A Clinicopathologic Correlation of the Idiopathic Hypereosinophilic Syndrome. II. Clinical Manifestations

By Robert T. Schooley, Morris A. Flaum, Harvey R. Gralnick, and Anthony S. Fauci

The idiopathic hypereosinophilic syndrome, a disorder characterized by peripheral blood and bone marrow eosinophilia associated with single or multiple organ system dysfunction attributable to tissue invasion by mature eosinophils, has, in the past, been associated with an extremely poor prognosis. Recently, we reported the favorable impact of a therapeutic protocol consisting of prednisone and/or hydroxyurea on the morbidity and mortality of this syndrome. We have reviewed the clinical and hematologic features upon admission and the subsequent clinical courses of 32 patients with this disease referred to the NIH between 1965 and 1979 in an effort to determine if these features suggest a more rapidly progressive course. A grading system based on 22 clinical features involving the 8 organ systems commonly affected by the illness was devised. The disease followed a more aggressive course in patients with evidence of cardiac or neurologic dysfunction at the time of initial NIH evaluation. Although splenomegaly, in and of itself, caused little morbidity, splenic enlargement at presentation appeared to be a predictor of a more aggressive course. The clinical grading system accurately predicted which patients would require no specific antihypereosinophilic therapy, which patients would respond adequately to corticosteroids, and which patients would require therapy with cytotoxic agents. It is proposed that this clinical grading system, and the hematologic grading system outlined in the accompanying report be used as aids in the selection of initial therapy in this group of patients.

The idiopathic hypereosinophilic syndrome (HES) is a disorder characterized by peripheral blood and bone marrow eosinophilia associated with single or multiple organ system dysfunction attributable to tissue invasion by mature eosinophils. The diagnostic criteria suggested by Chusid et al. include a peripheral blood eosinophilia of ≥1500 eosinophils/μm³ for 6 mo or longer, signs and symptoms of organ involvement, and a lack of evidence for parasitic, allergic, or other known causes of eosinophilia. In the past, the prognosis associated with this syndrome has been poor, with a median survival of 12 mo reported in the literature prior to 1976. Recently, however, a more favorable course has been noted for a group of patients managed with a regimen that includes prednisone or hydroxyurea. One of the difficulties with this protocol has been that it requires evidence of progression of organ system dysfunction prior to escalation and antihypereosinophilic therapy. We have reviewed the courses of 32 patients with the HES followed at the National Institutes of Health (NIH) between 1965 and March 1979 and March 1979 are included in this analysis. At the time of first admission to the NIH, patients were evaluated clinically and underwent baseline laboratory studies as outlined in Table 1.

Therapeutic Protocol

The regimen for administration of antihypereosinophilic therapy has been previously described in detail. In brief, after an initial evaluation, patients without evidence of organ system dysfunction are followed without specific antihypereosinophilic therapy, and reevaluated at 3–6 monthly intervals or as clinically indicated. Patients with evidence of organ system dysfunction are begun on prednisone at a dose of 60 mg/day. After 1–2 wk, these patients are gradually converted to an alternate-day schedule and are reevaluated at 3–6 monthly intervals or more frequently if clinically indicated. If the organ system dysfunction is arrested or improves on prednisone therapy, an attempt is made to reduce the drug to the lowest dose that maintains control of disease activity. Hydroxyurea is reserved for patients in whom evidence of disease progression is documented despite administration of prednisone.

Clinical Grading System

The initial NIH admission was retrospectively reviewed, and the data listed in Table 1 were extracted as available. Based on the clinical experience with patients with the HES, a clinical grading system was devised. This grading system was applied to the data available from each patient’s first NIH encounter. The grading system, which is summarized in Table 2, was weighted in such a fashion that features that have been historically associated with a poor prognosis, such as cardiac involvement, received proportion-

From the Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, and the Hematology Service, Clinical Pathology Department, Clinical Center, National Institutes of Health, Bethesda, Md.

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Address reprint requests to Dr. A. S. Fauci, National Institutes of Health, Building 10, Room 11B13, Bethesda, Md. 20205.

