PEMPHIGUS VULGARIS: UPDATE ON ETIOPATHOGENESIS, ORAL MANIFESTATIONS, AND MANAGEMENT

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ABSTRACT: Pemphigus is a group of potentially life-threatening diseases characterized by cutaneous and mucosal blistering. There is a fairly strong genetic background to pemphigus with linkage to HLA class II alleles. Certain ethnic groups, such as Ashkenazi Jews and those of Mediterranean origin, are especially liable to pemphigus. Pemphigus vulgaris (PV), the most common and important variant, is an autoimmune blistering disease characterized by circulating pathogenic IgG antibodies against desmoglein 3 (Dsg3), about half the patients also having Dsg1 autoantibodies. Oral lesions are initially vesiculobullous but readily rupture, new bullae developing as the older ones rupture and ulcerate. Biopsy of perilesional tissue, with histological and immunostaining examinations, is essential to the diagnosis. Serum autoantibodies to either Dsg1 or Dsg3 are best detected by both normal human skin and monkey esophagus or by enzyme-linked immunosorbent assay (ELISA). Before the introduction of corticosteroids, pemphigus vulgaris was typically fatal mainly from dehydration or secondary systemic infections. Current treatment is largely based on systemic immunosuppression using systemic corticosteroids, with azathioprine, dapsone, methotrexate, cyclophosphamide, and gold as adjuvants or alternatives, but mycophenolate mofetil and intravenous immunoglobulins also appear promising.

Key words. Pemphigus, autoimmune, corticosteroids, immunosuppressants, oral, bullous, vesiculobullous, skin.

Introduction

Pemphigus is a group of potentially life-threatening autoimmune mucocutaneous diseases characterized by epithelial blistering affecting cutaneous and/or mucosal surfaces, the term being derived from the Greek *Pemphix* (bubble or blister). Pemphigus affects 0.1-0.5 patients *per* 100,000 population *per* year (Ahmed *et al.*, 1980; Becker and Gaspari 1993).

Oral lesions of pemphigus are seen in up to 18% of patients at dermatology out-patient clinics (Ramirez-Amador *et al*., 2000), but despite the frequency of oral involvement, and novel therapeutic approaches (Stanley, 2000), there are surprisingly few recent studies of either the oral manifestations of pemphigus or their management (Mashkilleyson and Mashkilleyson, 1988; Lamey *et al*., 1992; Robinson *et al*., 1997; Scully *et al*., 1999; Sirois *et al*., 2000), and delays in diagnosis are still common (Sirois *et al*., 2000).

Pemphigus has been reviewed in the oral literature in the past decade (Eversole, 1994; Weinberg *et al*., 1997), but several advances in the understanding of the etiopathogenesis, pemphigus variants, and management warrant an update.

Epithelial Biology

An elementary knowledge of the biology of the oral epithelium is crucial to the understanding of pemphigus. The oral epithelium is a complex structure consisting of a range of cells, mainly keratinocytes, adherent to each other by desmosomes, and *via* hemidesmosomes, to an epithelial basement membrane and thereby to the underlying lamina propria. Each component is itself complex and consists of several proteins with important functions—not least the adherence of cells to adjacent structures, and cell-cell recognition and signaling.

Cell-basement membrane contact is largely *via* hemidesmosomes, which have a complex structure and come into contact with the superficial part of the basement membrane (the lamina lucida). Cell-cell contact is *via* occludens (tight junctions), adherens (desmosomes and adhesion plaques), and nexus junctions (gap junctions), each having a complex structure.

DESMOSOMES

Desmosomes guarantee the integrity of the epithelia, by functioning both as an adhesive complex and as a cell-surface attachment site for the keratin intermediate filaments of the cytoskeleton. Desmosomes are adhesion proteins that contain a series of proteins, particularly desmogleins and desmocollins—glycoproteins of the cadherin supergene family which link to cytokeratins *via* desmoplakins and plakoglobin (Buxton and Magee, 1992). Cadherins are composed of an extracellular domain involved in calcium-dependent binding to adjacent cells, a transmembrane domain, and an intracellular domain that binds to catenins and thence to actin (Gumbiner and McCrea, 1993).

