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Pemphigus Vulgaris and Paraneoplastic Pemphigus

■ Synonyms:	None
■ Etiology:	Circulating antibodies (IgG) against keratinocyte cell surface peptides including: PV—desmogleins PP—periplakin, envoplakin, desmoplakin, desmogleins
■ Associations:	PV—Myasthenia gravis, thymoma, penicillamine, and captopril PP—Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, Castleman's disease
■ Clinical:	Both variants show flaccid blisters with erosions and oral ulceration; PP is associated with variable features including targetoid- and lichenoid-appearing lesions with a tendency toward severe oral ulceration
■ Histology:	Intraepidermal acantholysis with bullae formation; PP may show a lichenoid/interface dermatitis or rarely, subepidermal bullae; both conditions show intraepidermal IgG and C3 on direct immunofluorescence (DIF)
■ IHC repertoire:	Immunohistochemical repertoire
■ Staging:	None
■ Prognosis:	PV—5-year ~90 % survival PP—5-year ~38 % survival
■ Adverse variables:	PV—Delay in diagnosis, advanced age, high-dose corticosteroids, and associated infection PP—Non-Hodgkin's lymphoma and chronic lymphocytic leukemia
■ Treatment:	PV—Corticosteroids, cyclophosphamide, azathioprine, mycophenolate mofetil, plasmapheresis, and IVIG PP—Problematic, treat underlying malignancy and corticosteroids

The disease pemphigus encompasses a group of related blistering conditions characterized by circulating antibodies against keratinocyte cell surface antigens important in mediating cell-to-cell adhesion [1, 2]. Of the various types and forms of the disease including pemphigus foliaceus, pemphigus erythematosus, IgA pemphigus, and pemphigus vegetans, it is pemphigus vulgaris (PV) and paraneoplastic pemphigus (PP) that constitute the most important causes of mortality. Overall, these disorders are quite rare, with an estimated prevalence of between 1 in 100,000 for PV and less than 1 in 1,000,000 for PP. Both disorders are seen principally in aged adults with a near equal gender distribution. PV is more commonly observed among Jews and individuals of Mediterranean descent, whereas there is no known ethnic predilection for PP.

The etiology of both disorders involves circulating IgG antibody against specific adhesion molecules present on the cell surface of keratinocytes that mediate cell-to-cell

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adhesion and are localized to the desmosome apparatus [3, 4]. The pathogenically important antigens differ among these two disorders. In mucosal PV, desmoglein 3 (130 kDa) is the predominant antigen, while both desmoglein 1 (160 kDa) and desmoglein 3 are targeted in mucocutaneous PV. In contrast, PP has multiple target antigens including plectin (500 kDa), desmoplakin I (250 kDa), bullous pemphigoid antigen 1 (230 kDa), envoplakin (210 kDa), desmoplakin II (210 kDa), periplakin (190 kDa), 170 kDa antigen, desmoglein 1, and desmoglein 3 [5, 6]. Of these antigens, antibodies against envoplakin and periplakin are the most specific for PP [7, 8]. Antibodies directed against these peptides disrupt cell-to-cell adhesion or desmosome assembly, resulting in acantholysis and blister formation. Despite a similarly evoked mechanism of blister formation, it is thought that the pathogenesis of antibody induction is different among these disorders. Patients with PV have a markedly increased frequency of certain class II major histocompatibility complex antigens including HLA-DR4 and HLA-DR14 that predispose to antibody induction against desmogleins [9, 10]. In contrast, the pathogenesis of PP is thought to involve tumor antigen cross-reactivity to normal cell surface constituents resulting in dysregulated immune modulation mediated by both humoral and cell-mediated mechanisms [11].

There are distinct disease associations with these disorders as well. PV is associated with myasthenia gravis and thymoma, as well as the administration of certain medications including penicillamine and captopril [12]. PP is invariably associated with the lymphoproliferative disorders, most commonly non-Hodgkin's lymphoma (39%), chronic lymphocytic leukemia (18%), Castleman's disease (18%), carcinoma (9%), thymoma (6%), sarcoma (6%), and Waldenstrom's macroglobulinemia (1%) [13]. There are rare associations between PP and the more common solid organ malignancies such as breast, lung, colorectal, or prostate adenocarcinoma.

