A Clinicopathologic Correlation of the Idiopathic Hypereosinophilic Syndrome. I. Hematologic Manifestations

By Morris A. Faum, Robert T. Schooley, Anthony S. Fauci, and Harvey R. Granick

A retrospective blind study of 32 patients with the hypereosinophilic syndrome was undertaken utilizing a hematologic scoring system that was based on peripheral blood and bone marrow findings, cytogenetics, B12 levels, and leukocyte alkaline phosphatase determinations. In addition to the grading system, which allowed formulation of a hematologic score, the data could also be normalized for individuals who did not have all tests performed by use of the hematologic quotient. This study clearly defined two groups of patients within the idiopathic hypereosinophilic syndrome. One group were those individuals with low hematologic scores and quotients who did not require therapy or who responded to prednisone therapy, while the second group of patients required cytotoxic therapy. These patients had significantly higher hematologic scores and quotients and a significant number of abnormalities similar to those seen in myeloproliferative syndromes, such as myelofibrosis and cytogenetic abnormalities. This type of hematologic scoring seems useful in predicting therapy and/or evaluating individuals or groups of patients with the hypereosinophilic syndrome.

THE IDIOPATHIC proliferation of eosinophils was initially recognized by Stillman in 1912. Since then, multiple designations have been used to describe this disorder, each drawing attention to the major organ system involved. These have included eosinophilic leukemia, disseminated eosinophilic collagen disease, and endomyocardial disease and eosinophilia. Hardy and Anderson introduced the term “hypereosinophilic syndromes” to encompass these nosologic entities and draw attention to the interrelationships among these disorders.

A constant feature of these disorders has been both peripheral blood and bone marrow eosinophilia with other organ systems variably involved. In a preliminary attempt to determine whether the degree and severity of the hematologic manifestation at initial evaluation of patients with the hypereosinophilic syndrome could be predictive of either progression of disease or response to therapy, we have studied retrospectively all available admission hematologic data of 32 patients with hypereosinophilic syndrome studied at the National Institutes of Health (NIH). In these patients, selected hematologic parameters correlated well with the severity of the disease and responsiveness to therapy. The hematologic scoring system described in this article may be useful in prospectively planning effective therapy in this disorder.

MATERIALS AND METHODS

Hypereosinophilia Patients: Criteria and Treatments

Since 1968, 32 patients have been admitted to the NIH and evaluated under the criteria described. Six patients were women and 26 were men. The criteria for the diagnosis of the idiopathic hypereosinophilic syndrome as outlined by Chusid et al. are: (1) a persistent eosinophilia of 1500 eosinophils/cu mm for longer than six mo or death before 6 mo associated with signs and symptoms of hypereosinophilic disease; (2) lack of evidence for other causes of eosinophilia; and (3) evidence of organ system involvement. Rationale and plan of management are outlined by Parrillo et al. and Schooley et al. Specific antieosinophil therapy is instituted unless patients manifest significant symptomatology or organ system involvement referable to eosinophil infiltration. Prednisone, initially 60 mg/day with a decrease to alternate days within 1–2 wk, is the drug regimen utilized initially. If progression of the disease is noted after 3 mo on this agent, patients are begun on busulfan, methotrexate, and vincristine.

Hematologic Evaluation

Initial peripheral blood smear and bone marrow obtained at NIH either by aspiration or biopsy, were reviewed by two hematologists (M.A.F. and H.R.G.) who were unaware of the course and response to therapy of the patients. Peripheral blood smears were evaluated for WBC number, differential count, morphological variation, and immaturity; red blood cell (RBC) morphological abnormalities; and platelet size and number. Biopsy specimens and aspirate sections were evaluated for cellularity, presence and degree of fibrosis, megakaryocyte content, and degree of eosinophilia. A 200-cell differential count was performed on all peripheral blood and aspirate smears available. Other features noted on examination of the aspirate smear were erythropoiesis and myelopoesis, and size, granularity, vacuolization, and maturation of eosinophils. Peripheral blood smears, bone marrow aspirations, and biopsy touch preparations were stained with a modified Romanowsky stain, and aspirate and biopsy sections were prepared as previously described.