ORAL EPITHELIUM

Oral epithelium is similar to skin but differs in several essentials, not least in that desmosomal components differ some-

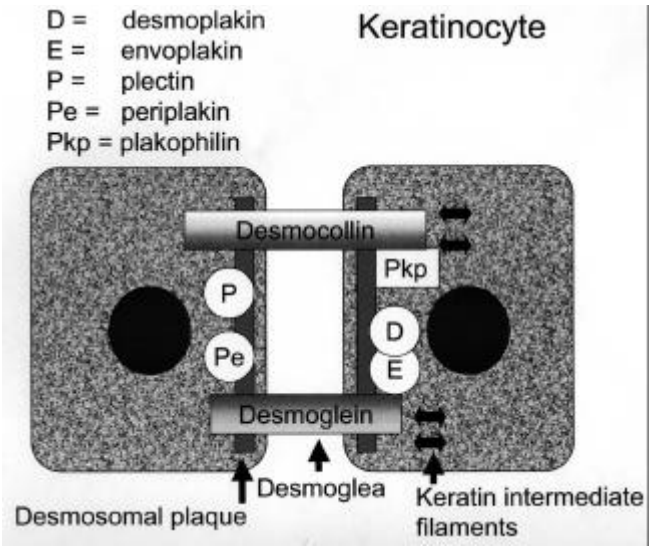

Figure 1. Epithelial structure.

what; for example, the cadherin-type adhesion molecules desmoglein 1 (Dsg 1) and Dsg 3 both are expressed in skin but oral epithelium expresses predominantly only Dsg 3 (Shirakata *et al*., 1998), the 130-kd molecule. This has consequences in terms of disease manifestations, as discussed below, as well as in antibody detection.

The epithelium thus has a complex structure (Fig. 1), and an array of molecules is required for epithelial integrity and health (Uitto and Pulkkinen, 1996; Lin *et al*., 1997; Cozzani *et al*., 2000). Damage to the intercellular area leads to separation of the keratinocytes-acantholysis—which, though typical of pemphigus, may be seen in other conditions (Table 1).

Pemphigus and Variants

Pemphigus affects the skin and may also affect the mucosae of the mouth, nose, conjunctivae, genitals, esophagus, pharynx, and larynx; it is found mainly in middle-aged and elderly patients. Pemphigus is a group of autoimmune disorders in which there is damage to desmosomes by antibodies directed against the extracellular domains of the cadherin-type epithelial cell adhesion molecules—the desmogleins (Dsg) (Nishikawa *et al*., 1996)—with immune deposits intra-epithelially, and loss of cell-cell contact (acantholysis), leading to intra-epithelial vesiculation.

TABLE 1
Causes of Acantholysis

- Primary
  - Pemphigus
  - Darier's disease
  - Transient acantholytic dermatosis
  - Warty dyskeratoma
- Secondary
  - Impetigo
  - Viral infections
  - Carcinoma

VARIANTS

There are several variants of pemphigus described (Table 2), with different autoantibody profiles and clinical manifestations.

PEMPHIGUS VULGARIS

Pemphigus vulgaris (PV) is the most common form and frequently involves the mouth (Weinberg *et al*., 1997; Scully *et al*., 1999). The main importance of PV is that it typically runs a chronic course, almost invariably causing blisters, erosions, and ulcers on the oral mucosae and skin. Before the introduction of corticosteroids, it was often fatal, mainly from dehydration or secondary systemic infections (Ahmed and Moy 1982; Robinson *et al*., 1997; Scully *et al*., 1999). The main antigen in pemphigus vulgaris is Dsg 3 (Amagai *et al*., 1992), whereas that in pemphigus foliaceus is Dsg 1 (Amagai *et al*., 1995). However, 50% of PV patients also have autoantibodies to Dsg1, and the proportion of Dsg1 and Dsg3 antibodies appears to be related to clinical severity (Harman *et al*., 2000a). Those PV which are predominantly oral have only Dsg3 antibodies (Harman *et al*., 2001). Typically, an individual patient develops a single variant of pemphigus, though cases have been described of transition to another variant (Ishii *et al*., 2000), presumably through epitope spread, and the clinical manifestations of a single variant can change over time, as discussed below. This change may be related to changes in the proportions of Dsg1 and Dsg3 autoantibodies (Harman *et al*., 2001).

PARANEOPLASTIC PEMPHIGUS

Apart from PV, the other important variant affecting the mouth is paraneoplastic pemphigus (PNP), usually associated with lymphoproliferative disease (Allen and Camisa, 2000), though one case with oral squamous carcinoma has been reported (Wong and Ho, 2000). Oral lesions may be the sole manifestation (Bialy-Golan *et al*., 1996) and have also been seen in all reported cases of paraneoplastic pemphigus (Laskaris *et al*., 1980; Anhalt *et al*., 1990; Camisa *et al*., 1992; Fullerton *et al*., 1992; Perniciaro *et al*., 1994).

OTHER VARIANTS

Oral lesions have been seen in less common pemphigus variants, especially in most cases with IgA pemphigus (intraepithelial IgA pustulosis [IEAP]), and in some cases of pemphigus associated with inflammatory bowel disease (Stone, 1971; Lubach *et al*., 1984; Delfino *et al*., 1986; Fabbri *et al*., 1986; Schwermann *et al*., 1988; Prendiville *et al*., 1994). In contrast, other types of pemphigus—such as pemphigus foliaceus (PF) and erythematosus and pemphigus vegetans—only rarely affect the oral mucosae (Ahmed *et al*., 1980; Virgili *et al*., 1992; Mahé *et al*., 1996).

