoid disease. BP predominantly affects the skin, involvement of the mucous membranes is seen in up to 20% of cases.

Epidemiology

BP most frequently affects elderly, with onset of disease usually after the age of 70 years. Incidences have been described from 1.21 to 2.17 per 100,000 persons per year. Moreover, the incidence rises substantially with age, up to 15–33 per 100,000 per year in people older than 80 years. The incidence of BP in Europe has more than doubled in the last decade, which might be related to both the increasing age of the general population, multi-drug use and the availability and quality of diagnostics. BP rarely occurs in infancy and childhood (see Chap. 24). BP has been associated with a high morbidity and a considerable 1-year mortality rate ranging from 20 to 40%. Most important risk factors for poor outcome are high age, widespread disease, a low Karnofsky score and high doses of oral corticosteroids [1].

Pathogenesis

BP is characterized by the presence of IgG autoantibodies against components of hemidesmosomes in the EBMZ, BP180 and BP230. Binding of autoantibodies to the antigens initiates a complex process, leading to separation of the epidermis and the dermis with subepidermal blister formation. Additionally, deposits of IgA, IgE and complement may also be found along the EBMZ. Most

Table 14.1 Target antigens, IF findings and clinical symptoms of subtypes of subepidermal autoimmune blistering diseases

Disease type	Target antigens	IF Findings		Clinical symptoms
		DIF	IIF SSS	
Bullous pemphigoid	BP180 BP230	n-serrated EBMZ IgG ± IgA, IgE, C3c	Epidermal	Pruritus, urticaria, tense blisters without predominant mucosal involvement
Nonbullous pemphigoid	BP180 BP230	n-serrated EBMZ IgG ± IgE, C3c	Epidermal	Erythematous papules or nodules, pruritus on primary nondiseased skin, eczematous lesions, urticarial plaques
Brunsting-Perry pemphigoid	BP180	n-serrated EBMZ IgG ± C3c	Epidermal	Erosions and blisters confined to the head, face, neck and upper trunk leaving atrophic scars
Lichen planus pemphigoides	BP180 BP230	n-serrated EBMZ IgG ± C3c	Epidermal	Tense blisters independent of the lichenoid plaques and papules of lichen planus
Pemphigoid gestationis	BP180 BP230	n-serrated EBMZ C3c ± IgG	Epidermal	Intense pruritic urticarial rash, papules and tense blisters starting around umbilicus and then spread over the body
Linear IgA bullous dermatosis	BP180 LAD-1, LABD-97	n-serrated EBMZ IgA ± IgG	Epidermal	Tense blisters and erosions in 'string of pearls', without predominant mucosal involvement
Anti-p200 pemphigoid	p200	n-serrated EBMZ IgG ± C3c	Dermal	Pruritus, tense bullae, vesicles, urticarial plaques, predominantly on the extremities and trunk
Epidermolysis bullosa acquisita	Type VII collagen	u-serrated EBMZ IgG ± IgA	Dermal	Mechanobullous variant: acral blistering that heal with scarring and milia Inflammatory variant: widespread vesicles and blisters, without scarring or milia

EBMZ epidermal basement membrane zone, *IF* immunofluorescence microscopy, *DIF* direct IF, *IIF SSS* indirect IF salt-split-skin, *IgG/IgA/IgE* immunoglobuline G/A/E, *C3c* complement C3, *BP* is characterized by subepidermal blister formation

BP patients have autoantibodies against the extracellular part of the 16th non-collagenous domain (NC16A) of BP180 (immunodominant region). BP230 is a 230-kDa intracellular component of the hemidesmosomal plaque. However, the pathogenic relevance of autoantibodies against BP230 is not fully elucidated. Isoforms of both BP180 and BP230 are also expressed in the central nervous system, which might explain the association between BP and neurological diseases, such as cognitive impairment, Parkinson's disease and stroke in up to half of patients with BP [1].

Main target antigens in BP are hemidesmosomal proteins BP180 and BP230

Diagnosis Paths

History and Physical Examination

BP typically presents with severe pruritus, localized or generalized tense blisters and erythema or urticarial plaques (Fig. 14.2). Nikolsky sign is negative. Predilection sites are the trunk, abdomen and flexural aspects of the extremities. Blisters may arise on both healthy and erythematous skin, often have a transparent or serous exudate and can persist for several days. Ruptured blisters leave erosions and crusts, but do not heal with scarring. Mucosal involvement is seen in 10–20% of BP patients, mostly the oral mucosa. Clinical and diagnostic clues are summarized in Table 14.2. A pitfall can be the prodromal phase that exists in a number of patients that only have pruritus and excoriated, eczematous or urticarial lesions that precede the development of blisters, or have persistent nonbullous pemphigoid [2]. A detailed medical history should be obtained, including a medication history with recent drug intake. Furthermore, the extent of BP should be assessed, for example with the BP Disease Area Index (BPDAI, see Chap. 2).

