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Case Study

Monocytic Crisis of Chronic Myeloid Leukemia in the Era of Tyrosine Kinase Inhibitor

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A 47-year-old man was diagnosed with Philadelphia chromosome-positive chronic myeloid leukemia (CML) in October 2005. He could not receive treatment with imatinib mesylate due to his economic circumstances. He was consequently treated with hydroxyurea with partial hematological remission until June 2008. Although imatinib mesylate was started thereafter, the adherence to this treatment was poor because of his occupational circumstances. In September 2009, imatinib mesylate was switched to nilotinib, with a subsequent phase of acceleration of the disease, presumably due to his poor adherence to the treatment. Dasatinib was started in September 2010, with transient hematological response and final blastic crisis of the disease in January 2011, regardless of improved adherence. Blast cells showed immature monocytic morphology and were positive for α-naphtylbutyrate esterase staining. They also expressed surface CD14 and CD64 antigens. A diagnosis of rare monocytic crisis of CML was made. He was treated with low-dose nilotinib following cytoreduction with MEC (mitoxantrone, etoposide, and cytarabine) chemotherapy. Severe leucopenia without circulating leukemic cells continued for about 2 months with sustained hepatosplenomegaly, and he died of pneumonia in March 2012. Necropsy showed severe bone marrow hypoplasia with focal infiltration of mature leukemic cells and similar infiltration in the liver. 〔*J Clin Exp Hematop 53(3) : 227-233, 2013*〕

Keywords: monocytic crisis, chronic myeloid leukemia, tyrosine kinase inhibitor, bone marrow necrosis

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the expansion of clonal hematopoietic cells that carry the Philadelphia (Ph) chromosome and are capable of terminal differentiation to every cell lineage during the chronic phase.[1] In terms of its natural history, CML typically progresses from the chronic phase to terminal blastic phase/blast crisis via an accelerated phase.[2] Blast crisis is often accompanied by additional chromosomal abnormalities in addition to the Ph chromosome as a result of secondary molecular evolution. The most common phenotype of the blasts at the time of crisis is a myeloid one, comprising approximately two-thirds of cases, which is followed by B lymphoid, megakaryocytic, erythroid, basophilic, and rarely monocytic, T lymphoid, and eosinophilic phenotypes.[3] The development of bcr-abl-targeted tyrosine kinase inhibitors (TKIs) as the treatment of chronic-phase CML has dramatically reduced the incidence of transformation of chronic-phase CML to blast crisis.[4,5] However, it is well known that the outcome of CML patients who exhibit failure or suboptimal response to the treatment with imatinib mesylate is poor,[6] indicating that poor responders to TKI treatment have a risk of developing blast crisis of CML. In this article, we report on a patient who developed rare monocytic crisis, presumably due to poor adherence to TKI treatment.

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CASE REPORT

A 47-year-old man came to Kobe City Medical Center General Hospital because of abdominal fullness in October 2005. Physically, the spleen was palpable 10 cm below the costal margin. Hematological tests revealed a white blood cell (WBC) count of 123×10^9/L with some immature granulocytes and a platelet count of 393×10^9/L. A bone marrow aspirate showed granuloid hyperplasia with 0.4% blast cells. Cytogenetic analysis of the marrow cells demonstrated an abnormal karyotype of t(9;22)(q34;q11.2) (Table 1).

Table 1. Graded accumulations of additional chromosomal abnormalities in addition to Ph chromosome along with the progression of CML in the present patient

Phase	Karyotype	No. of cells with abnormal karyotype/ No. of cells analyzed
CP	46, XY, t(9;22)(q34;q11.2)	19/20
	46, XY	1/20
AP	46, XY, t(9;22)(q34;q1.21), der(17), add(17)(p11.2), add(19)(p11), +der(22)t(9;22)	20/20
BC	53, X, −Y, +1, +3, +6, +8, +8, t(9;22)(q34;q11.2), +13, −17, +19, add(19)(q13), +21, +der(22)t(9;22)	5/13
	55, idem, +18, +21	6/13
	58, idem, +2, i(8)(q10), +17, +18, +18, +21	2/13

CP: chronic-phase; AP: accelerated phase; BC: blast crisis.

