Educational Case: Chronic Myeloid Leukemia

Britni R. E. Bryant, MD1,2, Juli-Anne Gardner, MD1,2
and Katherine A. Devitt, MD1,2

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.

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Primary Pathology Learning Objective
Objective HWC3.4: Morphology of Acute Versus Chronic Leukemia. Discuss the morphologic appearance of a blast and be able to distinguish acute myeloid leukemia (AML) from chronic myelogenous leukemia.

Competency 2: Organ System Pathology; Topic HWC—Hematopathology—White Cell Disorders; Learning Goal 3: Classification of Leukemia and Lymphomas

Secondary Pathology Learning Objective
Objective SP5.1: Special Studies. Describe the roles of immunohistochemistry, flow cytometry, cytogenetics, and molecular diagnostics in the diagnosis and classification of lymphoma and explain how, with examples, different techniques are most appropriate in diagnosis, staging, and management of disease.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic SP—Surgical Pathology; Learning Goal 5: Classification of Leukemia and Lymphomas

Patient Presentation
A 70-year-old man presented to his primary care physician with 2 months of fatigue and 10-pound weight loss. He noted a general sense of malaise and feeling poor. On physical examination, the clinician was able to palpate the spleen 4 cm below the costal margin (splenomegaly) but noted no palpable lymphadenopathy. Family history was noncontributory.

Diagnostic Findings, Part 1
Routine labs were drawn. Complete blood count (CBC) and differential results are shown in Tables 1 and 2. No imaging was performed.

Questions/Discussion Points, Part 1
What Is Your Interpretation of the Lab Values in Table 1?
The CBC reveals marked leukocytosis (elevated white blood cell [WBC] count) and mild normocytic anemia (decreased hemoglobin, with normal mean corpuscular volume). Platelets (PLTs) are within the normal range.

1 Department of Pathology and Laboratory Medicine, University of Vermont Medical Center, Burlington, VT, USA
2 Larner College of Medicine at the University of Vermont, Burlington, VT, USA

Corresponding Author:
Katherine A. Devitt, Department of Pathology and Laboratory Medicine, University of Vermont Medical Center, 111 Colchester Ave, Burlington, VT 05401, USA.
Email: katherine.devitt@uvmhealth.org

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What Is the Differential of Leukocytosis, and How Does the Complete Blood Count Differential Help Narrow This Down?

Leukocytosis in general is a nonspecific finding that can have a variety of etiologies, ranging from benign to neoplastic conditions, including infection, autoimmune disease, allergy, drug reaction, acute and chronic inflammation, leukemia, and myeloproliferative disorders. The next step is to look at the CBC differential to identify what types of cells are causing the WBC increase, as each type of WBC will be listed as a percentage of the total and in absolute counts. Are mature WBCs (lymphocytes and/or neutrophils) causing the increase or are they immature (blasts, promyelocytes, myelocytes, metamyelocytes)? Lymphocytosis may be caused by viral infection, hypersensitivity, leukemia, or lymphoma. Neutrophilia, on the other hand, may be caused by an acute inflammatory response to infection (usually bacterial), medication, bone marrow stimulation, or myeloproliferative disease. An increase in immature WBCs may be concerning for an underlying neoplasm.

What Entities Should Be Considered in This Patient?

