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Pemphigus

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Individual cells of the skin and mucosa, the keratinocytes, are anchored to one another and to the underlying connective tissue by a number of adhesive mechanisms that secure tissue integrity, resist mechanical trauma, prevent microorganisms from entering into the body, and protect from fluid loss. Epithelial cell-to-cell adhesion above the basal keratinocyte layer (ie, intraepithelial cell adhesion) is secured by specific adhesion complexes known as desmosomes [1–5]. In pemphigus patients, an autoimmune process disrupts desmosome function, leading to a breakdown of cutaneous and mucosal barriers. Characteristic is the presence of autoantibodies (IgG or IgA) against structural components of desmosomes resulting in epithelial cell separation (acantholysis) (Fig. 1). This process is clinically evident as intraepithelial blister formation, hence the term ''pemphigus,'' derived from the Greek word p*emphix* (bubble or blister). Research investigating epithelial blistering diseases led to the classification of more than 10 different disease types and subtypes currently categorized in the pemphigus group [6]. Of these, oral lesions are commonly seen in pemphigus vulgaris (PV), in paraneoplastic pemphigus (PNP), and in cases of pemphigus associated with inflammatory bowel disease [7–10]. PV and PNP warrant particular knowledge among dental professionals because the mucosal membranes are frequently involvement, even in early stages of disease. Recent evidence indicates that there are two phenotypes of PV, mucosal-dominant and mucocutaneous, with possible shifting from one to the other over time.

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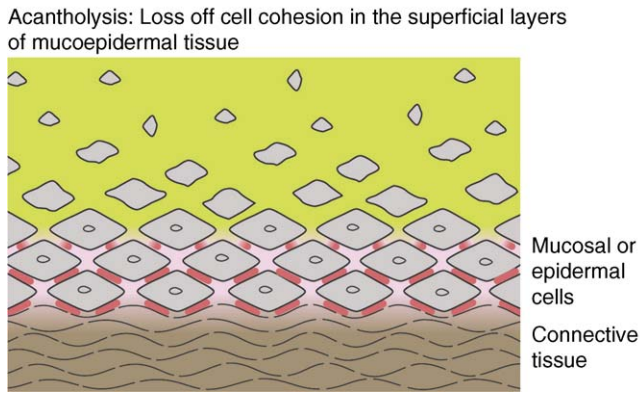

Fig. 1. Binding of antibodies to desmosomal components is associated with acantholysis in pemphigus.

Pemphigus vulgaris

Epidemiology

PV is an uncommon disease with an annual incidence of 1 to 5 per million population per year [11,12]. It most commonly develops in the fourth to sixth decades of life. A genetic predisposition linked to HLA class II alleles seems to be of some significance, because it has been shown to occur with increased frequency in certain ethnic groups and within families [13–17]. Ashkenazi Jews and persons of Mediterranean origin are especially at risk for pemphigus.

Pathophysiology

The origin of PV is unknown, but compelling evidence exists that the epithelial breakdown in PV is mediated by autoantibodies of the IgG type. This understanding stems from passive transfer experiments in which purified autoantibodies from PV patient sera were shown to induce blisters in skin-organ culture as well as in the skin and mucous membranes of neonatal mice [18–20]. When, on the other hand, the pathogenic autoantibodies were absorbed out from the patients' sera, bullae were no longer formed in the mice [21]. Blisters occur in the epidermis and the mucous membranes, where the IgG autoantibodies target two structural proteins of the desmosomes identified as desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3). A new pemphigus antigen, desmoglein 4, has recently been discovered and implicated in the pathogenesis of PV [22,23]. Research into the regional distribution of Dsg1 and Dsg3 revealed that Dsg1 is found throughout all layers of the skin, whereas Dsg3 is found only in two or three layers of the deep epidermis [24,25]. In contrast, Dsg3 is predominantly expressed

throughout mucous membranes (such as the oral epithelium), where Dsg1 is only minimally present [26]. Experimentally, animals can be genetically engineered so that they lack Dsg3 in skin and mucous membranes (so-called "Dsg3 knockout mice"). These mice develop acantholysislike lesions in the oral mucosa but not in the skin, thus providing strong evidence that Dsg3 is of primary importance in maintaining cell attachment of mucosal surfaces [27]. The binding of antibody to various desmogleins may have a direct effect on desmosomal adherence or may trigger a cellular process that results in acantholysis [28–30].

