Paraneoplastic Pemphigus

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Paraneoplastic disorders can be broadly defined as those that are caused by a remote effect of a cancer, not by direct tumor infiltration or tissue damage caused by metastases. These remote effects can be due to secretion of biologically active peptides or, in some cases, by immunologic effects of the tumor on the resident immune system. Paraneoplastic pemphigus (PNP) is an example of a paraneoplastic phenomenon caused by an autoimmune disease initiated by an underlying lymphoproliferative disorder (Anhalt et al, 1990). Its clinical presentation can be quite variable, which is why it remained unrecognized for so long (Redon et al, 1983; Matsuoka et al, 1989; Panielieyva, 1990). PNP can be defined and identified by the following features: (1) painful stomatitis and a polymorphous cutaneous eruption with lesions that may be blistering or lichenoid or may resemble erythema multiforme or a drug eruption; (2) histologic findings that reflect the variability of the cutaneous lesions, showing acantholysis, lichenoid, or interface change; (3) direct immunofluorescence demonstrating deposition of IgG and complement in the epidermal intercellular spaces, and often granular/linear complement deposition along the epidermal basement membrane zone; (4) serum autoantibodies that bind the cell surface of skin and mucous in a pattern typical for pemphigus, but in addition bind to simple, columnar, and transitional epithelia; (5) the serum autoantibodies identify desmogleins 1 and 3, as well as members of the plakin family of epithelial proteins, including desmoplakin I and II, envoplakin, periplakin, bullous pemphigoid antigen 1 (BPAgl), and plectin. The incidence of the disease is unknown, but it is less common than pemphigus vulgaris (PV) or foliaceus (PF). Clinical features of the disease can mimic those seen in a drug reaction, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis. Moreover, there is some evidence that the majority of cases are still not properly diagnosed.

PNP is associated in the majority of cases with non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, and Castleman’s disease. Treatment of the autoimmune disease is difficult, and most patients die from complications, including pulmonary involvement with respiratory failure.

CLINICAL FEATURES

Over the years, we have found that the most constant clinical feature of PNP is the development of painful and persistent stomatitis (Fig 1). In some patients only the oropharynx is affected, and skin lesions are never observed (Bialy Golan et al, 1996). Stomatitis is the earliest presenting sign and, despite treatment, is the one feature that persists throughout the course of disease, being extremely resistant to therapy. Stomatitis presents with erosions and ulcerations that can affect all surfaces of the oropharynx. The lesions are clinically distinctive. Because of the presence of epithelial necrosis and lichenoid changes, the lesions are much more necrotic and do not show the ragged superficial erosions characteristic of PV. They also preferentially localize to the lower and lateral borders of the tongue and characteristically extend onto and involve the vermilion of the lips. This involvement of the tongue appears to be the reason for the extreme oral pain reported by affected patients. The cutaneous lesions of PNP are much more variable than those seen in PV or PF, and different morphologies may be observed in an individual patient at different times. In some cases, there may be episodes of waves of blistering affecting the upper trunk, head and neck, and proximal extremities. These blisters rupture easily, leaving erosions. The blisters on the extremities can be quite tense, resembling those seen in bullous pemphigoid, or they can have surrounding erythema, thus clinically resembling erythema multiforme. On the upper chest and back, confluent erosive lesions can develop, producing a picture resembling toxic epidermal necrolysis (TEN). The similarity of the mucocutaneous features to erythema multiforme/TEN explains why this is the most common differential diagnosis for PNP. However, erythema multiforme and TEN are self-limited events that evolve and resolve over several weeks, whereas PNP is a relentlessly progressive disease that continuously evolves over months.

