BRIEF OBSERVATION

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Leukocytosis and Tobacco Use: An Observational Study of Asymptomatic Leukocytosis

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ABSTRACT

PURPOSE: This study aimed to characterize the white blood cell differential of tobacco smoking-induced leukocytosis and describe the longitudinal impact of smoking cessation on this peripheral blood abnormality.

METHODS: Medical records of patients undergoing evaluation by hematologists for persistent leukocytosis were reviewed. Patients in whom leukocytosis was determined to be secondary to tobacco use after exclusion of other causes were identified. Demographic and laboratory data were collected at time of diagnosis. Patients were longitudinally followed and information regarding smoking cessation and follow-up white blood cell values were recorded.

RESULTS: Forty patients were determined to have smoking-induced leukocytosis. The median age was 49.5 years (range: 28-75 years), 24 patients were female, and the mean body mass index (BMI) was 31.5 kg/m^2. The mean white blood cell count was 13.3 $\times$ 10^9/L (range: 9.8-20.9 $\times$ 10^9/L); 39 patients had absolute neutrophilia (98%), 21 had lymphocytosis (53%), 20 had monocytosis (50%), and 19 had basophilia (48%). During follow-up, 11 patients either quit (n = 9) or reduced (n = 2) tobacco use. Reduction in tobacco smoking led to a significant decrease in mean white blood cell count (13.2 $\times$ 10^9/L vs 11.1 $\times$ 10^9/L, P = 0.02). The median time to decrease in white blood cell count following reduction in tobacco use was 8 weeks (range: 2-49 weeks).

CONCLUSIONS: Tobacco-induced leukocytosis was characterized by a mild elevation in total white blood cell count and was most commonly associated with neutrophilia, lymphocytosis, monocytosis, and basophilia. Cessation of smoking led to improvement in leukocytosis. Tobacco history should be elicited from all patients presenting with leukocytosis to limit unnecessary diagnostic testing, and counseling regarding smoking cessation should be offered.

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KEYWORDS: Leukocytosis; Neutrophilia; Tobacco use

INTRODUCTION

Leukocytosis, defined as an elevated total white blood cell count, is a laboratory finding commonly detected on routine peripheral blood analysis.[1] In the absence of localizing symptoms, leukocytosis poses a diagnostic challenge for clinicians given the broad and potentially concerning associated differential diagnosis, which includes infection, inflammatory conditions, and malignancy.[2-4] The prevalence of this laboratory finding in asymptomatic individuals is incompletely understood, although prior investigators

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have reported elevated total white blood cell count in 7.8% of asymptomatic patients in the preoperative setting.[5]

Tobacco smoking is a recognized cause of leukocytosis.[6] Considering that in the United States 15.5% of adults smoke cigarettes,[7] the clinical significance of this association is apparent. Little is known regarding the peripheral blood phenotype of tobacco smoking-associated leukocytosis or the longitudinal impact of smoking cessation on total white blood cell count. This study aimed to characterize the complete blood count and white blood cell differential of tobacco smoking-induced leukocytosis and describe the longitudinal impact of smoking cessation on this peripheral blood abnormality.

CLINICAL SIGNIFICANCE

- In the absence of localizing symptoms, persistent leukocytosis poses a diagnostic challenge to clinicians, often prompting costly evaluations and unnecessary therapies.
- Tobacco use is a reversible cause of leukocytosis that is characterized by a mild elevation in total white blood cell count and the presence of neutrophilia, lymphocytosis, monocytosis, and/or basophilia.
- Tobacco history should be elicited from all patients presenting with leukocytosis to limit unnecessary diagnostic testing, and counseling regarding smoking cessation should be offered.

METHODS

Medical records of patients undergoing evaluation by hematologists for persistent leukocytosis between January 1, 2014, and December 31, 2018, were reviewed. Patients in whom leukocytosis was determined to be secondary to tobacco use after exclusion of other causes, including negative testing for breakpoint cluster region-Abelson (BCR-ABL) gene fusion (by either polymerase chain reaction or fluorescent in situ hybridization) were identified. Other studies used to exclude alternative diagnoses were recorded. Age, sex, body mass index (BMI), and complete blood cell count with white blood cell differentials were collected at the time of diagnosis. Leukocytosis was defined as a total white blood cell count $>9.6 \times 10^9$/L. Upper limit of normal for other components of the complete blood count are included in Supplementary Table 1, available online. Tobacco use was characterized as packs per day and pack-years. Reduction in smoking was defined as a 50% decrease in daily cigarette use. Patients were longitudinally followed, and information regarding smoking cessation and follow-up white blood cell values were recorded.

