Original Article

Chronic Idiopathic Neutrophilia: Experience and Recommendations

Alva B. Weir, MD, FACP, James B. Lewis Jr, MD, FACP, and Rafael Arteta-Bulos, MD

Objectives: To distinguish chronic idiopathic neutrophilia (CIN) in a cost-effective manner from neutrophilia caused by important underlying illnesses.

Methods: This was a retrospective review of patients visiting a Veterans Affairs Medical Center over the last 10 years with a diagnosis of leukocytosis or myeloproliferative disorder. Of this group, fifty-seven patients from 1999 to 2008 were identified with CIN. Clinical and laboratory parameters were examined to identify CIN and establish its course. Eighty-one patients who presented from 2005 to 2010 with myeloproliferative disorders were also studied at time of diagnosis to determine any possible confusion with CIN.

Results: The patients with CIN were followed for a mean of ≥7.3 years without progression to other serious disorders. Compared to non-CIN patients evaluated for neutrophilia, in multiple logistic regression analyses, smoking ($P = .001$) and increased BMI ($P = .004$) were significantly associated with CIN. No CIN patient developed a clinically apparent myeloproliferative disorder other than chronic myeloid leukemia (CML). Of the patients with myeloproliferative neoplasms reviewed at the time of their initial diagnosis, only CML occasionally presented with a picture consistent with CIN. For non-smokers, the BMI of CIN patients was significantly higher than the average VA population ($P < .001$).

Conclusion: Cigarette smoking and obesity are confirmed as factors associated with CIN and may be causative. CIN is unlikely to develop into a clinically recognizable myeloproliferative neoplasm other than CML. Cost-effective guidelines for the diagnostic evaluation of neutrophilia in otherwise healthy patients are presented.

Key Words: neutrophilia, myeloproliferative neoplasms, chronic myeloid leukemia, tobacco abuse, obesity, diagnostic evaluation

An elevated neutrophil count is a common laboratory finding among patients with a variety of diagnoses. Possible causes include infection, inflammatory disorders, leukemias, myeloproliferative neoplasms, drugs, endocrinopathies, and metastatic cancers. Chronic idiopathic neutrophilia (CIN) is an asymptomatic neutrophilia that persists for years with no apparent cause or harm to the patient. The most recent article in the English literature addressing an overview of CIN was published in the *Annals of Internal Medicine* nearly 40 years ago.[1] Since then, an association between cigarette smoking and neutrophilia has been established.[2–6] More recently an Israeli study by Herishanu et al proposed an association between obesity and neutrophilia.[7] An article published in the Japanese literature by Suzuki and Kitagawa briefly described 35 patients with chronic idiopathic neutrophilia, of whom 25 were cigarette smokers.[8] These three articles are the only case series focused on idiopathic neutrophilia published in the last 40 years. An association of leukocytosis with obesity and cigarette smoking was confirmed in 8635 patients participating in the National Health and Nutrition Examination Survey, 1976–1980. However, no discussion of neutrophils or chronic neutrophilia was presented.[9] Since 1971 a plethora of new tests, including JAK-2 mutation evaluation, Bcr-abl testing, and CT scans have become available. The primary care provider who first discovers the patient with neutrophilia must decide which tests are appropriate and which patients should be referred to the hematologist or for bone marrow evaluation. How aggressive, inconvenient and expensive should be the search for a cause for elevated neutrophil counts in otherwise healthy individuals?

We reviewed the charts of patients presenting to the Veterans Administration Hospital over a 10-year period,

Key Points

- Patients may live for many years with chronic idiopathic neutrophilia (CIN) and develop no apparent serious underlying illness.
- Cigarette smoking demonstrates a strong association with CIN and may be causative.
- In non-smokers, obesity is closely associated with CIN.
- Other than Chronic Myeloid Leukemia, it is unlikely that a chronic elevation of neutrophils might suggest an underlying myeloproliferative disorder, unless other blood abnormalities are present.

From the Veterans Affairs Medical Center, Memphis, TN; University of Tennessee Health Science Center, Memphis, TN; and Hematology/Oncology, University of Tennessee Health Science Center, Memphis, TN.

Reprint requests to Alva B. Weir, MD, FACP, VA Medical Center, 1030 Jefferson Avenue, Memphis, TN 38104. Email: Alva.Weir@va.gov

Funding for statistical analysis was provided by Research, Inc.

