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LETTER TO THE EDITOR

Coexistence of t(5;17)/NPM1-RARA and t(9;22)/BCR-ABL1 in chronic myeloid leukemia at initial diagnosis

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Dear Editor,

Additional chromosomal abnormalities (ACAs) occurs in < 10% of patients with newly diagnosed chronic myeloid leukemia (CML) in chronic phase (CP) [1, 2]. The most common ACAs are unbalanced chromosomal abnormalities, including +Ph, +8, i(17)(q10), and +19 [1, 3]. These changes are considered "major route" ACAs, whereas other infrequent aberrations are designated as "minor route" ACAs [1]. Several recurrent chromosomal rearrangements typically occurring in de novo acute myeloid leukemia (AML), such as t(8;21)(q22,q22), t(15;17)(q22;q21), and inv(16)(p13q22), have been infrequently observed as ACAs of CML (mainly the blast phase [CML-BP]) [4–8]. We here present a case diagnosed with CML-CP whose leukemia clone harboring both t(9;22)/BCR-ABL1 and t(5;17)/NPM1-RARA.

A 52-year-old man presented with a 2-month history of upper limb numbness. Mild splenomegaly was observed on physical examination. Laboratory tests showed leukocytosis (white blood cells, 66.27×10^9/L), anemia (hemoglobin, 93 g/L), and thrombocytopenia (platelets, 71×10^9/L). A peripheral blood smear demonstrated all stages of neutrophilic maturation, with 1% myeloblasts, 5% promyelocytes, 25% myelocytes, 10% metamyelocytes, 2% eosinophils, and 4% basophils. Bone marrow (BM) showed myeloid hyperplasia with markedly increased immature granulocytes (1.5% myeloblasts, 4% promyelocytes, 35% myelocytes, 17.5% metamyelocytes, and 2% eosinophils), confirming the diagnosis of CML. However, real-time quantitative reverse transcription PCR (RT-qPCR) revealed a p210 BCR-ABL1 transcript (7271 BCR-ABL1 copies /10000 ABL1 copies) and a NPM1-RARA transcript (1947 NPM1-RARA copies /10000 ABL1 copies). R-banding karyotype analysis showed 46,XY,t(9;22)(q34;q11) [7]/46,idem,t(5;17)(q32;q21) [3] (Fig. 1a). Fluorescence in situ hybridization (FISH) analysis also confirmed RARA rearrangement and BCR-ABL1 gene rearrangement (Fig. 1b, c). A diagnosis of CML-CP was rendered. The patient was treated with imatinib (400 mg/day). After 3 months of treatment, the patient achieved CCyR (complete cytogenetic response). The BCR-ABL1/ABL1 International Scale (IS) was 0.43% and NPM1-RARA decreased to 10 copies/10,000 ABL1 copies. At the 6-month evaluation, he achieved MMR (major molecular response) and NPM1-RARA was undetected by RT-qPCR. At the last evaluation, 15 months since imatinib commenced, loss of MMR occurred and BCR-ABL1/ABL1 IS increased to 1.87%. NPM1-RARA was still undetected and BM evaluation was hematologic complete remission. Then, the patient was lost to follow-up.

Reciprocal rearrangements involving RARA are the major cause of APL (acute promyelocytic leukemia) [9]. RARA rearrangements as ACAs of CML are extremely rare. t(15;17)/PML-RARA have been observed as secondary cytogenetic changes in CML [5–7]. t(5;17)/NPM1-RARA is associated with a rare APL variant and has never been reported as an ACA of CML.

Promyelocytic transformation of CML occurred when t(15;17)/PML-RARA appeared together with t(9;22)/BCR-ABL1. While, our patient harboring both t(9;22)/BCR-ABL1 and t(5;17)/NPM1-RARA transcripts was still at the stage of chronic phase. He treated with standard dose of imatinib and achieved optimal cytogenetic and molecular responses. Imatinib rapid eradicated CML cells with BCR-ABL1 and NPM1-RARA transcripts. In several CML patients