Since PNP has been recently reviewed (Allen and Camisa, 2000), the present review focuses on pemphigus vulgaris.

Etiopathogenesis

Pemphigus vulgaris is caused by autoantibodies against epithelial intercellular components, especially cadherins, and particularly desmogleins (Dsg 3 mainly but also Dsg1 in PV,

TABLE 2
Main Types of Pemphigus Involving the Mouth

Variant	Oral Lesions	Main Antigens (Ags)	Localization of Ags	Antibodies	References
Pemphigus vulgaris localized to mucosae (Mucosal)	Common	Dsg 3	Desmosomes	IgG	Harman *et al.*, 2000a, b, 2001
Pemphigus vulgaris also involving skin / other mucosae (Muco-cutaneous)	Common	Dsg 3 Dsg 1	Desmosomes	IgG	
Paraneoplastic pemphigus Periplakin	Common	Desmoplakin 1 Desmoplakin 2 BP 230	Desmosomes or hemi-desmosomes	IgG or IgA	Anhalt and Diaz, 2001; Anhalt *et al.*, 1990
Drug-induced pemphigus	Common	Dsg 3	Desmosomes	IgG	Korman, 2000; Korman *et al.*, 1991
Pemphigus foliaceus	Uncommon	Dsg 1	Desmosomes	IgG	
IgA pemphigus	Uncommon	Desmocollin 1 Desmocollin 2 Dsg 3	Desmosomes	IgA	

Dsg 1 in PF), and, though the precise initiating environmental or lifestyle factor is usually unclear, there is a genetic basis to many cases.

GENETIC BACKGROUND

Feel free to make corrections! There is a fairly strong genetic background to pemphigus vulgaris (PV), certain ethnic groups, such as Ashkenazi Jews and those of Mediterranean origin, being especially liable (Eller and Kest, 1941; Gellis and Glass, 1941; Pisanty *et al*., 1974). PV-IgG subclasses are detectable not only in patients but also in their first-degree relatives (Kricheli *et al*., 2000). Rare familial cases of PV have been reported (Starzycki *et al*., 1998).

HLA class II allele associations in PV are found with HLA-DR4 (DRB1*0402), DRw14 (DRB1*1041), and DQB1*0503 (Sinha *et al*., 1988; Ahmed *et al*., 1990, 1991, 1993; Matzner *et al*., 1995; Carcassi *et al*., 1996; Delgado *et al*., 1996, 1997; Lombardi *et al*., 1996; Nishikawa *et al*., 1996; Miyagawa *et al*., 1997; Mobini *et al*., 1997a; Loiseau *et al*., 2000). Asian alleles of the HLA-B15 family, including the allele B*1507, are significantly increased in comparison with normal controls, in Japanese patients with PV—but HLA class l alleles are not changed (Miyagawa *et al*., 2002). These HLA class II alleles appear critical to T-lymphocyte recognition of Dsg 3 peptides.

Two kinds of Dsg 3-derived peptides may be presented by HLA-DR according to the HLA polymorphism (DRB1*0402 or DRB1*14/0406). The DRB1*14/0406 PV-related molecules may be able to present Dsg 1 and Dsg 3 peptides, providing one explanation for cases of PV with combined responses to Dsg1 and to Dsg3 which are typified by a muco-cutaneous clinical phenotype (Loiseau *et al*., 2000).

PATHOGENESIS

Inevitably, any one or more of the desomosomal proteins can be defective or damaged, and this can result in loss of cell-cell adhesion leading to the clinical result of vesiculation, erosions, or ulcers which characterize pemphigus. Pemphigus vulgaris is an autoimmune disorder in which there is deposition of mainly IgG class antibodies intercellularly (Fig. 2) as well as damage to desmosomes by antibodies directed against the extracellular domains of cadherin-type epithelial cell adhesion molecules, particularly desmoglein 3 (Nishikawa *et al*., 1996). Since oral epithelium expresses largely Dsg 3 but skin expresses Dsg 1 as well as Dsg 3, damage by antibodies to Dsg 3, as in PV, results in oral lesions at an early stage, whereas skin integrity is maintained by Dsg 1; however, if Dsg 1 antibodies appear, cutaneous lesions appear to result and the disease tends to be more severe (Harman *et al*., 2000b) (Table 3).

