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Case report

Differential cytogenetic profile in advanced chronic myeloid leukemia with sequential lymphoblastic and myeloblastic blast crisis ☆

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ABSTRACT

Frequency of additional chromosomal abnormalities in chronic myeloid leukemia (CML) is estimated to be 7% in chronic phase and increases to 40–70% in advanced disease. Progression of CML from chronic phase to accelerated phase or blast crisis is often associated with secondary chromosomal aberrations. We report an exceptional case of CML as debut in lymphoblastic blast crisis and a subsequent progression in myeloblastic blast crisis with rare cytogenetic abnormalities.

1. Introduction

Chronic myeloid leukemia (CML) is a clonal malignant disorder of a pluripotent hematopoietic stem cell characterized by the presence of the reciprocal translocation t(9;22)(q34;q11), which generates the Philadelphia (Ph) chromosome. Frequency of additional chromosomal abnormalities has an incidence of 7% in chronic phase and increases to 40–70% in advanced disease/blast crisis [1,2]. Progression from chronic phase to accelerated phase or blast crisis is often associated with secondary chromosomal aberrations such as trisomy 8, trisomy 19, duplication of the Ph chromosome, isochromosome 17q (leading to the loss of p53 gene on 17p), acquisition of t(1;21) or translocations and inversions associated with AML/myelodysplasia [3], which translates a genomic instability of CML cells and the appearance of *BCR-ABL1* kinase mutations, both of which can confer resistance to tyrosine kinase inhibitors (TKIs) [4,5].

Herein we report an exceptional case of CML diagnosed in lymphoblastic blast crisis which subsequently suffered a progression to myeloblastic blast crisis with rare cytogenetic abnormalities.

2. Case report

A 65-year-old woman presented with profuse sweating and weakness for 3 months and a leukocytosis of 200 × 10e9/L with more than 80% blasts in peripheral blood. A bone marrow aspirate was performed showing 50% lymphoid blasts with aberrant myeloid markers: CD34+ CD45+w DR+ CD38+ cTdT+ cCD79a+ CD19+ CD10+ CD20− CD24+ cIgM− sIg− CD7+ CD13+ CD33+/−.

Genetic testing for Philadelphia chromosome was done by fluorescence in situ hybridization (FISH) and conventional cytogenetic analysis (karyotyping). The BCR-ABL fusion gene was assessed by RT-PCR. BCR-ABL rearrangement was detected by FISH in 96% of the bone marrow cell population and monosomy 7 in 71% of them (Fig. 1A and B). Cytogenetic features were as follows: 45,XX,-7,t(9;22)(q34;q11.2)[20] (Fig. 2A). The number of BCR-ABL transcripts at diagnosis was 70%.

The patient received chemotherapy based on anthracycline, vincristine and steroids and imatinib at doses of 600 mg daily with intrathecal chemotherapy, achieving complete remission of acute leukemia and chronic phase regression. Immediately after treatment, a new FISH assay in peripheral blood was performed and showed BCR-ABL rearrangement in 92% of cells, while monosomy 7 was not detected (Fig. 1C and D). Karyotype at that time was 46,XX,t(1;6),t(9;22)(q34;q11.2)[10]/46,XX[10].

Afterwards, the patient received consolidation therapy with vincristine and daunomycin plus imatinib, which was tapered to

