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A Case of Isolated Lymphoblastic Relapse of the Central Nervous System in a Patient with Chronic Myelogenous Leukemia Treated with Imatinib

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Isolated central nervous system (CNS) relapse is a rare, unpredictable event in patients with CML. Some studies have reported cases of isolated CNS relapse in CML [1-13]. However, very few studies have reported on isolated CNS relapse in the blast phase (BP) of CML in Korea [14, 15]. We report a case of BP CML with extramedullary lymphoblast proliferation in the CNS without evidence of disease in the peripheral blood (PB) and bone marrow (BM).

A 54-yr-old man was diagnosed as having *BCR/ABL1* (b2a2 type)-positive CML in July 2012. He was considered to be in the chronic phase on the basis of his blast count on PB smear and BM aspiration, and subsequently, he was administered imatinib (400 mg/day). Three months after diagnosis, he demonstrated a complete hematologic response, major cytogenetic response, and no major molecular response according to the National Comprehensive Cancer Network Guidelines in Oncology for CML (karyotype 46,XY,t(9;22)(q34;q11.2)[7]/46,XY[23], *BCR-ABL1* fusion transcript of 0.933% based on the International Scale [IS]) [16]. Seven months after initial diagnosis, he was readmitted with a complaint of headache since two months. Diffusion brain magnetic resonance imaging with magnetic resonance angiography revealed abnormal leptomeningeal enhancement of both paramedian gyri, suggesting involvement of leukemic cells. In cerebrospinal fluid (CSF) study, his CSF was turbid and had increased number of white blood cells (WBCs) (3.5×10^9/L), and almost all WBCs were lymphoid cells. Wright stain of cytospin-smeared CSF showed lymphoid cells with high nuclear-to-cytoplasmic ratio and coarse chromatin pattern with prominent nucleoli. Lymphoid cells were negative on periodic acid-Schiff staining. In flow cytometric analysis, the lymphoid cells had an early pre-B phenotype with an aberrant CD33 expression (positive for CD45, CD34, CD33, terminal deoxynucleotidyl transferase (TDT), HLA-DR, CD19, and CD10). The result of reverse transcriptase-PCR for detecting *BCR-ABL1* fusion transcript was positive (b2a2 type) in CSF. On complete blood count analysis, Hb level was 13.3 g/dL, WBC count was 11.41×10^9/L, and platelet count was 167×10^9/L. There was no morphologic evidence of lymphoblasts in PB and BM samples (Fig. 1). The patient was treated with dasatinib, intrathecal methotrexate, and cranial irradiation therapy. One week after initiation of treatment, CSF showed decreased WBCs (0.002×10^9/L) with no evident malignant cells. Two months after relapse, patient demonstrated a complete hematologic response, complete cytogenetic response, and major molecular response (karyotype

