

Letter to the Editor

Heterogeneity among characteristics of hyper-eosinophilic syndromes

To the Editor:

We read with interest the recent Journal article by Ogbogu et al¹ reporting the results from a multicenter analysis of patients with hypereosinophilic syndrome (HES). In retrospective and prospective studies, we have analyzed clinical and laboratory data from 88 patients who satisfied the stringent criteria by Chusid et al² for HES. We prospectively followed 55 patients; data from the remaining 33 were analyzed after chart review.

The patients were recruited from 2002 to 2009 from 3 institutions that treated patients with hematologic disorders; the coordinating center was located at Silesian Medical University in Katowice, Poland. Before patients were referred to the hematology units, potential secondary causes of hypereosinophilia were excluded. Informed consent was obtained from all patients according to the Declaration of Helsinki, and the study was approved by the institutional ethics committee. All patients included in the study exhibited symptoms, signs, and imaging or histologic evidence of eosinophilic organ involvement.

We performed complete blood count and differential analyses, routine chemistry tests, electrocardiograms, echocardiograms, chest x-rays, ultrasound/computed tomography/magnetic resonance studies, and analyses of bone marrow aspirates and biopsy samples. The methods of analysis of patients with HES, which included cytokine and tryptase measurements, immunophenotyping, and cytogenetic and molecular studies, are presented elsewhere.³ All laboratory tests were performed on treatment-naïve patients. Statistical methods were reported previously.³ Because this was a retrospective study, some results were not available for all cases.

Clinical responses were assessed after 1 month of treatment. A complete hematologic response was defined as a decrease in the absolute eosinophil count (AEC) to the normal range ($<0.7 \times 10^9/L$) with resolution of organ involvement. A partial response was defined as decrease in the AEC $\geq 50\%$ and/or symptomatic improvement. "No response" was defined as a stable or increasing AEC and/or stable or progressive organ dysfunction.

Forty-seven male and 41 female patients (median age at diagnosis, 56 years; range, 6-84 years) were included in the study. The median AEC was $6.6 \times 10^9/L$ (range, 1.5 - $136 \times 10^9/L$), and a median 31% of cells were eosinophils (range, 7% to 80%). Patients were divided into 5 subgroups according to Klion et al⁴; their characteristics are presented in Table I.

Of the 88 patients whose blood samples were tested by nested PCR analysis, 16 were found to have the *FIP1L1-PDGFR α* (Fip1-like 1-platelet-derived growth factor receptor α ; F/P) fusion transcript (18%; 14 male and 2 female patients). Three patients with F/P transcripts had no organ involvement. The remaining 13 cases had the following abnormalities: splenomegaly (n = 11), hepatomegaly (n = 7), cardiac failure (n = 3), lymph node enlargement (n = 2), pulmonary infiltrate (n = 2), and central nervous system involvement (n = 1). In 10 patients (12%), the diagnosis of chronic eosinophilic leukemia (CEL) was established on the basis of an increased number of blasts in peripheral blood and/or in bone marrow (n = 8) or the presence of molecular/cytogenetic markers, including 2 patients with the point mutation JAK2V617F (n = 2).

Splenomegaly was the most common form of organ involvement in this population. Twenty-six patients were found to have CEL (30%). Eight patients had a myeloproliferative variant of HES (etiology unknown) on the basis of at least 4 of the criteria proposed by Klion et al.⁴

Forty-two patients were tested for T-cell receptor (TCR) rearrangement by using multiplex PCR with heteroduplex analysis; clonality was detected in 18 patients (43%). Three patients were found to have aberrant T-cell phenotypes (by flow cytometry) and TCR clonal rearrangement (by PCR analysis). On the basis of the definition, these 3 patients (7%) were the only ones diagnosed with lymphocytic variant hypereosinophilic syndrome (L-HES).⁵ Fifty-one patients (including 15 not yet classified cases with clonal TCR) were diagnosed with idiopathic HES. The results of this analysis have been presented in detail.³

Serum tryptase and vitamin B12 levels were reported for 47 and 69 patients, respectively. Serum IgE levels were measured in 74 patients and were found to be increased compared with normal levels in 38 cases. Serum levels of IL-4 and IL-5 were documented for 49 and 51 patients, respectively.

