formation immediately above the basal layer. The dermal papillae, which are covered by basal cells in the single layer that is left in the lacunae, protrude and resemble villi. Dyskeratotic cells are occasionally found. Acantholytic cells in the lacunae are connected loosely to each other by a few desmosomes (Fig. 14.18). Autoantibodies to the epidermis are not detected by immunofluorescence.

**Diagnosis**

Hailey-Hailey disease is diagnosed by the clinical symptoms and pathological diagnosis. As it is autosomal dominantly inherited and frequently occurs within a family, it is important to take a thorough family history. Genetic diagnosis can identify the mutation in the ATP2C1 gene.

**Treatment**

Topical application of steroids and antibiotics ointments is useful. Oral etretinate (a vitamin A derivative) and surgical ablation may be performed in intractable cases.

### B. Autoimmune blistering diseases

#### a. Diseases with intra-epidermal blistering (pemphigus group)

**Outline**

- Middle-aged and elderly people are the most commonly affected. Intra-epidermal blistering with flaccid blisters occurs.
- The two main pemphigus groups are the pemphigus vulgaris group and the pemphigus foliaceus group.
- They are an autoimmune diseases. Acantholytic intra-epidermal blistering is produced by autoantibodies against desmoglein (intercellular substances; MEMO).
- Anti-desmoglein antibodies are detected by ELISA. In vivo IgG deposition and IgG antibodies are observed by immunofluorescence (IF). Nikolsky’s sign and Tzanck test are positive (i.e., for acantholytic cells).
- Oral steroids and immunosuppressants are mainly administered.

**Classification**

Diseases with intra-epidermal blistering (pemphigus group) are divided into two groups according to pathogenesis: pemphigus vulgaris and pemphigus foliaceus. Pemphigus vegetans is a type of pemphigus vulgaris; pemphigus erythematosus is a type of pemphigus foliaceus. The characteristics of each type are summarized in Table 14.2. Pemphigus vulgaris accounts for 60% of

**Hailey-Hailey disease and haploinsufficiency**

Both Hailey-Hailey disease and Darier’s disease are autosomal dominantly inherited. Mutation occurs in one of the allelic genes. In most cases, cutaneous symptoms do not appear until adulthood. Haploinsufficiency has been proposed as the mechanism of onset of these diseases. That is, the amount of protein produced by one allelic gene is sufficient in childhood, but shortages that emerge with age cause the later onset.
Table 14.2 Types of pemphigus groups.

<table>
<thead>
<tr>
<th></th>
<th>Pemphigus vulgaris</th>
<th>Pemphigus vegetans</th>
<th>Pemphigus foliaceus</th>
<th>Pemphigus erythematosus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>Middle age to elderly</td>
<td>Middle age to elderly</td>
<td>Middle age</td>
<td>Middle age to elderly</td>
</tr>
<tr>
<td><strong>Frequent site of skin lesion</strong></td>
<td>Whole body skin, oral mucosa</td>
<td>Intertriginous areas (e.g., axillary fossae)</td>
<td>Whole body skin</td>
<td>Oily areas of skin (e.g., face)</td>
</tr>
<tr>
<td><strong>Clinical finding</strong></td>
<td>Skin</td>
<td>Blisters, erosion</td>
<td>Blisters, erosion, papillary acanthosis, pustules</td>
<td>Erosion, lamellar exfoliation, crusts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Erosion, butterfly rash, seborrheic dermatitis-like skin lesion</td>
</tr>
<tr>
<td></td>
<td>Mucosal lesions</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Nikolsky’s sign</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Pathological finding</strong></td>
<td>Skin</td>
<td>Intraepidermal blisters (acantholysis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tzanck test</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Site of acantholysis</td>
<td>Lower epidermal layer (directly on basal cells)</td>
<td>Upper epidermal layer (granular cell layer)</td>
<td></td>
</tr>
<tr>
<td><strong>Targeted antigen</strong></td>
<td>Only Dsg3, Dsg3 and Dsg1</td>
<td></td>
<td>Only Dsg1</td>
<td></td>
</tr>
<tr>
<td><strong>ELISA</strong></td>
<td>Dsg1 (+/-), Dsg3 (+)</td>
<td>Dsg1 (+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immunofluorescence technique</strong></td>
<td>Direct (skin lesion)</td>
<td>IgG(+) in the epidermal intercellular space, C3(+) positive</td>
<td></td>
<td>IgG (+)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Steroids, immunosuppressants, plasmapheresis, human immunoglobulin therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 14.19 Distribution of desmoglein 1 and desmoglein 3 in the epidermis and pathomechanism of pemphigus.
Diseases with intra-epidermal blistering are classified according to the desmoglein molecules that are impaired (see also Fig. 14.23).