Fluorescence *in situ* hybridization showed a *bcr-abl* fusion signal in 94.6% of marrow cells analyzed. Reverse transcriptase-polymerase chain reaction also showed the major *bcr-abl* transcript. A diagnosis of Ph chromosome-positive CML in chronic phase was made and the Sokal score was intermediate risk. Although imatinib mesylate was available at this time, he could not receive the treatment with this agent because of his financial circumstances. Therefore, treatment with hydroxyurea was started without complete hematological response (CHR), presumably due to his poor adherence to this treatment associated with his occupational circumstances. Although treatment with imatinib mesylate (400 mg/day) became available to him in June 2008, CHR was not obtained because of his poor adherence to the treatment. Furthermore, he discontinued the treatment for 2 months owing to his occupational circumstances in July 2009. As a result, his WBC count elevated to 350×10^9/L with moderate anemia and a platelet count of 171×10^9/L. A bone marrow aspirate showed sustained chronic phase of CML with the same karyotype of t(9;22). Imatinib mesylate was switched to nilotinib (800 mg/day) to obtain CHR in February 2010. The treatment with nilotinib brought about CHR ; nevertheless, he again discontinued the treatment in May 2010. After 4 months of discontinuation, his WBC count elevated to 320×10^9/L, with a differential count of 1% blasts and 46% promyelocytes, and decreased platelet count of 59×10^9/L. Cytogenetic analysis of bone marrow cells showed t(9;22)(q34;q11) with additional abnormalities of der(17), add (17)(p11.2), add19(p11), and +der(22)t(9;22) in all 20 cells analyzed (Table 1), indicating progression to an accelerated phase of CML. Nilotinib was switched to dasatinib (140 mg/day) in September 2010. Although he continued to take dasatinib with a normal WBC count, he was admitted in January 2011 because of possible blast crisis of CML. Physical examination showed marked hepatosplenomegaly and small skin papules in the trunk, suggesting skin invasion of leukemic cells. Hematological examination showed a WBC count of 12.7×10^9/L with 5% blasts, 2% metamyelocytes, 4% band form, 3% segmented form, 1% eosinophils, 1% basophils, 29% monocytes, 55% lymphocytes, and 9% erythroblasts, a hemoglobin concentration of 9.1 g/dL, and a platelet count of 46×10^9/L. Hemostatic examination revealed that concentrations of fibrinogen and D-dimer were 1,174 mg/dL (normally 160 to 350 mg/dL) and 2.3 μg/mL (normally below 1.0 μg/mL), respectively. Biochemical tests showed that serum concentrations of aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, lactate dehydrogenase, blood urea nitrogen, and creatinine were 14 IU/L, 12 IU/L, 0.3 mg/dL, 285 IU/L, 445 IU/L (normally 120 to 230 IU/L), 13.0 mg/dL, and 1.12 mg/dL (normally 0.5 to 1.0 mg/dL), respectively. C-reactive protein was elevated to 17.1 mg/dL (normally below 0.3 mg/dL). Serum concentration of lysozyme was as high as 180 μg/mL (normally 4.2 to 11.5 μg/mL). A bone marrow aspirate revealed hypercellularity with 90% immature monocyte-like cells (Fig. 1A). Cytochemical analysis showed that these cells were strongly positive for α-naphthyl butyrate esterase staining (Fig. 1B), but negative for peroxidase (Fig. 1C) and naphthol ASD chloroacetate esterase staining (data not shown). Flow cytometric analysis demonstrated that these immature cells were positive for CD2, CD4, CD7, CD14, CD33, CD64, and HLA-DR, but negative for CD13 and CD34. Chromosomal analysis showed t(9;22) with further additional complex abnormalities including tetrasomy 8 and trisomy 19 (Fig. 2) (Table 1). These findings indicated the monocytic nature of these immature cells, and a diagnosis of monocytic crisis of CML was made. No known point mutations in *bcr-abl* were detected at this time point.

Since the WBC count increased from 12.7×10^9/L to 130.8×10^9/L 6 days after admission, he received combination chemotherapy consisting of mitoxantrone, etoposide, and cytarabine in addition to nilotinib at 400 mg/day. However, the effect of the combination chemotherapy was transient, with possible life-threatening infection ; therefore, a combination with nilotinib and hydroxyurea was started for the control of blast/immature monocyte counts. After 1 week of administration of this combination, the blast count decreased with severe neutropenia to less than 0.01×10^9/L, and severe pancytope-