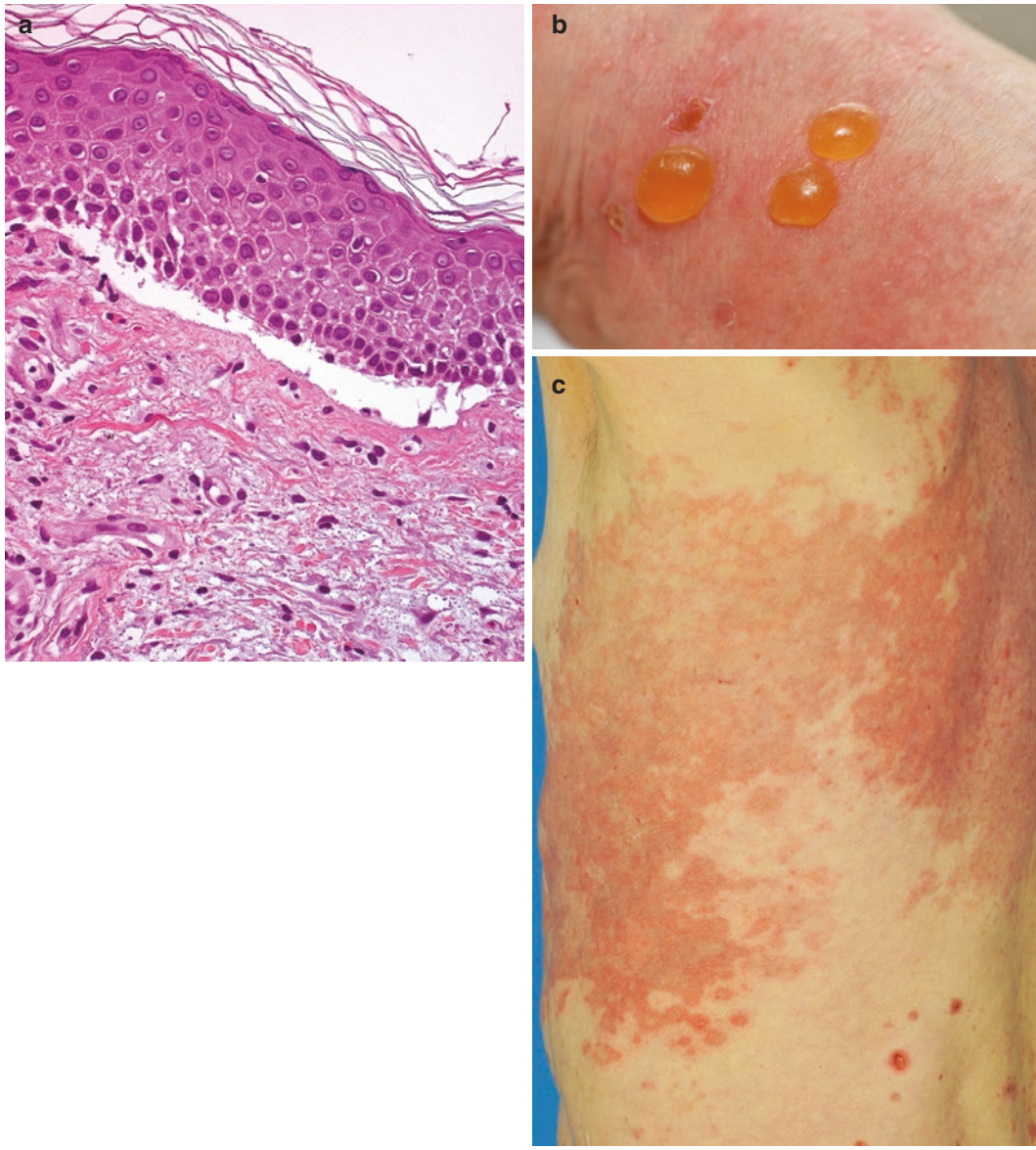

Fig. 14.2 Hallmarks of BP: (**a**) Histopathology of H&E section of lesional skin biopsy with subepidermal blister formation with eosinophils and a dermal inflammatory eosinophilic infiltrate (magnification 400×), (**b**) tense bullae on inflamed, erythematous skin, (**c**) confluent infiltrated urticarial plaques on the trunk

General Diagnostics

Which diagnostic steps are essential when bullous or nonbullous pemphigoid is suspected? The diagnosis of BP and NBP is based on a combination of criteria comprising clinical features and specific findings in direct IF and serology. Both DIF and IIF SSS should be performed for optimal diagnosis of BP and NBP. Based on a large diagnostic accuracy study, diagnostic criteria consist of at least two positive results out of three criteria: (1) pruritus and/or predominant cutaneous blisters, (2) linear IgG and/or C3c deposits (in an n-serrated pattern) by DIF on a skin biopsy specimen, and (3) positive epidermal side staining by IIF SSS on a serum sample [3]. A complete blood count often shows peripheral eosinophilia.