WBC counts, hemoglobin determinations, and platelet counts were obtained as previously described. Leukocyte alkaline phos-
hypoeosinophilic degranulation, and had cytoplasmic and nuclear changes. Abnormalities (blasts, promyelocytes, and cytoplasmic and nuclear changes) were evident in the bone marrow aspirate smear, although they were more readily identifiable in the peripheral blood smear. Charcot-Leyden crystals were commonly found in the bone marrow smear. The percentage of eosinophils found in the initial bone marrow differential count ranged from 7% to 57% with a mean of 33%.

The major abnormalities of the peripheral RBCs were tearad forms and nucleated RBCs. In the bone marrow, disorderly erythropoiesis was uncommon, with megaloblastic changes seen in only three patients. Large platelets were seen in five patients, but no abnormalities of megakaryocytopoiesis were identified.

Bone marrow biopsy and aspirate sections ranged from normocellular to markedly hypercellular. In all cases the bone marrow eosinophils were increased. Reticulin and collagen stains were performed in 17 patients. Of these, 6 revealed increase in reticulin fibers, although the majority were only mildly increased. Two specimens revealed increase in collagen fibers. Megakaryocytes were decreased in 13 of the 32 bone marrow specimens.

Correlation With Therapy

Patients Requiring No Therapy

Six patients, followed for a mean of 36.2 mo/patient (range 14–90 mo), have required no specific therapy. The hematologic data are summarized in Table 2. One patient presented with less than 1500 eosinophils/μl initially, but this increased soon after admission and has persisted above 1500/μl. The mean of the hemoglobin values and platelet counts were normal in this group. There were no major morphological abnormalities of the RBCs, nor was there blood or bone marrow basophilia, increase in mature WBCs, or fibrosis. Dyspoiesis and/or hypersegmentation of noneosinophil WBCs were seen in the peripheral blood of only one patient. Cytogenetic abnormalities and low LAP were seen in one patient, respectively. The most common abnormality was an elevation of the vitamin B12. The mean hematologic score (Table 2) in this untreated group was 2.33 (±0.61), which differed significantly (p < 0.005) from patients requiring therapy for the hypereosinophilic syndrome (Fig. 1). However, the hematologic score of patients who
responded to prednisone was not significantly different from the untreated group. The hematologic quotient of the untreated group was 9.83 ± 2.63, which was also significantly different from all patients receiving prednisone therapy (p < 0.005), but not significant when compared to the patient who responded to prednisone therapy. Although the mean (± SEM) WBC counts (9600 ± 1600 versus 30,500 ± 5100 per cu mm) and eosinophil counts (4100 ± 900 versus 4500 ± 3200 per cu mm) were higher in those patients who subsequently received therapy, these values were not significant (0.5 < p < 0.1). The interval from diagnosis to therapeutic intervention in the patients requiring therapy was significantly shorter (Gehan test, Z = 3.24, p < 0.001) when compared to the interval from diagnosis in the untreated group.

Patients Responding to Prednisone

Of the 26 patients who were placed on corticosteroid therapy, 9 responded adequately to prednisone. An adequate response to therapy is defined as lack of progression of disease or subjective and objective improvement in signs and symptoms of disease activity. Five of the six female patients are included in the prednisone-responsive group. The mean follow-up time for this group is 50 mo/patient (range 10 mo to 11 yr). The hematologic data for this group are presented in Table 3. The heterogeneous nature of the group is noteworthy. Most commonly noted were mild to moderate bone marrow hypercellularity (5 patients) and low or high LAP (6 patients). No peripheral blood WBC immaturity or abnormality in platelet count or cytogenetics was noted. Further, there was no increase in either fibrosis or myeloblasts and progranulocytes in the bone marrow.

The hematologic score in this subgroup was 3.44 ± 0.77, a value that did not differ significantly from the untreated patients, but was significantly different from the patients who required cytotoxic therapy (Fig. 2). The hematologic quotient showed similar differences (Fig. 3). The mean WBC count was significantly higher when compared to the untreated group (19,600 ± 3400 versus 9600 ± 1600, p < 0.05) but was not significantly different when compared to the cytotoxic therapy group (19,600 ± 3400 versus

<table>
<thead>
<tr>
<th>Table 2. Hematologic Findings. No Treatment Group</th>
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<tr>
<td><strong>Peripheral Blood</strong></td>
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<tr>
<td><strong>Bone Marrow</strong></td>
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<td><strong>Other</strong></td>
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<tr>
<td><strong>Patient</strong></td>
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<td>-----------</td>
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<td>1</td>
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<td>6</td>
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<td>7</td>
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</tbody>
</table>

