The immunopathology of pemphigus vulgaris: recent advances[1]

Maryann Fitzmaurice, M.D., Ph.D.

Aspects of the etiology, clinical presentation and course, diagnosis, and treatment of pemphigus vulgaris are reviewed. Recent advances in the immunopathology of pemphigus vulgaris are also discussed, with emphasis on studies in tissue-culture models with pathogenetic significance.

Index term: Pemphigus

Cleve Clin Q 53:283–289, Fall 1986

A rare but potentially devastating autoimmune blistering disease, primarily afflicting the aged, pemphigus vulgaris has only recently been treated successfully. Intense study of the disease has greatly advanced our knowledge and understanding of its immunopathology. Such study has uncovered a previously unrecognized mechanism of immunologic injury, which may help in the future to explain a host of as yet unexplained autoimmune diseases.

Pemphigus vulgaris was first described in 1791 when Wichman[1] published a case report of a patient with a devastating blistering disease affecting the skin and mucous membranes.

> When [the patient was] first seen . . . large areas of skin were deprived of their epithelium . . . denuded, like a like a scald. The mucous membranes of the mouth exhibited many wounds so that the patient could take only liquids. . . . The blisters were not raised but flat, the heighth and size of an almond and always broke soon. . . . Even when the [epithelium] was not detached by the underlying moisture it was loose and wrinkled, so that it could be moved.

[1] Department of Immunopathology, The Cleveland Clinic Foundation. Submitted for publication Dec 1985; accepted June 1986. pa

0009-8787/86/03/0283/07/$2.75/0

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Pemphigus vulgaris is one of a group of autoimmune skin diseases classified as noninflammatory vesiculobullous dermatoses, in which skin and mucous-membrane vesicles or bullae develop in association with deposits of antiepithelial antibodies of restricted specificity. This somewhat heterogeneous group of dermatoses includes several forms of pemphigus, several forms of pemphigoid, and dermatitis herpetiformis, among others.

Epidemiology

Currently, two forms of pemphigus are recognized: pemphigus vulgaris (and its variant pemphigus vegetans) and pemphigus foliaceus (and its variant pemphigus erythematosus).[2] Pemphigus vulgaris is the most common form, accounting for approximately 80% of cases. Still, it is a relatively rare disease, with an incidence of less than 1 per 100,000 in the United States.[3] In fact, a recent survey of dermatologists identified fewer than 300 patients nationwide.[4] Most of these patients are being cared for at a relatively small number of referral centers across the country, including The Cleveland Clinic Foundation and neighboring University Hospitals of Cleveland. Pemphigus vulgaris is also the most severe form of pemphigus: its generalized stage is one of the few medical emergencies in dermatology.

Clinical presentation and course

Pemphigus vulgaris is primarily a disease of the middle-aged and aged,[5] although an increasing number of cases of juvenile[6] and childhood[7] pemphigus are being reported each year. It shows no apparent sexual predilection, which is commonly seen in other autoimmune diseases. Although it is rarely reported to be familial, it is clearly not hereditary in the classical sense. There is, however, a higher incidence of pemphigus in Jewish and Mediterranean peoples as well as a higher-than-normal frequency of HLA-A10[8] and HLA-DRw4[9] histocompatibility types among pemphigus patients.

Pemphigus vulgaris is frequently associated with other autoimmune diseases, most commonly, systemic lupus erythematosus[10] and myasthenia gravis.[11] It is also frequently associated with neoplasia, most frequently with thymoma,[12] but is also associated with other lymphoid and nonlymphoid malignancies.[4]

Pemphigus vulgaris is rarely preceded by an identifiable prodrome, and no predisposing factors have been identified.[5] The disease classically presents with intraepithelial bullae on a nonerythematous base. The bullae are usually seen first in the oral mucosa,[13] followed by the glabrous skin of the trunk, axilla, and groin, but have also rarely been seen in the mucous membranes of the gastrointestinal[14] and female genital tracts.[15] Because of their characteristically superficial location within the epithelium, the bullae are flaccid, easily broken, heal with difficulty, and spread peripherally (the basis of the Nikolsky sign).[16] Fresh bullae may be painful, pustular, or hemorrhagic, but usually not pruritic. Older bullae occasionally heal with hyperpigmentation, but not scarring.

