Original Article

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. **(J Allergy Clin Immunol Pract 2015;■:■-■)**

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

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 guidelines[1] 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 1.5×10^9/L) and 393 (14.9%) had HE (absolute eosinophil count greater than 1.5×10^9/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-PDGFRA) 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-PDGFRA 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)