The authors have no financial relationships to disclose and no conflicts of interest to report.

Accepted April 8, 2011.

Copyright © 2011 by The Southern Medical Association

0038-4348/0–2000/104-499
DOI: 10.1097/SMJ.0b013e31821ec7cc

Copyright © 2011 The Southern Medical Association. Unauthorized reproduction of this article is prohibited.

1999–2008, with the diagnosis of leukocytosis to ascertain the incidence of chronic idiopathic neutrophilia and evaluate its outcome over time. The goal was to develop diagnostic guidelines that are both clinically and cost-effective.

Patients and Methods

The Veterans Affairs Medical Center (VAMC) in Memphis, TN, has an electronic medical record system that our hematology clinic began using about 1998. We reviewed the electronic charts of patients presenting with the CPT®-9 diagnostic codes representing neutrophilic leukocytosis between 1999 and 2008 and followed those charts to the present. We classified patients as CIN based on the following criteria: neutrophil counts of 8.0 $\times$ 10^9/L or greater on multiple determinations, persistence or recurrence of neutrophilia over six or more months, minimum medical follow-up of two years, no unexplained abnormality in the red cell or platelet counts, and no medical illness or drug usage known to produce prolonged neutrophilia.

Multiple clinical and laboratory parameters for each patient were specifically evaluated but statistical associations were evaluated only for smoking, BMI, anxiety/depression and African-American race.

We performed a second search to evaluate charts with diagnostic codes representing polycythemia vera, essential thrombocythemia, primary myelofibrosis, chronic myeloid leukemia, and myeloproliferative disorders not specified who presented to the Memphis VAMC between January 2005 and March 2010. We reviewed their charts to the time of diagnosis to determine whether any of these patients initially presented with an isolated neutrophilia. The study was approved by the institutional review board of the Memphis VAMC and a waiver of informed consent was granted.

Statistical Analysis

Multiple logistic regression analysis was used to establish the significance of race, depression/anxiety, BMI and smoking in the 57 CIN patients compared to the remaining 77 patients evaluated for neutrophilia who did not qualify for the diagnosis of CIN. Comparison of sample percent or proportion to population parameters was done using the normal curve approximation. Comparison of sample versus population BMI was done using the single sample test of a mean against a population parameter. This is also a normal curve approximation.

Results

Four hundred fifty patients were identified for the years 1999–2008 using the search parameters described. Their charts were evaluated from initial VAMC presentation to the present. One hundred thirty-four patients presented specifically with neutrophilia. Fifty-seven patients were identified who fit CIN criteria. Patients not fitting the criteria had other conditions including chronic myeloid leukemia, myeloproliferative disorders, transient neutrophilia due to infection and neutrophilia of a short duration (Table 1). Table 2 lists the patient characteristics for the 57 with CIN.

Neutrophils in CIN

Peak neutrophil counts ranged from 8.9 to 22.6 $\times$ 10^9/L. The mean neutrophil count on presentation was 9.448 $\times$ 10^9 L. Most patients experienced fluctuations in their neutrophil counts throughout their course but a preponderance of the counts remained elevated. When patients presented with acute infections, they experienced additional elevations in their neutrophil numbers, settling back down to a chronically elevated level when the infections subsided.

The mean duration of neutrophilia identified in these patients was ≥7.3 years with a range of 1 to 21 years. In four patients the neutrophilia resolved, one with tobacco cessation and two with weight loss.

Other Blood Elements in CIN

Erythrocytosis was present in five patients. Three of these had documented carbon monoxide levels of 8–9%. Of the other two, one was chronically hypoxic, and the other patient's evaluation strongly suggested secondary polycythemia.

Drug Exposure in CIN

None of the 57 patients with CIN was taking repetitive or chronic oral or parenteral corticosteroids or lithium. Two patients with alcohol abuse were documented. Three patients chronically abused cocaine, and one was a documented marijuana user.

Coexisting Illnesses in CIN

None of the patients with CIN had chronic inflammatory disorders over a significant period of their neutrophilia. No patient was post-splenectomy. Nine patients were eventually discovered to have solid tumor malignancies. In only one did the malignancy predate the discovery of the elevated neutrophil count. There was not a statistically increased number of psychiatric diagnoses compared to our non-CIN neutrophilic patients.