The clinical manifestations of PV consist of flaccid blisters with erosions that develop anywhere on the skin surface, frequently demonstrating a positive Nikolsky sign [14, 15]. The blisters may develop on normal appearing or erythematous skin (Fig. 38.1). Vegetative lesions with excessive granulation tissue may be seen in the intertriginous areas. Mucous membrane involvement, most importantly of the oral cavity, is present in nearly all cases of PV and is often a heralding symptom. It may antedate the development of skin lesions for several months and often persists following skin resolution. The most common presentation is of painful shallow ulcerations most frequently involving the buccal mucosa, palate, floor of the mouth, tongue, and less commonly the pharynx, larynx, conjunctiva, vagina, penis, or anus. The clinical findings in PP are more varied, although mucous membrane involvement is a characteristic of the disorder (Fig. 38.2). Stomatitis is usually the earliest sign of the condition, often persisting throughout the course of the disease, and is usually refractory to therapy. Painful erosions and ulcerations are typically encountered throughout the oropharynx, although lateral tongue

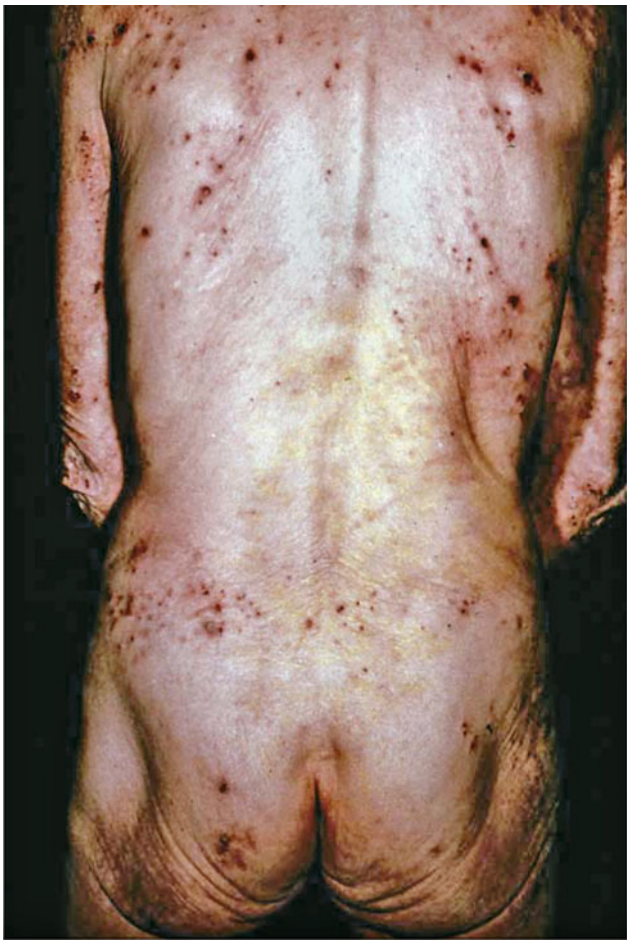

Figure 38.1. Widespread superficial ulcers in an elderly man with pemphigus vulgaris.

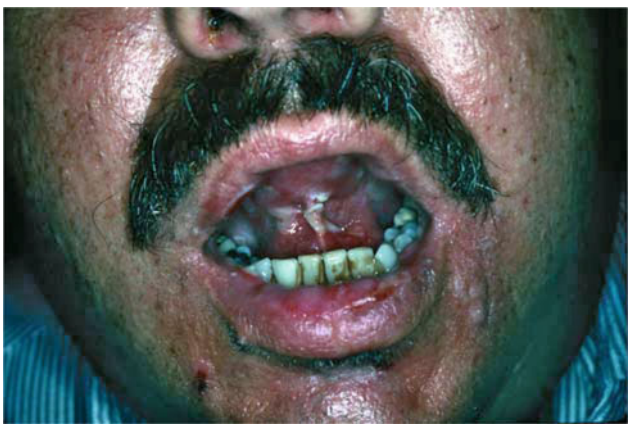

Figure 38.2. Severe mucositis seen in paraneoplastic pemphigus. Note involvement of the nasal mucosa.