Fig. 14.20 Direct immunofluorescence of pemphigus vulgaris.
Intercellular deposition of IgG is observed in the epidermis.
all pemphigus cases.

**Pathogenesis**

In pemphigus vulgaris, autoantibodies against desmoglein 3 are produced. Because the basal cell layer is rich in desmoglein 3, the action of autoantibodies against desmoglein 3 causes keratinocytes to lose adhesion: The basal cell layer erodes and blisters. In pemphigus foliaceus, however, autoantibodies against desmoglein 1 (and not desmoglein 3) are produced. Acantholysis occurs in the upper epidermal layer. Because the basal cell layer is not rich in desmoglein 1, the action of autoantibodies against desmoglein 1 has little adverse effect on basal cell adhesion: The basal cell layer remains largely intact. (Fig. 14.19).

**Pathology**

Dissociation of intercellular connections in the epidermis is called acantholysis. As dissociation progresses, epidermal cleavage and blistering occur. Keratinocytes deform to become spherical from loss of intercellular connection within the blisters (acantholytic cells). Tzanck test is positive. In pemphigus vulgaris, acantholytic blistering occurs immediately above epidermal basal cells; in pemphigus foliaceus and pemphigus erythematous, blistering occurs in the superficial epidermis, such as at sites immediately below the horny cell layer. In pemphigus vegetans, besides the findings of pemphigus vulgaris, acanthosis and papillomatosis are found, and eosinophil-filled pustules form in the epidermis.

**Laboratory findings**

Epidermal intercellular in-vivo-bound IgG in lesions are identified by direct immunofluorescence (IF). IgG anti-intercellular antibodies in the serum of patients are detected by indirect IF and ELISA (Fig. 14.20). Autoantibodies against desmoglein 1 and 3 are detected by ELISA. Tzanck test is also useful, in which the bottom of the blister is smeared and labeled to investigate the presence of acantholytic cells by Giemsa staining. Elevated levels of eosinophils may be found in the peripheral blood or in the blister contents.

### 1. Pemphigus vulgaris

**Outline**

- Acantholytic blisters form immediately above epidermal basal cells.
- The disease is caused by autoantibodies against desmoglein 3, which is a desmosomal adhesion factor in keratinocytes.
- The pathogenesis involves anti-desmoglein antibodies.
- When there is the involvement of autoantibodies against desmoglein 1, pemphigus vulgaris becomes systemic.
When anti-desmoglein 3 antibodies are exclusively involved, an oral mucosa type of the disease develops.

The disease most frequently occurs in the middle-aged and elderly. It tends to manifest as oral enanthema.

Nikolsky’s sign is positive.

Oral steroids and immunosuppressants are the first-line treatment.

Clinical features

Pemphigus vulgaris most frequently affects the middle-aged and elderly. Erosions and ulcers develop acutely in the oral mucosa in 70% to 80% of cases. Subsequently, blisters of various sizes occur on normal skin (Figs. 14.21-1 and 14.21-2). This blistering may occur anywhere on the body; however, it tends to appear at sites prone to pressure and friction, such as the back, buttocks and feet.

The blisters easily rupture to form large erosions and crusts. They are painful when touched. Blistering can be artificially produced by rubbing normal skin (Nikolsky’s sign). When the blisters are pressed without breaking, the fluid contents extend to the peripheral normal skin around the blisters (blister diffusion phenomena, or false Nikolsky’s sign).

