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Extramedullary B Lymphoblastic Crisis of CML, Presenting as a Leptomeningeal Tumor
– A Case Report –

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We report here on a rare case of a patient who presented with an extramedullary B lymphoblastic crisis as an initial manifestation of chronic myelogenous leukemia (CML). A 71-year-old man visited the emergency room due to suddenly developed dysarthria and right side weakness. Emergency craniotomy was done under the presumptive diagnosis of subdural hemorrhage. During the operation, a poorly demarcated firm mass was identified in the leptomeningeal space. Microscopically, the majority of the tumor was composed of monotonous immature cells with blast morphology, and these cells were immunoreactive for TdT, CD34, CD10 and CD20, indicating the precursor B-cell phenotype. The peripheral area of the tumor consisted of myeloid cells in various stages of maturation, and these cells were reactive for myeloperoxidase, chloroacetate esterase, CD43 and CD15. FISH analysis using the LSI *bcr-abl* dual color probe showed gene fusion signals in both the B-lymphoblasts and myeloid cells. The peripheral blood and bone marrow findings were consistent with CML with no evidence of a blast crisis. Cytogenetic study of the bone marrow demonstrated the 46, XY, t(9;22)(q34;q11) chromosome. A diagnosis of extramedullary B lymphoblastic blast crisis in a patient with Philadelphia chromosome-positive CML was made. Despite treatment, the patient died 3 months after he was diagnosed.

Key Words : Blast crisis; Chronic myelogenous leukemia; Fluorescent *in situ* hybridization; Philadelphia chromosome; Leptomeninges

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder that's characterized by the proliferation and accumulation of myeloid cells and their progenitors. These cells originate from a pluripotent hematopoietic stem cell and the CML is associated with the *BCR/ABL* fusion gene that is usually identified at the chromosome level as the Philadelphia chromosome or t (9;22)(q34;q11.2).[1] The development of CML is a multistep process that is initiated by the indolent proliferation of immature and maturing granulocytes in the peripheral blood and bone marrow. This stage, known as the chronic phase, eventually progresses to the accelerated phase and finally to the blast phase that represents a terminal transformation resembling acute leukemia.[1] The blast phase of the CML is defined as the presence of 20% or more blasts among the peripheral white blood cells or nucleated bone marrow cells, or an extramedullary blast proliferation is observed.[2] In 5-10% of the cases, the blast phase can present at extramedullary sites,[1] such as bone, lymph node, skin, soft tissue, and the central and peripheral nervous systems.[3] This condition, which is called extramedullary blast crisis, usually presents as a preceding event for the progression of CML or as an initial manifestation of relapse in patients with previously treated CML.[4] When an extramedullary blast crisis occurs as an isolated event without a previous history of CML, it is important to differentiate a CML patient in a blast crisis from *de novo* non-Hodgkin's lymphoma with blast morphology for administering the appropriate treatment. We report here on a rare case of an extramedullary B lymphoblastic crisis involving the leptomeninges as an initial manifestation of CML.

CASE REPORT

A 71-year-old man came to the emergency room in January 2008 with suddenly developed dysarthria and right side weakness. He had been treated for hypertension for 20 years and he had an attack of myocardial dysfunction 7 years previously. The

initial blood pressure was 150/90 mmHg. A CT scan of the head showed a crescent-shape enhancement in the left fronto-temporo-parietal area (Fig. 1A). Emergency craniotomy was done under the presumptive diagnosis of subdural hemorrhage. During the operation, a poorly demarcated firm mass with a smooth surface was identified in the leptomeningeal space. Piecemeal resection was done. The tumor was submitted to the pathology lab in fragments and the total weight of the pieces was 50 g. The cut surface showed a yellow to white homogenous appearance (Fig. 1B).