These experimental findings form the basis for an understanding of the clinical presentation. Specifically, it has been documented that some patients develop mucosal lesions without skin blisters, a phenotype of PV that has been categorized as mucosal-dominant PV [24,31]. The serum of these patients contains high titers of anti-Dsg3 antibodies and low or no titers of anti-Dsg1 antibodies. Hence, the preserved function of Dsg1 in the skin prevents development of cutaneous lesions, whereas the impaired adhesive function of Dsg3 causes acantholysis in the oral cavity. As PV progresses, many but not all patients develop cutaneous disease. Cutaneous lesions appear when antibodies to both Dsg1 and Dsg3 develop, and the clinical picture of mucocutaneous PV emerges. The clinical phenotype thus seems to be determined by the relative amounts of antibodies against Dsg1 and Dsg3. On rare occasions, anti-Dsg3 antibodies may disappear from the serum while anti-Dsg1 antibodies persist [32]. The then-emerging condition is pemphigus foliaceus, a pemphigus variant characterized by skin blisters without mucous membrane involvement. Fig. 2 and Table 1 summarize these variants of pemphigus. The observation that mucosal-dominant PV commonly precedes mucocutaneous PV puts the dentist in the forefront of diagnostic responsibility [33–42].

Besides IgG antibodies found in PV, IgA antibodies against Dsg3 also have been identified [43]. It is rare, however, to find oral lesions in IgA pemphigus (H. Hashimoto, personal communication, February 2004), possibly because autoantigens for IgA pemphigus may in fact not be a component of desmosomes [44] or because anti-Dsg autoantibodies may not act alone to cause pemphigus [45,46]. The traditional concept of pemphigus pathophysiology as described previously is being debated, and other autoantibodies that accompany antibodies directed against Dsg1 and Dsg3 may also play pivotal roles in the development of pemphigus [28–30].

What initiates the formation of IgG autoantibodies in PV patients at the very beginning of the disease is currently unknown (as is the case for most autoimmune diseases), although loss of tolerance for autoimmune target molecules may play a key role [47,48]. Exogenous factors capable of inducing or perpetuating pemphigus in genetically predisposed individuals include various medications, dietary components, and environmental factors [49–53].