*Hb, hemoglobin; RBC Abn, red blood cell abnormality; WBC, white blood cell count; 10^6/cu mm; Eos, eosinophils; 10^6/cu mm; WBC imm, white blood cell immaturity; 0—none, 1—myelocytes, metamyelocytes, 2—myeloblasts, progranulocytes; Myeloid Dyspl, myeloid dysplasias; Baso, basophils; Pt, platelet count; 10^9/cu mm; Cell, bone marrow cellularity; NC—normocellular, 1—mildly to moderately hypercellular, 2—markedly hypercellular; Myelo-Fibro, myelofibrosis; Mega, megakaryocytes; MB, PG, myeloblasts, progranulocytes; Cyto, cytogenetics; LAP, leukaocytes alkaline phosphatase.

0, not present; +, present; ND, not determined; N, normal; L, decreased; H, increased.

†Number abnormal over total number of patients.

Fig. 1. Hematologic score comparing the patients requiring no therapy versus patients requiring therapy. The treated group of patients included those patients receiving prednisone or cytotoxic therapy. The bar and brackets represent the mean ± SEM. The mean hematologic score of the treated group was 8.81 and for the group requiring no therapy 2.33.
36,200 ± 7300, p > 0.05). The mean of the eosinophil count was 9200 ± 2400/cu mm and did not differ significantly when compared to either the untreated group (4100 ± 900/cu mm), or the cytotoxic therapy group (21,900 ± 4500/cu mm).

Patients Requiring Cytotoxic Therapy

Seventeen patients, followed for a mean period of 38 mo/patient (range 1–108 mo) required cytotoxic therapy. When compared to the group responding to prednisone, the patients in this treatment category received prednisone for a significantly shorter period of time (Gehan test, Z = 3.76, p < 0.001). We found no significant difference in duration of prednisone treatment between those patients who ultimately responded to and those that ultimately failed cytotoxic therapy (Wilcoxon test, U = 26, p > 0.10); however, it is clear that prednisone responders had a score of 6 or
less while over 90% of the patients who eventually required cytotoxic therapy had a score greater than 6 (Fig. 4).

Therapeutically, this group can be divided into three subgroups. Four patients did not receive an adequate trial of cytotoxic therapy. One patient (no. 18) died within days of being admitted to the NIH and prior to institution of chemotherapy. The two remaining patients (nos. 17 and 19, Table 4) were placed directly on cytotoxic therapy but received no further therapy due to age and debility. One patient (no. 17) died prior to delivery of a course of therapy that could be evaluated for its efficacy. These patients received myleran and 6-mercaptopurine.

Nine patients, including the other female, nos. 20–28 in Table 4, responded to cytotoxic therapy. Seven patients were treated with hydroxyurea, while one received cyclophosphamide (no. 20) and another busulfan (no. 25).

The remaining four patients (nos. 29–32) failed to respond to cytotoxic therapy (hydroxyurea). The hematologic data of all the patients who required cytotoxic therapy are summarized in Table 4.

Multiple peripheral blood abnormalities appeared in patients in the cytotoxic therapy group. Greater than 75% of patients demonstrated anemia and RBC abnormalities, and more than 60% demonstrated abnormalities in platelet counts, dyspoiesis of noneosi- 

Table 4. Hematologic Findings. Cytotoxic Therapy Group

<table>
<thead>
<tr>
<th>Patient</th>
<th>RBC Abn</th>
<th>WBC Imm</th>
<th>Eos</th>
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<th>Myeloid</th>
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<td>12772</td>
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* Receiving chemotherapy.
The bone marrow demonstrated hypercellularity in 14 of the 16 patients in whom specimens were available for evaluation. Fibrosis occurred in 6 of 8 specimens, while megakaryocytes were decreased in 65%. Myeloid dyspoiesis also occurred commonly in 54%. Increase in myeloblasts and progranulocytes (>5%) occurred in only 2 patients. Abnormal cytogenetics, evaluation in the B<sub>12</sub>, and abnormal LAP were common findings.