On microscopic examination, the tumor involved the leptomeninges with a diffuse and nodular infiltrative growth pattern. The majority of the tumor was composed of monotonous immature cells with large nucleus, finely stippled chromatin, occasional nucleoli and relatively abundant cytoplasm. The cells were immunoreactive for CD34, TdT, CD10, CD20, and CD43. C-kit positive cells were rarely seen. However, the tumor cells showed negative results on the immunohistochemical staining for CD3 and CD15, and on the histochemical staining for myeloperoxidase and chloroacetate esterase (Table 1 and Fig. 2). The results of the ancillary studies indicated that the tumor cells were of the precursor B lymphoblast phenotype. The periphery of the lesion consisted of myeloid cells in various stages of maturation, and these cells were reactive for myeloperoxidase, chloroacetate esterase, CD43 and CD15, but they were non-reactive for CD34, c-kit, TdT, CD3 and CD20, indicating a CML component. Forty to 50 percent of the cells were CD10-positive (Table 1 and Fig. 2). The Ki-67 labeling was high in both the B lymphoblast and CML components (80-90%). The expression of p53 was high in the precursor B lymphoblast component (60-70%), but low in

Table 1. Summary of immunohistochemical and histochemical staining results in leptomeningeal tumor

	Blast component	CML component
CD34	+	–
TdT	+	–
CD10	+ (>95%)	+ (40-50%)
CD20	+	–
CD3	–	–
CD43	+ (60-70%)	+ (>95%)
CD15	–	+
Myeloperoxidase	–	+
Chloroacetate esterase	–	+

CML, chronic myelogenous leukemia.

Table 2. Differential count of WBC in peripheral blood smear

Blast	1%
Promyelocyte	4%
Myelocyte	9%
Metamyelocyte	11%
Band neutrophil	16%
Neutrophil	55%
Lymphocyte	1%
Monocyte	3%
Eosinophil	0%
Basophil	0%

WBC, white blood cell.

