Chronic Myelogenous Leukemia in a 66-Year-Old Male with Concurrent Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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CLINICAL HISTORY

Patient: A 66-year-old Caucasian male.

Chief Complaint: The patient felt tired and was eating less than usual. Previously, the patient could ride his bike for 3 miles, but now can barely complete 1 mile.

Medical History: Significant for persistent lymphocytosis for the past 10 years and recently diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) by flow cytometry on peripheral blood. He also has a history of hyperlipidemia, diabetes mellitus, and obstructive sleep apnea.

Social History: The patient does not smoke or use illicit drugs. He uses alcohol occasionally. The patient is married and is retired from an automobile supply company.

Family History: Noncontributory. None of his family members have a history of blood disorders.

Physical Examination: Significant for the following: alert; oriented to time, place, and person; neck: no palpable lymphadenopathy; heart and lung: unremarkable; abdomen: obese and soft, no palpable hepatosplenomegaly.

Vital signs: Blood pressure: 137/58 mmHg; pulse: 68/minute; respiratory rate: 12/minute; temperature: 37°C.

Principal Laboratory Findings: Laboratory test results are in Table 1.

Additional Testing: The molecular diagnostic test Janus kinase 2 (JAK2) V617F mutation was ordered. A peripheral blood smear at the hematologist’s office was abnormal 3 months later. Subsequently, on the peripheral blood specimen the molecular test assessing presence of BCR/ABL1 mRNA transcript producing the 210-kDa protein (p210) was ordered and a bone marrow biopsy with aspirate was performed. The bone marrow aspirate was also submitted for morphologic, cytogenetic, and flow cytometric evaluations (Images 1 and 2).

Keywords: flow cytometry, hematology, hematopathology, molecular diagnostics

Questions

1. What are the most significant clinical and laboratory findings in this patient?
2. What are the differential diagnoses and the most likely diagnosis?
3. What is the clinical presentation of this entity?
4. How is the disease diagnosed with the aid of clinical laboratory tests, a peripheral blood smear, and bone marrow exam?
5. How is the entity managed and treated?
6. How common is it for chronic lymphocytic leukemia to occur with this entity?
7. What is the clinical outcome of patients with this entity? How does the treatment differ?

Abbreviations

ABL1, Abelson oncogene; BCR, breakpoint cluster region; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CML, chronic myelogenous leukemia; FISH, Fluorescence in situ hybridization; JAK2, Janus kinase 2; Ph, Philadelphia; RT-PCR, reverse transcription polymerase chain reaction; TKI, tyrosine kinase inhibitor; WBC, white blood count

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Abbreviations

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Possible Answers

1. Clinically, the patient’s onset of fatigue and decreased appetite were the greatest concerns. His complete blood work showed a significantly elevated white blood cell (WBC) count with particularly striking bandemia, as well as eosinophilia, basophilia, and lymphocytosis. These findings could not be solely explained by the previously established diagnosis of CLL/SLL, so further diagnostic workup was necessary. Molecular testing for
the assessment of a JAK2 (V617F) mutation performed on peripheral blood was negative. Due to an abnormal peripheral smear 3 months later, a bone marrow biopsy with aspirate was performed. The bone marrow aspirate smears showed left shifted granulocytopoiesis with increased numbers of eosinophils and basophils. The clot section and decalcified biopsy were hypercellular with atypical megakaryocyctic proliferation. In addition, several small clusters of lymphocytes were seen in the decalcified biopsy section. By flow cytometry, those lymphoid cells were monotypic B-lymphoid cells with a composite antigen profile of CD19+, CD20+, CD23+, and CD5+, and were lambda positive. Conventional karyotype analysis of the bone marrow aspirate demonstrated the presence of Philadelphia (Ph) chromosome [t(9;22)(q34;q11)]. Fluorescence in situ hybridization (FISH) of the bone marrow aspirate revealed BCR/ABL1 fusion gene in 76% of the nuclei. In addition, molecular testing on the peripheral blood demonstrated presence of the BCR/ABL1 mRNA transcript (p210).

2. The WBC count raised the possibility of a myeloproliferative neoplasm. Myeloproliferative neoplasms are a heterogenous group of diseases characterized by a malignant transformation of 1 or more hematologic cell lines in the blood. Myeloproliferative neoplasms include chronic myelogenous leukemia (CML), polycythemia vera, essential thrombocythemia, primary myelofibrosis, chronic neutrophilic leukemia, and chronic eosinophilic leukemia. The pathophysiology of myeloproliferative neoplasms usually involves abnormal activation of 1 or more tyrosine kinase pathways. JAK2 mutation is commonly associated with polycythemia vera, essential thrombocythemia and primary myelofibrosis, whereas the causative factor in CML is the tyrosine kinase encoding BCR/ABL1 fusion gene. The JAK2 gene mutation was negative in this patient. The differential diagnosis from the bone marrow aspirate included CML, chronic myelomonocytic leukemia, chronic neutrophilic leukemia, and CLL/SLL. The histopathologic findings on bone marrow of left shifted granulocytopoiesis as well as the presence of Ph chromosome [t(9;22)(q34;q11)] on conventional karyotype, BCR/ABL1 fusion gene by FISH and BCR/ABL1 mRNA transcript by molecular testing established the diagnosis of CML.

