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.

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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). The SPD type shows subcorneal acantholysis and pustules with intercellular IgA deposits in the upper epidermis. The IEN type is characterized by pustules located deeper in the epidermis and by intercellular IgA deposits throughout the entire epidermis. Indirect immunofluorescence microscopy reveals circulating IgA antibodies to intraepidermal structures in only half the cases. 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 (Figure 1). There was no mucosal involvement. Bacterial cultures of the pustules were negative. The

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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 perilungal 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 ON COS7 CELLS

By indirect immunofluorescence that used COS7 cells transfected with desmocollin 1, 2, or 3, IgA autoantibodies in the serum of our patient clearly reacted with all of them (Figure 2). On the basis of these results, the patient was diagnosed as having the SPD-type IgA pemphigus, and oral therapy with dapsone, 50 mg twice daily, was started. This course resulted in complete clearing of skin lesions within 3 weeks.

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 Ca$$^{2+}$$-dependent cell adhesion molecules. Desmocollins show at least 3 isoforms 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

Figure 1. Bullous dermatosis in a 94-year-old woman. A, Right arm with pustules and crusts on an erythematous background. B, Histopathologic analysis of lesional skin that shows a subcorneal blister filled with neutrophilic granulocytes and erythrocytes (hematoxylin-eosin, original magnification ×100). C, Direct immunofluorescence microscopy of perilungal skin showing intercellular IgA deposits in the entire epidermis with stronger staining in the upper layers of the epidermis (original magnification ×200).
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.\textsuperscript{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 al\textsuperscript{19} 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.\textsuperscript{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 also 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.\textsuperscript{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.\textsuperscript{23}

Ebihara et al\textsuperscript{6} described 3 patients with SPD-type IgA pemphigus that reacted with desmocollin 1 and 2, and Hisamatsu et al\textsuperscript{21} 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.\textsuperscript{24-26} Recently, IgA autoantibodies to desmogleins 1 and 3 could also be found.
in patients with pemphigus vulgaris and pemphigus foliaceous, in addition to IgG antibodies to these desmogleins.24 Furthermore, a few patients with IgA pemphigus have been shown to react with desmoglein 1 and 3 via IgA ELISA.22 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.27 Autoantibodies to desmocollins have also been described in certain pemphigus serum samples,18,21 which may be owing to the epitope spreading concept.29 However, as in mucocutaneous-type pemphigus vulgaris with IgG antibodies to both desmoglein 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.

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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.

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