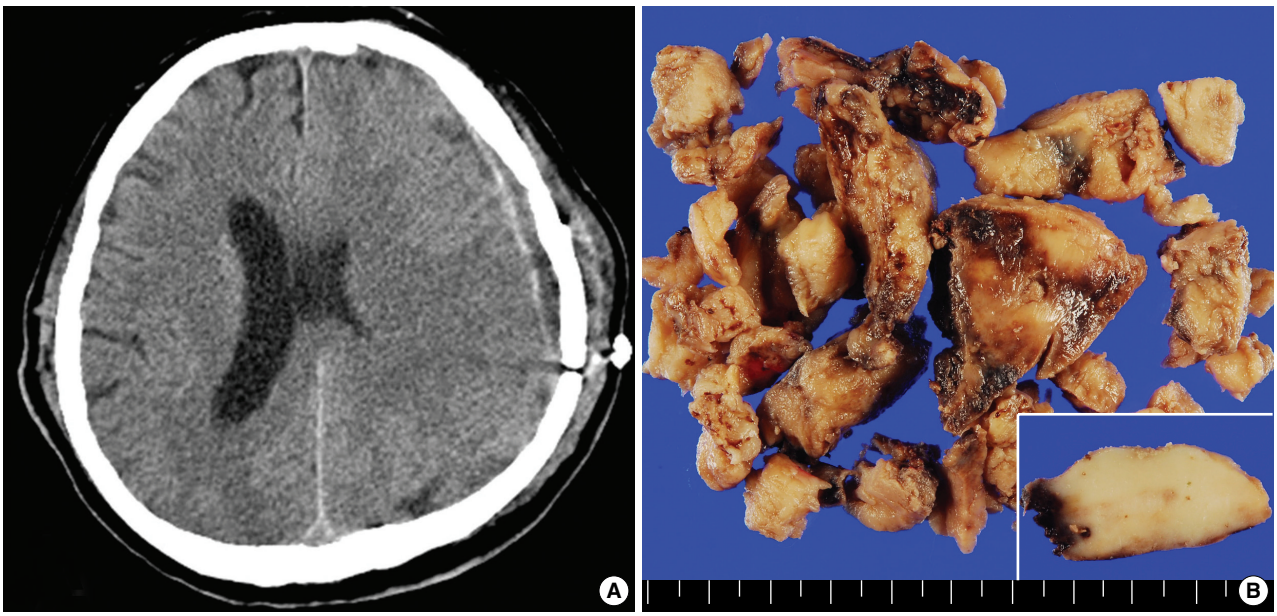

Fig. 1. CT scan of the head shows a crescent-shape enhancement in the left fronto-temporo-parietal area, and deviation of the left ventricle to the right side due to diffuse brain edema (A). The tumor masses submitted in fragments are gray white and firm (B).

