

Case Report 4

Neutrophilic-chronic myeloid leukemia: A case report

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Abstract

Neutrophilic-chronic myelogenous leukemia (CML-N) is a rare chronic myelogenous leukemia (CML) variant characterized by *BCR-ABL1* positive chronic neutrophilia. It has a BCR breakpoint on chromosome 22 between exons 17 and 20 in a region designated as micro-BCR. It is thought to have a more benign course than classical CML. This case report describes a 41-year-old Saudi woman diagnosed with CML-N. The peripheral blood and bone marrow picture for her were dominated by segmented neutrophils and fluorescent in situ hybridization was positive for *BCR/ABL* fusion of t(9;22). Our patient eventually required a stem cell transplant because of imatinib intolerance and bone marrow failure believed to be induced by nilotinib.

Key words

Neutrophilic-chronic myeloid leukemia (CML-N); Chronic myeloid leukemia (CML); Neutrophilia

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Introduction

Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm (MPN) characterized by the presence of the *BCR-ABL1* fusion gene located on the Philadelphia (Ph) chromosome. ⁽¹⁾ Ph chromosome is pathognomonic for CML and never occurs in reactive neutrophilia or chronic neutrophilic leukemia. ^(1, 2) The CML rare variant, neutrophilic-CML (CML-N), is associated with persistent neutrophilia in addition to a distinctive molecular defect on the Ph chromosome, resulting in a novel *BCR/ABL1* protein. ⁽²⁾ CML-N was thought to have a more benign course than classic CML; however, the majority of cases suggest otherwise. ⁽³⁾ The aims of this report are to detail the clinical case of a 41-year-old woman with initial presentation of neutrophilia in order to demonstrate the laboratory and clinical criteria utilized to establish a diagnosis of CML-N.

Case Report

A 41-year-old Saudi woman was diagnosed with leukocytosis in a routine complete blood count (CBC) April 2013. She had no chronic diseases or relevant family history. She was clinically asymptomatic and maintained normal vital signs. The patient had pallor and splenic enlargement 4 cm below the left costal margin.

CBC showed the following results: white blood cell, 81.8×10^9 cells/L; red blood cell, 3.24×10^{12} cells/L; hemoglobin, 7.68 g/L; and platelets, 244×10^9 cells/L. Peripheral smear confirmed the marked leukocytosis with significant neutrophilia (91%), with increased granulation in some cells. Basophils were prominent (7%), and there were no circulating blasts. Bone marrow (BM) appeared hypercellular with an expansion of the granulopoietic population and marked neutrophilic proliferation (**Figure 1**).

Conventional cytogenetic study for the patients revealed $46, XX, t(9;22)(q34;q11.2)[2]$, and fluorescent in situ hybridization (FISH) was positive for *BCR/ABL* fusion of $t(9;22)$ on all interphase nuclei (**Figure 2**). The patient was diagnosed with chronic CML-N; she was started on imatinib, which was switched to nilotinib 300 mg po bid owing to imatinib intolerance. One month later, she developed thrombocytopenia (65×10^9 cells/L), and the nilotinib dose was reduced to 200 mg po bid.

Cells counts continued to decrease, and she developed pancytopenia. Repeated BM biopsy revealed severe hypocellularity (5% cellularity), consistent with BM failure (**Figure 3**). There was no morphological sign of myelodysplastic syndrome, indicating that it was most likely drug induced (when the patient maintained on nilotinib for 2 month). A chromosome breakage study ruled out Fanconi anemia, and paroxysmal nocturnal hemoglobinuria was negative according to flow cytometry.

The patient received peripheral blood allogeneic stem cell transplantation (SCT) from her ABO-compatible, fully matched brother. She tolerated the procedure well, and engraftment was achieved day +15 post-SCT.

