

[CASE REPORT]

A Rare Monocytic Crisis of Chronic Myelogenous Leukemia Presenting with Unusual Extramedullary Manifestations and an Atypical (14;22)(q24;q11.2) Translocation in the Bone Marrow

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Abstract:

A 48-year-old man was admitted due to marked leukocytosis. Bone marrow examinations resulted in a diagnosis of Philadelphia (Ph) chromosome-positive chronic myeloid leukemia. One month later, massive muscle and bone invasion by leukemic cells was detected. After induction chemotherapy, he complained of a headache and visual loss, which was caused by a leukemic infiltration in the central nervous system. After temporary remission in response to chemotherapy, the disease relapsed in the form of an intracranial tumor. The unusual t(14;22)(q24;q11.2) translocation of the Ph-chromosome and the significant increase in monocytes observed might have contributed to the unique and aggressive clinical course.

Key words: monocytic crisis, Philadelphia (Ph) chromosome positive chronic myelogenous leukemia, (14;22)(q24;q11.2) translocation, extramedullary manifestations

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by a marked proliferation of myeloid lineage mediated by BCR-ABL fusion gene. The translocation of BCR and ABL is typically detected as t(9;22)(q34;q11), as known as Philadelphia (Ph) chromosome, but some CML cases present variant translocation. We report a case of CML with t(14;22) translocation and atypical clinical manifestation.

Case Report

A 48-year-old man presented with pain in his shoulder, waist, and upper legs in January 2014. One month later, he visited a clinic, and a peripheral blood (PB) analysis showed a white blood cell count of 33,500/mm³ and a blast frequency of 1% (Table). He was referred to our hospital, and

a bone marrow (BM) examination demonstrated hypercellularity, with a predominance of myeloid cells. As significant dysplastic changes were observed (Fig. 1), and the absolute number of PB monocytes exceeded 1,000/mm³ (Table), the patient was tentatively diagnosed with the myeloproliferative type of chronic myelomonocytic leukemia (CMML).

A karyotype analysis using the G-banding method demonstrated a unique (14;22)(q24;q11.2) translocation (Fig. 2), and a fluorescence hybridization (FISH) analysis detected the BCR-ABL fusion gene signal at a frequency of 87%. As the number of blast cells in the patient's BM had not increased, he was ultimately diagnosed with Ph chromosome-positive CML in the chronic phase (CP). His Sokal score was 0.6 (low), and the Hasford score was 227.15 (low). Two weeks later, massive leukemic cell invasion was observed in the patient's muscle and bone (Fig. 3). A histological examination of the right iliac muscle revealed the extramedullary infiltration of CML cells with monocytic features, while no significant increase in the number of blasts was detected

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Table. Laboratory Data at Admission.

WBC	33,400 / μ L	TP	4.9 g/dL	NAP score	173 pts
blast	0.5 %	Alb	2.2 g/dL	O	29 %
pro	0.0 %	BUN	17.8 mg/dL	I	12 %
myelo	3.5 %	Cre	0.74 mg/dL	II	27 %
meta	1.0 %	UA	6.7 mg/dL	III	21 %
stab	5.5 %	AST	18 IU/L	IV	11 %
seg	67.0 %	ALT	12 IU/L	V	0 %
eos	2.0 %	LDH	550 IU/L		
bas	2.5 %	ALP	231 IU/L	PT	11.5 s
mono	8.5 %	T-Bil	0.4 mg/dL	APTT	33.5 s
lymph	9.5 %	Na	139 mEq/L	Fbg	499 mg/dL
Hb	17.2 g/dL	K	3.5 mEq/L	FDP	2.7 mg/dL
Plt	21.8×10^4 / μ L	Cl	97 mEq/L		
		Ca	12.8 mg/dL		
		CRP	12.15 mg/dL		