RESULTS

Forty patients were determined to have smoking-induced leukocytosis after extensive evaluation. Patient demographic and laboratory data are summarized in Table. The median age was 49.5 years (range: 28-75 years), 24 patients were female, and the mean body mass index was 31.5 kg/m^2. Additional studies commonly used to exclude other causes of leukocytosis included flow cytometry in 27 patients (68%), peripheral blood smear evaluation in 24 patients (60%), serum protein electrophoresis in 8 patients (20%), and bone marrow biopsy in 4 patients (10%). On average, patients smoked 0.9 packs per day for a median of 34 pack-years (range: 3-59 pack-years). Mean complete blood count values are summarized in Table. A total of 39 patients had absolute neutrophilia (98%), 21 had lymphocytosis (53%), 20 had monocytosis (50%), 19 had basophilia (48%), 12 had erythrocytosis (30%), 9 had eosinophilia (23%), and 8 had thrombocytosis (20%). None of the patients were noted to have circulating blasts, myelocytes, promyelocytes, metamyelocytes, or nucleated red blood cells on peripheral blood analysis.

A total of 28 patients (70%) were counseled to quit smoking at time of diagnosis. During longitudinal follow-up, 11 of these patients (39%) either quit (n = 9) or reduced (n = 2) tobacco use. In patients who decreased tobacco use, total white blood cell count values were assessed over a 12-month period (Figure). Compared to the initial white blood cell count, reduction in tobacco smoking led to a significant decrease in leukocytosis (mean white blood cell count 13.2 $\times$ 10^9/L vs 11.1 $\times$ 10^9/L, $P = 0.02$). Overall, 10 of the 11 patients (91%) who reduced their smoking had reduction in total white blood cell count. The median time to improvement of leukocytosis was 8 weeks following

Table Patient Demographic, Diagnostic, and Laboratory Information

Patient Demographic	Value (Range)
Median Age	49.5 years (28-75 years)
Female Sex	N = 24
Mean BMI	31.5 kg/m^2 (18.8-50.2 kg/m^2)
Mean Packs per Day Smoked	0.9 packs per day (0.1-2.5 packs/d)
Median Pack-Years Smoked	34 pack-years (3 -59 pack-years)
Diagnostic Testing Performed	**Number of Patients (%)**
BCR-ABL	40 (100%)
Flow Cytometry	27 (68%)
Peripheral Blood Smear	24 (60%)
Serum Protein Electrophoresis	8 (20%)
Bone Marrow Biopsy	4 (10%)
Advanced Imaging (CT/PET CT)	4 (10%)
T-Cell Receptor Gene Rearrangement Studies	3 (8%)
Serum Tryptase	2 (5%)
Colony Stimulating Growth Factor 3	1 (3%)

Table (*Continued*)

Diagnostic Testing Performed	Number of Patients (%)
Chronic Lymphocytic Leukemia — FISH	1 (3%)
Cysteine-Rich Hydrophobic Domain 2 — FISH	1 (3%)
Laboratory Study	**Mean Value (Range)**
White Blood Cell Count	13.3 × 10^9/L (9.8-20.9 × 10^9/L)
Hemoglobin	15.0g/dL (12.3-18.6 g/dL)
Platelet Count	298 × 10^9/L (90-418 × 10^9/L)
Absolute Neutrophil Count	8.8 × 10^9/L (5.95-17.02 × 10^9/L)
Absolute Lymphocyte Count	3.2 × 10^9/L (1.1-6.14 × 10^9/L)
Absolute Monocyte Count	0.87 × 10^9/L (0.35-1.47 × 10^9/L)
Absolute Eosinophil Count	0.34 × 10^9/L (0.05-1.49 × 10^9/L)
Absolute Basophil Count	0.09 × 10^9/L (0-0.24 × 10^9/L)
Peripheral Blood Abnormality	**Number of Patients (%)**
Neutrophilia	39 (98%)
Lymphocytosis	21 (53%)
Monocytosis	20 (50%)
Basophilia	19 (48%)
Erythrocytosis	12 (30%)
Eosinophilia	9 (23%)
Thrombocytosis	8 (20%)

BCR-ABL = breakpoint cluster region-Abelson; BMI = body mass index; CT = computed tomography; FISH = fluorescent in situ hybridization; PET = positron emission tomography.

reduction in tobacco use (range: 2-49 weeks). Of the patients who did not reduce smoking, none had resolution of their leukocytosis.

DISCUSSION

These observations support the notion that tobacco use leads to mild elevation of total white blood cell count and may be associated with other peripheral blood leukocyte abnormalities, including neutrophilia, lymphocytosis, monocytosis, and basophilia. The predominance of neutrophilia within this study is in line with prior investigations.[8] Interestingly, almost half of patients in this study had basophilia. To our knowledge, an association between basophilia and tobacco smoking is not well described.

