Pemphigus is an autoimmune bullous disorder characterized by autoantibodies to keratinocyte cell surface antigens and is divided into 2 major forms, pemphigus foliaceus and pemphigus vulgaris. Pemphigus vegetans, a variant of pemphigus vulgaris, is characterized clinically by hypertrophic vegetating skin lesions on the right inguinal region with typical histopathological features. Immunoblotting using normal human epidermal extracts detected IgG antibodies to Dsg1 and Dscs. Enzyme-linked immunosorbent assays (ELISAs) revealed IgG antibodies to Dsg1 but not to Dsg3. Complementary DNA (cDNA) transfection method to COS-7 cells and novel ELISAs using eukaryotic recombinant proteins of human Dsc1, Dsc2, and Dsc3 confirmed specific IgG reactivity with Dsc3.

Case Report/Case Series
Two Cases of Pemphigus Vegetans With IgG Anti–Desmocollin 3 Antibodies

Hiroshi Saruta, MD; Norito Ishii, MD; Kwesi Teye, PhD; Fumitake Ono, MD; Bungo Ohyama, MD, PhD; Hiroshi Koga, MD; Chika Ohata, MD; Minao Furumura, MD, PhD; Daisuke Tsuruta, MD, PhD; Takashi Hashimoto, MD

IMPORTANCE Pemphigus vegetans shows clinically vegetating and/or pustular skin lesions mainly on the intertriginous areas and histopathologically neutrophilic and eosinophilic pustules in the epidermis. Pemphigus vegetans shows IgG reactivity mainly with desmoglein (Dsg) 3, but also with other autoantigens, including Dsg1 and desmocollins (Dscs).

OBSERVATIONS We examined antigen profiles in 2 cases of pemphigus vegetans. (1) A woman in her 80s presented with typical vegetating skin lesions on the right inguinal region with typical histopathological features. Immunoblotting using normal human epidermal extracts detected IgG antibodies to Dsg1 and Dscs. Enzyme-linked immunosorbent assays (ELISAs) revealed IgG antibodies to Dsg1 but not to Dsg3. Complementary DNA (cDNA) transfection method to COS-7 cells and novel ELISAs using eukaryotic recombinant proteins of human Dsc1, Dsc2, and Dsc3 confirmed specific IgG reactivity with Dsc3. (2) A woman in her 70s presented with pustular skin lesions on the left fingers with typical histopathological features. Immunoblotting and ELISAs did not detect antibodies to either Dsg1 or Dsg3. Conversely, immunoblotting detected IgG antibodies to Dscs, cDNA transfection method revealed IgG reactivity only with Dsc3, and findings from ELISAs showed that IgG reacted weakly with Dsc2 and strongly with Dsc3.

CONCLUSIONS AND RELEVANCE Autoantibodies to Dscs, particularly to Dsc3, may play a pathogenic role in some cases of pemphigus vegetans.

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Author Affiliation: Department of Dermatology, Kurume University School of Medicine, and Kurume University Institute of Cutaneous Cell Biology, Kurume, Fukuoka, Japan (Saruta, Ishii, Teye, Ono, Ohyama, Koga, Ohata, Furumura, Tsuruta, Hashimoto).

Corresponding Author: Takashi Hashimoto, MD, Department of Dermatology, Kurume University School of Medicine, and Kurume University Institute of Cutaneous Cell Biology, 67 Asahimachi, Kurume, Fukuoka 830-0011, Japan (hashimot@med.kurume-u.ac.jp).
although the patient did not remember the onset of the lesion owing to dementia.

Physical examination revealed a slightly gray-colored vegetating plaque, with several surrounding erythemas and small pustules, on the right inguinal area (Figure 1A). Laboratory tests revealed elevations in erythrocyte sedimentation rate (29 mm/h [reference range, <15 mm/h]), presence of antihuman T-cell lymphoma/leukemia virus-1 antibodies (2048 s/co [signal to cutoff] [reference range, <16 s/co]), carcinoembryonic antigen level (7.3 ng/mL [reference range, <5.0 ng/mL]), and squamous cell carcinoma antigen level (6.5 ng/mL [reference range, <15 ng/mL]). ELISAs detected anti-Dsg1 antibodies (ELISA index value, 101 [reference range, <14]) but not anti-Dsg3 antibodies (index, <5 [reference range <14]).

Chest radiography, abdominal ultrasonography, gastrointestinal endoscopy, electrocardiogram, and vaginal examination revealed no abnormal findings. Enhanced computed tomography of the abdomen and pelvis revealed hypertrophic
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Discussion

We extensively analyzed autoantigens for 2 cases of clinically and histopathologically typical pemphigus vegetans. Three serological tests, including immunoblotting, cDNA transfection method, and novel ELISAs for Dsc1, Dsc2, and Dsc3, indicated that case 1 had IgG anti-Dsc3 antibodies, in addition to IgG anti-Dsg1 antibodies. Case 2 also showed strong IgG reactivity with Dsc3, although lower reactivity with Dsc2 was detected by ELISA but not cDNA transfection method. Intriguingly, case 2 showed no antibodies to either Dsg3 or Dsg1.