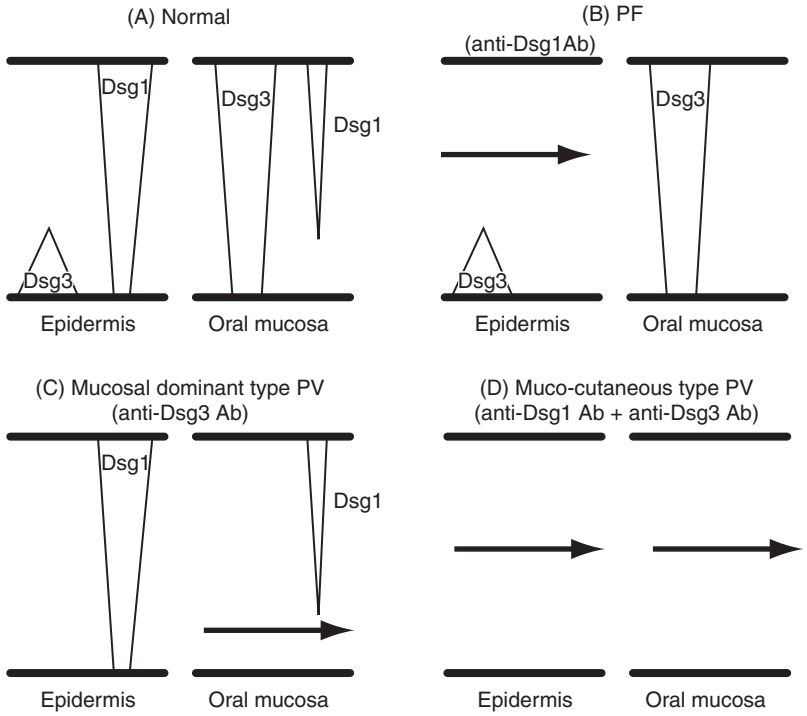

Fig. 2. (*A*) The distribution of Dsg 1 and Dsg3 varies among epidermis and oral mucosa depending of the types of antibody (*Ab*) present. (*A*) Normal distribution. (*B*) Blisters occur in skin with anti-Dsg1 Ab, resulting in pemphigus foliaceus (*PF*). (*C*) Blisters occur in mucosa with anti-Dsg3 Ab, resulting in mucosal-dominant pemphigus vulgaris (*PV*). (*D*) Blisters occur in skin and mucosa with anti-Dsg1 and anti-Dsg3 Ab, resulting in mucocutaneous pemphigus vulgaris (*PV*). Arrows indicate the levels of blister formation. *From* Hashimoto T. Recent advances in the study of the pathophysiology of pemphigus. Arch Dermatol Res 2003;295(Suppl 1):S2–11. Epub@2003 Jan 9.:S2-11; Available at: http://springerlink.metapress.com/openurl.asp?genre=article &eissn=1432-069X&volume=295&supp=1&spage=S2. Accessed January 25, 2004; with permission.

Clinical presentation

PV affects the mucosa and the skin, resulting in superficial blisters and chronic ulceration. Various mucosal surfaces may be involved, including ocular, nasal, oral, pharyngeal, laryngeal, upper respiratory, and anogenital

Table 1
Antigens targeted by autoantibodies and corresponding forms of pemphigus

Antigens	Forms of pemphigus
Desmoglein 3	Mucosal-dominant pemphigus vulgaris
Desmoglein 3, desmoglein 1, and possibly desmoglein 4	Mucocutaneous pemphigus vulgaris
Desmoglein 1	Pemphigus foliaceus
Desmoglein 3, desmoglein 1, and plakin proteins	Paraneoplastic pemphigus

mucous membranes. Because the clinical presentation is the first indicator for further investigations (histology, serum analysis), it is critical that clinicians recognize the variety of lesions, which may be a sign of PV [54]. Oral mucosal lesions are almost invariably present, underlining the decisive role of the dental professional in promptly diagnosing the pathology. Chronic ulcerations (lasting longer than 2 weeks) on any oral mucosal surface that cannot be attributed to some other factor should prompt the clinician to include PV (and PNP) in the differential diagnosis. Often, tissue fragility becomes overt in areas of trauma from toothbrushing or from frictional forces caused by removable prosthetics (Fig. 3). In fact, the formation of a lesion after gentle mechanical pressure (eg, blowing air or applying pressure with mirror handle) on affected tissue may be used as a diagnostic tool in the assessment of patients presenting with oral ulcerations. This test is known as Nikolsky's sign, named after Pyotr Vasilyewich Nikolsky, who first described this sign in 1896 (Fig. 4) [55]. This test is not specific for PV, however, because it can be provoked in other diseases such as paraneoplastic pemphigus, oral lichen planus, mucous membrane pemphigoid, epidermolysis bullosa, linear IgA disease, lupus erythematosus, dermatomyositis, chronic erythema multiforme, or graft-versus-host disease [56]. Although PV accounts for only approximately 2% of intraoral ulcerative lesions, the serious nature of the disease justifies its consideration in nearly any situation in which multiple chronic oral ulcerations are present. Clinicians should therefore not hesitate to pursue a definitive diagnosis by using proper laboratory investigations.

Laboratory tests

A biopsy specimen studied by both routine histopathologic and immunopathologic methods is fundamental to identifying the cause of chronic mucosal erosions and ulcerations. These laboratory tests contribute critically to differentiating between pemphigus, paraneoplastic pemphigus, lichen planus, mucous membrane pemphigoid, epidermolysis bullosa, linear IgA disease, lupus erythematosus, dermatomyositis, chronic erythema multiforme, and graft-versus-host disease.