In PV and PF, the tissue injury is mediated exclusively by autoantibody, and the blistering acantholytic lesions are evident. In PNP, there is substantial evidence that the autoantibodies alone do not cause all of the tissue injury—hence the variable clinical and histologic presentation. There is cell-mediated cytotoxicity, which can cause the clinical and histologic findings of lichenoid change, individual cell necrosis or confluent cell necrosis that causes lichenoid lesions, or lesions that resemble erythema multiforme or TEN (Nguyen et al, 2001). Cutaneous lichenoid lesions may be the only cutaneous signs of the disease, or they may develop in lesions that had previously been blistered, which is a distinctive finding in PNP (Stevens et al, 1993). These lesions consist of infiltrated erythematous papules and plaques, and are always accompanied by stomatitis. In the chronic form of the disease and after treatment, this lichenoid eruption may predominate over blistering on the cutaneous surface. Both blisters and lichenoid lesions affecting the palms and the soles, as well as the paronychial tissues, are common; they help to distinguish PNP from PV, in which acral and paronychial lesions are uncommon. PNP has also been identified in a horse (Williams et al, 1995) and a dog (de Bruin et al, 1999). In animal species, it has the same associated neoplasms and clinical outcomes.

PNP is the only form of pemphigus that has involvement of tissues not covered by stratified squamous epithelium. Approximately 30–40% of cases will develop pulmonary injury, often with a
Plasm in almost all patients (Mimouni more striking in pediatric cases, where it is the underlying neo-
ophilic hyperplasia), 10%; (4) thymoma (malignant and benign), 6%; (5) sarcoma, 6%; (6) Waldenström's macroglobulinemia, 6% (Fig 2). The majority of cases are associated with NHL and CLL, but an unusual finding is the disproportionate frequency of Castle-
mania's disease. This is a very rare lymphoproliferative disorder, and so this association must give us some clues as to the etiology of the autoimmunity. The association with Castleman’s is even more striking in pediatric cases, where it is the underlying neo-
plasm in almost all patients (Mimouni et al, 2002). Prior to the description of PNP, there were many cases of Castleman’s disease associated with atypical forms of pemphigus, and we suspect most were cases of PNP (Tagami et al, 1978; Plewig et al, 1990). More common cancers, such as adenocarcinomas of breast, bowel, and lung or basal cell and squamous cell carcinoma of skin have not been associated with PNP. There are a very few reports of PNP occurring with tumors, such as squamous cell carcinoma. Most of these diagnoses have not been confirmed by immuno-
chemical testing, however, so the association remains unproven.

At present, we can only speculate about the potential mechanisms by which these tumors induce autoimmunity against epithelial proteins. Initially, we thought that the tumors might constitutively or anomalously express epithelial proteins. This phenomenon does occur in several neurologic paraneoplastic syn-
dromes where the tumor expresses a normal host protein. When presented by the tumor cells, however, these proteins are targeted by the antitumor immune response and cross-react with normal constitutive proteins (Korneguth, 1989). In PNP, however, we have no evidence that the tumors themselves anomalously express epithelial proteins. We also have no evidence that the tumor cells produce the pathogenic autoantibody. For example, in cases of Waldenström’s the autoantibody produced is polyclonal, IgG class, so it could not be produced by the myeloma and is a prod-
uct of the host immune response.

There is at least one attractive alternative hypothesis, given the evidence that dysregulated cytokine production by tumor cells may drive the development of autoimmunity. For example, it has been observed that treatment with cytokines may induce PNP (Kirsner et al, 1995), raising the possibility of more complex interactions between the tumor cells and the immune system. Interleukin 6 (IL-6) has received some attention, as patients with PNP show markedly elevated serum levels of this cytokine (Fig 3) (Nouisari et al, 1999b). It has been observed that the tumor cells iso-
lated from some cases of Castleman’s disease, non-Hodgkin’s lymphoma, and CLL (Yee et al, 1989) secrete large amounts of IL-6 in vitro. It is tempting to think that this might be the link to the frequent association of Castleman’s with PNP. IL-6 promotes B cell differentiation and drives immunoglobulin production, and dysregulated IL-6 production has been implicated in specific auto-
immune diseases. Castleman’s tumors are known to be associated with other autoimmune phenomena such as myasthenia gravis and autoimmune cytopenias, and Castleman’s patients have also been shown to have high serum levels of IL-6. Symptoms attributable to Castleman’s tumors can be abolished by complete excision of the affected node(s) and, coincidentally, serum IL-6 levels revert to normal. Perhaps the most compelling evidence arises from the observation that administration of anti-IL-6 monoclonal
antibodies can effectively reverse systemic manifestations of Castleman’s disease. This was shown in a case of autoimmune thrombocytopenia associated with Castleman’s. Administration of anti-IL-6 caused a prompt elevation of platelet counts and elimination of the patient’s “B” symptoms (Beck et al, 1994). These observations are intriguing, but further study of cytokine regulation in these complex and very ill patients is challenging.