Left untreated, pemphigus vulgaris follows a chronic, progressive, and ultimately fatal course. The bullae spread and coalesce, denuding large areas of the skin and mucous membranes. Involvement of the oral mucosa frequently results in severe dysphagia and subsequent malnutrition. Loss of the epidermal barrier frequently results in severe fluid and electrolyte imbalance and overwhelming infection, as seen in traumatic burn victims. In fact, the most common cause of death in pemphigus vulgaris patients is staphylococcal septicemia.[17]

Diagnosis

Today, the diagnosis of pemphigus vulgaris is based not only on its clinical presentation but also on the results of histologic and immunologic evaluation of skin and mucous membrane biopsies as well as on serologic studies. At one time, cytologic examination of material scraped from the base of skin or mucous membrane bullae (the Tzank test)[18] was used almost exclusively for the diagnosis of pemphigus vulgaris. However, a biopsy taken from the peripherally spreading border of a new bulla is now considered crucial in making the diagnosis.

In 1953, Lever[19] was the first to make clear the histologic distinction between pemphigus vulgaris and clinically similar noninflammatory vesiculobullous dermatoses. The earliest histologic change seen in skin and mucous membrane biopsy specimens in pemphigus vulgaris is epithelial spongiosis, with both intercellular edema and loss of intercellular bridges. This is sometimes associated with intraepithelial collections of eosinophils, in which case the histologic change is re-

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ferred to as *eosinophilic spongiosis*. As pemphigus vulgaris lesions progress, epithelial acantholysis (loss of cell-to-cell cohesion) becomes prominent. Eventually, intraepithelial clefts form and coalesce to produce distinct acantholytic bullae. The bullae characteristically lie suprabasilarly within the epithelium and are filled with proteinaceous fluid and free-floating acantholytic cells. These cells are histologically distinct (having large hyperchromatic nuclei and condensed eosinophilic cytoplasm) and, although not pathognomonic, are the hallmark of pemphigus vulgaris.

Auspitz[20] was probably the first to observe acantholysis in pemphigus vulgaris. However, Civatte[21] is credited as being the first to recognize its pathologic significance in bulla formation. Acantholysis was once thought to result instead from disruption of desmosomal attachments between epithelial cells. However, electron microscopy has shown acantholysis to result directly from dissolution of the intercellular substance, a glycocalyx-like substance thought to be partly responsible for epithelial cell cohesion, with only secondary loss of desmosomal attachments.[22]

The most significant advance in the diagnosis of pemphigus vulgaris was the detection of tissue-bound and circulating pemphigus antibodies using immunofluorescence techniques, first reported by Jordon[23] and Beutner et al.[24] Tissue-bound pemphigus antibodies are detected by direct immunofluorescence in skin and mucous membrane lesions from virtually 100% of pemphigus vulgaris patients. Circulating pemphigus antibodies are detected by indirect immunofluorescence on a variety of tissue substrates in sera from 80% to 90% of untreated patients. In both cases, pemphigus antibodies are seen as a network of fluorescence within the intercellular spaces of the epithelium. The fluorescence due to pemphigus antibodies is linear, indicating the presence of specific antiepithelial antibodies rather than nonspecific immune complexes.

Tissue-bound pemphigus antibodies detected by direct immunofluorescence and circulating pemphigus antibodies detected by indirect immunofluorescence are almost exclusively IgG immunoglobulins and are probably both κ and λ light-chain types[25] of all four subclasses, G1, G2, G3, and G4.[26] It was once thought that these pemphigus antibodies were directed against desmosomal constituents. However, electron microscopy has shown that they are actually directed against antigens (pemphigus antigens) in the glycocalyx-like intercellular substance.[27]

Tissue-bound pemphigus antibodies detected by direct immunofluorescence are virtually pathognomonic of pemphigus vulgaris. However, circulating "pemphigus-like" antibodies detected by indirect immunofluorescence may rarely be seen in other diseases. Fortunately, the few serologic false positives for pemphigus vulgaris are generally not seen in patients with other bullous dermatoses, but rather in patients with severe thermal burns, drug reactions, or abnormally high isohemagglutinin titers.[28] There are, however, a few reports of "pemphigus-like" antibodies in patients with bullous or cicatricial pemphigoid.[29]

Circulating pemphigus antibody titers determined by indirect immunofluorescence have been found to correlate well with disease activity in pemphigus vulgaris.[30] However, the use of pemphigus antibody titers to evaluate clinical status and response to treatment is still controversial. This is, at least in part, because the tissue substrates used to determine the antibody titers by indirect immunofluorescence vary.[31]

The most recent advance in the diagnosis of pemphigus vulgaris is the use of complement studies.[32] Total hemolytic complement has been found to be lower in blister fluid than in serum in pemphigus patients, indicating local activation of complement within pemphigus bullae. In fact, the individual complement components C1q, C4, C2, C3, C5, and C3PA have all been found to be lower in blister fluid. Direct immunofluorescence has also occasionally shown complement deposition, principally C3 but also C1, C4, properidin, and factor B, in both skin and mucous membrane lesions from pemphigus patients, indicating activation of both the classical and alternate complement pathways. Only recently, however, have pemphigus antibodies been shown to fix complement in vitro.[33–35] In fact, indirect immunofluorescence has shown C1q, C4, and C2 to be fixed in vitro by at least some pemphigus antibodies.

