Paraneoplastic Pemphigus Herpetiformis With IgG Antibodies to Desmoglein 3 and Without Mucosal Lesions

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Background: Pemphigus herpetiformis (PH) is a rare clinical entity that combines the clinical features of dermatitis herpetiformis and the immunopathologic features of pemphigus. The target antigen is usually desmoglein 1, with exceptional cases manifesting autoantibodies against desmoglein 3. More recently, it has been found that many patients with PH also demonstrate autoantibodies against desmocollin. The association of PH with a malignant neoplasm is rare.

Observations: We describe a patient with PH and a lung neoplasm. Immunologic studies demonstrated IgG antibodies to desmoglein 3 and to an unknown 178-kDa protein but no antibodies to desmocollin.

Conclusions: The association of PH with a thoracic malignant neoplasm has been reported in only 4 previous cases, and the neoplasm could be responsible for the unusual immunologic profile in the patient described herein. To our knowledge, this is the first report of PH with an associated neoplasm in which only anti–desmoglein 3 antibody was detected.

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EMPHEGUS HERPETIFORMIS (PH) is a rare clinical entity that combines the clinical features of dermatitis herpetiformis and the immunopathologic features of pemphigus. It affects patients aged 30 to 80 years and manifests as a subacute onset of erythematous urticarial plaques and clusters of vesicles in a herpetiform arrangement. The mucous membranes are usually not involved. Histologic findings of PH include eosinophilic spongiosis with various degrees of acantholysis, which is usually minimal.1-3 Eosinophilia may be present in some patients.4,5 Direct immunofluorescence (IF) shows IgG antibodies on keratinocyte cell surfaces, and the target antigen has been shown to be desmoglein (Dsg) 1 in most cases.3,6,7 Anti-Dsg antibodies in PH are thought to induce spongiosis with eosinophil infiltration but rarely produce acantholysis, in contrast to classic pemphigus. Although the association of cancer with immunobullous diseases can be seen in patients with paraneoplastic pemphigus (PNP) and pemphigus vulgaris (PV),8,9 it is rare in patients with PH. We describe a patient having PH with IgG autoantibodies to Dsg3 and to an unknown 178-kDa protein associated with pulmonary neoplasia.

REPORT OF A CASE

A 68-year-old Hispanic woman was seen with a 2-week history of diffuse pruritic lesions on the trunk and extremities. She denied any mucosal involvement or history of similar lesions. Her medical history was positive for hypothyroidism secondary to treated Graves disease, benign mucinous cystadenoma of the ovary after total hysterectomy, osteoporosis, and smoking. Her medications included levothyroxine sodium, calcium carbonate, vitamin D, alendronate sodium, aspirin, albuterol sulfate nebulization, and fluticasone propionate and salmeterol xinafoate inhaler. A review of systems was positive for decreased appetite, weight loss (12 kg in 2 years), shortness of breath on exertion, and constipation. On physical examination, several large erythematous annular plaques with central crust and scales were noted on the trunk and extremities. The lesions ranged from 1 to 10 cm, and some lesions were coalescing (Figure 1 A and B). Intact blisters with serous content were present on the proximal right anterior thigh and left calf. There were no mu-
cosal lesions. Hematoxylin-eosin staining of skin demonstrated an intraepidermal suprabasilar vesicle with a single row of keratinocytes attached to the basement membrane and acantholytic keratinocytes within the vesicle. The superficial dermis contained a mild inflammatory infiltrate with eosinophils (Figure 1C). Direct IF demonstrated IgG deposition on the cell surfaces of keratinocytes. Indirect IF detected IgG antibodies at a titer of 1:100 that bound to the cell surfaces of monkey esophagus epithelium.

Enzyme-linked immunosorbent assay (ELISA) demonstrated marked elevation of autoantibodies to Dsg3 (193 U/mL). ELISA was negative for IgG antibodies to Dsg1, bullous pemphigoid (BP) 180, and BP230. The clinical presentation and histologic and laboratory findings were consistent with PH. The patient’s condition improved significantly with systemic corticosteroid therapy, with almost complete clearing of the lesions within 1 week.