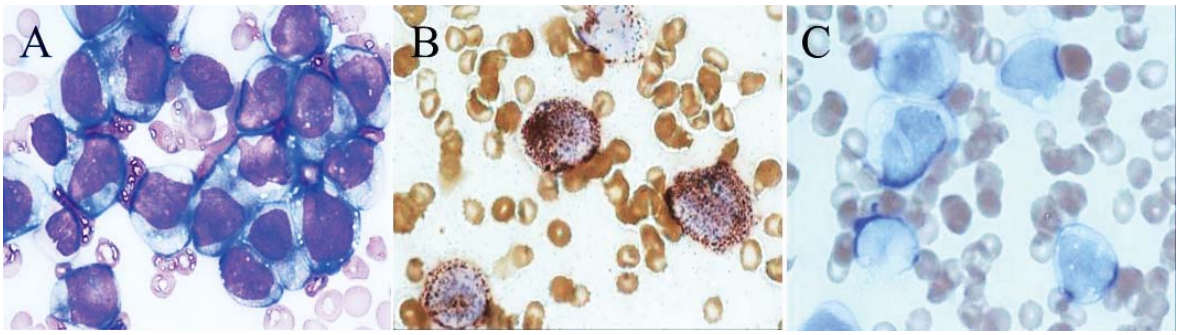

Fig. 1. Smear preparations of a bone marrow aspirate at the diagnosis of blast crisis. Many monocytoid blast cells with abundant cytoplasm containing some vacuoles are seen (*1A*; Wright-Giemsa stain, × 1,000). Cytochemical analysis shows that these cells are strongly positive for α-naphthyl butyrate esterase stain (*1B*; × 1,000), but negative for myeloperoxidase staining (*1C*; × 1,000).

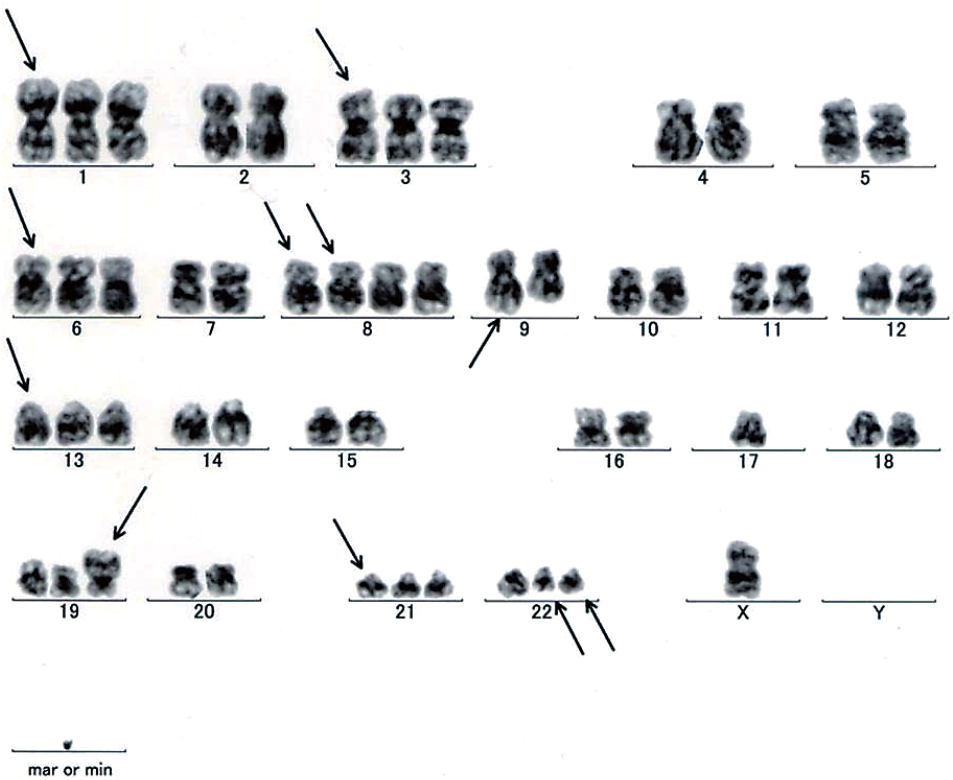

Fig. 2. Abnormal karyotype observed at the time of blast crisis. The karyotype is 53, X, −Y, +1, +3, +6, +8, +8, t(9;22)(q34;q11.2), +13, −17, +19, add(19)(q13), +21, +der(22)t(9;22).

nia continued thereafter. He had an HLA-matched sibling donor ; therefore, he was moved to Shinko Hospital for possible bone marrow transplantation in February 2011. The pancytopenia with few blasts and neutrophils continued with the combination of nilotinib and hydroxyurea, although prominent hepatosplenomegaly persisted. A bone marrow biopsy performed in March 2011 revealed extensive bone marrow necrosis (Fig. 3A). Although we conducted bone marrow transplantation at this time, he developed leukemic meningitis accompanied by convulsion and blindness of the left eye. Intrathecal chemotherapy improved the convulsion ; however, he developed recurrent massive melena. These complications made us unable to perform marrow transplantation, and he ultimately died of pulmonary hemorrhage due to