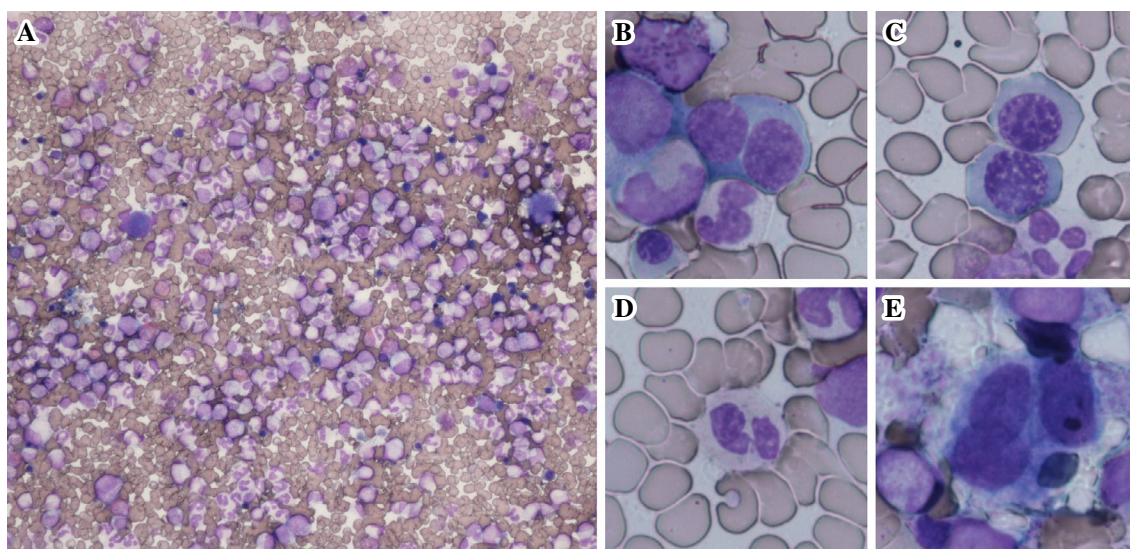


Figure 1. Bone marrow smear obtained at presentation (A). Dysplastic changes, such as erythroblasts with multinuclearity (B), megaloblastoid changes (C), hypo-segmented neutrophils (D), and megakaryoblasts with multiple widely separated nuclei (E), were observed. Magnification: A, $\times 100$; B-E, $\times 1,000$.

during an immunohistochemical study or FISH analysis (Fig. 4), which suggested the disease had progressed to extramedullary monocytic crisis (BC). Before the Ph positivity was proven, under the diagnosis of CMML with extramedullary disease (EMD), induction chemotherapy with daunorubicin and cytarabine was administered, which reduced the size of the extramedullary tumor. However, one month later, the patient complained of a severe headache and right visual loss. Fundoscopy revealed right optic disc edema. One week later, he suffered bilateral complete vision loss and bilateral optic disc edema due to optic neuritis.

Computed tomography (CT) and magnetic resonance imaging (MRI) demonstrated a subdural hematoma in the left frontal lobe and shaggy enhancement involving the falx cerebri, which were suggestive of pachymeningitis, along

with thickening of the bilateral optic nerves. Lumbar puncture was also performed. Again, it was found that mature myeloid cells (CD33/13-positive but CD34-negative) rather than blasts predominated, and the mature myeloid cells were determined to be of CML origin by a FISH analysis, with BCR-ABL fusion signal positivity at a frequency of 99%. BM aspiration revealed a complex karyotype together with the t(14;22)(q24;q11.2) translocation: 46XY, +i(1)(q10), der(14)t(14;22)(q24;q11.2), der(15;22)(q10;q10)t(14;22) [7]/47, idem,+mar1 [2]/46,idem,-der(15;22) t(14;22),+mar2 [3]/48, idem,-der(14)t(14;22),+15,-der(15;22)t(14;22),+der(22)t(14;22),+mar3,+mar4 [4], and the blast count was only 0.4%. The amount of major bcr-abl chimeric mRNA as measured by a reverse transcription polymerase chain reaction (RT-PCR) assay was 4.4×10^4 copies per microgram mRNA.

