

Hematologic Malignancies Identified in Patients with Hypereosinophilia and Hypereosinophilic Syndromes

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What is already known about this topic? Certain hematologic malignancies are associated with peripheral or tissue eosinophilia.

What does this article add to our knowledge? Hematologic malignancy is a rare cause of peripheral eosinophilia. These patients may be at greater risk of less common T-cell-derived non-Hodgkin's lymphomas.

How does this study impact current management guidelines? Peripheral eosinophilia in a patient suspected of having hematologic malignancy should alert clinicians to less common cancers and prompt expedited subspecialty evaluation.

BACKGROUND: Certain hematologic malignancies are associated with hypereosinophilia or tissue eosinophilia. It is unclear if patients with hypereosinophilia are more likely to develop one of these malignancies.

OBJECTIVE: This study sought to quantify the specific hematologic malignancies that developed in patients with preexisting hypereosinophilia.

METHODS: Adult patients with eosinophilia associated with the development of hematologic malignancy were identified by a retrospective review of the Mayo Clinic patient database between 2000 and 2013.

RESULTS: Of 2642 patients identified with eosinophilia, hypereosinophilia, or hypereosinophilic syndrome, 25 (aged 28.8 to 86.1 years; 13 male; 12 female) had a diagnosis of either lymphoma or leukemia. The majority of these patients had non-Hodgkin lymphoma (17 of 25). T-cell-derived lymphomas were more common (12 of 17) than B-cell-derived lymphomas (4 of 17). In patients with leukemia (8 of 25), chronic lymphocytic leukemia (4 of 8) was most common, followed by chronic eosinophilic leukemia (3 of 8). Approximately 5.1% of patients with hypereosinophilia developed a hematologic malignancy. On average, the malignancy developed 30.0 ± 42.7 months after the onset of hypereosinophilia.

CONCLUSIONS: The development of hematologic malignancies in this referral population with eosinophilia was rare (0.2%), but more common in those with hypereosinophilia (5.1%). Non-Hodgkin's lymphomas, particularly T-cell-derived malignancies, were most commonly diagnosed. Patients with preexisting hypereosinophilia were diagnosed with hematologic conditions that were rarer within the general population. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:920-5)

Key words: Hematologic malignancy; Hypereosinophilia; Hypereosinophilic syndrome; Lymphoma; Leukemia

Eosinophilia can occur in certain hematologic malignancies, either as a primary clonal condition or as a secondary reactive process.¹ Prior reports have identified eosinophilia as an associated finding in Hodgkin's lymphoma (HL), non-Hodgkin's lymphomas (NHLs), and various leukemias.² In one study of HL, peripheral eosinophilia was estimated to occur in approximately 15% of patients and had been associated with a survival advantage.³ A later study, however, found that tissue eosinophilia within lymph nodes predicted worse survival in nodular sclerosing HL.⁴ In adult T-cell lymphoma/leukemia (ATLL), eosinophilia ($>0.5 \times 10^9/L$) was an independent prognostic factor for worse performance status and survival.⁵ For cutaneous T-cell lymphomas including Sézary syndrome, peripheral eosinophilia at diagnosis was the only factor that predicted a greater probability of disease progression and mortality in multivariate analysis.⁶ Such data are not readily available for other NHLs or leukemias.

Recently, a large population-based study determined the odds ratios of developing a hematologic malignancy within 3 years of documented eosinophilia ($>1.0 \times 10^9/L$) on a single cell count differential. That study found increased odds ratios for the diagnosis of HL, chronic lymphocytic leukemia (CLL), and classic myeloproliferative neoplasms. Classic myeloproliferative neoplasms were defined as a large group encompassing polycythemia vera, myelodysplastic syndromes, myeloid leukemias, and monocytic leukemias.⁷ The odds ratios and incidence rates