The patients who responded to cytotoxic agents differed from the group as a whole by demonstrating a lower incidence of thrombocytopenia (3/9), myelofibrosis (1/3) and bone marrow myeloid dyspoiesis (2/8). The mean WBC count was 39,400 ± 11,000/cu mm and eosinophil count was 23,000 ± 6500/cu mm. The mean hematologic score for this subgroup was 11.1 ± 1.4, a value that did not differ significantly from that of the patients who did not respond to chemotherapy (0.05 < p < 0.1). The mean of the hematologic quotients was likewise not statistically significant (50 versus 66, p > 0.10).

Each of the four patients who failed to respond to chemotherapy demonstrated thrombocytopenia, decreased megakaryocytes, abnormalities of myeloid maturation in the bone marrow, and elevation of vitamin B<sub>12</sub> levels. Myelofibrosis was demonstrated in all 3 patients in whom biopsies were available. Further, the 2 patients who had greater than 5% myeloblasts and progranulocytes fell into this treatment failure category. The mean of the hematologic score and quotient, 15.8 ± 1.5 and 66.3 ± 5.8, respectively, was not significantly different from the chemo-therapy responsive group. The mean of the WBC count of these 4 patients was 13,500 ± 4100/cu mm; eosinophil count was 8000 ± 3000/cu mm. One patient was receiving chemotherapy at the time that these values were obtained.

Discriminant Analysis

Stepwise discriminant analysis, utilizing hematologic score and eosinophil count, yielded classification functions for each group. These values resulted in the classification of cases into the correct group with an accuracy of 79%. The results of the classification matrix are presented in Table 5. As noted in the table, no error of classification was made in the group that did not respond to cytotoxic therapy. In only two instances was a patient advanced in group, one from the nontherapy to prednisone response group and one patient from cytotoxic responder to nonresponder.

**DISCUSSION**

The clinical and laboratory heterogeneity of the idiopathic hypereosinophilic syndrome(s) and the great variability in progression of organ system involvement from patient to patient suggested to us that we might be able to subdivide the hypereosinophilic syndrome on the basis of hematologic findings. We felt that the entire hematologic picture would be important in subclassifying the hypereosinophilic syndromes. We arbitrarily set a hematologic scoring system that included findings in the peripheral blood, bone marrow, and certain other studies previously shown to be useful in classifying hematologic disorders, i.e., B<sub>12</sub> levels, cytogenetics, LAP. Since this was a retrospective study, it was readily obvious that all patients might not have all studies performed during their initial admission. In order to apply the hematologic scoring system to each patient, we devised the hematologic quotient, which allowed for “comparison” of each hematologic score. It is important to restate that the two individuals who were involved in the development of the hematologic scoring system, analysis of the initial laboratory data, and interpretation of the bone marrow and peripheral blood smears had no prior knowledge of the patients’ courses. We feel that this type of objective grading system can be implemented in other studies of individuals or groups of patients with the hypereosinophilic syndromes.

The morphological abnormalities of the eosinophils in this disorder, notably increased size, irregular cytoplasmic granulation and vacuolization, and nuclear hypo- and hypersegmentation, have been commented on previously. In our study, the abnormalities in the

<table>
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<th>Table 5. Classification Matrix</th>
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<tr>
<td>No Therapy Required</td>
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<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>No therapy required</td>
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<tr>
<td>Prednisone responders</td>
</tr>
<tr>
<td>Cytotoxic therapy responders</td>
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<td>Total</td>
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For personal use only.on October 22, 2017. by guest
the finding of abnormal chromosomal analysis is both urea, 2 were shown to have aneuploidy. It appears that sis. Seven of these patients required cytotoxic therapy.

of the neoplastic nature of this disorder. Eight of our authors have considered these findings to be indicative of patients who required cytotoxic therapy.

cytotoxic therapy.

count greaten than 100,000/cu mm, the 9-mo survival of disease to the extent that all patients who failed chemotherapy had both thrombocytopenia and decreased megakaryocytes. Thrombocytopenia was found in two-thirds of the cases and thrombocytosis in 3% of the cases reviewed by Benvenisti and Ultmann. An incidence of 31% and 16%, respectively, was found in our series, and decreased megakaryocytes were found in 3 patients. The findings of thrombocytopenia and decreased megakaryocytes correlated with the severity of disease to the extent that all patients who failed chemotherapy had both thrombocytopenia and decreased megakaryocytes.