Table 14.2 Clues to diagnosis of BP

Clinical clues for diagnosis of BP	Diagnostic clues for diagnosis of BP
Elderly with severe pruritus	Peripheral eosinophilia
Eczematous lesions, papules or nodules	Subepidermal splitting
Urticarial plaques	Dermal inflammatory infiltrate of eosinophils
Localized or generalized tense blisters	DIF IgG/C3c along EBMZ n-serrated pattern
Mucosal lesions	IIF on monkey esophagus IgG positive
Polypharmacy	IIF SSS IgG positive epidermal binding
Nikolsky sign negative	BP180 NC16A ELISA positive
Good response to oral corticosteroids	Immunoblot BP180 positive

Main clinical symptoms of BP are tense blisters, urticarial plaques and pruritus

Histopathology of a bullous lesion shows subepidermal splitting and an inflammatory infiltrate composed of mainly eosinophils and neutrophils. However, in absence of blistering, the histopathology may be non-specific, and be limited to eosinophilic spongiosis or an eosinophilic infiltrate in the upper dermis. Direct immunofluorescence microscopy reveals a linear n-serrated immunodeposition of IgG and/or complement C3 along the EBMZ. Other Ig subclasses can be found, such as IgA, IgM and occasionally IgE.

Diagnosis of bullous and nonbullous pemphigoid is based on clinical features, DIF and immunoserology

Specific Diagnostics

Diagnosis of BP and NBP can be confirmed with very high specificity by serology using IIF on 1.0 M NaCl-split skin (SSS) substrate showing binding of antibodies to the epidermal side (roof) of the artificial split [3]. IIF on monkey esophagus is less sensitive. Combining the IIF SSS technique (epidermal or dermal binding) with serration pattern analysis (n-serrated versus u-serrated) allows to differentiate between different subtypes of pemphigoid and EBA (see Chap. 4). BP180 NC16A and BP230 ELISA's are not recommended for initial diagnosis, due to frequent borderline findings [3]. After confirmed diagnosis of BP, the BP180 NC16A ELISA can be used to monitor disease activity. Immunoblot can be used to test the patient's serum reactivity to BP180, BP230 and/or other rare targeted antigens.

Case Study: Part 2

Histopathology of a lesional biopsy of an intact blister showed a subepidermal blister with a dense inflammatory infiltrate of eosinophils. A perilesional skin biopsy for DIF showed linear depositions of IgG 3+, IgA 1+ and C3c 3+ in an n-serrated pattern along the EMBZ. Serologic testing by IIF SSS was positive for IgG on the epidermal side of the salt-split-skin. BP180 NC16A and BP230 ELISA IgG indexes were 51 (positive), and 7 (negative), respectively. Immunoblot was positive on BP180 and BP230 IgG. The diagnosis was made of BP, which initially presented only with pruritus.

Treatment Tricks

Initial Treatment and Therapeutic Ladder

BP can have a clinical course that may last from several months to years. The high age of BP patients and the possible presence of co-morbidities can make the treatment management more difficult. Recommended first-line therapy for mild, moderate and severe disease is superpotent topical steroids (clobetasol propionate) 30–40 g/day applied daily over the whole body, including blisters, erosions and healthy skin, but sparing the face [4]. Whole body application of superpotent topical corticosteroids is considered to be effective and save and has a lower cumulative dose of corticosteroids and less side-effects compared to oral corticosteroids. Patients with localized BP can be treated with superpotent topical corticosteroids applied to lesional skin only. Oral corticosteroids (prednisone 0.5 up to 0.75 mg/kg/day) are often used in treatment of moderate to severe BP and

may be accompanied by adjunctive superpotent topical corticosteroids and/or immunosuppressive or -modulating agents [4]. Low-dose methotrexate (2.5–12.5 mg/week) was reported to be an effective and relatively safe therapeutic option in elderly BP patients [5]. Systemic anti-inflammatory antibiotics (doxycycline) may be used as alternative treatment when oral corticosteroids are contraindicated. Other therapeutic options include dapsone, azathioprine, mycophenolate mofetil, or mycophenolic acid. Rituximab treatment may be considered when these agents are contraindicated or in refractory cases of BP (see box XX pemphigus) [6]. Subsequently, the combination of intravenous immunoglobulin (IVIG) and Rituximab may be considered if Rituximab monotherapy is ineffective.

Whole body application of superpotent topical steroids is first-choice therapy in BP

Case Study: Part 3

First-line therapy with whole body application of superpotent topical corticosteroids (40 g/day) improved her complaints, but appeared to be insufficient. Therefore, the patient received adjunctive treatment with Methotrexate 7.5 mg/day, later increased to 10 mg/day. Pruritus and the frequency of blistering reduced, after 3 month the patient reached complete remission and methotrexate was lowered to 7.5 mg/day again. When mild symptoms of itch returned, adjunctive treatment with lesional superpotent topical corticosteroids was sufficient to maintain complete remission.

Follow-Up and Tapering

BP can last for several years and has the tendency to relapse. Determination of anti-BP180 NC16A IgG antibodies by ELISA follows disease activity and severity and can also be used to identify patients with a high risk of relapse. Current evidence suggests to continue initial topical treatment until 15 days after disease control, when no new lesions arise and lesions begin to heal. Then treatment of superpotent topical corticosteroids should be reduced by a tapering schedule, with daily treatment in the 1st month, every 2 days in the 2nd month, 2 times a week in the 3rd month and once a week starting in the 4th month. Tapering of oral corticosteroids after disease control is based on clinical course, and when available on serum levels of anti-BP180 NC16A IgG [3].