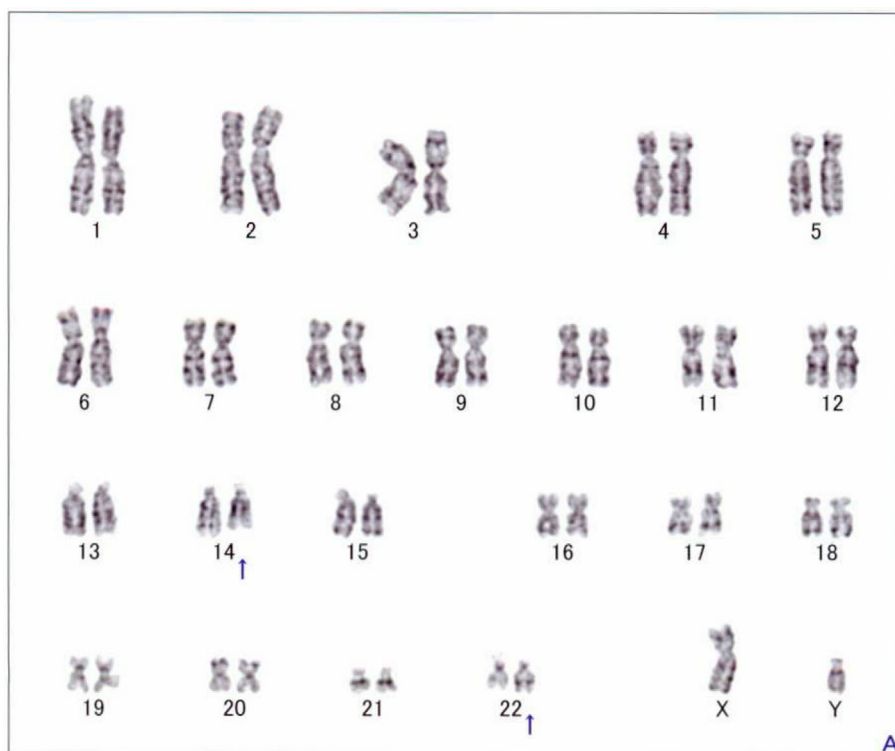


Figure 2. Karyogram of G-banding assay of BM at the initial presentation. The two arrows indicate the 14th and 22nd chromosomes, which seem to be translocated with each other. BM: bone marrow

Intensive chemotherapy involving high-dose cytarabine and dasatinib, a second-generation tyrosine kinase inhibitor (TKI), together with repeated intrathecal infusions of cytarabine, was administered. The Bcr-abl mRNA level in PB was measured monthly by a transcription mediated amplification assay (Amp-CML[®]; Fuji Rebio, Tokyo, Japan) and achieved a major molecular response (24 copies per 0.5 microgram RNA) after 2 months. When the second CP was achieved, we started to search the Japanese BM registry for unrelated human leukocyte antigen-matched donors. Three months later, although a major molecular response was maintained less than 5 copies by Amp-CML assay, the patient was transferred to our hospital due to the emergence of behavioral disturbance, which was found to have been caused by a tumor in the left frontal lobe. The cerebrospinal fluid (CSF) cell counts were increased, and BCR-ABL fusion signals in the CSF were positive at a frequency of 100% by a FISH analysis but were not detected in the BM (data not shown), suggesting the central nervous system (CNS) relapse of CML. The same chemotherapy regimen involving high-dose cytarabine and intrathecal injections of cytarabine was administered; however, the patient eventually died due to the progression of his disease.

Discussion

An extramedullary BC of CML is defined as the development of tumors composed mainly of CD34-positive blasts, irrespective of the presence/absence of blast proliferation in

the BM. The prevalence of extramedullary BC has been reported to range from 7-17% among patients with CML-BC (1-3).

In general, EMD in CML most commonly develops in the lymph nodes, skin, bone, or CNS (1, 4). In the present case, tumors were detected in the patient's bone and muscle at presentation and spread to the CNS, including the optic nerves, after induction chemotherapy. Bone invasion is not uncommon in cases of acute leukemia, and the bone is the most common site of EMD in CML (1, 5). Such invasion generally occurs in the terminal part of the blastic phase (6, 7), but it can be seen at the initial presentation in rare cases (8, 9). In contrast, skeletal muscle invasion is rarely observed, and only a few cases have been reported in the literature (6).

