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Lichenoid paraneoplastic pemphigus in the absence of detectable antibodies

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Paraneoplastic pemphigus (PNP) has been described as an antibody-mediated mucocutaneous disease occurring almost exclusively in patients with lymphocytic neoplasms. We describe 4 patients with the clinical features of the lichenoid variant of PNP in the absence of detectable autoantibodies. On the basis of these findings, we conclude that the spectrum of PNP likely includes patients with disease predominantly or exclusively mediated by cytotoxic T cells rather than autoantibodies. The pathophysiology and range of PNP disease are likely more complex than was initially believed. (J Am Acad Dermatol 2007;56:153-9.)

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Paraneoplastic pemphigus (PNP) is a blistering and erosive mucocutaneous disease associated with malignant lymphocytic neoplasms, most commonly chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), Castleman's disease, and thymoma. Contrary to other variants of pemphigus, PNP may involve not only stratified epithelium, but also the columnar epithelium of the lungs, resulting in progressive bronchiolitis obliterans that is refractory to treatment and almost always results in death.[1] The clinical and histologic findings associated with PNP are highly variable. Whereas some patients have mucocutaneous blisters that mimic pemphigus vulgaris,[2] many have inflammatory lesions that resemble T-cell–mediated diseases, such as lichen planus,[3] graft-versus-host disease,[4] and erythema multiforme.[5,6] In one series of 6 consecutive patients with PNP, 5 had lesions that were clinically and histologically similar to lichen planus.[3]

The diagnostic criteria for PNP are based on the initial case reports and these include (1) polymorphous mucocutaneous blisters and erosions; (2) histopathologic findings of epidermal acantholysis, dyskeratosis, and vacuolar interface changes; (3) epidermal intercellular deposition of IgG and C3 with or without linear deposition at the basement membrane zone as demonstrated by direct immunofluorescence(DIF); (4) serum autoantibodies to epithelia as demonstrated by indirect immunofluorescence (IIF) with murine tissue (bladder, heart, liver, and tongue); and (5) immunoprecipitation findings of antibodies to a complex of 5 polypeptides (250-kd desmoplakin 1, 230-kd BP antigen BPAg1, 210-kd desmoplakin 2 and envoplakin, 190-kd periplakin, and the yet unidentified 170-kd antigen).

Although detection of the plakin and desmosomal cadherin autoantibodies is diagnostic for PNP, recent reports suggest that clinical PNP can present with a restricted repertoire of these antibodies[3,7]; moreover, according to one case report, the antibodies may be absent or undetectable in affected organs, such as the lungs.[8] We report 4 cases that clinically and histologically represent the lichenoid variant of PNP, but lack autoantibodies detectable by DIF, IIF, or immunoprecipitation. These patients with lymphoproliferative neoplasms demonstrated aggressive and refractory ulcerative mucocutaneous lesions with prominent interface dermatitis on histologic examination. Additionally, in one patient pulmonary disease developed that was consistent with bronchiolitis obliterans and two patients had severe esophageal ulceration.

All 4 patients in this series were treated with rituximab before the development of PNP. It is possible that rituximab altered the disease course by preventing development of the antibody-mediated component, leaving the T-cell–mediated portion of the disease to proceed. It is also plausible that these patients represent a distinct lichenoid variant of PNP independent of B-cell depletion. Less likely, rituximab may have simply lowered antibody levels so as to make them undetectable.

Abbreviations used:

CLL: chronic lymphocytic leukemia
CT: computed tomographic
DIF: direct immunofluorescence
IIF: indirect immunofluorescence
IL: interleukin
NHL: non-Hodgkin lymphoma
PNP: paraneoplastic pemphigus

In light of this cohort of seronegative patients described, we propose that the diagnostic criteria for PNP be modified to include patients with a seronegative lichenoid variant. In particular, the diagnosis of seronegative PNP must be considered in patients previously treated with rituximab. Finally, we elaborate on our expanding understanding of the pathophysiology and treatment options for PNP.

METHODS

DIF

Frozen sections were stained with fluoresceinated antibodies specific for human IgG, IgA, IgM, complement, and fibrin by standard immunohistochemical techniques that have been well described.[9]

IIF

Serum samples were analyzed for autoantibodies that bound desmosomal and plakin components of monkey esophagus and murine bladder and/or tongue.[10]

Immunoprecipitation

Immunoprecipitation was performed with a technique based on that described by Stanley, Koulu, and Thivolet.[11] ^{14}C-labeled cultured normal human keratinocytes were incubated with sera from each of the patients. Normal human sera and sera from a patient with known PNP were used as negative and positive controls, respectively.

CASE REPORTS

Index case

A 71-year-old Caucasian woman presented with a 1-year history of dysphagia secondary to severe esophagitis and esophageal stricture. Ten years before presentation (1993), the patient had been diagnosed with NHL (mixed diffuse and follicular small cleaved cell) for which she had received 4