44-Year-Old Man With Fatigue, Weight Loss, and Leukocytosis

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A 44-year-old man with a medical history notable for subclinical hypothyroidism, hypertension, hyperlipidemia, and irritable bowel syndrome presented for outpatient evaluation of progressive fatigue and weight loss. The patient initially sought medical care for fatigue 2 years previously, but he described sudden worsening of his symptoms over the months leading up to his current evaluation. Most notably, he reported a profound impact on his exercise capacity. Previously, the patient would participate in multiple triathlons annually, but this past year, he only participated in one marathon. Over the preceding 2 months, he experienced further decline in exercise capacity, only participating in physical activity for 20 minutes at a time. He disclosed that following any physical activity, he required a prolonged period of recovery.

Regarding the patient’s irritable bowel syndrome, he described frequent cramping, bloating, and increased frequency of loose stools. His symptoms were mild and transient. He reported no nausea, vomiting, constipation, or melena. The previous year, he was evaluated by a gastroenterologist who performed an endoscopy that revealed a normal esophagus, stomach, and duodenum. Duodenal biopsies yielded unremarkable findings. *Helicobacter pylori* antibodies were absent. A colonoscopy was not performed.

On review of systems, the patient reported a 9-kg weight loss over the preceding 5 months that had stabilized over the past month. He reasoned that this decrease in weight was predominantly secondary to lost muscle mass in the setting of decreased exercise. He had no night sweats, palpitations, early satiety, exertional dyspnea, or angina symptoms. Subclinical hypothyroidism had been diagnosed when the patient was in his mid-30s and had since been managed with levothyroxine. His hypertension and hyperlipidemia were managed with lisinopril, diet, and exercise. On social history, the patient reported no current or former tobacco or illicit substance use. He consumed 3 to 7 alcoholic beverages per week. He had a 4-year college degree and worked in an office setting.

On examination, the patient was well-appearing. His blood pressure was 134/71 mm Hg, pulse rate was 75 beats/min, and body mass index was 22.46 kg/m². Physical examination revealed normal conjunctiva, and his neck circumference was normal with no thyroid abnormalities. Cardiopulmonary examination findings were unremarkable, and no adenopathy was detected. The patient’s abdomen was soft without any tenderness or organomegaly. Neurologic examination findings were within normal limits, and the patient’s muscle bulk and tone were appropriate.

1. Which one of the following diagnostic studies would be least appropriate at this time?
   a. Serum thyrotropin measurement
   b. Complete blood cell count (CBC) with white blood cell (WBC) differential
   c. Serum chemistry and metabolic panel
d. Screening for HIV
e. Serum carbohydrate antigen (CA 19-9) test

Fatigue is a common problem encountered in ambulatory clinics and poses a diagnostic challenge for clinicians given the broad and potentially concerning differential diagnosis. Thyroid function abnormalities could contribute to the patient’s fatigue, and given his history of subclinical hypothyroidism.
roidism treated with thyroid hormone replacement therapy, it would be prudent to investigate for thyroid dysfunction. A CBC would be a reasonable screening tool in this setting to evaluate for potential anemia. The addition of the WBC differential affords the opportunity to screen for potential lymphoproliferative or myeloproliferative states. Because electrolyte, hepatic, or renal abnormalities may contribute to fatigue and the patient reported gastrointestinal symptoms, a chemistry and metabolic panel would be a reasonable diagnostic test in this setting. If this patient has not been tested for HIV previously, performing this test would be reasonable because HIV can lead to fatigue and weight loss and screening is recommended by the US Preventive Services Task Force.\(^2\)

CA 19-9 is a validated biomarker for pancreatic cancer and provides useful information regarding response to chemotherapy, prognosis, and surveillance in patients already diagnosed with such malignancy. However, the utilization of this biomarker in screening patients for pancreatic cancer is not recommended.\(^3\) Although the patient had gastrointestinal symptoms and reported weight loss, other diagnostic studies would be more appropriate at this time.

