Antiepiigrin Cicatricial Pemphigoid

An Underdiagnosed Entity Within the Spectrum of Scarring Autoimmune Subepidermal Bullous Diseases?

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Background: Antiepiigrin cicatricial pemphigoid (AECP) is a chronic autoimmune subepidermal blistering disease characterized by autoantibodies to laminin 5 and clinical features of cicatricial pemphigoid. Only a few patients with AECP have been described to date. The aim of the present study was to analyze the relative frequency of AECP among patients with the clinical phenotype of cicatricial pemphigoid.

Observations: Serum from 16 consecutive patients with the clinical phenotype of cicatricial pemphigoid were included in this study. Nine patients had circulating IgG autoantibodies by indirect immunofluorescence on sodium chloride–split skin; patients' IgG bound to the epidermal side (n = 2), dermal side (n = 5), or both sides (n = 2) of this test substrate. Interestingly, all 5 cases with dermal binding immunoprecipitated laminin 5 from extracts and media of cultured keratinocytes, and 4 of these serum samples reacted with the α3 subunit of laminin 5 by immunoblotting. None of the patients with dermal binding of IgG demonstrated autoantibodies to type VII collagen.

Conclusion: Our data suggest that, among patients with the clinical phenotype of cicatricial pemphigoid, AECP may be more frequent than previously assumed.

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Cicatricial pemphigoid (CP) is a chronic, subepidermal autoimmune blistering disease of mucous membranes and skin. It may involve oral, ocular, nasal, pharyngeal, laryngeal, esophageal, and anogenital mucous membranes. Skin lesions appear in about 30% of patients with CP.1-4 Cicatricial pemphigoid is a heterogeneous disease with respect to the isotype of the associated autoantibodies in these patients (ie, IgG, IgA, or both), the side of skin split by 1-mol/L sodium chloride (NaCl) that is bound by their circulating autoantibodies, and the specific antigens targeted by their autoimmune response.

To date, the best characterized IgG autoantibodies in patients with CP and skin involvement (ie, patients whose disease is not limited to the eyes) are directed to BP180 (also referred to as type XVII collagen or BPAG2), laminin 5, or type VII collagen.3-6 In 1992, Domloge-Hultsch et al7 described a group of patients with CP who had IgG autoantibodies against a set of disulfide-linked polypeptides referred to as epiligrin. This protein, also designated nicein, kalinin, and BM 600 at that time, is now known to be identical to laminin 5, which is a heterotrimer consisting of α3β3γ2 subunits.

The aim of the present study was to analyze the relative frequency of antiepiigrin cicatricial pemphigoid (AECP) among patients with the clinical phenotype of CP in a regional referral center. The patients' skin and/or mucosa were analyzed by direct immunofluorescence (IF) microscopy. In addition, serum samples were studied by indirect IF for the presence of circulating IgG autoantibodies against BP180, the β4 subunit of α6β4 integrin, laminin 5, or type VII collagen. Of 16 consecutive patients with CP identified, 9 had IgG anti–basement membrane autoantibodies. We report the clinical features of these patients as well as their response to treatment. Our data suggest that, among patients with the clinical phenotype of CP, AECP represents an important subset.

RESULTS

IMMUNOFLORESCEENCE

All 16 patients included in this study had linear deposits of immunoreactants at the...
PATIENTS AND METHODS

PATIENTS

Between June 1, 1989, and May 31, 1998, we analyzed the serum of 16 consecutive patients with the clinical phenotype of CP (all with a frankly scarring phenotype) at the immunofluorescence laboratory of the Department of Dermatology, University of Würzburg, Würzburg, Germany. Thirteen patients were treated at our department; the serum of 3 patients was sent to us from other institutions. Thirteen patients were women and 3 were men; their mean age was 65.3 years (range, 47-76 years). All patients showed different degrees of scarring involvement of oral (n = 15), ocular (n = 9), nasal (n = 5), pharyngeal (n = 6), laryngeal (n = 6), esophageal (n = 1), or anogenital (n = 7) mucous membranes as well as the skin (n = 8).

IF MICROSCOPY STUDIES

Perilesional skin or mucosa was studied by direct IF for deposits of IgG, IgA, IgM, and C3. For indirect IF, serum samples of patients and normal volunteers were reacted with 1-mol/L NaCl-split human skin as described previously. Slides for IF microscopy were examined independently by 2 investigators (including D.Z.).