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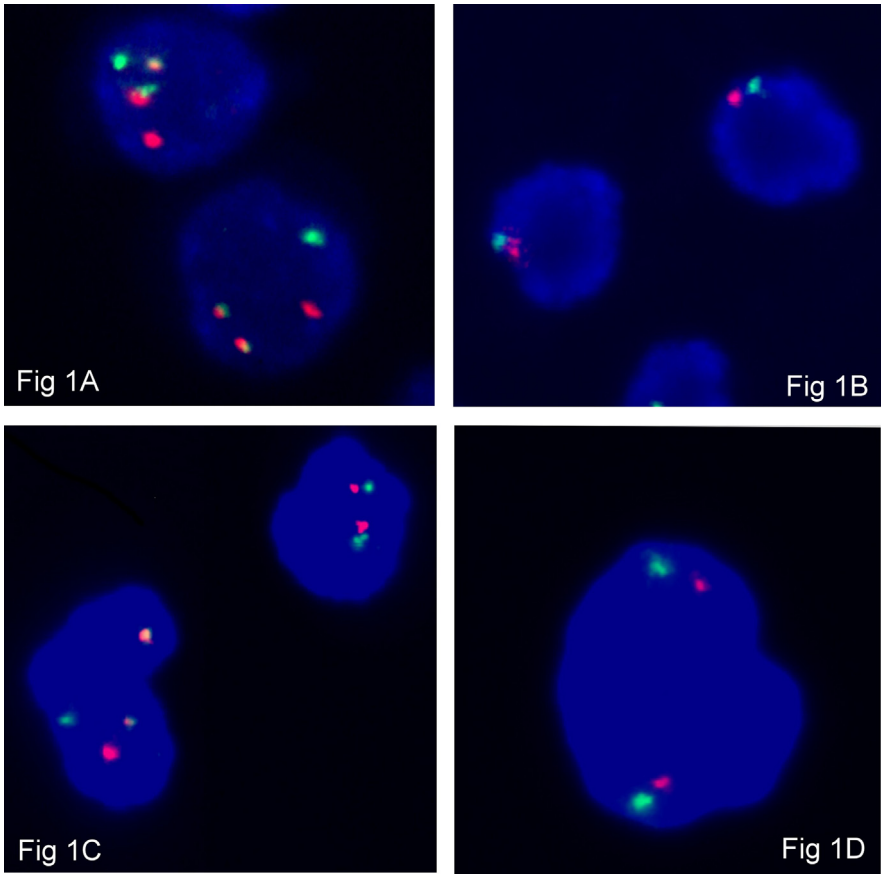

Fig. 1. (A) At diagnosis. Interphase FISH, Vysis dual-fusion probe set. Green: BCR; red: ABL; yellow: fused BCR and ABL signals corresponding to der(9) and der(22) translocation products. (B) At diagnosis. Interfase FISH, Vysis dual color probe set. Green: chromosome 7 centromere; red: locus 7q31. Interphase cells showing one centromere and one 7q31 signal indicating monosomy 7. (C) After treatment: rearrengement BCR/ABL (92%). (D) After treatment: monosomy 7 = 0%. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