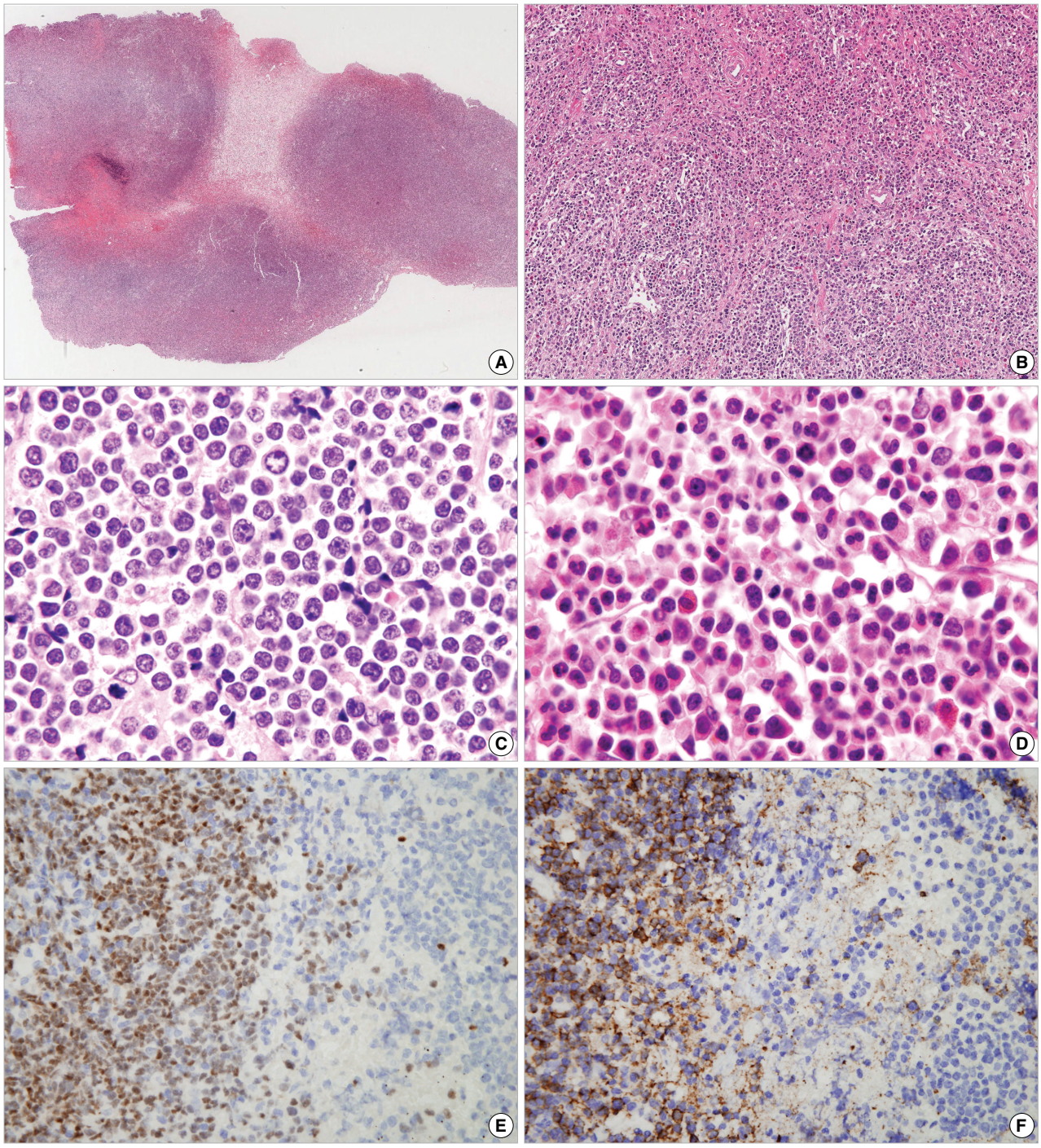

Fig. 2. The leptomeningeal tumor shows diffuse and nodular growth pattern (A). The junction area (B) shows mophologically distinct, blast (C) and CML (D) components. The cells in blast component are positive for TdT (E) and CD20 (F). *(Continued on the next page)*

the CML component (<5%). FISH analysis performed on the formalin-fixed paraffin-embedded tissue section using the LSI® *bcr/abl* dual color probe (Vysis Inc., Des Plaines, IL, USA) showed gene fusion signals in both the B lymphoblast and CML components (Fig. 3). Since the cells in the paraffin-embedded tissue section were piled up one on another, quantitatively analyzing this positive signal was difficult to do. The leptomeningeal tumor was considered to be a localized B lymphoblastic transformation in CML.

On admission, the patient's white blood cell count was

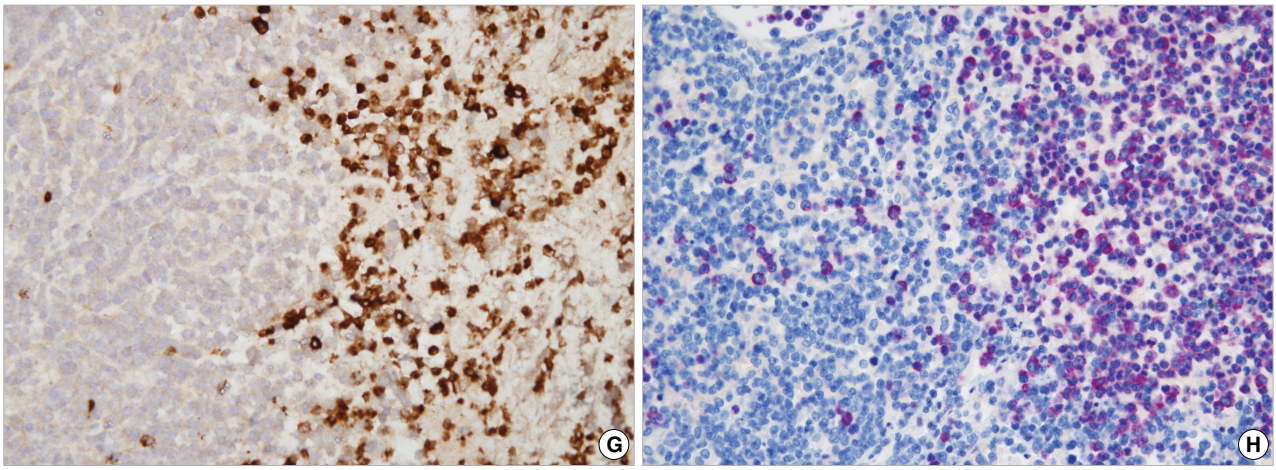

Fig. 2. *(Continued from the previous page)* Whereas the cells in CML component are positive for myeloperoxidase (G) and chloroacetate esterase stain (H).

