



Pemphigus: Etiology, pathogenesis, and inducing or triggering factors: Facts and controversies

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Abstract Pemphigus includes a group of autoimmune bullous diseases with intraepithelial lesions involving the skin and Malpighian mucous membranes. Pemphigus vulgaris (PV), the most frequent and representative form of the group, is a prototypical organ-specific human autoimmune disorder with a poor prognosis in the absence of medical treatment.

The pathomechanism of PV hinges on autoantibodies damaging cell–cell cohesion and leading to cell–cell detachment (acantholysis) of the epidermis and Malpighian mucosae (mainly oral mucosa). A controversy exists about which subset of autoantibodies is primarily pathogenic: the desmoglein-reactive antibodies or those directed against the acetylcholine receptors of the keratinocyte membrane.

The onset and course of PV depend on a variable interaction between predisposing and inducing factors. Genetic predisposition has a complex polygenic basis, involving multiple genetic loci; however, the genetic background alone (“the soil”), although essential, is not by itself sufficient to initiate the autoimmune mechanism, as proven by the reports of PV in only one of two monozygotic twins and in only two of three siblings with an identical PV-prone haplotype. The intervention of inducing or triggering environmental factors (“the seed”) seems to be crucial to set off the disease. The precipitating factors are many and various, most of them directly originating from the environment (eg, drug intake, viral infections, physical agents, contact allergens, diet), others being endogenous (eg, emotional stress, hormonal disorders) but somehow linked with the subject’s lifestyle. As to certain drugs, their potential of provoking acantholysis may be implemented by their interfering with the keratinocyte membrane biochemistry (biochemical acantholysis) and/or with the immune balance (immunologic acantholysis). Viral infections, especially the herpetic ones, may trigger the outbreak of PV or simply complicate its clinical course. The precipitating effect might be due to interferons and other cytokines released by the host as a consequence of the viral attack, which overactivate the immune response. Inductions of PV by physical agents (ultraviolet or ionizing radiation, thermal or electrical burns, surgery and cosmetic procedures), contact allergens (in particular, organophosphate pesticides), dietary factors (eg, garlic, leek, onion, black pepper, red chili pepper, red wine, tea), and emotional stress are rare, but well-documented events.

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The possible intervention of the environment in the outbreak of PV has been overlooked in the past, but nowadays clinicians perceive it more frequently. The assumption that genetic factors alone are not sufficient to cause the outbreak of the disease, inevitably instills the idea that PV may not occur spontaneously, but always results from an interaction between an individual predisposing genetic background and environmental precipitating factors, often concealed or apparently harmless.

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Introduction

Pemphigus, a word derived from the Greek πέμφιξ-ίγος (read pemphix-igos) meaning blister (or bulla, from the Latin), refers to a group of autoimmune bullous diseases characterized by widespread blistering and erosions of the skin and mucous membranes. There are six main variants of pemphigus: pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, pemphigus erythematous, paraneoplastic pemphigus, and drug-induced pemphigus. This contribution focuses only on pemphigus vulgaris (PV), which is the most frequent and representative form of the pemphigus group, as well as a prototypical organ-specific human autoimmune disease. Its incidence is estimated at one to five cases per 1 million inhabitants per year but is much higher in some Ashkenazi Jewish populations and in Eastern countries, such as India, Malaysia, China, and Japan. It involves both men and women with a mean age between 40 and 60 years, although some cases have been described in children.¹

Initial lesions consist in cell–cell detachment (acantholysis) in the deep part of the epithelium, just above the basal layer (suprabasal acantholysis), resulting in a splitting that gives rise to blister formation (intraepithelial bulla). In two-thirds of cases, the oral mucosa is the site of onset and the disease may remain confined there for several months (oral pemphigus). Intact bullae are quite an uncommon finding in the mouth, where painful and poorly healing erosions represent the hallmark lesions. Skin involvement usually occurs subsequently, with flaccid blisters evolving into erosive areas. Lesions often appear on the trunk, intertriginous areas (axillar, inframammary, and inguinal regions), and scalp, but every site may be involved. Pruritus and the degree of pain are variable. Other stratified squamous epithelial mucosal surfaces (pharynx, larynx, esophagus, conjunctiva, urethra, cervix, anal mucosa) also may be affected in patients with more severe disease.

If left untreated, PV becomes generalized (new crops of bullae appear anywhere, more and more areas of skin present eroded and crusted), the outcome often being fatal within 1 to 3 years due to uncontrolled fluid and protein loss or opportunistic infection. The use of systemic steroids and immunosuppressants has completely modified the natural course and dramatically improved the prognosis of the disease. Currently, the mortality rate of PV is estimated at 5% to 10%¹; however, although mortality from PV is low, deaths from treatment side effects or complications are not rare.

Etiopathogenesis

Beutner and Jordon found the key to the etiopathogenesis of pemphigus in 1964.² They demonstrated antibodies directed against an intercellular antigen of Malpighian epithelia (skin and mucous membranes) in sera of patients with pemphigus. Clinical and experimental observations (Table 1) proved that these antibodies are pathogenic, being the “culprit” and not simply the “witness” of the acantholytic phenomenon.