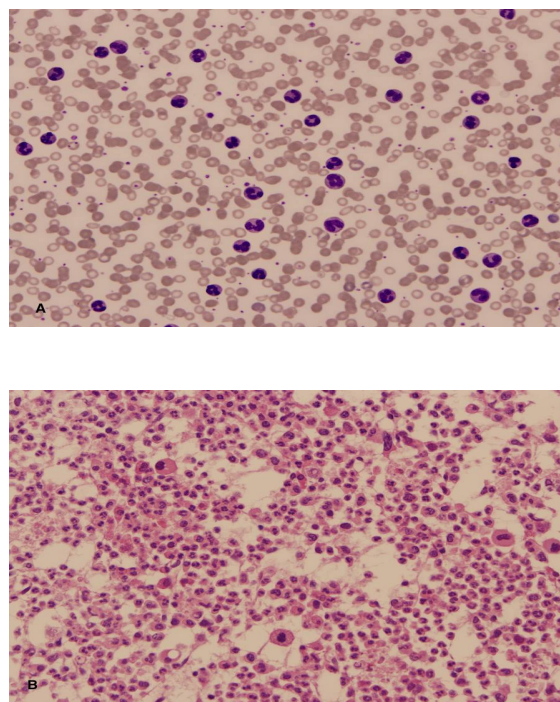


Figure 1: **A**, peripheral blood smear confirmed the marked leukocytosis with neutrophilia (May-Grünwald-Giemsa stain x50). **B**, bone marrow appeared hypercellular with mature granulocytic hyperplasia (H&E stain x50).

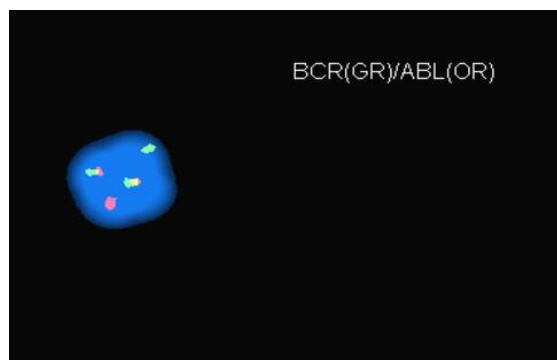


Figure 2: FISH study with dual color and dual fusion translocation probe on interphase preparation from the patient's BM cell. The BCR and ABL probe are labeled with SpectrumGreen and SpectrumOrange respectively. In our patient there is one green (normal 22q11.2), one orange (normal 9q34) and two green/orange (yellow) signals, representing derivative 22q11.2 and 9q34, respectively, are detected.

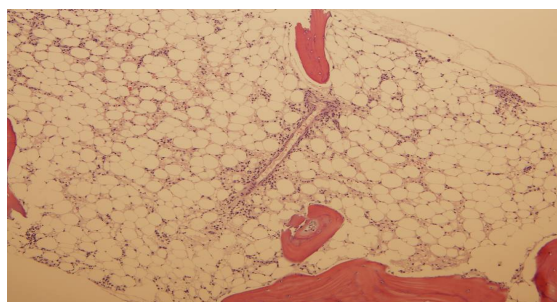


Figure 3: Bone marrow biopsy appeared markedly hypocellular after 2 month of nilotinib (H&E stain x10).

Discussion

CML shows granulocytic hyperplasia with peaks in the percentage of myelocytes and neutrophils, but in CML-N, the picture is dominated by segmented neutrophils. Chronic neutrophilia with *BCR-ABL1* positivity should be considered a CML variant, not chronic neutrophilic leukemia. ^(1, 4, 5) Such patients (CML-N) are thought to have a benign clinical course, showing lower white blood cell counts,

minimal basophilia, milder anemia, and less prominent or absent splenomegaly. In the peripheral blood, most circulating myeloid cells are mature granulocytes, and blastic transformation occurs rarely. ⁽³⁾

CML-N has a BCR breakpoint on chromosome 22 occurring downstream from M-BCR between exons 17 and 20 in a region designated as micro-BCR, and a larger fusion protein, p230, is encoded. ^(1, 6) When present, translocation can be detected using FISH analysis and subtyped by **Reverse Transcription-Polymerase Chain Reaction (RT-PCR)**. In our case, the FISH probe is a pan-probe that detects the three known breakpoints for the Ph chromosome, one of which is micro-BCR. RT-PCR subtyping measures the quantity of the two types of BCR-ABL fusion transcripts, p210 and p190, which are seen in CML and acute lymphoblastic leukemia, respectively, with the Ph chromosome. ^(7, 1)

Although the presence of the fusion transcript for p230 could not be confirmed here, positive FISH analysis for *BCR/ABL* fusion in t(9;22) with hypercellular BM dominated by neutrophilia was sufficient for CML-N diagnosis.

Verstovsek et al. reviewed 23 CML-N patients and suggested that chromosomal abnormalities and Ph chromosome appear to be associated with a more malignant disease course. However, presence of Ph chromosome as a single abnormality does not confer an indolent course. ⁽³⁾

Even without additional chromosomal abnormalities, this rare variant of CML may show an unfavorable clinical course with marked anemia, splenomegaly, and intolerance to imatinib and nilotinib, leaving SCT as the last resort.

Conflict of interest: None declared.

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