We compared the results of laboratory studies between patients with F/P⁺ and F/P⁻ CEL and those of patients with HES (including idiopathic HES, L-HES, and myeloproliferative variant HES). Patients with CEL had significantly increased white blood cell counts, AECs, and levels of serum vitamin B12 and tryptase compared with patients with HES. Patients with HES had increased platelet counts and serum levels of IL-5 compared with patients with CEL (see this article's Table E1 in the Online Repository at www.jacionline.org).

Results of cytogenetic analyses were available for 48 patients (54%); karyotypes were normal in 84%. The cytogenetic abnormalities were as follows: -Y (n = 2), complex karyotypes (n = 2), translocation t(6;11) (n = 1), -7 (n = 1), and -17 (n = 1).

In our series, 76 patients (86%) began corticosteroid monotherapy at doses varying from 20 to 60 mg daily; clinical responses were observed in 64% (49 patients). Forty-one patients continued to receive a low dose of corticosteroid maintenance therapy (5-20 mg daily). Discontinuation of corticosteroids led to eosinophilia recurrence in most patients. Ten patients remained in remission even after therapy ended, but the follow-up period was less than 3 months (see this article's Table E2 in the Online Repository at www.jacionline.org). Serum levels of IL-5 were available for 31 responders and 19 nonresponders. Median levels of serum IL-5 were significantly increased among patients who responded to steroids compared with nonresponders (18.6 vs 11.0; $P = .01$).

Sixteen patients who had the F/P fusion transcript had a rapid response to imatinib at starting doses from 100 to 400 mg daily (100%; range, 6-65 months); they remained in sustained hematologic and molecular remission after a median of 42 months of therapy.

Sixteen of 26 patients with CEL were resistant to corticosteroid monotherapy. The maximum starting dose was 1 mg/kg daily. The 10 patients with F/P⁻ CEL were treated with a median number of 3 therapeutic approaches, including allogeneic hematopoietic stem cell transplantation. Imatinib (400 mg daily) was ineffective in 2 patients with F/P⁻ CEL. Of the 10 patients with F/P⁻ CEL, 70% died: 3 from progression to acute myeloid leukemia, 1 from concurrent development of lymphoblastic lymphoma, and 3 from

TABLE I. Characteristics of patients included in the study

Parameter	Idiopathic HES	F/P ⁺ CEL	F/P ⁻ CEL	M-HES	L-HES
No. of patients (%)	51 (58)	16 (18)	10 (12)	8 (9)	3 (3) [†]
Sex: male/female	19/32	14/2	7/3	5/3	2/1
Age (y), median (range)	54 (6-84)	52 (19-80)	64 (23-77)	59 (19-78)	45 (37-64)
WBC count ($\times 10^9/L$), median (range)	12.4 (5.2-120)	23 (5-105)	23.9 (9.3-175)	19.3 (7.6-32.9)	9.7 (6.4-26.2)
WBC >N	28/51 (55%)	15/16 (94%)	8/10 (80%)	7/8 (88%)	1/3 (33%)
Hemoglobin (g/dL), median (range)	13.1 (8.8-17.7)	12.7 (8.2-16.1)	11.8 (9.1-16)	13.4 (9.1-15.6)	12.9 (11.8-13.2)
Hemoglobin <N	3/51 (6%)	3/16 (19%)	4/10 (40%)	2/8 (25%)	0/3 (0%)
Platelet count ($\times 10^9/L$), median (range)	289 (43-605)	166 (26-700)	269 (40-891)	180 (47-380)	240 (192-364)
Platelet count >N	7/51 (14%)	2/16 (13%)	2/10 (20%)	0/8 (0%)	0/3 (0%)
Platelet count <N	2/51 (4%)	2/16 (13%)	4/10 (40%)	4/8 (50%)	0/3 (0%)
AEC ($\times 10^9/L$), median (range)	4.2 (1.5-88)	11.5 (2.5-40)	9.6 (1.5-136)	6.6 (1.5-24)	6.1 (1.6-13.8)
Eosinophils in bone marrow (%), median (range)	30.5 (11-80)	35 (7-61)	37 (14-64)	31 (24-40)	29 (15-40)
Serum IgE >N (IU/mL)*	27/40 (68%)	2/16 (13%)	5/8 (63%)	2/7 (29%)	2/3 (67%)
Serum vitamin B12 >N (pg/mL)*	3/38 (8%)	2/16 (13%)	2/8 (25%)	1/4 (25%)	0/3 (0%)
Serum IL-5 >N (pg/mL)*	10/27 (37%)	0/8 (0%)	0/8 (0%)	1/5 (20%)	0/3 (0%)
Serum IL-4 >N (pg/mL)*	4/24 (17%)	1/11 (9%)	1/6 (17%)	1/5 (20%)	1/3 (33%)
Serum tryptase level >N (ng/mL)*	1/24 (4%)	2/7 (29%)	4/8 (50%)	1/5 (20%)	0/3 (0%)

