CASE REPORTS

Acquired C1 inhibitor deficiency associated with systemic lupus erythematosus affecting the central nervous system

Shotaro Nakamura, Mototaka Yoshinari, Yoshiyuka Saku, Katsuya Hirakawa, Chiaki Miishima, Koichiro Murai, Kunihiro Tokiyama, Masatoshi Fujishima

Abstract
A 22 year old woman with systemic lupus erythematosus affecting the central nervous system had acquired C1 inhibitor deficiency. She was admitted for treatment of psychiatric behaviour, but showed no signs of angioedema. The serum complement profile of the patient showed normal C3 concentration and a depletion of C4, C2, C1 inhibitor, and Clq. Her parents had normal complement profiles. An extremely reduced C4 concentration may lead to involvement of the central nervous system in systemic lupus erythematosus.

Complement deficiency, especially deficiencies of the early complement components of the classical pathway, may be associated with systemic lupus erythematosus and other lupus-like diseases. Genetic deficiency of C1 inhibitor is associated with hereditary angioneurotic oedema, which in some cases has been associated with systemic lupus erythematosus. The trait of hereditary angioneurotic oedema is proposed as autosomal dominant. The acquired form of C1 inhibitor deficiency, first described by Constanzi et al in 1969, is usually associated with B cell lymphoproliferative disorders, such as lymphoma, lymphosarcoma, chronic lymphocytic leukaemia, para-proteinemia, or macroglobulinaemia. As far as we know, no case of acquired C1 inhibitor deficiency associated with systemic lupus erythematosus has been described previously.

Case history
A 22 year old unmarried woman was admitted because of fever (39°C) in November 1987. Seven years before the admission, at the age of 14, she had received corticosteroid treatment because of fever, facial oedema, and a positive test for antinuclear antibody. She had had no previous episodes of angioedema. On admission she had a malar rash, lymphopenia, a positive test for antinuclear antibody, and an abnormal titre for antibody to DNA. After steroid treatment she convalesced and left the hospital. In April 1988 she was admitted again because of a recurrence of fever and worsening of the laboratory findings for inflammation. After an increased dose of steroid (40 mg/day prednisolone) she left the hospital again. The dose of prednisolone was tapered, and she became manic and was transferred to our hospital in October 1988.

On examination the patient was talkative and febrile with a temperature of 38°C. A malar rash on her face and thrombophlebitis on both legs were seen. Blood pressure was 140/80 mmHg and pulse rate 104/min. An ejective systolic murmur was heard at the apex of the heart. Breath sound was normally audible. Neither the liver nor the spleen was palpable. Results of a neurological examination were normal.

The urine was normal. The white cell count was 3·7 × 10⁹/l, with 67% neutrophils, 23% lymphocytes, 8% monocytes, 2% eosinophils; haemoglobin concentration was 112 g/l. Platelet count was 264 × 10⁹/l and the erythrocyte sedimentation rate 29 mm/h. Total protein was 81 g/l (19–27 γ globulin), albumin 43 g/l, urea nitrogen 3·9 mmol/l, and creatinine 53 μmol/l. Electrolytes, aspartate aminotransferase, and creatine kinase were normal. Creatinine clearance was 1·57 ml/s.

Serum C reactive protein was 0·012 g/l (normal <0·004). Serological tests for syphilis were negative. Serum immunoglobulin concentrations were IgG 23·45 g/l (normal 9·0–23·0), IgA 3·37 g/l (normal 0·80–4·50), IgM 0·89 g/l (normal 0·80–3·00). LE tests were negative. The anticardiolipin antibody titre was 1/320, with a speckled pattern, and the titre for antibody to DNA was 21·2 units/ml (normal <18). There was no antibody detectable against the ribonucleoprotein or Sm fractions. Circulating immune complexes were undetectable. Total haemolytic complement (CH50) was too low to measure in both serum and plasma. Serum complement studies are described later.

A lumbar puncture showed clear cerebrospinal fluid, which contained 11 × 10⁶ lymphocytes and 10⁶ neutrophils per litre with a raised initial pressure of 200 mmH₂O. The cerebrospinal fluid protein was increased to 1·2 g/l (normal 0·1–0·4), lactate concentration was 2·11 mmol/l (normal 1·33–1·67), and pyruvate 0·127 mmol/l (normal 0·082–0·114). An electroencephalogram disclosed a diffuse slow wave. Computed tomography showed mild cerebral atrophy.

After admission the patient showed manic symptoms. She was diagnosed as having psychosis associated with systemic lupus erythematosus, as her psychotic symptoms appeared
together with fever when the erythrocyte sedimentation rate and C reactive protein increased after tapering the steroid treatment. Additionally, the high concentrations of protein, lactate, and pyruvate in the cerebrospinal fluid and diffuse slow waves in the electroencephalogram indicated involvement of the central nervous system.20 21

The patient was treated with pulsed methylprednisolone 1000 mg/day for three days, which markedly improved her psychotic symptoms and the abnormalities in the cerebrospinal fluid and electroencephalogram. After pulse therapy serum concentration of CH50 rose to normal, C3 concentration remained normal, and C4 concentration increased slightly (figure).