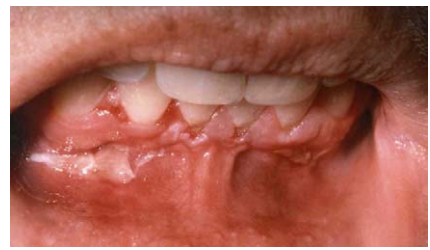

Fig. 3. Tissue fragility in a PV patient. Note tissue sloughing in areas traumatized by toothbrushing.

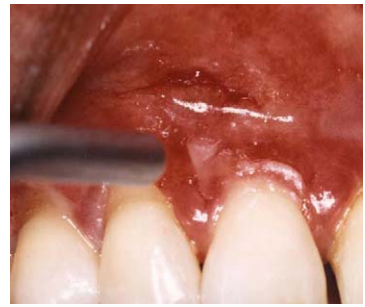

Fig. 4. Application of light mechanical forces to tissue may induce blisters in PV patients, known as Nikolsky's sign.

Ideally, two tissue samples including lesional and perilesional tissue are obtained. Each specimen is stored in a different transport medium. Including healthy-appearing tissue may not always be easily accomplished, because the fragile tissue tends to peel away during the surgical procedure (Fig. 5). The first biopsy needs to be immersed in 10% neutral buffered formalin and sent for routine histopathologic analysis, which may reveal characteristic acantholysis (Fig. 6). Because the tissue components tend to fragment, the sensitivity of light microscopy is compromised. Considering the potential seriousness of the disease, direct immunofluorescence (DIF) is recommended as a complementary diagnostic tool. DIF in affected tissues allows visualization of antibodies, complement, and fibrin that are invisible under light microscopy. To obtain accurate results with DIF, it is important to obtain biopsy material from the appropriate site, place it in the correct transport medium, and get it to the testing facility without delay. Failure at any of these points contributes to false-negative outcomes. Consequently, the second biopsy is taken from perilesional tissue and placed on a gauze

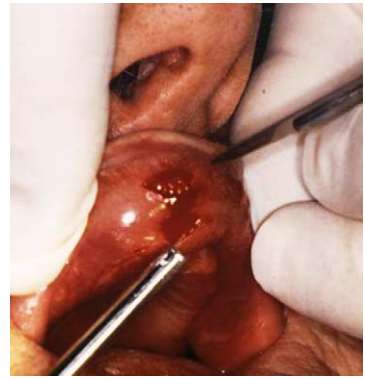

Fig. 5. Difficulties in obtaining a proper tissue specimen may arise because the fragile tissue tends to peel with minimal suction.

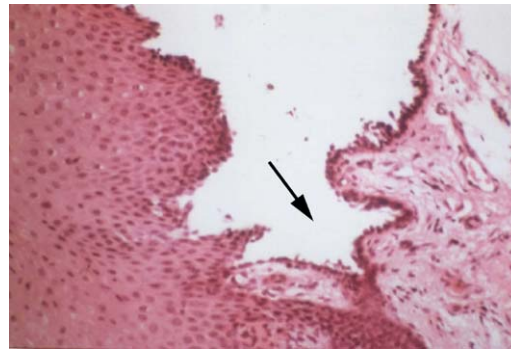

Fig. 6. Histologic picture of acantholysis in PV. Arrow indicates cleft formation above the basal cell layer caused by disintegration of epidermal cell-to-cell adhesion.

pad soaked with a holding solution for storage and transportation [57]. Normal saline can be used when express mail or a courier service to a dermatopathology laboratory is available. Specimens transported in normal saline need to reach the laboratory within 24 hours. If transportation of the biopsy sample is expected to exceed this time limit, a special transport medium known as Michel's solution should be used. This fixative prevents tissue degradation without damaging the immunoreactants (ie, immunoglobulins, complement, and fibrin). Once specimens are received in the laboratory, the holding solution is rinsed off in a neutral buffer. The specimens are then embedded, frozen, sectioned, and placed on slides. Various sections of the slide are incubated with fluorescein-labeled antibodies directed against different human immunoglobulins, complement, fibrin, and fibrinogen. When the slides are examined under the microscope, DIF typically demonstrates homogeneous epithelial cell surface staining with IgG (and possibly also C3, C1 properdin, and properdin factor B) (Fig. 7) [58,59].