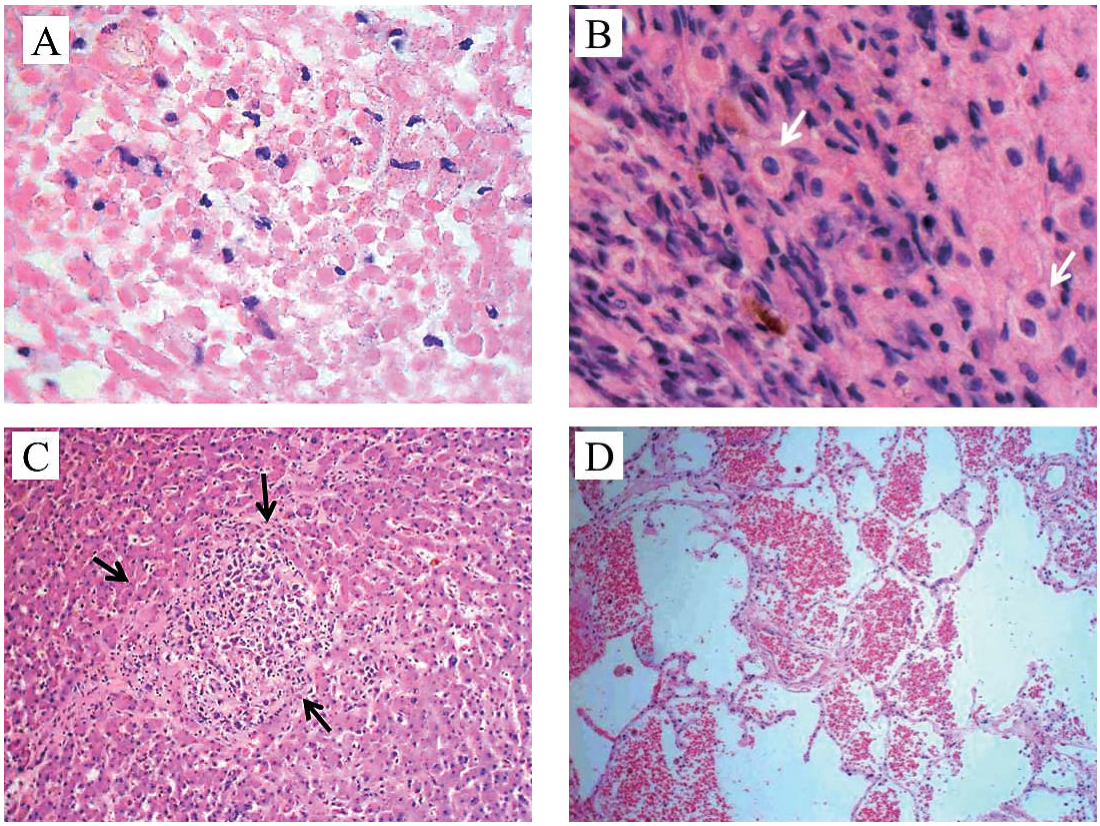

Fig. 3. Histological examination of biopsy and necropsy specimens from the bone marrow, liver, and lung. (***3A***) The marrow tissue shows extensive necrosis, and no viable cells are seen. Biopsy specimen, H&E stain, × 400. (***3B***) A focal infiltrate of residual leukemic cells in the necrotic tissue of the bone marrow. *Arrows* indicate large leukemic cells with abundant cytoplasm, suggesting partial differentiation toward monocyte in each infiltrate. Necropsy specimen, H&E stain, × 400. (***3C***) A focal infiltrate of leukemic cells in the portal area of the liver. *Arrows* indicate the extent of the infiltrate/portal area. Necropsy specimen, H&E stain, ×100. (***3D***) Extensive alveolar hemorrhage is seen due to *Stenotrophomonas maltophilia* infection. Necropsy specimen, H&E stain, × 100.

Stenotrophomonas maltophilia in April 2011. Necropsy showed severe bone marrow hypoplasia with focal infiltration of mature leukemic cells (Fig. 3B) and similar infiltration in the portal area of the liver (Fig. 3C) and spleen (data not shown). In addition, necropsy specimen of the lung showed extensive alveolar hemorrhage, possibly due to *Stenotrophomonas maltophilia* infection (Fig. 3D).