Much is known but much remains controversial about the exact nature and molecular structure of the antibodies responsible for the development of the disease (pemphigus antibodies) as well as about their targets (pemphigus antigens). For a long time it has been accepted that PV resulted only from the binding of autoantibodies to calcium-dependent adhesion molecules (desmogleins 1 and 3), which are normal components of keratinocyte cell membranes belonging to the cadherin supergene family, and which are primarily involved in cell–cell cohesion. Desmogleins 1 and 3 have so represented the main antigens of pemphigus and still represent the main autoantibody target in most clinical variants. Being desmoglein 3 overexpressed in non-keratinized epithelia (mucous membranes) and desmoglein 1 overexpressed in keratinized epithelia (skin), as a rule, oral pemphigus has mainly been related to antidesmoglein 3 antibodies, whereas the full-blown disease with both mucosal and skin involvement has been related to the concurrent action of antidesmoglein 3 and antidesmoglein 1 antibodies. Recently, it has been claimed that

Table 1 Evidence of the pathogenicity of the ICAb of pemphigus

Clinical observations

The transplacental passage of ICAb from pemphigus patient to newborn causes in the latter cutaneous lesions with clinical, histologic, and immunologic characteristics of pemphigus, which resolve spontaneously within a few weeks (*transient neonatal pemphigus*).

In pemphigus patients, the removal of large quantities of ICAb from the blood through plasmapheresis produces temporary clinical remissions.

Experimental research

In vitro: ICAb cause acantholysis in cultures of normal human skin, even in the absence of complement.

In vivo: The injection of human ICAb in the peritoneum of newborn mice produces, in the animals, skin lesions very similar to those of human disease in regard to the clinical, histologic, and immunologic aspects.

ICAb, intercellular antibodies.

the role of desmoglein-reactive antibodies in the pathomechanism of acantholysis has been overestimated, despite desmogleins 1 and 3 still being the main autoantigens in most clinical variants of pemphigus and despite their corresponding antibodies still having a diagnostic importance. In fact, if the integrity of Malpighian epithelia relied entirely on desmogleins 1 and 3, the epidermis would disintegrate to a suspension of single cells in the presence of both antidesmoglein 1 and antidesmoglein 3 antibodies, which normally never occurs. Therefore, detachment of keratinocytes from one another also could depend on a different subset of nondesmoglein pemphigus antibodies that recognize and block keratinocyte acetylcholine receptors. Noteworthy, these receptors play a crucial role in mediating cell–cell cohesion, in particular by regulating the intraepithelial expression of desmogleins. The keratinocyte acetylcholine receptors can thus be considered nondesmoglein pemphigus antigens. In this light, the earliest sign of keratinocyte detachment (cell shrinkage) would be sustained by autoantibodies directed toward these acetylcholine receptors located on the keratinocyte membrane, whereas only subsequently antidesmoglein antibodies would enter into action and provoke cell–cell dishesion. The synergistic effect of different subsets of autoantibodies, which target different antigens that are anyway aimed at maintaining cell–cell cohesion, could explain the clinical and biological variability of the disease in different patients. In fact, the severity of the disease and its clinical picture may greatly depend on the ratio of these different antibody subsets in each patient. Therefore, PV acantholysis seems to result from cooperative and finely coordinated biological signals that control cell adhesion in Malpighian epithelia.³ From this new point of view, cell–cell dishesion in PV is depicted as a multistep mechanism initiating with the autoantibody binding to keratinocytic membrane and subsequent activation of the apoptotic machinery; continuing with basal cell shrinkage (early acantholysis) and internalization of the extra-desmosomal desmogleins; ending up with complete cell–cell detachment, formation of suprabasal clefts (advanced acantholysis), rounding up and apoptotic death of isolated parabasal keratinocytes (Tzanck cells), and “tombstoning” of the surviving basal cells. This pathomechanism, which emphasizes how apoptotic enzymes contribute to the acantholytic phenomenon in PV both in terms of molecular events and chronologic sequence, has been termed *apoptolysis*.⁴

The primary initiating stimulus for the production of pemphigus antibodies often remains an enigma, but a predisposing genetic background for the disease to develop is thought to be essential.

Genetic background (the soil)

The existence of a complex polygenic basis, involving multiple genetic loci, is clearly established for PV. Most of these loci still remain unknown, being twin and adoption

studies unavailable because of the low prevalence of the disease among the general population. Additional support to this genetic basis comes from the increased incidence of autoimmunity disorders in PV patients (autoimmunity comorbidity) and in their blood relatives, who may be affected by type 1 diabetes, autoimmune thyroid disease, less commonly PV itself. Multiple familial PV cases, despite being rare, are likely to occur particularly in first-degree relatives.

