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 immunoenzymetric 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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edematous area of the thigh. On days 16 and 17, leukaphereses were performed, yielding a total of 3 × 10^9 eosinophils. Prednisone, 80 mg/d, was begun on day 17 following the leukapheresis. Between days 17 and 19, total leukocyte count and eosinophil count rapidly decreased; urine output increased slowly, weight remained stable, and hemoglobin decreased from 13.4 g/dL to 10.4 g/dL. On the night of days 19 to 20, while still receiving 80 mg of prednisone daily, she experienced an acute episode of sinus bradycardia (42 bpm) and orthopnea. Clinical examination showed jugular venous distension, bibasilar lung dullness, and epigastric tenderness. Chest roentgenogram showed bilateral pleural effusions and bibasilar infiltrates. An echocardiogram showed elevated pulmonary and systemic venous pressures and normal cardiac output consistent with volume overload. Administration of furosemide, 80 mg intravenously, resulted in diuresis of 6,100 mL, weight loss, and clinical improvement during the next 24 hours. The diuresis was sustained with metolazone 5.0 mg/d. The patient was discharged on day 22 with a tapering course of prednisone and diuretics and was discharged on day 22 with a tapering course of prednisone and metolazone.

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 two monoclonal antibodies, JES1-39D10 as coating antibody, and JES1-5A10 derivatized with the hapten nitroiodophenyl, as the detecting antibody in conjunction with L-cell-derived recombinant IL-5 as the standard. This assay has been used to quantify IL-5 in 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). Assays were performed on day 6 (immediately before onset of her attack), on day 16 (during the peak of the eosinophilia), and during clinical attacks following discharge.

Immunodermatologic studies. Immunophenotyping of infiltrating dermal lymphocytes was performed on lesional skin obtained by punch biopsy from the right thigh. Biopsy sections were stained for eosinophil granule major basic protein by indirect immunofluorescence. A specimen from this biopsy was also examined after routine hematoxylin and eosin staining.

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 activation markers. Subsequent T-cell analyses performed during attacks were likewise negative for in-vitro neutralizing anti-CD20, -CD4, or -CD8. Subsequent T-cell analyses performed during attacks were likewise negative for increased percentages of T cells bearing 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 cosin 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>
</tr>
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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/mm³, 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/mm³, 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/mm³, 13% eosinophils. IL-5, undetectable.</td>
</tr>
</tbody>
</table>

Data from Gleich et al, Patient 4.

**DISCUSSION**

The T-lymphocyte dependency of blood eosinophilia was recognized around 1970. Subsequent studies showed that T-cell-deficient mice (Nu/Nu) fail to develop primary or secondary eosinophilia when infected with *Ascaris suum* larvae or *Schistosoma mansoni* cercariae. Eosinophil colony-stimulating factors have been demonstrated in the supernatants of sensitized T cells from patients with allergic eosinophilia, from cultured T-cell leukemia-lymphoma cells, and from murine T-cell hybridomas. Sanderson et al identified a murine T-cell–derived eosinophil differentiating factor that caused production of eosinophils in vitro. The cDNA for this factor coded for a protein identical to murine IL-5. IL-5 prolonged in vitro survival of eosinophils and converted normodense human eosinophils to hypodense cells. Recombinant human IL-5 has been shown to selectively stimulate production of eosinophils in human bone marrow cultures, to act as a chemotactic factor, and to cause a selective activation of human eosinophil function, inducing changes in cell morphology, polarization of granules, membrane ruffling, production of oxygen radicals, and degranulation.

The IL-5 immunoenzymatic assay in this series for the determination of serum IL-5 has proven to be relatively robust. It has been used to determine serum IL-5 levels longitudinally both in cancer patients treated with IL-2 and in onchocerciasis patients undergoing the Mazotti reaction in response to antihelminth treatment. Serum IL-5 has been undetectable by this immunoassay in large numbers of serum samples unassociated with eosinophilia, indicating that normal serum levels are below the assay threshold of detection. In a study involving serum IL-3 associated with a chromosomal translocation event in acute lymphocytic leukemia with eosinophilia, the absence of serum IL-5 was documented both by this immunoassay and a bioassay for IL-5, rendered monospecific using specific neutralizing anti–IL-5 monoclonal antibodies. In this study, the immunoassay precision was clearly good enough to discriminate fluctuations of IL-5 serum levels longitudinally within a particular patient, a finding that we believe to be important in future investigation of this disease.

Here, we report elevated serum levels of immunoreactive IL-5 in patients with the syndrome of episodic angioedema and eosinophilia and show that an increase in the serum IL-5 level was detected before peak eosinophil numbers in the peripheral blood. In three of the four patients studied, as shown in Figs 1, 2, and 3, IL-5 levels spontaneously decreased during the latter stages of the attacks. The presence of eosinophilia and leukocytosis before an increase in IL-5 values (Fig 3) could be explained by a cyclic increase in IL-5 which antedated our period of observation. Alternatively, the biologic activity of IL-5 in vivo may be greater than our current ability to detect this lymphokine in vitro. During treatment with prednisone, IL-5 levels became undetectable in three of four patients (Figs 1 and 3, Table 1), with associated clinical improvement, decreased eosinophil numbers, and weight loss. Because IL-5 levels were already decreasing before prednisone administration, the contribution of this therapy to the final IL-5 levels must...
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 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 eosinophils 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 circulation; importantly, however, 32% of the CD4 cells expressed the HLA-DR activation antigen (normal value, <2%). In the case presented here, we found a similar percentage (28%) of CD3+ T cells expressing for the DR activation antigen 10 days before the maximal eosinophil count. However, we have no direct evidence that the activated T cells were responsible for the elevated IL-5 values detected and the underlying reason for increased IL-5 production in this disorder remains to be elucidated. One must remain cognizant of the possibility that activated lymphocytes may not be the sole, or even predominant, source for elevated IL-5 detected in this syndrome. Recent studies have shown that most cells may express mRNA for IL-5, as well as other cytokines, in response to cross-linkage of Fcε receptors or to calcium ionophores. Because of its multiple recognized effects on eosinophil proliferation, chemotaxis, and survival, we believe the elevated serum levels of IL-5 in the syndrome of episodic angioedema and eosinophilia may be of importance in explaining many of the pathophysiologic aspects of this disorder.

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