Nonbullous Pemphigoid

Short Definition in Layman Terms

Nonbullous pemphigoid (NBP) is the subset of patients with immunopathological findings of BP and pruritus, but no blister development. Similar to BP, the onset of disease is often at high age. Patients may present with chronic itch or with various nonbullous inflammatory skin lesions. NBP patients are frequently misdiagnosed as drug reaction or dermatitis, and therefore the diagnostic delay is long. Clinicians should be aware of this pemphigoid subtype when encountering elderly patient with pruritus.

Definitions and Classification

In 1953 Walter F. Lever added the pleonasm "bullous" to the name pemphigoid in an attempt to separate it from mucous membrane pemphigoid. We now know that BP is not always bullous. In the literature there is no unanimity on how to name the subset of patients with pemphigoid without blistering. The coined terms include, pruritic nonbullous pemphigoid, pemphigoid nodularis, papular pemphigoid, prurigo-nodularis like pemphigoid, non-bullous BP, prodromal BP and BP incipiens. Because these patients have pemphigoid of the skin without blistering, we classify this subtype as NBP [2].

Epidemiology

Of all patients presenting with BP, approximately 20–25% does not have blistering. The majority of the patients with NBP is above 70 years of age. Probably NBP is underdiagnosed in elderly with chronic itch, because of unfamiliarity of clinicians with the diagnosis of NBP.

Approximately 20% of patients with bullous pemphigoid do not show skin blistering, a variant termed nonbullous pemphigoid

Pathogenesis

The pathogenesis of NBP shows great resemblance to that of BP, and also relies on the production of IgG autoantibodies that target hemidesmosomal proteins BP180 and BP230. It is unknown why patients with NBP do not develop blisters, while the diagnostic immunological findings can be similar to BP. In contrast to BP with mainly BP180 autoreactivity, predominant reactivity to BP230 is seen in NBP that might lead to a less extensive inflammatory response. Moreover, less frequent complement activation is observed in NBP versus BP skin.

Clinical Symptoms

The clinical presentation of NBP is heterogeneous and may mimic other inflammatory diseases. Patients most commonly present with severe pruritus, accompanied by erythematous papules and nodules [2]. Moreover, eczematous lesions, urticarial plaques, and pruritus on primary nondiseased skin could be observed (Fig. 14.3).

Think of NBP in elderly with chronic itch

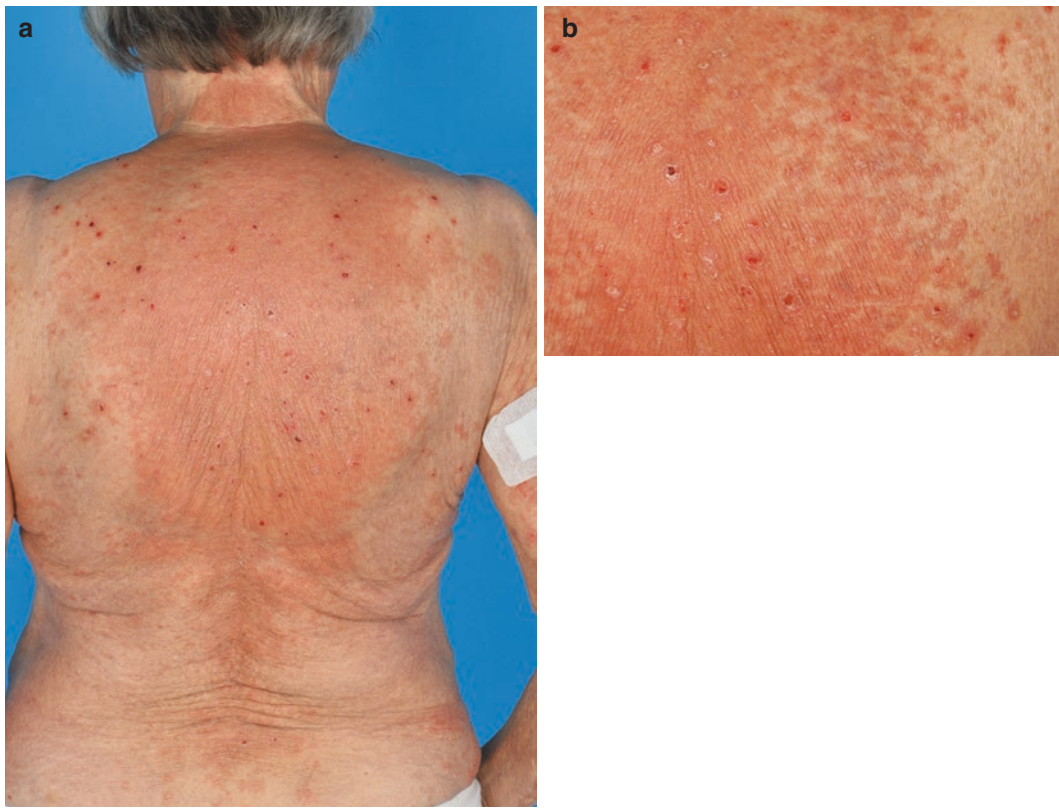

Fig. 14.3 An elderly NBP patient with pruritic, excoriated eczematous lesions on the back (**a**), and in detail (**b**); DIF showed lineair IgG along the BMZ in the n-serrated pattern

Diagnosis Paths

Similar to diagnosis of BP (above), diagnosis of NBP is based on a combination of criteria comprising clinical features and specific findings in direct IF and serology [3]. In the absence of blisters we recommend a biopsy for DIF in NBP from lesional skin. Diagnosis of NBP can be made by positive IIF on SSS (epidermal binding) in combination with a compatible clinical phenotype [3]. Other serological tests like immunoblot or NC16A ELISA can support the diagnosis. However, single positive results by BP180 NC16A or BP230 ELISA should not be considered as having BP or a BP variant, because of frequent borderline results.