Table 1. Diagnoses of patients presenting with chronic neutrophilia (n = 134)

Diagnosis	No. patients
Chronic idiopathic neutrophilia	57
Neutrophilia lasting <6 mo	29
Chronic infection	4
Post splenectomy	7
Myeloproliferative neoplasm with neutrophilia	20
Neutrophils <8000 $\times$ 10^6/L	9
Chronic myeloid leukemia	3
Prednisone/lithium use	5
Total	134

© 2011 Southern Medical Association

Copyright © 2011 The Southern Medical Association. Unauthorized reproduction of this article is prohibited.

Table 2. Chronic idiopathic neutrophilia—patient data

Patient	Age at presentation, y	Race	Sex	Duration, y	Total neutrophils at presentation ($\times 10^9$/L)	Peak neutrophils ($\times 10^9$/L)	Drugs	Psychiatric diagnosis	Smoker	BMI, kg/m^2
1	64	W	M	7.5	9.80	11.60	Albuterol	No	Yes	23
2	52	W	M	7, resolved	10.00	17.10	None	No	Yes	36
3	34	W	M	5, resolved	8.20	22.60	Albuterol, beclomethasone inhaler and nasal spray	No	Yes	33
4	60	W	M	6, resolved	8.10	9.90	Flunisolide nasal spray	No	Yes	32
5	39	W	M	15.5[a]	8.40	12.90	None	Anxiety/depression	Yes	34
6	54	AA	M	11	10.58	13.90	None	No	Yes	40
7	37	AA	M	15[a]	8.40	13.60	Cocaine	Schizophrenia	Yes	31
8	49	W	M	1.5[a]	8.30	15.30	Albuterol, flunisolide nasal spray	Depression/borderline	Yes	29
9	56	W	M	9.5[a]	8.10	11.30	None	No	Yes	34
10	65	W	M	9, resolved	9.50	9.90	Albuterol	Anxiety/PTSD	Yes	21
11	63	W	M	1.5, resolved	8.40	14.00	Beclomethasone inhaler and nasal spray	Depression	Yes	30
12	40	W	F	6[a]	9.51	14.40	Cannabinoids, pain meds	Depression/pain	Yes	33
13	46	W	M	12[a]	8.17	12.40	None	No	Yes	28
14	55	W	M	6, resolved	8.30	10.70	Flunisolide nasal spray	No	Yes	34
15	46	AA	F	11[a]	9.78	14.80	None	Depression	Quit	33
16	58	W	M	3, resolved	8.10	10.40	Albuterol	Depression	Yes	37
17	47	W	M	15[a]	14.80	18.68	None	Depression	Yes	23
18	47	W	M	3[a]	9.50	12.00	None	Depression/PTSD	Yes	27
19	74	W	M	3.5[a]	10.80	13.40	Fluticasone nasal spray	No	Yes	27
20	59	W	M	1[a]	11.20	12.00	None	No	Yes	27
21	56	W	M	10	8.90	11.20	None	No	Yes	32
22	48	W	M	14[a]	8.90	11.00	None	Depression/anxiety	Quit	32
23	36	W	M	14.5[a]	10.20	11.10	None	Depression	Yes	29
24	49	AA	F	11.5	8.70	15.10	Albuterol	Depression	Yes	32
25	58	W	M	5.5, resolved	8.40	10.40	Albuterol, flunisolide nasal spray and inhaler, formoterol	Adjustment disorder	Yes	40
26	50	AA	M	4, resolved	8.40	10.50	None	Mood disorder	Yes	26
27	42	AA	M	13.5[a]	8.40	10.20	None	No	Yes	30
28	49	AA	M	7, resolved	8.40	10.40	None	No	Yes	28
29	79	W	M	3.5[a]	8.50	9.70	None	No	No	23
30	63	W	M	4	9.60	10.90	None	Depression	Yes	33
31	65	W	M	6.5	8.80	12.80	None	None	No	31
32	60	W	M	2	8.40	9.40	None	None	No	50
33	49	AA	F	2.75	8.9	8.9	None	None	Yes	29
34	51	AA	M	15	10.3	10.8	None	None	Yes	25
35	40	W	M	15	9.3	10.4	None	None	Yes	113[b]
36	50	AA	M	11	14.9	14.9	None	None	Yes	29
37	36	?	M	11	9.6	12.6	None	None	Yes	26
38	53	W	M	2.25	8.8	10.7	Albuterol/flunisolide	None	Yes	29
39	25	AA	M	16	8.4	9.8	None	None	Yes	23
40	64	W	M	5.5	9.5	11.3	None	Depression	Yes	27
41	51	W	M	3	10.7	11.2	None	None	Yes	33
42	31	AA	M	9.5	8.2	10.5	None	PTSD/depression	Yes	23
43	38	W	M	21	10.5	17.9	Cocaine	Schizophrenia	Yes	34
44	62	W	M	1.1	10.1	10.1	None	Depression/anxiety	Yes	25
45	48	AA	M	8	8.6	10.7	None	Depression	No	32
46	66	W	M	4.5	10.2	11.1	Albuterol	Depression	No	42
47	55	W	M	6	9	9.9	Flunisolide	None	Yes	28
48	68	W	M	3.5	9.4	13.1	Lithium[c]	Depression	Yes	25