The Dsg autoantibodies are of the IgG class and in active PV are predominantly IgG4 polyclonal antibodies but IgG1 while in remission (Bhol *et al*., 1995; Tremeau-Martinage *et al*., 1995). Dsg 1 autoantibodies are found in over 50% of cases of

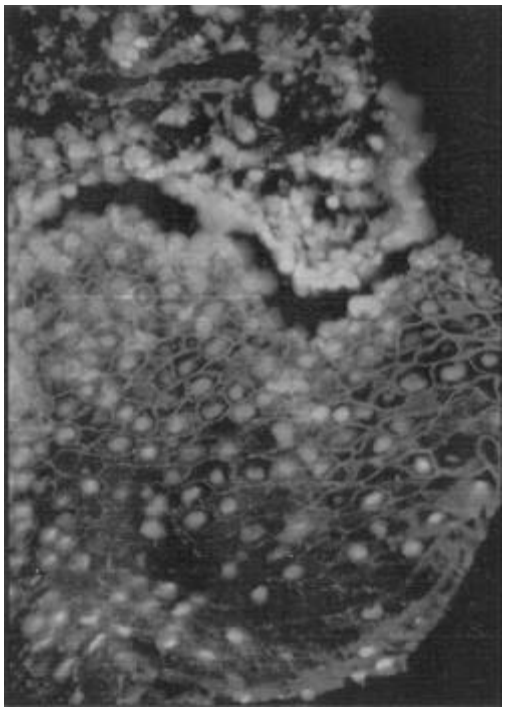

Figure 2. Immune deposits in PV.

PV, and the frequency may differ with race, since they are found in a significantly greater proportion of patients of Indian origin than in white northern Europeans (Harman *et al*., 2000b).

There is direct evidence that autoantibodies against desmoglein 3 (Dsg3) are critical in the pathogenesis (reviewed by Kalish, 2000; Anhalt and Diaz, 2001; Kowalewski *et al*., 2001), since the transfer of PV serum IgG antibodies against Dsg3 into newborn mice induces a bullous skin disease resembling PV (Nishikawa *et al*., 1996; Ding *et al*., 1999; Hertl, 2000), and recombinant Dsg 1 and Dsg 3 absorb the antibodies that cause PV-like skin blisters in neonatal mice. Loss of tolerance against Dsg3 in both B- and T-cells appears important for the development of PV (Tsunoda *et al*., 2002). Dsg 3 forms from two types of small clusters on the nondesmosomal plasma membrane, *i.e.*, either half-desmosome-like clusters with keratin intermediate filament (KIF) attachment or simple clusters without KIF attachment. PV-IgG-induced internalization of the nondesmosomal simple clusters of Dsg3 may represent the primary effects of PV-IgG on keratinocytes (Sato *et al*., 2000). Furthermore, there is evidence that the disease activity in general correlates with the level of serum autoantibodies, and *in vivo* injection produces the disease in monkeys and mice and human skin (Schiltz and Michel, 1976).

The precise mechanism of the acantholysis after pemphigus IgG binds to Dsg 3 on the cell surface is unknown but may involve proteinases (reviewed by Kalish, 2000; Anhalt and Diaz, 2001; Kowalewski *et al*., 2001). PV- IgG causes a transient increase in intracellular calcium and inositol 1,4,5-trisphosphate concentration, and subsequent activation of protein kinase C (PKC) in cell lines. The phosphatidylcholine (PC)-specific phospholipase C (PLC) pathway plays a major role in P-IgG-induced transmembrane signaling by causing long-term activation of PKC (Seishima *et al*., 1999). Plasminogen activation and apoptosis may also be involved (reviewed by Kalish, 2000; Anhalt and Diaz, 2001; Kowalewski *et al*., 2001). Late development of Dsg 1 antibodies in PV correlates with disease progression (Miyagawa *et al*., 1999); the appearance of antibodies against Dsg1 heralds involvement of skin and mucosae other than oral (Ding *et al*., 1997; Harman *et al*., 2000b).

TABLE 3
Antibodies to Desmogleins in PV

PV lesions	Dsg 3	Dsg 1
Mucosal mainly	+	-
Mucocutaneous	+	+

After Harman *et al*. (2000).

ANTIGENS OTHER THAN DESMOGLEIN

Pemphigus autoimmunity may not be limited to antidesmoglein antibodies. Nondesmoglein antibodies induce pemphigus-like lesions in neonatal mice. Non-Dsg PV IgGs also cause gross skin blisters with PV-like suprabasal acantholysis and staining perilesional epithelium in a fishnet-like pattern, indicating that the PV phenotype can be induced without anti-Dsg 3 or anti-Dsg 1 antibody (Nguyen *et al*., 2000a,b).