To date, the association between HLA class II genes and PV is the strongest and, at the same time, the best documented,⁵ whereas other associations still need to be confirmed. Early serological studies supported PV association with DR4 (more frequent in women than men, thus suggesting the role of genetics in determining the “female bias,” which is typical of several autoimmune conditions, although non-genetic mechanisms also may be involved), and with DR14, which is a split antigen of the older HLA-DR6 serotype group (in Italian patients it is clearly predominant compared with DR4).⁵ Molecular gene subtyping highlighted two alleles that are known as DRB1* 0402 and DQB1* 0503. In fact, more than 95% of PV patients carry one of them.^{5,6} Molecular analysis of DRB1 polymorphisms revealed first a significant increase of DRB1* 14 and DRB1* 04; then, further analyses looking for a more stringent association with some particular allele subtypes, showed a highly significant increase of DRB1* 0402 (which is prevalent in the Ashkenazi Jewish population and often associated with DQB1* 0503), DRB1* 1401, DRB1* 1404, and more recently DRB1* 1454. Regarding DQB1* polymorphisms, molecular analysis showed a significant increase of subtype DQB1* 0503 (in linkage with DRB1* 14) as well as a meaningful presence of DQB1* 0302 (in linkage with DRB1* 04).⁵ Analysis of the sequence and structure of these PV susceptibility alleles reveals key HLA peptide-binding site pockets and residues that distinguish these molecules from non-disease-associated sequences. These data highlight the exquisite specificity of the immune response and suggest mechanisms by which autoimmune reactions are initiated. HLA II associations in PV are consistent with the prevailing model of disease development in which the activation of class II restricted, desmoglein-specific CD4 T-effector cells drives autoreactive B-cell activity and autoantibody production.⁶

Despite the great number of studies on the association between HLA II and PV, very few have been performed lately to detect other genes, different from HLA II genes, responsible for susceptibility to the disease.⁶ The findings still seem unclear. Some of them focus on the HLA class I A antigens (A3, A10, A26, B15, B35, B38, B44, and B60), whereas others on HLA class I B antigens. As for class I B, an increased frequency of a deletion variant of HLA-G has been reported in patients with PV and an association has been found with the allele HLA-E* 0103, which is significantly increased in some PV patients (as well as in other autoimmune patients).⁶ Because PV is considered a

disease with polygenic susceptibility, even non-HLA genes, particularly with reference to polymorphisms in autoantigens, have been recently thought to take a part in its onset.

To date, the link between the genetic background (HLA and non-HLA) and different biological/clinical profiles of PV (localization of lesions, disease severity, antibody titers, response to immunosuppressive treatment) has not been found yet. A better understanding of the genes responsible for the susceptibility to the disease, and particularly of the association of certain genes with a definite risk for falling ill with PV, will lead, in the near future, to a more individually tailored therapy hinged on patient's genetic background.

Yet the genetic predisposition alone, although basic, is not by itself sufficient to initiate the autoimmune pathomechanism leading to the disease, as proven by reports of pemphigus in one of two monozygotic twins⁷ and in only two of three siblings with identical predisposing haplotype.⁸ Therefore, the intervention of environmental-inducing factors seems to be crucial to set off the disease at the beginning (initiating factors) and to maintain it in the subsequent course (perpetuating factors).⁹

Inducing or triggering factors (the seed)

In the majority of patients with pemphigus, no inducing agent seems to exist and the disease apparently starts in a spontaneous manner (spontaneous or idiopathic pemphigus); however, in several cases, a meticulous clinical history detects the presence, often just a slight hint, of facilitating factors (induced or triggered pemphigus).

Induced pemphigus proper refers to a condition where exogenous factors, very often thiol drugs (eg, penicillamine or captopril), play such a major role for the outbreak of lesions that the disease regresses after the inducing factor has been eliminated, even in the absence of any treatment. This condition, which represents the prototype of the previously mentioned variant drug-induced pemphigus, usually differs from true PV for clinical features (resembling pemphigus foliaceus or pemphigus herpetiformis), histology (acantholysis being irregular and not neatly suprabasal), pathogenesis (cell–cell detachment may be non–antibody-mediated but merely due to biochemical mechanisms, ie, formation of thiol drug–cysteine bonds instead of normal cysteine–cysteine bonds with consequent disturbance to keratinocyte cohesion).^{10,11} Thiol-induced pemphigus may have so few characteristics of true pemphigus that the term *pemphigus-like syndrome* often appears more appropriate for this condition.

In *triggered pemphigus*, endogenous predisposing factors are so prevailing that the inducing factor(s) seem(s) to only trigger or facilitate, in a casual and nonspecific manner, a dysimmune mechanism previously programmed and ready to be set off. In this case, despite elimination of the precipitating factor(s), the disease self-perpetuates with all

characteristics of spontaneous pemphigus, in particular of PV (mucocutaneous involvement, suprabasal antibody-mediated acantholysis). Factors able to facilitate PV in genetically predisposed individuals are many and various. Most of them are exogenous, directly originating from the environment (eg, drug intake, viral infections, physical agents, contact allergens, diet); however, also endogenous factors, such as emotional stress, being related to the individual life style, anyway depend on the environmental situation of the subject.⁹

Drug intake

In our experience, drug intake is the most common cause of the outbreak of PV. Grouped according to their chemical structure, the medications suspected of triggering PV on the basis of circumstantial evidence are thiol drugs, phenol drugs, and others (non-thiol non-phenol drugs) (Table 2).