(continued next page)

Copyright © 2011 The Southern Medical Association. Unauthorized reproduction of this article is prohibited.

Table 2. *(Continued)*

Patient	Age at presentation, y	Race	Sex	Duration, y	Total neutrophils at presentation ($\times 10^9$/L)	Peak neutrophils ($\times 10^9$/L)	Drugs	Psychiatric diagnosis	Smoker	BMI, kg/m^2
49	59	W	M	3	9.8	9.8	None	Depression/anxiety	Yes	26
50	60	W	M	2.7	8.8	11.9	None	Depression	Yes	36
51	60	W	M	1.5	10	13.2	None	Depression	Yes	22
52	70	AA	M	7	12.2	14.1	Albuterol/flunisolide	None	No	40
53	52	W	F	8	8.4	11.4	None	None	Yes	31
54	66	W	M	2	9.1	10.3	Albuterol	None	Yes	33
55	58	AA	F	5	10.2	12.9	Albuterol/flunisolide	None	Yes	37
56	59	W	F	3.1	8.0	9.2	None	None	No	32
57	64	AA	M	2.9	12.7	12.7	None	None	Yes	32

[a]*Leukocytosis present when first seen in clinic. Number with superscript "a" is years observed.*
[b]*Bilateral amputee. BMI not included in calculating mean BMI or used in statistical analysis.*
[c]*Neutrophilia was present when lithium was not in use.*
AA, African American; F, female; M, male; PTSD, posttraumatic stress disorder; W, white.

Cigarette Smoking in CIN

Forty-seven (82.4%) of the 57 CIN patients were active cigarette smokers. Among the 10 nonsmokers, eight had never smoked and two patients had quit smoking 15 and 20 years before. Sixty-one percent of 77 patients evaluated for neutrophilia with causes other than CIN were smokers. In multiple logistic regression analysis of 57 CIN patients compared to 77 patients with neutrophilia from other causes, controlling for race, BMI, and depression/anxiety, CIN was significantly associated with smoking ($P = 0.001$).

Obesity in CIN

Thirty-one of 57 patients with CIN were obese at some time during their neutrophilia with BMI > 30. Eighteen were overweight with a BMI of 25 to 30. Only eight patients had normal body weight. The two patients with CIN who had quit smoking prior to our evaluation had BMIs of 33 and 32 at the time their neutrophilia was initially discovered. One of the seven patients who had never smoked had a BMI of 23, one was overweight, and five were obese. In multiple logistic regression analysis of 57 CIN patients compared to 77 patients with neutrophilia from other causes, controlling for race, depression/anxiety, and smoking, increased BMI was significantly associated with CIN ($P = 0.004$). Compared to the population of all patients who attend the VAMC in Memphis, BMI was not significantly different in smokers with CIN ($P = .301$), but there was a significant association of increased BMI (35.3 kg/m^2) for nonsmokers with CIN compared to the VA patients at large (28.8 kg/m^2) ($P = < 0.001$).

Relationship to Known Myeloproliferative Disorders

Between January 2005 and March 2010, 81 patients were seen at the VAMC in Memphis with probable or definite diagnoses of myeloproliferative disorders. None of the myeloproliferative disorders other than CML presented with neutrophilia as an isolated blood count abnormality. None of our CIN patients developed a clinically significant, non-CML myeloproliferative neoplasm (Ph- MPN) over the mean follow-up period of > 7.3 years.

