

## Pathologic Quiz Case

### A 29-Year-Old Woman With Thrombocytosis

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A 29-year-old woman, gravida 1, para 0, at 41 weeks of gestation underwent a cesarean section because of failure to progress. On admission, a complete blood count showed a white blood cell (WBC) count of  $13.4 \times 10^3/\mu\text{L}$ ; hemoglobin, 11.3 g/dL; red blood cell count,  $3.74 \times 10^6/\mu\text{L}$ ; and platelet count,  $321 \times 10^3/\mu\text{L}$ . She delivered a healthy female infant and was discharged. The woman's past medical history was remarkable for Hodgkin lymphoma, nodular sclerosing type, which was diagnosed at the age of 22 years and treated with mantle radiation. Subsequent to therapy, she developed hypothyroidism and stomatitis. At a follow-up visit 1 month after delivery, she had a WBC count of  $9.8 \times 10^3/\mu\text{L}$ ; hemoglobin, 13.0 g/dL; platelets,  $703\,000 \times 10^3/\mu\text{L}$ ; with 55% neutrophils, 30% lymphocytes, 5% monocytes, 7% eosinophils, and 3% basophils. Three months later, a bone marrow biopsy was performed. At that time, her WBC count was  $19.3 \times 10^3/\mu\text{L}$ ; hemoglobin, 12.7 g/dL; platelets,  $870 \times 10^3/\mu\text{L}$ ; with 63% neutrophils, 1% bands, 27% lymphocytes, 4% monocytes, 1% eosinophils, and 4% basophils (Figure 1). At the time of bone marrow biopsy, there was no fever, sweating, weight loss, diarrhea, lymphadenopathy, or hepatosplenomegaly. The aspirate smear was very cellular and noteworthy for displaying a myeloid-erythroid ratio of approximately 10:1, eosinophilia, and small megakaryocytes with hypolobated nuclei (Figure 2). The core biopsy was approximately 85% cellular; the findings morphologically recapitulated those of the aspirate smear.

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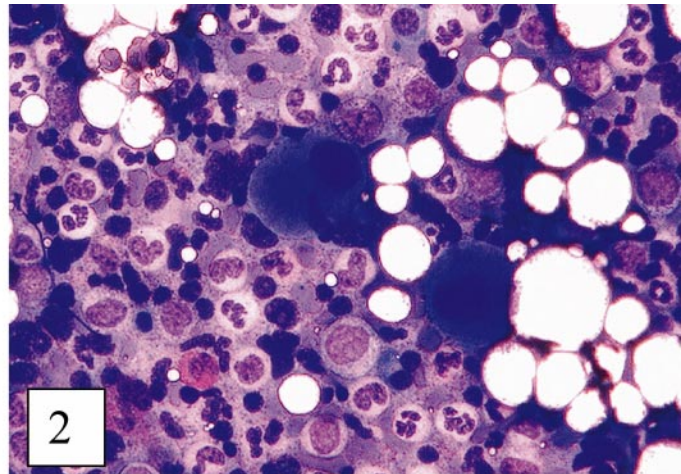
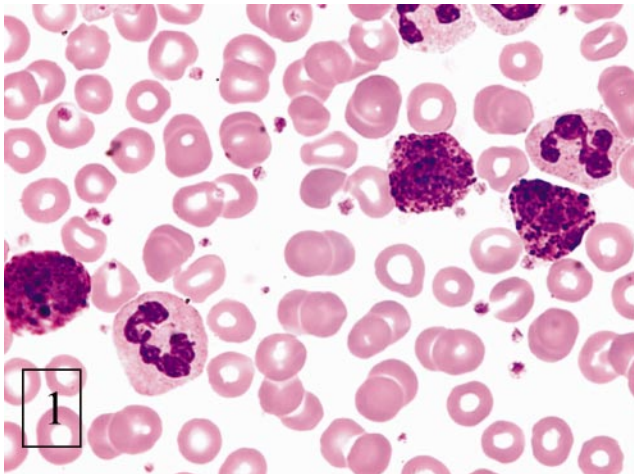
**What is your diagnosis?**

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## Pathologic Diagnosis: Chronic Myelogenous Leukemia