Laboratory studies revealed mild normocytic anemia, with a hemoglobin level of 11.1 g/dL (to convert hemoglobin level to grams per liter, multiply by 10.0), no eosinophilia, and normal results on thyrotropin, basic metabolic panel, and hepatic function tests. Her electrocardiogram was normal. Further evaluation of her weight loss, shortness of breath, and decreased appetite was recommended, but the patient did not undergo a chest radiograph until 4 months later, when it revealed a 7 × 6.5-cm mass on the mid right lung without pleural effusion. Chest computed tomography with intravenous contrast was then performed and demonstrated a large mass in the lower right upper lobe and right middle lobe with central necrosis. Right hilar masses consistent with lymph nodes were also found. The pulmonary artery branches were found to be obliterated around this mass, and probable tumor thrombus seemed to extend into the left atrium likely through the right superior pulmonary vein, forming an intra-atrial polypoid structure. Signs of severe emphysema were also noted. An attempt was made to contact the patient with the results the next day, but the patient had died.

To further characterize the immunologic profile of this patient, ELISA and IF using transfected COS-7 cells for desmocollin (Dsc)12,13 as well as immunoblotting using normal human epidermal extracts as the source of antigens,14 were performed. ELISA using antibodies against recombinant proteins of the entire extracellular domains of human Dsc1, Dsc2, and Dsc3 expressed by a baculovirus system was negative for IgG anti-Dsc1, anti-Dsc2, and anti-Dsc3 antibodies (the optical density cutoff value was 0.15). Immunofluorescence of transfected COS-7 cells also confirmed the absence of antibodies against Dsc1, Dsc2, and Dsc3 in our patient’s serum: whereas a control serum sample from a patient with atypical pemphigus, who was known to have IgG anti-Dsc1, anti-Dsc2, and anti-Dsc3 antibodies, demonstrated granular staining of the cell surface; no staining was observed in COS-7 cells incubated with our patient’s serum (Figure 2). Immunoblotting demonstrated IgG autoantibodies against a 130-kDa antigen (which corresponded to Dsg3 when using a serum sample from a patient with PV as a positive control) and against an unknown 178-kDa protein (Figure 3). The patient’s serum was negative for autoantibodies against the BP230,
BP180, 160-kDa Dsg1, 210-kDa envoplakin, 190-kDa periplakin, and 110-kDa Dsc a-form and b-form antigens (Figure 3). Because of the patient’s unexpected death and limited amount of serum available for studies, indirect IF on rat bladder was not performed.

**COMMENT**

The association of cancer with immunobullous diseases can be seen in patients with PNP and in patients with typical PV. Paraneoplastic pemphigus is a specific diagnostic entity, first described in 1990 by Anhalt et al. Most patients with PNP have anti-Dsg3 antibodies; however, a disease mechanism relying exclusively on anti-Dsg3 antibody is thought to be unlikely. Ohyama et al demonstrated that the association between clinical phenotype and anti-Dsg autoantibody profile in PNP is not as clear as that in classic PV, and they suggested that the skin blisters in PNP can be caused not only by anti-Dsg antibodies but also by other pathologic mechanisms, such as a lichenoid reaction and interface dermatitis. In contrast, Amagai et al showed that affinity-purified anti-
Dsg3 from serum samples of patients with PNP caused gross blisters in neonatal mice and that the removal of anti-Dsg3 eliminated this ability, suggesting that anti-Dsg3 IgG has a primary pathogenic role in inducing loss of cell adhesion between keratinocytes and in causing blister formation. It is possible that much of the initial damage may be the result of anti-Dsg antibodies and that the polymorphous nature of the condition is likely caused by further interaction of antibodies directed against the plakin family of proteins.

Our patient had a negative ELISA for anti-BP230 antibodies, and immunoblotting was negative for the 210-kDa envoplakin and the 190-kDa periplakin. Her immunologic profile, lack of mucosal involvement, and excellent response to therapy are consistent with the diagnosis of PH and render the diagnosis of PNP unlikely. However, the association of a pulmonary malignant neoplasm with this unusual skin presentation may indicate that this patient in fact represents a case of paraneoplastic PH.

