Int J Clin Exp Pathol 2019;12(5):1811-1815
www.ijcep.com /ISSN:1936-2625/IJCEP0093221

Case Report

Co-existence of t(9;22) and t(8;21) in primary blast phase of chronic myelogenous leukemia: clinical experience and literature review

Yuanfeng Zhang[1*], Yinghui Liu[1*], Xiaoqian Liu[1], Licai An[1], Baohua Huang[3], Jie Li[3], Guili Zhang[3], Xiaolu Zhang[3], Jinying Gong[4], Guohua Yu[2], Xiaoxia Chu[1]

Departments of [1]Hematology, [2]Pathology, Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai 264000, Shandong Province, China; [3]Laborary Department of Hematology, Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai 264000, Shandong Province, China; [4]Department of Pathology, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Tianjin 300020, China. [*]Equal contributors.

Received March 1, 2019; Accepted March 28, 2019; Epub May 1, 2019; Published May 15, 2019

Abstract: Rare chronic myelogenous leukemia (CML) patients manifested as the primary blast phase without a chronic and accelerated phase. The occurrence of a t(8;21) translocation in secondary blast phase of CML or Philadelphia chromosome positive acute myelogenous leukemia (Ph+ AML) has been reported previously. No case of primary blast phase of chronic myelogenous leukemia (CML-BP) bearing one clone with t(9;22) and t(8;21) simultaneously has been reported. One Chinese patient presenting with extensive spontaneous ecchymosis and enlarged spleen diagnosed as acute myelogenous leukemia (AML) by smear and immunophenotype was given chemotherapy including daunorubicin 3 days and cytarabine 7 days without a tyrosine kinase inhibitor (TKI) drug at the beginning. Fresh frozen plasma and 4-factor prothrombin complex concentrate was also transfused for coagulation disorder. However, fusion genes BCR/ABL p210 and AML1/ETO were both positive and karyotype analysis showed the abnormalities of t(9;22) and t(8;21) in the same clones. Bone marrow aspirate on 7th day of chemotherapy indicated hypocellularity with 45% blasts remaining. Cytarabine was prolonged to nine days combined with imatinib 600 mg per day. His bone marrow aspirate after complete remission revealed t(8;21) clones disappearing, especially FISH of bone marrow smear detecting the BCR/ABL fusion signals in the basophilic erythroblasts, which confirmed his diagnosis as primary blast phase of CML rather than Ph+ AML. Thus, we report for the first time one patient diagnosed as primary blast phase of CML presenting with t(9;22) and t(8;21) simultaneously.

Keywords: Chronic myelogenous leukemia, primary blast phase, coagulation disorder, case report, chromosome translocation

Introduction

CML is a clonal myeloproliferative disorder of pluripotent hematopoietic stem cells characterized by specific hematologic and chromosomal changes [1]. The clinical course of patients with CML generally is divided into three phases: chronic phase, accelerated phase, and blast phase. The specific chromosomal abnormality is the Philadelphia chromosome (Ph), which results from a translocation involving the abl gene at chromosome 9q34 and the bcr gene at chromosome 22q11 [2]. The encoded chimeric protein, BCR/ABL is the target of TKI drug therapy [3]. Rare CML patients manifested as primary blast phase without a chronic and accelerated phase [4]. The t(8;21)(q22;q22) typically is associated with a distinct type of AML with characteristic morphologic features and a favorable clinical outcome [5]. The occurrence of this translocation in secondary blast phase of CML or Ph+ AML has been reported previously [6-12]. Here we report for the first time one patient diagnosed in the primary blast phase of chronic myelogenous leukemia bearing one clone with t(9;22) and t(8;21) simultaneously.

Case presentation

A 45-year-old Chinese man with chief complaints of jaw pain for two months was admitted into our hospital on June 6, 2017. No positive