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Abbreviations used

<i>AICL</i>	<i>Angioimmunoblastic T-cell leukemia</i>
<i>AML</i>	<i>Acute myelogenous leukemia</i>
<i>ATLL</i>	<i>Adult T-cell lymphoma/leukemia</i>
<i>BE</i>	<i>Blood eosinophilia</i>
<i>CEL</i>	<i>Chronic eosinophilic leukemia</i>
<i>CI</i>	<i>Confidence Interval</i>
<i>CLL</i>	<i>Chronic lymphocytic leukemia</i>
<i>CTCL</i>	<i>Cutaneous T-cell lymphoma</i>
<i>DLBCL</i>	<i>Diffuse large B-cell lymphoma</i>
<i>FISH</i>	<i>Fluorescence in situ hybridization</i>
<i>FIP1L1</i>	<i>Fip-1-like-1</i>
<i>HE</i>	<i>Hypereosinophilia</i>
<i>HE-N</i>	<i>Hypereosinophilia from apparent eosinophil clone</i>
<i>HE-R</i>	<i>Reactive hypereosinophilia</i>
<i>HES</i>	<i>Hypereosinophilic syndrome</i>
<i>HL</i>	<i>Hodgkin's lymphoma</i>
<i>ICD</i>	<i>International Classification of Diseases</i>
<i>IL-5</i>	<i>Interleukin-5</i>
<i>MALT</i>	<i>Mucosa-associated lymphoid tissue</i>
<i>NHL</i>	<i>Non-Hodgkin's lymphoma</i>
<i>NOS</i>	<i>Not otherwise specified</i>
<i>PDGFRA</i>	<i>Platelet-derived growth factor receptor alpha</i>
<i>PTCL</i>	<i>Peripheral T-cell lymphoma</i>

of the specific entities included in this category were not reported.

What remains to be elucidated is the frequency with which the specific hematologic malignancies are diagnosed in patients presenting with eosinophilia. This question is of interest because eosinophilia has been shown to be a poor prognostic indicator in entities such as ATLL and HL, but can also contribute to the comorbid complications stemming from eosinophil toxicity. A better understanding of the epidemiology may also help clinicians to determine proper surveillance periods, expedite the necessary workup, and recommend the most appropriate treatment for patients with these conditions.

Our study identified the specific hematologic malignancies encountered most commonly in patients presenting with eosinophilia by a retrospective review of the Mayo Clinic patient database from January 2000 to March 2013. Our findings are reported in the context of severity of eosinophilia and the temporal relationship between eosinophilia onset and diagnosis of hematologic malignancy.

METHODS

With approval of the Mayo Clinic Institutional Review Board, a retrospective chart review of patients diagnosed with eosinophilia or eosinophilia-related disorder and a hematologic malignancy between the years 2000 and 2013 was conducted. Adult (>18 years of age) patients with eosinophilia based on International Classification of Diseases (ICD)-9 diagnostic codes were initially identified. This subset of charts was reviewed only for ICD-9 diagnostic codes corresponding to lymphomas and leukemias occurring in association with the onset of eosinophilia. Data were collected by the chart review up until March 31, 2013. Patient protected health information was kept confidential and secure according to Health Insurance Portability and Accountability Act and institutional guidelines.

The diagnosis of peripheral blood eosinophilia (BE) ($>0.5 \times 10^9/L$), hypereosinophilia (HE) ($>1.5 \times 10^9/L$), reactive hypereosinophilia

(HE-R), primary hypereosinophilia from an apparent eosinophil clone (HE-N), hypereosinophilic syndrome (HES), and eosinophilia-related disorders (eg, episodic angioedema with eosinophilia [Gleich's syndrome], eosinophilic granulomatosis with polyangiitis, and eosinophilic pneumonia) was confirmed based on the most recent consensus guidelines¹ using data extrapolated from documented laboratory values and clinical findings. The frequency of all hematologic malignancies was identified, and each specific leukemia or lymphoma diagnosis was determined. The interval of time from the onset of eosinophilia to hematologic malignancy diagnosis was calculated. The duration of survival after the diagnosis of hematologic malignancy was also calculated.

Interleukin-5 (IL-5) levels (normal reference range in adult population <7.8 pg/mL) were quantitated by sandwich immunoassay utilizing electrochemiluminescence detection (limit of detection 0.5 pg/mL; Viracor-IBT Laboratories, Lee's Summit, Mo).