IMMUNOPRECIPITATION STUDIES

Subconfluent monolayers of normal human keratinocytes were biosynthetically radiolabeled with methionine labeled with sulfur 35 (1.85 MBq/mL; New England Nuclear, Boston, Mass) in methionine-free medium for 2 hours (for studies of cell extract) or overnight (for studies of conditioned medium). Samples were collected, processed, and studied by immunoprecipitation (IP) by means of serum from patients and normal controls as described previously.

IMMUNOPRECIPITATION ASSAY STUDIES

Dermal and epidermal extracts were prepared and analyzed as described. BP180 NC16A and fusion protein 4575 representing a C-terminal portion of the BP180 ectodomain were expressed as glutathione S transferase (GST) fusion proteins and affinity purified by means of glutathione agarose. Immuno blot analysis and enzyme-linked immunosorbent assay studies with recombinant BP180 NC16A were performed as described previously. Lammin 5 was isolated from the extracellular matrix of cultured human keratinocytes, reduced, and studied by immunoblotting with serum from patients and reference controls. Alkaline phosphatase–conjugated goat F(ab’)2 anti–human IgG was used as a secondary antibody (dilution of 1:1000). Immunoblots were developed with an alkaline phosphatase–conjugate substrate kit (Bio-Rad, Hercules, Calif.).

ANTIGEN EXTRACTION IMMUNOBLOT AND ENZYME-LINKED IMMUNOSORBENT ASSAY STUDIES

Basement membrane zone (BMZ) in biopsy specimens from perilesional skin and/or mucosa. In 14 of 16 patients, deposits of IgG were found; in 12 patients, deposits of C3; and in 2 patients, deposits of IgA. Indirect IF microscopy studies of NaCl-split skin identified IgG anti-BMZ autoantibodies in 9 of these patients; titers ranged from 10 to 320. In contrast, none had circulating IgA anti-BMZ autoantibodies. In 2 cases, an epidermal staining pattern was observed; in another 2, a combined dermoepidermal staining pattern; and in 5 cases, a dermal staining pattern.

IMMUNOPRECIPITATION

In studies of conditioned medium from biosynthetically radiolabeled human keratinocytes, all 5 patients with IgG directed against the dermal side of NaCl-split skin (as well as a reference control patient with AECP) immunoprecipitated a series of disulfide-linked polypeptides that correspond to laminins 5 and 6, as previously described (see "Patients and Methods" section). The relative stoichiometry of polypeptides identified by patients 1 to 4 (lanes 3-6) as well as the reference positive control (lane 2) was approximately the same; the reactivity of autoantibodies from patient 5 (lane 7) dominated against laminin 5. Serum from a normal volunteer (negative control, lane 1) showed no specific reactivity to these proteins. The markers at the left margin indicate molecular weight (× 10^3).
Figure 2 shows representative results of IP studies of biosynthetically radiolabeled extracts from cultured human keratinocytes. While normal human serum (negative control, lanes 2 and 12) showed no reactivity to this preparation, serum from a reference patient with bullous pemphigoid immunoprecipitated BPAG1 (bullous pemphigoid antigen 1) as a distinct 230-kd band (lane 3, marked by arrow). Serum from patients with anti-epiligrin cicatricial pemphigoid (patients 1, 2, and 5 and a reference positive control [lanes 5, 7, 8, and 13, respectively]) immunoprecipitated a complex of disulfide-linked, comigrating polypeptides from keratinocyte extracts (delimited by brackets) as described previously.20 Serum from patients with cicatricial pemphigoid with IgG directed against the epidermal side of 1-mol/L sodium chloride–split skin showed no specific reactivity (patient 6, lane 15) or bound only “patient-specific” bands (patient 7, lane 9, faint bands of 150 and 100 kd). Similarly, serum from patients with cicatricial pemphigoid with IgG directed against both sides of 1-mol/L sodium chloride–split skin showed no specific reactivity (patient 9, lane 10) or only “patient-specific” bands (patient 8, lane 14, a band of 110 kd). Serum from a patient with an undefined blistering disease containing IgG directed against the epidermal side of 1-mol/L sodium chloride–split skin (titer, 40) showed no specific reactivity to this preparation (lane 4). A set of radiolabeled molecular weight markers is shown in lanes 1, 6, and 11 on each Tris-glycine polyacrylamide gel; the numbers in the left margin indicate their molecular weight (×10^3).