Though the underlying mechanisms of tobacco smoking-induced leukocytosis are multifactorial, habitual smoking ultimately results in the induction of a chronic systemic inflammatory response.[9] Prolonged exposure to tobacco smoke causes impaired function of alveolar macrophages, leading to decreased clearance of intracellular apoptotic material and likely propagating inflammation.[10] The predominance of neutrophils on the white blood cell differential is further supported by prior studies that have demonstrated shortened transit time of polymorphonuclear leukocytes within the bone marrow of patients who smoke.[11] The underlying mechanisms of other abnormalities of the white blood cell differential are less understood, though one could postulate multiple potential signaling pathways given the cytokine release associated with tobacco use.[12,13]

Of note, counseling regarding smoking cessation was documented by the diagnosing hematologist in only 70% of patients (n = 28). When considering that 39% of patients receiving this counseling ultimately reduced their tobacco use, the impact of this intervention cannot be overstated. The tobacco use reduction rate associated with counseling by a hematologist was far higher than expected in light of prior studies.[14] This finding should encourage clinicians to provide counseling regarding smoking cessation, especially in the setting of newly attributed leukocytosis.

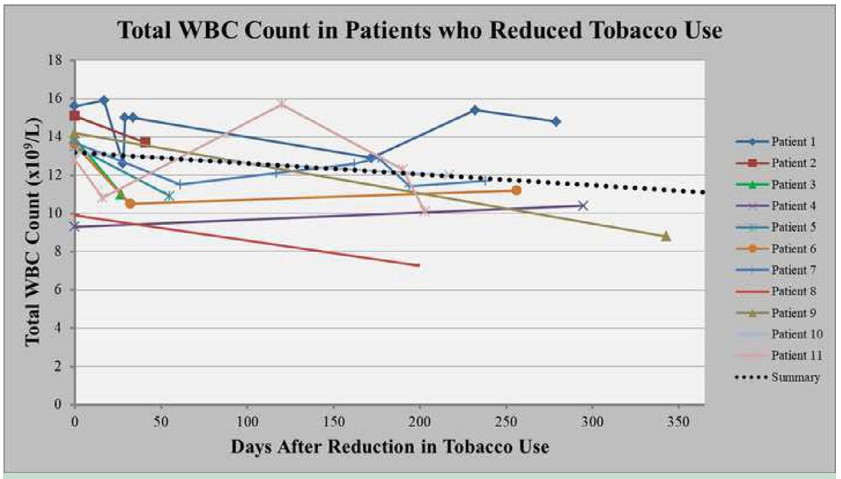

Figure Total white blood cell count in patients who reduced tobacco use.

Of the patients who reduced their tobacco use, 91% experienced improvement in leukocytosis. Though prior investigations have noted that smoker's leukocytosis may be reversible,[15] they were limited by cross-sectional study design and reliance on associations between self-reported tobacco use and cessation rather than subspecialist diagnosis and longitudinal follow-up. Given that the median time to improvement of total white blood cell count following reduction in tobacco use was 8 weeks, it may be prudent to advise smoking cessation and perform repeat peripheral blood analysis instead of pursing advanced diagnostic testing in patients with mild asymptomatic leukocytosis.

CONCLUSION

In conclusion, tobacco-induced leukocytosis was characterized by a mild elevation in total white blood cell count and was most commonly associated with neutrophilia, lymphocytosis, monocytosis, and basophilia. Counseling regarding smoking cessation provided by the diagnosing clinician appeared to result in a higher reduction rate of tobacco use than expected. Cessation of smoking led to improvement in leukocytosis. Tobacco history should be elicited from all patients presenting with leukocytosis to limit unnecessary diagnostic testing, and counseling regarding smoking cessation should be offered.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2020.05.038.

Supplementary Table 1 Upper Limit of Normal of Complete Blood Count and White Blood Cell Differential Components per Institutional Lab Parameters

Laboratory Value	Upper Limit of Normal
Total white blood cell count	9.6×10^9/L
Absolute neutrophil count	6.45×10^9/L
Absolute lymphocyte count	3.07×10^9/L
Absolute monocyte count	0.81×10^9/L
Absolute eosinophil count	$0.48 \times 10^{9/}$/L
Absolute basophil count	0.08×10^9/L
Absolute erythrocyte count (women)	5.13×10^9/L
Absolute erythrocyte count (men)	5.65×10^9/L
Platelet count (women)	371×10^9/L
Platelet count (men)	317×10^9/L