Immunoblotting of normal human epidermal cell extracts revealed that IgG antibodies in a serum sample from the patient reacted with the 110-kDa a-form and the 100-kDa b-form of Dscs, as well as the 230-kDa BP230-like band and the 190-kDa periplakin-like band, but did not react with Dsgs (Figure 2E). cDNA transfection method revealed that IgG, but not IgA, antibodies reacted only with Dsc3 (Figure 2F). Novel Dsc ELISAs revealed that IgG antibodies reacted with Dsc2 (OD, 0.142 [cutoff, 0.070]) and strongly with Dsc3 (OD, 1.324 [cutoff, 1.200]), but not with Dsc1 (OD, 0.103 [cutoff, 0.200]).

From the typical clinical and histopathological findings, the diagnosis of pemphigus vegetans was made. We treated the patient first with a topical corticosteroid because the lesions were limited to the fingers. Although the treatment was effective, oral mucosal lesions and pustular skin lesions on the left inguinal area subsequently appeared. Oral prednisolone, 20 mg/d, completely controlled the lesions. We tapered the prednisolone dose to 5 mg/d without any recurrence. The clinical course was well correlated with serum eosinophil numbers.

Case 2

A woman in her 70s presented with erosive skin lesions on the left fingers. The patient had no remarkable family history. She first noticed an erosion on the left third finger web 3 months prior to presentation. Antifungal cream, which was prescribed by an internist under the putative diagnosis of tinea interdigitale, was ineffective. The lesion increased in number and size.

Physical examination revealed erosive skin lesions with pustules and scaly erythemas on the left third and fourth fingers (Figure 2A). Laboratory tests revealed an elevated number of eosinophils (580.5/μL) and presence of antinuclear antibodies with speckled pattern (+40), with no abnormality in other test results. ELISAs did not detect antibodies to either Dsg3 or Dsg1.

Histopathological analysis of a biopsy specimen of the skin lesion showed acanthotic epidermis with no apparent acantholysis and extensive inflammatory infiltrates in the dermis (Figure 2B). Typical large eosinophilic pustules with a few neutrophils were also present in the epidermis (Figure 2C).

Direct immunofluorescence detected no deposits of IgG, IgA, IgM, or C3. Results of indirect immunofluorescence of normal human skin sections were negative for both IgG and IgA antibodies, while indirect immunofluorescence of monkey esophagus sections detected IgG (Figure 2D), but not IgA, anti-epithelial cell surface antibodies.

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tibodies in indirect immunofluorescence, and the 230-kDa band is occasionally shown in serum samples from patients with nonbullous pemphigoid.

Clinically, both case 1 and case 2 showed Hallopeau-type clinical features. Both cases showed almost identical histopathological features, characteristic of pemphigus vegetans. In addition, both cases showed strong IgG reactivity with Dsc3. Considering that clinical features of both Neuman- and Hallopeau-types concur in some cases of pemphigus vegetans, the results of the present study may suggest a common pathomechanism in the Hallopeau-type of pemphigus vegetans.

To date, autoantibodies to Dscs were identified only occasionally in patients with nonclassic types of pemphigus, in-
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including pemphigus vegetans, pemphigus herpetiformis, paraneoplastic pemphigus, and atypical pemphigus. However, precise prevalence of IgG anti-Dsc autoantibodies in various types of pemphigus, including pemphigus vegetans, has not been fully elucidated. To answer this question, extensive studies using Dsc ELISAs in large numbers of patients with pemphigus should be performed.

The pathogenic role of anti-Dsc antibodies is not well understood in any types of pemphigus. In our study, case 2 is particularly interesting because this case showed typical clinical features of pemphigus vegetans but no anti-Dsg antibodies, supporting our previous speculation of pathogenic role of anti-Dsc autoantibodies in pemphigus vegetans.

The studies of knockout mice of Dsc1 and Dsc3 showed pemphigus-like skin fragility with defective epidermal barrier function. In addition, the pathogenic role of anti-Dsc3 antibodies were demonstrated in a single pemphigus case with anti-Dsg3 antibodies and by an in vitro cell culture study. These previous studies suggested that anti-Dsc antibodies play a pathogenic role by influencing keratinocyte cell adhesion. Further functional studies should be required to elucidate the pathogenic relevance of anti-Dsc antibodies in pemphigus.

REFERENCES