In addition to being responsible for typical drug-induced pemphigus via biochemical mechanisms only (see previously), thiol drugs also can be implicated in precipitating a true, antibody-mediated PV. In fact, the incorporation of thiol drugs into the keratinocyte molecular structure may lead to changes in the antigenic conformation of membrane desmogleins, resulting in the production of anti-desmoglein 1 and 3 antibodies, responsible for immune acantholysis and subsequent true PV. Additionally, by directly interfering

Table 2 Drugs involved in inducing or triggering pemphigus grouped according to their chemical structure

Thiols (drugs containing or releasing a sulfhydryl radical)

- Penicillamine
- Captopril
- Penicillin and its derivatives (aminopenicillins)
- Cephalosporins *
- Piroxicam
- Gold sodium thiomalate
- Thiamazole

Phenols (drugs containing a phenol ring)

- Cephalosporins *
- Aspirin
- Rifampin
- Levodopa
- Heroin
- Pentachlorophenol
- Phenobarbital

Non-thiol non-phenol drugs

- ACE inhibitors other than captopril
- Most NSAIDs
- Nifedipine
- Biological modifiers of the immune response (vaccines, interferons and other cytokines)
- Others

ACE, angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drug.

* Some cephalosporins are both thiol and phenol drugs.

with immunocompetent cells, thiol drugs may cause a general immune imbalance thus amplifying the acantholytic self-injury.^{9,11} The thiol drugs more frequently involved in triggering PV are penicillamine, captopril, and penicillin and its derivatives (chiefly aminopenicillins), piroxicam, gold sodium thiomalate, and thiamazole. It is worth noting that captopril, when added to normal human skin *in vitro* cultures, exactly behaves like pemphigus antibodies, because it: (1) triggers apoptosis¹²; (2) modulates acetylcholinesterase thus reducing the normal aggregating function of keratinocyte acetylcholine receptors and paving the way for cell–cell dishesion¹³; and (3) causes overt acantholysis.¹⁴ As to gold sodium thiomalate, it is a contradictory datum to find this drug among those that can facilitate the onset of pemphigus as well as among those that are used to treat it, being gold salts still included in the alternative therapies for pemphigus.

The mechanism whereby phenol drugs can trigger PV might be related to interleukin (IL)-1 α and tumor necrosis factor- α that phenol-exposed keratinocytes release. These cytokines are known to be involved in the development of acantholysis in PV. They also play a role in the regulation and synthesis of complement and proteases, like plasminogen activator, which also are involved in the acantholytic phenomenon.⁹ Cephalosporins (chiefly the injectable ones, eg, ceftriaxone) and aspirin are widely used phenol drugs often responsible for starting PV in genetically predisposed subjects.

Among the non-thiol, non-phenol drugs capable of facilitating the outbreak of PV, we mention non-thiol angiotensin-converting enzyme (ACE) inhibitors (eg, enalapril), most nonsteroidal anti-inflammatory drugs (NSAIDs), nifedipine, and above all, the biologic modifiers of the immune response such as vaccines, interferons (IFNs), and other cytokines, that may promote the immune acantholysis in several ways: (1) overexpression of target antigens on keratinocyte membrane; (2) overactivation of the immune system with stimulation of antibody production; (3) amplification of the local immune response; and (4) release of plasminogen activators by keratinocytes. Several case reports of PV were associated with vaccinations against influenza or tetanus and diphtheria, IFNs and IL-2 therapy, some of which had a fatal outcome.⁹ Importantly, one study detected pemphigus antibodies in the sera of non-pemphigus patients who were on long-term treatment with IFN- α .¹⁵

Interestingly, some drugs able to promote PV belong to two different categories of “guilty” drugs (eg, captopril is both a thiol and an ACE inhibitor; some cephalosporins have a chemical structure with both a thiol and a phenol ring), which can well account for their high potential of setting up PV in patients with the predisposing genetic background.

Viral infections

Clinical reports and experimental investigations have pointed to the possible role of viral infections, in

particular herpesvirus infections, in the pathogenesis of PV.⁹ In a study of 20 consecutive patients with pemphigus, DNA sequences of herpes simplex virus (HSV), Epstein-Barr virus (EBV), human herpesvirus (HHV)-6 (but not of varicella-zoster virus, cytomegalovirus [CMV] and HHV-8) were detected in the circulating lymphomonocytes and skin lesions of some patients.¹⁶ Pathogenically, it can be supposed that herpetic infection may induce upregulation of humoral and cellular pro-inflammatory factors, thus facilitating the outbreak of PV. In fact, HSV infection has been shown to induce high levels of IFN- γ , IL-4, and IL-10 that, in genetically predisposed subjects, may trigger or increase autoantibody production. Furthermore, herpetic infection can induce the production of autoantibodies through molecular mimicry ensuing from epithelial tissue damage by HSV, with subsequent exposure of immunologically protected autoantigens (such as desmogleins 1 and 3); however, a role of HSV in perpetuating (or slowing down the healing of) preexisting PV lesions cannot be excluded, especially if one considers the lack of normal epithelial barrier in PV lesions and the frequent coexistence in these patients of iatrogenic immunosuppression (steroids and immunosuppressants). The observation that HSV infection is not accompanied by an increase of antidesmogleins antibodies in PV patients questions the role played by HSV in triggering PV.¹⁷ Anyway, the controversy remains,¹⁸ also concerning HHV-8.^{19,20}