3. CML accounts for 15%-20% of adult leukemias (primarily in middle-aged adults), but is rare in young or elderly patients. CML can present in 3 phases: chronic phase, accelerated phase, and blast crisis; the clinical manifestations depend on the phase of the disease.

Most cases of CML are discovered incidentally in the chronic phase when elevated WBC counts are observed or an enlarged spleen palpated on physical examination. Nonspecific symptoms include fatigue and weight loss, with decreased exercise tolerance occurring after several months in the chronic phase. Additional symptoms include abdominal pain (secondary to splenomegaly), along with headaches and blurred vision related to increased blood viscosity. The most common physical finding is splenomegaly, with the size of the spleen directly correlating with peripheral blood granulocyte count. Splenomegaly can be marked with the splenic edge felt below the umbilicus. Occasionally, patients present with an acute abdomen secondary to splenic infarction. Hepatomegaly may also be present.

In the accelerated phase, patients experience symptoms such as bleeding, petechiae, and ecchymoses.

In blast crisis, symptoms are similar to the accelerated phase but include a rapidly enlarging spleen and failure of medication to control leukocytosis and splenomegaly.

4. The diagnostic workup for CML includes a complete blood count with differential, peripheral blood smear, bone

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**Table 1. Principal Laboratory Findings**

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient’s Result</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC count</td>
<td>157</td>
<td>3.8-10.6 × 10⁹/L</td>
</tr>
<tr>
<td>Neutrophil count, Abs</td>
<td>24.62</td>
<td>1.8-7.7 × 10⁹/L</td>
</tr>
<tr>
<td>Bands, Abs</td>
<td>13.85</td>
<td>0.0-0.8 × 10⁹/L</td>
</tr>
<tr>
<td>Metamyelocytes, Abs</td>
<td>3.08</td>
<td>0.0 × 10⁹/L</td>
</tr>
<tr>
<td>Myelocytes, Abs</td>
<td>7.7</td>
<td>0.0 × 10⁹/L</td>
</tr>
<tr>
<td>Lymphocyte count, Abs</td>
<td>90.79</td>
<td>1.1-4.0 × 10⁹/L</td>
</tr>
<tr>
<td>Basophil count, Abs</td>
<td>3.08</td>
<td>0.0-0.2 × 10⁹/L</td>
</tr>
<tr>
<td>Monocyte count, Abs</td>
<td>6.16</td>
<td>0.0-0.8 × 10⁹/L</td>
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<tr>
<td>Eosinophil count, Abs</td>
<td>4.62</td>
<td>0.0-0.7 × 10⁹/L</td>
</tr>
<tr>
<td>Nucleated RBCs</td>
<td>2/100 WBC</td>
<td>N/A</td>
</tr>
<tr>
<td>RBC</td>
<td>4.79</td>
<td>4.40-6.00 × 10⁹/L</td>
</tr>
<tr>
<td>HBG</td>
<td>13.5</td>
<td>13.5-17.0 g/dL</td>
</tr>
<tr>
<td>HCT</td>
<td>42.2</td>
<td>41%-53%</td>
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<tr>
<td>MCV</td>
<td>88.2</td>
<td>80-100 FL</td>
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<tr>
<td>Platelet count</td>
<td>390</td>
<td>150-450 × 10⁹/L</td>
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<tr>
<td><strong>Chemistry</strong></td>
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<tr>
<td>Lactate dehydrogenase</td>
<td>371</td>
<td>100-190 U/L</td>
</tr>
<tr>
<td>Uric acid, serum</td>
<td>8</td>
<td>3.5-7.2 mg/dL</td>
</tr>
</tbody>
</table>

Abs, absolute; HBG, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; RBC, red blood cell; WBC, white blood cell.
Images 1A, 1B, 1C, and 1D

A, The bone marrow aspirate smear shows marked granulocytic bulge with basophilia (500× magnification, Wright Stain). B, The decalcified bone biopsy shows a small cluster of lymphocytes identified by red arrow (400× magnification, hematoxylin and eosin stain). C, Conventional karyotype demonstrates the Philadelphia chromosome on chromosome 22 resulting from the t(9;22) identified by the blue arrows. D, FISH demonstrates the BCR-ABL1 fusion gene as indicated by the yellow arrows. 69×52 mm (300×300 DPI)

Image 2

Flow cytometry of bone marrow aspirate. The composite antigen profile of CD19+ and 5+ (left), CD23+ (middle), and lambda restricted (right) lymphocytes are essentially diagnostic of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). 22×8mm (300×300 dpi)
marrow aspiration and biopsy, and cytogenetic analysis of a bone marrow aspirate. Based on findings in the peripheral blood smear, bone marrow cytology, and the presence of the Ph chromosome, a diagnosis of CML can be confirmed. The blood count will have an elevated WBC count (20,000–60,000 cells/μL) with an absolute increase of granulocytic component and left shift with myeloid bulge, normal lymphocytes, and mildly elevated eosinophil and basophil counts.

