Subcorneal Pustular Dermatosis–Type IgA Pemphigus With Autoantibodies to Desmocollins 1, 2, and 3

Imke Düker, MD; Jörg Schaller, MD; Christian Rose, MD; Detlef Zillikens, MD; Takashi Hashimoto, MD; Johannes Kunze, MD

Background: IgA pemphigus is a rare neutrophilic acantholytic autoimmune disease that is characterized by IgA deposits on keratinocyte cell surfaces. Clinically and histologically, IgA pemphigus is divided into 2 major subtypes: subcorneal pustular dermatosis and intraepidermal neutrophilic IgA dermatosis. We report the first case of subcorneal pustular dermatosis–type IgA pemphigus that showed reactivity to all 3 isoforms of the desmocollin family by indirect immunofluorescence microscopy of COS7 cells transfected with desmocollin 1, 2, or 3.

Observations: We describe a 94-year-old woman with IgA pemphigus with a unique immunopathologic pattern. Direct immunofluorescence microscopy revealed IgA deposits throughout the entire epidermis, with stronger staining in the upper epidermis. The autoantibodies from this patient did not show IgA or IgG reactivity with desmogleins via immunoblotting or enzyme-linked immunosorbent assay. By indirect immunofluorescence by the use of COS7 cells transfected with desmocollin 1, 2, or 3, IgA autoantibodies in a serum sample from our patient clearly reacted with all of them.

Conclusions: The pathophysiology and autoantigen profile of bullous autoimmune diseases, especially pemphigus and its subforms, are more complex than previously believed. Because pemphigus seems to be a heterogeneous disorder, further studies are needed to evaluate the complexity of the disease.

Arch Dermatol. 2009;145(10):1159-1162

IgA pemphigus is a rare autoimmune blistering disease characterized by epidermal IgA immunoglobulin deposits. The presence of IgA in the epidermis was first reported by Varigos. In the past, various terms have been used to describe this condition, such as intraepidermal neutrophilic IgA dermatosis, intercellular IgA vesiculopustular dermatosis, and IgA pemphigus foliaceus. Currently, IgA pemphigus is considered to be a distinct clinical entity that includes 2 subtypes with different histologic features and different IgA deposition patterns in the epidermis: intraepidermal neutrophilic IgA dermatosis (IEN) and subcorneal pustular dermatosis (SPD). In the SPD type, desmocollin 1, one of the desmosomal cadherins, has been identified as a target autoantigen. In most cases of the IEN type, the autoantigen remains to be fully characterized, whereas, in single cases, desmoglein 1 and desmoglein 3 have been demonstrated to be targets of the autoantibodies in this variant. Clinically, patients commonly present with flat pustules, often on a slightly erythematous base, which tend to coalesce to form annular patterns. The regions mainly affected are the trunk, axillae, and groin. Mucosal involvement is usually lacking.

REPORT OF A CASE

A 94-year-old woman presented with a 2-week history of bullous dermatosis. Results of physical examination revealed a disseminated vesiculopustular eruption on an erythematous base and erosions with yellow crusts. The sites of predilection were the axillae, groin, and proximal portions of the extremities. There was no mucosal involvement. Bacterial cultures of the pustules were negative. The
results of laboratory investigations, such as serum immunofixation of IgG, IgA, and IgM, were within normal ranges.

HISTOPATHOLOGIC ANALYSIS

Histopathologic examination of a lesional skin biopsy specimen showed a subcorneal cleft with acantholysis. The blister was filled by fibrin, erythrocytes, and numerous neutrophilic granulocytes (Figure 1). In the upper dermis, there were also neutrophils that infiltrated the epidermis.

DIRECT IMMUNOFLUORESCENCE MICROSCOPY

Direct immunofluorescence microscopy of a perilesional skin biopsy specimen revealed intercellular deposits of IgA in the entire epidermis with a stronger staining of the superficial layers (Figure 1). Fluorescein isothiocyanate–conjugated goat anti-human IgA (specific to α chains) and IgG (specific to γ chains) were used as secondary antibodies (DiaMed Inc, Windham, Maine).

INDIRECT IMMUNOFLUORESCENCE MICROSCOPY

The results of indirect immunofluorescence microscopy performed on monkey esophagus and healthy human skin were negative for circulating IgA or IgG autoantibodies. Interestingly, when performed on sodium chloride split human skin, IgA autoantibodies that stained the interface of the stratum corneum and stratum granulosum were detected at a titer of 1:320.

IMMUNOBLOT ANALYSIS AND ENZYME-LINKED IMMUNOSORBENT ASSAY

Immunoblot analysis of healthy human epidermal extracts showed no specific IgA or IgG reactivity in the serum of the patient. Enzyme-linked immunosorbent assay (ELISA) that used recombinant desmoglein 1 and 3, expressed in the baculovirus system, showed no IgA or IgG reactivity.

COMMENT

We present a case of SPD-type IgA pemphigus with a unique immunopathologic pattern. Direct immunofluorescence microscopy revealed IgA deposits on keratinocyte cell surfaces, but unexpectedly the staining was throughout the epidermis, which showed stronger intensity in the superficial and weaker staining in the basal layers. Usually, autoantibodies from patients with SPD-type IgA pemphigus do not react with the basal layers of the epidermis because of the epidermal distribution of the autoantigen (ie, desmocollin 1). Staining of the entire epidermis in the skin of our patient, which resembled the pattern of the IEN type, suggested desmoglein 3 or desmocollin 3 as potential additional autoantigens. In fact, in addition to reactivity with desmocollin 1, the serum of our patient bound to both desmocollins 2 and 3 by indirect immunofluorescence microscopy of COS7 cells transfected with the different desmocollin isoforms. In contrast, no IgA or IgG reactivity was found with desmogleins 1 and 3.