CNS relapse has been documented in approximately 20% of CML patients that suffer from BC (10, 11). Isolated CNS relapse in patients who maintained at least hematological remission has also been reported (12, 13). In the latter cases, contrary to the findings of the present case, immature blasts were the predominant cells in the patients' cerebrospinal fluid. Dural metastasis of CML is rare, but it has been reported (14, 15), and leukemic infiltration of the dura mater is considered to be a cause of chronic subdural hematoma (15). Hypertrophic panmeningitis is a rare disorder characterized by fibrosis and thickening of the dura matter, and it can occur idiopathically or secondary to an infection, autoimmune disorder, or malignancy, including CML (16).

The optic nerve is another rare site of CNS inva-

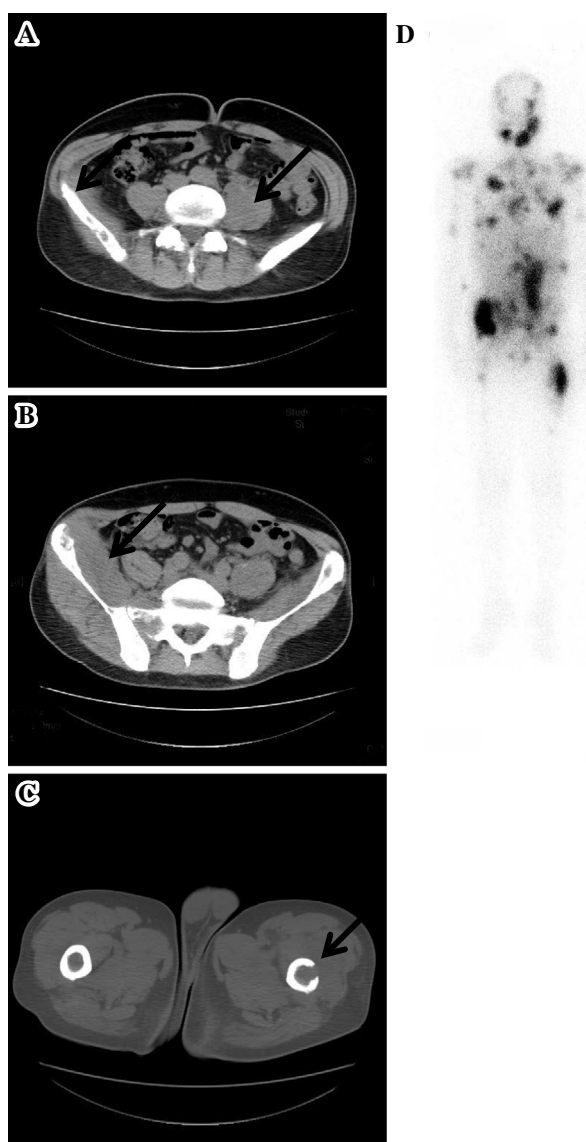


Figure 3. CT images showing muscle (A, B) and bone (C) invasion by leukemia cells. Gallium-67 scintigraphy (D) revealed extensive infiltration by extramedullary tumor cells.

sion (17-19). In an autopsy study, 16% of CML cases showed optic nerve involvement (20). The combination of decreased vision and leukemic infiltration into the optic nerve is considered to be an ophthalmologic emergency, and urgent radiotherapy is useful for treating such visual disturbance (21). In the present case, we selected combined chemotherapy involving high-dose cytarabine and repeated intrathecal infusions of cytarabine. Dasatinib was also administered, as it has been reported to be effective in resolving such optic nerve infiltration (22). Unfortunately, the patient's visual acuity did not recover, even after the disappearance of the dural and meningeal infiltration.