Note that in this case, the patient has absolute neutrophilia, eosinophilia, and basophilia. There is also a "left shift," meaning there is an increase in immature myeloid cells (bands, metamyelocytes, myelocytes). Both of these findings suggest chronic myeloid leukemia (CML), a clonal disease of myeloid cells (cells that are made in the bone marrow), but are not specific. In this age-group, acute leukemia must be considered with a presentation of leukocytosis and anemia. There are myeloid and lymphoid types of both chronic and acute leukemias depending on the lineage of the malignant cells, but in contrast to chronic leukemias, which are characterized by increases in mature cells, acute leukemias are characterized by increases in very immature cells (blasts). Acute leukemias are more aggressive clinically, as the cells proliferate much more rapidly. There are many types of AMLs, but the CBC in AML often shows decreased mature WBCs and increased blasts (very immature WBCs). You would also expect pancytopenia (decrease in all 3 cell lines: mature WBCs, red blood cells, and PLTs) as the neoplastic cells take over the bone marrow. In addition, infectious etiologies may enter the differential here, as infection can present with leukocytosis with a left shift. This is termed a “leukemoid reaction.” There are not strict cutoffs for differentiating between benign and reactive causes; however, WBC counts greater than 100 000/cmm are almost always due to leukemia or myeloproliferative diseases. A WBC count of 50 000 to 100 000/cmm is in the gray zone, as some infections and solid tumors may cause these levels. Even these numbers, however, are not specific, as the patient in our scenario had a relatively low WBC count in comparison.

Diagnostic Findings, Part 2

The abnormal CBC required pathologist review. A peripheral smear was made and is shown in Figure 1.

Questions/Discussion Points, Part 2

How Does Examination of the Peripheral Smear Help With the Differential?

Review of the peripheral smear is essential to both verify the automated CBC differential and assess morphology of the cells. In this case, we can confirm an increase in mature WBCs, with a predominance of neutrophils and their precursors. Compare this to a case of acute leukemia (Figure 2), which shows a predominance of immature cells, or blasts, characterized by increased nuclear:cytoplasmic ratios, immature chromatin, nucleoli, and lack of nuclear segmentation. Patients with acute leukemia often present with leukocytosis, and it is essential to be able to distinguish blasts from mature WBCs.
What Ancillary Studies May Be Helpful?

Flow cytometry is always a good thought with hematologic processes. Flow cytometry analyzes individual cells for the expression of multiple antigens and physical characteristics through the use of fluorescently tagged antibodies. It allows for characterization of hematopoietic cells within a sample. It is limited, however, in its utility to diagnose myeloproliferative disorders such as CML, generally showing the nonspecific finding of increased myeloid cells, though may be helpful in classifying blasts when present. For other cases of leukocytosis, however, this test is essential and is crucial for classifying cases of acute leukemia and lymphoproliferative disorders. In our case, cytogenetics and molecular testing are essential ancillary studies that will provide the diagnosis. Cytogenetic analysis allows for visualization of a patient’s chromosomes and is most useful for identifying numerical and large structural abnormalities. Molecular tests are able to identify even smaller changes.

Diagnostic Findings, Part 3

Cytogenetic analysis was performed. The karyotype is provided in Figure 3, and fluorescence in situ hybridization (FISH) results are provided in Figure 4.

Questions/Discussion Points, Part 3

What Is Your Interpretation of This Karyotype?

The first thing to notice is that there is an appropriate number of chromosomes (46) and that the patient is male (XY). Each chromosome pair should look fairly similar. Notice the white arrows referring to abnormal chromosomes 9 and 22. The abnormal chromosome 9 has a piece of the long arm of chromosome 22 on it, and the abnormal chromosome 22 looks shorter than normal as the piece of DNA it received from chromosome 9 is smaller than the one it gave away. This apparently balanced translocation between chromosomes 9 and 22 is classic for CML and is seen in the vast majority of cases (up to 95%). It forms what is known as the Philadelphia chromosome, resulting in fusion of the BCR gene on chromosome 22 and ABL1 gene on chromosome 9 and giving rise to the BCR-ABL1 fusion protein. This translocation can be identified on conventional karyotype or by FISH testing (Figure 4).

What Is Your Interpretation of the Fluorescence In Situ Hybridization Results?

Interpreting FISH may seem intimidating. The basic concept is that we can use very specific fluorescent probes that will bind to known DNA regions in the nucleus and allow us to see where they are located. This case is an example of interphase FISH, so the nucleus is not actively dividing and the chromosomes are stretched out. This is also an example of dual fusion FISH, which allows us to see whether an abnormal gene fusion has occurred. In this case, the ABL1 gene on chromosome 9 has been tagged with a red signal and the BCR gene on chromosome 22 has been tagged with green. In a normal cell, you would see 2 red signals and 2 green signals, and they would not be next to each other as they are on different chromosomes. Here, though, you can see that there is 1 normal red signal representing the normal chromosome 9, 1 normal green signal representing the normal chromosome 22, and 2 yellow signals (yellow occurs when red and green are very close together, or fused).
representing the abnormal chromosome 9 and 22 that have exchanged DNA, that is, there are 2 fusion signals. This is a classic example of the pattern in CML.