Of the CML patients, 10 had accessible laboratory results prior to their diagnosis. Of these, at least two and possibly three of the patients presented with isolated neutrophilias and no other hematological disorder for at least six months prior to the diagnosis of CML.

Discussion

The human body may elevate its neutrophil count as a response to inflammation, infection, injury, metastatic malignancy, or acute stress. These responses are mediated by granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), colony stimulating factor-1 (CSF-1), interleukin 5 (IL-5) and other factors.[10] Certain drugs may mimic these physiologic responses, especially corticosteroids, beta agonists, and lithium. Almost always, physiologic neutrophilia can be explained after a thorough history and physical examination with appropriate laboratory and radiological evaluations.

A number of malignant disorders, primarily the myeloproliferative neoplasms, can produce non-physiologic elevations of the neutrophil count. These occur through mutations that lead to constitutive activity of signaling pathways resulting in either increased cell growth or decreased apoptosis.[11] Additional testing, including PCR or FISH techniques for bcr-abl, JAK-2 mutational testing, erythropoietin levels, and bone marrow examination with cytogenetics, may be warranted for patients suspected of having a myeloproliferative neoplasm. Almost always, such disorders present with abnormalities of the blood that a hematologist or pathologist can recognize with examination of the blood smear and cell counts. Polycythemia vera demonstrates an elevated red cell count unless iron deficiency is present,[12] and CML usually demonstrates early white cells such as myelocytes and metamyelocytes or increased basophils in the peripheral blood smears.[13] Primary

© 2011 Southern Medical Association

Copyright © 2011 The Southern Medical Association. Unauthorized reproduction of this article is prohibited.

Table 3. Evaluation for persistent neutrophilia

History and physical examination
Complete blood count
Chemistry profile to include liver function tests
Chest x-ray
Other laboratory and imaging based on identified abnormalities
Review of blood smear by hematologist or pathologist
Repeat focused history and physical examination, complete blood count, and chemistry profile at 2, 6, and 12 mo and annually thereafter

myelofibrosis usually demonstrates abnormalities in the red cell or platelet numbers and almost always has abnormal red cell morphology on the peripheral smear.[14] Chronic myelomonocytic leukemia is recognized peripherally by an increase in monocytes or dysplastic changes in the blood cells.[15]

Over a period of 10 years with multi-year follow-up, we have identified 57 patients in the VAMC's hematology clinic with isolated neutrophilia of greater than 8.0×10^9/L who suffered no apparent harm from their neutrophil elevation and in whom evaluation beyond history, physical examination and testing appropriate to their medical condition would have been wasted.

Most of our patients were cigarette smokers. In the original series of chronic idiopathic leukocytosis in English literature, 25 of 35 patients were cigarette smokers.[1] Two subsequent less well characterized studies both found an association with-smoking.[7,8] Forty-seven (82.4%) of our 57 patients with CIN were active cigarette smokers, and two were former smokers. As a comparison, 61% of patients evaluated for neutrophilia at the VA who were not CIN were smokers. It is possible that most of the patients in our series developed an elevated neutrophil count due to their cigarette smoking. Cigarette smoking causes an increase in neutrophil band percent, an increase in L-selection expression on neutrophils, and increased myeloperoxidase in neutrophils suggesting an accelerated release of neutrophils from the bone marrow.[16] Alveolar macrophages release factors such as TNF-d, IL-1, IL-8 and GM-CSF when stimulated by cigarette smoking.[17] Cigarette smokers have an increase in inflammatory markers such as C-reactive protein and fibrinogen.[18,19] Most of these mediators stimulate hematopoiesis and cause neutrophil release from the bone marrow.

Obesity is another likely etiology of CIN. In an article on the possible contribution of obesity to leukocytosis, Herishanu et al described a series of 327 patients referred to their clinic for persistent leukocytosis.[7] Of those patients, 15.3% were asymptomatic, nonsmoking and obese with a female-to-male ratio of 4:1. Adipose tissue produces proinflammatory cytokines and, specifically, leptin has been found to be increased in obese patients and correlated with neutrophilia.[20] Eighty-six percent of our patients were either overweight or obese. The average BMI of all patients visiting VAMC Memphis in 2001 was 28. The average BMI of nonsmokers and those who had quit smoking for greater than 10 years in our study was 35.5, suggesting obesity as an associated factor in nonsmokers.