All means were reported with standard deviations and compared using 2-sided Student's *t*-test with statistical significance established at $P < .05$. All statistical analyses were carried out using JMP software (Version 9.0.1, SAS Institute, Inc., Cary, NC).

RESULTS

Patient characteristics

The initial database search identified 2642 unique patients with an ICD-9 diagnostic code corresponding to BE, HE, HES, or an eosinophilia-related disorder as defined by Valent et al.¹ Of these patients, 2249 (85.1%) had BE (absolute eosinophil count between 0.5 and $1.5 \times 10^9/L$) and 393 (14.9%) had HE (absolute eosinophil count greater than $1.5 \times 10^9/L$), which included 55 (2.1%) with HES or myeloproliferative variant of HES.

Lymphoma or leukemia was diagnosed in a total of 25 patients (age range 28.8 to 86.1 years, median age 70.4 years; 13 male; 12 female) during the study period. The frequency of hematologic malignancy diagnosis in patients with HE was 20 of 393 (5.1%) and 5 of 2249 (0.2%) in those with BE (odds ratio 22.9; 95% CI 8.5 to 61.3, $P < .0001$). The other patients in these groups did not develop a hematologic malignancy during the study period.

Lymphomas. Lymphomas were found in 17 patients (Table I). Among lymphomas, NHLs occurred with the greatest frequency accounting for 16 of the 17 cases. Specific entities within this subcategory included peripheral angioimmunoblastic T-cell lymphoma (AICL; 4 cases), Sézary syndrome (4 cases), and peripheral T-cell lymphoma not otherwise specified (PTCL NOS; 3 cases). The remainder were single cases of cutaneous T-cell lymphoma (CTCL), mucosa-associated lymphoid tissue (MALT) lymphoma of breast tissue, gastric MALT lymphoma (associated with *Helicobacter pylori* infection), and diffuse large B-cell lymphoma (DLBCL; Table I).

Leukemias. Leukemias were noted in 8 patients (Table I). Among leukemias, CLL (4 cases) occurred most frequently followed by chronic eosinophilic leukemia (CEL; 3 cases) and acute myelogenous leukemia (AML; 1 case). For the CEL cases, one clearly had the Fip-1-like-1 - platelet-derived growth factor receptor alpha (FIP1L1-PDGFRα) fusion mutation by fluorescence *in situ* hybridization (FISH) analysis. The second only exhibited a trisomy 8 anomaly on karyotype analysis in a patient with a long history of HES. The third was negative for FIP1L1-PDGFRα fusion by FISH, but had an apparent eosinophil clone on bone marrow biopsy with no other signs of end-organ damage or splenomegaly. This patient's eosinophilia was thus classified as primary (clonal/neoplastic)

TABLE I. Hematologic malignancies identified by type

Type (n = 25)	Subtype (n)	Specific malignancies (n)
Leukemia (8)	Acute (1)	Acute myelogenous leukemia (1)
	Chronic (7)	Chronic lymphocytic leukemia (4)
		Chronic eosinophilic leukemia (3)
Lymphoma (17)	Non-Hodgkin (16)	
	T-cell derived (12)	Angioimmunoblastic T-cell lymphoma (4)
		Sézary syndrome (4)
		Peripheral T-cell lymphoma NOS (3)
		Cutaneous T-cell lymphoma (1)
	B-cell derived (4)	MALT lymphoma of breast (1)
		Gastric MALT lymphoma (1)
		Splenic marginal zone lymphoma (1)
		DLBCL (1)
	Hodgkin (1)	Classic Hodgkin's lymphoma (1)

DLBCL, Diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; NOS, not otherwise specified.

hypereosinophilia (HE-N). We were unable to contact the reading pathologist to determine how the eosinophil clone was identified.