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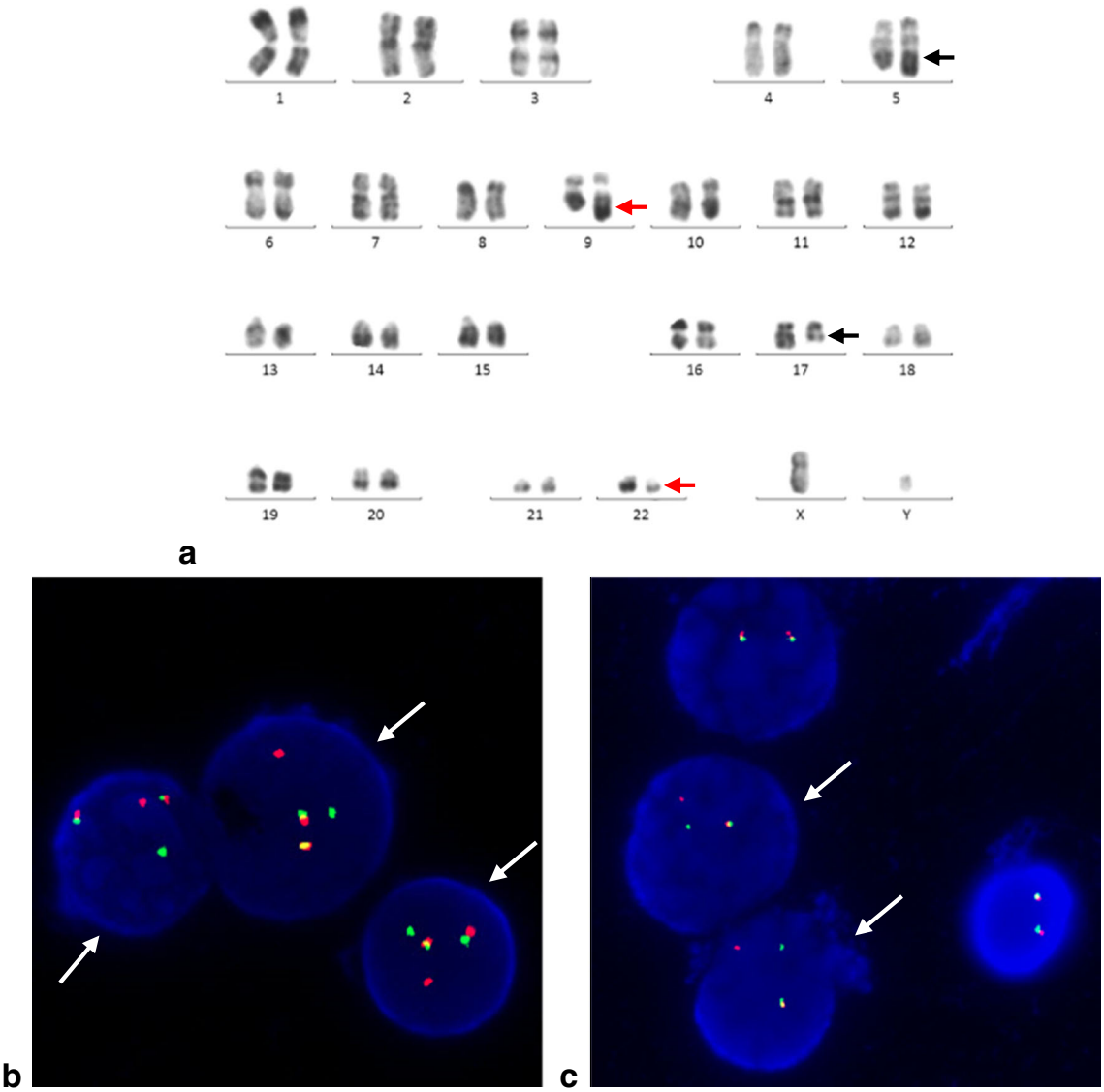

Fig. 1 **a** R-band karyotyping showed 46,XY, t(5;17)(q32;q21), t(9;22)(q34;q11). **b** FISH analysis (Vysis LSI BCR/ABL1 Dual Color, Dual Fusion Translocation Probe) showed two fusion signals (yellow) and separate red and green signals, indicating that only one allele each of the BCR gene and the ABL1 gene were disrupted and translocated to each other (white arrow). **c** FISH analysis (Vysis LSI RARA Dual Color, Break Apart Rearrangement Probe) showed one yellow signal and separate red and green signals, indicating that one allele of the RARA gene was disrupted (white arrow)

[5–7], promyelocytic blast crisis occurred during imatinib treatment. Imatinib-resistant/intolerant was existent in these patients. Concurrent treatment of TKIs and ATRA was still a good choice to achieve complete remission.

Compared with the current case, CML patients with promyelocytic crisis always had inferior outcomes and died within a relatively short time after diagnosis, similar to the overall survival in CML-BP [5]. The detection of ACAs have been associated with inferior outcomes in accelerate phase (AP) and BP [10, 11]. While several studies showed the presence of ACA at diagnosis did not confer worse prognosis for patients with CML treated with TKI [1, 12]. t(15;17)/PML-RARA as an ACA of CML always emerged in promyelocytic blast crisis during the course of therapy. This may explain CML patients with ACA of t(15;17)/PML-RARA had inferior outcomes but our patient had not.

This is the first CML case of coexistence of t(9;22)/BCR-ABL1 and t(5;17)/NPM1-RARA. The case indicated that imatinib is still the best choice for treatment of CML with concurrence of t(9;22)(q34;q11)/BCR-ABL1 and t(5;17)(q32;q21)/NPM1-RARA at the time of diagnosis.

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Compliance with ethical standards

Informed consent Informed consent was obtained from the patient described.

Conflict of interest The authors declare that they have no conflict of interest.

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