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.

In 1984, Gleich et al reported four cases of a novel syndrome of recurrent angioedema, urticaria, fever, and weight gain. Symptomatic episodes were associated with marked weight increase and eosinophilia; histologic studies showed eosinophil infiltration and degranulation in the dermis. IgM levels were increased in all four patients. Since the initial series, additional reports have appeared in the literature, the youngest patient was a 2½-year-old child. In contrast to patients with the idiopathic hypereosinophilic syndrome, patients with episodic angioedema and eosinophilia have no increased risk of cardiovascular morbidity or mortality. Because interleukin (IL)-5 is a specific stimulator of human eosinophil differentiation, as well as a selective eosinophil chemotractant and eosinophil activation factor, we assayed serum IL-5 levels from four patients with episodic angioedema and eosinophilia: three previously reported cases and one new case. Here, we report that serum IL-5 levels are increased in this syndrome and fluctuate in relationship to blood eosinophilia and clinical findings.

MATERIALS AND METHODS

Case report. A 19-year-old nonatopic woman was referred to the Mayo Clinic for diagnosis and treatment of a 3½-year history of episodic angioedema and eosinophilia. In the months before her evaluation, she had experienced recurrent attacks of increasingly severe edema of the face, hands, feet, and legs associated with dyspnea on exertion, fever to 40°C, and weight gain of up to 18 kg. Leukocyte counts ranged from 31,000 to 51,000/mm³, with 70% to 84% eosinophils. The attacks had occurred approximately once per month and had lasted an average of 2 weeks. She had derived no benefit from therapy with indomethacin or cimetidine. Although injections of glucocorticoids initially afforded relief of her symptoms, prednisone (20 to 40 mg/d) administration in the weeks before her referral was not clinically helpful. The patient had not used aspirin and no allergies to medications were known. She denied any relation of attacks to her menstrual cycle and had discontinued the use of oral contraceptives 3 weeks before evaluation. She rarely drank alcoholic beverages, did not smoke or use illicit drugs, and had traveled only to Canada. There was no history of connective tissue disorders, parasitic disease, chronic urticaria, or other diseases commonly associated with eosinophilia. The family history did not reveal relatives with similar symptoms.

On physical examination, vital signs were normal. A congenital palsy of the proximal right arm was present. Nonpitting edema of both legs, feet, the dorsa of the hands, and the right periorbital skin was evident. Excoriated papular, erythematous skin lesions were present on the dorsa of the hands and feet. Cardiovascular and neurologic systems were normal, as was the remainder of the physical examination.

Initial laboratory values showed a total leukocyte count of 10,500/mm³ with 53% eosinophils, 26% neutrophils, 18% lymphocytes, and 2% monocytes (Fig 1); hemoglobin and platelet counts were normal. IgM was 484 mg/dL (normal range, 60 to 300 mg/dL). Negative or normal values included the following: chest roentgenogram, mammogram, electrocardiogram, echocardiogram, serum chemistry values, serum B₁₂ and folate, AM and PM cortisol levels, total hematocrit complement, C₃, C₄, and C₁ esterase inhibitor (both quantitative and functional assays), serum protein electrophoresis, antinuclear antibody, rapid plasma reagin, serologies for toxoplasmosis and echinococcosis, urinalysis, and stools for ova and parasites. Lymphocyte studies showed normal numbers of T cells, normal percentages of T-helper and T-suppressor cells, and a normal T-helper to T-suppressor ratio. Bone marrow aspiration and biopsy showed 30% eosinophils and megakaryocytic hyperplasia, without evidence of malignancy. The karyotype was 46XX.

Clinical course. The patient was admitted to the Clinical Research Center where her course was monitored (Fig 1). Clinical and laboratory studies performed were approved by the Institutional Review Board of the Mayo Clinic. Informed consent was obtained before all studies. During days 1 to 7, the patient remained asymptomatic; her weight increased by 2.5 kg. During days 8 to 14, she developed pronounced facial swelling, painful leg edema, and occasional nausea and vomiting. Her weight increased by 4 kg. Twenty-four-hour urinary volumes were 402 mL, 247 mL, and 274 mL on days 12, 13, and 14, respectively. Eosinophils were increased by 4.6 kg. Leukocytes and eosinophils increased to maxima of 57,900/mm³ and 48,350/mm³ on day 16. The patient underwent skin biopsy of an indurated lesion in an
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edematous area of the thigh. On days 16 and 17, leukaphereses were performed, yielding a total of \( 3 \times 10^9 \) 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 clinical attacks following discharge.

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\(^1\) 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 blood mononuclear cell supernatants.\(^6\) The sera from the previously reported cases had been collected during observation of attacks and had been stored at \(-20^\circ\text{C}\).

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 fluorescein 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 9 (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.\(^1\) Biopsy sections were stained for eosinophil granule major basic protein by indirect immunofluorescence.\(^1\) A specimen from this biopsy was also examined after routine hematoxylin and eosin staining.
were increases found in the percent of T cells bearing other activation markers. Subsequent T-cell analyses showed an increased percentage, 28% (normal 2% to 3%), 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.

Immunodermatologic 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 eosinophilic granule major basic protein deposition was observed in the dermis.

The T-lymphocyte dependency of blood eosinophilia was recognized around 1970.33-35 Subsequent studies showed that T-cell-deficient mice (Nu/Nu) fail to develop primary or secondary eosinophilia when infected with Ascaris suum larvae36 or Schistosoma mansoni cercariae.37 Eosinophil colony-stimulating factors have been demonstrated in the supernatants of sensitized T cells from patients with allergic eosinophilia,14 from cultured T-cell leukemia-lymphoma cells,19 and from murine T-cell hybridomas.20 Sanderson et al identified a murine T-cell-derived eosinophil differentiating factor that caused production of eosinophils in vitro.21,22 The cDNA for this factor coded for a protein identical to murine IL-5.23 IL-5 prolonged in vitro survival of eosinophils and converted normodense human eosinophils to hypodense cells.24 Recombinant human IL-5 has been shown to selectively stimulate production of eosinophils in human bone marrow cultures,25 to act as a chemoattractant,23 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.26-28

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-229 and in onchocerciasis patients undergoing the Mazotti reaction in response to antihelminth treatment.30 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,31 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.32 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

### 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>
</thead>
<tbody>
<tr>
<td>8/20/81</td>
<td>Attack of angioedema, 7.3-kg weight gain, leukocyte count 3.75 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 3.14 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 urine 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 CD4+ 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 mast 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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