COMPLEMENT STUDIES

Functional complement assays were measured on fresh serum. Total haemolytic activity of the classical pathway (CH50) was measured as described by Mayer.22 Total haemolytic activity of the alternative pathway (ACH50) was determined by the method of Platts-Mills and Ishizaka.23 Haemolytic activities of C1, C4, C2, C3, C5, C6, C7, C8, and C9 were measured by methods of Nelson et al.24 C1 inhibitor activity was determined according to the method of Lachmann and Hobart.25

Protein concentrations of C4, C3, and C5 were determined by nephelometry (Behring).26 Proteins of C1q, C6, C7, C8, C9, and C1 inhibitor were measured by single radial immunodiffusion27 using monospecific antisera.

Table 1 shows the complement profile of the patient. CH50 was less than 6 units/ml (normal 30–50). C1 was depressed to 11% of functional activity and C1q protein was less than 0.030 g/l (normal 0.087–1.146). C4 activity was 0% and C4 protein was less than 0.01 g/l (normal 0.11–0.46). C2 was 8% of functional activity. Functional activities and protein concentrations of C3, C5, C6, C7, C8, C9 were normal except for the raised activity of C9. C1 inhibitor activity was less than 25% and C1 inhibitor protein was less than 0.048 g/l (normal 0.154–0.338). A follow up study showed persistently low levels of functional activities and protein concentrations of C1 inhibitor after pulse therapy.

The possible presence in the patient's serum of antibodies to C1 inhibitor was tested for by determining the recovery of C1 inhibitor activity of the control serum both with and without the addition of the patient's serum. Table 2 shows that the activity of C1 inhibitor in

![TREATMENT](image)

Clinical course of the patient as pulsed methylprednisolone 1000 mg/day was given intravenously for three days. Normal range of total protein in cerebrospinal fluid is 0.1–0.4 g/l and of lactate 1.33–1.67 mmol/l. Shaded areas indicate normal ranges. CSF = cerebrospinal fluid; ESR = erythrocyte sedimentation rate; CRP = C reactive protein.
**Acquired C1 inhibitor deficiency in SLE**

**Table 3 Complement profile of the patient’s parents**

<table>
<thead>
<tr>
<th></th>
<th>Father</th>
<th>Mother</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH50 (U/ml)</td>
<td>42</td>
<td>42</td>
<td>30-50</td>
</tr>
<tr>
<td>C4 activity (% NHS*)</td>
<td>180 6</td>
<td>76 4</td>
<td></td>
</tr>
<tr>
<td>C4 protein (g/l)</td>
<td>0.30 0.15</td>
<td>0.11-0.46</td>
<td></td>
</tr>
<tr>
<td>C3 protein (g/l)</td>
<td>0.80 0.67</td>
<td>0.38-0.96</td>
<td></td>
</tr>
<tr>
<td>C1 inhibitor activity (% NHS)</td>
<td>165 87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1 inhibitor protein (g/l)</td>
<td>0.321 0.286</td>
<td>0.154-0.338</td>
<td></td>
</tr>
</tbody>
</table>

*NHS=normal human serum.*

**Table 4 Underlying disorders and incidence of cutaneous angioedema in 56 previously reported patients with acquired C1 inhibitor deficiency**

<table>
<thead>
<tr>
<th>Underlying disorders</th>
<th>Total number of cases</th>
<th>Number of cases with cutaneous angioedema</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoglobulinaemia</td>
<td>3</td>
<td>6, 11</td>
<td></td>
</tr>
<tr>
<td>Lymphosarcoma</td>
<td>3</td>
<td>2, 8</td>
<td></td>
</tr>
<tr>
<td>Monoclonal gammopathy</td>
<td>5</td>
<td>2, 8, 16, 17, 19</td>
<td></td>
</tr>
<tr>
<td>Lymphocytic leukaemia</td>
<td>15</td>
<td>7, 8, 9, 11, 12, 14</td>
<td></td>
</tr>
<tr>
<td>Lymphoproliferative disorder (undefined)</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma (rectum)</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Macroglobulinaemia</td>
<td>5</td>
<td>4, 10, 11, 14</td>
<td></td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>1</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>5</td>
<td>9, 11, 14, 18, 19</td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>3</td>
<td>2, 10, 14, 15</td>
<td></td>
</tr>
<tr>
<td>Teratoma (ovary)</td>
<td>1</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>9</td>
<td>9, 16, 27, 28, 29, 30</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Low serum concentrations of early components of the complement system are occasionally found in patients with systemic lupus erythematosus, and are associated with the presence of antibody to DNA, or continuing nephritis or vasculitis. The degradation of C1, C4, and C2 is known to be accelerated in this disease. The normal serum concentration of C3 and the persistently low concentrations of C4, C2 with depleted activity of CH50 are compatible with the deficiency of C1 inhibitor in this patient. 1, 2

