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### BCR-ABL Transcript With an e19a2 (c3a2) Junction in Classical Chronic Myeloid Leukemia

To the Editor:

In a recent issue of *Blood*, Pane et al<sup>1</sup> reported three cases of neutrophilic-chronic myeloid leukemia (CML-N) that exhibited a t(9;22) chromosomal translocation. In all cases, a rare type of BCR-ABL rearrangement with a breakpoint between exons e19 (c3) and e20 (c4) of the BCR gene (designated the  $\mu$ -bcr region) was documented. The same group first described such a breakpoint in 1990<sup>2</sup> and, interestingly, now believe that their initial two cases would be better reclassified as CML-N, rather than as typical or classical CML.<sup>1</sup> They speculate that the inclusion of additional BCR sequences in the BCR-ABL fusion gene, coding for a large p230<sup>BCR-ABL</sup> product, enables more of the leukemic granulocytes to proceed to complete maturity. A further patient reported by Wada et al<sup>3</sup> was similarly described as atypical Ph<sup>+</sup> CML. In contrast to the above-mentioned reports, we present a case with the e19a2 BCR-ABL transcript that exhibits all the features of typical or classical CML.

A 70-year-old man presented with a history of malaise and weight loss. His hemoglobin level was 9.5 g/dL, white blood cell count  $68.3 \times 10^9/L$ , neutrophils 44%, lymphocytes 5%, monocytes 2%, eosinophils 5%, basophils 5%, metamyelocytes 24%, myelocytes 7%, promyeloblasts 2%, myeloblasts 6%, and platelet count  $373 \times 10^9/L$  and he had a leukocyte alkaline phosphatase (LAP) score of 11 (normal range, 20 to 110). The spleen was palpable 15 cm from the costal border and there was 2 cm hepatomegaly. Trepine biopsy showed a marked increase in bone marrow cellularity, eosinophilia, megakaryocytes with some mononuclear forms, and an increased reticulin (grade 3). Cytogenetic analysis of 20 bone marrow metaphases, using G-banding, showed 45,X-Y, t(9;22)(q34;q11) in all cells. BCR-ABL mRNA was analyzed by multiplex polymerase chain reaction (PCR),<sup>4</sup> using four primers to generate PCR products from BCR-ABL and normal BCR gene transcripts. This resulted in a band of approximately 900 bp, in addition to the 808-bp band representing the BCR transcript. Using two of the multiplex primers (B2B, 5' ACAGAATTCCGCTGACCATCAATAAG 3'; and CA3, 5' TGTGACTGGCGTGATGTAGTTGCTTGG 3'), the 900-bp product was still generated, indicating that the additional sequence was due to exons downstream of e14(b3). The product was sequenced on a PE Applied Biosystems 373 automated sequencer (Applied Biosystems, Foster City, CA) and shown to represent an in-frame BCR-ABL e19a2 transcript.<sup>2,3</sup>

CML-N, also known in the literature as chronic neutrophilic leukemia, is characterized by a more benign course when compared with classical CML,<sup>1,5</sup> with a lower white blood cell count with minimal basophilia, a milder anemia, less prominent splenomegaly, and a normal LAP score. In contrast, our case was typical of CML, with a significant basophilia, a relatively high proportion of circulating immature granulocytes, a low LAP score, and a marked splenomegaly. BCR-ABL transcripts with the e19a2 junction, therefore, are not restricted to atypical cases but may occur in classical CML.

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