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LETTER TO THE EDITOR

BCR-ABL1- and *CBFB-MYH11*-positive chronic myeloid leukemia presenting with primary blast crisis and marrow fibrosis

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Dear Editor,

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the *BCR-ABL1* fusion gene [1]. Bone marrow fibrosis leading to dry tap aspiration has been reported in patients with CML, frequently in association with blast crisis [2]. *CBFB-MYH11* is a genomic abnormality in acute myeloid leukemia (AML) that predicts a favorable prognosis [1]. Here, we report a case of *BCR-ABL1*- and *CBFB-MYH11*-positive CML with primary blast crisis (CML-pBC) and marrow fibrosis.

A previously healthy 69-year-old woman was admitted to our hospital because of severe pneumonia and acute hypoxemic respiratory failure that required intubation and mechanical ventilation. Her hemoglobin level was 8.6 g/dL; white blood cell count was 234×10^9/L with 32% blasts, 2% promyelocytes, 6% myelocytes, 2% metamyelocytes, 29% neutrophils, 6% basophils, 13% eosinophils, 7% monocytes, and 3% lymphocytes; and platelet count was 648×10^9/L. The blasts were positive for myeloperoxidase and both naphthol AS-D chloroacetate and alpha-naphthyl butyrate esterases. A multiplex quantitative real-time polymerase chain reaction panel revealed chimeric major *BCR-ABL1* and *CBFB-MYH11* transcripts (Table 1). Interphase fluorescence in situ hybridization (FISH) analysis confirmed *BCR-ABL1* fusion and *CBFB* rearrangement signals in circulating blasts and neutrophils. Leukemic cells expressed CD34, CD33, CD13, and HLA-DR and were characterized as 46, XX, t(9;22)(q34.1;q11.2), inv(16)(p13.1q22). Repeated bone marrow aspirations were dry tap. A biopsy specimen showed hypercellular marrow with approximately 30% blasts and grade 2 fibrosis according to the marrow fibrosis scoring system [3]. Computed tomographic scanning showed an enlarged spleen (17 cm in length).

The patient received induction chemotherapy with cytarabine and daunorubicin, and the circulating blast percentage dropped to 1%. FISH analysis revealed disappearance of the *CBFB*-rearranged cells, but the percentages of *BCR-ABL1*-positive cells remained unchanged (Table 1). Bone marrow aspirations remained dry taps. The biopsy specimen showed expansion of myeloid progenitor cells at various stages of maturation with approximately 2% blasts and a high myeloid-to-erythroid ratio of 10:1. The patient started taking ponatinib after tracheal extubation, and a hematological response was obtained within 1 month.

Differentiation of CML-pBC from *BCR-ABL1*-positive AML, which has been included as a provisional entity in the 2016 revised WHO classification [1], is difficult. We applied the recently proposed algorithm for the initial differential diagnosis, which supported the diagnosis of CML-pBC [4]. *BCR-ABL1* and *CBFB*-rearranged cells were sensitive to chemotherapy, whereas the founding *BCR-ABL1* cells were resistant to chemotherapy, implying that *CBFB-MYH11* operated as a minor route aberration for the blast crisis. In addition, t(9;22) has been an independent unfavorable prognostic factor in de novo AML [5]. Future studies will clarify whether *BCR-ABL1*-positive de novo AML requires a specific treatment strategy.

Marrow fibrosis is an independent unfavorable prognostic factor for CML [6, 7], although it has not been described in *CBFB-MYH11* AML. *JAK2*, *CALR*, and *MPL* mutations, which may initiate marrow fibrosis, were not detected in our case. As some BCR-ABL1 tyrosine kinase inhibitors reduce bone marrow fibrosis in CML, it is of interest to know whether ponatinib, a potent BCR-ABL1 inhibitor, can mitigate marrow fibrosis while maintaining remission [8].

Keisuke Kidoguchi and Kensuke Kojima contributed equally to this work.

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Table 1 Cytogenetic and molecular data before and after induction treatment

		At diagnosis		After induction treatment	
		Blasts	Neutrophils	Blasts	Neutrophils
FISH (%)	*BCR-ABL1* fusion signals	100	95	87	99
	CBFB rearranged signals	58	5	0	0
Chromosome analysis		46,XX,t(9;22)(q34.1;q11.2), inv.(16)(p13.1q22) [20]		46,XX,t(9;22)(q34.1;q11.2) [19]/ 46, idem, inv(16) (p13.1q22) [1]	
qRT-PCR	*BCR-ABL1*	300,000		210,000	
(copies /μg RNA)	*CBFB-MYH11*	200,000		840	

FISH fluorescence in situ hybridization, *qRT-PCR* quantitative reverse transcription-polymerase chain reaction

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Compliance with ethical standards Written informed consent was obtained from the patients for publication.

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

References

1. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM et al (2016) The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 127: 2391–2405
2. Gralnick HR, Harbor J, Vogel C (1971) Myelofibrosis in chronic granulocytic leukemia. Blood. 37:152–162
3. Thiele J, Kvasnicka HM, Facchetti F, Franco V, van der Walt J, Orazi A (2005) European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica. 90:1128–1132
4. Neuendorff NR, Burmeister T, Dörken B, Westermann J (2016) BCR-ABL-positive acute myeloid leukemia: a new entity? Analysis of clinical and molecular features. Ann Hematol 95:1211–1221
5. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, Dombret H, Ebert BL, Fenaux P, Larson RA, Levine RL, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz M, Sierra J, Tallman MS, Tien HF, Wei AH, Löwenberg B, Bloomfield CD (2017) Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 129:424–447
6. Buesche G, Hehlmann R, Hecker H, Heimpel H, Heinze B, Schmeil A et al (2003) Marrow fibrosis, indicator of therapy failure in chronic myeloid leukemia - prospective long-term results from a randomized-controlled trial. Leukemia. 17:2444–2453
7. Dekmezian R, Kantarjian HM, Keating MJ, Talpaz M, McCredie KB, Freireich EJ (1987) The relevance of reticulin stain-measured fibrosis at diagnosis in chronic myelogenous leukemia. Cancer. 59: 1739–1743
8. Bueso-Ramos CE, Cortes J, Talpaz M, O'Brien S, Giles F, Rios MB, Medeiros LJ, Kantarjian H (2004) Imatinib mesylate therapy reduces bone marrow fibrosis in patients with chronic myelogenous leukemia. Cancer. 101:332–336