

MUCOSAL DISEASES SERIES

Number 11 Pemphigus vulgaris

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Pemphigus is a group of potentially life-threatening autoimmune diseases characterized by cutaneous and/or mucosal blistering. Pemphigus vulgaris (PV), the most common variant, is characterized by circulating IgG antibodies directed against desmoglein 3 (Dsg3), with about half the patients also having Dsg1 autoantibodies. There is a fairly strong genetic background to pemphigus with linkage to HLA class II alleles and ethnic groups such as Ashkenazi Jews and those of Mediterranean and Indian origin, are especially liable. 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 examination are essential to the diagnosis. Serum autoantibodies to either Dsg1 or Dsg3 are best detected using both normal human skin and monkey oesophagus or by enzyme-linked immunosorbent assay. Before the introduction of corticosteroids, PV was typically fatal mainly from dehydration or secondary systemic infections. Current treatment is largely based on systemic immunosuppression using corticosteroids, with azathioprine or other adjuvants or alternatives but newer therapies with potentially fewer adverse effects, also appear promising.

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Introduction

Pemphigus is a term derived from the Greek *Pemphix* (bubble or blister) for a group of potentially life-threatening autoimmune mucocutaneous diseases characterized by epithelial blistering affecting cutaneous and/or mucosal surfaces. Pemphigus affects 0.1–0.5

patients per 100 000 population per year (Ahmed *et al*, 1980; Becker and Gaspari, 1993).

Pemphigus affects the skin and oral mucosa and may also affect the mucosae of the nose, conjunctivae, genitals, oesophagus, pharynx and larynx and is found mainly in middle aged and elderly patients. 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.

Pemphigus has been reviewed in the oral literature in the past decade (Eversole, 1994; Weinberg *et al*, 1997; Scully and Challacombe, 2002) but a number of advances in the understanding of the aetiopathogenesis, pemphigus variants, and management, warrant an update. This paper focuses mainly on pemphigus vulgaris (PV).

Epithelial biology

The epithelium has a complex structure and an array of molecules is required for epithelial integrity and health. The oral epithelium consists mainly of keratinocytes, adherent to each other by desmosomes, and via hemidesmosomes, to an epithelial basement membrane and thereby to the underlying lamina propria/dermis. Desmosomes are adhesion proteins that function both as an adhesive complex and as a cell-surface attachment site for the keratin intermediate filaments (KIFs) of the cytoskeleton (see Article 1).

Oral epithelium

Oral epithelium is closely similar to skin but differs in several essentials, not least in that desmosomal components differ somewhat; for example, the cadherin-type adhesion molecules Dsg1 and Dsg3 are both expressed in skin but in oral epithelium the 130 kD molecule Dsg3 is preferentially expressed (Shirakata *et al*, 1998). This has consequences in terms of disease manifestations as discussed below as well as in antibody detection. Damage to the intercellular area leads to separation of

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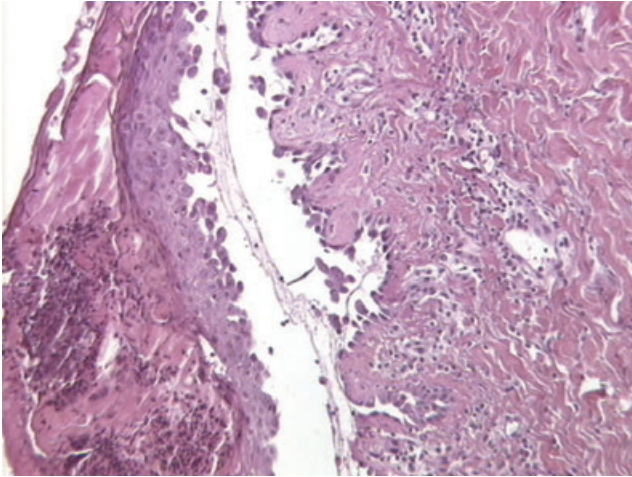


Figure 1 Acantholysis

Table 1 Causes of acantholysis

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

the keratinocytes-acantholysis – which, although typical of pemphigus (Figure 1), may be seen in other conditions (Table 1).