In the patients reviewed, none of the CIN patients developed a clinical picture consistent with a Ph- MPN. None of our patients with myeloproliferative disorders other than CML presented with a CIN picture. Three of 10 patients with CML had the potential to be confused initially with CIN. Identifying these patients early is not likely urgent since fewer than 5% of CML patients without peripheral blasts convert to an acute leukemia within the first year of their diagnosis.[21]

Eighteen patients with CIN were using beta agonists or inhaled or nasal steroids, mostly for chronic obstructive pulmonary disease, but only six throughout the period of neutrophilia. Beta agonists can increase peripheral neutrophil counts[22] but we provide no evidence that these drugs cause neutrophilia.

Twenty-four of the 57 patients with CIN carried the diagnoses of depression, anxiety, post traumatic stress disorder, mood disorder or schizophrenia. It is possible that stress-related products such as epinephrine or corticosteroids were elevated chronically in these patients and a chronic elevation of such mediators could theoretically contribute to a chronic neutrophilia,[23,24] but we could not demonstrate a statistical increase in CIN among these diagnoses in our patients.

Seventy-two percent of our patients were white, and 28% African American. This contrasts to the 41% of Memphis VAMC patients in 2001 who were African American. This difference approached but did not reach statistical significance ($P = 0.066$). African Americans have lower average neutrophil counts than whites with the difference possibly explained by the presence of a single nucleotide polymorphism in the Duffy antigen/receptor chemokine gene in African Americans.[25]

Table 4. Indications for additional testing in persistent neutrophilia

Abnormalities on history and physical suggesting inflammation or malignancy
Abnormalities on a chest x-ray or chemistry panel suggesting inflammation or malignancy
Abnormalities in the red cell, platelet, monocyte, eosinophil, or basophil counts
Myelocytes or earlier white cell precursors on smear
Abnormalities on blood smear reviewed by a hematologist or pathologist
Change in history and physical, chemistry, or complete blood count testing on follow-up surveillance
Patient without obesity or smoking history
Fluorescence in situ hybridization or polymerase chain reaction testing for bcr-abl mutation for persistent leukocytosis >12 mo, a rise in neutrophil count by >50%, a total neutrophil count >15,000, or presence of myelocytes, basophilia, eosinophilia, or monocytosis
Evaluation by hematologist and possible bone marrow examination if anemia, elevated hematocrit, thrombocytosis, basophilia, eosinophilia, monocytosis, peripheral blasts, or anyone who develops an abnormally low hematocrit or platelet count

Copyright © 2011 The Southern Medical Association. Unauthorized reproduction of this article is prohibited.

Conclusion

In summary, there is a strong association within our population between cigarette smoking and CIN and between obesity in nonsmokers and CIN. In fact, these associations may be strong enough to identify chronic neutrophilia of smoking and chronic neutrophilia of obesity as valid populations, thus making the true chronic idiopathic neutrophilia population quite small. The associations of CIN with anxiety/depression and race are not statistically significant in our study and therefore remain as hypothesis-generating findings. The possibility of evolving a Ph- MPN from CIN is very unlikely, but early CML may mask itself as CIN.

We began with the question, "Which patients with isolated, elevated neutrophil counts need an extensive evaluation?" Reasonable management for a healthy patient presenting with a neutrophilic leukocytosis would include the studies listed in Table 3. Circumstances requiring additional testing are listed in Table 4.

Chronic neutrophilia in asymptomatic patients is a complex problem that requires clinical judgment but usually does not require extensive and costly testing. We believe the guidelines presented will identify important diseases in a timely manner while minimizing the burdens of time and expense we place upon our patients.

Acknowledgments

The authors thank Marshall J. Graney, PhD, for statistical assistance and Catherine Lewis for editorial assistance.