The inability to consistently detect a specific herpesvirus in PV patients suggests that viral infection may only be an occasional factor triggering the outbreak or exacerbation of the autoimmune disorder through a nonspecific way in a genetically susceptible host. The same could be said for some anecdotal inductions of PV by other common viral infections (such as flu, cold, other infections of the upper respiratory tract), although in these cases a concurrent facilitating effect might be due to the use of drugs (such as penicillin derivatives, cephalosporins, pyrazolones, and other NSAIDs) usually employed in the management of these infections. The combined effect of viruses and drugs in the induction of certain dysimmune reactions is a well-known event (eg, ampicillin rash in infectious mononucleosis, Reye's syndrome in children with varicella or influenza treated with aspirin). Therefore, it is not senseless to envisage the same combination in some cases of PV. A typical instance is featured by the case report of PV appeared 2 weeks after a coxsackievirus infection treated with an oral cephalosporin (cefixime) to prevent bacterial complications.²¹ A possible explanation for these both virus- and drug-related reactions, often named *paraviral eruptions*, is that virus-infected cells may release endogenous activating substances that, in the presence of external antigenic stimuli (ie, drugs), can function as natural adjuvants to evoke a primary immune response, thus representing the natural initiators of some forms of autoimmunity.²¹

Physical agents

Several physical agents, such as sunburns, ionizing radiation, thermal or electrical burns, and surgical and even cosmetic procedures proved to be able to trigger pemphigus in predisposed individuals.

Ultraviolet (UV) radiation is the most important physical factor in inducing pemphigus. In some cases sunlight induced a transient form of pemphigus *ex novo* in apparently healthy individuals, in others only exacerbated a preexisting PV.⁹ Reports of PV induced by psoralen and ultraviolet A (PUVA) therapy suggest that the A band alone of UV radiation is responsible for the inducing effect.

Ionizing radiation can trigger PV as repeatedly reported in the literature. Skin lesions usually begin in the irradiated area and subsequently spread to other cutaneous or mucosal sites. The relationship between ionizing radiation and onset of pemphigus lesions is usually clear and sometimes even impressive, as documented by the outbreak of PV with cutaneous involvement confined to the skin within the therapeutic radiation portal.²² In many cases, however, the inducing role of ionizing radiation can be questioned by the coexisting tumor that required radiotherapy and that itself might have been pathogenically linked with the bullous disease (paraneoplastic or radiation-induced pemphigus?). It has been known for a long time that UV and ionizing radiations can alter on one side the biochemistry of epidermis, and on the other the regulatory mechanisms of autoimmunity.^{9,23}

As with ionizing radiation, pemphigus lesions following thermal or electrical burns^{24,25} usually appear within and adjacent to the burned areas and subsequently extend to other skin regions and often to the oral cavity. The operating pathomechanism may hinge on the release of self-antigens (desmogleins 1 and 3), pro-inflammatory mediators, and possibly cryptic peptides that is provoked by the thermal or electrical tissue injury.²⁵ These stimuli, in pemphigus-prone individuals, can set off the specific antibody production (antidesmoglein antibodies) responsible for the immune-mediated acantholysis.

Surgery and cosmetic procedures also have been reported to be exogenous factors capable of favoring the onset or the recurrence of PV.⁹ No relation has been found between the type of surgical procedure and the outbreak of pemphigus lesions because they appeared following skin grafting, electrosurgery (here with a concurring thermal effect), hair transplantation, facelift, reduction mammoplasty, and so on. In some patients, the onset or recurrence of the pemphigus lesions occurred in drainage sites. Dermabrasion and chemical peels also favored acantholytic lesions in pemphigus-prone individuals, but a synergic chemical effect (phenol is itself a pemphigus-inducing substance) cannot be excluded in these cases. In all the circumstances just cited, mechanical, chemical, and inflammatory stimuli may concurrently have a part in paving the way for the outbreak

of PV in predisposed individuals. Sometimes simple Koebner isomorphic response may be evoked.⁹

