Elevated Serum Levels of Interleukin-5 in Patients With the Syndrome of Episodic Angioedema and Eosinophilia


The syndrome of episodic angioedema and eosinophilia is characterized by cyclic edema, marked peripheral blood eosinophilia, and eosinophil degranulation in the dermis. Using a sensitive immunoenzymometric method, we measured serum interleukin (IL)-5 levels in four patients with this syndrome. We also determined the percentage of activated T cells in the peripheral blood of a new patient before and during an attack. In the patient presented, IL-5 levels peaked several days before maximal eosinophilia and then declined. This patient's lymphocytes showed an increased percentage, 28% (normal 2% to 3%), of activated T cells staining for both CD3 and HLA-DR 10 days before maximal eosinophilia, but no increase at the time of peak eosinophilia. In serum from three previously reported cases, elevated serum IL-5 levels were found during attacks. After glucocorticoid administration, IL-5 levels became undetectable in three of the four patients. Production of IL-5 is likely an important determinant of the pathophysiology of this syndrome.

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from the circulation. IL-5 was measured in duplicate samples of jugular venous distension, bibasilar lung dullness, and epigastric tenderness. The reported IL-5 value represents the mean, corrected for sample dilution. The assay detection threshold was 50 to 100 pg/mL per sample.

IL-5 assay. Sera from this patient, as well as from three previously reported cases of this syndrome (Gleich et al., cases 1, 3, and 4), were assayed for IL-5 by an immunoenzymetric assay using T-cell clone supernatants, as well as mitogen-activated peripheral blood mononuclear cell supernatants. The sera from the previously reported cases had been collected during observation of attacks and had been stored at -20°C.

Activated T-cell analysis. Two-color flow cytometric assays of peripheral blood lymphocytes were used to determine the percentage of activated T cells in the present patient's peripheral blood. Assays were performed using a fluorescent activated cell sorter (Becton Dickinson, San Jose, CA) and monoclonal antibodies (Becton Dickinson) to the following cell surface markers: CD3 (Leu 4), HLA-DR, CD25 (IL-2 receptor), CD71 (transferrin receptor), CD20 (Leu 16), CD4 (Leu 3A), and CD8 (Leu 2A).

RESULTS

Serum IL-5 levels. Serum IL-5 values for the patient presented in the case report are shown in Fig 1. IL-5 levels showed a biphasic increase with peaks on days 9 and 14. Interestingly, days 13 and 14 were the days of lowest 24-hour urine output (247 mL and 274 mL, respectively). By the day of maximal blood eosinophilia, day 16, serum IL-5 level had decreased and it became undetectable following prednisone administration.

Serum IL-5 levels from two previously reported cases of the syndrome of episodic angioedema and eosinophilia along with other clinical features are shown in Figs 2 and 3. Both patients showed serum IL-5 levels that were elevated or became elevated during clinical attacks with marked eosinophilia. Another reported case showed elevated levels of IL-5 during two attacks of angioedema (Table 1). In the present case (Fig 1) and in patient 4 (Fig 3), IL-5 levels were decreasing before treatment with prednisone and...
were increases found in the percent of T cells bearing other increased percentages of T cells bearing activation markers. Perivascular infiltration of activated T cells staining both for CD3 and HLA-DR on day 6. On day 16, at the peak of eosinophilia, no increase in activated T-cell numbers was observed, and on neither date were increases found in the percent of T cells bearing other activation markers (CD71 or CD25), or labeling with anti-CD20, -CD4, or -CD8. Subsequent T-cell analyses performed during attacks were likewise negative for increased percentages of T cells bearing activation markers.

Immunodermatology studies. The skin biopsy specimen stained with hematoxylin and eosin showed perivascular mononuclear cell infiltration throughout the dermis with occasional eosinophils. Immunocytochemical analyses of the skin biopsy specimen showed that the majority of infiltrating cells were T-helper cells possessing CD2, CD3, and CD4 markers. As in previously reported cases, extensive extracellular eosinophil granule major basic protein deposition was observed in the dermis.