Treatment Tricks

Treatment of this intense pruritic condition is essential. Treatment recommendations for NBP are similar as in BP, with first-line treatment of whole body application of superpotent topical corticosteroids. If not responsive, systemic treatment with low-dose methotrexate is the next recommended step [2]. In other cases maintenance treatment with low dose oral corticosteroids is necessary, or Rituximab might be considered in refractory cases.

Brunsting-Perry Cicatricial Pemphigoid

Short Definition in Layman Terms

Brunsting-Perry cicatricial pemphigoid is a form of localized pemphigoid affecting the skin and limited to the head and neck area, leading to scarring. Brunsting-Perry cicatricial pemphigoid is rare, but difficult to recognize for clinicians. A skin biopsy for DIF must be performed for a correct diagnosis.

Facts and Figures

In 1957, Brunsting and Perry described a rare localized form of cicatricial pemphigoid patients who presented with itchy erosions with blisters that heal with scarring at the site of the scalp, face and neck [7]. Circulating IgG autoantibodies target BP180, and occasionally LAD-1. Subepidermal split formation occurs in most cases at the level of the lamina lucida. The target, the C-terminal domain of BP180 that is located in the lamina densa, might be responsible for the scarring phenotype. The average age at onset of symptoms is 58 years and the male/female ratio is 2:1.

Clinical Symptoms

Brunsting-Perry cicatricial pemphigoid clinically presents with erosions and blisters of the head, neck and shoulder area that heal with scarring and milia (Fig. 14.4). The scarring of the scalp will develop in permanent alopecia. Mucosal involvement is rarely seen. Because of its rarity and resemblance with other diseases like epidermolysis bullosa acquisita, erosive pustular dermatosis of the scalp, chronic infection, squamous cell carcinoma, folliculitis decalvans it may be difficult to recognize.

Brunsting-Perry cicatricial pemphigoid is localized on head, neck and shoulders

Diagnosis Paths

Histopathological biopsy of the border of an erosion of the scalp shows subepidermal blistering with lymphocytes, neutrophils and eosinophils, and the presence of extensive scarring in the der-

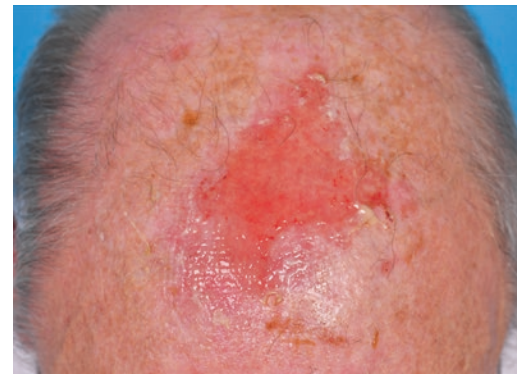

Fig. 14.4 Sharply bordered erosions on the scalp with scarring alopecia in a patient with Brunsting-Perry pemphigoid

mis, with loss of hair follicles. DIF on perilesional skin shows linear deposits of IgG and C3 in the n-serrated pattern along the epidermal BMZ. DIF of normal healthy skin of the upper arm may also show deposits of IgG and C3c. The indirect immunofluorescence examination is often negative.

Treatment Tricks

The disease is responding well to oral corticosteroids (prednisolone 0.5–0.75 mg/kg/day) in combination with immunosuppressive agents like azathioprine (2–3 mg/kg/day). For painful erosions using a wound dressing with a silicon layer is useful.

Lichen Planus Pemphigoides

Introduction and AIMS

Lichen planus pemphigoides (LPP) is a rare variant of pemphigoid diseases characterized by a combination of clinical, histological and immunological features of both lichen planus (LP) and BP. In the bullous form of LP blistering is restricted to LP lesions, however, in LPP blisters appear also on normal appearing skin.

Facts and Figures

The term lichen planus pemphigoides or 'lichen ruber pemphigoides' was first used by Kaposi in 1892, describing a dermatosis with lichen planus lesions with additional blistering. The pathogenesis of LPP is not completely understood yet, LPP is associated with an autoimmune response directed mostly against the NC16A domain of BP180. A suggested theory is that LP lesions damage the basal keratinocytes and expose the BP180 antigens, leading to a secondary autoimmune reponse with autoantibodies to the EBMZ [1]. The mean age of onset is usually younger (50–60 years) than in BP.

Diagnosis Paths

LPP clinically presents with a lichenoid eruption of papules and plaques preceding bullous lesions on both LP lesions and previously normal skin. LPP predominantly affects the extremities and tends to be less severe than BP. Histopathology shows typical findings of LP in papular lesions and subepidermal blistering in biopsies of bullous lesions. The diagnosis of LPP is confirmed by detection of IgG autoantibodies or C3c directed against the EBMZ by DIF of a perilesional biopsy, and detection of circulating IgG autoantibodies against BP180 NC16A, and enables to distinguish LPP from bullous LP.