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Table 1. Initial Clinical Evaluation in the Idiopathic Hypereosinophilic Syndrome

<table>
<thead>
<tr>
<th>Organ System</th>
<th>History and Physical Examination</th>
<th>Laboratory Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cardiovascular</td>
<td>Congestive heart failure</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td></td>
<td>Angina</td>
<td>Echocardiogram</td>
</tr>
<tr>
<td></td>
<td>Mitral regurgitation</td>
<td>Chest x-ray</td>
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<td></td>
<td>S3 or S4 gallop</td>
<td></td>
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<tr>
<td>2. Nervous system</td>
<td>Transient ischemic attack or cerebrovascular accident</td>
<td>Cerebral angiogram if clinically indicated</td>
</tr>
<tr>
<td></td>
<td>Diffuse CNS dysfunction</td>
<td>Nerve conduction</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>Nerve biopsy if clinically indicated</td>
</tr>
<tr>
<td>3. Lungs</td>
<td>Asthmatic symptomatology</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td>4. Liver</td>
<td>Size, rarely pain</td>
<td>SGOT, SGPT, alkaline phosphatase Scan</td>
</tr>
<tr>
<td>5. Spleen</td>
<td>Size, pain</td>
<td>Scan</td>
</tr>
<tr>
<td>6. Muscles</td>
<td>Pain or weakness</td>
<td>CPK, LDH, aldolase</td>
</tr>
<tr>
<td>7. Gastrointestinal</td>
<td>Diarrhea or malabsorption</td>
<td>Radiographic contrast studies or biopsy if clinically indicated</td>
</tr>
<tr>
<td>8. Cutaneous</td>
<td>Pruritis</td>
<td>Biopsy if clinically indicated</td>
</tr>
<tr>
<td></td>
<td>Angioedema</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maculopapular or pustular eruption</td>
<td></td>
</tr>
<tr>
<td>9. Kidneys</td>
<td></td>
<td>Urinalysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Creatinine, blood urea nitrogen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biopsy if clinically indicated</td>
</tr>
</tbody>
</table>

Patients Responding to Prednisone

Twenty-six patients ultimately required specific antihypereosinophilic therapy with either prednisone or cytotoxic agents. Nine of these patients followed for a mean of 39 mo showed improvement or stabilization of organ system dysfunction on prednisone therapy. As seen in Fig. 1, the clinical grading system was highly effective in separating those patients who responded to prednisone (mean clinical score 3.33 ± 1.09), from those patients in groups 3, 4, and 5 who manifested an incomplete response to prednisone (mean clinical score 9.18 ± 0.72) (p < 0.001). However, the clinical score could not separate those patients in whom no therapy was required from those who were prednisone responders (Fig. 1). Only 3 of the 9 patients responding to prednisone had cardiac abnormalities on presentation compared to 14 of 17 who failed to respond adequately to prednisone ($\chi^2 = 6.25, p < 0.02$). Splenic enlargement was present at the initial NIH evaluation in only 3 of 9 patients who responded to prednisone therapy as compared to 14 of 17 who failed to respond adequately to prednisone ($\chi^2 = 6.25, p < 0.02$).

Patients Failing to Respond to Prednisone

The therapeutic response to prednisone was judged inadequate in 17 patients. Thirteen of these patients received what was considered an adequate trial of
cytotoxic agents. Of these 13 patients, 10 received hydroxyurea; cyclophosphamide was administered to 2 patients and 6-mercaptopurine to 1 patient. Of the 4 remaining patients in this group, 3 received cytotoxic therapy but they died before an adequate course of cytotoxic therapy had been delivered to assess adequacy of the response; 1 patient was judged to be too debilitated to be a candidate for cytotoxic therapy.

As noted above, the clinical grading system was quite accurate in predicting which patients would ultimately require cytotoxic therapy (Fig. 1). Sixteen of the 17 patients deemed to be candidates for cytotoxic therapy compared to 4 of the 15 who either required no therapy or who responded to prednisone therapy had clinical scores of 6 points or more ($\chi^2 = 19.39, p < 0.001$). As noted above, cardiac involvement and splenomegaly were present at the initial NIH evaluation in most patients who ultimately required cytotoxic therapy.

Patients Failing to Respond to Cytotoxic Therapy

Disease manifestations were not controlled by cytotoxic therapy in 4 patients. These patients had significantly more organ system disease at presentation (mean clinical score 12.00 ± 1.35 points) than patients manifesting a satisfactory response to cytotoxic therapy (mean clinical score 7.78 ± 0.92 points) ($p < 0.05$). As noted in the companion report, the group of patients in whom cytotoxic therapy failed tended to have lower white blood cell counts and total eosinophil counts prior to the initiation of therapy than those who responded to cytotoxic agents despite the presence of significant organ disease.