Table 1. IL-5 Levels in a Patient With Episodic Angioedema Associated With Eosinophilia

<table>
<thead>
<tr>
<th>Date</th>
<th>Clinical Course</th>
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<tbody>
<tr>
<td>8/20/81</td>
<td>Attack of angioedema, 7.3-kg weight gain, leukocyte count 37.5 x 10^9/mm^3, 75% eosinophils. IL-5, 345 pg/mL (normal; undetectable).</td>
</tr>
<tr>
<td>2/2/82</td>
<td>Attack of angioedema. Leukocyte count 31.4 x 10^9/mm^3, 76% eosinophils. IL-5, 251 pg/mL.</td>
</tr>
<tr>
<td>2/3/82</td>
<td>Prednisone begun with a dosage schedule of 60 mg for days 1 and 2, 40 mg for days 3 and 4, 20 mg for days 5 and 6, and 10 mg on day 7.</td>
</tr>
<tr>
<td>2/10/82</td>
<td>Patient well. Leukocyte count 8 x 10^9/mm^3, 13% eosinophils. IL-5, undetectable.</td>
</tr>
</tbody>
</table>

Data from Gleich et al, Patient 1.
remain somewhat speculative. During each of the leukaphereses on days 16 and 17, approximately 220 mL of cells was removed, but approximately 500 mL of a volume expander was infused. Therefore, it is possible that in the present case the leukaphereses may have had a dilutional effect on serum IL-5 values. Interestingly, in the patient reported here, an intravascular fluid-overloaded state developed following prednisone administration. This resulted clinically in acute bradycardia, orthopnea, and the presence of bibasilar infiltrates on chest x-ray; echocardiogram showed no evidence of cardiac dysfunction. The fluid overload may have occurred because of differences between the rate of fluid mobilization from tissue and excretion by the kidneys. Intravenous administration of furosemide resulted in rapid diuresis and resolution of clinical symptoms. Chronologically, maximum IL-5 levels occurred on days 13 and 14; interestingly, these 2 days were also the days with the lowest urinary output (247 mL/24 h, 274 mL/24 h, respectively), while maximum eosinophil levels occurred on days 16 and 17, respectively. It is interesting that the peak eosinophilia lagged behind the peak serum IL-5 level by approximately 3 to 4 days. This may represent the time it takes for late-stage eosinophil progenitors to fully differentiate into mature eosinophils. It is not known whether IL-5 affects renal function; however, one possibility for the peak values on days 13 and 14 was decreased urinary excretion of this lymphokine. It is also noteworthy that the increased percentage of activated T-helper cells occurred before the development of elevated IL-5 values. In a previous report of a patient with the syndrome of episodic angioedema and eosinophilia, normal percentages of CD4 helper cells and CD8 suppressor cells were reported in the peripheral lymphocytes; however, one possibility for the peak values on days 13 and 14 was decreased urinary excretion of this lymphokine. It is also noteworthy that the increased percentage of activated T-helper cells occurred before the development of elevated IL-5 values. In a previous report of a patient with the syndrome of episodic angioedema and eosinophilia, normal percentages of CD4 helper cells and CD8 suppressor cells were reported in the peripheral lymphocytes; however, one possibility for the peak values on days 13 and 14 was decreased urinary excretion of this lymphokine. It is also noteworthy that the increased percentage of activated T-helper cells occurred before the development of elevated IL-5 values. In a previous report of a patient with the syndrome of episodic angioedema and eosinophilia, normal percentages of CD4 helper cells and CD8 suppressor cells were reported in the peripheral lymphocytes; however, one possibility for the peak values on days 13 and 14 was decreased urinary excretion of this lymphokine. It is also noteworthy that the increased percentage of activated T-helper cells occurred before the development of elevated IL-5 values. In a previous report of a patient with the syndrome of episodic angioedema and eosinophilia, normal percentages of CD4 helper cells and CD8 suppressor cells were reported in the peripheral lymphocytes; however, one possibility for the peak values on days 13 and 14 was decreased urinary excretion of this lymphokine. It is also noteworthy that the increased percentage of activated T-helper cells occurred before the development of elevated IL-5 values.
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