Erosions form in the oral cavity and esophageal mucosa, causing dysphagia. When the eruptions are widespread, electrolyte abnormalities resulting from loss of body fluid or hypoproteinemia are found; this can be fatal when there is secondary infection. Complications include thymoma or myasthenia.

Pathology, Laboratory findings

Acantholysis causes intra-epidermal blistering. Blisters often form leaving one basal layer at the bottom; such blistering is described as “tombstone-like” (Fig. 14.22). Highly eosinophilic infiltration occurs in the blisters and the dermal upper layer. Anti-desmoglein 3 antibodies are detected by ELISA.

Diagnosis

In diagnosis, it is necessary to identify intercellular in vivo IgG deposition by immunofluorescence (IF), and to detect anti-desmoglein antibodies by ELISA. The quantity of antibodies in

<table>
<thead>
<tr>
<th>ELISA</th>
<th>Diagnostic name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Dsg1 IgG antibody Anti-Dsg3 IgG antibody</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
the serum is known to reflect the pemphigus condition. When only desmoglein 3 is detected, the disease is membrane-dominant pemphigus vulgaris, in which there is only minor blistering of the skin. When both desmoglein 1 and 3 are detected, blistering is often seen in the oral mucosa and systemic skin (Table 14.3, Fig. 14.23).

**Differential diagnosis**

It is necessary to differentiate the disease from dermatitis herpetiformis, bullous pemphigoid, impetigo, burns, bullous drug eruptions, erythema multiforme and Stevens-Johnson syndrome.

**Treatment**

Systemic application of steroids is the first-line treatment. According to the severity, 0.5 mg to 1.0 mg prednisolone per 1 kg of body weight per day is administered. The dosage is tapered off to a maintenance dose or until it can be discontinued. Immunosuppressants (mycophenolate mofetil, cyclophosphamide, azathioprine, methotrexate and cyclosporine) may be used. In intractable cases, plasma exchange therapy and mega-dose gamma-globulin therapy are also performed. Antibiotic
application, fluid replacement and nutrition management are conducted supplementarily.

2. Pemphigus vegetans

Clinical features

Pemphigus vegetans is a subtype of pemphigus vulgaris whose onset is marked by the formation of vesicles and erosions that do not re-epithelialize but gradually proliferate and elevate. Lesions are often accompanied by vesicles and pustules. There is a strong odor, and the disorder frequently occurs on areas exposed to friction, such as the axillary fossa, umbilical fossa, and the periphery of the oculonasal and perioral regions. Pemphigus vegetans can be of Neumann type or Hallopeau type. The onset of the Neumann type is marked by blistering, and pemphigus-vulgaris-like blistered erosions form. Pustules mainly occur in the Hallopeau type, which has a better prognosis.

Differential diagnosis

Pemphigus vegetans should be differentiated from condyloma latum, condyloma acuminatum, proliferative chronic pyoderma and fungal granuloma.

Treatment

The treatment is the same as for pemphigus vulgaris.

3. Pemphigus foliaceus

Clinical features

Unlike pemphigus vulgaris, pemphigus foliaceus does not involve the mucosa. Nikolsky’s sign is positive.

Outline

Autoantibodies are produced exclusively against desmoglein 1.

Acantholysis and blistering are seen in the superficial epidermis (in the granular cell layer).

Fragile blisters, scaling and erosion, accompanied by crusts, occur systemically. Lesions are not produced in the mucosa.

Examinations and treatments are the same as for pemphigus vulgaris. The steroid dosage is usually less than for pemphigus vulgaris.

Clinical features

Pemphigus foliaceus most commonly affects the middle-aged and elderly. Extremely fragile flaccid vesicles are produced, some of which dry to become leafy and to exfoliate successively. The face, head, back and chest are most commonly affected. When the disorder progresses and spreads over the whole body, it resembles exfoliative erythroderma (Figs. 14.24-1 and 14.24-2). Unlike pemphigus vulgaris, pemphigus foliaceus does not involve the mucosa. Nikolsky’s sign is positive.
Pathology, Laboratory findings

Acantholytic blistering is found in and between the epidermal horny cell layer and the epidermal upper layer. Intercellular in vivo IgG deposition is observed by immunofluorescence. Anti-desmoglein 1 antibodies can be detected by ELISA.