The immunopathology of PNP is more complex than that of PV and PF, where the tissue injury is secondary to autoantibody binding to epidermal cells alone. There is evidence of cell-mediated cytotoxicity, which could explain the histologic and clinical features of lichenoid change and individual cell necrosis. Almost all patients have autoantibodies against desmogleins, demonstrable by ELISA, and we know that these antibodies are pathogenic. If the desmoglein autoantibodies from these patients are injected into neonatal mice, acantholytic skin lesions are demonstrable (Amagai et al, 1998; Reich et al, 1999). However, no other internal organs are involved and there is no lymphocyte-mediated cell damage. None of features of the disease that suggest cell-mediated autoimmunity, then, are recreated by immunoglobulin injections alone. This is also an indication that humoral immunity by itself will reproduce features of acantholysis, but reproduction of the cell-mediated immune attack may be necessary to reproduce all of the features of the disease in an animal model.

LABORATORY FINDINGS

PNP is clinically complex, and so far we have found that the most reliable serologic markers for it are identification of polyclonal IgG autoantibodies against plakin proteins and, in most cases, desmogleins 1 and 3. The plakins are a group of sequence-related proteins found in the intracellular plaque of desmosomes and hemidesmosomes; they mediate attachment of cytoskeletal intermediate filaments to transmembrane adhesion molecules such as the desmogleins. Autoantibodies against these proteins are the most reliable markers for the disease. The most characteristic and consistently recognized plakin antigens are envoplakin (Kim et al, 1997) and periplakin (Mahoney et al, 1998) (210 and 190 kDa, respectively). The next most frequently detected are antibodies against desmoplakins I and II (250 and 210 kDa, respectively). Less commonly, patients recognize bullous pemphigoid Ag 1 (230 kDa), plectin, and plakoglobin. The identity and frequency of an antigen band at 170 kDa is not well defined. PNP patients may also have clinical and serologic evidence of other autoimmune phenomena such as myasthenia gravis and autoimmune cytopenias.

To screen for PNP autoantibodies, we can test for IgG autoantibodies by indirect immunofluorescence (IF) reactive with rodent urinary bladder epithelium. A positive result implies the presence of plakin autoantibodies; however, the sensitivity and specificity of this serologic test are only about 75% and 83%, respectively (Helou et al, 1995). More specific and sensitive tests include immunoblotting against epidermal cell extracts, which can effectively detect antibodies against envoplakin, periplakin, and desmoplakin, and immunoprecipitation using radiolabeled keratinocyte extracts, which can detect antibodies against any of the plakin proteins.

This autoantibody profile is more complex than that observed in PV or PF, where autoantibodies are produced only against the desmogleins. The humoral immunity in PNP may represent an example of epitope spreading in which patients develop autoantibodies against structurally related plakin proteins and structurally unrelated transmembrane cell surface proteins (the desmogleins) that are physically linked to the plakin proteins in the desmosome and hemidesmosome (Bowen et al, 2000).

PATHOLOGY

The clinical features of paraneoplastic pemphigus are variable, and this is reflected by potential variability in the histopathology of lesions (Horn and Anhalt, 1991; Mehregan et al, 1993). The stomatitis is extremely severe, and many biopsies from ulcerative lesions yield nonspecific changes of inflammation and ulceration. If we can biopsy perilesional epithelium, suprabasilar acantholysis of the oral mucosa may be observed.