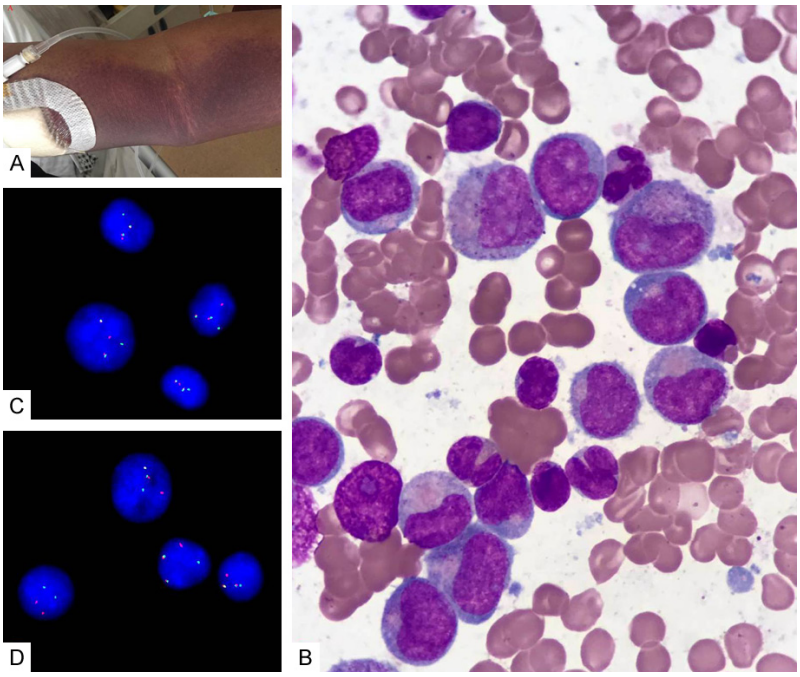

Figure 1. Clinical manifestations, morphology and FISH results before treatment. A. Obvious bleeding of the arm. B. Bone marrow blasts showing abundant granular cytoplasm with clear nucleoli and perinuclear clearing. C. In cells with t(8;21), the hybridization produces fused yellow signals (AML1/ETO), orange signals (ETO), and green signals (AML1). D. In cells with t(9;22), the hybridization produces fused yellow signals (BCR/ABL), red signals (native ABL), and 1 green signal (native BCR).

past history was obtained. One week before admission extensive spontaneous ecchymosis and subcutaneous nodules were found. Enlarged spleen was 5 cm under the costal margin. Complete blood count showed hemoglobin 107 g/L, thrombocytopenia 49×10^9/L, leukocytosis 172.26×10^9/L with 37% neutrophils, 2% monocytes, 9% lymphocytes, 3% myelocytes, 4% metamyelocytes, 45% blasts, and coagulation testing showed partial thromboplastin time 20.2 sec (11-15), activated partial thromboplastin time 28.5 sec (20-40), fibrinogen 3.75 g/L, thrombin time 20.4 sec (14-21), d-dimer 28 mg/L (**Figure 1A**). Bone marrow smear disclosed markedly increased cellularity with 33% myeloblasts, 18% promyelocytes, 18% myelocytes, 6% metamyelocytes, 20% mature neutrophils, 1% eosinophils, 0.5% basophils, 8% lymphocytes, and 0.5% normoblasts (**Figure 1B**). Flow cytometric immunophenotyping of bone marrow showed the blasts were positive for CD33, CD123, CD38, MPO, partially positive for CD15, CD13, CD11b, CD9 and were negative for CD34, HLA-DR, CD19. He was given a regimen including daunorubicin 80 mg/m^2×3 day and cytarabine 100 mg/m^2×7 day on hospital day 3 after admission. At the beginning, fresh frozen plasma and 4-factor prothrombin complex concentrate was transfused for coagulation disorder. Reverse transcription polymerase chain reaction (RT-PCR) of AML fusion genes BCR/ABL p210 and AML1/ETO were both positive. The BCR/ABL and ABL1/ETO nuclear fusion signals were also detected by fin situ hybridization (FISH) in the interphase cells (**Figure 1C**, **1D**). Karyotype analysis revealed chromosomal abnormalities t(9;22) and the t(8;21) in all 15 evaluated mitoses (**Figure 2A**). His T315I mutation was negative. Bone marrow aspirate on 7th day of chemotherapy indicated hypocellularity with 45% blasts remaining. Then cytarabine was prolonged to nine days combined with imatinib 600 mg/day. The third bone marrow aspirate on July 7, 2017 showed hypocellularity without excess blasts and fusion gene BCR/ABL was still positive but AML1/ETO turned out as negative, which indicated his disease was back to the chronic phase of CML. After complete remission, the karyotype analysis of fourth aspirate showed t(9;22) abnormality without t(8;21) (**Figure 2B**), correlating with FISH results (**Figure 2C**, **2D**). BCR-ABL fusion signal was also detected in the basophilic erythroblasts on the bone marrow smear which definitely confirmed his diagnosis of CML-BP, not Ph+ AML (**Figure 3A**, **3B**). Because of donor and financial limitation, he could not receive allogenic stem cell transplantation and died from early relapse and resistance to chemotherapy two months later.