Treatment

Treatment of pemphigus vulgaris today is less empirical and symptomatic than in the past. Nonspecific immunosuppressants, including systemic corticosteroids and cytotoxic agents, are the mainstays of therapy. Currently, the treatment of choice for most patients is a combination of

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tapering, alternate-day prednisone (frequently requiring initial doses of 100 mg/day or higher) and low-dose methotrexate[36] or azathioprine.[37] Gold therapy[38] may have a role in long-term maintenance or in treatment of patients who do not respond to more conventional therapy. Adjuvant immunotherapies, such as plasmapheresis,[39] are still largely experimental and have been used in only a few clinical trials. In any event, the side effects of such aggressive immunosuppressive therapy can be as severe as the disease itself. Therefore, despite treatment, mortality from pemphigus vulgaris remains at about 10%.

Etiology

A wide variety of etiologies has been proposed for pemphigus vulgaris over the years. One of the earliest proposed was enzymic lysis. This was based, first, on detection of proteolytic activity in blister fluid from pemphigus patients[40] and, second, on the experimental induction of bullae in human volunteers by topical application of proteolytic enzymes such as chymotrypsin.[41] This early concept has now been overshadowed by an autoimmune etiology for pemphigus vulgaris.

Immunopathologic studies

Although there is little question as to the autoimmune etiology of pemphigus vulgaris, questions remain concerning its pathogenesis. What is pemphigus antigen exactly? Are pemphigus antibodies truly pathogenic? And, if so, by what mechanism do they produce immunologic injury?

What is pemphigus antigen? Early immunofluorescence and electron microscopy studies showed pemphigus antigen to be localized in the intercellular substance. Beyond this, little was known about the nature of the antigen itself.

Most of what was known about pemphigus antigen had been learned from studies of the antigen in situ. It had long been known that the intercellular substance was rich in carbohydrates. This was initially shown by staining the intercellular substance with carbohydrate-specific histochemical stains (such as periodic acid Schiff's silver,[42] phosphotungstic acid,[43] and lanthanum[44]). Next, the intercellular substance was shown to consist of carbohydrate-rich macromolecules (such as glycoproteins and glycolipids), which contain the monosaccharides glucose, glucosamine, galactose, galactosamine, and mannose as part of their carbohydrate moieties. This was shown by staining the intercellular substance with a variety of lectins, a class of plant and animal agglutinins with more restricted, antibody-like monosaccharide-binding specificity (including concanavilin A, wheat germ agglutinin, *Ricinus communis* agglutinin, *Limulus polyphemus* agglutinin, *Ulex europaeus* agglutinin, and lotus A), using direct fluorescence techniques.[45–47] More recently, Fitzmaurice and Deodhar[48] showed that the monosaccharides glucose, galactose, and galactosamine are not only part of the carbohydrate moiety of pemphigus antigen itself, but are, more specifically, a part of its antigenic site. This was shown by inhibiting the binding of pemphigus antibody to pemphigus antigen with these monosaccharides, using an indirect immunofluorescence technique.

Early attempts to isolate pemphigus antigen for further physicochemical characterization in vitro were limited by the lability of the antigen under harsh extraction and purification conditions. More recent attempts to isolate pemphigus antigen from both tissue (human epidermis[49]) and body fluids (human saliva[50] and urine[51]) using gentler extraction and purification techniques have proved more successful: Stanley et al[52] isolated a glycoprotein (210,000 molecular weight) from human epidermal-cell cultures that reacts with pemphigus antibodies in an immunoblot assay. Their in vitro work suggests that the earlier in situ work characterizing pemphigus antigen as a carbohydrate-rich macromolecule, specifically a glycoprotein, was correct. Perhaps further physicochemical characterization of the glycoprotein in vitro will also confirm the conclusion of the earlier in situ work that the carbohydrate moiety of pemphigus antigen is part of its antigenic site.