The present case is unique, as no significant increase in the number of blast cells was observed in the patient's BM at presentation or during disease progression. Extramedullary BC is quite a rare event in CML-CP. Furthermore, it is unusual for EMD to involve the proliferation of monocytic cells, rather than blasts. In the past, there have been a few

reports of CML-derived tumor formation due to extramedullary hematopoiesis without being composed of blastomas (5, 23, 24).

In the current case, the initial tentative diagnosis was CMML due to significant dysplastic changes in the BM accompanied by an elevated monocyte count in the PB. CMML was also suspected, as the patient's neutrophil alkaline phosphatase score had not decreased and the typical Ph chromosome was not detected on a G-band analysis. Mild-to-moderate dysplastic changes can occur in typical cases of CML that progress to severe dysplasia in the latter stages of the condition; however, this does not match the initial presentation seen in the present case (25). Monocyte production increases during the course of Ph-positive CML, until monocytes account for as many as 10-20% of PB cells (26). To avoid the misdiagnosis of CML as CMML, it was proposed that the absence of relative monocytosis (a PB monocyte frequency of >8%; it was 8.5% in the present case) should be a criterion for the diagnosis of CML when the total number of leukocytes is higher than $20 \times 10^9/L$ (25). Ph-positive CML rarely expresses the p190^{BCR-ABL} transcript, which is often accompanied by prominent monocytosis and a hematological phenotype that is intermediate between those of CML and CMML (27-29). In our case, the conventional p210^{BCR-ABL} transcript, but not the p190^{BCR-ABL} transcript, was detected during an analysis based on the reverse transcription polymerase chain reaction. In 10% of CML cases, the Ph chromosome is detected as a variant translocation, where the deleted segment on chromosome 22 is translocated to a chromosome other than chromosome 9, or a complex translocation involving a different chromosome (30-32). The (14;22)(q24;q11.2) translocation has not been reported before. These types of variant Ph chromosome are usually mediated by three-way translocation, but the mechanism in this case was not proven by spectrum karyotyping or a multi-color banding assay. Such atypical chromosomal changes together with the presence of marked PB monocytosis and significant dysplasia delayed the diagnosis of CML in the present case. The mechanism responsible for the development of this complex rearrangement and its clinical significance need to be elucidated in future.

With the transition from CML-CP to the BC phase, chromosomal changes other than the typical changes involving the Ph chromosome occur in 60 to 80% cases, such as double Ph chromosomes, trisomy 8 or 19, or isochromosome 17 (33). It is speculated that BCR-ABL affects DNA repair, leading to genomic instability, which causes clonal evolution, including blast crises. In the present case, in addition to the typical chromosomal changes a complex karyotype was detected in the BM sample obtained after the induction chemotherapy, even though it did not exhibit significant blast proliferation. Tsunemine et al. reported a case of CML involving a monocytic crisis (34). In their case, the blast cells displayed an immature monocytic morphology and expressed monocytic markers (i.e., CD14 and 64 antigens) on their surfaces. They also summarized 12 cases of CML in-