Notably, certain hematologic malignancies previously shown to be associated with eosinophilia, including primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, adult T-cell leukemia/lymphoma, acute B-cell lymphoblastic leukemia, and T-cell prolymphocytic leukemia, were not found in this series of patients.⁸⁻¹²

Temporal relationships

When taking into account the temporal relationship between eosinophilia and lymphoma or leukemia, 11 of 25 patients had HE that predated the onset of malignancy (Table II). Of these 11, 7 met criteria for HE, whereas the remaining 4 had HES (3 cases) or Gleich's syndrome (1 case). The most common hematologic malignancies identified in this subgroup of 11 patients were AICL (3 cases) and CEL (3 cases). The time between the onset of eosinophilia and the diagnosis of AICL ranged from 0.8 months to 24.4 months. Two cases of CEL occurred in the context of HES. The third case of CEL occurred in a patient with HE but no end organ dysfunction attributable to eosinophils. The time between the onset of eosinophilia and the diagnosis of CEL ranged from 5.4 months to 37.9 months. The remaining hematologic malignancies identified in this subgroup were single cases of AML, nodular sclerosing HL, Sézary syndrome, and DLBCL. The cases of AML and nodular sclerosing HL were diagnosed within 1 month of eosinophilia onset. Sézary syndrome occurred in the patient with Gleich's syndrome 82.2 months after the first documentation of HE. DLBCL occurred in a patient with idiopathic HES nearly 12 years after the diagnosis of HES and was thought to be related to chronic immunosuppressive therapy and EBV infection. This patient had been treated with high-dose prednisone, hydroxyurea, interferon-alpha, then switched to alemtuzumab for refractory hypereosinophilia approximately 9 months before the diagnosis of DLBCL from a soft tissue mass arising within the right orbit. The median time from the onset of hypereosinophilia to the diagnosis of hematologic malignancy was 10.0 months. The mean time was 30.0 ± 42.7 months, which was skewed by 2 individuals who developed a hematologic malignancy 82.2 and 143.7 months after the onset of Gleich's syndrome and HES, respectively.

The duration of survival (in months) after the diagnosis of malignancy was calculated for those patients who died during the

study time period (Table II). Not enough cases of each malignancy were identified to determine meaningful survival or mortality data.

Hypereosinophilia and blood eosinophilia with diagnosis of hematologic malignancy. Seven patients had HE-R after the diagnosis of hematologic malignancy. In these patients, the malignancy was diagnosed before the first documented elevation in eosinophil levels (Table II). The specific malignancies identified in this subgroup were PTCL NOS (2 cases), Sézary syndrome (2 cases), and single cases of CTCL that could not be further characterized, MALT lymphoma of breast tissue, and CLL. In these patients, eosinophilia was temporally related to the diagnosis of the hematologic malignancy and occurred after the diagnosis of the malignancy.

Five patients exhibited peripheral BE before or concomitant with the diagnosis of a hematologic malignancy (Table II). These patients were diagnosed with CLL (2 cases) and 1 case each of AICL, Sézary syndrome, and gastric MALT lymphoma associated with *H. pylori* infection. The relationship between BE and hematologic malignancy was less clear. Of these 5 patients, 3 had time-limited increases in eosinophil levels close to the time of hematologic malignancy diagnosis without a history of eosinophil elevations on previously documented blood counts. The patient diagnosed with Sézary syndrome had a time-limited elevation in eosinophil count without identifiable cause, which then returned to normal. However, the diagnosis of Sézary syndrome occurred 93.4 months after the brief period of eosinophilia that had been noted on peripheral blood counts. The patient with *H. pylori* associated gastric MALT lymphoma was the only one of these 5 patients who had a persistent low-level eosinophilia for many years. The eosinophilia did not increase or decrease nearer to the time of malignancy diagnosis. This patient continued to have persistent low-level eosinophilia even after treatment of *H. pylori*.

Organ-specific eosinophilia and malignancy. Two patients had documented hypereosinophilia because of eosinophilic pneumonia and eosinophilic granulomatosis with polyangiitis. These 2 patients subsequently developed CLL and splenic marginal zone lymphoma, respectively, without a clear relationship between their eosinophilia and the hematologic malignancy (Table II).