In LPP blisters may arise on LP lesions and previously normal skin

Treatment Tricks

Simultaneous treatment of LP lesions and bullous lesions is needed to avoid an ongoing stimulation of the autoimmune process at the EBMZ. Treatment follows algorithms as for LP and BP [1]. The prognosis is good, with a reported low rate of recurrence of blistering.

Pemphigoid Gestationis

Short Definition in Layman Terms

Pemphigoid gestationis (PG) is a pregnancy-associated subtype of pemphigoid which manifests in the 2nd or 3rd trimester of pregnancy. Sporadically this disease presents within 4 weeks after birth.

PG usually manifests in the 2nd and 3rd trimester of pregnancy

Facts and Figures

Holmes and Black suggested in 1982 to name the disease pemphigoid gestationis instead of herpes gestationis, because of the correlation of the clin-

ical spectrum and immunlogical findings with pemphigoid diseases. PG is characterized by autoreactivity to the NC16A domain of BP180.

Epidemiology

The annual incidence of PG is 1:50,000 pregnancies. No difference in phenotype is seen in both Caucasians and Afro-Americans. PG can arise at any moment in childbearing age.

Pathogenesis

The pathogenesis of PG is not fully known. It is believed that PG is caused by loss of protection of the feto-placental unit against allogeneic recognition by the mother. In normal pregnancy, there is no expression of MHC II antigens on the trophoblast. This is a mechanism that protects the fetus against recognition by the maternal immune system. Within PG patients, however, there is an aberrant expression of MHC class II molecules in the placenta. Consequently, BP180 present in the placenta is presented to the maternal immune system, leading to an immune response with the formation of autoantibodies against BP180 and affection of the skin [8].

Clinical Symptoms

PG presents with pruritic urticarial plaques, vesicles and tense blisters starting around the umbilicus, followed by expansion over the trunk and the distal extremities (Fig. 14.5). Remission is usually seen within 6 months. In the minority of the patients (<5%) PG persists and converts into BP. Recurrence of PG occurs in more than 90% of the additional pregnancies. Exacerbation may occur prior to menses or after starting oral anticonception. Because of placental insufficiency, there is a risk of growth retardation and premature delivery of the fetus. There is no increased risk of stillbirth or spontaneous abortion. In 10% of the neonates a transient form of BP is seen. Neonatal disease has a mild course with remission within days to weeks [8].

Inform the patient about the possibility of recurrence of PG in following pregnancies

Diagnosis Paths

Histopathology shows subepidermal blistering with eosinophilic infiltrate. Final diagnosis can be made by DIF showing C3c and IgG depositions in the n-serrated pattern along the EBMZ. IgG1 and IgG3 having strong complement binding properties cause the presence of C3c. IIF performed on 1 M NaCl-split skin substrate showing binding of antibodies to the epidermal site (roof) of the split and by immunoblot analysis revealing immunoglobulin binding to the 180-kDa antigen.

Treatment Tricks

The first-line therapy for PG is (super) potent topical corticosteroids in combination with H1-receptor antagonist. Oral corticosteroids can be introduced at an initial dose of 0.25–0.5 mg/kg/day when (super) potent topical corticosteroids are not sufficient enough. A multidisciplinary approach with the gynecologist is recommended.

Anti-p200 Pemphigoid

Introduction

Anti-p200 pemphigoid is a recently defined, rare subtype of pemphigoid diseases characterized by autoantibodies against a 200-kDa protein (p200) of the EBMZ. The molecular identity of the pathogenic autoantigen has yet to be defined. Anti-p200 pemphigoid is probably misdiagnosed and classified as BP or inflammatory EBA, because of low availability of diagnostics test.