M-HES, Myeloproliferative variant of HES; WBC, white blood cell.

*Normal ranges (N): IgE <100 IU/mL; vitamin B12 level, 157-1057 pg/mL; tryptase level, <11.5 ng/mL; IL-4 and IL-5, <5.8 pg/mL and <25.8 pg/mL, respectively.

[†]Three percent among all included patients, but 7% among patients tested for T-cell abnormality, both by flow cytometry and PCR.

refractory CEL with subsequent cardiac complications while on therapy with hydroxyurea and prednisone.

Hydroxyurea was administered to 17 patients, alone or in combination with corticosteroids. The other patients were treated with the following: IFN- α (n = 5), busulfan (n = 4), vincristine (n = 2), cyclosporine (n = 2), autologous stem cell transplantation (n = 2), etoposide, mercaptopurine, or cytarabine (n = 5). Imatinib was given to 11 patients with F/P⁻ HES who were refractory to several other treatment strategies, including steroids (as monotherapy or in combination). It was effective only in 2 cases (18%): 1 patient (given imatinib, 100 mg daily) achieved complete hematologic remission of a follow-up period of 6 years (the F/P fusion transcript was undetectable, even after temporary imatinib withdrawal and eosinophilia recurrence), and another patient (given imatinib, 400 mg daily) had a complete response that lasted more than 2 years.

In accord with the results obtained by Ogbogu et al.¹ we confirmed male predominance of CEL (21 male and 5 female patients); most patients with idiopathic HES were female. In assessing eosinophilic organ damage and dysfunction, we observed splenomegaly in most patients with CEL, but cardiac and pulmonary involvement were the most common organ defects observed in patients with HES. Ogbogu et al.¹ most frequently observed dermatologic and pulmonary damage in patients with CEL. The discrepancies between studies might have arisen from referral bias in our cohort and our use of very sensitive techniques to assess organ dysfunction. In some patients, a variety of diagnostic methods, including cardiac magnetic resonance and endomyocardial biopsy analysis, were used to confirm eosinophilic involvement. However, we emphasize that the clinical efficacy of these techniques has not been studied prospectively. In our cohort of patients with idiopathic HES, cardiac manifestations included the following: congestive heart failure (n = 9), mitral valve regurgitation (n = 4), and asymptomatic echocardiographic abnormalities (n = 2). In 3 of the 9 patients with cardiac failure, endomyocardial damage was confirmed by magnetic resonance and biopsy.

We reached conclusions that are similar to those of Ogbogu et al.¹ regarding patients with CEL and F/P mutations; patients with the F/P fusion transcript had increased serum levels of vitamin B12 and tryptase compared with patients with HES. We observed a higher proportion of F/P⁺ patients (18% in this study vs 11% with HES). The increased number of patients with CEL who were F/P⁻ in our study (12%) compared with Ogbogu et al.¹ might result from selection bias or the bone marrow aspiration/biopsy assessments we performed at the initial evaluations. Some patients are asymptomatic when they first visit their doctor, with unexplained hypereosinophilia as their only disorder.