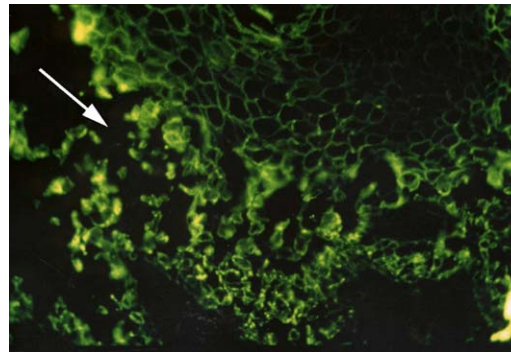

Fig. 7. Direct immunofluorescence demonstrates homogeneous epithelial cell surface staining with IgG. Arrow indicates cleft formation above the basal cell layer as shown in Fig. 6.

Indirect immunofluorescence studies (IIF) enable a search for circulating autoantibodies in the patient's serum and are usually performed after DIF studies reveal antibody deposits in the mucosa or skin. IIF requires serum specimens that are collected without anticoagulant. The blood sample is centrifuged, and the serum refrigerated until it is mailed, if arrival time at the laboratory is expected to exceed 2 days. For analysis, the serum is incubated with an epithelial substrate, usually monkey esophagus, and then incubated with fluoresceinated anti-human IgG. As outlined previously, the exact identification of circulating antibodies supports the clinical assessment for differentiating between mucosal-dominant and mucocutaneous PV [31]. The quantification of serum titers with IIF is useful to observe disease progression over time and to evaluate therapeutic interventions. IIF studies are also performed on rodent bladder to rule out paraneoplastic pemphigus (as discussed later). Fig. 8. illustrates the differences between DIF and IIF.

Therapy

Improvements in the mortality rate during the past 50 years are mainly the result of the availability of prednisone, which even today is the mainstay of therapy [60]. Various medications are being used as steroid-sparing agents in an attempt to reduce the adverse effects of long-term steroid treatment [61], and a range of other therapies are being developed and tested [62–68]. Clearly, PV patients should be managed by clinicians with special expertise in this field. The British Association of Dermatologists published guidelines for the management of PV patients, reflecting the most recent evidence of effective treatment options [69]. Topical therapies cannot replace systemic medication but may be useful for palliative treatment of painful oral lesions [70]. Maintaining or improving the oral hygiene and minimizing irritation of the lesions are part of a general supportive regimen [71]. The finding that induction of complete remission seems in part related to the initial severity and extent of disease underscores the importance of early recognition by the dental professional [72].

Paraneoplastic pemphigus

In general, paraneoplastic syndromes are markers of internal malignancies and are defined as being caused by a remote effect of a neoplasm. After various reports on an association between mucocutaneous blistering diseases and malignancy [73–77], Anhalt first defined PNP as a clinically and immunologically distinct disease [78]. He initially suggested five criteria for the diagnosis of PNP and recently presented four revised minimal criteria for diagnosis of PNP [79]:

1. Painful, progressive stomatitis, with preferential involvement of the tongue. This finding is so consistent that it is unreasonable to consider the diagnosis in its absence.