Similarly, if we biopsy intact cutaneous blisters, suprabasilar acantholysis is present. Unlike other forms of pemphigus, in PNP there may be substantial inflammatory cell infiltration of early lesions. Nonblistering lesions can show individual keratinocyte necrosis with lymphocytic infiltration into the epidermis, reminiscent of that seen in erythema multiforme or graft versus host disease. In addition, vacuolar interface change with sparse lymphocytic infiltrate of the basilar epithelium can be seen in some areas; they resemble cutaneous lupus erythematosus. The lichenoid skin lesions show areas of dense lymphocytic infiltrate in the upper
demonstrated that cell-mediated immunity is not seen in PV or PF—hence the unique histopathologic features and, presumably, the unique clinical features as well.

Patients should have evidence of IgG autoantibodies bound to the cell surface of affected epithelium by direct immunofluorescence. False negatives are more common in PNP than in PV, however, and repeated biopsies may be necessary to demonstrate this finding. In a minority of cases, we might also see a combination of both cell surface and basement membrane zone deposition of IgG and complement components, but the absence of this combined cell surface/basement membrane zone staining does not negate the diagnosis.

DIAGNOSIS

Not all patients demonstrate all of the five criteria that were originally proposed to define the disease. We propose that the following represent the minimal criteria for diagnosis of PNP with a high degree of confidence.

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.

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 this 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. Direct IF is very frequently 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 are the key serologic markers for the entity. Positive indirect IF on rodent bladder is readily available but not highly reliable. Immunohistochemical techniques are much more precise and should demonstrate, at a minimum, autoantibodies against periplakin and/or envoplakin (Kiyokawa et al., 1998). Patients with PNP should have a positive indirect IF test on monkey esophagus and have antibodies against desmoglein 3 by ELISA. This will not discriminate between PV and PE, however.

4. Demonstration of an underlying lymphoproliferative neoplasm. Approximately two-thirds of cases arise in the context of known malignant disease, most often NHL or CLL. 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 computerized tomography scan of the chest, abdomen, and pelvis.

The major differential diagnosis for patients with just oral involvement should include PV, oral lichen planus, and major aphthous stomatitis. More lichenoid skin lesions and mucositis can closely resemble extensive lichen planus. Patients with skin and oral involvement most closely resemble erythema multiforme, TEN, or PV. A small number of patients with recurrent erythema multiforme major have antibodies against desmoplakins and will therefore have a positive indirect IF on bladder epithelium. These cases are distinguished from PNP in several ways: (1) they do not have an underlying malignancy; (2) they do not have antibodies against the plakin proteins that are more specific for PNP, that is, envoplakin and periplakin; and (3) the antibodies are transient and are only detectable during episodes of active disease (Foedinger et al., 1995). The autoantibodies in PNP are constantly present.

A small number of patients appear to have PNP, but do not have demonstrable circulating autoantibodies. These patients tend to have predominantly lichenoid skin and mucosal lesions, but they behave in most other ways like antibody-positive patients and have the same underlying neoplasms. Because the definition of the disease relies so heavily on demonstration of the specific autoantibody markers, further study is required to know how to classify these patients.

TREATMENT AND PROGNOSIS

The prognosis for PNP depends on the nature of the underlying malignancy. Although the disease is initiated by the tumor, simply debulking the tumor or reducing tumor burden through chemotherapy will not halt disease progression. It seems that once the autoimmune disease is initiated, it progresses independently of the underlying neoplasm. An example of the disconnect between tumor burden and autoimmunity is found in a case reported by Fullerton and colleagues (Fullerton et al., 1992) in which PNP developed after successful autologous bone marrow transplantation for non-Hodgkin’s lymphoma. This patient was free of detectable tumor burden at the time of his death, but he died of pulmonary injury secondary to PNP. The patient did receive an autologous bone marrow transplant and therefore received his own memory T cells, which may have induced the disease even after successful treatment of the malignancy. It is also possible that individual malignant lymphoid cells that were not detectable by routine autopsies methods persisted after the transplant and were adequate to induce the PNP. In any case, this would indicate that autologous bone marrow transplantation is probably not a potential treatment for the autoimmune disease.

To date, there have been no reports of patients receiving an autologous bone marrow transplant in the setting of PNP, so it is not known what effect that treatment might have.

