Acquired Hemophilia Associated with Autoimmune Bullous Diseases: A Report of Two Cases and a Review of the Literature

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Abstract

Acquired hemophilia (AHA) is a relatively rare and life-threatening disease caused by autoantibodies against factor VIII. Autoimmune bullous diseases (ABD) are also caused by autoantibodies against specific skin proteins. We herein report two cases of AHA associated with ABD. These coincidences are extremely rare, and only 14 documented cases have been reported previously. We further analyzed the properties of the autoantibodies in our patients. The epitopes were the A2 domain in patient 1, and both the A2 domain and the light chain in patient 2. Their isoforms were predominantly IgG4. Cross-reactivity could not be demonstrated. An accumulation of cases is required to unveil the pathogenesis of AHA.

Key words: acquired hemophilia A, pemphigus, bullous pemphigoid, autoantibody, factor VIII inhibitor and cross-reactivity

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Introduction

Acquired hemophilia (AHA) is a relatively rare disease that occurs at a rate of approximately 1.5 persons per million each year, and is a sometimes life-threatening autoimmune disease caused by the spontaneous development of autoantibodies against factor VIII (1). The clinical manifestations include spontaneous hemorrhages into skin, muscles or soft tissues, and excessive bleeding during surgery. Hemarthrosis seldom occurs in AHA, in contrast to congenital hemophilia. About half of the cases are associated with pregnancy, the post-partum period, autoimmune diseases, malignancies or drug allergies (2). Although some knowledge of the condition has been accumulated, the pathogenesis remains unclear.

We herein describe two rare cases of AHA associated with autoimmune bullous diseases (ABDs), pemphigus and bullous pemphigoid, which are also caused by autoantibodies against specific skin proteins, desmogleins and BP180, respectively. To the best of our knowledge, only 16 documented cases of AHA associated with ABDs have been reported, including the two present cases (3-13). These ABDs may be related to the pathogenesis of AHA, however, the characterization of the autoantibodies has been limited, as well as the clinical features, and the accumulation of additional cases will be necessary to provide a better picture of these diseases.

In this study, we analyzed the properties of the autoantibodies in these two cases of AHA associated with ABD, and discuss the clinical relevance.

Case Reports

Patient 1

Patient 1 was a 44-year-old Japanese woman who was treated for pemphigus foliaceus six years prior with high dose methyl-prednisolone, tailing to a maintenance dose of 5 mg prednisolone daily. About a week before the admis-
tions suggested hematothorax. On admission, she manifested hemorrhagic shock and investigations suggested hematothorax. On admission, she manifested hemorrhagic shock and investigated for about two weeks. However, these abnormal coagulation tests were gradually improved, and the inhibitor activity was eventually diminished after three months of treatment with prednisolone combined with cyclophosphamide.

**Patient 2**

Patient 2 was an 80-year-old Japanese woman who was diagnosed with bullous pemphigoid that resolved with prednisolone treatment for eight months without any recurrence. Three months later, she was referred to our hospital, presenting with massive subcutaneous bleeding of her arms and a gingival hemorrhage after she fell. An investigation showed a normal platelet count, microcytic anemia and a prolonged APTT (87.1 seconds). The factor VIII levels were less than 1% and the factor VIII inhibitor activity measured 28 BU/mL.

Twenty-five mg of prednisolone was administered for four weeks and gradually tapered. The inhibitor activity has been successfully reduced to undetectable levels even after discontinuation of the corticosteroid.

**Determination of the isoforms and the epitopes of the autoantibodies**

We performed a Western blot analysis to identify the epitope fragments of autoantibodies, using recombinant factor VIII that was either thrombin-treated or untreated as the antigen. For the secondary antibodies, we used peroxidase-conjugated anti-human immunoglobulin specific for IgG1, IgG2, IgG3, IgG4, IgM or IgA, to determine the isoforms of the autoantibodies (Cygnum Technologies, Inc., Southport, NC).