Laboratory studies revealed the following (reference ranges provided parenthetically): thyrotropin, 1.0 mIU/L (0.3 to 4.2 mIU/L); sodium, 141 mmol/L (135 to 145 mmol/L); potassium, 4.3 mmol/L (3.6 to 5.2 mmol/L); bicarbonate, 30 mmol/L (22 to 29 mmol/L); serum urea nitrogen, 16 mg/dL (8 to 24 mg/dL); creatinine, 1.3 mg/dL (0.74 to 1.35 mg/dL); alanine aminotransferase, 33 U/L (7 to 55 U/L); aspartate aminotransferase, 24 U/L (8 to 48 U/L); alkaline phosphatase, 47 U/L (40 to 129 U/L); C-reactive protein, less than 3.0 mg/L (≤8.0 mg/L). The CBC with WBC differential was notable for the following: hemoglobin, 14.4 g/dL (13.2 to 16.6 g/dL); platelet count, 167 × 10^9/L (135 to 317 × 10^9/L); total WBC count, 20.2 × 10^9/L (3.4 to 9.6 × 10^9/L); absolute neutrophil count, 13.33 × 10^9/L (1.56 to 6.45 × 10^9/L); lymphocyte count, 2.63 × 10^9/L (0.95 to 3.07 × 10^9/L); monocyte count, 0.81 × 10^9/L (0.26 to 0.81 × 10^9/L); eosinophil count, 0.0 × 10^9/L (0.03 to 0.48 × 10^9/L); and basophil count, 0.81 × 10^9/L (0.01 to 0.08 × 10^9/L); metamyelocytes and myelocytes comprised 5% (<1.0%) and 8% (<0.5%) of circulating peripheral blood cells, respectively. Screening for HIV was negative.

2. Which one of the following is the best interpretation of this patient’s CBC with differential?

- a. The neutrophilia suggests the presence of infection
- b. The absence of eosinophils suggest an immunodeficiency syndrome
- c. The leukocytosis and differential are suggestive of a myeloid malignancy
- d. The leukocytosis indicates the need for positron emission tomography
- e. The normal hemoglobin level excludes the possibility of sleep apnea

Neutrophilic leukocytosis is commonly attributed to acute infectious or inflammatory conditions. However, the absence of localizing infectious symptoms, the patient’s normal C-reactive protein level, and the presence of other notable abnormalities on the WBC differential, make this a less likely conclusion. There are no common primary immunodeficiency syndromes that result in isolated eosinophilopenia. The presence of basophilia and myeloid precursors in this patient are highly suspicious for a myeloid malignancy. Prior investigators have noted that an absolute basophil count of 0.4 × 10^9/L or greater in patients with leukocytosis has a 99.0% specificity for myeloid cancer.\(^4\) The patient’s WBC differential is not consistent with a lymphoproliferative process, and therefore, further evaluation for lymphoma, specifically with positron emission tomography, would not be prudent. Although hypoxia from obstructive sleep apnea is a recognized cause of erythrocytosis, the presence of a normal hematocrit value does not rule out this diagnosis.\(^5\)

The patient’s CBC with WBC differential was repeated the following week and revealed persistent leukocytosis, basophilia,
and circulating myeloid precursors. Due to concern about an indolent infection, bacterial and fungal cultures of the patient’s blood were obtained and a urinalysis with culture was performed. Consultation with the hematology department was requested and scheduled for the following week.