Acantholytic autoantibodies target a novel human alpha 9 acetylcholine receptor regulating keratinocyte adhesion, a novel keratinocyte annexin-like molecule binding acetylcholine and termed pemphaxin (Nguyen *et al*., 2000b), and catenin (Mignogna *et al*., 2001). This is an area of controversy reviewed elsewhere (Kalish, 2000; Anhalt and Diaz, 2001; Kowalewski *et al*., 2001).

CELLULAR IMMUNITY IN PV

Although the PV autoantibodies are pathogenic, the role of the cellular immune system in acantholysis is unclear. Although CD4 T-cells that recognize the extracellular domain of these desmosomal cadherins are present, any role for these is as yet undefined. There is only a sparse cellular infiltrate around the basement membrane zone, but autoreactive T-cell responses to Dsg 3 may be critical to the pathogenesis, since antibody production generally requires T-cell help, and the strong association with distinct HLA class II alleles (see above) suggests the involvement of CD4+ T-lymphocytes. These T-cells recognize epitopes of Dsg 3. Most of the T-cells are CD45RO (Hertl *et al*., 1998a,b), which help autoreactive B-lymphocytes to produce autoantibodies (Nishifuji *et al*., 2000). CD28-deficient mice (lacking a co-stimulatory signal for T-lymphocyte activation) are much more sensitive to the development of PV than are wild-type mice (Toto *et al*., 2000). T-cell recognition of epitopes of Dsg 3 may be crucial for the initiation and perpetuation of the production of Dsg 3-specif-

ic autoantibodies by B-lymphocytes (Hertl and Riechers, 1999). These autoreactive CD4+ T-cells preferentially produce TH2 cytokines such as interleukin 4 (IL-4), IL-6, and IL-10 (Wucherpfennig *et al*., 1995; Lin *et al*., 1997), but also TH1 cytokines such as gamma interferon (Hertl *et al*., 1998a,b; Hertl and Riechers, 1999). Autoantibodies of the TH2-dependent IgG4 subtype are preferentially seen in active PV, while autoantibodies of the TH1-dependent IgG1 subclass predominate upon remission. Healthy individuals who carry HLA class II alleles similar or identical to those highly prevalent in PV also develop autoreactive T-cell responses to Dsg 3. Autoreactive T-cells from PV patients produce both TH1 and TH2 cytokines, while autoreactive T-cells from healthy persons produce TH0 cytokines (Hertl and Riechers, 1999). Cytokines including interleukin-10 (Toto *et al*., 2000), interleukin-6, interleukin-15, and tumor necrosis factor-alpha (Ameglio *et al*., 1999) are probably involved in PV (Feliciani *et al*., 2000).

Possible Etiological Factors

DIET

The role of diet in the etiology of pemphigus is reviewed elsewhere (Brenner *et al*., 1998; Tur and Brenner, 1998), but garlic in particular may cause occasional cases of pemphigus (Ruocco *et al*., 1996a).

DRUGS

Traditionally, drugs that are capable of inducing pemphigus are divided into two main groups according to their chemical structure:

- drugs containing a sulfhydryl radical (thiol drugs or SH drugs), such as penicillamine and captopril (Laskaris *et al*., 1980; Korman *et al*., 1991; Wolf *et al*., 1991; Laskaris and Satriano, 1993; Ruocco *et al*., 1996a; Shapiro *et al*., 2000);
- nonthiol or other drugs, the latter often sharing an active amide group in their molecule (Wolf and Brenner, 1994). Phenol drugs (Goldberg *et al*., 1999), rifampicin (Gange *et al*., 1976), diclofenac (Matz *et al*., 1997), captopril (Korman *et al*., 1991), and other ACE inhibitors (Kaplan *et al*., 1992; Ong *et al*., 2000) are occasionally implicated.
- Cosmetics have been implicated in the high prevalence of PV in Tunisia (Bastuji-Garin *et al*., 2002).

VIRUSES

The initiating factor in PV remains enigmatic but particularly in view of the apparently transmissible nature of some pemphigus variants (fogo selvagem), the role of viruses has been suggested (reviewed by Ruocco *et al*., 1996b). Most recently, attention has been directed toward the herpesviruses. Very occasionally, the onset of PV has been reported concurrently with (Takahashi *et al*., 1998), or following, herpesvirus infections, and the possibility of epitope spreading or molecular mimickry has been suggested as the pathogenesis (Goon *et al*., 2001). Herpesvirus DNA has been detected, by polymerase chain reaction, in peripheral blood mononuclear cells and skin lesions of patients with pemphigus (Tufano *et al*., 1999). Human herpesvirus 8 (HHV-8) DNA was detected in lesions of patients with PV, while all specimens of non-pemphigus blistering skin diseases were negative (Memar *et al*., 1997; Jang *et al*., 2000). When PCR products were sequenced, the sequences were almost identical to the prototypic sequence for HHV-8, and a few base-pair substitutions at 1086C-T and 1139A-C were detected, suggesting that HHV-8 might have trophism for pemphigus lesions (Jang *et al*., 2000). In contrast, others have failed to detect HHV-8 DNA in lesional skin of pemphigus vulgaris patients (Cohen *et al*., 1998; Bezold *et al*., 2000).

