CORRESPONDENCE

De Novo Philadelphia Chromosome (*BCR/ABL1*) Positive Myelodysplastic Syndrome: Is it a Distinct Molecular and Clinical Entity?

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To the Editor,

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders characterized by dysplastic changes of bone marrow and blood cells, peripheral blood cytopenias, and increased risk for transformation to secondary leukemia. A numerous acquired somatic mutations involved in epigenetic regulation, RNA splicing, DNA damage response, transcriptional regulation and signal transduction such as *SF3B1*, *TET2*, *RUNX1*, *ASXL1*, *SRSF2*, *TP53*, *U2AF1*, *NRAS/KRAS*, *DNMT3A*, *ZRSR2* and *EZH2*, *ZNF554*, *ZNF557*, *GLTSCR1*, *GLTCCR2* etc. have been already detected in the patients with MDS [1–3]. Copy number alterations (mostly of them amplifications and deletions) of all parts of chromosome 5, 7, 8 and 2, Trisomy 8, Monosomies 5, 7 and 20 as well as the loss of the Y chromosome contribute to MDS pathophysiology and are among the most common cytogenetic abnormalities observed in MDS [1]. However, MDS with Philadelphia chromosome (Ph) positivity is reported to be extremely rare and features *BCR/ABL1* rearrangements that produce p210 fusion protein in the majority of cases [2]. We would like to draw attention to the case of a female patient with de novo diagnosed MDS with *BCR/ABL1* fusion gene that produce p190 fusion protein.

A 68-year-old woman originally presented with persistent microcytic anemia (hemoglobin 6.1 g/L), granulocytopenia (3.2, range 4.5–11 × 10⁹/L) and thrombocytopenia

(98, range 150–350 × 10⁹/L) two weeks before hospital admission. She had fatigue and pal skin without any clinical signs of bleeding. Consequently, she received two blood transfusions and was clinically stable.

Bone marrow biopsy showed hypercellularity (70%) with trilineage dyspoiesis, numerous ring sideroblasts (75/100 nucleated erythroblasts), absence of fibrosis (reticulin stain: 0 points according to the Bauermeister Scale), all consistent with a diagnosis of MDS with multilineage dysplasia (MDS-RS-MLD according to WHO classification) (Fig. 1a, b).

Cytogenetically, a total of 23 metaphases were analyzed from the bone marrow cultures. 13 out of 23 cells showed a normal female chromosome set (46, XX) while 7 metaphases showed a derivative chromosome 11, which had deposited additional material from chromosome 14 on the long arm. The analysis also showed a derivative chromosome consisting of the short arms of a chromosome 16 and the short arm of a chromosome 19, resulting in a monosomy for the long arm of chromosomes 16 and a trisomy for the short arm of chromosome 19. Moreover, using FISH analysis on interphase nuclei, we have found a reciprocal translocation between the long arm of a chromosome 9 and the long arm of a chromosome 22 which leads to a *BCR/ABL1* rearrangement at the molecular level (Fig. 1c). So, there were two cytogenetically independent clones: (a) small *BCR/ABL1* positive clone, and (b) the clone with the derivative chromosome 11 which could be probably assigned to the MDS. Additionally, the two-color FISH analysis was performed with a *BCR/ABL1* probe. The total of 500 interphase nuclei were evaluated, 496 have showed a normal signal constellation, whereas 4 nuclei have had a signal constellation typical for a low *BCR/ABL1* rearrangement (%*BCR-ABL1*/*ABL1* = 0.243). Consecutively, the RNA

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Fig. 1 The laboratory features. The bone marrow aspirate revealed megaloblastoid erythroid precursors with numerous ringed sideroblasts. Storage iron was present. The bone marrow biopsy was hypercellular (ca. 70% cellularity) due to hyperplasia. Blasts were not

increased. All features were consistent with the diagnosis of MDS according to WHO criteria (**a, b**, Giemsa stain, original magnification $\times 400$). A metaphase cell showing positivity for the *BCR-ABL1* rearrangement using FISH (**c**)

was isolated. After reverse transcription, a *BCR/ABL1* fusion transcript of the type m-bcr (e1a2 corresponding to p190) was detected. Furthermore, the two-color FISH analysis was carried out with probes which mark the genes *ZNF554* and *ZNF557* (19p13) and the genes *GLTSCR1* and *GLTSCR2* (19p13). Corresponding to trisomy 19p, 4 of the 200 analyzed interphase nuclei had three signals for the genes on the short arm of chromosome 19. Corresponding to the partial trisomy 14q, 7 out of 100 analyzed interphase nuclei showed three signals for the IGH locus localized on the long arm of chromosome 14 in band 14q32. Unfortunately, three weeks after the diagnosis, patient developed a septic condition (leukocytes 4.2, range $4.5\text{--}11 \times 10^9/\text{L}$; C-reactive protein 350, range 0–5 mg/L; procalcitonine 4.5, range 0–5 $\mu\text{g/L}$) and died as a result of multiple organ failure.

In 1960, Nowell and Hungerford first reported the discovery of Ph chromosome, corresponding to the reciprocal translocation between chromosome 9 and 22, t(9; 22)(q34; q11) [3]. The final result of this translocation is the *BCR/ABL1* chimeric gene which is in 95% of cases the cytogenetic hallmark of chronic myelogenous leukemia (CML), but is also found in acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML) with frequency of 0.5–3%. As already pointed out, MDS with Ph chromosome is reported to be extremely rare and the significance of this anomaly is unknown [2]. In the rare instances of patients with Ph chromosome + MDS controversy exists regarding whether these patients showed true acute leukemia or CML in blast crisis. The current literature does not provide convincing results and no standardized treatment for *BCR-ABL1* + MDS or AML exists. Drummond et al. reported a case of a female patient who demonstrated a complete cytogenetic response to imatinib 600 mg/day within 3 months and complete molecular remission after

14 months [4]. Keung et al. reported a patient treated with imatinib 400 mg/day and cytopenia worsened. The disease progressed to AML [5]. Considering the small number of cases, a randomized trial testing different treatment regimens can hardly ever be expected so that the distinction between *BCR-ABL1* + MDS or AML and CML in blast crisis remains a therapeutic enigma.

BCR-ABL1 + MDS could be definitely classified as a distinct molecular and clinical entity. However, the significance of *BCR-ABL1* translocation in patients with MDS is still poorly understood and only about 40 cases are documented in the literature from which less than 20 belonging to de novo category. Overall analysis of these cases has pointed toward a poor prognosis or aggressive disease course [2, 4, 5]. The presence of *BCR-ABL1* translocation in MDS patients could suggest a stronger proliferation in the bone marrow because of increased tyrosine kinase activity but further clinical studies are needed to confirm this prediction as well as studies that include the molecular characterization of the patient's genome. Finally, the mechanism of Ph chromosome acquisition in MDS as well as different therapy options continuing to be challenging in every single case.

Compliance with Ethical Standards

Conflict of interest The author declares that there is no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Consent for the publication of this case report and any additional related information was taken from the next of kin of the patient involved in the study.

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