Discussion

As to our literature review, this is the first case diagnosed as primary blast phase of CML with co-existence of t(9;22) and t(8;21). Early in 1978, Dr. Francesconi found a 13-year old patient diagnosed as AML with t(8;21); howev-

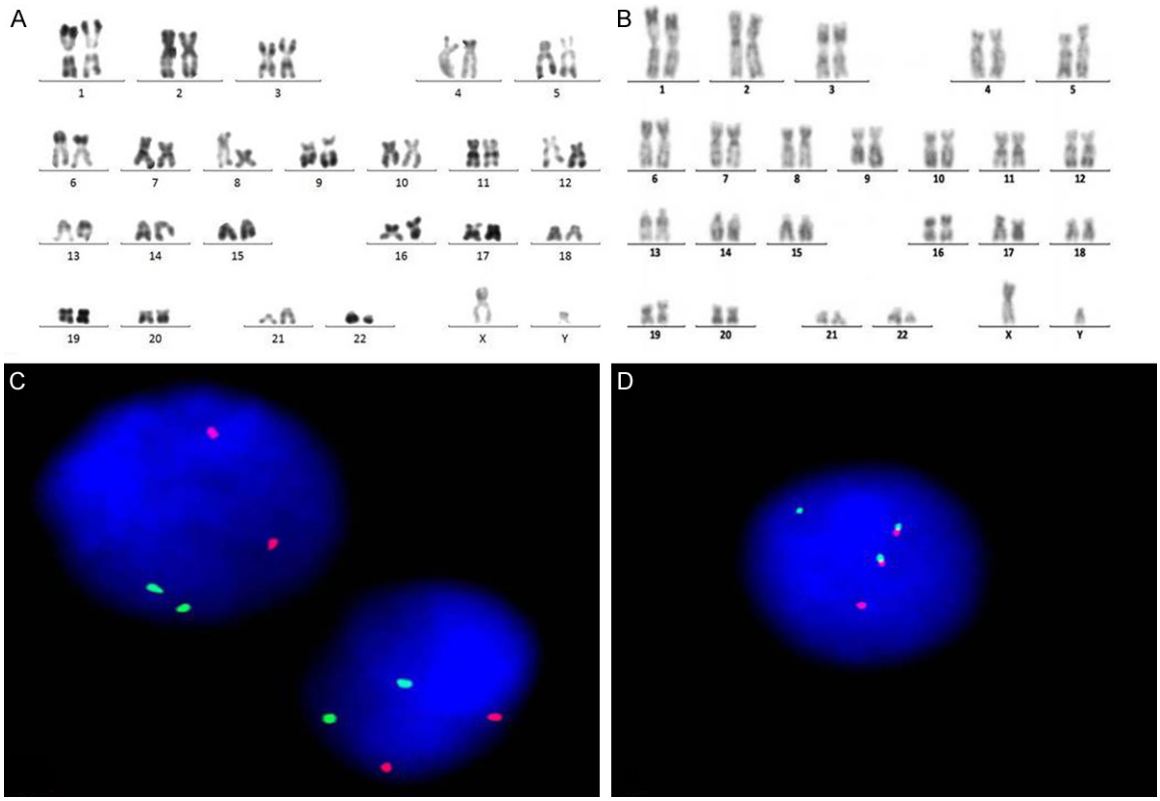

Figure 2. Karyotype of bone marrow before and after chemotherapy and FISH results of bone marrow after chemotherapy. A. Karyotype of the bone marrow before treatment showing t(9;22) and t(8;21) abnormality in the same leukemic clone cells. B. Karyotype of the bone marrow after treatment: t(9;22) without t(8;21) abnormality. C. FISH showing disappearance of fused yellow signals (AML1/ETO) after effective treatment. D. FISH showing remaining fused yellow signals (BCR/ABL) after effective treatment.