Desmocollins, together with the desmogleins, are major desmosomal glycoproteins and are members of the cadherin superfamily of Ca²⁺-dependent cell adhesion molecules.²⁷ Desmocollins show at least 3 isoforms³ and contribute to the adhesive core of the desmosome, whose basic function is to guarantee the epidermal integrity by the mediation of cell-cell adhesion. The isoforms of desmocollins are expressed in a differentiation-specific manner: desmocollin 1 expression is weak in suprabasal layers and increases further upward; it shows strong
expression in the upper spinous layers. Desmocollin 2 shows similar expression to desmocollin 1 but is most strongly expressed at the base of the rete ridges. Desmocollin 3 is most strongly expressed in the basal layers and weaker in the suprabasal layers.15,17,18

In our case, the detection of IgA autoantibodies not only to desmocollin 1 but also to the 2 other desmocollin isoforms may explain the finding of the staining throughout the epidermis by direct immunofluorescence microscopy. Kopp et al19 recently described another case of SPD-type IgA pemphigus in which the autoantibodies reacted not only with the uppermost layers but throughout the entire epidermis. In this previous case, antibodies to both desmocollin 1 and desmoglein 1 were detected.

A staining pattern throughout the epidermis by direct and indirect immunofluorescence microscopy along with a histologic characteristic of the SPD-type IgA pemphigus was also seen by Niimi et al.20 However, target antigens of IgA antibodies in this case remained unknown: they did not react with desmogleins or desmocollins as determined by immunoblotting, ELISA, or immunofluorescence microscopy of complementary DNA-transfected cells. In our case, via immunoblotting, we could not detect any IgA reactivity in the serum of our patient. As reported, a possible explanation for the failure to detect desmocollins by this method is that the effect of conformation-dependent epitopes on desmocollins may have been altered by the extraction procedure or sodium dodecyl sulfate–polyacrylamide gel electrophoresis.11,21,22 Not only immunoblotting but also ELISA may fail to detect reactivity in some cases in which the results of indirect immunofluorescence microscopy on complementary DNA–transfected cells are positive; this factor suggests that there may be differences in conformation between desmocollin 1 produced by baculovirus-infected cells and protein produced by COS7-transfected cells.23

Ebihara et al6 described 3 patients with SPD-type IgA pemphigus that reacted with desmocollin 1 and 2, and Hisamatsu et al21 detected IgA antibodies to both desmocollin 2 and 3 in one case of so-called atypical pemphigus. We report the unique detection of IgA antibodies to desmocollins 1, 2, and 3 in a patient with SPD-type IgA pemphigus.

In recent years, it has become evident that the different subtypes of IgA pemphigus may be associated with a number of different autoantibody specificities. It is becoming more obvious that certain autoantibodies are not restricted to just one form of pemphigus.24-26 Recently, IgA autoantibodies to desmogleins 1 and 3 could also be found.

Figure 2. Indirect immunofluorescence microscopy of COS7 cells transfected with desmocollins 1, 2, and 3. The IgA antibodies of the serum of our patient reacted with the transfected cells that express desmocollin 1 (A), desmocollin 2 (B), and desmocollin 3 (C). IgA antibodies of a control individual with subcorneal pustular dermatosis–type IgA pemphigus reacted with COS7 cells transfected with desmocollin 1 (D) but not IgA antibodies of a healthy control serum (E).
in patients with pemphigus vulgaris and pemphigus foliaceous, in addition to IgG antibodies to these desmogleins. Furthermore, a few patients with IgA pemphigus have been shown to react with desmoglein 1 and 3 via IgA ELISA. These cases, in which IgA antibodies react exclusively with desmogleins 1 or 3, should be named IgA pemphigus foliaceous and IgA pemphigus vulgaris, respectively. In a few cases, neutrophilic infiltration can be lacking. Autoantibodies to desmocollins have also been described in certain pemphigus serum samples, which may be owing to the epitope spreading concept. However, as in mucocutaneous-type pemphigus vulgaris with IgG antibodies to both desmogleins 1 and 3, individual cases may show antibodies to multiple antigens. Autoantibodies to these different antigens are not necessarily considered to be produced by epitope spreading. It is therefore feasible, in our case, that IgA antibodies to desmocollins 1, 2, and 3 may be produced independently. Because pemphigus seems to be a heterogeneous disorder, further studies are needed to evaluate the complexity of the disease.

Accepted for Publication: February 27, 2009.

Correspondence: Imke Düker, MD, Department of Dermatology and Venerology, St. Barbara Hospital, Catholic Clinic, Barbarastrasse 67, 47167 Duisburg, Germany (imkeduerker@gmail.com).

Author Contributions: Drs Düker, Schaller, Rose, Zillikens, Hashimoto, and Kunze had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Düker, Schaller, and Kunze. Acquisition of data: Düker, Schaller, Rose, Zillikens, Hashimoto, and Kunze. Analysis and interpretation of data: Düker, Schaller, Rose, Zillikens, Hashimoto, and Kunze. Drafting of the manuscript: Düker. Critical revision of the manuscript for important intellectual content: Düker, Schaller, Rose, Zillikens, Hashimoto, and Kunze. Administrative, technical, or material support: Düker, Schaller, Rose, Zillikens, Hashimoto, and Kunze. Study supervision: Düker, Schaller, and Kunze.

Financial Disclosure: None reported.

References

12. Hashimoto T, Ebihara T, Nishikawa T. Two different isoforms of desmocollin are recognized by autoantibodies in various types of pemphigus. Dermatology. 1994;189(suppl 1):124-125.