Are pemphigus antibodies pathogenic? The most persuasive answers to this question have come from classic passive-transfer studies. Early attempts to passively transfer pemphigus were only moderately successful: passive transfer of human pemphigus antibody via intravenous infusion into adult monkeys produced antibody deposits but did not produce skin or mucous membrane bullae.[53] Recently, however, Anhalt et al[54] produced both antibody deposits and bullae in skin and mucous membranes by passive transfer of human pemphigus antibody via intraperitoneal injection into newborn mice. Finally, nature has performed the ultimate passive-transfer experiments. Wasserstrum and Laros[55] re-

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cently reported transplacental transmission of pemphigus vulgaris in a pregnant woman, resulting in intrauterine fetal death. These studies strongly suggest that pemphigus antibodies are, in fact, pathogenic.

What is the mechanism by which the immunologic injury is produced? The most persuasive answers to this question have come from work in a variety of tissue-culture models. This work has unified the early concept of enzymic lysis with the later concept of an autoimmune etiology and has proposed a previously unrecognized mechanism of immunologic injury.

In the 1970s there were a number of reports, including the initial reports of Michel and Ko,[56,57] of acantholytic bullae production in human skin organ-cultured with pemphigus antibody but without complement. Histologic studies showed these bullae are indistinguishable from those seen in pemphigus vulgaris patients. Electron microscopic studies confirmed that the acantholysis resulted from dissolution of the intercellular substance rather than loss of desmosomal attachments.[58] These findings suggested that pemphigus antibody produced its acantholytic injury by a mechanism other than the classic, immunologic mechanism of antibody-dependent, complement-mediated lysis.

More recently, Fitzmaurice and Deodhar[59] reported production of acantholytic bullae in human skin organ-cultured with two lectins, *Ricinus communis* agglutinin 60 and 120, which bind like pemphigus antibody to the intercellular substance but do not have the antibody-related functions of complement fixation, etc. Histologic studies showed these bullae are similar to those seen in pemphigus vulgaris patients. Electron microscopic confirmation is in progress. These studies again suggest that acantholysis is not necessarily the result of antibody-dependent, complement-mediated lysis, but perhaps of some other mechanism.

In 1979, Schiltz et al[60] isolated an "acantholytic factor," believed to be a nonlysosomal epidermal proteinase, produced by human skin organ-cultured in the presence of pemphigus antibody. In 1981, Moroika et al[61] showed that certain nonspecific proteinase inhibitors, including soybean trypsin inhibitor, can inhibit pemphigus antibody–mediated acantholysis in organ-cultured human skin. These findings strongly suggest that pemphigus antibody produces its acantholytic injury, not by the classical immunologic mechanism of antibody-dependent, complement-mediated lysis, but rather by stimulating the release of epidermal proteinases, which digest the intercellular substance.[62] More recently, Moroika et al[63] suggested that the serine proteinases of the plasminogen-plasminogen activator system may be among those involved in pemphigus antibody–mediated acantholysis in the in vitro organ-culture model.

Work done in a cell-culture model has lent further support to the newly proposed mechanism of acantholysis via epidermal proteinase activation. In 1978, Diaz and Marcelo[64] and Farb et al[65] reported acantholylic detachment from plastic substrates of epidermal cells cultured with pemphigus antibody. Again, pemphigus antibody apparently produced acantholylic detachment by activating epidermal proteinases that could be inhibited by nonspecific proteinase inhibitors, including soybean trysin inhibitor. In 1983, Hashimoto et al[66] also suggested that the serine proteinases of the plasminogen-plasminogen activator system may be among those involved in pemphigus antibody–mediated detachment in the in vitro cell-culture model. In 1985, Kawana et al[67] further suggested that the complement system may enhance the effects of pemphigus antibody and the proteinases it activates in this model.

Although we now have some understanding of the nature of pemphigus antigen, the pathogenicity of pemphigus antibody, and the mechanism of immunologic injury in pemphigus vulgaris, one question remains. How are pemphigus antibodies produced in the first place? The answer may come from work in a mitogen-stimulated, peripheral-blood cell-culture model that allows manipulation of the immunocyte populations involved (B lymphocytes, T lymphocytes, and monocytes). Using this model system with pokeweed-mitogen stimulation, both Ahmed et al[68] and Fitzmaurice and Deodhar[69] recently found that the peripheral-blood mononuclear cells from pemphigus vulgaris patients produced pemphigus antibodies. However, future application of the peripheral blood cell–culture model to study of the immunopathogenesis of pemphigus will require a more sensitive assay for pemphigus antibody than the currently available indirect immunofluorescence assay. Fortunately, more sensitive assays for pemphigus antibody, such as a solid-phase, enzyme-linked immunoassay or radioimmunoassay,[70] are being developed.

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Maryann Fitzmaurice, M.D., Ph.D.
Department of Immunopathology
The Cleveland Clinic Foundation
9500 Euclid Ave.
Cleveland, OH 44106

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