By immunoblotting of epidermal extracts, 3 of the 14 patients with epidermal basement membrane deposits of IgG or C3 had autoantibodies to BP230, and 1 patient demonstrated antibodies to BP180. None of the 14 patients had autoantibodies to type VII collagen by immunoblot analysis of dermal extracts. With the use of recombinant forms of BP180, 2 of the 14 serum samples reacted with BP180 NC16A by both immunoblot analysis and enzyme-linked immunosorbent assay, and 3 serum samples immunoblotted a GST fusion protein containing a 49–amino acid stretch of the C-terminal region of BP180.11 Representative results of these analyses are shown in Figure 4. Three of the 14 serum samples were negative by indirect IF yet positive for reactivity with epidermal and recombinant proteins.

**IMMUNOBLOTTING**

Immunoblot studies of laminin 5 isolated from the extracellular matrix of cultured human keratinocytes found that IgG from patients 1 to 4 with AECP bound both the 200- and 165-kd unprocessed and processed subunits, respectively, of laminin α3 (Figure 3). These findings accounted for the ability of these serum samples to immunoprecipitate both laminins 5 and 6, since the α subunits of these laminin isoforms are immunologically cross-reactive.30,31 Serum from patient 5 with AECP showed no immunoblot reactivity to any purified laminin α subunits, a finding that has been previously ascribed to the reactivity of such patients’ IgG to conformational determinants of this protein.19,32 These studies included reference serum samples from patient with AECP who had IgG autoantibodies directed exclusively against laminin α3 as well as a normal volunteer with no evidence of anti-laminin 5 IgG.

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**CLINICAL AND IMMUNOPATHOLOGIC FEATURES AND COURSE OF DISEASE OF THE 5 PATIENTS WITH AECP**

Clinical characteristics of the 5 patients with AECP are summarized in Table 1, and examples are shown in Figure 5. Immunopathologic features of these patients are demonstrated in Table 2, and representative examples of direct and indirect IF are depicted in Figure 6 and Figure 7. The response to treatment in the 5 patients with AECP is briefly summarized below.

Patient 1 underwent intravenous pulse therapy, including dexamethasone (100 mg/d on 3 consecutive days) and cyclophosphamide (500 mg on day 1), for 10 cycles as described previously.18,33 Adenocarcinoma of the colon was detected after the sixth pulse, and the patient un-
derwent hemicolectomy. Subsequently, symptoms improved markedly. Cyclophosphamide was discontinued, and the patient is currently treated with pulses of dexamethasone (100 mg/d on 3 consecutive days) every 10 weeks. Under this regimen, no new blisters have formed during the past 6 months, whereas antibodies to laminin 5 are still detectable by IP. The patient continues to suffer from severe scarring of the larynx.

Patient 2 had stable disease for 2 years with tapering doses of oral methylprednisolone (initially 80 mg/d) and azathioprine (initially 150 mg/d). She underwent surgical treatment for ectropion on 3 occasions, then was unavailable for follow-up.

In patient 3, treatment with dexamethasone and cyclophosphamide pulses was initiated and supplemented with 125 mg of cyclophosphamide orally daily between cycles, therapy that resulted in a good clinical response and stable disease. After 9 cycles of dexamethasone and cyclophosphamide treatment, the patient developed multiple enlarged lymph nodes that were found to signify metastases from a carcinoma of the cervix uteri for which hysterectomy had been performed 6 years earlier. The patient died of metastatic disease 1 year after diagnosis of AECP.

Patient 4 experienced clinical improvement with dexamethasone and cyclophosphamide pulse therapy. The patient died of pneumonia 6 weeks after the initiation of treatment.

Patient 5 showed no substantial improvement after different treatment regimens, including dapsone, colchicine, systemic glucocorticosteroids, high-dose intravenous immunoglobulins, and cyclosporine. The patient died of a perforated duodenal ulcer 2½ years after initiation of treatment.