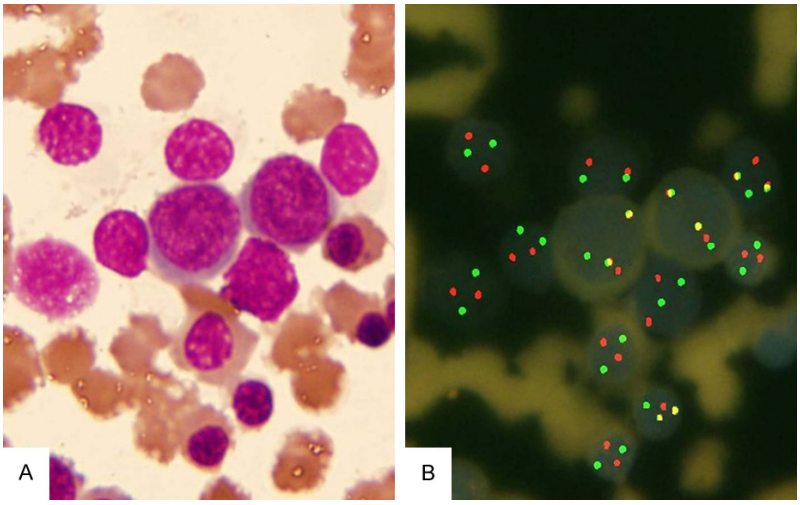

Figure 3. FISH results of the BCR/ABL signals in the basophilic erythroblasts on the bone marrow smear. A. Two basophilic erythroblasts on the bone marrow smear. B. FISH of bone marrow smear showing fused yellow signals (BCR/ABL) in the two basophilic erythroblasts.

er, treatment was unsatisfactory and eight months after diagnosis and courses of therapy were given, chromosome analysis showed presence of a Ph+ chromosome [6]. Xue et al [7] reported one case of basophilic leukemia bearing simultaneous translocations of t(8;21) and t(9;22); however, differential diagnosis between CML and Ph+ AML was undetermined. The presence of a t(8;21) alteration can be detected as an additional chromosom in blast phase of CML with disease progression [8, 9]. Ammatuna et al have described cases of acute myeloid leukemia with simultaneous occurrence of t(9;22) and t(8;21) [10-12].

It is difficult to distinguish primary blast phase of CML from Ph+ AML; however, history of ante-

cedent blood anomaly, basophilia >2% in white blood cells, and 100% BCR/ABL metaphases would be helpful for diagnosis of CML [4]. CML originates from pluripotent hematopoietic stem cells and BCR-ABL is the main driving event in CML, sufficient to initiate the disease while BCR-ABL in AML is a secondary event [11, 13]. The presence of the Ph chromosome in erythroblasts, neutrophilic, eosinophilic, basophilic granulocytes, macrophages and megakaryocytes is specific for CML [14]. For this reason, when a CML-BP patient is back to chronic phase, Ph chromosome is always still present. In our case, the Ph+ clone remained while disappearance of t(8;21) clones after effective treatment indicated a CML-BP diagnosis. Identification of BCR/ABL fusion signals in these cells in the bone marrow or peripheral blood smears by FISH is a well way to differentiate CML from AML [15, 16], just as the method we used in our case.

Patients with CML in primary blast crisis should be treated with a TKI drug with or without chemotherapy, with the goal of reversion to chronic phase and proceeding to allogenic stem cell transplantation as quickly as possible [17]. Our patient was treated according to acute myelogenous leukemia by his bone marrow morphology and immunophenotye at the beginning. However, coagulation disorder deteriorated during chemotherapy. More importantly, the second bone aspirate showed 45% blasts remaining, but he achieved complete remission after adding a TKI drug, which indicated the importance of TKI drugs in treating CML-BP.

Acknowledgements

Thanks to Dr. Tong Wang of Hebei Yanda Lu Daopei Hospital, Langfang, China for contributing FISH results of the bone marrow smear. This work was supported by Yantai Key Research and Development Project (2017WS101).

Written informed consent was obtained from the patient for publication of this case report.

Disclosure of conflict of interest

None.

Abbreviations

CML, Chronic myelogenous leukemia; Ph+ AML, Philadelphia chromosome positive Acute Myelogenous Leukemia; AML, Acute Myelogenous Leukemia; TKI, Tyrosine kinase inhibitor; CML-BP, blast phase of chronic myelogenous leukemia; Ph, Philadelphia chromosome; RT-PCR, reverse transcription polymerase chain reaction; FISH, fluorescence in situ hybridization.

