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
erythema (Figs. 14.28-1 and 14.28-2) and is much less invasive to the mucous membranes (about 20% of the mucous membrane is involved) than is pemphigus vulgaris. The general condition of the patient is favorable; however, it may be complicated by malignant tumors in the internal organs.

**Pathogenesis**

Autoantibodies are produced against hemidesmosome (HD) structural proteins, Type XVII collagen (COL17, BP180) and BP230 (BPAG1) in the epidermal basement membranes, which leads to blistering. Autoantibodies against the membrane-proximal NC16a domain of BP180 play a major role in pathogenesis.

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**Differential diagnosis between bullous pemphigoid and epidermolysis bullosa acquisita using salt-split-skin analysis**

Differentiating between bullous pemphigoid and epidermolysis bullosa acquisita is often difficult because of the similar clinical courses and immunofluorescence (IF) findings. Normal human split skin processed with 1M NaCl is used for differential diagnosis.

When normal human skin is soaked in 1M NaCl for 48 hours at 4 °C, the epidermis and dermis separate in the lamina lucida and artificial blistering occurs. The patient’s serum is reacted to skin with this epidermal-dermal separation as the matrix for IF: In the case of bullous pemphigoid, the serum reacts to hemidesmosomes on the epidermal side; in the case of epidermolysis bullosa acquisita, the serum reacts to anchoring fibrils on the dermal side. Using this split-skin method, it is possible to distinguish between the diseases by the location of the blisters.

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Fig. 14.28-2 Bullous pemphigoid.

e, f, g: Tense bullae on the trunk. h, i: Tense bullae on the palms, fingers and toes.
In bullous pemphigoid, subepidermal blistering is accompanied by eosinophilic infiltration (Fig. 14.29). Linear IgG and C3 deposition in the basement membranes of the lesions is observed by direct immunofluorescence (IF) (Fig. 14.30). Anti-epidermal basement membrane antibodies in the serum of the patients are detected by indirect IF; autoantibodies against Type XVII collagen proteins are identified by ELISA. High IgE values and elevated levels of eosinophils are found in peripheral blood in some cases.

**Diagnosis**

Bullous pemphigoid is diagnosed by clinical and pathological features and by IF and ELISA (Table 14.4). In vivo linear IgG deposition on the epithelial basement membranes is seen in all patients with bullous pemphigoid, which is a necessary criterion for diagnosis. Indirect IF using normal human split skin processed with 1M-NaCl is conducted to distinguish this disease from other subepidermal blistering diseases such as epidermolysis bullosa acquisita (MEMO).

**Treatment**

Oral steroids (0.5 mg/kg/day) are administered; and then gradually reduced. Combination therapy of immunosuppressants such as cyclophosphamide, DDS, tetracyclines and nicotinic-acidamide is also useful. Dehydration and secondary infections should be carefully avoided, and nutrition management is important for elderly patients. Topical steroid application may be sufficient in cases with mild symptoms. Plasma exchange therapy may also be performed in severe cases.

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**2. Herpes gestationis***

**Clinical features**

Multiple urticarial erythema appears on the abdomen, buttocks and extremities between the fourth month of pregnancy and immediately following delivery, and vesicles form in the periphery of the erythema. The mucosa is rarely involved. Intense itching is present. Although herpes gestationis disappears 2 to 3 months after delivery in most cases, it becomes more recurrent and aggravated with each successive pregnancy.

**Pathogenesis**

It is thought to be a bullous pemphigoid that is specific to pregnant women. Herpes gestationis occurs in 1 in 5,000 to 1 in 10,000 deliveries. Autoantibodies against Type XVII collagen proteins are found in hemidesmosomes.

**Diagnosis**

Itching is intense. Herpes gestationis resembles dermatitis...
herpetiformis; however, it is distinguished by the absence of IgA deposition and the presence of linear C3 deposition (Table 14.4).

**Treatment**

Topical steroids are mainly applied. In severe cases, oral steroids are administered.

### 3. Cicatricial pemphigoid

**Synonym:** Benign mucous membrane pemphigoid

Blasting and erosive lesions occur, mostly in the oral cavity and conjunctiva, leaving scarring (Fig. 14.31). Lesions may occur in the genitalia, perianal region, pharynx, esophagus and nasal mucosa. Prompt treatment is required if there is blepharosynechia or respiratory difficulty. Autoantibodies against Type XVII collagen proteins and laminin 332 are found.

### 4. Epidermolysis bullosa acquisita

**Outline**

- Autoantibodies against type VII collagen, which is a structural component of anchoring fibrils, are produced.
- Subepidermal blisters form. They leave milium when they heal.
- Differential diagnosis from bullous pemphigoid is clinically difficult.
- Steroids are administered orally. The disease is intractable.

**Clinical features**

In epidermolysis bullosa acquisita, friction erosions and blisters appear on the knees, elbows, palms and soles. They may leave scarring or progress in a course similar to bullous pemphigoid. Healing often leaves scarring and milium (Figs. 14.32-1 and 14.32-2).

**Pathogenesis**

Autoantibodies against type VII collagen, which is a structural component of anchoring fibrils that connect the epidermis and the dermis, are produced. Subepidermal blisters form as a result.

**Laboratory findings**

Linear IgG deposition is observed by direct immunofluorescence on the epidermal basement membrane of the lesions. Autoantibodies against type VII collagen of 290kD are found by immunoblot procedure using the patient’s serum.

**Diagnosis**

The absence of a hereditary history of blistering formation is
an important aid for diagnosis. The most reliable methods of diagnosing epidermolysis bullosa acquisita are indirect immunofluorescence using 1M-NaCl split skin as a substrate (MEMO), and immunoblot procedure.