How Is This Disease Treated?
Chronic myeloid leukemia can often be treated effectively for many years with the use of tyrosine kinase inhibitors (TKIs), which target the activated BCR-ABL1 fusion protein. The BCR-ABL1 protein can be monitored over time in a patient’s blood. With consistent monitoring, most patients will now live a normal life span. Some cases, however, are resistant to TKIs, and these patients have a worse prognosis.

What Is the Natural Clinical Course of This Disease?
There are 3 phases of CML. Most patients present in chronic phase (CP), which is relatively indolent, meaning that it is not aggressive and patients often remain in CP for a long time as they are treated. If the disease is left untreated, it will progress, generally through an accelerated phase (AP), and ending in blast phase (BP). As this occurs, the neoplastic cells gain more mutations and become less and less mature. There are certain criteria to identify patients in AP, evidenced by worsening CBC counts, physical examination, and cytogenetic progression. Blast phase occurs when the criteria for acute leukemia are met, with ≥20% blasts in the blood or bone marrow or the presence of a mass of blasts elsewhere in the
Interestingly, while myeloid blasts comprise the majority of BP cases, it is not uncommon to find the blasts are of lymphoid lineage.4,5

Teaching Points
- Leukocytosis is a nonspecific lab finding with a variety of etiologies. Identifying the type of cell causing the WBC increase is essential, both by analyzing the CBC differential and examination of the peripheral smear.
- Leukemoid reactions present with marked neutrophilia and left shift and can mimic neoplastic conditions.
- The CBC findings of leukocytosis with neutrophilia, basophilia, and left shift are classic for CML.
- Acute leukemia is an aggressive malignancy that often presents with increased blasts and decreased mature WBCs, red blood cells, and PLTs. It can be further classified as myeloid or lymphoid, like chronic leukemias. Morphologically, blasts show high nucleus:cytoplasm ratios, round nuclei, smooth fine chromatin, and prominent nucleoli.
- Chronic myeloid leukemia has a characteristic translocation t(9;22) resulting in BCR/ABL1 gene fusion and the BCR-ABL1 fusion protein which is therapeutically targeted by TKIs.
- Most cases of CML are diagnosed in CP and, if left untreated, naturally progress through AP and ending in BP (acute leukemia).
- Flow cytometry, cytogenetics, and molecular analysis are all useful ancillary tests in the diagnosis and monitoring of hematologic malignancies.

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ORCID iD
Katherine A. Devitt https://orcid.org/0000-0001-8816-9203

References
1. Knollmann-Ritschel BEC, Regula DP, Borowitz MJ, Conran R, Prystowsky MB. Pathology competencies for medical education and educational cases. Acad Pathol. 2017:4. doi:10.1177/2374289517715040.
2. Riley LK, Rupert J. Evaluation of patients with leukocytosis. Am Fam Physician. 2015;92:1004-1011.
3. Cherian S, Wood B. Flow Cytometry in Evaluation of Hematopoietic Neoplasms: A Case-Based Approach. Northfield, IL: CAP Press; 2012:99-101.
4. Vardiman JW, Melo JV, Baccarani M, Radich JP, Kvasnicka HM. Chronic myeloid leukemia, BCR-ABL1-positive. In: Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Rev 4th ed. Lyon, France: International Agency for Research of Cancer; 2017:30-36.
5. Vardiman JW. Myeloproliferative neoplasms. In: Jaffe ES, Arber DA, Campo E, et al, eds. Hematopathology. 2nd ed. Philadelphia, PA: Elsevier; 2017:847-881.