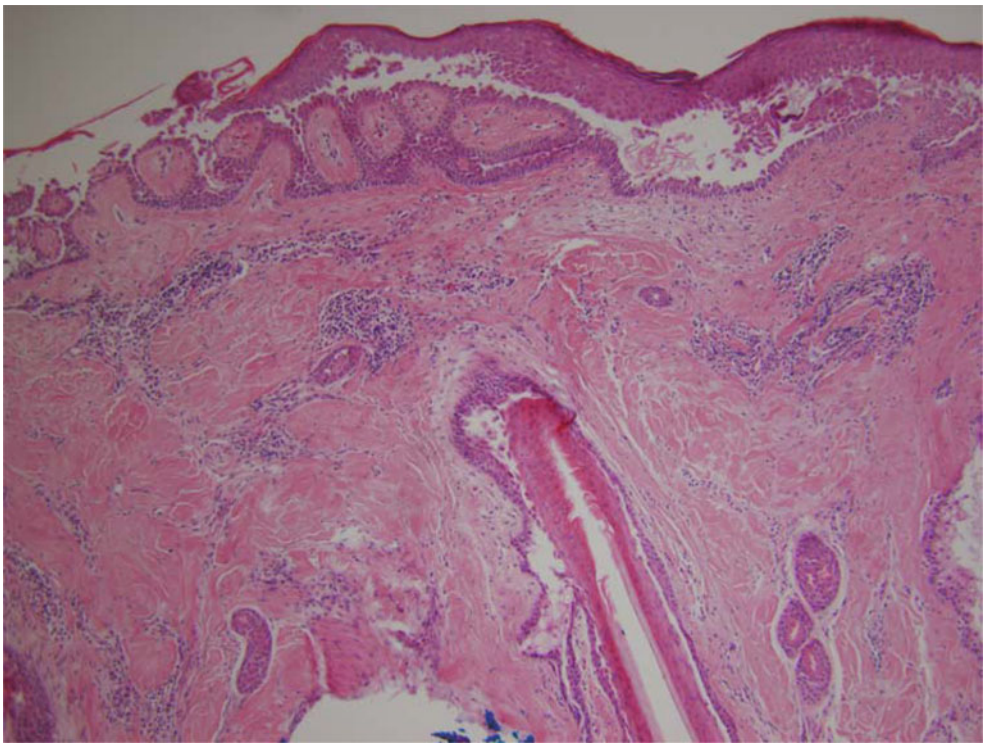

Figure 38.3. Low power photomicrograph depicting suprabasilar acantholysis with follicular involvement.

involvement with extension to and involvement of the vermilion border of the lips is characteristic. The skin lesions often occur episodically as waves of tense or flaccid blisters surmounted on an erythematous base situated on the trunk or extremities. Individually, the lesions may appear as shallow ulcerations similar to PV, as tense blisters similar to bullous pemphigoid, as confluent and erosive patches similar to erythema multiforme/toxic epidermal necrolysis, or as flat-topped papules similar to lichen planus [16–19]. Lichenoid-appearing lesions may be observed on the palms and soles as well as the paronychial skin in established cases, constituting an important means of clinically distinguishing this disorder from PV.

The histopathology of PV is distinctive. Early lesions show exocytosis of neutrophils with accompanying intercellular spongiosis and focal acantholysis. Established lesions show a mixture of dermal and epidermal neutrophils and eosinophils with conspicuous epidermal acantholysis and bullae formation (Fig. 38.3). The acantholysis characteristically spares the basilar layer of the epithelium, imparting an appearance likened to that of "tombstones." Chronic lesions, particularly derived from intertriginous areas, are apt to show acanthosis with neutrophilic and eosinophilic abscesses. Although the histopathology of PP may be identical to that of PV, more often, considerable histologic variation capable of simulating lichenoid/interface dermatitis or bullous pemphigoid is encountered. This histologic diversity may be seen in disparate lesions biopsied synchronously or in metachronous lesions from the same individual. The lichenoid interface pattern often shows striking dyskeratosis with a tendency toward confluent basilar necrolysis (Fig. 38.4). The inflammatory infiltrate of PP often shows a predominance of lymphocytes. Oral biopsies obtained from patients with both disorders show a variable degree of acantholysis with intramucosal or submucosal vesiculation. The inflammatory infiltrate characteristically shows a predominance of neutrophils.

The direct immunofluorescence (DIF) findings are similar and consist of intraepithelial staining with antibodies to IgG and C3 of the lesional skin [20, 21]. DIF is more likely to be negative among patients with PP or to additionally show basement membrane staining. Distinction of these disorders can also be attained with indirect immunofluorescence as monkey esophagus is a more sensitive substrate in PV (anti-Dsg3 autoantibodies) while rat bladder is more sensitive with PP (antiplakin autoantibodies) [22]. Additional methods for identifying the pemphigus autoantibodies include enzyme-linked immunosorbent assay (ELISA), immunoprecipitation, and immunoblotting.