Address correspondence to: Dr. Xiaoxia Chu, Department of Hematology, Affiliated Yantai Yuhuangding Hospital of Qingdao University, 20 East Yuhuangding Road, Yantai 264000, Shandong Province, China. E-mail: lucychu126@126.com; Dr. Guohua Yu, Department of Pathology, Affiliated Yantai Yuhuangding Hospital of Qingdao University, 20 East Yuhuangding Road, Yantai 264000, Shandong Province, China. E-mail: ygh0535@hotmail.com

References

[1] Sawyers CL. Chronic myeloid leukemia. N Engl J Med 1999; 340: 1330-40.
[2] Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, Kantarjian HM. The biology of chronic myeloid leukemia. N Engl J Med 1999; 341: 167-72.
[3] Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J, Lydon NB. Effects of a selective inhibitor of the ABL tyrosine kinase in the growth of BCR-ABL positive cells. Nat Med 1996; 2: 561-6.
[4] Neuendorff NR, Burmeister T, Dörken B, Westermann J. BCR-ABL-positive acute myeloid leukemia: a new entity? Analysis of clinical and molecular features. Ann Hematol 2016; 95: 1211-21.
[5] Downing JR. The AML1/ETO chimaeric transcription factor in acute myeloid leukemia: biology and clinical significance. Br J Haematol 1999; 106: 296-308.
[6] Battaglia D, Dubé I, Pinkerton P, Senn J. Acquisition of additional primary chromosome abnormalities in the course of karyotype evolution in a case of FAB-M2 acute leukemia. Cancer Genet Cytogenet 1989; 40: 105-10.
[7] Xue YQ, Guo Y, Lu DR, Gu J, Lu DW, Gong JX, Wang MH, Zhu WY, Lin BJ. A case of basophilic leukemia bearing simultaneous translocations t(8;21) and t(9;22). Cancer Genet Cytogenet 1991; 51: 215-21.
[8] Ferro MT, Steegman JL, Escribano L, Heiurichs B, Parada L, García-Sagredo JM, Resino M, Cabello P, San Román C. Ph-positive chronic myeloid leukemia with t(8;21) (q22;q22) in blastic crisis. Cancer Genet Cytogenet 1992; 58: 96-9.
[9] Kojima K, Yasukawa M, Ishimaru F, Dansako H, Matsuo Y, Kimura Y, Nawa Y, Hara M, Harada

M. Additional translocation (8;21)(q22;q22) in a patient with Philadelphia-positive chronic myelogenous leukaemia in the blasted phase. Br J Haematol 1999; 106: 720-2.

[10] Ammatuna E, Divona M, Curzi P, Panetta P, Zaza S, Postorino M, Cantonetti M, Amadori S, Lo Coco F. Simultaneous occurrence of BCR/ABL1 and RUNX1/RUNX1T1 in a case of therapy-related acute myeloid leukemia. Cancer Genet Cytogenet 2009; 195: 189-91.

[11] Bacher U, Haferlach T, Alpermann T, Zenger M, Hochhaus A, Beelen DW, Uppenkamp M, Rummel M, Kern W, Schnittger S, Haferlach C. Subclones with the t(9;22)/BCR-ABL1 rearrangement occur in AML and seem to cooperate with distinct genetic alterations. Br J Haematol 2011; 152: 713-20.

[12] Dallorso S, Sessarego M, Garré ML, Haupt R, Pasino M, Sansone R. Secondary acute promyelocytic leukemia with t(8;21) and t(9;22) at onset and loss of the Philadelphia chromosome at relapse. Cancer Genet Cytogenet 1990; 47: 41-6.

[13] Gilliland DG. Molecular genetics of human leukemias: new insights into therapy. Semin Hematol 2002; 39: 6-11.

[14] Spiers AS, Bain BJ, Turner JE. The peripheral blood in chronic granulocytic leukemia: a study of 50 untreated Philadelphia positive cases. Scand J Haematol 1977; 18: 25-38.

[15] Ruiz S, Chen YH. Acute myeloid leukemia with coexistence of t(9;22) and inv(16). Blood 2018; 131: 1263.

[16] Kamoda Y, Izumi K, Iioka F, Akasaka T, Nakamura F, Kishimori C, Tsuda K, Fukutsuka K, Okumura A, Hayashida M, Ohno H. Philadelphia chromosome-positive acute lymphoblastic leukemia is separated into two subgroups associated with survival by BCR-ABL fluorescence in situ hybridization of segmented cell nuclei: report from a single institution. Acta Haematol 2016; 136: 157-66.

[17] Hehlmann R. How I treat CML blast crisis. Blood 2015; 120: 737-47.