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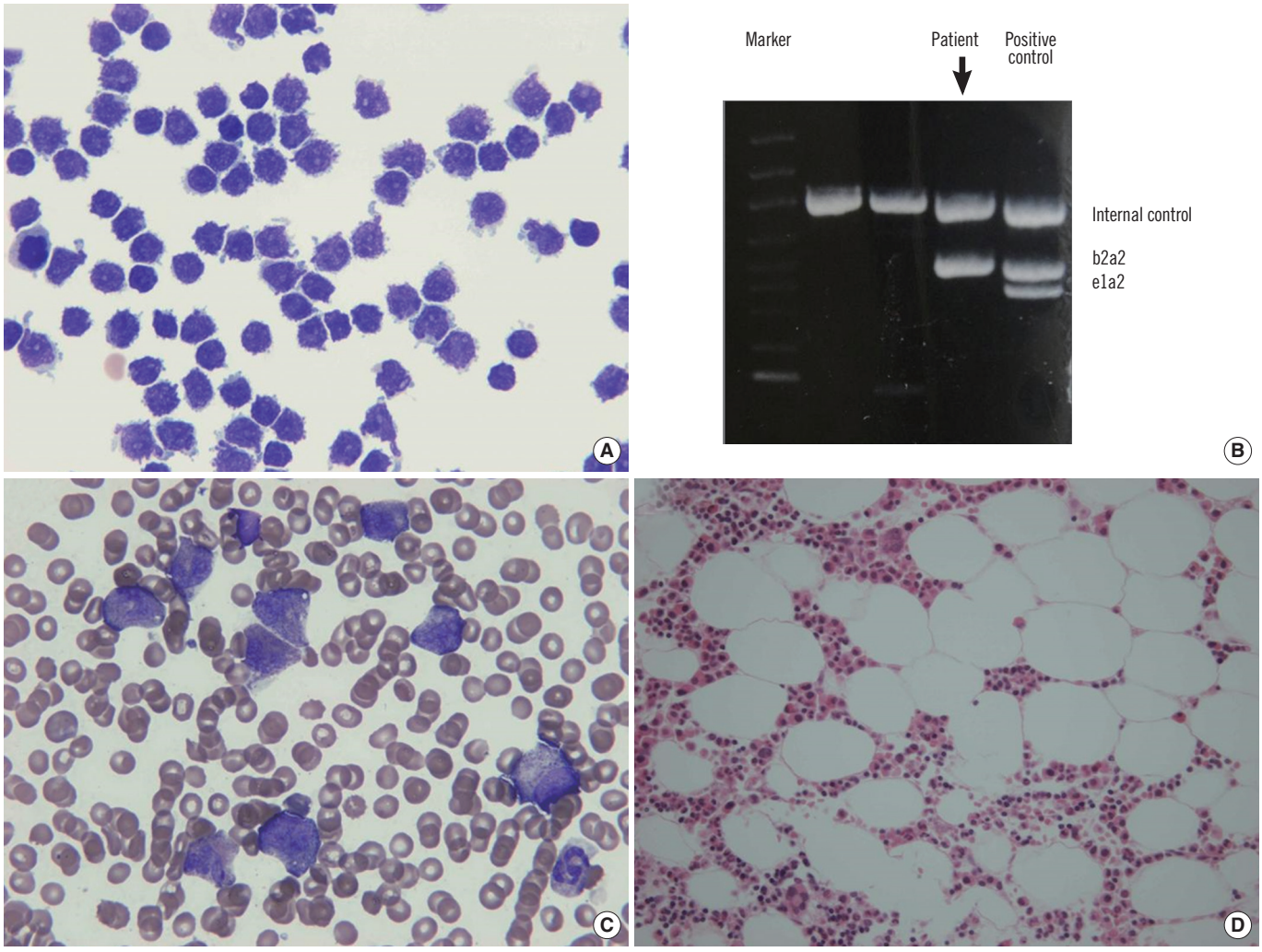

Fig. 1. Cerebrospinal fluid (CSF) findings at seven months after initial diagnosis of CML. (A) Cytospin-smeared CSF showing numerous lymphoid cells with high nuclear-to-cytoplasmic ratio and coarse chromatin pattern with prominent nucleoli (Wright stain, ×1,000). (B) The major *BCR-ABL1* fusion transcript (b2a2 type) was detected in the CSF sample using reverse transcriptase-PCR. (C) Peripheral blood smear showing slightly increased white blood cell count including neutrophils with left-shiftness. No malignant lymphoid cells are seen (Wright stain, ×1,000). (D) Bone marrow aspirate smear showing myeloid hyperplasia without definite lymphoblasts (Wright stain, ×1,000).

46,XY[30], *BCR-ABL1* fusion transcript of 0.011% by IS). His laboratory findings are summarized in Table 1.

This patient showed optimal response to imatinib therapy that was administered according to the European Leukemia Net recommendation [17]. However, spontaneous, isolated CNS relapse occurred after 7 months of imatinib therapy. In previous reports, isolated CNS relapse was observed in patients with imatinib-treated CML or Philadelphia chromosome-positive acute lymphoblastic leukemia [1-15]. This phenomena raised the possibility that imatinib may poorly penetrate the blood-brain barrier. Some studies have demonstrated that imatinib does not reach therapeutic levels in CSF, and therefore, imatinib therapy alone may lead to a potential risk of CNS involvement [1, 10].