3. Which one of the following laboratory tests would be the best next step in evaluating the patient’s abnormal WBC differential?
   a. Analysis for mutation of JAK2
   b. Peripheral blood evaluation for fusion transcripts of the BCR-ABL oncogene
   c. Serum protein electrophoresis and assessment of the ratio of \( \kappa \) and \( \lambda \) free light chains
   d. Flow cytometry
   e. CALR mutation analysis

JAK2 mutations are commonly detected in patients with polycythemia vera, essential thrombocytopenia, and myelofibrosis. Although these diseases are included in classic myeloproliferative neoplasms, this patient does not have findings suggestive of these disorders. The best next step at this time would be to evaluate for the fusion of the BCR-ABL oncogene, a gene product formed by translocation of chromosomes 9 and 22. This oncogene is located on shortened chromosome 22, otherwise known as the Philadelphia chromosome.\(^6\) Thus, chromosome 22 with the BCR-ABL oncogene is the pathognomonic finding of chronic myelogenous leukemia (CML). Although many disease states can result in basophilia, the degree of basophilia and the presence of myeloid precursors in our patient are highly suggestive for a diagnosis of CML.\(^4\) Serum protein electrophoresis and free light chains are diagnostic studies utilized to screen for multiple myeloma; a malignancy that would not be consistent with this patient’s presentation. Flow cytometry is performed to assess for clonality in patients with lymphocytosis and/or circulating blasts. Because the patient’s WBC differential exhibits abnormalities in cells of myeloid lineage, flow cytometry would not likely be beneficial at this time. Mutations involving CALR can be detected in a minority of patients with essential thrombocythemia and myelofibrosis. Given the absence of thrombocytosis and splenomegaly in our patient, these diagnoses would be less likely.

Results of the patient’s infectious studies were unremarkable. Fungal serologies and QuantiFERON-TB results were negative. Given the presence of circulating myeloid precursor cells and basophilia, polymerase chain reaction for BCR-ABL gene fusion was performed and revealed the presence of messenger RNA for BCR-ABL p210 fusion form. Bone marrow biopsy evaluation revealed a markedly hypercellular marrow, with increased myeloid precursors, megakaryocytes, and myeloid to erythroid ratio. No lymphocyte abnormalities were identified. Given the patient’s clinical presentation and laboratory evaluation findings, CML was diagnosed.

4. Which one of the following treatment options is most appropriate at this time?
   a. Hydroxyurea
   b. Therapeutic phlebotomy
   c. Imatinib
   d. Supportive care and 81 mg aspirin
   e. Bone marrow transplant

Hydroxyurea is a cytoreductive agent that is typically reserved for patients with CML who experience blast crisis that is refractory to first-line therapy and temporarily in patients with severe leukocytosis (total WBC >30 × 10^9/L).\(^7\) Interval phlebotomy is a therapeutic modality utilized in polycythemia vera and would not benefit this patient. A tyrosine kinase inhibitor, such as imatinib, is considered first-line therapy in patients with CML and therefore is the most appropriate option.\(^6\) Supportive care and low-dose aspirin are utilized in essential thrombocythemia and would not be considered adequate therapy for this patient. Allogeneic stem cell transplant is a therapy reserved for patients with CML who are experiencing a blast crisis that is refractory to other therapeutic modalities and would not be considered in this patient at this time.
Imatinib was prescribed. Two months later, the patient presented for outpatient evaluation and reported improvement of his fatigue. Laboratory studies were notable for the following: WBCs, \(4.5 \times 10^9/L\); absolute neutrophils, \(3.4 \times 10^9/L\); lymphocytes, \(0.7 \times 10^9/L\); monocytes, \(0.2 \times 10^9/L\); eosinophils, \(0.0 \times 10^9/L\); and basophils, \(0.0 \times 10^9/L\). No circulating myeloid precursor cells or nucleated red blood cells were detected. The patient reported interest in reinitiating exercise and triathlon training. He inquires about a medical opinion regarding his prognosis because he is unsure if he should continue to pursue age-appropriate preventive health screenings given his new cancer diagnosis.