An elevated WBC count has been recognized as an indicator of a poor prognosis. In patients with a WBC count greater than 100,000/cu mm, the 9-mo survival was 25%. Both the WBC and eosinophil counts in our series showed a trend to higher counts in patients requiring therapy and statistically significant differences were evident when those patients who remained untreated were compared to the patients who required cytotoxic therapy.

Data from the literature is inconclusive regarding the level or significance of vitamin B₁₂ in hypereosinophilic syndromes, while elevations are present in disparate disorders, including the leukemoid reaction, myeloid metaplasia with myelofibrosis, and the accelerated phase of CGL. Although there were no striking intergroup differences, there was a tendency to increased frequency of LAP abnormality in the patients requiring more aggressive therapy. Seven of the 10 patients in the chemotherapy group who had abnormal values had low LAP scores.

Myelofibrosis has been seen previously and has been associated with either a rapidly progressive course or blastic transformation. The two patients with increases in myeloblasts and progranulocytes had concomitant myelofibrosis, one of whom has subsequently developed blastic transformation. Myelofibrosis was demonstrated in each of the three patients who had biopsies performed in the group that failed hydroxyurea therapy. Myelofibrosis, in the hypereosinophilia syndrome, is thus associated with a more progressive and less therapeutically responsive disorder. A similar situation exists in CGL.

The compilation of these entities to form a hematologic score, and its derivative, the hematologic quotient, allows one to separate those patients who require no therapy or prednisone therapy from those who will subsequently require chemotherapy. As can be seen from Fig. 3, all patients who did not receive therapy had hematologic scores of 5 or less with a mean score of 2.33, while only 30% of patients who were felt to require prednisone or cytotoxic agents had scores in this range. The mean score of this latter group was 8.81. The low mean hematologic score in the untreated group is a reflection of the fact that many of the factors that comprise this score were absent in this subgroup, i.e., RBC abnormalities; WBC immaturity; peripheral blood and bone marrow basophilia; myelofibrosis; dyspoiesis and hypersegmentation of the bone marrow noneosinophil myeloid cells; and increase in myeloblasts and progranulocytes. Greater differences, however, are evident when a comparison of treatment groups are made. Figure 2 demonstrates that the hematologic score of all predi- sone responders is 6 or less, while 90% of patients who required cytotoxic therapy were above this value. The mean of the hematologic quotients is also significantly different. In comparing patients with scores of 6 or less with those greater than 6, several differences were evident. No patient with a score of 6 or less had WBC
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immaturity in the peripheral blood, bone marrow myelofibrosis, or an elevated percentage of myeloblasts and progranulocytes. The significance of peripheral blood WBC immaturity has been previously recognized as a poor prognostic indicator.11

The classification of the idiopathic hypereosinophilic syndrome has been a major issue of controversy. Some have considered the syndrome a form of leukemia,2,4 while others doubted that the syndrome was even a neoplastic proliferation.7,35,36

From our data, we can divide the hypereosinophilic syndrome into a benign phase and an accelerated phase. The benign phase consists of those individuals who have increased eosinophil counts (over 1500/µl), low hematologic scores and quotients, and who require no specific therapy or respond to prednisone. The second group, the accelerated phase, appears to be comprised of two subgroups. The first, a group of patients who tend to have abnormalities of other cell series and generalized hyperplasia of the marrow, do not respond to steroid therapy. In addition, these individuals have biochemical evidence, i.e., B2, LAP, cyto genetics, to suggest that they truly have a myeloproliferative disorder. These patients require cytotoxic therapy to control their disease. The second group of the accelerated phase appears to be that group of patients who are not responsive to cytotoxic chemotherapy. This group of patients is characterized by a very high incidence of myelofibrosis, myeloblasts, and progranulocytes in the bone marrow or peripheral blood, thrombocytopenia, and decreased megakaryocytes. In the accelerated phase there appears to be a true continuum of diseases; we have seen one patient in the accelerated group who developed acute leukemia.

In this study we were able to define separate subgroups of patients with the hypereosinophilic syndrome and have been able to predict from the hematologic values at the time of presentation those patients who would not require therapy or only corticosteroids for control of their disease, and those who require more intensive therapy to control their disease. In this last group of patients, their disease may be an eosinophilic form of myeloproliferative or myelodysplastic syndrome.

ACKNOWLEDGMENT

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