Antibody Titers to Desmogleins 1 and 3 in a Patient With Paraneoplastic Pemphigus Associated With Follicular Dendritic Cell Sarcoma

Mariko Seishima, MD; Makiko Oda, MD; Zuici Oyama, MD; Tomoaki Yoshimura, PhD; Futoshi Yamazaki, PhD; Takahiko Aoki, MD; Mariko Nei, MD; Takashi Hashimoto, MD

Background: Most paraneoplastic pemphigus (PNP) cases reported to date have been associated with lymphoproliferative neoplasms. Patients with PNP have autoantibodies against the plakin family (e.g., envoplakin and periplakin). Antibodies against desmoglein 3 (Dsg3) and Dsg1, antigens for classic types of pemphigus, have also been reported to play an important role in the initial stage of PNP.

Observations: We describe a patient with PNP associated with follicular dendritic cell sarcoma. Antibodies to envoplakin and periplakin were detected. When only mucosal lesions were observed at the early stage, the antibody to Dsg3 but not to Dsg1 was detected by enzyme-linked immunosorbent assay. After skin lesions appeared, antibodies to Dsg1 and Dsg3 were detected. These titers were elevated, with exacerbation of skin lesions.

Although the patient received corticosteroid therapy, double-filtration plasmapheresis, and intravenous human immunoglobulin therapy after surgical resection of follicular dendritic cell sarcoma, she died of fungal infective lung embolisms. A direct immunofluorescence study of autopsy samples showed IgG deposition in the epidermis of the skin and oral mucosal membrane, but not in the lungs and kidneys and follicular dendritic cell sarcoma of the para-aortic area.

Conclusion: In this patient with PNP and follicular dendritic cell sarcoma, there was an association between the clinical phenotype and the anti-Dsg antibody profile, as seen in pemphigus vulgaris.

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P ARANEOPLASTIC PEMPHIGUS (PNP) is an autoimmune bullous disease characterized by severe mucosal membrane involvement, polymorphous skin lesions, and underlying neoplasms. Most cases reported to date have been associated with lymphoproliferative neoplasms. Patients with PNP have IgG autoantibodies against a characteristic set of antigens, most of which have been identified as cytoplasmic proteins of the plakin family (desmoplakin I and II, bullous pemphigoid [BP] 230, envoplakin, periplakin, and plectin), and an unidentified 170-kDa antigen. Recently, antibodies against desmoglein 3 (Dsg3) and Dsg1, which are antigens for classic types of pemphigus, have also been reported to play an important role in the initial stage of PNP.

We describe a patient with PNP associated with follicular dendritic cell sarcoma (FDCS). At the early stage, when only mucosal lesions were observed, the antibody to Dsg3 but not to Dsg1 was detected by enzyme-linked immunosorbent assay (ELISA). When skin lesions appeared 3 months later, antibodies to Dsg1 and Dsg3 were detected. These findings indicate that the pathogenesis of PNP is similar to that of pemphigus vulgaris and pemphigus foliaceus. This patient died despite receiving various therapies, including corticosteroid therapy and double-filtration plasmapheresis, and we present the autopsy findings.