In contrast to PNP, the association of PH with neoplasia is rare, and only 6 cases have been reported in the literature to our knowledge, including 4 patients with lung cancer, 1 patient with esophageal cancer, and 1 patient with prostate cancer. Because of the few cases and limited description, it is difficult to draw any conclusions regarding the immunologic profiles of these patients. No circulating antibodies were found in 1 case, autoantibodies against 150-kDa and 230-kDa antigens were reported in 1 case, low-titer IgG antibodies against cell surfaces of the epithelium of guinea pig esophagus were demonstrated in 1 case, and detailed information was unavailable from another case report of a patient with lung neoplasia. The patient with prostate cancer showed anti-Dsg1 and anti-Dsg3 antibodies, and the specificity of circulating antibodies found on indirect IF in the patient with esophageal cancer was unidentified. Among all cases, a strict parallel course between dermatosis and the malignant neoplasm was reported only by Palleschi and Giomi, who suggested that some cases of PH may in fact represent a tumor-related cutaneous disease and that these may be included in a wider definition of PNP.

It is unclear why the clinical presentations of PH and classic pemphigus are so different, despite the common presence of anti-Dsg1 or anti-Dsg3 autoantibodies. It has been speculated that the phenotypic variations may be caused by differences in epitopes recognized by the autoantibodies. Whereas autoantibodies in pemphigus foliaceus and PV recognize functionally important regions on Dsg and inhibit their adhesive function, autoantibodies in PH may recognize a functionally less important part of the molecule, thereby inducing no acantholysis but inflammatory processes via complement activation or cytokine release by keratinocytes, leading to intercellular edema and eosinophilic spongiosis. Changes in epitopes recognized by anti-Dsg autoantibodies may also explain the transformation of PH into pemphigus foliaceus or PV. Few patients with PH demonstrate autoantibodies to Dsg3, and our patient’s immunologic profile supports the concept that Dsg3 is also a target antigen in this disease. Many of these cases, including our patient, did not have mucosal involvement, and this further reinforces that the pathogenesis of PH autoantibodies differs from that of classic pemphigus and that other unknown factors may be involved.

There is a growing body of evidence in the literature demonstrating the importance of Dsc3 in cellular adhesion of the epidermis. It has recently been shown that many patients with PH have anti-Dsc autoantibodies (K. Ishii, MD, and TH, unpublished data, 2009). However, in our patient, 3 different methods (ELISA, immunoblotting, and IF of transfected COS-7 cells) failed to demonstrate IgG anti-Dsc1, anti-Dsc2, or anti-Dsc3 antibodies. However, immunoblot analysis in our patient demonstrated an unknown 178-kDa protein in the serum. Unfortunately, because of the patient’s unexpected death, we were unable to further investigate the characteristics of this protein. It is unclear if the presence of these autoantibodies was associated with the unique clinical presentation of our patient with acantholysis or with the underlying neoplasm. Further case
reports and investigation with detailed immunologic profiles are required to fully understand the underlying immunopathogenic nature of this disease.

Herein, we described a patient having PH with IgG autoantibodies to Dsg3 and to an unknown 178-kDa protein who had an underlying lung neoplasm. To our knowledge, this is the first report of PH with an associated neoplasm in which only anti-Dsg3 antibody was detected. It is unclear if other factors such as non-IgG autoantibodies or the anti–178-kDa protein were involved in our patient’s unusual presentation.

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Study concept and design: Prado, Brice, Fukuda, Hashimoto, and Fujita. Acquisition of data: Fukuda and Hashimoto. Analysis and interpretation of data: Prado, Brice, Fukuda, Hashimoto, and Fujita. Drafting of the manuscript: Prado. Critical revision of the manuscript for important intellectual content: Prado, Brice, Fukuda, Hashimoto, and Fujita. Obtained funding: Hashimoto. Administrative, technical, or material support: Prado, Brice, Fukuda, Hashimoto, and Fujita. Study supervision: Fujita.

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