We observed the same proportion of patients with L-HES (7%) as Ogbogu et al.¹ In contrast, we observed an increased number of cases that had clonal TCR (43%) based on PCR analysis—a very sensitive technique for detection. However, demonstrating isolated clonal TCR rearrangement is insufficient to diagnose a patient with L-HES⁵; clonal T cells are also found in peripheral blood of the elderly⁶ and in patients with severe viral infections.⁷

In conclusion, further prospective evaluations are needed of the different techniques to diagnose eosinophilic-related organ damage and classify HES variants. A multicenter study is also required to overcome referral bias.

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TABLE E1. Significant differences in laboratory findings between HES and CEL

Parameter	F/P ⁺ CEL N = 16	F/P ⁻ CEL N = 10	IHES+M-HES+L-HES N = 62	P value [‡]
WBC count ($\times 10^9/L$)	23.1 (5.3-105)	23.9 (9.3-175)	14.6 (5.2-120)	.008
Platelet count ($\times 10^9/L$)	165 (26-700)	269 (40-891)	268 (43-605)	.03
AEC ($\times 10^9/L$)	11.5 (2.5-40.8)	9.6 (1.5-136)	5.0 (1.5-88.8)	.02
Median serum vitamin B12 level (pg/mL)	868 (220-2000)	813 (410-3359)	456 (60-3115)	.002
Median serum tryptase (ng/mL)	11.8 (3-80.9)	40.4 (4.8-49)*	4.7 (1.5-190)	.004
Median serum IL-5 (pg/mL)	†8.3 (0.0-11.1)	14.9 (13.7-16.2)	16.6 (0.0-81.5)	.01

IHES, Idiopathic HES; M-HES, myeloproliferative variant of HES.

*Significant differences were found only between F/P⁻ CEL and HES.

†Significant differences were found only between F/P⁺ CEL and HES.

‡Comparisons were made for each of 2 CEL groups individually vs the HES subgroup.

TABLE E2. Organ involvement and steroid responsiveness

Parameter	IHES	F/P ⁺ CEL	F/P ⁻ CEL	M-HES	L-HES ³
Organ involvement					
Cardiac	15/51 (29%)	3/16 (19%)	2/10 (20%)	4/8 (50%)	NA
Pulmonary	16/51 (31%)	2/16 (13%)	0/10 (0%)	1/8 (12%)	NA
Cutaneous	8/51 (16%)	0/16 (0%)	0/10 (0%)	1/8 (12%)	2/3 (66%)
Splenomegaly	7/51 (14%)	11/16 (69%)	6/10 (60%)	4/8 (50%)	2/3 (66%)
Hepatomegaly	4/51 (8%)	6/16 (38%)	4/10 (40%)	2/8 (25%)	1/3 (33%)
Neurologic	4/51 (8%)	1/16 (6%)	2/10 (20%)	NA	NA
Gastrointestinal	5/51 (10%)	0/16 (0%)	1/10 (10%)	1/8 (12%)	NA
Others	Lymph nodes	Lymph nodes	No	No	Lymph nodes
Constitutional symptoms (fever, weakness, weight loss, sweats, cough)	Yes	Yes	Yes	Yes	Yes
Steroids treatment					
Response to monotherapy with steroids (%)	53	0	33 (steroids + HU)	12	100
CR (n)	27/51	NA	NA	NA	NA
PR (n)	18/51	NA	2/6	1/8	3/3
NR (n)	6/51	12/12	4/6	5/8	NA
Current treatment and disease status	35 in PR/CR on maintenance dose, 10 in CR off therapy, 6 resistant	16 in CR on imatinib	2 in PR on HU + steroids, 1 in CR after AlloSCT, 7 died	2 in CR on imatinib, 4 in PR on steroids + HU, 2 died	2 in PR on steroids 1 in CR after ABCT (NHL transformation)

ABCT, Autologous blood cell transplant; AlloSCT, allogeneic stem cell transplant; CR, complete remission; HU, hydroxyurea; IHES, idiopathic HES; M-HES, myeloproliferative variant of HES; NA, not applicable; NHL, non-Hodgkin lymphoma; NR, no response; PR, partial response.