**Differential diagnosis**

It is essential to differentiate this disease from other blistering diseases such as bullous pemphigoid, pemphigus, porphiria, drug-induced eruptions and amyloidosis. In progressive cases, cutaneous symptoms similar to dystrophic epidermal bullosa (nail deformity, coalescence of fingers and toes) may be present.

**Treatment**

Epidermolysis bullosa acquisita is resistant to treatment. Oral steroids, immunosuppressants (e.g., cyclosporine) and plasma exchange are administered.

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5. *Dermatitis herpetiformis (Duhring)*

**Outline**

- It is characterized by extremely intense itching and irritation, chronically recurrent erythema, and vesicles. The vesicles tend to form circular patterns.
- HLA-B8, DR3 and DQ2 are involved. The disease is rarely seen in ethnic Japanese. It is common in Caucasians.
- Granular IgA deposition is found in the dermal papillary.
- Gluten-induced enteropathy develops as a complication in many cases.
- Oral DDS is effective.

**Clinical features**

Extremely intense itching is present. Erythema and urticarial wheals occur, with vesicles produced in a ring-shaped pattern at the periphery ([Fig. 14.33](#)). The severe itching causes the patient to scratch, resulting in crusts, including bloody crusts. The eruptions heal with abnormal pigmentation or depigmentation. Eruptions appear symmetrically on the entire body, especially on the elbows, knees and buttocks. However, the palms, soles and mucosa are hardly affected. Gluten-induced enteropathy is found in more than 90% of cases. As in celiac disease, in which there is hypersensitivity to gluten, atrophic changes in jejunal villi are found in dermatitis herpetiformis.

**Pathogenesis**

In recent years, it has been discovered that patients with this disease have IgA antibodies against tissue transglutaminase in the serum. The granular IgA deposition in the skin is an immunocomplex.
Subepidermal blistering is present. Micro-abscesses are caused in dermal papillary by neutrophilic infiltration.

**Laboratory findings**

Granular IgA deposition is observed by direct immunofluorescence (IF) in the dermal papillary. Anti-cutaneous autoantibodies are not seen in the patient’s serum by IF. The patient’s serum does not contain IgA-class anti-transglutaminase antibodies. Involvement of HLA-B8 in dermatitis herpetiformis has been found. There are elevated levels of eosinophils in the peripheral blood.

**Diagnosis**

Dermatitis herpetiformis is diagnosed by the clinical features, such as rashes, intense itching, subepidermal blistering, and granular IgA deposition in the papillary dermis. The symptoms are reduced remarkably by DDS; this fact has diagnostic significance. Dermatitis herpetiformis is rare in ethnic Japanese.

**Differential diagnosis**

Dermatitis herpetiformis should be distinguished from linear IgA bullous dermatosis, bullous pemphigoid, herpes gestationis and erythema multiforme.

**Treatment**

Sulfa drugs such as DDS are effective. A gluten-free diet and antihistamines are also useful.

6. **Linear IgA bullous dermatosis (LAD)**

**Clinical features**

Linear IgA bullous dermatosis (LAD) is divided into childhood LAD, whose symptoms appear in children under age 10, and adult LAD, which occurs in adults age 40 or older. Multiple erythema and tense blisters accompanied by intense itching occur over the entire body, as in dermatitis herpetiformis (Fig. 14.34). Lesions may occur in the mucous membranes. The lesions tend to aggregate on the genitalia and inner regions of the thighs in childhood LAD and heal spontaneously in some cases.

**Pathogenesis, Epidemiology**

LAD is caused by linear IgA deposition on the epidermal basement membrane; the deposition pattern differs from that in granular dermatitis herpetiformis. In Japan, most cases of IgA deposition on the epidermal basement membrane are LAD; dermatitis herpetiformis is rare.

**Pathology**

Subepidermal blistering is found. Neutrophilic infiltration is
seen. Linear IgA deposition is found in the epidermal basement membranes. C3 may also deposit in some cases.

**Laboratory findings, Diagnosis**

Linear IgA deposition on the epidermal basement membranes can be identified by direct immunofluorescence (IF). Anti-epidermal basement membrane IgA autoantibodies may be detected in the patient’s serum by indirect IF.

**Differential diagnosis**

LAD should be differentiated from dermatitis herpetiformis. In LAD, there is a histopathological finding of linear patterns of in vivo IgA deposition, there are anti-basement membrane IgA auto-antibodies in serum in some cases, there is no involvement of HLA-B8, DR3, or DQ2, there is involvement of the mucosa, and there is no sensitivity to gluten.

**Treatment**

DDS is effective, as are oral steroids.

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**Pustular diseases**

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**1. Palmoplantar pustulosis (PPP)**

Synonym: Pustulosis palmaris et pustulosis

**Outline**

- Multiple sterile pustules form symmetrically on the palms and soles of the middle-aged and elderly, becoming chronic.
- Smoking, bacterial infection (tonsillitis), dental caries and dental metal allergy are associated with occurrence of PPP.
- Sternocostoclavicular ossification and pain may develop as complications.
- Topical steroid application, smoking cessation and tonsillectomy are the main treatments.

**Clinical features**

Multiple vesicles occur on the thenar and antithenar regions of the palms and arches of feet, and these become pustular. Erythema develops at the periphery of the lesions and fuses into plaques (Fig. 14.35). Itching may be present. Punctate depressions and thickening occur frequently in the nails. Pustules recur in 2- to 4-week cycles and progress chronically. They may appear on the knees, lower extremities and scalp. In 10% of palmoplantar pustulosis (PPP) cases, sternocostoclavicular ossification accompanied by chest pain develops as a complication.