References

1. Ward HN, Reinhard EH. Chronic idiopathic leukocytosis. *Ann Intern Med* 1971;75:193–198.
2. Stemmelin GR, Doti CA, Shanley CM, et al. Smoking as a cause for mild chronic neutrophilia. *Blood* 2004;104. Abstract 3796.
3. Parry H, Cohen S, Schlarb JE, et al. Smoking, alcohol consumption and leukocyte counts. *Am J Clin Pathol* 1997;107:64–67.
4. Corre F, Lellouch J, Schwartz D. Smoking and leukocyte counts. Results of an epidemiological survey. *Lancet* 1971;2:632–634.
5. Noble RC, Penny BB. Comparison of leukocyte count and function in smoking and nonsmoking young men. *Infect Immun* 1975;12:550–555.
6. Smith MR, Kinmonth A, Luben RN, et al. Smoking status and differential white cell count in men and women in the EPIC-Norfolk population. *Atherosclerosis* 2003;169:331–337.
7. Herishanu Y, Rogowski O, Polliack A, et al. Leukocytosis in obese individuals: possible link in patients with unexplained persistent neutrophilia. *Eur J Haematol* 2006;76:516–520.
8. Suzuki K, Kitagawa S. Chronic idiopathic leukocytosis. *Ryoikibetsu Shokogun Shirizu* 1998;21(Pt 2):17–18.
9. Schwartz J, Weiss S. Host and environmental factors influencing the peripheral blood leukocyte count. *Am J Epidemiol* 1991;134:1402–1409.
10. Koury MJ, Mahmud N, Rhodes MM. Origin and development of blood cells. In: Greer JP, Foerster J, Rodgers GM, et al (eds): *Wintrobe's Clinical Hematology.* 12th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2009:95.
11. Campbell PJ, Green AR. The myeloproliferative disorders. *N Engl J Med* 2006;355:2452–2466.
12. Spivak JL, Silver RT. The revised World Health Organization diagnostic criteria for polycythemia vera, essential thrombocytosis, and primary myelofibrosis: an alternative proposal. *Blood* 2008;112:231–239.
13. Quintás-Cardama A, Cortes JE. Chronic myeloid leukemia: diagnosis and treatment. *Mayo Clin Proc* 2006;81:973–988.
14. Tefferi A, Barbui T. Bcr/abl-negative, classic myeloproliferative disorders: diagnosis and treatment. *Mayo Clin Proc* 2005;80:1220–1232.
15. Komrokji RS, Zhang L, Bennett JM. Myelodysplastic syndromes classification and risk stratification. *Hematol Oncol Clin North Am* 2010;24:443–457.
16. Van Eeden SF, Hogg JC. The response of human bone marrow to chronic cigarette smoking. *Eur Respir J* 2000;15:915–921.
17. Francus T, Romano PM, Manzo G, et al. IL-1, IL-6, and PDGF mRNA expression in alveolar cells following stimulation with a tobacco-derived antigen. *Cell Immunol* 1992;145:156–174.
18. Wannamethee SG, Lowe GDO, Shaper AG, et al. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic inflammatory markers for cardiovascular disease. *Eur Heart J* 2005;26:1765–1773.
19. Yanbaeva DG, Dentener MA, Creutzberg EC, et al. Systemic effects of smoking. *Chest* 2007;131:1557–1566.
20. Laharrague P, Oppert JM, Brousset P, et al. High concentration of leptin stimulates myeloid differentiation from human bone marrow $CD34^+$ progenitors: potential involvement in leukocytosis of obese subjects. *Int J Obesity* 2000;24:1212–1216.
21. Reichard KK, Larson RS, Rabinowitz I. Chronic myeloid leukemia. In: Greer JP, Foerster J, Rodgers GM, et al (eds): *Wintrobe's Clinical Hematology.* 12th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2009:2009.
22. Athens JW, Raab SO, Haab OP, et al. Leukokinetic studies. III. The distribution of granulocytes in the blood of normal subjects. *J Clin Invest* 1961;40:159–164.
23. Bremner JD, Krystal JH, Southwick SM, et al. Noradrenergic mechanisms in stress and anxiety: II. Clinical studies. *Synapse* 1996;23:39–51.
24. Arranz L, Guayerbas N, De la Fuente M. Impairment of several immune functions in anxious women. *J Psychosom Res* 2007;62:1–8.
25. Grann V, Ziv E, Joseph C, et al. Duffy (Fy), DARC, and neutropenia among women from the United States, Europe, and the Caribbean. *Br J Haematol* 2008;143:288–293.

© 2011 Southern Medical Association

Copyright © 2011 The Southern Medical Association. Unauthorized reproduction of this article is prohibited.