TABLE II. Classification of eosinophilia and hematologic malignancies

Classification of eosinophilia	Hematologic malignancy	Eosinophils ($\times 10^9/L$)*	IL-5 (pg/mL)	Time (mo)†	Survival (mo)‡
Hypereosinophilia predated malignancy diagnosis					
HE-R	Acute myelogenous leukemia	2.17	NC	1.0	A
HE-R	Classic Hodgkin's lymphoma§	13.82	NC	0.5	21.6
HE-R	Angioimmunoblastic T-cell lymphoma	2.02	47.1	24.4	27.1
HE-R	Angioimmunoblastic T-cell lymphoma	2.63	7.0	19.3	13.3
HE-R	Angioimmunoblastic T-cell lymphoma	2.35	NC	0.8	8.2
HE-R	Peripheral T-cell lymphoma NOS	2.23	0	4.5	31.0
Gleich's syndrome	Sézary syndrome	10.23	50.7	82.2	28.4
HE-N	Chronic eosinophilic leukemia	2.39	44.0	37.9	61.0
HES-N	Chronic eosinophilic leukemia¶	3.20	NC	10.0	A
HES-N	Chronic eosinophilic leukemia#	6.00	9.0	5.4	A
Idiopathic HES	Diffuse large B-cell lymphoma**	10.30	0	143.7	A
Malignancy diagnosis predated hypereosinophilia					
HE-R	Chronic lymphocytic leukemia	2.12	NC	NA	A
HE-R	MALT lymphoma of breast††	4.60	NC	NA	A
HE-R	Peripheral T-cell lymphoma NOS	4.33	0	NA	3.9
HE-R	Peripheral T-cell lymphoma NOS	3.33	NC	NA	A
HE-R	Cutaneous T-cell lymphoma‡‡	1.68	NC	NA	65.3
HE-R	Sézary syndrome	2.60	0	NA	55.4
HE-R	Sézary syndrome	2.14	NC	NA	24.6
Eosinophilia associated with hematologic malignancy					
BE	Chronic lymphocytic leukemia	1.04	NC	3.0	11.5
BE	Chronic lymphocytic leukemia	1.39	NC	1.0	47.7
BE	Gastric MALT lymphoma§§	0.53	NC	49.9	A
BE	Angioimmunoblastic T-cell lymphoma	1.45	NC	NA	A
BE	Sézary syndrome	0.78	NC	93.4	A
Organ specific hypereosinophilia and malignancy					
EoPNA	Chronic lymphocytic leukemia	2.98	0	NA	A
EGPA	Splenic marginal zone lymphoma	5.06	NC	NA	27.6

A, Alive at end of study period; BE, blood eosinophilia; EGPA, eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome); EoPNA, eosinophilic pneumonia without other organ involvement or damage to suggest HES; IL, interleukin; MALT, mucosa-associated lymphoid tissue, NA, not applicable; NC, not checked; NOS, not otherwise specified.

*Initial elevation in eosinophil count.

†Interval between eosinophilia onset and malignancy diagnosis.

‡After diagnosis of malignancy.

§Nodular sclerosing type.

||Atypical mast cells noted on bone marrow biopsy with negative Fip-1-like-1 - platelet-derived growth factor receptor alpha (FIP1L1/PDGFRα), FGFR3, JAK2, and BCR/Abl testing.

¶Trisomy 8 clonality.

#FIP1L1/PDGFRα mutation.

**Related to long-term immunosuppression and EBV infection, HE-N, HES, HES-N, and HE-R as defined by Valent et al.¹

††Subsequently developed follicular lymphoma and then diffuse large B-cell lymphoma.

‡‡T-cell receptor gene rearrangements noted.

§§Associated with *Helicobacter pylori* infection.

Mediators of eosinophilia and malignancy. IL-5 levels were elevated in 5 of the 10 patients in whom these levels were measured. The 5 patients with elevated IL-5 levels had HE-R (2 patients), HE-N, HES, and Gleich's syndrome. The malignancies that these patients developed included CEL (2 cases), AICL (2 cases), and Sézary syndrome (1 case; Table II). An elevated IL-5 level was discovered in a patient with CEL whose bone marrow biopsy showed atypical, spindled mast cells in vague clusters, but did not exhibit the FIP1L1-PDGFRα fusion by FISH. This patient's bone marrow sample was not further analyzed for other FIP1L1-PDGFRα gene locus deletions or for the *c-Kit* Asp816Val mutation. This patient was treated with hydroxyurea and lived for 61 months after the diagnosis of CEL.