Pemphigus and variants

There are several variants of pemphigus described (Table 2; Figure 2) with different autoantibody profiles and clinical manifestations. Typically an individual patient develops a single variant of pemphigus, although cases have been described of transition to another

variant (Ishii *et al*, 2000), presumably through epitope spreading (intermolecular), 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).

Pemphigus vulgaris

Pemphigus vulgaris is the most common form and it frequently affects 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 and, before the introduction of corticosteroids, 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 PV is Dsg3 (Amagai *et al*, 1992), but 50% of patients also have autoantibodies to Dsg1. The proportion of Dsg1 and Dsg3 antibodies appears to be related to the clinical severity of PV (Harman *et al*, 2000a); those with only Dsg3 antibodies have oral lesions predominantly (Harman *et al*, 2001).

Other variants with oral lesions

Apart from PV, the other important variant affecting the mouth is paraneoplastic pemphigus (PNP), usually associated with lymphoproliferative disease (Allen and Camisa, 2000; Kaplan *et al*, 2004) although one case with oral squamous carcinoma has been reported (Wong and Ho, 2000). Oral lesions have 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; Kaplan *et al*, 2004) and may be the sole manifestation (Bialy-Golan *et al*, 1996). Oral lesions have been seen in most cases of IgA pemphigus (intra-epithelial 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).

Table 2 Main types of pemphigus with oral involvement

Variant	Localisation of Ags	Main antigens (Ags)	Antibody class	Oral lesions	Ref
PV localised to mucosae (Mucosal)	Desmosomes	Dsg3	IgG	Common	Emery Harman Hashimoto Amagai Harman
PV also involving skin/other mucosae (Muco-cutaneous)	Desmosomes	Dsg3 Dsg1	IgG	Common	
Pemphigus foliaceus	Desmosomes	Dsg1	IgG	Uncommon	Emery
Drug-induced pemphigus	Desmosomes	Dsg3	IgG	Common	Korman
IgA pemphigus	Desmosomes	Dsg3	IgA	Uncommon	Hashimoto
Paraneoplastic pemphigus	Desmosomes or Hemi-desmosomes	Desmocollin 1 Desmocollin 2 Desmoplakin 1 Desmoplakin 2 BP 230 Periplakin	IgG or IgA	Common	Anhalt Hashimoto Oursler Kaplan

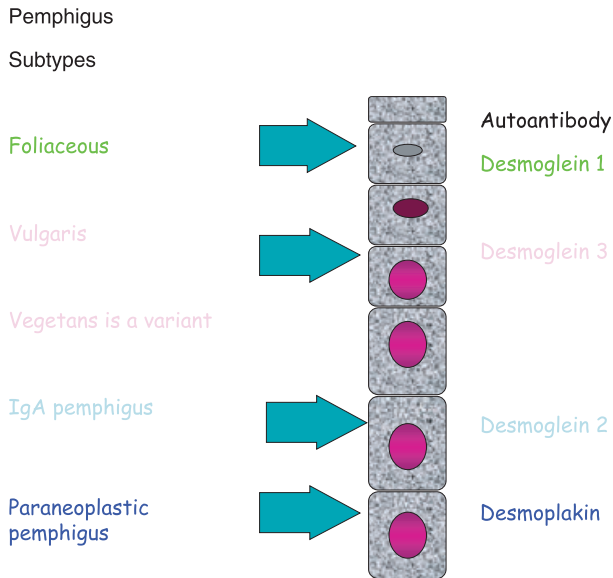


Figure 2 Pemphigus variants

In contrast, other pemphigus variants such as pemphigus foliaceus, pemphigus erythematosus and pemphigus vegetans only rarely affect the oral mucosae (Ahmed *et al*, 1980; Virgili *et al*, 1992; Mahe *et al*, 1996).

Pemphigus vulgaris

Genetic background

There is a fairly strong genetic background to PV; certain ethnic groups, such as Ashkenazian Jews and those of Mediterranean and South Asian origin being especially liable (Eller and Kest, 1941; Gellis and Glass, 1941; Pisanti *et al*, 1974). Rare familial cases of PV have been reported (Starzycki *et al*, 1998).