The C1 inhibitor deficiency of this patient is thought to be acquired as her parents had normal complement profiles and her serum concentrations of C1q and C1 were undetectable.2 8 The acquired C1 inhibitor deficiency had no normal or slightly increased synthesis of C1 inhibitor in contrast with hereditary angio-neurotic oedema.10 14 Increased activation of C1 has been proposed as a cause of accelerated catabolism of C1 inhibitor in the acquired disorder.

Since Kohler et al reported the first case of hereditary angio-neurotic oedema with systemic lupus erythematosus in 1974, 18 subjects with hereditary C1 inhibitor deficiency have developed lupus erythematosus.1-3 As many as 2% of patients with hereditary angio-neurotic oedema may develop systemic lupus erythematosus, which is a significantly higher incidence than the 0.4-1.6 cases per 100 000 per year seen in the general population.2 The marked reduction of C4 concentrations seems to have an important role in the pathogenesis of systemic lupus erythematosus associated with hereditary angio-neurotic oedema. 1, 2 Blocking of the classical pathway would facilitate the establishment of a virus infection,2, 5 but the inadequate clearance or solubilisation of immune complexes may be more important.4, 5

Acquired C1 inhibitor deficiency is rare, though there have been about 56 reported cases. Most of those patients had associated underlying diseases, such as B cell lymphoproliferative disorders, and had symptoms of angioedema, like hereditary angio-neurotic oedema (table 4).6-9, 27-30 As far as we know, no such cases associated with systemic lupus erythematosus have been reported. Our patient may have a special form of acquired C1 inhibitor deficiency because she had no symptoms of angioedema, which is occasionally associated with acquired C1 inhibitor deficiency in patients with lymphoproliferative disorders.

Although, occasionally, low concentrations of C1 inhibitor have been seen in patients with an acute exacerbation of systemic lupus erythematosus, 3, 11 those patients were clearly different from ours in the following points: (a) their C1 inhibitor concentrations were temporarily depleted in the acute phase and returned to normal after treatment; (b) the depletions of C1 inhibitor were accompanied by decreased concentrations of C3 and C9.

Two hypotheses can be proposed for the pathogenesis of our case. One is that the markedly activated B cells in systemic lupus erythematosus by some uncertain mechanism might have induced C1 inhibitor deficiency.5 There is a close relation between the concentrations of C1 inhibitor and certain immunoglobulins produced by abnormal B cells.10 14 A reaction between the immunoglobulin (idiotype) and the anti-idiotypic antibody might fix C1q and consequently consume C1 inhibitor at a rapid rate on the surface of the B cells.10 Another possibility is that systemic lupus erythematosus might have developed from C1 inhibitor deficiency caused by some unknown background disease, by the same mechanism proposed in systemic lupus erythematosus associated with hereditary angio-neurotic oedema.1, 2 On the other hand, the association might be purely coincidental.

It is not clear why our patient did not develop the features of angioedema. Possibly, excessive consumption of the complement system in systemic lupus erythematosus might not have left sufficient peptide derived from C2 or C4-like molecules for the generation of significant quantities of kinin-like peptides.8

A few years ago, a new type of acquired C1 inhibitor deficiency associated with C1 inhibitor antibodies was reported.28 29 In that case such diseases as lymphoproliferative disorders and B cell abnormalities with anti-idiotype antibodies were not associated. The molecular weight of the purified C1 inhibitor was 96 kilodaltons, which is less than 105 kilodaltons of normal C1 inhibitor. The concentrations of C1 inhibitor protein were reported to be only slightly reduced (60-70% of normal v <30% of normal in the 'classical' case), which is in contrast with the
almost null levels of Cl inhibitor in our patient. Furthermore, Cl inhibitor antibodies were negative in our patient.

Interestingly, the central nervous system in this patient was affected. The increased vascular permeability in the choroid plexus, instead of peripheral angioedema,8 27 might have accelerated the passage of anti-nervous tissue autoantibodies into the central nervous system through the blood-brain barrier,21 31 32 although anti-nervous tissue autoantibodies may be directly produced within the central nervous system.33 35

The markedly reduced C4 concentration may play a part in the genesis of profound central nervous system disease in this patient, though the precise mechanism of Cl inhibitor depletion associated with systemic lupus erythematosus remains to be defined.

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1 Agnello V. Lupus diseases associated with hereditary and acquired deficiencies of complement. Springer Semin Immunopathol 1986; 8: 161–78.
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