Correlation of Clinical and Hematologic Grading Systems

The clinical grading scores for patients with HES are listed in Table 3. In the companion report, we have outlined a number of hematologic parameters that appear to have prognostic significance for this group of patients. A hematologic scoring system, developed in a fashion similar to the clinical scoring
system described here, was also applied to this group of patients. The hematologic grading system was even more effective in dividing patients into subsequent treatment groups than was the clinical grading system. In an effort to determine whether a positive correlation existed between clinical and hematologic characteristic for this group of patients, the two scoring systems were compared by the Spearman rank method. As can be seen in Fig. 2, the correlation between the two scoring systems was highly significant \((r = 0.689, \ p < 0.001)\). By contrast, the correlations between the initial clinical score and either the initial total eosinophil count \((r = 0.344)\) (Fig. 3) or the initial white blood cell count \((r = 0.309)\) (data not shown) are much weaker. As noted in the companion report,4 neither the initial total eosinophil count nor the initial white blood cell count accurately predicted the final treatment group.

**DISCUSSION**

Specific therapy for the idiopathic HES has been associated with a favorable impact on survival.2 In the past, decisions regarding initiation or escalation of therapy have been based solely on clinical parameters. Major therapeutic changes were generally made after evidence of significant disease progression.2 This approach, combined with careful medical management of complications of the illness, has significantly improved survival of patients with this illness.2 The requirement for demonstration of progression of the disease prior to an escalation of therapy places
patients at risk for the development of complications of the illness which may not always be reversible. In this and the companion report, we have attempted to identify factors that would predict at the patient's initial presentation which patients will ultimately require more aggressive therapy. In addition, we have developed formal scoring systems for clinical and hematologic parameters that provide guidance in the early identification of these patients.

The presence of cardiac manifestations at the first NIH encounter received a relatively heavy weighting in the clinical grading system (Table 2). Previous observers have noted that the cardiac manifestations of this illness contribute to much of the morbidity and most of the mortality associated with this syndrome. Optimal medical management of the cardiac manifestations has recently been reviewed. Application of the clinical and hematologic grading systems to patients with this disease may identify those patients in whom more intensive early therapy will arrest the illness prior to the development of significant restrictive cardiomyopathy or mitral regurgitation.

A relatively heavy weight was assigned to the presence of nervous system disease at the initial encounter. Although nervous system involvement was seen in only 5 patients at first encounter, 4 of these patients required cytotoxic therapy. Hepatosplenic involvement was also seen more frequently in patients requiring cytotoxic therapy. In contrast to cardiac and nervous system disease, hepatosplenic involvement in and of itself produced little morbidity or mortality. Splenomegaly was sometimes associated with pain from capsular swelling or from segmental infarcts documented by radioisotope scanning. It is likely, however, that hepatosplenic involvement serves as a marker for the more aggressive myeloproliferative elements of the syndrome.

The presence of pulmonary involvement was seen in 15 of our patients at presentation and appeared to correlate with the requirement for more aggressive therapy. However 11 of these patients also had cardiac involvement. The paucity of patients in our study with pulmonary involvement alone rendered generalizations about the prognostic significance of pulmonary involvement per se difficult. Referral patterns to a tertiary care center such as NIH probably account for the infrequency of our patient group of isolated pulmonary infiltrates with eosinophilia, a condition generally associated with an excellent prognosis.

Gastrointestinal involvement was seen initially in only 4 of our patients and was not associated with the need for aggressive therapy, and in general, it was not associated with extensive extraintestinal manifestations. Although fatalities have been reported with eosinophilic gastroenteritis, the prognosis associated with this syndrome is usually quite good. Dermatologic manifestations of the illness occurred in 11 patients in this series. As previously reported, episodes of angioedema correlated with a good prognosis and responsiveness to corticosteroid therapy.

The correlation of initial clinical and hematologic parameters in patients with the idiopathic HES is further supportive evidence of the pathophysiologic role played in this syndrome by disordered eosinophilic production. The poor correlation between initial clinical score and white blood cell and eosinophil counts suggests that factors other than the absolute number of circulating eosinophils contribute to the severity of the disease. These factors may include the maturity, granule content, and migrational patterns of the eosinophils observed in this illness. This may also account for the observation that corticosteroids may occasionally be beneficial in an individual case without significantly affecting the number of circulating eosinophils. In contrast, hydroxyurea therapy, which has not been shown to affect granulocyte adherence, chemotaxis, or margination, which are affected by corticosteroids, has failed to be clinically beneficial except when associated with a significant reduction in the number of circulating eosinophils.

Thus, these scoring systems are presented to provide guidance in the early selection of appropriate therapy for patients with the idiopathic HES. We do not
propose that either scoring system should be used as absolute determinants of initial therapy of all patients with this illness. Rather, attention to the factors identified in these systems should alert physicians to patients with potentially more severe disease, and hence, help to identify patients who might be candidates for earlier, more aggressive specific antihypereosinophilic therapy.

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REFERENCES

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RT Schooley, MA Flaum, HR Gralnick and AS Fauci