DISCUSSION

Monocytic crisis is a rare phenotype of blast crisis in CML. To the best of our knowledge, only 11 cases of monocytic crisis have been described in the English literature or abstracts, and all cases except for the present one were reported before the availability of imatinib mesylate.[7-17] Clinical data of these 11 and the present patients are summarized in Table 2. Furthermore, in the era of TKI of the second generation, blast crisis itself is rare. Therefore, the facts that the present patient could not initially start treatment with imatinib mesylate and that his adherence to subsequent TKI treatments was very poor may be instructive in terms of risky situations regarding blast crisis. Indeed, the adherence to imatinib mesylate as the critical factor for achieving a cytogenetic or molecular response has been reported.[18,19]

It is speculated that *bcr-abl* affects the DNA repair process, and altered DNA repair leads to genomic instability, which consequently causes clonal evolution and, finally, blast crisis.[20] In the present patient, uncontrolled and sustained *bcr-abl* activity in CML cells may have caused the accumulation of genetic instability. Indeed, a leukemic cell line was established from bone marrow cells at the initial period of the blast crisis in the present patient. Interestingly, multiple amplification of *bcr-abl* was demonstrated in these cultured cells (Arima *et al*., personal communication). This highly ampli-

Table 2. Clinical data of cases of CML monocytic crisis in the literatures

Ref. No.	Age/ Sex	Year of onset	Cyto-chemistry	Surface antigen	Lyso-zyme	Karyotype at the time of BC	Therapy prior to BC	Extra-medulary disease
7	38/M	1973	MPO(+) α-NB(+) ASD(+)	N.D.	N.D.	N.D.	BU	N.D.
8	26/M	1978	MPO(−) α-NB(+)	N.D.	N.D.	54, XY, +3, +6, +7, +8, +19, +21, t(9;22)(q34;q11), +der(22)t(9;22)(q34;q11), +der(22)t(9;22)(q34;q11)[5]	BU	liver
9	22/M	1978	MPO(+−) α-NB(+) ASD(+−)	Fcg(+) OKMI(+)	35.6	t(9;22)	BU, 6-MP, ACNU, VCR, DNR	liver, LN, kidney, adrenal
10	69/M	1979	MPO(+−) α-NB(+) ASD(−)	OKM1(+), 4F2(+), OKIA(+), OKT10(+)	N.D.	Double Ph[13/21]	BU, HU	liver
11	56/F	N.D.	MPO(+) α-NB(+)	N.D.	N.D.	62, XX, +1, +2, +3, +5, +6, +8, +der(9), +10, +der(11), +13, +16, +17, +18, +19, +21, −22, +del(22)(q11), [5]/46, XX, t(9;11;22)(p13;p15;q11)[20]	BU, 6-MP	N.D.
12	72/F	1981	α-NB(+)	N.D.	460	47XX, t(9;22)(q34;q11), +8, del(11) [11]/48, XX, t(9;22)(q34;q11), t(9;22)(q34;q11)[42]	BU	pleural effusion
13	17/F	1982	MPO(+) α-NB(+) ASD(+)	CD13(+), CD14(+), CD33(+), CD36(+)	203	50, XX, +8, +9, +19, t(9;22)(q34;q11), +der(22) t(9;22)(q34;q11)	BU	liver, LN, skin
14	62/F	1987	MPO(+) α-NB(+)	CD13(+), CD14(+), CD36(+)	63	N.D.	ranimustin	lung
15	63/F	1984	MPO(−) α-NB(+) ASD(−)	CD13(+), CD33(+), CD4(+), CD14(−)	< 2.0	60-66, XX, t(9;22)(q34;q11), +additional abnormality	none	rib
16	63/F	1990	MPO(+) α-NB(+)	CD13(+), CD33(+)	31	+8, +13, del(13)(q?) ×2, +18, der(22) t(9;22)(q34;q11)	IFN	none
17	69/F	1998	N.D.	CD68(+), CD45(+), CD34(+), lysozyme(+)	N.D.	t(9;22;22)(q34;q31;q13)	IFN, HU	sacrum
Our case	47/M	2005	MPO(−) α-NB(+) ASD(−)	CD4(+), CD14(+), CD33(+), CD64(+), CD34(+), CD13(−)	180	53, X, Y, +1, +3, +6, +8, +8, t(9;22)(q34;q11.2), +13, −17, +19, add(19)(q13), +21, +der(22)t(9;22)[5], 55, idem, +18, +21[6], 58, idem, +2, i(8)(q10), +17, +18, +18, +21, [2]	HU, imatinib, nilotinib, dasatinib	liver, skin