Treatment

Treatment is the same as for pemphigus vulgaris. The oral steroid dosage may be less than that for pemphigus vulgaris. Topical steroids are sufficient in some cases.

4. Pemphigus erythematous

Synonym: Senear-Usher syndrome

Clinical features

Pemphigus erythematous is a subtype of pemphigus foliaceus, and it occurs most commonly in the middle-aged and elderly. It frequently affects the seborrheic zones on the head, face, chest and back. Systemic lupus erythematosus (SLE) like erythema or seborrheic dermatitis-like eruptions occur on the face, and pemphigus foliaceus-like intra-epidermal blisters form on the trunk (Fig. 14.25). The mucosa is not involved. Involvement of SLE is seen in some cases.

Treatment

The treatment is the same as for pemphigus foliaceus.

5. Paraneoplastic pemphigus

Outline

- The disease accompanies malignant or benign neoplasm (lymphoproliferative diseases in particular). Severe mucosal lesions with erosion, and various cutaneous lesions, appear.
- Autoantibodies against several epidermal proteins, such as desmogleins and plakin family molecules, are found.

Clinical features

Erosions, ulceration and bloody crusts are widespread on mucous membranes in the oral cavity, pharynx and lips. Pseudomembranous conjunctivitis may lead to blepharosynechia. Various cutaneous lesions occur. It is important to test for IgG autoantibodies and to identify tumors accompanying paraneoplastic pemphigus.

Treatment

The neoplasms underlying paraneoplastic pemphigus are treated. Treatment is the same as for severe pemphigus vulgaris.

MEMO

Transient acantholytic dermatosis

This is also called Grover’s disease. Itching papules and blisters with acantholysis occur on the trunk and extremities, subsiding within three months. The pathogenesis is unknown. Autoantibodies against skin are not present.
Drug-induced pemphigus is a catchall for diseases that cause lesions that resemble pemphigoid clinically and immunologically. It has various clinical symptoms and various histological and immunohistological findings (Fig. 14.26). Acantholysis is found in the epidermis of the lesions. In vivo IgA deposition is found in the epidermis of the lesions. Drug-induced pemphigus is most frequently induced by drugs that contain SH residue, such as d-penicillamine.

Neonatal pemphigus is seen in newborns of mothers with pemphigus. The mother’s IgG autoantibodies pass into the placenta, affecting the newborn infant’s skin. The clinical symptoms, and histological and immunohistological findings of pemphigus are transiently observed in neonatal pemphigus.

Intercellular IgA dermatosis is a rare disease that causes epidermal intercellular IgA deposition. Vesicles and pustules are transiently observed in neonatal pemphigus.