Contact allergens

Some chemicals can exacerbate or even trigger PV with mediation of allergic contact dermatitis (ACD).⁹ The chemicals more implicated in this condition often are known as common sensitizers in various fields of work, such as photographic developing, dry cleaning, industrial solvent work, gardening, and chiefly intensive agriculture. In fact, several cases of PV following repeated contact with pesticides have been reported, the most paradigmatic of which is the one that occurred in a young farmer, in whom blistering started as an ACD to 1,3-dichloropropene (a soil fumigant he used as a field pesticide) and then shifted to PV, probably because of the patient's pemphigus-prone genetic background.²⁶ An international survey showed that exposure to pesticides is actually associated with an increased risk for PV.²⁷ The same study and another one²⁸ revealed that PV is more common in nonsmokers than in smokers. Taken together, these data support the pathogenic role of the keratinocyte–acetylcholine axis in PV (see Etiopathogenesis section). In fact, nicotine, a cholinergic agonist, by interfering with these antiacetylcholine receptor antibodies, can act as a protective factor against cell–cell detachment, accounting for the inverse association between smoking and PV. Conversely, organophosphate pesticides are known to block the nicotinic acetylcholinesterase channel, resulting in the accumulation of acetylcholine at cholinergic receptors. Chronic exposure to pesticides induces tolerance to their toxicity with consequent decrease of muscarinic and nicotinic receptors in the nervous system and in the skin (down-regulation). As a result, reduction of cell–cell adhesion ensues in the epidermis, which accounts for the direct association between exposure to pesticides and occurrence of PV.^{9,27}

Dietary factors

Nutritional factors are rarely mentioned as possible pemphigus inducers²⁹; however, epidemiologic, clinical, and experimental data collected on the subject in recent years have allowed the inclusion of dietary factors into the ever growing list of environmental agents capable of facilitating PV in genetically predisposed individuals. For a long time, the high incidence of PV in Russian Jews has been linked with the strong presence of spices in the diet habits of this ethnic group. Several cases of PV related to dietary factors have been reported⁹ and most of them point to a high consumption of edible plants belonging to the genus *Allium* (ie, garlic, leeks, and onion). These plants are rich in thiol allyl compounds with an *in vitro* proven acantholytic potential.³⁰ Also tannins, polyphenolic compounds contained in several edible plants, fruits, and their derivatives

(eg, black pepper, red chili pepper, cherry, cranberry, blackberry, red wine, and tea), have been suspected of favoring the onset of PV in pemphigus-prone patients. Interestingly, tannins are immunologically reactive and also able to cause *in vitro* acantholysis.^{31,32} In this view, one might wonder whether high consumptions of garlic, red chili pepper, and tea are linked to the high incidence of PV in India. Who can say or deny it?

Taken together, these epidemiologic, clinical, and experimental data support the belief that some nutrients, with chemical structures similar to those of certain pemphigus-inducing drugs (thiol and phenol drugs), may actually have an acantholytic potential over time. Because acantholysis-prone individuals are probably pemphigus-prone individuals due to their easier releasing of keratinocyte-sequestered antigens, the possibility exists that, in genetically predisposed individuals, the abundant and continual ingestion of thiol allyl compounds and/or tannins favors the onset or the maintenance of PV lesions. In fact, these substances may either be incorporated into keratinocytes, thus leading to simple biochemical acantholysis, or may release sequestered desmoglein antigens from immunologically privileged sites and also interfere with the immune balance, thus leading to antibody-mediated immunologic acantholysis. As it occurs with the thiol drugs, a combined mechanism is also possible.^{9,29}

Emotional stress

The skin, nervous system, and immune system are interconnected, use the same language (cytokines and neurotransmitters), and functionally represent a unique neuroimmunocutaneous system,³³ which can well account for a pathogenic link between an intensive emotional stress and the onset (or the worsening) of an autoimmune skin disorder. Several cases of PV triggered by emotional stress have been reported.^{9,34,35} The stressing events more frequently associated were environmental disasters, war, terrorism, partner's or near relative's death, separation from partner, sexual aggression or sex-related disturbance. In each case, these events had been lived in a highly emotional way. In our opinion, the role of psychological stress in triggering PV is still underestimated and, in most cases of apparently spontaneous PV, both patient and doctor overlook the intervention of an emotional precipitating factor. In fact, a clinical investigation of 13 consecutive pemphigus patients with personality disorders revealed that 12 of them had experienced a stressful event during the year preceding the onset of the immune disorder.³⁴ A more recent study has shown that stress can play a triggering part in pemphigus apart from any underlying personality disorders.³⁵

Finally, bearing in mind the previously discussed link between herpesvirus and PV, it is of interest to recall here that the immune response to latent herpesvirus (HSV, CMV, EBV) is altered by stressful events,³⁶ as proven by the common observation of herpes simplex recurrences triggered

by psychological stress. Therefore, three events can be pathogenically interconnected: emotional stress, herpetic infections, outbreak or worsening of PV.