**Cross-reactivity of autoantibodies against factor VIII to human skin protein extracts**

After incubation (or absorption) with the indicated amount of human skin protein extracts (BioChain Institute, Inc., Newark, CA), the patients’ plasma samples were examined for reactivity to factor VIII by a Western blot analysis in the same manner as described above.

**Ethics**

All blood samples were obtained after the patients had provided informed consent, and this study was approved by the Institutional Review Board.

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**Results**

As shown in Figure A, an analysis of antibody binding site on the factor VIII molecule by immunoblotting was performed utilizing thrombin-treated factor VIII. The patient’s plasma recognized the 43 kDa fragment of the heavy chain (A2 domain) in patient 1 and the A2 domain and the 72 kDa fragment of the light chain in patient 2. In both patients, only the anti-human IgG4-specific secondary antibody detected factor VIII (or its fragments), demonstrating that the autoantibodies against factor VIII were predominantly of the IgG4 isofrom.

In order to clarify the immunological relationships be-
Table. Acquired Hemophilia Associated with Autoimmune Bullous Diseases (ABD)

<table>
<thead>
<tr>
<th>No.</th>
<th>y/o sex</th>
<th>ABD</th>
<th>Response to Tx of ABD</th>
<th>Onset after B(P)</th>
<th>Ig iso epitope Titer (BU/mL)</th>
<th>Treatment Prognosis</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45 M</td>
<td>Pem</td>
<td>Getting improved before AH</td>
<td>48D</td>
<td>ND</td>
<td>ND</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>65 M</td>
<td>BP</td>
<td>AH occurred at relapse of BP</td>
<td>2-3M</td>
<td>ND</td>
<td>ND</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>67 F</td>
<td>BP</td>
<td>Relapsed after self-discontinuation (6 months) concurrently with relapse</td>
<td>IgG1</td>
<td>ND</td>
<td>24/76</td>
<td>mPSL pulse, FFP, FVIII, CPA, PSL</td>
</tr>
<tr>
<td>4</td>
<td>56 M</td>
<td>Pem</td>
<td>Resolved by PSL, before AH</td>
<td>4M</td>
<td>ND</td>
<td>ND</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>68 M</td>
<td>BP</td>
<td>Rapid response to topical CS</td>
<td>6 M</td>
<td>ND</td>
<td>ND</td>
<td>&gt;2</td>
</tr>
<tr>
<td>6</td>
<td>78 M</td>
<td>BP</td>
<td>Resolved by PSL</td>
<td>4 M</td>
<td>ND</td>
<td>ND</td>
<td>839</td>
</tr>
<tr>
<td>7</td>
<td>49 F</td>
<td>BP</td>
<td>Resolved with CS, CPA</td>
<td>7 M</td>
<td>IgG1 &gt; IgG1 (44kD)</td>
<td>147.8</td>
<td>FFP, PSL, PE, CPA Good</td>
</tr>
<tr>
<td>8</td>
<td>84 F</td>
<td>BP</td>
<td>ND</td>
<td>2 M</td>
<td>ND</td>
<td>ND</td>
<td>29.4</td>
</tr>
<tr>
<td>9</td>
<td>81 F</td>
<td>BP</td>
<td>Slight improve, but not cured more than 13W</td>
<td>4 W</td>
<td>ND</td>
<td>ND</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>68 F</td>
<td>BP</td>
<td>Resolved with clobetasol propionate Topical concurrently with relapse</td>
<td>ND</td>
<td>ND</td>
<td>1.4</td>
<td>FEIBA, Topical steroid Good</td>
</tr>
<tr>
<td>11</td>
<td>83 F</td>
<td>P</td>
<td>Effective to topical CS (3yrs), but relapsed concurrently with relapse</td>
<td>ND</td>
<td>ND</td>
<td>17</td>
<td>rFVII, CS Died of severe hemorrhage</td>
</tr>
<tr>
<td>12</td>
<td>24 M</td>
<td>BP</td>
<td>PSL</td>
<td>2Y</td>
<td>ND</td>
<td>ND</td>
<td>256</td>
</tr>
<tr>
<td>13</td>
<td>60 F</td>
<td>BP</td>
<td>No medication for 3M concurrently</td>
<td>ND</td>
<td>ND</td>
<td>(+)</td>
<td>FFP, rFVIII, CPA, IVIg mPSL Complete remission</td>
</tr>
<tr>
<td>14</td>
<td>88 M</td>
<td>BP</td>
<td>Not improved with PSL</td>
<td>4M</td>
<td>ND</td>
<td>ND</td>
<td>7.0</td>
</tr>
<tr>
<td>15</td>
<td>80 F</td>
<td>BP</td>
<td>Resolved with PSL before AH</td>
<td>12M</td>
<td>IgG1 (73kD)</td>
<td>20</td>
<td>PSL Good</td>
</tr>
<tr>
<td>16</td>
<td>44 F</td>
<td>PF</td>
<td>Improved with PSL before AH</td>
<td>6Y</td>
<td>IgG1 (44kD)</td>
<td>45</td>
<td>mPSL puls PSL CPA, Good</td>
</tr>
</tbody>
</table>