Associations of PV with HLA class II alleles 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; Lombardi *et al*, 1996; Nishikawa *et al*, 1996; Delgado *et al*, 1997; Miyagawa *et al*, 1997; Mobini *et al*, 1997a; Loiseau *et al*, 2000). In Japanese patients with PV, Asian alleles of the HLA-B15 family, including the allele B*1507, are significantly increased in comparison with normal controls, but HLA class I alleles are unchanged (Miyagawa *et al*, 2002).

The HLA class II alleles appear critical to T lymphocyte recognition of Dsg3 peptides. Genes in the HLA class I region may also have a role in the development or progression of PV (Gazit *et al*, 2004; Loewenthal *et al*, 2004). Two kinds of Dsg3-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 Dsg1 and Dsg3 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).

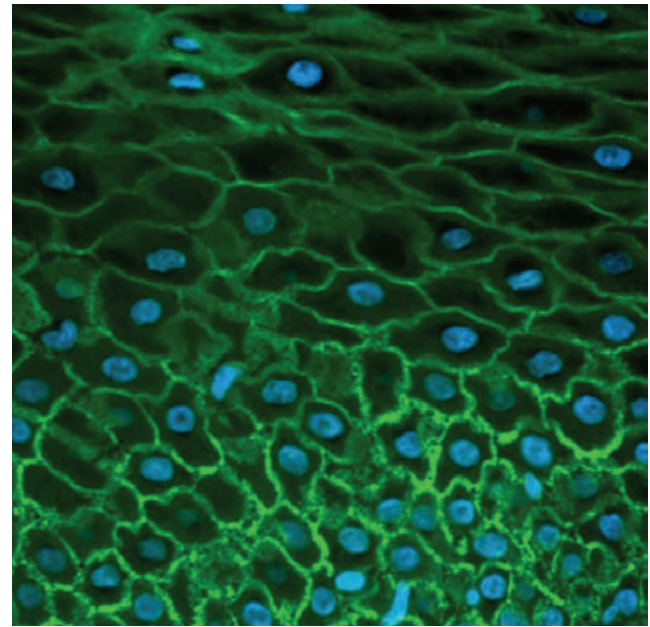


Figure 3 Immune deposits in pemphigus vulgaris

The PV-IgG subclasses are detectable not only in patients with PV but also in their first-degree relatives (Kricheli *et al*, 2000).

Pathogenesis

In PV mainly IgG antibodies are deposited intercellularly (Figure 3) directed against the extracellular domains particularly of Dsg3 (Nishikawa *et al*, 1996) and as oral epithelium expresses largely Dsg3 (skin expresses Dsg1 as well as Dsg3), oral lesions appear at an early stage. Development of Dsg1 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). Dsg1 autoantibodies are found in over 50% of cases of PV, and the frequency may differ with race as they are found in significantly greater proportion of patients of Indian origin than white northern Europeans (Harman *et al*, 2000b).

There is direct evidence that autoantibodies against Dsg3, are critical in the pathogenesis (Kalish, 2000; Anhalt and Diaz, 2001; Kowalewski *et al*, 2001), as 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 Dsg1 and Dsg3 absorb the antibodies

Table 3 Antibodies to desmogleins in pemphigus vulgaris (PV)

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

After Harman *et al* (2000b).
Dsg, desmoglein.

that cause PV-like skin blisters in neonatal mice. Furthermore, the homozygous deletion mutation (2079del14) in the Dsg3 gene in mice (Dsg3bal-Pas mice) could determine loss of cell adhesion (Pulkkinen *et al*, 2002). Loss of tolerance against Dsg3 in both B and T cells appears important for the development of PV (Tsunoda *et al*, 2002) but is not determinant (Veldman *et al*, 2004). Dsg3 forms from two types of small clusters on the non-desmosomal plasma membrane, i.e. either half-desmosome-like clusters with KIF attachment or simple clusters without KIF attachment. PV-IgG-induced internalization of the non-desmosomal 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 (HS) (Schiltz and Michel, 1976).