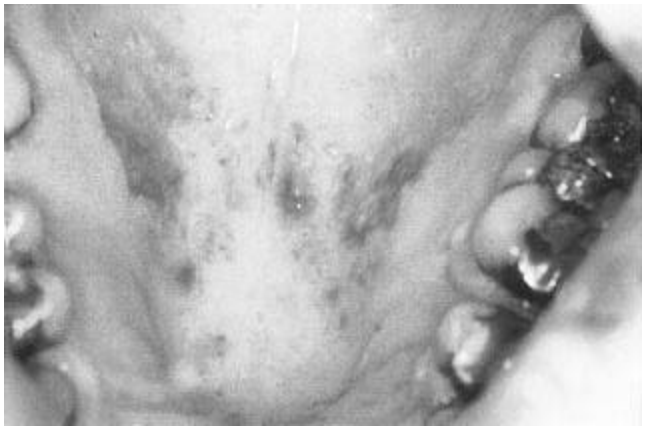

Figure 3. Oral lesions in PV.

OTHER FACTORS

A recent multicenter study at outpatient services of teaching hospitals in Bulgaria, Brazil, India, Israel, Italy, Spain, and the USA revealed lower numbers of smokers among patients with PV, higher exposure rates to pesticides, and a higher number of female patients who had been pregnant. These findings suggested that this may point to the contribution of estrogens in the disease process (Brenner *et al*., 2001).

ASSOCIATION WITH OTHER DISORDERS

Pemphigus vulgaris may occasionally be associated with other autoimmune disorders, such as rheumatoid arthritis, myasthenia gravis, lupus erythematosus, or pernicious anemia (Ahmed *et al*., 1980).

Oral Lesions

Oral lesions of PV are typically seen in adults, rarely in childhood (Laskaris *et al*., 1980). Oral lesions are common and early manifestations (Eversole *et al*., 1972) and typically run a chronic course, causing blisters, erosions, and ulcers (Fig. 3). However, the prevalence of oral involvement varies: One recent multicenter study in several countries showed that Bulgarian patients less frequently had oral mucous membrane lesions (66%) compared with Italian (83%) and Israeli (92%) patients (Brenner *et al*., 2001). Initially vesiculobullous, the oral lesions readily rupture, new bullae developing as the older ones rupture and ulcerate (Sciubba, 1996), and thus erosions and ulcers are the main features and are seen primarily in the

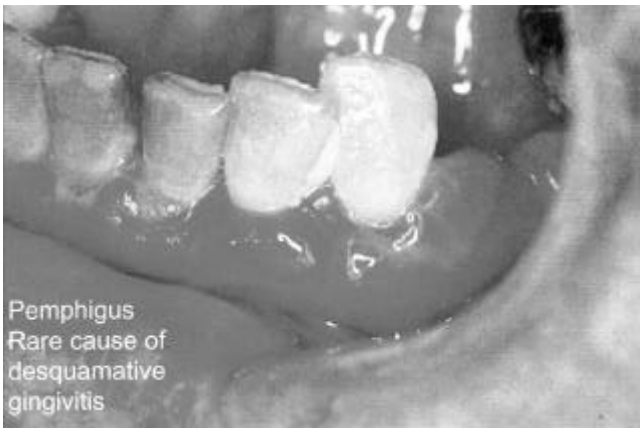

Figure 4. Oral lesions in PV.

buccal mucosa, palate, and lips (Pisanty *et al*., 1974; Meurer *et al*., 1977; Zegarelli and Zegarelli, 1977; Orlowski *et al*., 1983; Shah and Bilimoria, 1983; Sklavounou and Laskaris, 1983; Lamey *et al*., 1992; Kanwar and Dhar, 1995; Weinberg and Abitbol, 1995; Scully *et al*., 1999; Davenport *et al*., 2001). Ulcers heal slowly, but scarring is rare (Zegarelli and Zegarelli, 1977; Shklar *et al*., 1978). Gingival lesions are less common and usually comprise severe desquamative or erosive gingivitis, where bullae have ruptured to leave flaps of peeling tissue with red erosions or deep ulcerative craters mainly on the attached gingivae (Shklar *et al*., 1978; Markitziu and Pisanty, 1983; Orlowski *et al*., 1983; Barnett 1988). Desquamative gingivitis (DG) may be seen, but this is a term that denotes a particular clinical picture and is not a diagnosis in itself (Scully and Porter, 1997) (Fig. 4).

