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

Yuanfeng Zhang1*, Yinghui Liu1*, Xiaqian Liu1, Licai An1, Baohua Huang3, Jie Li3, Guili Zhang3, Xiaolu Zhang3, Jinying Gong4, Guohua Yu2, Xiaoxia Chu1

Departments of 1Hematology, 2Pathology, Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai 264000, Shandong Province, China; 3Laboratory Department of Hematology, Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai 264000, Shandong Province, China; 4Department 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
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m²×3 day and cytarabine 100 mg/m²×7 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 T3-15I 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 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).
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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.

It is difficult to distinguish primary blast phase of CML from Ph+ AML; however, history of antecedent 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 chromosome 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].
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.

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.

References

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