5. Which one of the following represents this patient’s most likely prognosis?
   a. Likely need for bone marrow transplant in the future
   b. Disease cure after completion of 12 months of therapy
   c. Shortened life expectancy due to opportunistic infections
   d. His laboratory studies indicate that he is cured and can terminate therapy
   e. Normal lifespan following treatment

Although bone marrow transplant is a treatment option for CML, it is reserved for patients whose CML is refractory to multiple tyrosine kinase inhibitors. The rate of resistance to tyrosine kinase therapy is approximately 2% per year. It is not likely that the patient will require transplant for his CML. Following 1 year of treatment, patients are not considered “cured” of CML. Although opportunistic infections have been reported in patients with CML, such infections are not considered a major driver of mortality in patients with CML. This patient has received tyrosine kinase inhibitor therapy for only 2 months, and follow-up data regarding his molecular response have not yet been obtained. Prior studies note that patients who had received at least 2 years of imatinib therapy had a relapse rate of 61% following therapy discontinuation. It would be premature to assume resolution of his disease, and termination of imatinib therapy would not be advised. It is reasonable for this patient to expect a high probability of sustained molecular response and normal lifespan given the low rate of tyrosine kinase inhibitor resistance per year, the availability of 5 US Food and Drug Administration–approved tyrosine kinase inhibitors, and the presence of other therapies including allogeneic stem cell transplant.

The patient continued his imatinib therapy. Two years following diagnosis, fusion transcripts for the BCR-ABL oncogene remain undetected on peripheral blood analysis. His exercise tolerance has improved, and he continues to work toward his previous level of physical activity.

DISCUSSION
Fatigue is a problem commonly encountered in ambulatory clinics and poses a diagnostic challenge for clinicians given the broad and potentially concerning differential diagnosis. Myeloid malignancies, such as CML, should be considered in patients presenting with fatigue who are noted to have leukocytosis with concomitant basophilia and/or myeloid precursor cells on peripheral blood analysis. Approximately 85% of patients with CML will present in the chronic phase, often characterized by vague symptoms such as fatigue, weight loss, and joint pain.

Considering this clinical presentation, primary care physicians should note that they may be the initial health care contact for patients with this hematologic malignancy.

Chronic myelogenous leukemia is a myeloid neoplasm with an annual incidence of 1 to 2 cases per 100,000 adults and accounts for nearly 15% of new leukemia diagnoses among adults in the United States. The BCR-ABL fusion oncogene is the underlying pathogenesis of this myeloproliferative malignancy, and it can be detected through either fluorescence in situ hybridization or polymerase chain reaction testing. Imatinib is a tyrosine kinase inhibitor that specifically targets this fusion gene product and is recognized as a first-line therapy for this cancer. Following US Food and Drug Administration approval of imatinib in 2001, the annual mortality of
CML in the United States decreased substantially, which led to a subsequent increase in disease prevalence. Projections estimate that by 2040, the prevalence of CML in the United States may be between 180,000 and 450,000 patients. When considering this increase in disease prevalence, the importance of primary care physician familiarity with this condition becomes apparent as many will find patients with CML under their longitudinal care. Furthermore, physicians should be aware of toxicities and drug interactions related to the tyrosine kinase inhibitors utilized by their patients. For example, imatinib interacts with multiple pharmacological agents through inhibition of cytochrome P450 3A4 and can cause adverse effects such as peripheral edema, weight gain, fatigue, and myalgias. Other tyrosine kinase inhibitors used in CML have been associated with pulmonary arterial hypertension, QT interval prolongation, hyperglycemia, and renal and hepatic dysfunction.

Chronic myelogenous leukemia is a myeloproliferative neoplasm that is marked by the presence of the BCR-ABL fusion gene and is characterized by increased production of myeloid cells. The clinical presentation of this illness is often indolent, and in many circumstances, diagnostic evaluation will be initiated by primary care physicians. In patients with fatigue, the presence of unexplained leukocytosis with concomitant basophilia and/or myeloid precursor cells should prompt suspicion for CML, and appropriate referral to a hematologist should be pursued. Primary care physicians should become familiar with this malignancy and recognize the importance of continued age-appropriate preventive care because many patients with CML will have a normal life expectancy.

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REFERENCES

CORRECT ANSWERS: 1. e. 2. c. 3. b. 4. c. 5. e