Diagnosis

Many disorders damaging epithelial adhesion molecules are of autoimmune etiology, may have systemic manifestations (Eversole, 1994; Weinberg *et al*., 1997), and can be difficult to differentiate clinically. Therefore, without further investigation, it can be difficult if not impossible to determine the molecular basis of vesiculobullous, erosive, or ulcerative disorders affecting the oral mucosa or gingivae. Something as apparently homogeneous as desquamative gingivitis is thus a catch-all term which encompasses a range of disorders, and management can be carried out on a firm basis only if an accurate diagnosis is achieved (Scully and Porter, 1997). Clinical features such as a positive Nikolsky sign are not specific.

Therefore, in addition to a full history and examination, biopsy examination and appropriate histopathological and immunological investigations are frequently indicated. Biopsy of perilesional tissue, with histological and immunostaining examination, is essential to the diagnosis. Assay of serum antibody titers by indirect immunofluorescence (IIF) may also help guide prognostication and therapy. A recent critical evaluation of two ELISAs for the detection of antibodies to Dsg 1 and 3 comparing two substrates, normal human skin (HS) and monkey esophagus (MO), showed that, when PV serum was used, the sensitivity of IIF was 83% on HS and 90% on MO, and that this combination of substrates should not only increase the sensitivity of detecting pemphigus antibodies, but would also aid in the differentiation of PV from PF (Harman *et al*., 2000a). This strongly suggests that both substrates should be used in the diagnosis of PV, since patients with predominantly oral disease may have only Dsg3 antibodies, which are not always detectable in human skin.

TABLE 4
Monitoring Protocol for Patients with Pemphigus on Systemic Corticosteroid Therapy during the First 3 Months of Therapy

Daily	Weekly	Monthly
Diet low in sodium and carbohydrate	clinical oral examination	titer of serum anti-epithelial antibodies
Blood pressure estimation	body weight estimation	
Recording of symptomatology	hematological examination for first month, then every 15-30 days	

Management

Oral lesions of pemphigus vulgaris may respond partially to topical or intralesional corticosteroids or other immunosuppressants. The treatment of DG consists of improving the oral hygiene, minimizing irritation of the lesions (Checchi *et al*., 1988), the use of specific therapies for the underlying disease where available, and often local immunosuppressive treatment (Lozada-Nur *et al*., 1991), but systemic immunosuppressive therapy, notably corticosteroids (Nisengard and Rogers, 1987), is almost inevitably required in PV.

In any event, in the absence of systemic treatment, oral lesions of PV are almost invariably followed by involvement of the skin or occasionally other epithelia such as the esophagus (Mignogna *et al*., 1997), when systemic immunosuppression will almost invariably be required.

Global immunosuppression is still largely used, though recently there have been attempts at more specific modulation of the autoimmune response which requires autoreactive helper T-cells that regulate immunoglobulin isotype switching. Systemic corticosteroids remain the mainstay of therapy of patients with oral lesions, transforming an invariably fatal disease into one whose mortality is now below 10% (Scully *et al*., 1999; Mignogna *et al*., 2000).

Current treatment, therefore, is largely based on systemic immunosuppression by systemic corticosteroids, with azathioprine, dapsone, methotrexate, cyclophosphamide, gold, and cyclosporin as adjuvants or alternatives, and this has significantly reduced the mortality (Mourellou *et al*., 1995; Bystryn and Steinman, 1996; Carson *et al*., 1996; Mobini *et al*., 1997b; Korman, 2000). The recognition that the severity of the disease is related to

the proportions of Dsg3 and Dsg1 antibodies (Harman *et al*., 2000a) and to the titer of each (Harman *et al*., 2001b) suggests that sequential assays to monitor the specificity and titer of antibodies, along with the clinical features, may be useful in determining the degree of immunosuppression needed.

Hence, topical corticosteroids may suffice for a time if there are only localized oral lesions, with low-titer serum antibodies, but otherwise systemic immunosuppressants (*e.g.*, prednisolone) are essential (Muller and Stanley, 1990; Lamey *et al*., 1992; Chrysomallis *et al*., 1994; Scully *et al*., 1999), and patients should be closely monitored (Table 4). Some use corticosteroids intravenously (Chrysomallis *et al*., 1995; Werth, 1996; Femiano *et al*., 2001) or use steroids with perhaps fewer adverse effects such as deflazocort (Mignogna *et al*., 2000). Once the disease is under clinical control, the dose of corticosteroid can be tapered (Rosenberg *et al*., 1976) or adjuncts added.