Tryptase levels were also measured in 9 patients, but only 1 had an elevated level of 14.3 ng/mL (upper limit of normal: 11.5 ng/mL). This patient developed PTCL NOS 4.5 months after the onset of HE and survived for 31.0 months after the diagnosis.

Hypereosinophilia treatment, chemotherapy, and eosinophil levels. In the 11 patients who demonstrated hypereosinophilia before the diagnosis of a hematologic malignancy, 63.6% (7 of 11) had eosinophil counts that increased further at the time of malignancy diagnosis and subsequently decreased with initiation of chemotherapy or HE-related treatment (Figure 1). All 4 patients who had lower eosinophil counts at the time of hematologic

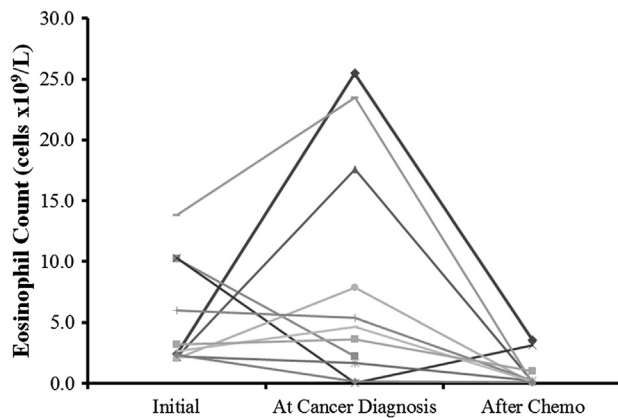


FIGURE 1. Eosinophil counts before the diagnosis of malignancy, at the time of malignancy diagnosis, and after the initial cycle of chemotherapy or hypereosinophilia directed therapy. Each line represents a single patient.

malignancy diagnosis were being treated with either prednisone (3 of 4) or interferon-gamma. Three patients had eosinophil counts greater than $10.0 \times 10^9/L$ at the time of initial evaluation at our institution. The patient with the highest initial eosinophil count ($13.8 \times 10^9/L$) was diagnosed with nodular sclerosing HL within a month of eosinophilia onset (diagnosis occurred at age 80). The eosinophil count had increased further to $23.5 \times 10^9/L$ at the time of cancer diagnosis. This patient received vincristine, carmustine, cyclophosphamide, procarbazine, and prednisone, and survived for 21.9 months. After the first round of chemotherapy, the eosinophil count decreased to less than $0.5 \times 10^9/L$. The other 2 patients with initial eosinophil counts greater than $10.0 \times 10^9/L$ had Gleich's syndrome and HES. They were both being actively treated for their underlying condition at the time of hematologic malignancy diagnosis, which accounted for their decreased eosinophil count.

Nine patients required treatment for HE separate from the chemotherapy directed at their hematologic malignancy. These patients were all given prednisone initially. Other medications used to treat HE were interferon-alpha (3 patients), hydroxyurea (2 patients), cyclosporine (1 patient), or alemtuzumab (1 patient). The patient with CEL with FIP1L1-PDGFR mutation received prednisone initially, but then was switched to imatinib mesylate once the mutational analysis was available.

DISCUSSION

This retrospective case series revealed that the severity of initial eosinophilia made a significant difference in the odds ratio of being diagnosed with a hematologic malignancy. This finding corroborates an earlier study by Andersen et al,⁴ which showed increased odds ratios of being diagnosed with HL, CLL, and classic myeloproliferative neoplasms in patients with an elevated eosinophil count (greater than $1.0 \times 10^9/L$) in the preceding 3 months. In contrast to the report by Anderson et al, the majority of patients who eventually developed NHL in our case series were diagnosed with their malignancy after 3 months from eosinophilia onset. By examining a time frame beyond 3 months, our study shows that NHLs are the most common diagnostic entity encountered in patients presenting with eosinophil counts in the hypereosinophilic range. As other diseases known to cause

hypereosinophilia are ruled out, clinicians may need to consider a hematologic malignancy. The diagnosis of hematologic malignancy can occur up to 30 months or longer after the onset of hypereosinophilia. The relevance of low-level eosinophilia in hematologic malignancy is less clear. A larger population-based study is likely to help clarify whether hypereosinophilia is associated with hematologic malignancy beyond a 3-month time frame. On the basis of Anderson et al and our study, we propose that HL, CLL, and myeloproliferative neoplasms be considered in the first 3 months from eosinophilia onset. However, with persistence of hypereosinophilia beyond 3 months, rarer forms of NHLs should be strongly considered. This situation would require appropriate diagnostic workup and referral for subspecialty evaluation.