The Dsg autoantibodies in active PV are predominantly IgG4 polyclonal antibodies but IgG1 whilst in remission (Bhol *et al*, 1995; Tremereau-Martinage *et al*, 1995; Ayatollahi *et al*, 2004). The precise mechanism of the acantholysis after the pemphigus IgG (PV-IgG) binds to Dsg3 on the cell surface is unknown but may involve proteinases (reviewed by Kalish, 2000; Anhalt and Diaz, 2001; Kowalewski *et al*, 2001). PV-IgG increases the intracellular calcium and inositol 1,4,5-trisphosphate concentration, and subsequently activates protein kinase C (PKC) in cell lines. The phosphatidylcholine (PC)-specific phospholipase C (PLC) pathway plays a major role in PV-IgG-induced transmembrane signalling by causing long-term activation of PKC (Seishima *et al*, 1999). Plasminogen activation may also be involved with apoptosis via caspase activation (reviewed by Kalish, 2000; Anhalt and Diaz, 2001; Kowalewski *et al*, 2001; Lo Muzio *et al*, 2002; Puviani *et al*, 2003; Wang *et al*, 2004).

Antigens other than desmoglein

Pemphigus autoimmunity may not be limited to antidesmoglein antibodies but this is an area of controversy reviewed elsewhere (Kalish, 2000; Anhalt and Diaz, 2001; Kowalewski *et al*, 2001).

Acantholytic autoantibodies target a human alpha 9 acetylcholine receptor regulating keratinocyte adhesion, a keratinocyte annexin-like molecule binding acetylcholine and termed pemphaxin (Nguyen *et al*, 2000b) and catenin (Mignogna *et al*, 2001). Non-desmoglein antibodies (non-Dsg PV-IgGs) induce pemphigus-like lesions in neonatal mice and cause gross skin blisters with suprabasal acantholysis and staining in perilesional epithelium in a fishnet-like pattern (Nguyen *et al*, 2000a,b).

Cellular immunity in PV

Although the PV autoantibodies are pathogenic, the role of the cellular immune system in acantholysis is unclear. CD4 T cells that recognize the extracellular domain of these desmosomal cadherins are present, but 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 Dsg3 may be critical to the pathogenesis as 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 Dsg3. 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 costimulatory 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 Dsg3 may be crucial for the initiation and perpetuation of the production of Dsg3-specific autoantibodies by B lymphocytes (Hertl and Riechers, 1999) but they alone are not sufficient (Veldman *et al*, 2004). 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) and 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 Dsg3. Autoreactive T cells from PV patients produce both TH1 and TH2 cytokines whilst autoreactive T cells from the healthy persons produce TH0 cytokines (Hertl and Riechers, 1999). Cytokines including interleukin-10 (Toto *et al*, 2000), IL-6, IL-15 and tumour necrosis factor-alpha (Ameglio *et al*, 1999) and IL-1alpha and tumour necrosis factor-alpha are probably involved in PV (Feliciani *et al*, 2000; Torzecka *et al*, 2003). Tumour necrosis factor-alpha and interleukin-1alpha induce *in vitro* the expression of urokinase plasminogen activator (Feliciani *et al*, 2003).

Possible aetiological factors

Diet

Garlic may cause occasional cases of pemphigus (Ruocco *et al*, 1996a) and this and other dietary factors are reviewed elsewhere (Brenner *et al*, 1998; Tur and Brenner, 1998).

Drugs

Drugs capable of inducing pemphigus fall into two main groups according to their chemical structure –

- drugs containing a sulphhydryl radical (thiol drugs or SH drugs) e.g. penicillamine and captopril (Laskaris *et al*, 1980; Korman *et al*, 1991; Wolf *et al*, 1991; Laskaris and Satriano, 1993; Ruocco *et al*, 1996b; Shapiro *et al*, 2000).
- non-thiol drugs, often sharing an active amide group in their molecule (Wolf and Brenner, 1994) e.g. phenol drugs (Goldberg *et al*, 1999), rifampicin (Gange *et al*,

1976), diclofenac (Matz *et al*, 1997), and other ACE-inhibitors (Kaplan *et al*, 1992; Ong *et al*, 2000) are occasionally implicated.