Thus, treatment is still largely with systemic corticosteroids, with steroid-sparing agents, and it remains to be seen whether newer therapies discussed below, such as mycophenolate mofetil or intravenous immunoglobulin therapy, prove in the longer term to offer significant advantages over the systemic corticosteroids.

Alternative treatments to corticosteroids

Adjuncts or alternatives to corticosteroids in the treatment of PV include several other immunosuppressive therapies. Chlorambucil (Shah *et al*., 2000), azathioprine (Roenigk and Deodhar, 1973), or cyclophosphamide (Lever and Schaumburg-Lever, 1977, 1984; Fellner *et al*., 1978; Piamphongsant, 1979; Ruocco, 1988; Pasricha *et al*., 1988, 1995) may be effective, the latter sometimes being effective when azathioprine is not (Ahmed and Hombal, 1987). Immunoablative high-dose cyclophosphamide without stem cell rescue has been successful in one patient (Hayag *et al*., 2000). Cyclosporin has proved effective in some hands (Balda and Rosenzweig, 1986; Cunliffe, 1987; Barthelemy *et al*., 1988; Mobini *et al*., 1997b) but not in others as an adjuvant to corticosteroids (Ioannides *et al*., 2000). However, methotrexate is not recommended (Carson *et al*., 1996). Adverse effects of these drugs are common (Scully and Cawson, 1998), but mycophenolate mofetil offers the hope of relatively safe immunosuppression with no nephrotoxicity or hepatotoxicity (Enk and Knop, 1997, 1999; Bredlich *et al*., 1999), and tacrolimus may have a place (Wu *et al*., 2002).

Other drugs

Other agents used with variable benefit include gold (Penneys *et al*., 1976; Salomon and Saurat, 1986), dapsone (Piamphongsant, 1979; Basset *et al*., 1987), etretinate (Orfanos and Bauer, 1983), prostaglandin E_2 (Morita *et al*., 1995), and minocycline (Gaspar *et al*., 1996).

Plasmapheresis

Plasmapheresis (Cotterill *et al*., 1978; Blaszczyk *et al*., 1981; Swanson and Dahl, 1981; Roujeau *et al*., 1982; Bystryn, 1988; Roujeau, 1993; Turner *et al*., 2000) sometimes with cyclosporin (Ruocco, 1988) or cyclophosphamide (Kiel synchronization protocol) and extracorporeal photophoresis (Edelson, 1984) have also been reported to be of benefit.

Intravenous immunoglobulins

Intravenous immunoglobulins have proved successful and safe in steroid-resistant PV (Mobini *et al*., 1995; Bewley and Keefe, 1996; Bystryn and Steinman, 1996; Engineer *et al*., 2000; Sibaud *et al*., 2000).

Remission

The incidence of remissions in pemphigus is unclear, because these are usually reported at a single point in the evolution of the disease. Thus, it is uncertain whether treatment simply suppresses the manifestations of the disease and consequently must be continuously administered, or induces complete and long-lasting remissions that permit therapy to be discontinued. However, a recent long-term longitudinal study examined the induction of complete and long-lasting remissions (defined as "lesion-free with no systemic therapy for at least 6 months") in 40 patients with PV treated conventionally and followed up for an average of 7.7 yrs, and showed that five (5%) of the patients died of the disease but that complete and long-lasting remissions were induced in 25%, 50%, and 75% of patients 2, 5, and 10 yrs, respectively, after diagnosis (Herbst and Bystryn, 2000). Most of the remaining patients were in partial remission or had mild disease controlled with a small dose of corticosteroids. The course of the disease followed different patterns, with some patients rapidly entering complete and long-lasting remissions, whereas others never entered into a complete remission. The induction of complete remission was related to the initial severity and extent of disease and to early response to treatment (Herbst and Bystryn, 2000).

It is thus possible, eventually, to induce complete and durable remissions in most patients, permitting systemic therapy to be safely discontinued without a flare in disease activity. The proportion of patients in whom this can be achieved increases steadily with time, and therapy can be discontinued in approximately 75% of patients after 10 years (Herbst and Bystryn, 2000).

Future Directions

The pathogenesis of PV is rapidly being unraveled, and the search for etiological factors may soon bear fruit. New, more effective, more specific, and safer treatments are emerging, over and above the recent newer immunosuppressive agents such as mycophenolate and tacrolimus, and include:

- proteinase inhibitors (Dobrev *et al*., 1996),
- chimeric molecules for specific recognition and elimination of the autoimmune B-cells (Proby *et al*., 2000),
- suggestions for targeting Dsg 3-specific T-cells for the eventual modulation of the T-cell-dependent production of pathogenic autoantibodies in PV (Hertl and Riechers, 1999), and
- suggestions for a novel avenue for the development of a non-steroidal treatment for PV using the anti-acantholytic activity of cholinergic agonists (Grando, 2000).

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