We present a summary of 15 cases of isolated CNS relapse in CML patients in Table 2. Isolated CNS relapse was predominantly observed in men (M:F=11:4) with a median age of 42 yr (range, 17-73 yr). The major presenting symptom of isolated CNS relapses was headache with or without other neurologic symptoms. Nine of 15 cases (60%) had complete cytogenetic response state at CNS relapse. The median time from treatment initiation to CNS relapse was 25 months (range, 4-58 months) in 15 cases. Findings from these cases show that isolated CNS relapse has no correlation with a response to imatinib therapy. No other sites were involved, except for CNS in all of the 15 cases, and eight cases had B-cell lymphoid phenotype of blasts [2-15]. In our case, the patient was a middle-aged man experi-

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Table 1. Brief laboratory data of the case

	At diagnosis: CML onset	After 3 months	After 6 months	After 7 months: CNS relapse	After 9 months	After 12 months
Peripheral blood samples						
WBC ($\times 10^9$/L)	98.75	3.46	5.69	11.41	2.75	2.5
PLT ($\times 10^9$/L)	351	157	206	167	171	57
Blast (%)	0	0	0	0	0	0
Bone marrow samples						
Blast (%)	1.8	0.2	1.0	0.4	0.4	2.4
Karyotype	46,XY,t(9;22)(q34;q11.2)[20]	46,XY,t(9;22)(q34;q11.2)[7]/46,XY[23]	46,XY,t(9;22)(q34;q11.2)[1]/46,XY[11]	46,XY,t(9;22)(q34;q11.2)[3]/46,XY[27]	46,XY[30]	46,XY[20]
BCR-ABL1 fusion gene (RT-PCR)	Positive (b2a2)	Positive (b2a2)	Positive (b2a2)	Positive (b2a2)	Positive (b2a2)	Negative
BCR-ABL1 fusion gene (qPCR) IS%	26.280	0.933	0.317	NA	0.011	0
CSF samples						
WBCs ($\times$ 10/L)	NA	NA	NA	3.527	4	NA
BCR-ABL1 fusion gene (RT-PCR)	NA	NA	NA	Positive (b2a2)	Negative	NA

Abbreviations: CNS, central nervous system; WBC, white blood cell; PLT, platelet; RT-PCR, reverse transcriptase PCR; qPCR, quantitative PCR; CSF, cerebrospinal fluid; IS, international scale; NA, not available.

encing headaches as the initial manifestation of CNS relapse. Excluding the case in a 17-yr-old patient [6], the time interval from the diagnosis to CNS relapse in our case was shorter (7 months) than the previously reported cases. Most of the previous cases had received additional treatment with intrathecal chemotherapy and cranial irradiation, and had showed good response [2-15]. Nishimoto et al. [13] reported a case with successful treatment with dasatinib and allogeneic hematopoietic stem cell transplantation (HSCT). Our patient was also treated with dasatinib after CNS relapse in BP of CML, and is currently being prepared to receive HSCT. Brain imaging, CSF study, or CNS prophylaxis are not routinely undertaken in patients with chronic phase CML at diagnosis. To our knowledge, there are no recommendations on the evaluation of CNS disease in CML patients. There are prognostic classifications using four factors, such as age, size of spleen, platelet count, and blast count at diagnosis and they remain valid for imatinib treatment [18-20]. Our patient was at high risk according to risk stratifications by Hasford et al. [19] and Sokal et al. [20] (Hasford score 1,509 and Sokal score 1.35). However, risk factors of CNS relapse have not been investigated. Further studies are needed to identify risk factors of CNS relapse.

To our knowledge, this is the third report of isolated CNS lymphoblast proliferation in a Korean CML patient. It is important to consider CNS relapse in chronic phase CML patients optimally treated with imatinib, especially in patients presenting with neurological symptoms, including headache. This emphasizes the need for brain imaging study and CSF monitoring in imatinib-treated CML patients even without evidence of disease progression on PB smear and BM studies.