Viruses

The apparently transmissible nature of some pemphigus variants (fogo selvagem), has suggested a role for viruses (Ruocco *et al*, 1996b). The onset of PV has occasionally been reported concurrently with (Takahashi *et al*, 1998), or following, herpesvirus infections, and the possibility of epitope spreading or molecular mimicry has been suggested as the pathogenesis (Goon *et al*, 2001). Herpesvirus DNA has been detected in peripheral blood mononuclear cells and skin lesions of patients with pemphigus by PCR (Tufano *et al*, 1999). Human herpesvirus 8 (HHV-8) DNA was detected in lesions of patients with PV compared with non-pemphigus blistering skin diseases which were negative (Memar *et al*, 1997; Jang *et al*, 2000) but HHV-8 might have tropism for pemphigus lesions (Jang *et al*, 2000). Indeed, others have failed to detect HHV-8 DNA in lesional skin of patients with PV (Cohen *et al*, 1998; Bezold *et al*, 2000).

Other factors

A recent multicentre 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 and suggested that this may point to the contribution of oestrogens 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 anaemia (Ahmed *et al*, 1980).

Oral lesions

Oral lesions of PV are seen in up to 18% of patients at dermatology outpatient clinics (Ramirez-Amador *et al*, 2000) but the prevalence of oral involvement varies: one recent multicentre study in several countries showed that Bulgarian patients less frequently had oral mucous membrane lesions (66%) compared with Italians (83%) and Israeli (92%) patients (Brenner *et al*, 2001). There are surprisingly few studies either of the oral manifestations or their management (Mashkilleysen and Mashkilleysen, 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).

Oral lesions of PV are rare in childhood (Laskaris *et al*, 1980) but common and early manifestations in adults (Eversole *et al*, 1972) where they typically run a chronic course (Figure 4). 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 seen mainly in the buccal mucosa, palate and lips (Pisanti



Figure 4 Oral lesions in pemphigus vulgaris

et al, 1974; Meurer *et al*, 1977; Zegarelli and Zegarelli, 1977; Orłowski *et al*, 1983; Shah and Bilimoria, 1983; Sklavounou and Laskaris, 1983; Lamey *et al*, 1992; Kanwar and Dhar, 1995; Weinberg and Abitbol, 1995; Scully and Porter, 1997; Davenport *et al*, 2001). Ulcers heal slowly usually without scarring (Zegarelli and Zegarelli, 1977; Shklar *et al*, 1978). Gingival lesions are less common and at the onset, may frequently appear as isolated blisters and/or erosions mainly located on free gingivae, very little in extension and hard to recognize as bullous lesions (Mignogna *et al*, 2001). Advanced manifestations 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; Orłowski *et al*, 1983; Barnett, 1988).

Diagnosis

Vesiculobullous, erosive or ulcerative disorders affecting the oral mucosa or gingivae can be very difficult to differentiate clinically and clinical features such as a positive Nikolsky sign are not specific. There is also considerable discussion between experts (Mimouni *et al*, 2003).

It is crucial to establish the diagnosis of PV clearly, and as early as possible, so that adequate treatment can be commenced. In addition therefore, 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 are essential to the diagnosis.

Assay of serum antibody titres by indirect immunofluorescence (IIF) may also help guide prognostication and therapy. A recent critical evaluation of two enzyme-linked immunosorbent assays (ELISAs) for the detection of antibodies to Dsg1 and 3 comparing two substrates, normal human skin (HS) and monkey oesophagus (MO) showed that using PV serum 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 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 as patients with predominantly oral disease may only have Dsg3 antibodies which are not always detectable using HS. With appropriate dilution, ELISA detection of autoantibodies to Dsg3 and Dsg, can provide useful information for assessing disease activity (Cheng *et al*, 2002).

Management

In the absence of systemic treatment, oral lesions of PV are almost invariably followed by skin involvement or occasionally lesions in other epithelia such as the oesophagus (Mignogna *et al*, 1997). Systemic immunosuppression will thus almost invariably be required (Nisengard and Rogers, 1987; Harman *et al*, 2003). Systemic corticosteroids remain the mainstay of therapy for 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). Some use corticosteroids intravenously (Chrysomallis *et al*, 1995; Werth, 1996; Femiano *et al*, 2002; Mignogna *et al*, 2002) or use steroids with perhaps fewer adverse effects such as deflazacort (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. The recognition that the severity of the disease is related to the proportion of Dsg3 and Dsg1 antibodies (Harman *et al*, 2000a) and to the titre of each (Harman *et al*, 2001) suggests that sequential assays to monitor the specificity and titre of antibodies, along with the clinical features may be useful in determining the degree of immunosuppression needed (Cheng *et al*, 2002).