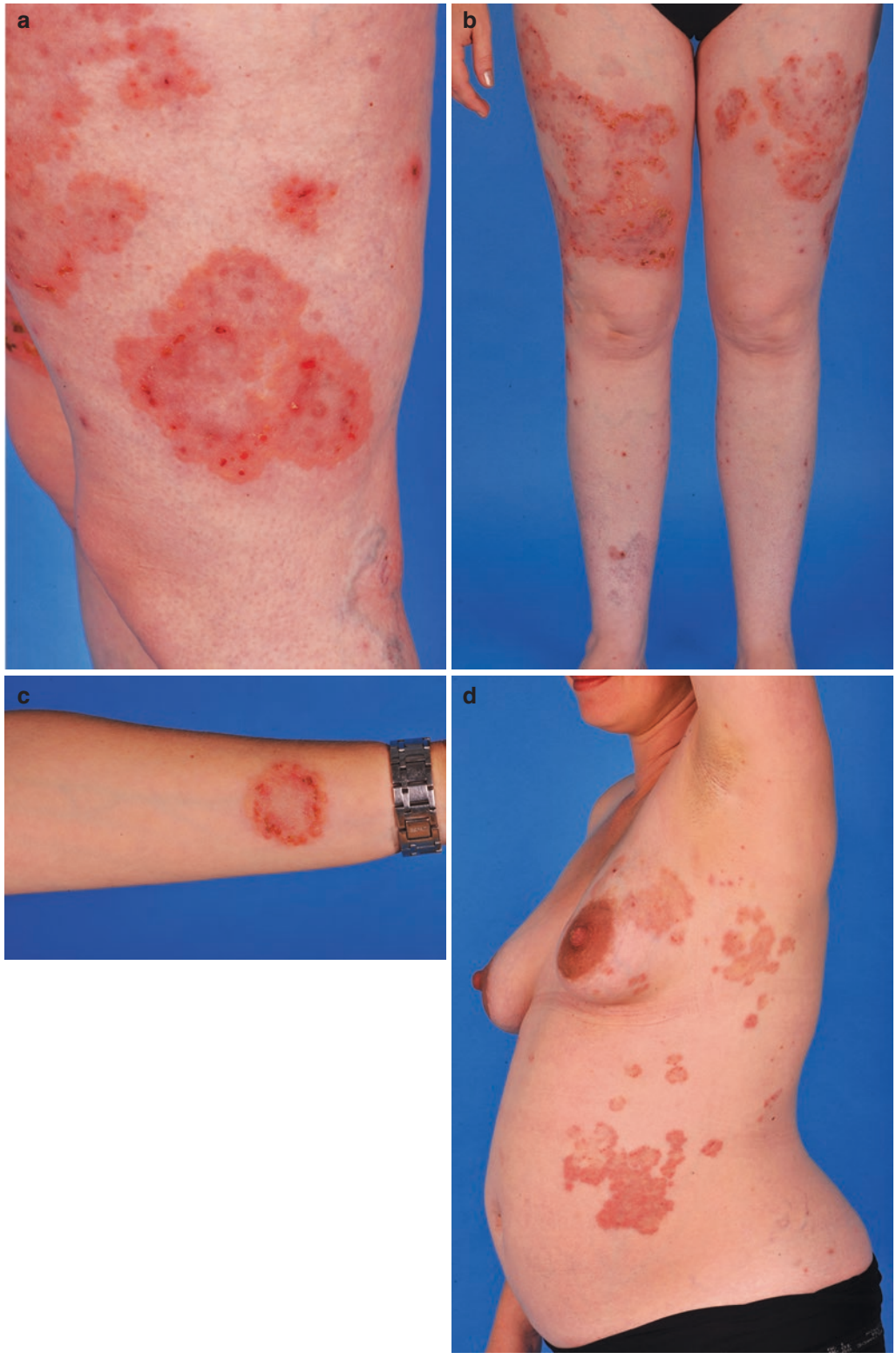

Fig. 14.5 Pemphigoid gestationis in a woman in the 24th week of gestation with pruritic eruption of circinate vesicles on urticarial plaques (**a**–**d**) [Reprinted with permission from *Ned Tijdschr Geneeskd*. 2009;153: B36. Diagnostic image. A pregnant female with blisters]

Facts and Figures

Originally described in 1996 as a novel subepidermal autoimmune blistering disease with autoantibodies against an unknown 200-kDa component of the EBMZ, the disease was consequently termed anti-p200 pemphigoid [9]. Since then, it was renamed to laminin γ1 pemphigoid as a new entity, because serum samples of 90% of anti-p200 patients appeared to recognize the glycoprotein laminin γ1, mainly the C-terminus region. However, *ex vivo* and *in vivo* studies were unable to show pathogenic activity of laminin γ1 [10].

The autoantigen in anti-p200 pemphigoid is a 200-kDa protein in the lower EBMZ

Clinical Symptoms

The clinical presentation of anti-p200 pemphigoid is heterogeneous and may mimic BP, LAD and inflammatory EBA. Most patients present with pruritus and tense bullae, vesicles and erythematous or urticarial plaques, predominantly on the extremities and trunk. When monomorphic blistering occurs solitary on hands and feet, it may resemble dishydrotic pemphigoid (Fig. 14.6a, b). In approximately 10–20% of patients mucous membranes are involved, but not as predominant as in anti-LN-332 MMP. Lesions normally heal without scarring. Patients tend to be younger than in BP. An association with psoriasis was seen in about 30% of reported cases, mostly in Japanese patients [10].

Diagnosis Paths

Anti-p200 pemphigoid is characterized by subepidermal blistering with a mainly neutrophilic inflammatory infiltrate, in contrast to a typical eosinophilic infiltrate in BP. However, histopathology alone cannot differentiate anti-p200 pemphigoid from other pemphigoid diseases. DIF of a perilesional biopsy shows linear deposits of IgG