There does seem to be more hope if the patient has an associated benign or localized tumor. For example, if a patient has an encapsulated Castleman’s tumor or a benign thymoma that has been entirely surgically excised, the disease can improve substantially or enter a complete remission (Plewig and Jansen, 1991). This remission may take one to two years after surgery, however, and continued immunosuppression is required, and many patients succumb to complications in this prolonged postoperative period. A suggested regimen involves combined use of prednisone, 0.5 mg/kg; cyclosporine, 5 mg/kg; and oral cyclophosphamide, 2 mg/kg. These medications should be tapered as symptoms improve. In pediatric cases with respiratory disease, the persistent autoimmunity immediately post-surgery can cause ongoing pulmonary injury, and lung transplantation might be required for long-term survival (Chin et al., 2000).

On the other hand, there is no evidence that any individual therapeutic regimen is consistently effective in patients with malignant neoplasms. For unknown reasons, cases associated with NHL seems to be more difficult to treat than those associated with CLL. Although there are a couple of individual reports of long-term survivors (Camisa et al., 1992), almost all patients with NHL or CLL will succumb within three months to two years after diagnosis. Oral corticosteroids in a dose of 0.5–1 mg/kg will produce partial improvement but not complete resolution of lesions. Cutaneous lesions respond more quickly to therapy, whereas the stomatitis is generally more refractory; the pulmonary disease seems to progress even if the mucositis improves. Aside from corticosteroids, many other agents have been tried in individual cases on an anecdotal basis, but none have proved to be particularly effective. Methods that have been tried and have often failed include immunosuppression with cyclophosphamide or azathioprine, gold, dapsone, plasmapheresis, photopheresis, and...
high-dose intravenous immunoglobulins. A subset of patients, usually with CLL as an underlying neoplasm, responded to a combination of prednisone, 0.5–1 mg/kg/day, and cyclosporine, 5 mg/kg/day (Stähle-Backdahl et al., 1995). Additional treatment with intermittent pulse cyclophosphamide to control the underlying CLL was usually also used in these cases and may have contributed to the good outcome. Some patients show improvement after treatment with rituximab in combination with prednisone and cyclophosphamide (Borradori et al., 2001). It is not known why this autoimmune disease is so refractory to the kind of immunosuppressive treatments that usually work well in PV or other autoimmune diseases.

The exact cause of death in PNP has been attributed to multiple factors including sepsis, gastrointestinal bleeding, “multiorgan failure,” and respiratory failure. Patients with B cell neoplasms are known to have a high frequency of autoimmune cytopenias, and they may develop more than one neoplasm-associated autoimmune disease. In some cases of PNP, fatal episodes of sepsis are suspected to have occurred because of sudden and unexplained neutropenia, possibly due to this mechanism.

Respiratory failure is increasingly recognized as a common terminal event. It had been unrecognized earlier because in the earliest phase of the disease the patient complains of shortness of breath with no remarkable imaging changes and with an obstructive pattern on pulmonary function tests that is often attributed to a history of smoking, asthma, and the like. Despite its benign-appearing onset, however, the development of shortness of breath with obstructive disease, progressing to bronchiolitis obliterans, is a terminal pathway in most cases. The exact mechanisms by which this pulmonary disease occurs are not clear. We do know that these patients have autoantibodies that react with desmoplakins and that desmoplakins are present in respiratory epithelium. It is thus possible that respiratory failure may be due to autoantibody-mediated injury to bronchial epithelium, with plugging of terminal alveoli with airflow obstruction and ventilation perfusion abnormalities. Additionally, direct damage to alveolar epithelium can cause a diffusion barrier and subsequent intractable hypoxia. We have no insight into possible cell-mediated pulmonary injury, however, which might be an important factor. The pulmonary injury does not respond to medical treatment, and the development of shortness of breath and hypoxia in a patient with this syndrome is an ominous prognostic sign.

CONCLUSION

Although our knowledge of PNP has progressed substantially in the last decade, much is still unknown. The disease occurs rapidly, has a short and stormy progression in many patients, and leaves us with a limited window of opportunity in which to study it in individual cases. We hope that with increased recognition of PNP more details of the mechanisms of autoimmune injury will be defined, allowing us to better treat these affected patients.

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