Alternative treatments to corticosteroids

Azathioprine (Roenigk and Deodhar, 1973), chlorambucil (Shah *et al*, 2000), or cyclophosphamide (Lever and Schaumburg-Lever, 1977; Fellner *et al*, 1978; Piamphongsant, 1979; Lever and Schaumburg-Lever, 1984; Pasricha *et al*, 1988, 1995; Ruocco, 1988) can be effective. Immunoablative high-dose cyclophosphamide without stem cell rescue has been successful in one patient (Hayag *et al*, 2000). Ciclosporin has proved effective in some hands (Balda and Rosenzweig, 1986; Barthelemy *et al*, 1988; Mobini *et al*, 1997b) but not in others as an adjuvant to corticosteroids (Ioannides *et al*, 2000). However, methotrexate in high doses is not recommended (Carson *et al*, 1996) but a low dose schedule may be of benefit (Smith and Bystry, 1999).

Adverse effects of these drugs are common (Scully and Bagan, 2004). Other agents used with variable benefit include gold (Penneys *et al*, 1976; Salomon and Saurat, 1986), dapsone (Piamphongsant, 1979; Basset *et al*, 1987), etretinate, prostaglandin E₂ (Morita *et al*, 1995), minocycline (Gaspar *et al*, 1996), and mycophenolate mofetil (Enk and Knop, 1997, 1999; Bredlich *et al*, 1999), although others have not confirmed this (Powell *et al*, 2003) and tacrolimus may have a place (Wu *et al*, 2002).

New drugs

However, although global immunosuppression is still largely used, recently there have been attempts to use cholinergic agonists, which are a promising possibility (Grando, 2000; Nguyen *et al*, 2004) or to more specifically modulate the autoimmune response which requires autoreactive helper T cells that regulate immunoglobulin isotype switching, and Rituximab (anti-CD20 monoclonal antibody) shows promise (Dupuy *et al*, 2004). Other possibilities include proteinase inhibitors (Dobrev *et al*, 1996), chimeric molecules for specific recognition and elimination of the autoimmune B cells (Proby *et al*, 2000), targeting Dsg3-specific T cells to eventually modulate the T-cell-dependent production of pathogenic autoantibodies in PV (Hertl and Riechers, 1999) and removal of pathogenic autoantibodies with immunoadsorption (Lufth *et al*, 2003; Schmidt *et al*, 2003).

Plasmapheresis

Plasmapheresis (Cotterill *et al*, 1978; Blaszczyk *et al*, 1981; Swanson and Dahl, 1981; Roujeau *et al*, 1982; Bystry, 1988; Roujeau, 1993; Turner *et al*, 2000) sometimes with ciclosporin (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; Bystry and Steinman, 1996; Engineer *et al*, 2000; Sibaud *et al*, 2000; Sami *et al*, 2003; Herzog *et al*, 2004).

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 years and showed that five (5%) patients died of the disease but complete and long-lasting remissions were induced in 25, 50 and 75% of patients 2, 5 and 10 years, respectively, after diagnosis (Herbst and Bystry, 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 Bystry, 2000).

It is thus possible to eventually 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).

Oral care

Topical corticosteroids may suffice for a time if there are only localized oral lesions, with low titre serum antibodies, but otherwise systemic immunosuppressants (e.g. prednisolone) are essential (Muller and Stanley, 1990; Lamey et al, 1992; Chrysomallis et al, 1994; Scully and Porter, 1997) and patients should be closely monitored. Oral lesions of PV may respond poorly to systemic immunosuppression, and topical or intralesional corticosteroids or other immunosuppressants may help. The treatment of DG also consists of improving the oral hygiene, minimizing irritation of the lesions (Checchi et al, 1988), and often local immunosuppressive treatment (Lozada-Nur et al, 1991).

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