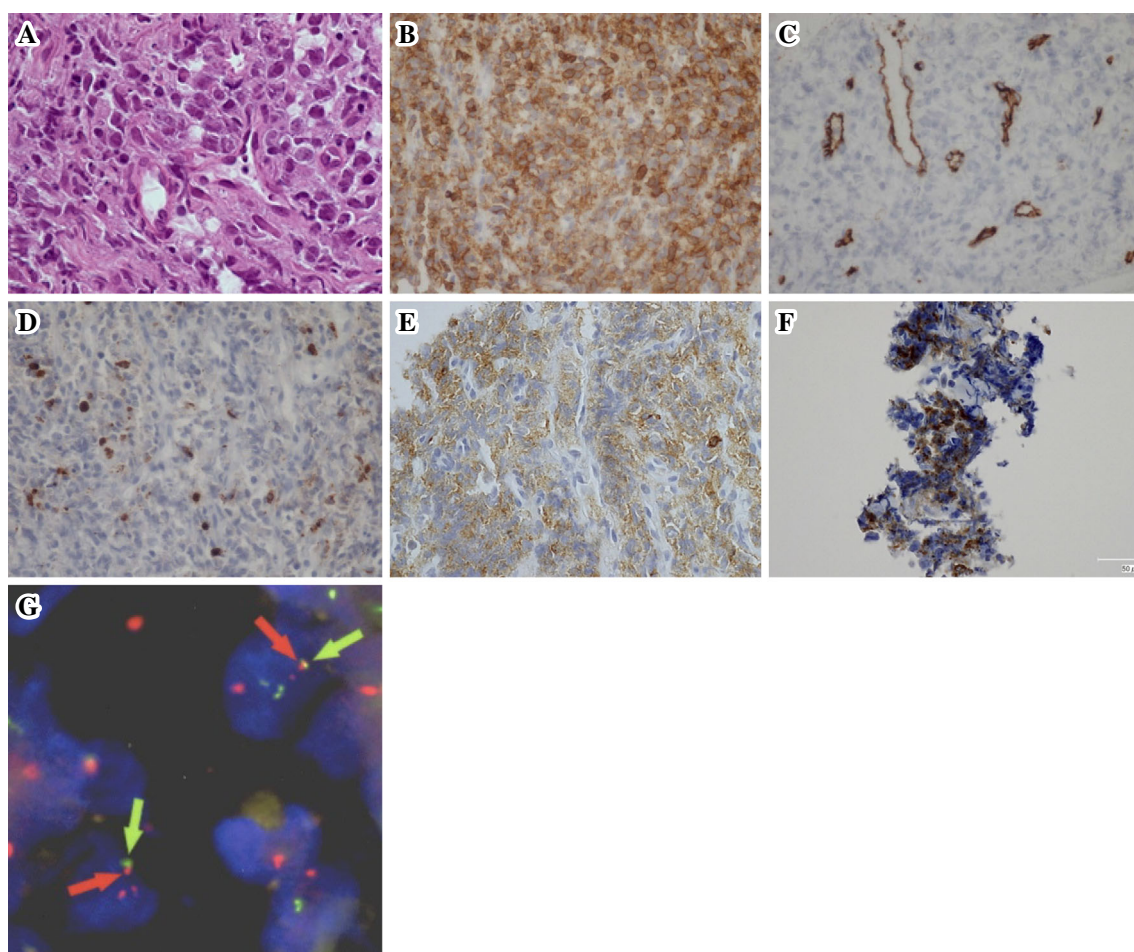


Figure 4. An immunohistochemical study and FISH analysis of right iliac muscle samples. (A: Hematoxylin and Eosin staining, B: positive CD45 staining, C: negative CD34 staining, D: negative myeloperoxidase staining, E: positive CD68 staining, F: positive CD168 staining, G: positive BCR-ABL fusion signal staining). Magnification: A, $\times 600$; B-F, $\times 400$. FISH: fluorescence hybridization

volving monocytic crises that exhibited features similar to our case [i.e., additional chromosomal changes (in 9 out of 10 cases) and/or EMD (in 9 out of 10 cases)]. The present case can also be categorized as a monocytic crisis of CML that resulted in numerous high-risk genetic mutations (similar to those seen in CMML), which might have contributed to the aggressive and resistant nature of the disorder.

In the current case, even after intensive chemotherapy combined with dasatinib, which crosses the blood-brain barrier and is considered to be an effective treatment for CNS invasion of Ph-positive leukemia (35), the disease relapsed as a cerebral tumor. A case reported by Tsunemine et al. also progressed to BC during dasatinib treatment, and the patient subsequently developed leukemic meningitis, which prevented them from undergoing a BM transplant (34). Even in the TKI era, cases of CML-BC are sometimes observed and are considered to be candidates for stem cell transplants (SCT) (36). Rare cases of monocytic CML-BC might be suitable as candidates for SCT as soon as the second CP is achieved; SCT is the sole curative treatment for CML-BC and CMML (37), as CNS involvement is difficult to overcome.

The authors state that they have no Conflict of Interest (COI).

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