### Table 14.4 Autoimmune blistering diseases that cause subepidermal blisters.

<table>
<thead>
<tr>
<th></th>
<th>Bullous pemphigoid</th>
<th>Herpes gestationis</th>
<th>Cicatricial pemphigoid</th>
<th>Epidermolysis bullosa acquisita</th>
<th>Dermatitis herpetiformis (Duhring)</th>
<th>Linear IgA bullous dermatosis (LAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>Elderly (youth in some cases)</td>
<td>4-month-pregnant to postpartum women</td>
<td>Adults and elderly</td>
<td>Adults and elderly</td>
<td>Middle age</td>
<td>&lt;10 or 40</td>
</tr>
<tr>
<td><strong>Frequent site</strong></td>
<td>Whole body</td>
<td>Abdomen, buttocks, extremities</td>
<td>Oral cavity, ocular mucosa</td>
<td>Intercrinosus areas (e.g., elbows, knees,)</td>
<td>Whole body (especially elbows, knees, buttocks)</td>
<td>Whole body</td>
</tr>
<tr>
<td><strong>Clinical findings</strong></td>
<td>Findings of skin</td>
<td>Tense blisters, edematous erythema, itching</td>
<td>Urticaria-like erythema, itching</td>
<td>Erosion, blisters, scarring</td>
<td>Itching, erythema, urticaria-like wheal</td>
<td>Erythema, tense blisters, itching</td>
</tr>
<tr>
<td></td>
<td>Mucosal infiltration</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pathological findings</strong></td>
<td>Eosinophilic infiltration</td>
<td>Eosinophilic infiltration</td>
<td>Neutrophilic infiltration, microabscess</td>
<td>Neutrophilic infiltration</td>
<td>97kD (Degradation products of BP180)</td>
<td></td>
</tr>
<tr>
<td><strong>Autoantigen</strong></td>
<td>BP180, BP230</td>
<td>BP180</td>
<td>BP180, laminin-332</td>
<td>Type VII collagen</td>
<td>Granular deposition of IgA in the papillae of upper dermal layer</td>
<td>Linear deposition of IgG (sometimes C3) in BMZ</td>
</tr>
<tr>
<td><strong>Immunofluorescence findings</strong></td>
<td>Direct</td>
<td>Linear deposition of IgG and C3 in the epidermal basement membrane zone (BMZ)</td>
<td>Linear deposition of C3 in BMZ</td>
<td>Linear deposition of IgG in BMZ</td>
<td>Granular deposition of IgA in the papillae of upper dermal layer</td>
<td>Linear deposition of IgG (sometimes C3) in BMZ</td>
</tr>
<tr>
<td></td>
<td>Indirect (Serum)</td>
<td>Detection of anti-basement membrane antibody</td>
<td>Detection of autoantibody against type VII collagen (290kDa)</td>
<td>Anti-autoantibody not detected</td>
<td>Detection of anti-IgA antibody in BMZ</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Oral steroids, immunosuppressant, DDS</td>
<td>Topical and oral steroids</td>
<td>Oral steroids, immunosuppressant, plasmapheresis</td>
<td>Oral DDS, gluten-free diet</td>
<td>DDS, oral steroids</td>
<td></td>
</tr>
</tbody>
</table>
produced on the trunk and extremities, and they become chronic. Some cases are not clinically differentiable from subcorneal pustular dermatosis.

### 9. Fogo selvagem, Brazilian pemphigus foliaceus

Fogo selvagem (Brazilian pemphigus foliaceus) is endemic to Brazil and certain other areas of South America. Autoantibodies recognize desmoglein 1, which is the same as in pemphigus foliaceus. Transmission is thought to involve black flies of the family Simuliidae.

### b. Diseases with subepidermal blistering (pemphigoid group)

#### Outline
- These are autoimmune blistering diseases in which subepidermal blistering occurs as a result of autoantibody action against epidermal basement membrane structural proteins.
- Unlike the flaccid intra-epidermal blisters of pemphigus, these subepidermal blisters are tense and do not rupture easily (Fig. 14.27).
- Bloody blisters and milium may occur together.
- The disease is divided into pemphigoid, linear IgA bullous dermatosis, epidermolysis bullosa acquisita and other (Table 14.4).
- Immunofluorescence is useful for diagnosis.
- Steroids and DDS (dapsone) are applied.

#### 1. Bullous pemphigoid (BP)

##### Outline
- Autoantibodies against hemidesmosomes in the epidermal basement membranes are found.
- The major pathogenic antigen is Type XVII collagen (COL17, BP180). The roof of the blister has the full thickness of the epidermis.
- Elderly people account for the majority of cases.
- The disease is characterized by subepidermal blisters that do not rupture easily, itching and enanthema.
- Oral steroids are administered.

##### Clinical features

The elderly are more commonly affected by bullous pemphigoid than are young people. Multiple relatively large and severe subepidermal blisters form immediately below the epidermis. Bullous pemphigoid is often accompanied by edematous...

---

*Clinical images are available in hardcopy only.*

---

**Fig. 14.28-1 Bullous pemphigoid.**

a: Itching, edematous erythema and tense bullae on the extremities. This is a typical skin manifestation of bullous pemphigoid. b: Skin lesions on the chest. c: Affected back. d: Comparatively large erythema.