The peripheral blood smear will show leukocytosis, manifested by presence of left shift, basophilia, eosinophilia, and thrombocytopenia. The bone marrow will have increased myeloid precursors.

Diagnosis of CML is based on an elevated total WBC count with an absolute increase in mature granulocytes, and demonstration of Ph chromosome by conventional karyotype, abnormal BCR/ABL1 fusion gene by FISH, or the presence of BCR/ABL1 mRNA transcript (p210) by quantitative real time reverse transcription polymerase chain reaction (RT-PCR).

The Ph chromosome is a reciprocal translocation between the long arms of chromosomes 9 and 22 [t(9;22) (q34;q11)], resulting in fusion of the oncogene ABL1 on chromosome 9 with the BCR on chromosome 22. This translocation results in the fusion gene BCR/ABL1, which encodes a protein with potent tyrosine kinase activity. This chromosomal abnormality is the hallmark of CML and is found in almost all patients with the disease. The translocation is present throughout the clinical course of CML and will disappear in remission. Conventional karyotype analysis of bone marrow cells identifies the Ph chromosome by looking at individual chromosomes in metaphase. FISH can detect the BCR/ABL1 fusion gene by using labeled probes that are hybridized to chromosomes and detected by fluorochrome. Quantitative real time RT-PCR will identify and amplify the BCR/ABL1 transcript if present.

5. The initial therapy for CML is imatinib mesylate (Gleevec), a tyrosine kinase inhibitor (TKI) that inhibits proliferation and induces apoptosis in cells that express the BCR/ABL1 fusion gene. Patients are monitored for hematologic remission characterized by a normal complete blood count and no symptoms, cytogenetic remission with absence of Ph chromosome positive cells, and molecular remission defined as a 3-log reduction in the BCR/ABL1 fusion gene transcript copy numbers detected by quantitative real time RT-PCR.

The prognosis for CML patients has improved: the current median survival time is 5 or more years and the 5-year survival rate is 57.2%. The prognosis is best if the disease is diagnosed in the chronic phase, and worst if diagnosed in the blast phase. The only proven cure is allogenic bone marrow transplantation.

6. CML and CLL/SLL occurring concomitantly is rare. To our knowledge, this is only the 11th reported case of CLL/SLL with subsequent development of CML. CLL/SLL is the most common leukemia in adults, and comprises 25%-30% of all leukemias. It is estimated that more than 14,990 people (8870 men and 6120 women) were diagnosed with CLL/SLL in 2010. The median age at diagnosis of CLL/SLL is 72 years with an overall 5-year survival of 78.0%. Patients with CLL/SLL may be predisposed to development of a second malignancy due to an impaired immune system or previous chemotherapy. The second malignancy typically occurs several years after the diagnosis of CLL/SLL, with the majority of cases being non-hematologic. In most cases reported in the literature, CLL/SLL precedes development of CML as observed in this case; however, there have been reports of both types of leukemia developing simultaneously and CML developing before CLL/SLL.

7. Current literature addressing management and outcome of concomitant CML and CLL/SLL is limited. While targeted therapy with TKIs such as imatinib and dasatinib is well-established for CML, use of TKIs in CLL/SLL has not been investigated until recently. Studies suggest a potential role for TKIs in the treatment of CLL/SLL. For example, Herman and colleagues propose a role for phosphatidylinositol 3-kinase (PI3K) inhibitor CAL-101 based on demonstrated expression of PI3K-δ isoform in CLL/SLL and its inhibition by CAL-101 in primary CLL/SLL cells in a time and dose dependent fashion. The role of dasatinib, a dual SRC/ABL kinase inhibitor currently used to target imatinib-resistant cases of CML, was investigated in CLL/SLL by Veldurthy and colleagues. The authors found an increased sensitivity for dasatinib, particularly in the subgroup of CLL/SLL cases with unfavorable prognostic indicators such as unmutated IgVh status, CD38 positivity, and ZAP70 expression. In 2010, Serpa and colleagues reported a case of sequential CML and CLL/SLL. The CLL/SLL component partially responded to dasatinib, a second-generation TKI, with reduction in lymph node enlargement, reduction in lymphocyte count, and improvement of neutrophil counts. In summary, the treatment of concomitant CML and CLL/SLL needs...
further investigation; however, novel kinase inhibitors may have a role as demonstrated by the partial respond in symptoms and counts in recent studies.

**Patient Follow-up**

The patient is currently being treated with Gleevec at 400 mg once a day. Hematologic remission was established 6 months later with normalization of peripheral blood smear and 7 months later on bone marrow aspirate with normalized myeloid population (2% myelocyte, 7% bands, and 6% neutrophils). Both the peripheral blood smear and bone marrow demonstrated persistent CLL/SLL. Cytogenetic remission was achieved 7 months later on bone marrow aspirate with conventional karyotype showing a normal male karyotype and on FISH the BCR/ABL1 fusion gene was within the normal limits. The patient achieved molecular remission as confirmed by lack of detection of the BCR/ABL1 mRNA transcript after 6 months, 7 months, and 15 months.

**References**