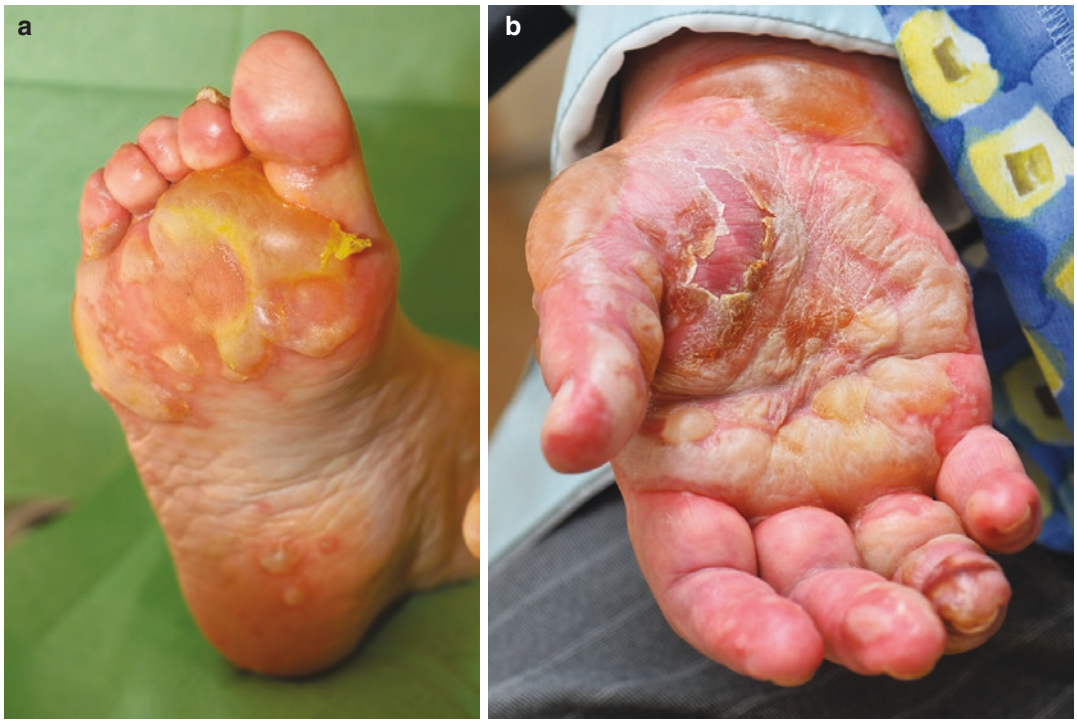

Fig. 14.6 Anti-p200 pemphigoid. Resembling dyshidrotic pemphigoid with multiple tense blisters on (**a**) the right foot and the palm of (**b**) the right hand

and/or IgA and complement C3 along the EBMZ in an n-serrated pattern. Using serration pattern analysis, anti-p200 pemphigoid can be differentiated from EBA with a u-serrated pattern along the EBMZ. Autoantibodies in anti-p200 pemphigoid bind to the lower lamina lucida, therefore IIF on salt-split-skin reveals binding of circulating autoantibodies along the dermal side of the artificial split. This method allows differentiating anti-p200 pemphigoid from BP, but not from anti-LN-332 MMP and/or EBA. Specific serological diagnostic tests are needed to distinguish these subtypes of pemphigoid diseases, such as IIF analysis on knockout skin (see Chap. 5) or immunoblotting of dermal extract with a 200-kDA protein band.

Anti-p200 pemphigoid is characterized by a mainly neutrophilic infiltrate in histology, IgG n-serrated pattern along EBMZ in DIF, and dermal binding in IIF SSS

Treatment Tricks

Treatment of anti-p200 pemphigoid follows the same guidelines as for BP, but anti-p200 pemphigoid is not a milder form of BP. First choice treatment in mild to moderate disease is superpotent topical steroids (clobetasol propionate 0.05%). In severe disease, oral corticosteroids (prednisolone 0.5 mg/kg/day) and adjunctive immunosuppresive therapy can be used (see BP section).

Review Questions

1. What are the three main clinical symptoms of BP?
   (a) Eczema, urticaria and tense blisters
   (b) Pruritus, urticarial plaques and tense blisters
   (c) Pruritus, nodules and tense blisters
   (d) Papules, nodules and tense blisters
2. Nonbullous pemphigoid may mimick:
   (a) Dry skin (xerosis cutis)
   (b) Scabies
   (c) Atopic dermatitis
   (d) All of mentioned above
3. First-line treatment of mild and severe BP is
   (a) Superpotent topical corticosteroids whole body application
   (b) Oral corticosteroids
   (c) Azathioprine
   (d) Dapsone
4. Patients with Brunsting-Perry cicatricial pemphigoid present with:
   (a) Predominant mucosal involvement
   (b) Tense blisters predominantly on the extremities and trunk
   (c) Erosions and blisters at the head, neck and shoulder area
   (d) Itch, urticaria and flat blisters
5. Lichen planus pemphigoides is characterized by:
   (a) Autoantibodies targeting collagen VII
   (b) Blisters on both lichen planus lesions and normal skin
   (c) Blisters solitary on lichen planus lesions
   (d) Vesicles and tense blisters starting around the umbilicus
6. Which statement about pemphigoid gestationis is correct
   (a) Pemphigoid gestationis manifests in the 1st trimester of pregnancy
   (b) The BP180 C-terminal domain is the target antigen.
   (c) Exacerbation may occur before menstruation or after starting oral anticonception
   (d) There is an increased risk of stillbirth
7. Clinical features of anti-p200 pemphigoid include:
   (a) Psoriasis
   (b) Blisters on acral sites
   (c) Predominant mucosal lesions
   (d) Scarring of lesions

Answers

1. (b)
2. (d)
3. (a)
4. (c)
5. (b)
6. (c)
7. (b)

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