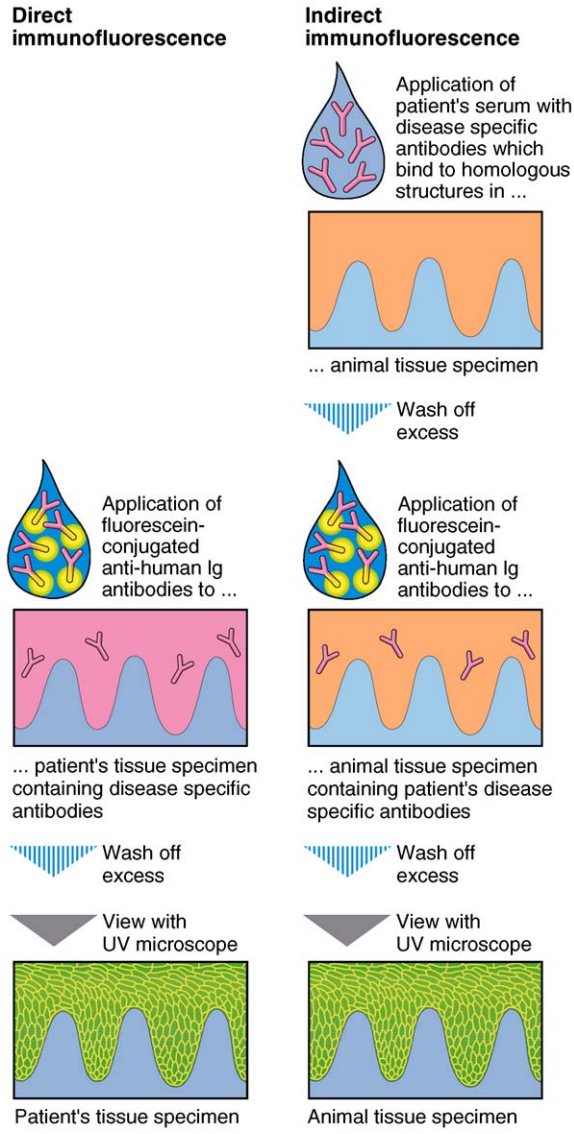

Fig. 8. Direct immunofluorescence studies reveal antibody deposits in the patient's mucosa or skin tissue. Circulating autoantibodies in the patient's serum may be visualized by indirect immunofluorescence, because they bind to homologous structures in animal tissue (monkey esophagus or rodent bladder).

2. Histologic features of acantholysis or lichenoid or interface dermatitis. Although acantholysis is most readily detected in oral lesions, the necrosis and secondary inflammation make it difficult to detect without repeated biopsies. Some patients never develop skin lesions; some show

only lesions that clinically and histologically are lichenoid or resemble erythema multiforme. DIF frequently is negative, and the serologic markers for the disease are so specific that demonstration of tissue-bound autoantibodies is not an essential criterion.

3. Demonstration of antiplakin autoantibodies. These autoantibodies are the key serologic markers for the entity. Positive IIF on rodent bladder is readily available but is not highly reliable. Immunochemical techniques are much more precise and should demonstrate, at a minimum, autoantibodies against periplakin and/or envoplakin. Patients with PNP should have a positive IIF test on monkey esophagus and have antibodies against Dsg 3 by ELISA. This test does not discriminate between PV and PF, however.
4. Demonstration of an underlying lymphoproliferative neoplasm. Approximately two thirds of cases arise in the context of known malignant disease, most often non-Hodgkin's lymphoma or chronic lymphocytic leukemia. In approximately one third of cases, there is no known neoplastic lesion at the time the mucocutaneous disease develops. These cases tend to be associated with Castleman's disease, abdominal lymphoma, thymoma, or retroperitoneal sarcomas. In most cases, the occult neoplastic lesion can be detected by CT scan of the chest, abdomen, and pelvis.

PNP and PV have common features, such as involvement of mucous membranes, histologic finding of suprabasilar acantholysis, and immunopathologic finding of in vivo bound IgG in epidermal surfaces. The clinical and histologic differences are discussed later.

