Acantholytic disorders

Introduction

The term acantholysis derives from the Greek *akantha*, a thorn or prickle, and *lysis*, a loosening. In its simplest definition, the term is used to reflect a primary disorder of the skin (and sometimes the mucous membranes) characterized by separation of the keratinocytes at their desmosomal junctions (Fig. 5.1). A wide range of conditions are characterized by this feature, from inherited disorders such as Darier’s disease and Hailey-Hailey disease in which a calcium pump gene mutation results in desmosomal instability through to the autoimmune pemphigus group of diseases whereby autoantibodies directly damage desmosomes with resultant keratinocyte separation and blister formation (Table 5.1). Desmosomes may also be damaged by secondary phenomena, for example following severe edema, either intercellular (spongiosis) or intracellular (e.g., ballooning degeneration as is seen in various viral infections). Such processes, however, are not included in the acantholytic category and are discussed elsewhere. The histological features of the conditions described in this chapter show considerable overlap. The diagnosis is therefore dependent upon adequate clinical information and the results of immunofluorescence investigations.

Pemphigus

Pemphigus (Gr. *pemphix*, blister) refers to a group of chronic blistering diseases which develop as a consequence of autoantibodies directed against a variety of desmosomal proteins. The condition as a whole is rare, with an annual incidence ranging from 0.1–0.7 per 100,000 of the general population. It is commoner in the Jewish population in which the annual incidence rises to 1.6–3.2 per 100,000. Ashkenazi Jews are the most frequently affected. The incidence in India also appears to be higher than in other countries. There is no sex predilection.

Table 5.1

<table>
<thead>
<tr>
<th>Antigens targeted in the pemphigus variants</th>
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<td><strong>Pemphigus variant</strong></td>
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<tr>
<td>Pemphigus vulgaris</td>
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<td>Pemphigus vegetans</td>
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<tr>
<td>Pemphigus foliaceus</td>
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<td>Pemphigus erythematosus</td>
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<td>Fogo selvagem</td>
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<td>IgA pemphigus</td>
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<td>Herpetiform pemphigus</td>
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<td>Paraneoplastic pemphigus</td>
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<td>Drug-induced pemphigus</td>
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The clinical features and, therefore, classification of these disorders depends upon the level of separation within the epidermis:

- In pemphigus vulgaris (p. vulgaris) and pemphigus vegetans (p. vegetans) the blisters are suprabasal.
- In pemphigus foliaceus (p. foliaceus), pemphigus erythematosus (p. erythematosus) and fogo selvagem, the blisters are situated more superficially.

Pemphigus vulgaris is by far the most common variant, accounting for 80% of cases.8,9 In addition to affecting humans, pemphigus has been described in a variety of animals including dogs, cats, goats, and horses.10

**Pemphigus vulgaris**

**Clinical features**

Pemphigus vulgaris (p. vulgaris) particularly affects the middle aged (onset typically at 40–60 years of age) although occasionally (up to 2.6%) children are affected.1–7 Self-limiting neonatal disease through transplacental transfer of maternal autoantibodies has also rarely been documented (see pathogenesis).8–11 The disease begins in the mouth (Figs 5.2, 5.3) in 50–70% of patients with painful erosions or bullae and, after a period of weeks or months, the blisters spread to involve the skin.12–15 Oral lesions most commonly affect the buccal, palatine, and gingival mucosae.5,14–17 Pemphigus vulgaris is only rarely confined to the skin.9,10

The typical skin lesion is a fragile, flaccid blister, which develops on normal or erythematous skin, and readily ruptures, leaving a painful, crusted, raw, bloody erosion (Figs 5.4, 5.5). Lesions are most often seen on the scalp, face, axillae, and groin, although in some patients they are generalized (Figs 5.6–5.8). Blisters can be induced by rubbing the adjacent, apparently normal skin with a finger – the Nikolsky sign. Direct pressure applied to the center of the blister is also followed by lateral extension – the Asboe-Hansen sign.7 Healing is often accompanied by postinflammatory hyperpigmentation but scarring is not a feature.2

Before the introduction of corticosteroid therapy, the lesions usually became more extensive and in the past often led eventually to death. Treatment with high doses of corticosteroids, immunosuppressants, such as azathioprine and more recently biologicals has significantly reduced the mortality to 5–15% and prolonged remissions without treatment are now being reported.2 A considerable proportion of the deaths that do occur, however, are due to the side effects of therapy and include staphylococcal infections and, to a lesser extent, pulmonary embolism.2 Severe opportunistic infections due to a wide range of organisms including listeria, nocardia, enterococci, herpes virus, cryptococcus and candida may further complicate the disease.21–27

Fig. 5.2

Pemphigus vulgaris: painful erosions are present on the buccal mucosa. By courtesy of R.A. Marsden, MD, St George’s Hospital, London, UK.

Fig. 5.3

Pemphigus vulgaris: in this patient there is an intact blister on the floor of the mouth. Pemphigus commonly presents in the mouth. By courtesy of the Institute of Dermatology, London, UK.

Fig. 5.4

Pemphigus vulgaris: since the blisters are superficial, erosions are more commonly encountered. By courtesy of the Institute of Dermatology, London, UK.

Fig. 5.5

Pemphigus vulgaris: extensive erosions and blisters are present on the shin. By courtesy of R.A. Marsden, MD, St George’s Hospital, London, UK.
Pemphigus

Chronic inflammatory cell infiltrate with conspicuous eosinophils, although sometimes these are scanty or even absent. Mucous membrane lesions show similar histology.

Ultrastructurally, there is dilatation of the intercellular space with consequent stretching of the desmosomal attachment points (Figs 5.14, 5.15). With progression, these separate and eventually disappear, residual cell membranes often showing a pseudovillous morphology. Hemidesmosomes are morphologically normal. Immunoelectron microscopy confirms that the immunoreactants are located within the intercellular space.

**Endemic pemphigus vulgaris**

Patients with clinical and histological presentation of pemphigus vulgaris but epidemiological features of fogo selvagem were identified in the Goiania and Brasilia regions of Brazil, known endemic areas of pemphigus foliaceus. These patients demonstrate classical mucocutaneous disease and antibodies to both Dsg1 and Dsg3, but are remarkable for early onset of disease, frequently before the age of 20.