Vascular Endothelial Growth Factor Is Involved in Angioedema Associated with Eosinophilia

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Summary: Angioedema associated with eosinophilia is a disorder characterized by angioedema and eosinophilia. However, the pathogenesis of this disorder has not been fully understood. We experienced 4 patients with angioedema associated with eosinophilia. All patients were young, 3 were female and 1 was male. All patients revealed edema of the limbs and eosinophilia. The symptom was rapidly improved after the initiation of low or medium dose of prednisolone. We evaluated the serum concentration of interleukin 5 (IL-5) and the plasma concentration of vascular endothelial growth factor (VEGF) in 1 patient. Both cytokines were markedly elevated before the treatment and decreased after the treatment. Angioedema associated with eosinophilia is not so rare, and IL-5 and VEGF are involved in the pathogenesis of this disease.

Key words angioedema, eosinophilia, vascular endothelial growth factor

INTRODUCTION

Angioedema associated with eosinophilia was first described by Gleich et al. [1] in 1984, and is characterized by angioedema, urticaria, leukocytosis, eosinophilia, fever, increased body weight and benign clinical course without involvement of the internal organs. A number of patients with angioedema associated with eosinophilia has been accumulated, and this clinical entity has been truly established [2-5]. Although the pathogenesis of this disorder has not been fully understood, interleukin 5 (IL-5), which stimulates eosinophil proliferation and differentiation, has been reported to be associated with this disease [2-4]. However, the mechanism of edema in this disease has not been clear. Vascular endothelial growth factor (VEGF), also known as vascular permeability factor, is a cytokine that exerts several important actions on the vascular endothelium and induces capillary hyperpermeability [6,7]. We experienced 4 patients with angioedema associated with eosinophilia. In one patient, we evaluated the serum concentration of IL-5 and the plasma concentration of VEGF, and found marked elevation of these cytokines.

CASE REPORT

The clinical features of the patients are shown in Table 1. All patients were referred to our hospital due to a history (from 1 week to 1 month) of nonpitting edema. Laboratory investigations showed an elevation of white blood cells and eosinophilia in all patients. Prednisolone rapidly resolved the edema and eosinophilia in all patients. A local doctor had already treated Case 1 with 30 mg per day of prednisolone before his visit to our hospital. In Case 4, a liver function test revealed mild abnormalities, serum aspartate aminotransferase of 43 U/L and serum alanine aminotransferase of 38 U/L. Neither hepatitis B surface antigen nor anti-hepatitis C virus antibody was positive. She had received some medications
TABLE 1.  
Clinical features of the four patients

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>male</td>
<td>female</td>
<td>female</td>
<td>female</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35</td>
<td>37</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Edema of the face</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Edema of the arms</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Edema of the legs</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urticaria</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>White blood cell count (/mm³)</td>
<td>8,900</td>
<td>10,400</td>
<td>17,600</td>
<td>19,000</td>
</tr>
<tr>
<td>Eosinophil count (/mm³)</td>
<td>1,060</td>
<td>2,704</td>
<td>8,008</td>
<td>13,110</td>
</tr>
<tr>
<td>Hepatic function</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>abnormal</td>
</tr>
<tr>
<td>Renal function</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Dose of prednisolone (mg)</td>
<td>30</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>

including antibiotics from a local doctor. After the cessation of the drugs, her liver function improved rapidly.

In Case 3, an informed consent form was obtained from the patient and we measured the serum concentration of IL-5 and the plasma concentration of VEGF by enzyme immunoassay before and after the treatment with prednisolone. The serum concentration of IL-5 was 63.7 pg/mL (normal, below 7.8) before the treatment, and it had decreased to below the detectable level at 1 and 5 weeks after the initiation of prednisolone. The plasma concentration of VEGF was 226 pg/mL (normal, below 38.3) before the administration of prednisolone, and it had decreased to 47.8 pg/mL at 1 week and below 15.6 pg/mL at 5 weeks after the initiation of prednisolone.

DISCUSSION

Angioedema associated with eosinophilia was first described by Gleich et al. [1] in 1984, and is characterized by edema, urticaria, leukocytosis, eosinophilia, fever, increased body weight and benign clinical course without involvement of the internal organs. A number of patients with angioedema associated with eosinophilia has been accumulated, and this clinical entity has been truly established [2-5]. We experienced 4 cases during 5 years. Among them, 3 cases were referred during the last 2 years. Therefore, this disorder is not so rare, and physicians should be aware of this disease as a cause of edema of the limbs.

IL-5, which stimulates eosinophil proliferation and differentiation, has been reported to be associated with this disease [2-5]. However, the mechanism of edema in this disease has not been clear. VEGF, also known as vascular permeability factor is a potent multifunctional cytokine that exerts several important actions on the vascular endothelium and induces capillary hyperpermeability [6,7]. In one patient, we evaluated the serum concentration of IL-5 and the plasma concentration of VEGF, and found marked elevation of these cytokines. IL-5 stimulates production of eosinophils in bone marrow and causes selective activation of eosinophils [8,9]. In the patient, the serum concentration of IL-5 before the treatment was apparently elevated, and decreased with improvement, indicating that IL-5 was involved in the pathogenesis of this disease.

Eosinophils synthesize a number of cytokines that may contribute to the pathogenesis of various diseases [10]. Eosinophils spontaneously release VEGF, and this release is regulated by IL-5 [11], which is involved in pathogenesis of this disease. However, the relationship between angioedema associated with eosinophilia and VEGF has not been evaluated yet. In the patient, the plasma concentration of VEGF was markedly elevated before the treatment with prednisolone. This evidence suggests that VEGF may contribute to generation of edema in this disease. IL-5 induces proliferation and activation of eosinophils, eosinophils release VEGF, and VEGF induces capillary hyperpermeability, resulting in edema. Thus, the edema in this disease is clearly explained by the actions of IL-5 and VEGF.

A low or medium dose of prednisolone was...
effective for the edema and eosinophilia in all cases. After the initiation of the prednisolone, serum IL-5 and plasma VEGF levels were decreased with improvement of edema. Corticosteroid also suppresses IL-5 synthesis by T cells [12]. It has been reported that VEGF release by eosinophils was suppressed by corticosteroid [11]. Therefore, VEGF is closely associated with the edema in this disorder, and prednisolone improves this symptom by suppressing the production of IL-5 from T cells or mast cells and that of VEGF from eosinophils. Thus, the association of IL-5 and VEGF with this disease is probable, although further studies with a large number of patients will be needed.

Liver function abnormality was detected in Case 4. One of the characteristics of this disease is the lack of involvement of the internal organs [1-5]. Case 4 had received some antibiotics from a local doctor, and the abnormality was rapidly improved after the cessation of the drug. Therefore, we considered that the abnormality was drug-induced liver injury.

We experienced 4 cases with angioedema associated with eosinophilia. Plasma VEGF and serum IL-5 levels were markedly elevated in a patient. Therefore, we suggest that VEGF as well as IL-5 may be involved in the pathogenesis of angioedema associated with eosinophilia.

REFERENCES