A provocative question

The possible intervention of the environment in the outbreak of PV is ever more perceived by clinicians. In fact, there are some reports of induced or triggered pemphigus claiming more than one environmental factor as causal or precipitating agent (eg, penicillamine and captopril acting simultaneously³⁷), two viral infections (common cold and herpes simplex labialis) treated with a combination drug composed of paracetamol, caffeine, chlorpheniramine maleate and phenylephrine HCl,³⁸ surgical trauma and sunbathing occurring in different times,³⁹ concurring action of sunbathing, aspirin, other NSAIDs, and progesterone,⁴⁰ combined effect of contact dermatitis and sun exposure.⁴¹

It is also of note that several drugs that are capable of inducing pemphigus share an active amide group in their molecule,⁴² which might lead to considering further and so far unexplored pathomechanisms of induction.

Probably, in the future, the more patients' clinical history and laboratory investigations (aimed at the search for possible environmental-inducing factors) are meticulous and exhaustive, the fewer cases of spontaneous pemphigus will be found. Even today, the assumption that genetic factors alone are not sufficient to provoke the outbreak of pemphigus,^{7,8} inevitably raises a provocative question: Does spontaneous pemphigus actually exist or is the outbreak of the disease always a result of an interaction between an individual pemphigus-prone genetic background and environmental-inducing agents, often concealed or apparently harmless such as diet ingredients or emotional stress?

We think that a thorough investigation on induced or triggered pemphigus, aimed at detecting environmental-provoking or precipitating factors and relative pathogenic mechanisms, is of the utmost importance for both speculative and practical purposes. From the conjectural view, the study of the mechanisms operating in induced pemphigus will also elucidate some obscure etiopathogenic aspects pertaining to idiopathic pemphigus (if it really exists). In routine practice, avoiding or limiting the interaction of environmental-triggering factors with the pemphigus-prone genetic background is a useful precaution in the management of pemphigus patients because it can improve the efficacy of conventional treatments, reduce risks for relapses and, in some cases (induced pemphigus proper), even result in a cure.⁴³

References

1. Joly P, Litrowski N. Pemphigus group (vulgaris, vegetans, foliaceus, herpetiformis, brasiliensis). Clin Dermatol 2011;29:432-6.