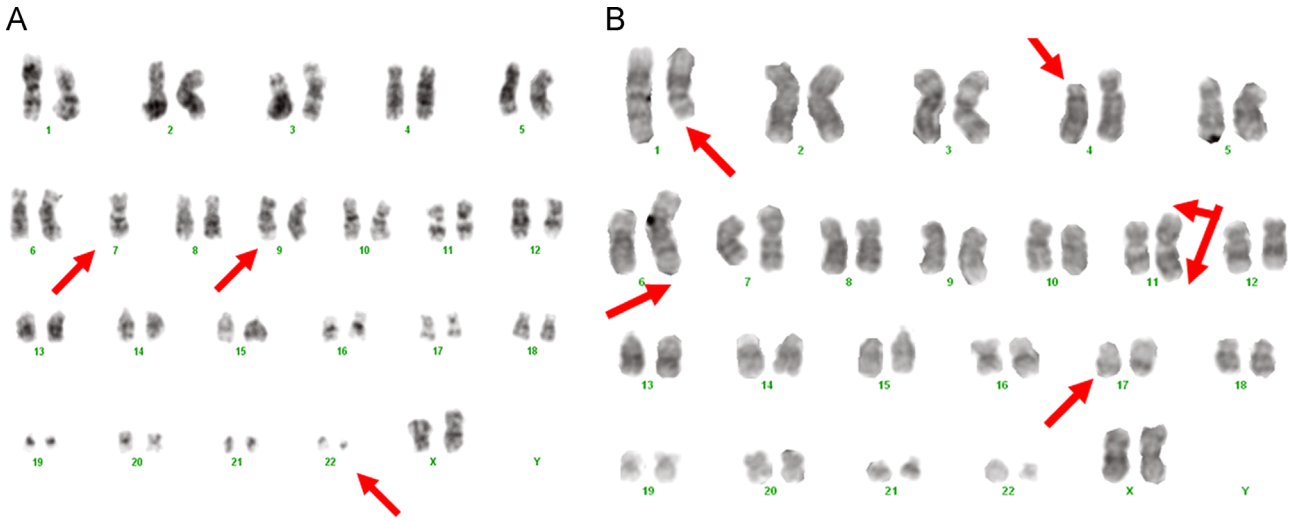

Fig. 2. (A) Karyotype at diagnosis (lymphoblastic blast crisis): 45,XX,-7,t(9;22)(q34;q11.2)[20]. (B) Karyotype at relapse (myeloblastic blast crisis): 46,XX,t(1;6)(q22;q21), del(4)(p14),t(9;22)(q34;q11.2),der(11)add(11)(p14)add(11)(q23),add(17)(q12∼21)[20].

400 mg daily due to dyspnea and marked palpebral and ankle edema. Overall, she showed a good clinical outcome with 3.3% bcr-abl transcripts three months after diagnosis.

Nevertheless, one week after this last determination, the patient returned to consultation due to headache and B symptoms. WBC showed leukocytosis of 258 × 109/L with 87% blasts. A new bone marrow had infiltration by 75% blasts of myeloid lineage consistent with myeloid blast crisis of CML. Immunophenotype of this blastic population was CD45+ CD34+d CD117+d DR+ CD38+ CD13+ CD33+ CD11b− CD64− CD56− CD7+/− CD9+d CD123+ showing the following karyotypic changes: 46,XX,t(1;6)(q22;q21),del(4)(p14),t(9;22)(q34;q11.2),der(11)add(11)(p14)add(11)(q23),add(17)(q12∼21)[20] (Fig. 2B). The patient also developed a T315I bcr-abl mutation detected by DNA sequencing.

In spite of treatment with steroids, she suffered a seizure and a parenchymal hematoma was observed in a cranial TC-scan, and subsequently died.

3. Discussion

In the current study we report on a patient with CML diagnosed with lymphoblastic blast crisis with monosomy 7 in 71% of bone marrow cells; karyotype was 45,XX,-7,t(9;22)(q34;q11.2)[20] at diagnosis. After treatment, monosomy 7 was not detected and a t (1;6) was observed upon regression into chronic phase. Afterwards, a subsequent myeloid blast crisis was associated with the following karyotype: 46,XX,t(1;6)(q22;q21),del(4)(p14),t(9;22)(q34;q11.2),der(11)add(11)(p14)add(11)(q23),add(17)(q12–21)[20]. In addition, the T315I bcr-abl mutation was also detected.

These findings would suggest the presence of a leukemic stem cell carrying the t(9;22) as the primary event in the onset of the disease. A second hit would be the acquisition of a monosomy 7 in a cell committed to lymphoid lineage, which might confer a proliferative advantage giving rise to the lymphoid blast crisis, when diagnose was made. At this time point, it was also observed the presence of a small fraction of leukemic cells, which would be committed to myeloid lineage, carrying a t(1;6) in addition to the t (9;22), which latter on gave rise to the myeloid blast crisis. At this time, the emergence of several additional cytogenetic abnormalities was observed and T315I mutation was found, as an indicative fact of refractoriness to treatment.

Thus, treatment for acute lymphoblastic leukemia based on chemotherapy and imatinib successfully erradicated the clone involved in lymphoblastic blast crisis while allowing a clonal selection and subsequent expansion of myeloid cells carrying the t(1;6). Very few cases of lineage switch in CML have been reported in the literature before [6–9] and during the imatinib era [10]. Furthermore, to our knowledge, this is the first report describing sequential lymphoid and myeloid blast crisis with differentiated cytogenetic abnormalities.

In summary, this is an interesting case depicting the underlying clonal heterogeneity of CML in evolution as well as the clonal selection under combined treatment with chemotherapy plus TKIs.

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