According to the most recent National Cancer Institute Surveillance, Epidemiology, and End Results Program statistics, NHLs are more common than HL and leukemias in the general US population.¹³ However, NHLs encompass a highly diverse group of individual malignancies, which each have a unique incidence and prevalence. Among NHLs, AICL and Sézary syndrome were most frequently diagnosed. Both of these entities are T-cell-derived malignancies known to cause peripheral eosinophilia.^{6,14} T-cell-associated cytokines, specifically Th2 cytokines, have previously been associated with eosinophilopoiesis in peripheral T-cell lymphomas and HL.^{15,16} We found elevated IL-5 levels in 5 of 10 patients. These 5 patients had either T-cell-derived malignancies or CEL. Notably, 5 patients did not have elevated IL-5 levels despite having HE on peripheral cell counts. This may implicate other cytokines and cellular factors in the development of eosinophilia or reflect the unknown sensitivity of the assay. The elucidation of these mechanisms is beyond the scope of this study. However, nearly half (12 of 25; 48%) of the malignancies identified in this study were rare T-cell-derived lymphomas (Table 1). According to previous estimates, PTCL NOS, AICL, and Sézary syndrome account for 7.0%, 1.5%, and <1% of NHLs, respectively.^{17,18} Thus, in patients presenting with hypereosinophilia and a suspicion for hematologic malignancy, the rank order of potential hematologic malignancy diagnoses may be different than the general population. This alteration in rank order can have significant clinical implications. Biopsies are likely to be needed of skin lesions thought to be unrelated, in difficult to access lymph nodes, or from specific organs. These considerations may make it necessary to refer patients to a medical center with greater resources and experience with diagnosing and treating these rare hematologic malignancies.

We were also able to retrospectively review changes in eosinophil levels longitudinally showing a potential relationship between eosinophil levels and malignancy diagnosis, treatment, and recurrence. In 63.6% of cases (7 of 11 patients), the hypereosinophilia that developed before the diagnosis of a hematologic malignancy increased further until the underlying malignancy was diagnosed and treated. The 4 patients with decreased eosinophil counts at the time of hematologic malignancy diagnosis had received a course of prednisone or interferon-gamma, which suppressed the peripheral eosinophil counts. The majority of the chemotherapy regimens utilized included prednisone (or other glucocorticoid), which may partially account for the response noted in the eosinophil levels as would the change in cytokine milieu with treatment of the underlying malignancy. In selected examples, the eosinophilia returned with recurrence of the malignancy. Eosinophilia can be an important prognostic indicator for certain hematologic malignancies. For example, in HL, peripheral eosinophilia predicted better survival,³

whereas in Sézary syndrome, peripheral eosinophilia at diagnosis predicted greater chance of disease progression and mortality.⁶ Unfortunately, our series did not identify enough cases of each specific malignancy to generate meaningful survival or mortality data. It may be of interest to determine if eosinophil counts could be used reliably to predict malignancy recurrence. This would provide simple and cost-effective means of monitoring patients where hypereosinophilia was associated with their malignancy.

Our study was limited by its design as a retrospective chart review at a single tertiary referral institution. The results may not be generalizable to the general population and should be carefully interpreted in the context referral bias. Many of the patients identified in this study were specifically referred for specialized workup of hypereosinophilia in the context of nonspecific symptoms. The frequency of rare NHLs that were diagnosed may be overestimated in this population.

Based on our retrospective review, the overall frequency of hematologic malignancy among patients with HE or HES was 5.1% with NHLs occurring most commonly. Clinicians should be aware that hematologic malignancy can develop many months to years after the onset of hypereosinophilia and that T-cell-derived hematologic malignancies may be more likely to occur in these patients.

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