2. Beutner E, Jordon R. Demonstration of skin antibodies in sera of pemphigus vulgaris patients by indirect immunofluorescent staining. *Proc Soc Exp Biol Med* 1964;117:505-10.
3. Baroni A, Lanza A, Cirillo N, Brunetti G, Ruocco E, Ruocco V. Vesicular and bullous disorders: pemphigus. *Dermatol Clin* 2007;25:597-603.
4. Grando SA, Bystryk JC, Chernyavsky AI, et al. Apoptolysis: a novel mechanism of skin blistering in pemphigus vulgaris linking apoptotic pathways to basal cell shrinkage and suprabasal acantholysis. *Exp Dermatol* 2009;18:764-70.
5. Lombardi ML, Mercurio O, Ruocco V, et al. Common human leukocyte antigen alleles in pemphigus vulgaris and pemphigus foliaceus Italian patients. *J Invest Dermatol* 1999;113:107-10.
6. Sinha AA. The genetics of pemphigus. *Dermatol Clin* 2011;29:381-91.
7. Ruocco V, Peluso G, Pisani M. Pemphigus vulgaris in only one of two monozygotic twins. *J Am Acad Dermatol* 1985;12:587-9.
8. Revenga-Arranz F, Martínez-Lasso J, Vanaclocha-Sebastián F. Pemphigus in two MHC-haploidentical brothers. *Dermatology* 1996;193:71-2.
9. Ruocco V, Ruocco E. Pemphigus and environmental factors. *G Ital Dermatol Venereol* 2003;138:299-309.
10. Ruocco V, Pisani M, de Angelis E, Lombardi ML. Biochemical acantholysis provoked by thiol drugs. *Arch Dermatol* 1990;126:965-6.
11. Ruocco V, de Angelis E, Lombardi ML. Drug-induced pemphigus. II. Pathomechanisms and experimental investigations. *Clin Dermatol* 1993;11:507-13.
12. Baroni A, Buommino E, Paoletti I, Orlando M, Ruocco E, Ruocco V. Pemphigus serum and captopril induce shock protein 70 and inducible nitric oxide synthase overexpression, triggering apoptosis in human keratinocytes. *Br J Dermatol* 2004;150:1070-80.
13. Baroni A, Buommino E, Ruocco E, et al. Captopril modulates acetylcholinesterase in human keratinocytes. *Arch Dermatol Res* 2011;303:491-7.
14. Ruocco V, de Angelis E, Lombardi ML, Pisani M. In vitro acantholysis by captopril and thiopronine. *Dermatologica* 1988;176:115-23.
15. Fleischmann M, Célérier P, Bernard P, Litoux P, Dreno B. Long-term interferon-alpha therapy induces autoantibodies against epidermis. *Dermatology* 1996;192:50-5.
16. Tufano MA, Baroni A, Buommino E, Ruocco E, Lombardi ML, Ruocco V. Detection of herpesvirus DNA in peripheral blood mononuclear cells and skin lesions of patients with pemphigus by polymerase chain reaction. *Br J Dermatol* 1999;141:1033-9.
17. Caldarola G, Kneisel A, Hertl M, Feliciani C. Herpes simplex virus infection in pemphigus vulgaris: clinical and immunological considerations. *Eur J Dermatol* 2008;18:440-3.
18. Hocar O, Zidane W, Laissaoui K, Akhdari N, Amal S. L'infection herpétique au cours du pemphigus. *Médecine et maladies infectieuses* 2009;39:64-5.
19. Meibodi NT, Nahidi Y, Mahmoudi M, et al. Evaluation of coexistence of the Human Herpesvirus type 8 (HHV-8) infection and pemphigus. *Int J Dermatol* 2010;49:780-3.
20. Esmaili N, Hallaji Z, Abedini R, Soori T, Mortazavi H, Chams-Davatchi C. Pemphigus vulgaris and herpesviruses: is there any relationship? *Int J Dermatol* 2010;49:1261-5.
21. Ruocco E, Lo Schiavo A, Baroni A, et al. Pemphigus vulgaris after coxsackievirus infection and cephalosporin treatment: a paraviral eruption? *Dermatology* 2008;216:317-9.
22. Robbins AC, Lazarova Z, Janson MM, Fairley JA. Pemphigus vulgaris presenting in a radiation portal. *J Am Acad Dermatol* 2007;56:S82-5.
23. Ruocco V, Pisani M. Induced pemphigus. *Arch Dermatol Res* 1982;274:123-40.
24. Vignale R, Espasandin J, Cassinelli A, Casella de Vilboa E, Gonzalez V. Pemphigus vulgaris after electrosurgery (thermal-heat therapy) of a basal cell carcinoma. *Int J Dermatol* 1993;32:307-8.
25. Tan SR, McDermott MR, Castillo CJ, Sauder DN. Pemphigus vulgaris induced by electrical injury. *Cutis* 2006;77:161-5.
26. Voza A, Ruocco V, Brenner S, Wolf R. Contact pemphigus. *Int J Dermatol* 1996;35:199-201.
27. Brenner S, Tur E, Shapiro J, et al. Pemphigus vulgaris: environmental factors. Occupational, behavioral, medical, and qualitative food frequency questionnaire. *Int J Dermatol* 2001;40:562-9.
28. Valikhani M, Kavusi S, Chams-Davatchi C, et al. Pemphigus and associated environmental factors: a case-control study. *Clin Exp Dermatol* 2007;32:256-60.
29. Ruocco V, Brenner S, Ruocco E. Pemphigus and diet: does a link exist? *Int J Dermatol* 2001;40:161-3.
30. Brenner S, Ruocco V, Wolf R, de Angelis E, Lombardi ML. Pemphigus and dietary factors. In vitro acantholysis by allyl compounds of the genus *Allium*. *Dermatology* 1995;190:197-202.
31. Brenner S, Ruocco V, Ruocco E, et al. In vitro tannin acantholysis. *Int J Dermatol* 2000;39:738-42.
32. Feliciani C, Ruocco E, Zampetti A, et al. Tannic acid induces in vitro acantholysis of keratinocytes via IL-1 α and TNF- α . *Int J Immunopathol Pharmacol* 2007;20:289-99.
33. Misery L. Skin, immunity and nervous system. *Br J Dermatol* 1997;137:843-50.
34. Cremniter D, Baudin M, Roujeau JC, et al. Stressful life events as potential triggers of pemphigus. *Arch Dermatol* 1998;134:1486-7.
35. Morell-Dubois S, Carpentier O, Cottencin O, et al. Stressful life events and pemphigus. *Dermatology* 2008;216:104-8.
36. Ader R, Cohen N, Felten D. Psychoneuroimmunology: interactions between the nervous system and the immune system. *Lancet* 1995;345:99-103.
37. Blanken R, Doeglas HMG, de Jong MCJM, Kardaun SH, van Leeuwen M. Pemphigus-like eruption induced by D-penicillamine and captopril, in the same patient. *Acta Derm Venereol (Stockh)* 1988;68:456-7.
38. Brenner S, Hodak E, Dasclu D, Lurie R, Wolf R. A possible case of drug-induced familial pemphigus. *Acta Derm Venereol (Stockh)* 1990;70:357-8.
39. Arpaia N, Loconsole F, Mastrodonato M, Rantuccio F. Isomorfismo reattivo da fotoesposizione in un caso di pemfigo volgare. *Dermatologia Clinica* 1993;13:232-4.
40. Satriano RA, Fiorentini E, Tripodi Cutri F, Muto L. A case of multi-triggered pemphigus vulgaris. *G Ital Dermatol Venereol* 1999;134:595-8.
41. Orion E, Barzilai D, Brenner S. Pemphigus vulgaris induced by diazinon and sun exposure. *Dermatology* 2000;201:378-9.
42. Wolf R, Brenner S. An active amide group in the molecule of drugs that induce pemphigus: a casual or causal relationship? *Dermatology* 1994;189:1-4.
43. Ruocco E, Aurilia A, Ruocco V. Precautions and suggestions for pemphigus patients. *Dermatology* 2001;203:201-7.