**COMMENT**

Antiepiligrin cicatricial pemphigoid is a recently defined chronic subepidermal autoimmune vesiculobullous disease that primarily affects mucous membranes.\(^5,20\) It was previously considered to comprise a small subgroup of patients with CP. Direct IF examination of perilesional mucous membrane or skin biopsy specimens from patients with AECP demonstrates linear deposits of IgG and C3 at the BMZ. Indirect IF studies show binding of the IgG autoantibodies to the dermal side of NaCl-split human skin.\(^7,20\) By IP of radiolabeled condi-

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**Figure 3.** Immunoblot studies of laminin 5 purified from the extracellular matrix of human keratinocytes, showing that IgG from patients 1 to 4 with antiepiligrin cicatricial pemphigoid (lanes 6-9, respectively) and a reference control patient with antiepiligrin cicatricial pemphigoid (lane 5) immunoblotted the 200-kd (unprocessed) and 185-kd (processed) \(\alpha\) subunit of laminin 5 (marked by arrows). Although the reactivity of IgG from patient 1 was weak (lane 6), the identified bands comigrated with those bound by IgG from other patients with antiepiligrin cicatricial pemphigoid and darkened on prolonged development. Serum from patient 5 with antiepiligrin cicatricial pemphigoid (lane 10) as well as a normal volunteer (negative control, lane 4) showed no reactivity to these polypeptides. Because IgG from patients 1 to 4 with antiepiligrin cicatricial pemphigoid recognized laminin subunit \(\alpha\)3, they immunoprecipitated laminins 5 (\(\alpha\3\beta\3\gamma\2\) and 6 (\(\alpha\3\beta\1\gamma\1\)) as shown in Figure 1. Rabbit laminin 5 antiserum bound all subunits of this protein (lane 3) as described previously;\(^23\) normal rabbit serum tested as a control was negative (lane 2). A set of molecular weight markers is shown in lane 1; the numbers in the left margin indicate molecular weight (\(\times 10^{-3}\)).
tioned keratinocyte medium or by immunoblot analysis of extracellular matrix of cultured human keratinocytes, the autoantibodies were found to recognize laminin 5. Laminin 5 is an anchoring filament–lamina densa associated heterotrimer (α3β3γ2). More recently, it was found that most patients’ autoantibodies bind to the α3 subunit of this protein.14,16 Some patients have antibodies to laminin β3, and some show reactivity to both the

<table>
<thead>
<tr>
<th>Patient No./Sex/</th>
<th>Involvement*</th>
<th>Associated Diseases and Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mouth</td>
<td>Eye</td>
</tr>
<tr>
<td>1/F/76</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/F/75</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/F/60</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/F/65</td>
<td>+</td>
<td>−</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/F/74</td>
<td>+</td>
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*Plus sign indicates present; minus sign, absent.
The pathogenic relevance of autoantibodies to laminin 5 has been demonstrated in an animal model. When rabbit anti–laminin 5 antibodies were passively transferred into neonatal mice, the animals developed subepidermal bullous disease that duplicated the findings seen in patients with AECP.

In this study, we characterized the immune response in 16 consecutive patients with clinical and immunopathologic features of CP that were identified at the Department of Dermatology at the University of Würzburg during a period of 9 years. All patients were studied by direct and indirect IF microscopy and for reactivity of serum antibodies with dermal and epidermal extracts, recombinant forms of BP180, and extracts and media of radiolabeled human keratinocytes by immunoblot and/or IP analysis. Nine of the 16 patients had circulating IgG antibodies to components of the BMZ. Five of these 9 patients were found to have antibodies to laminin 5. In none of our patients with CP was reactivity to type VII collagen detected. A total of 6 of our patients with CP showed autoantibodies to BP180; 2 serum samples reacted with NC16A and 3 others with a C-terminal stretch of BP180. One serum sample bound to BP180 extracted from epidermis, whereas 3 serum samples contained antibodies to epidermal BP230. Some serum samples were negative by indirect IF but recognized native or recombinant forms of the BP autoantigens, or both. Three serum samples (patients 7 through 9) bound recombinant forms of BP180 yet showed no specific corresponding IP or immunoblot reactivity to human keratinocyte or epidermal extracts. This finding may have occurred because immunoblotting with recombinant BP180 is more sensitive than IP or immunoblot analysis with BP180 extracted from keratinocytes or epidermis, as was previously shown.