Epidemiology

Approximately 150 cases have been reported in the 10 years after Anhalt first described five cases in 1990 [78,80]. Patients of all ages and races can be affected [81,82]. A significant association of PNP with HLA-DRB1*03 allele has been reported [83]. PNP is associated with benign and malignant tumors. It occurs either before, during, or after diagnosis of the associated disease. It can be detected as long as 16 years after the onset of the tumor [84]. Rarely, the neoplasm remains occult. PNP has been reported in association with various malignancies, such as non-Hodgkin's lymphoma, chronic lymphocytic leukemia, Castleman's disease, thymoma, Waldenstrom's macroglobulinemia, sarcomas, pancreatic carcinoma, bronchogenic squamous cell carcinoma, intraductal breast carcinomas, and others. Approximately 80% of cases are linked to just three neoplasms: non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and Castleman's disease (giant follicular hyperplasia) [79,85]. The association with Castleman's disease is particularly striking in children, in whom this rare lymphoproliferative disorder is the underlying neoplasm in almost all cases

[81]. The recent observation of PNP-associated oral lesions in animals raises hope for better possibilities to study the disease in research models [86,87].

Pathophysiology

As with PV, it has been demonstrated that the majority of patients with PNP possess antibodies to Dsg3 and Dsg1 in their serum [88,89], but molecular differences, particularly regarding Dsg3 epitopes, have been characterized [90]. More importantly, an additional second group of antibodies are present, targeting molecules of the plakin family (Table 1) [78,91–95]. The plakin proteins (desmoplakin I and II, BPAG1, envoplakin, periplakin, and plectin) form the portion of the desmosome just under the plasma membrane, linking the cytoskeleton to the transmembrane protein of the desmosome (desmogleins), and they are essential in maintaining cell adhesion. Autoantibodies against these plakin proteins are the most reliable marker for PNP. The route by which circulating antibodies come into contact with these cytoplasm proteins [88] and the potential mechanisms by which malignant tumors may induce autoimmunity against epithelial proteins remain speculative. One hypothesis suggests that pathologic antigens derived from the associated malignancy may stimulate the generation of antibodies that then cross-react with normal epithelial proteins [89,96,97]. Such abnormal expression of epithelial proteins by tumors has not been substantiated, however, nor has it been shown that tumor cells produce the pathogenetic antibodies that cause epithelial breakdown. On the other hand, it has been observed that subpopulations of tumors or cell lines from many neoplasms associated with PNP secrete cytokines, specifically interleukin-6 (IL-6), and that serum levels of IL-6 in PNP patients are elevated [98]. This enhanced expression of IL-6 is thought to promote autoimmunity against intercellular proteins, although a causative link has not been proven. Some authors discuss the phenomenon of epitope spreading as a potential mechanism underlying the development of PNP, possibly resulting from necrotic keratinocytes that fuel the autoimmune response [99,100]. Desmoglein autoantibodies from PNP patients induce acantholytic skin lesions when injected into neonatal mice, although no internal organ is affected and lymphocyte-mediated cell damage is absent [88,101]. These experimental findings indicate that complex mechanisms underlie the perplexing clinical features of PNP, which to date have not been fully elucidated.

Clinical presentation

The most constant and earliest presenting sign in PNP is the presence of intractable, painful oral erosions [78,79,96,102,103]. These erosions affect all surfaces of the oropharynx and characteristically involve the lateral borders of the tongue and the vermilion of the lips, often with hemorrhagic crusting

[79,96]. The lesions differ in appearance from those seen in PV because of the presence of epithelial necrosis and lichenoid changes. Their presence, alone or in combination with polymorphous skin eruptions, is an important diagnostic criterion. One might expect that this high prevalence of oral lesions in PNP patients is related to the almost invariable finding of anti-Dsg3 antibodies [88], but, puzzlingly, undetectable levels of anti-Dsg3 despite the presence of severe mucosal disease have been reported [89]. Conjunctival involvement is also seen and may result in scarring. The mucosal ulcerations and erosions mimic many other autoimmune diseases with mucosal manifestations, and clinicians are therefore urged to restrain from initiating palliative therapy without clear diagnosis.