Abbreviations: BC, blastic crisis; lysozyme, serum lysozyme (μg/ml); MPO, myeloperoxidase; α-NB, alpha-naphthylbutyrate BU, busulfan; 6-MP, mercaptopurine; ACNU, nimustine; DNR, Daunorubicin; VCR, vincristin; IFN, interferon; ASD, naphthol ASD chloroacetate; HU, hydroxyurea; N.D., not described;

fied *bcr-abl* may have contributed to the genomic instability in the present patient. The loss of 17p due to −17, which was observed in the karyotype at the time of blast crisis in the present patient might have diminished the function of the *p53* gene and subsequently enhanced the progression of CML.[21]

In relation to possible *bcr-abl*-caused genetic evolution, blast crisis is often associated with additional cytogenetic and secondary molecular changes that contribute to the enhanced proliferation and survival, as well as differentiation arrest, of CML cells.[22] With the transition from CML chronic phase to blast crisis, 60% to 80% of patients acquire chromosomal changes in addition to the Ph chromosome.[23] The most common changes include double Ph chromosome, trisomy 8, trisomy 19, and isochromosome 17.[23] Previous cases of monocytic crisis also showed chromosomal abnormalities involving chromosomes 8, 19, and 22, as observed in the present case ; however, these abnormalities are not specifically restricted to monocytic crisis. Of interest, the karyotype at the time of blast crisis was quite different from that during the accelerated phase in the present patient (Fig. 2) ; the karyotype during the crisis was hyperdiploid with 53 to 58 chromosomes and contained many trisomies and some monosomies. As a speculation for the mechanism of hyperdiploid change, previous treatment with hydroxyurea may have contributed to the development of chromosomal abnormalities because a review regarding cytogenetic evolution in CML[20] indicated a close relationship between previous treatment with hydroxyurea or busulfan and hyperdiploid changes with+8, +Ph, i(17q), +19, +21, +17, −7, or −17 during the advanced stage of CML, many of which were present in the karyotype during the crisis in the present patient. Therefore, previous hydroxyurea treatment and *bcr-abl* amplification might have caused multi-step molecular genetic evolution resulting in the hyperdiploid tumor cells from the period of accelerated phase to that of blast

crisis in the present patient.

Resistance of CML cells to TKIs is induced by several mechanisms and is frequently associated with a specific point mutation in the *bcr-abl* kinase domain.[24] There have been several reports regarding other mechanisms of resistance, including the amplification of *bcr-abl*, over-expression of the multidrug resistance P-glycoprotein, and activation of alternative signaling pathways, such as those involving the *Src* family kinases, *Ras*, phosphatidylinositol 3-kinase, Janus kinase, and the signal transducer and activator of transcription.[25] CML cells in the present patient apparently showed resistance to imatinib and dasatinib, although the exact efficacy and resistance were unclear because of poor adherence to each treatment. Nevertheless, no known and available *bcr-abl* point mutation was detected at any phase of CML. The amplification of *bcr-abl* as observed in the established cell line, therefore, may have contributed to the resistance to imatinib in the present patient.

After the onset of blast crisis, we treated the present patient with nilotinib, which had brought about CHR in the chronic phase of CML. The efficacy of nilotinib for CML in the accelerated phase or blast crisis may have been established.[26,27] This agent suppressed the proliferation of leukemic cells in the peripheral blood for a long time in the present patient, although normal hematopoiesis hardly recovered, and focally residual leukemic cells were present in the bone marrow, liver, and spleen. Extensive bone marrow necrosis observed during the period of severe leucopenia under the treatment with nilotinib may have contributed to the recovery failure of normal hematopoiesis. Bone marrow necrosis in CML has been reported in at least 14 patients, most of whom were in the blastic phase.[28] The necrosis results from cellular hypoxia due to ischemia of marrow microcirculation as a consequence of inflammatory damage or mechanical obstruction.[29] Bone marrow necrosis has also been associated with the use of imatinib mesylate.[29-31] These reports suggest that overgrowth of leukemic cells during blast crisis of CML causes failure of the microcirculation. Thus, the causative role of nilotinib in bone marrow necrosis should be investigated in patients with CML blast crisis in future.

DISCLOSURE

We have no conflicts of interest with regard to any companies or individuals.

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