REPORT OF A CASE

A 64-year-old woman had received surgical treatment for FDCS of the retroperitoneum 18 months before she consulted the Department of Dermatology, Ogaki Municipal Hospital (Ogaki, Japan), on October 30, 2001, with a 2-week history of painful erosions on the lips and conjunctivae (Figure 1). Recurrence of retroperitoneal tumor had been detected by computed tomography 3 months previously. Histologic findings from a biopsy specimen from the lip skin showed acantholysis in the lower epidermis and slight lymphocytic infiltration in the upper dermis. Direct immunofluorescence of the lip...
skin sample showed IgG deposition to the cell surface in the lower epidermis. By indirect immunofluorescence using normal human skin, the patient’s serum sample showed IgG anti-epidermal cell surface antibodies at a titer greater than 1:160, and the study using rat transitional epithelium indicated these antibodies at a titer greater than 1:40. Antibodies to envoplakin and periplakin were also detected by immunoblot analysis using normal human epidermal extracts as a substrate (Figure 2A). Antibodies to N-terminal globular domains, entire central rod domains, and C-terminal globular domains of envoplakin and periplakin were detected in the serum samples by immunoblot analysis using recombinant proteins of envoplakin and periplakin (Figure 2B). Antibody titers against Dsg1, Dsg3, and BP180 were determined using Dsg1-, Dsg3-, and BP180-coated ELISA plates (MBL, Nagoya, Japan), including the positive and negative controls according to the protocols provided by the manufacturer. The results are expressed as ELISA scores calculated from optical density according to the instructions. We also collected serum samples from control subjects and from patients with confirmed pemphigus vulgaris, pemphigus foliaceus, and BP. The test result for anti-Dsg3 antibody was positive (index, 29.6; reference range, <10) using ELISA of desmoglein, whereas the test result for anti-Dsg1 antibody was negative (index, 7.8; reference range, <11). Antibody against BP180 was not detected in serum samples by ELISA of BP180. Laboratory data were within reference ranges. The serum interleukin 6 level measured by enzyme immunoassay was 4.5 pg/mL, which is within the reference range (<8.0 pg/mL). Based on these findings, a diagnosis of PNP was made.

Corticosteroid therapy, including corticosteroid pulse therapy, and double-filtration plasmapheresis after surgical resection of the recurrent retroperitoneal tumor reduced the oral erosions, but they still persisted. Histologically, the retroperitoneal tumor consisted of atypical large spindle or ovoid cells that stained positive for CD21 and p53 but negative for CD3, CD20, CD30, CD68, CD45RB, p80, and S100 protein. A diagnosis of FDCS was made according to the World Health Organization classification. No additional therapy for the tumor, such as chemotherapy, was given after surgical resection.

Papules appeared on the trunk and extremities after 3 months of therapy (Figure 3), and the papules soon turned to erosions. At this time, laboratory examinations demonstrated slight anemia. Her leukocyte count was $5.45 \times 10^9/\mu L$ (neutrophils, 70.3%; lymphocytes, 25.9%; monocytes, 3.1%; and eosinophils, 0.7%). Flow cytometry analysis of peripheral lymphocytes showed 83.4% T cells, 12.5% B cells, and 4.1% null cells. The peripheral lymphocyte marker test showed 21.3% CD4 and 44.5% CD8. Histologic findings of papules on forearm skin showed liquefaction degeneration in the basal layer, eosinophilic bodies in the epidermis, and perivascular mononuclear cell infiltration in the dermis. A direct immunofluorescence study of papules on the forearm showed IgG deposition in the cellular surface and cytoplasms of the epidermis. By indirect immunofluorescence of a normal human skin section, the patient’s serum showed IgG anti-epidermal cell surface antibodies at a titer greater than 1:160, and the study using rat transitional epithelium indicated these antibodies at a titer greater than 1:40. Antibodies to envoplakin and periplakin were also detected by immunoblot analysis using normal human epidermal extracts as a substrate (Figure 2A). Antibodies to N-terminal globular domains, entire central rod domains, and C-terminal globular domains of envoplakin and periplakin were detected in the serum samples by immunoblot analysis using recombinant proteins of envoplakin and periplakin (Figure 2B).
tracts as a substrate. At that time, antibodies to Dsg1 and Dsg3 were detected by ELISA; indices were 77.8 and 56.5, respectively (Figure 4). These titers were elevated with exacerbation of the skin lesions and reached 115.3 (Dsg1) and 103.8 (Dsg3) after 2 months (Figure 4). Although corticosteroid therapy, including 3 courses of corticosteroid pulse therapy; double-filtration plasmapheresis; and intravenous human immunoglobulin therapy were given, severe erosions over the whole skin (Figure 5) and oral and genital mucosal membrane did not improve. The patient died of fungal infective embolisms in the lungs after 7 months of therapy.