Cytogenetic studies revealed 46,XX,t(9;22)(q34;q11.2), confirming the morphologic impression. The usual presentation of chronic myelogenous leukemia (CML) consists of marked peripheral leukocytosis with numerous granulocytic cells mimicking a bone marrow aspirate smear. The mean WBC count on presentation is 20 to 500  $\times 10^3/\mu\text{L}$ , with a mean of between 134 and 225  $\times 10^3/\mu\text{L}$ . Platelet counts range from a mean of 399 to 484  $\times 10^3/\mu\text{L}$  and can increase to more than 1000  $\times 10^3/\mu\text{L}$ . Thrombocytopenia is uncommon.<sup>1</sup>

This case is unusual because of the relatively low numbers of circulating WBCs, but it shows other features characteristic of CML, the most noteworthy being basophilia and the presence of clustered, small, hypolobated megakaryocytes.<sup>1,2</sup> In the other common myeloproliferative disorders, essential thrombocythemia, polycythemia vera, and idiopathic myelofibrosis, megakaryocytes are large. Cytogenetic studies and sometimes fluorescence in situ hybridization are necessary for characterization of the myeloproliferative disorders.<sup>2</sup>

Chronic myelogenous leukemia was found to be associated with the 9;22 translocation in 1970. Its presence is considered sine quo non for the diagnosis, and in cases in which conventional cytogenetic studies are negative, fluorescence in situ hybridization will reveal a masked translocation. The 9;22 translocation has been identified as corresponding to a fusion gene, *BCR/ABL*, which produces an abnormal tyrosine kinase. The breakpoint cluster region (*BCR*) is on chromosome 22 and *ABL*, named after the Abelson murine leukemia virus, is on chromosome 9.<sup>3</sup>

The type of fusion protein is believed to impact the clinical course of the disease. Three main variants of the *BCR/ABL* gene have been described, with different breakpoints in the *BCR* gene and splicing patterns. Major *BCR/ABL* that is translated into the b2-a2p210*BCR-ABL* or b3-a2p210*BCR-ABL*, is encountered in 99% of CML cases. The second fusion minor *BCR/ABL* e1-a2p190*BCR/ABL* is encountered rarely in CML. A third fusion protein  $\mu$ -*BCR* c3/a2 (e19/a2)p230 is found in CML cases with increased platelets. The  $\mu$ -*BCR* breakpoint is downstream from the major-*BCR* and minor-*BCR* regions and permits the inclusion of additional *BCR* sequences in the fusion gene, encoding for a larger p230 protein product.<sup>4,5</sup> While analysis of the *BCR* was not performed in our case, the  $\mu$ -*BCR* breakpoint appears quite likely.

Clinically, CML occurs in 3 phases: chronic phase, accelerated phase, and blast phase. Most patients present in

the chronic phase and progress to other phases, but different presentations may occur.<sup>1-3</sup>

Diagnosis of the chronic phase can often be inferred from the absolute and relative WBC counts with marked leukocytosis, a spectrum of maturing granulocytes with numerous myelocytes (myelocyte bulge), and absolute basophilia. The neutrophil alkaline phosphatase score is low. At diagnosis, circulating blasts are uncommon. Platelets are usually increased in number, often to more than 1000  $\times 10^3/\mu\text{L}$ . Mild anemia is usually present. The bone marrow is characteristically hypercellular, primarily due to myeloid hyperplasia. Myeloid blasts make up less than 5% of marrow cells. The myeloid-erythroid ratio is usually 10:1 or higher. The number of megakaryocytes is initially normal, but usually increases as the disease progresses and may occur scattered throughout the bone marrow or in small groups. The megakaryocytes tend to be smaller than normal, in contrast to the abnormally large megakaryocytes in other chronic myeloproliferative disorders. Reticulin fibrosis may be present in 50% of cases. Increased fibrosis has been associated with shortened survival.

Traditionally, conventional chemotherapy was the method of treatment for CML. More recently, interferon- $\alpha$  and allogeneic bone marrow or stem cell transplants have improved survival and cured some patients. Imatinib mesylate, a specific inhibitor of the *BCR/ABL* tyrosine kinase, recently has been demonstrated to be very effective in the treatment of CML in chronic phase and is associated with high rates of hematologic and cytogenetic remissions.<sup>6,7</sup> Resistance to therapy can develop, however, and transformation to blast crisis may occur, particularly in patients without a cytogenetic response.<sup>3,6,7</sup>

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