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Table 2. Immunopathologic Findings in 9 Patients With CP With Circulating IgG Autoantibodies to Epidermal BMZ

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Indirect IF†</th>
<th>HK Media IP‡</th>
<th>HK Extract IP§</th>
<th>HK ECM IB</th>
<th>BP180 4575 IB</th>
<th>BP180 NC16A IB</th>
<th>Epidermal Extract IB</th>
<th>Dermal Extract IB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dermal (20)</td>
<td>L5 and L6</td>
<td>L5</td>
<td>α3¶</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>2</td>
<td>Dermal (160)</td>
<td>L5 and L6</td>
<td>L5</td>
<td>α3</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>3</td>
<td>Dermal (10)</td>
<td>L5 and L6</td>
<td>L5</td>
<td>α3</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>4</td>
<td>Dermal (320)</td>
<td>L5 and L6</td>
<td>L5</td>
<td>α3</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>5</td>
<td>Dermal (40)</td>
<td>L5 (L6 faint)</td>
<td>L5</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>6</td>
<td>Epidermal (10)</td>
<td>−</td>
<td>−</td>
<td>ND</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>7</td>
<td>Epidermal (40)</td>
<td>−</td>
<td>−</td>
<td>150, 100 kd</td>
<td>ND</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>8</td>
<td>Dermal and epidermal (160)</td>
<td>120 kd</td>
<td>110 kd</td>
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<tr>
<td>9</td>
<td>Dermal and epidermal (10)</td>
<td>−</td>
<td>−</td>
<td>ND</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
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</table>

*CP indicates cicatrical pemphigoid; BMZ, basement membrane zone; IF, immunofluorescence; HK, human keratinocyte; IP, immunoprecipitation; ECM, extracellular matrix; IB, immunoblot; minus sign, absent; plus sign, present; and ND, not done. All patients had linear deposits of IgG and C3 at the BMZ of perilesional skin biopsy specimens.
†Indirect immunofluorescence microscopy on 1-mol/L sodium chloride–split human skin; results in parentheses correspond to titers of anti-BMZ IgG.
‡Because HK medium has been shown to be a source of immunoreactive laminin 5 (L5) and laminin 6 (L6), the results are presented accordingly. The IgG autoantibody reactivity in patient 5 dominated against L5.
§Laminin 5 is the dominant isoform identified in biosynthetically radiolabeled keratinocyte extracts; hence, all results are noted accordingly.
¶BP180 4575 represents a C-terminal stretch of BP180 consisting of 49 amino acids.
†The α3 chain of laminin 5.
patients with CP. However, our study selected patients on the basis of the clinical finding of a scarring phenotype, whereas Chan et al selected their patients on the basis of the finding of involvement of mucous membranes (i.e., a scarring phenotype was not a requirement for inclusion in their study).

Summary data regarding clinical and immunopathologic features of 14 cases of AECP have been reported to date. The clinical features of these patients have been indistinguishable from those of patients with other forms of CP. All of our patients with AECP had involvement of the oral mucosa, and in all but 1 patient the oropharynx and larynx were also affected. Interestingly, all of our patients were women. This is in contrast to the previous cases, in which 8 of 13 patients were male. Our observation may be an incidental finding or may represent regional or racial differences within our population of northwestern Bavaria. Two of our 5 patients with AECP suffered from an associated malignant tumor. In 1 patient, metastatic disease from a cervical carcinoma was detected shortly after AECP was diagnosed. In a second patient, disease activity was markedly reduced when an adenocarcinoma of the colon was removed. After surgery, no new blisters occurred, and this patient has currently tapered off treatment.

Five other cases of AECP have been reported in association with cancer. Whether these findings indicate a causal relation between AECP and malignant neoplasms or rather represent a coincidence requires further study of a larger group of patients during a longer period. The survival rate of our patients with AECP was not favorable. Two patients with AECP died of complications of immunosuppressive treatment. Another patient died of metastatic carcinoma of the cervix 1 year after the diagnosis of AECP. The characterization of different subgroups among patients with different subtypes of CP may identify individuals at risk for severe disease, certain spectrums of involvement, or specific associations. Moreover, such distinctions may eventually lead to the development of more effective and specific treatment regimens as advances in immunotherapy are forthcoming.

We add 5 new cases of AECP to the literature concerning this recently identified entity. Five of 9 patients with clinical features of CP and detectable levels of circulating IgG anti-BMZ autoantibodies suffered from this disease. Our findings suggest that, among patients with the clinical phenotype of CP, AECP may represent an important subset.

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REFERENCES


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Clinicians, local and regional societies, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern and be submitted double-spaced and in triplicate. Photomicrographs and illustrations must be clear and submitted as positive color transparencies (35-mm slides) or black-and-white prints. Do not submit color prints unless accompanied by original transparencies. Material should be accompanied by the required copyright transfer statement, as noted in “Instructions for Authors.” Material for this section should be submitted to George J. Hruza, MD, Cutaneous Surgery Center, 1 Barnes Hospital Plaza, Suite 16411, St Louis, MO 63110. Reprints are not available.

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