Histologic findings from autopsy specimens showed recurrence of FDCS in the retroperitoneum and small intestine with a lesional diameter of 15 cm and multiple embolisms of fungi in the lungs and kidneys. However, there was no constrictive bronchiolitis obliterans. Direct immunofluorescence of autopsy specimens showed IgG depositions to the cell surface in the epidermis of the skin and oral mucosal membrane, whereas the lungs, kidneys, liver, and retroperitoneal tumor showed negative staining for the depositions.

**COMMENT**

Paraneoplastic pemphigus shows antibodies against multiple antigens, including desmogleins and members of the plakin family (desmoplakins, BP230, envoplakin, periplakin, and plectin).3,4 In classic pemphigus vulgaris, the mucosal dominant type has only anti-Dsg3 antibodies, whereas the mucocutaneous type has antibodies to Dsg1 and Dsg3.14,15 In this patient, there was an association be-

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**Figure 3.** Papules on the trunk 3 months after the first consultation.

**Figure 4.** Clinical course and time course of the change in antibody indices of desmoglein 1 (Dsg1) and Dsg3.

**Figure 5.** Severe erosions are observed over the whole skin in April 2002.
tween the clinical phenotype and the anti-Dsg antibody profile, as seen in pemphigus vulgaris.\(^{14}\) When only mucosal lesions were observed, antibodies to Dsg3 but not to Dsg1 was detected. In contrast, antibodies to Dsg1 and Dsg3 were detected after skin lesions appeared. However, Ohyama et al\(^{8}\) showed that there is no clear association between the clinical phenotype and the anti-Dsg antibody profile in PNP in their study. This finding suggests that besides anti–Dsg IgG, other pathologic mechanisms, such as lichenoid reaction or interface dermatitis, may be involved in blister formation in PNP.\(^{16}\)

Autoantibodies to desmogleins are not detected in all patients with PNP.\(^{8,17}\)

Paraneoplastic pemphigus is often associated with an underlying neoplasm.\(^{18}\) It is unclear at present why underlying malignancies produce such a wide range of symptoms. Two hypotheses have been proposed.\(^{19}\) First, an antitumor immune response cross-reacts with normal epithelial proteins. However, in the present case, the tumor in the retroperitoneum did not show IgG deposits to the cell surface with direct immunofluorescence. In addition, most patients with PNP have lymphomas and chronic leukemia of B-cell origin, which do not normally produce desmosomes or express desmoplakins. However, the expression of desmoplakin was described in non-Hodgkin lymphomas, thymomas, and Castleman tumors. Second, the induction of autoimmunity may be the result of dysregulated cytokine production by tumor cells. For example, interleukin 6 is known to promote B-cell differentiation and to drive immunoglobulin production.\(^{20}\) Second, the induction of autoimmunity may be the result of dysregulated cytokine production by tumor cells. For example, interleukin 6 is known to promote B-cell differentiation and to drive immunoglobulin production, and dysregulated interleukin 6 production has been demonstrated in certain autoimmune diseases.\(^{17}\)

Dysregulation of cytokines may cause the synthesis of anti–Dsg3 IgG autoantibodies, which initiates the acantholytic process and damages the cell membranes. Once the membrane is damaged, antiplakin autoantibodies are induced, which then enter the cell and bind the target autoantigens (desmoplakins I and II, BP230, envoplakin, and periplakin) by an epitope-spreading phenomenon.\(^{18,19}\)

This is a case of PNP associated with FDCS. A similar case has also been reported by Lee et al,\(^{20}\) but their case arises from a Castleman tumor. Although the serum interleukin 6 level was within the reference range in our case, dysregulation of other cytokines may cause the initial pathologic process in PNP. Because dendritic cells present antigens to T cells, the autoimmune reaction may be enhanced by disturbed cytokine production of the tumor cells in the present patient.

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Correspondence: Mariko Seishima, MD, Department of Dermatology, Ogaki Municipal Hospital, Minaminokawacho 4-86, Ogaki 503-8502, Japan (tosyo1@omh.ogaki .gifu.jp).

REFERENCES