The cutaneous lesions of PNP are quite variable and are more polymorphic than those of PV [79]. PNP may consist of lichen planus–like skin lesions, morbilliform lesions, or even erythema multiforme–like lesions in addition to blisters and erosions. In addition to the mucocutaneous symptoms, approximately 30% to 40% of cases develop pulmonary involvement, which never is found in patients with PV. The earliest symptoms are progressive dyspnea and reduced pulmonary functions without radiographic signs of disease. Endoscopic biopsy may reveal inflammation and acantholysis of bronchial respiratory epithelium. The patients eventually develop changes characteristic of bronchiolitis obliterans, which is often the cause of death [79].

Laboratory tests

The guidelines for obtaining oral mucosal biopsies apply to patients with PNP. The importance of obtaining perilesional oral epithelium, if at all possible, must be emphasized because biopsies from ulcerative lesions are likely to reveal only nonspecific inflammatory changes. Specimen handling also is analogous to cases with PV. The variability of mucocutaneous appearance is reflected in the histopathologic findings. These findings may include lichenoid changes, vacuolar interface change, or keratinocytes necrosis, alone or in addition to suprabasilar acantholysis. PNP tissue samples analyzed by DIF usually show IgG deposits bound to cell surface, similar to those seen in PV tissue. Staining is often only focal and weaker, and repeated biopsies may be necessary because of false-negative results [79]. Occasionally, basement membrane zone deposition of IgG and complement components may be observed in addition to the cell surface staining [79].

The most important initial laboratory test for diagnosing PNP is IIF. As mentioned previously, in cases of suspected PNP, rodent bladder is used as a substrate in addition to monkey esophagus because the technique can distinguish PNP from the other types of pemphigus with approximately 75% to 80% sensitivity and specificity [57,104]. This technique works because PNP autoantibodies bind to simple, columnar, transitional, and

stratified squamous epithelia, whereas PV autoantibodies bind only to stratified squamous epithelium. False-negative and false-positive results can occur, the latter in a subset of patients with erythema multiforme major who have antibodies against desmoplakin [79]. In doubtful cases, more specific and sensitive tests can be employed, including immunoblotting against epidermal cell extracts and immunoprecipitation using radiolabeled keratinocyte extracts.

Therapy

The management of oral manifestations of PNP is extremely difficult, as is the overall therapy of this disease. The prognosis is strongly influenced by the nature of the underlying neoplasm. The disease may resolve in 6 to 12 months when an underlying benign or localized tumor can be completely excised [105–107], and some patients with chronic lymphocytic leukemia might respond to immunosuppressive treatment [108,109]. Plasmapheresis may be useful in controlling severe disease in the initial period by reducing the amount of circulating antibodies [110,111]. Unlike PV, however, the correlation between antibody profile and clinical presentation is variable in PNP patients, and therefore the antibody profile is not useful for treatment monitoring [112]. Multiple other remedies have been tried and have failed to control the disease, including immunosuppression (corticosteroids, cyclophosphamide, cyclosporine, azathioprine), gold, dapsone, photopheresis, rituximab, and high-dose intravenous immunoglobulins [79,113]. Astonishingly, PNP can follow its own independent course even after surgical resection of the underlying neoplasm or chemotherapy [114]. A common sequel of the disease is respiratory failure, resulting from pulmonary involvement caused by respiratory infections, from direct involvement of the tracheo-bronchial tree by the underlying malignancy, or from bronchiolitis obliterans [98,115]. Lung transplantation has been reported to be successful in a single pediatric report [116].

Summary

PV and PNP are potentially life-threatening autoimmune diseases with similar underlying pathophysiologies and clinical presentations. In both conditions, the oral cavity is frequently a site of early disease manifestation. Patient histories reveal that oral lesions are less promptly recognized than the more characteristic cutaneous appearance [42], resulting in more clinician consultations, and unfortunate diagnostic delays. Use of appropriate diagnostic tests is of critical importance in identifying these two serious diseases. In addition to history and clinical examination, the diagnostic approach requires biopsy submitted for both routine histologic and DIF examination. Analysis of serologic markers is useful for diagnostic clarification and possibly for therapeutic monitoring.

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