Table: Acquired Hemophilia Associated with Autoimmune Bullous Diseases (ABD)

between AHA and ABD, we examined the cross-reactivity between factor VIII and human skin extract proteins. Preabsorption of each patient’s plasma with adult skin extracts did not lead to any significant changes in the binding to recombinant factor VIII (Figure). Therefore, no cross-reactivity was demonstrated.

No significant reactivity of the plasma to normal human skin extract proteins was observed, probably because the AHA occurred after the remission of ABD induced by immunosuppressive therapies in both patients.

**Discussion**

To the best of our knowledge, only 16 documented cases of AHA associated with autoimmune bullous disease (ABD) have been reported, including the two present cases. Among these cases, the age distribution was from 24 to 88 years old. The median of the time from the onset of ABD to that of AHA was four months, and varied between coincidence and six years. None of the AHA cases developed prior to the onset of ABD. The treatment of AHA involves two main goals; the eradication of autoantibodies and maintaining effective hemostasis during a bleeding episode. The former includes bypass therapies with recombinant activated factor VIIa or/and activated prothrombin complex concentrate, and neutralization therapy with factor VIII concentrates. The latter requires immunoadsorption and plasmapheresis, immunosuppression (corticosteroids, cyclophosphamide, azathioprine, rituximab, etc). Based on our literature review, no distinct trend was observed among the cases of AHA associ-
ated with ABD, while interestingly, topical corticosteroid administration induced remission in some cases.

The characterization of autoantibodies has been performed in only limited cases. In only two of the previous cases were the isoforms identified, which were predominantly IgG4, as was observed in both of the present cases (3, 6). In another single case, the epitope mapping was analyzed, which demonstrated that the autoantibodies recognized the A2 domain as an epitope (6). In the present cases, the autoantibodies recognized the A2 domain in patient 1 and the A2 domain and the light chain in patient 2. These findings were consistent with other AHA cases without ABD (14). No unique properties of autoantibodies in patients who had AHA with ABD were identified in this study.

According to our literature search, the cutaneous disorders associated AHA were almost invariably ABD (15), which may imply that there is some relationship between these two autoimmune diseases. We examined the cross-reactivity of the autoantibodies between the skin proteins and factor VIII, but no cross-reactivity was demonstrated in the present cases.

As shown in Table, the clinical features of AHA with ABD varied, and could be affected by the characteristics of the autoantibodies. Both of our cases of AHA occurred after ABD was relieved or controlled, while in some cases, the conditions occurred and improved concomitantly. In such cases, the autoantibodies might have some cross-reactivity.

The mechanisms underlying the development of the autoantibodies associated with AHA seem to be heterogeneous and complicated, and the precise characterization of the autoantibodies may shed light on the pathogenesis of AHA. An accumulation of such cases and a more detailed analyses are required to reveal the pathogenesis of AHA.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

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References