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CLINICAL VIGNETTE

Outpatient Evaluation of Leukocytosis: Unexpected Diagnosis of Chronic Leukemia

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Leukocytosis is one of the most common reasons for outpatient hematology referrals. Leukocytosis is often an incidental finding on a routine complete blood count (CBC), and the ambulatory patients are usually asymptomatic. In this setting, the clinical concern lies in the uncommon possibility of an underlying hematologic malignancy. The following two cases illustrate leukocytosis evaluations that led to the diagnosis of chronic leukemia. Both patients had been in good health with no significant medical comorbidities and were referred by their primary care doctors to hematology clinic for the evaluation of persistent mild leukocytosis.

Case 1

A 70-year-old woman presented with a white blood cell (WBC) count that had been normal but newly increased to 13,000 cells/ μ L in 01/2017 with subsequent fluctuations between 10,000 and 13,000. On her visit in 09/2017, her WBC count was 12,000 with 59% neutrophils and 23% lymphocytes. Of note, monocytosis of 1,400 cells/ μ L was present. Hemoglobin, platelet count, and other CBC parameters were all within normal range. She was clinically doing well with no signs or symptoms in the way of infection. Peripheral blood flow cytometry did not reveal any abnormalities. She was assessed for chronic myeloid leukemia (CML) via PCR testing for the BCR-ABL1 fusion transcript, which came back positive (albeit at a low level of 4.17% IS). With the early diagnosis of CML, she was started on a BCR-ABL tyrosine kinase inhibitor with normalization of the WBC count.

Case 2

A 74-year-old man presented with a WBC count that had been normal but newly increased to 11,900 cells/ μ L in 10/2016 with subsequent WBC counts up to 13,000. On initial hematology consultation in 02/2018, his WBC count was 13,000 with 44% neutrophils and 44% lymphocytes. Absolute lymphocyte count was 5,720. His lymphocyte proportion had been very gradually rising for the last 5 years. Hemoglobin, platelet count, and other CBC parameters were all within normal range. Flow cytometry revealed monotypic B-lymphocytosis co-expressing CD5 (dim) and CD23, immunophenotypic of chronic lymphocytic leukemia (CLL). Subsequent FISH analysis was consistent with deletion of 13q, which is the most common cytogenetic abnormality identified in CLL (approximately 50% of CLL) and is associated with a favorable prognosis. He has been observed without treatment to date.

Discussion

The above cases are more exceptions than norms, where the majority of leukocytosis cases referred to hematologists turn out to be benign or reactive. In fact, we simply repeat the CBC during the first visit and not uncommonly see normalization of the WBC count.

The normal range of WBC count is defined as being within 2 standard deviations above and below the mean. This definition necessarily labels 2.5% of the population to be leukocytic (and the other 2.5%, leukopenic). In absolute terms, leukocytosis is defined by most laboratories as a WBC count above 11,000 cells/ μ L in adults. The WBC differential consists of neutrophils, lymphocytes, monocytes, eosinophils, and basophils. There are normal variations in WBC count and WBC differential percentages depending on age, ethnicity, and pregnancy.^{1,2} Neutrophilia (a neutrophil count of greater than 7,700 cells/ μ L in adults) is the most common type of leukocytosis and may be physiologic in some cases. Serial measurements over time may be all that is needed to determine the absence of underlying pathology. One study looked at 34 apparently healthy subjects with persistent leukocytosis from neutrophilia, with a normal hemoglobin, and without known underlying etiologies. During an average follow up of 7 years, none acquired leukemia and the vast majority did not develop diseases known to be responsible for leukocytosis.³

Reactive causes of neutrophilia are numerous and can often be determined based on history or clinical presentation. Infection and inflammation are common causes of neutrophilia. Underlying inflammatory conditions associated with neutrophilia include connective tissue disease and inflammatory bowel disease. Certain medications, including corticosteroids, catecholamines, and lithium, may be the causative agent, in which case cessation of the drug would normalize the WBC count.² Corticosteroids and catecholamines can cause abrupt leukocytosis due to demargination of peripheral blood neutrophils (half of circulating neutrophils are reversibly adherent to the endothelium).⁴ Cigarette smoking and obesity have also been associated with chronic neutrophilia and may be causative.⁵ Compared with never smokers, total WBC count was 27% higher in current smokers and 14% higher in former smokers who quit less than 5 years ago.⁶ Neutrophilia has been associated with many types of "stress," including exercise, surgery, seizures, and panic attacks.^{2,7} Solid tumors have been associated with extreme leukocytosis (WBC >40,000), via suspected

mechanisms including hematopoietic growth factors production and paraneoplastic leukemoid reaction.⁸

In the absence of an obvious reactive etiology, autonomous leukocytosis needs to be considered. Specifically, malignant disorders such as leukemias and myeloproliferative neoplasms are of concern. As hematologists, we consider a variety of factors to assess for malignant leukocytosis, including the clinical presentation, chronicity of the leukocytosis, aberration of WBC differential, and associated abnormalities in the red blood cell and platelet lineages. Examination of the peripheral blood smear allows for direct visualization of cellular morphology and identification of atypical or immature WBCs and blasts. Blast percentage of greater than 20% is diagnostic of acute leukemias, but acute leukemias can be present in an individual with a lower percentage of blasts or no blasts in the peripheral blood.¹ When clinical suspicion is sufficient for underlying malignancy, additional hematologic testing may include peripheral blood flow cytometry and/or bone marrow aspirate and biopsy. Molecular testing for genetic alterations is also used to aid in the diagnoses of malignant leukocytosis. Since a left-shifted (increase in immature granulocytes) leukocytosis is found in both chronic myeloid leukemia and reactive causes, FISH or PCR testing for the BCR-ABL fusion is needed to make a diagnosis of CML. Neutrophilia may accompany other myeloproliferative neoplasms such as polycythemia vera, essential thrombocythemia, primary myelofibrosis, atypical CML, and chronic neutrophilic leukemia. Testing for mutations in JAK2, CALR, MPL, and CSF3R can aid in the diagnostic workup.⁹

Lymphocytosis in adults is defined as a lymphocyte count greater than 3,500 cells/ μ L and is more often related to underlying clonal disorder than reactive causes in an adult population as compared to a pediatric population.^{1,10} Peripheral blood flow cytometry can determine if the lymphocytosis is monoclonal. Chronic lymphocytic leukemia (CLL) is the most common adult leukemia and can be diagnosed using this method, as mentioned in case 2. Monoclonal B-cell lymphocytosis (MBL) is differentiated from CLL by a B-lymphocyte count of less than 5,000 cells/ μ L and lack of other signs of a lymphoproliferative disorder.¹¹ MBL can be found in up to 12% of healthy individuals over age 40 years and usually has a benign course. Other lymphoproliferative disorders associated with lymphocytosis include splenic marginal zone lymphoma, mantle cell lymphoma, hairy cell leukemia, and Burkitt lymphoma. Immunophenotyping by flow cytometry and cytogenetics are used to make the specific diagnoses.

In conclusion, leukocytosis is a common reason for referral to hematology and can be a cause for patients' anxiety as leukemia is a potential but uncommon diagnosis. Evaluation includes thorough history taking, physical exam, CBC and WBC differential review (past and current), peripheral smear, and additional laboratory testing based on suspected etiologies. Reactive leukocytosis is most commonly encountered and the underlying condition can be addressed. If a hematologic malignancy is a reasonable possibility, further workup may involve

peripheral blood flow cytometry, bone marrow aspiration and biopsy, and/or molecular testing. Once the diagnosis of a specific hematologic malignancy is made, the hematologist will be able to recommend appropriate treatment.

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