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Table 2. Cases of isolated CNS blast crisis in CML

Reports	Age	Sex	Prior disease status	Treatment	First symptom at CNS involvement	BM status at CNS involvement	Time to CNS disease	Other involved sites	Phenotype of blasts	Additional treatment after CNS disease	Outcome
Rajappa et al. (2004) [2]	39	M	CP	Imatinib	Headache and vomiting	CCyR	17 months	None	NA	IT+RT	Alive
Bornhauser et al. (2004) [3]	56	F	NA	Interferon-α, hydroxyurea→imatinib	Sensorimotor deficit (blurred vision and ataxia)	Major CyR	24 months	None	Lymphoblast	IT+RT+ allo-PBSCT	Dead
Bujassoum et al. (2004) [4]	42	F	BP (lymphoblast)	Interferon-α, hydroxyurea→imatinib	Headache	CCyR	12 months	None	Lymphoblast	IT+allo-PBSCT +RT	Alive
Johnson et al. (2005) [5]	50	M	CP	Interferon-α→imatinib	Headache, nausea, and vomiting	Major CyR	16 months	None	Early pre-B lymphoblast	IT+allo-SCT	Dead
Matsuda et al. (2005) [6]	17	M	CP	Imatinib	Headache	CCyR	4 months	None	Mixed myeloid/ B-cell blasts	IT+RT	Alive
Kim et al. (2006) [14]	42	M	CP	Imatinib	Headache and vertigo	Major CyR	25 months	None	B lymphoblast	Craniotomy +IT	Dead
Aichberger et al. (2007) [7]	52	M	CP	Interferon-α→imatinib	Headache and ataxia	CCyR	58 months	None	Myeloblast	IT+RT	Alive
	73	F	CP→AP	Interferon-α→imatinib	Vertigo and blurred vision	CCyR+MMR	55 months	None	Myeloblast	IT+CT	Alive
Altintas et al. (2007) [9]	39	M	CP→AP	Hydroxyurea→imatinib	Headache, nausea, and vomiting	Minor CyR	7 months	None	Lymphoblast	IT+RT	Alive
Barlow et al. (2008) [8]	68	M	CP	Imatinib	Headache, leg cramp, tremor, and poor balance	CCyR	25 months	None	B-lymphoblast (pre-B)	IT+RT	Alive
Lee et al. (2009) [15]	39	M	NA	Imatinib	Headache and diplopia	CCyR	37 months	None	Lymphoblast	IT	Alive
Isobe et al. (2009) [10]	61	M	CP	Imatinib	Visual disturbance and vomiting	CCyR	16 months	None	B-lymphoblast (pre-B)	IT+autoPBSCT	Alive
Thomas et al. (2010) [11]	33	M	AP→BP	Hydroxyurea, imatinib→ cytosine arabinoside, dasatinib, and allo-PBSCT	Upper back pain, bilateral upper extremity weakness, dysarthria, and diplopia	CMR	33 months	None	Myeloblast	IT+RT	Alive
Fuchs et al. (2012) [12]	64	F	BP	Imatinib→dasatinib, allo-PBSCT	Cognitive and psychomotorical impairment	Major CyR+MMR	46 months	None	NA	OP+IT	Dead
Nishimoto et al. (2013) [13]	22	M	NA	Imatinib	Headache, fever, and impaired vision	CCyR	29 months	None	Lymphoblast	IT+RT+allo-SCT	Alive
Present case	56	M	CP	Imatinib	Headache	Major CyR	7 months	None	B-lymphoblast (early pre-B)	IT+RT	Alive

Abbreviations: CNS, central nervous system; BM, bone marrow; CP, chronic phase; AP, accelerated phase; BP, blast phase; CyR, cytogenetic response; CCyR, complete cytogenetic response; MMR, major molecular response; IT, intrathecal chemotherapy; RT, cranial irradiation; PB, peripheral blood; SCT, stem cell transplantation; NA, not available.

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