Systemic steroids are first-line treatment for PV. Various regimens and tapering schedules have been employed and cited in the literature. Other reported nonsteroidal therapies include azathioprine, mycophenolate mofetil, dapsone, cyclophosphamide, cyclosporine, methotrexate, rituximab, and intravenous immunoglobulin. These agents

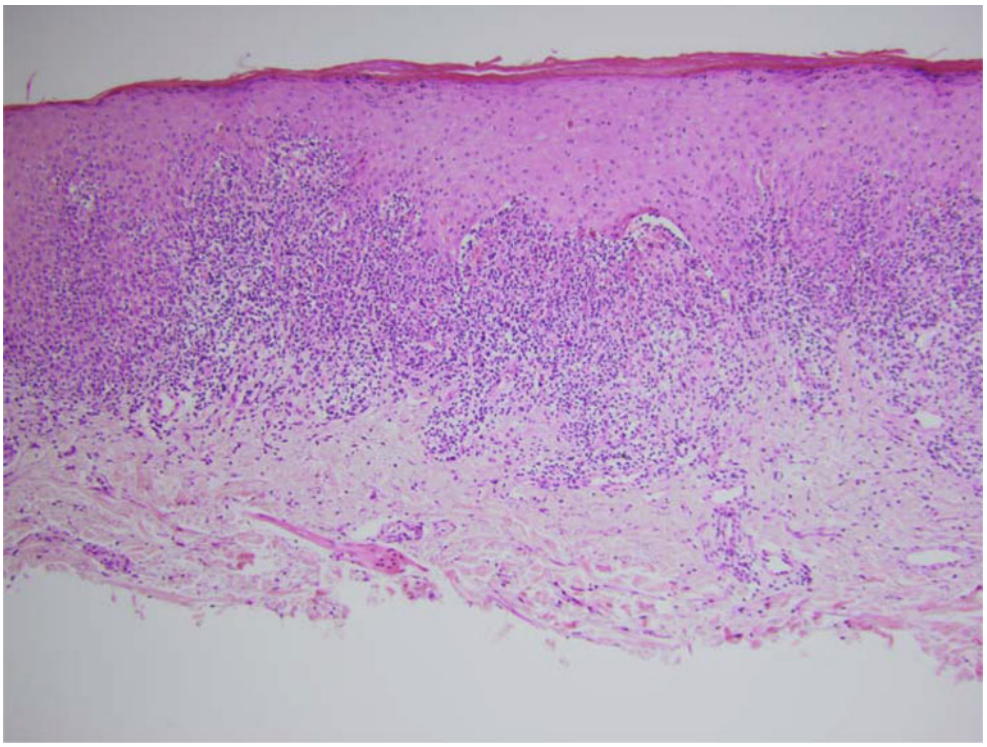

Figure 38.4. Dense lichenoid inflammatory infiltrate with increased necrotic keratinocytes and incipient subepidermal blister formation seen in paraneoplastic pemphigus.

are often used in combination with systemic steroids as adjuvant therapy for PV. The prognosis of PV is generally much more favorable today, particularly since the advent of multifactorial immunosuppressive therapy [23]. The mortality rate is approximately 10 %. Opportunistic infection and fluid/electrolyte imbalances are the main causes of morbidity and mortality. The prognosis of younger patients with PV or those cases associated with medications, myasthenia gravis, and/or thymoma is generally more favorable. In contrast, the prognosis of PP is grave with a 1-, 3-, and 5-year survival rate of 49 %, 41 %, and 38 % respectively [24]. Of note, in patients who present with PP prior to being diagnosed with any internal malignancy, an extensive examination for an occult neoplasm is warranted. It is recommended that a CT of the chest, abdomen, pelvis as well as CBC, LDH, and serum protein electrophoresis be performed [5]. In addition to the association with malignancy, an increased risk of bronchiolitis obliterans contributes to the high mortality rate in PP patients [25]. The mainstay of treatment is addressing the underlying neoplasm. Patients with resectable lesions such as thymoma or Castleman's disease have more favorable outcomes compared to those with indolent lymphoproliferative disorders such as chronic lymphocytic leukemia. Immunosuppressive agents are usually employed to suppress the symptoms of PP, often with very variable responses.

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