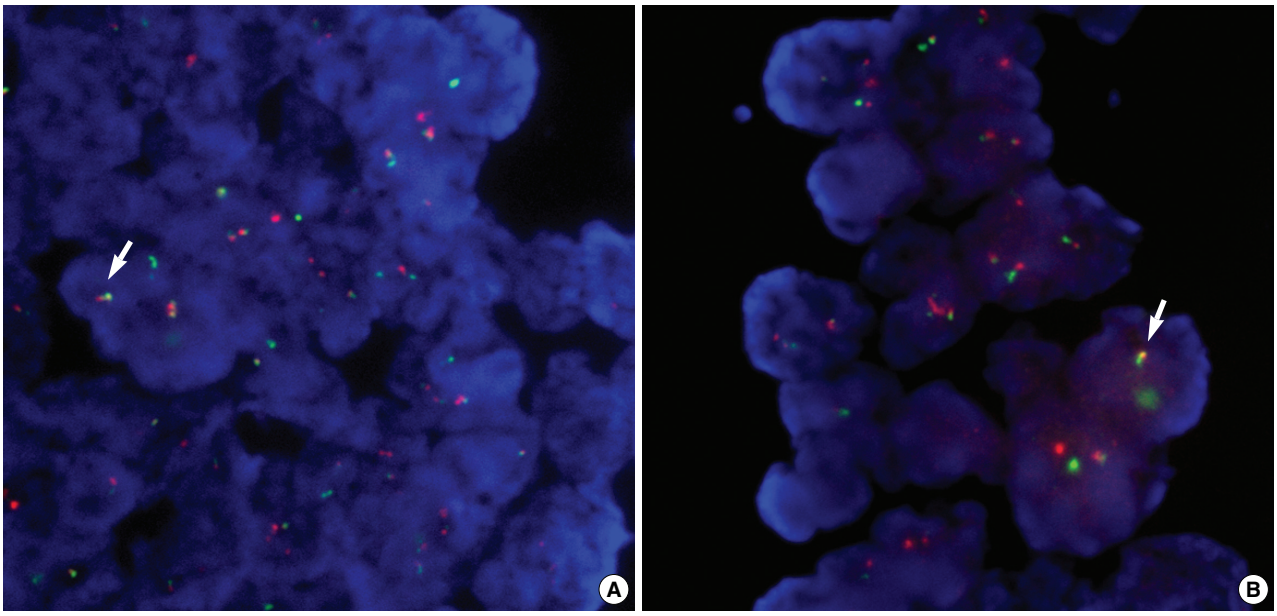

Fig. 3. FISH analysis on the formalin-fixed paraffin-embedded tissue section shows *bcr-abl* fusion signal (yellow dots) (arrows) in both blast (A) and CML components (B).

190,000/μL, and the WBCs were comprised of 1.0% blasts, 4.0% promyelocytes, 9.0% myelocytes, 11.0% metamyelocytes, 16.0% band-form neutrophils, 55.0% segmented neutrophils, 1.0% lymphocytes and 3.0% monocytes. The hemoglobin level was 10.3 g/dL, and the platelet count was 141,000/μL (Table 2). The leukocyte alkaline phosphatase (LAP) score was 15 (reference value: score 30-130). The peripheral blood smear showed increased numbers of granulocytes with a wide range of maturing myeloid cells (Fig. 4A). The bone marrow aspiration smear showed increased numbers of mature and immature myeloid cells, including 1.9% blasts, 2.3% promyelocytes, 17.8% myelocytes, 31.9% metamyelocytes, 15.9% band-form neutrophils, 25.2% segmented neutrophils and 1.7% eosinophils (Fig. 4B and Table 3). The bone marrow was hypercellular (cellularity: 90-95%) and nearly packed by myeloid cells at all stages of maturation (Fig. 4C, D). Some small, dwarf megakaryocytes and scattered eosinophils were seen. There was no evidence of a blast crisis in the bone marrow. Cytogenetic analysis of the bone marrow showed the Philadelphia chromosome 46, XY, t(9;22)(q34;q11.2) (Fig. 5). FISH analysis on the peripheral blood revealed *bcr/abl* fusion in 99.0% of the cells.

He was diagnosed with CML and being in an extamedullary

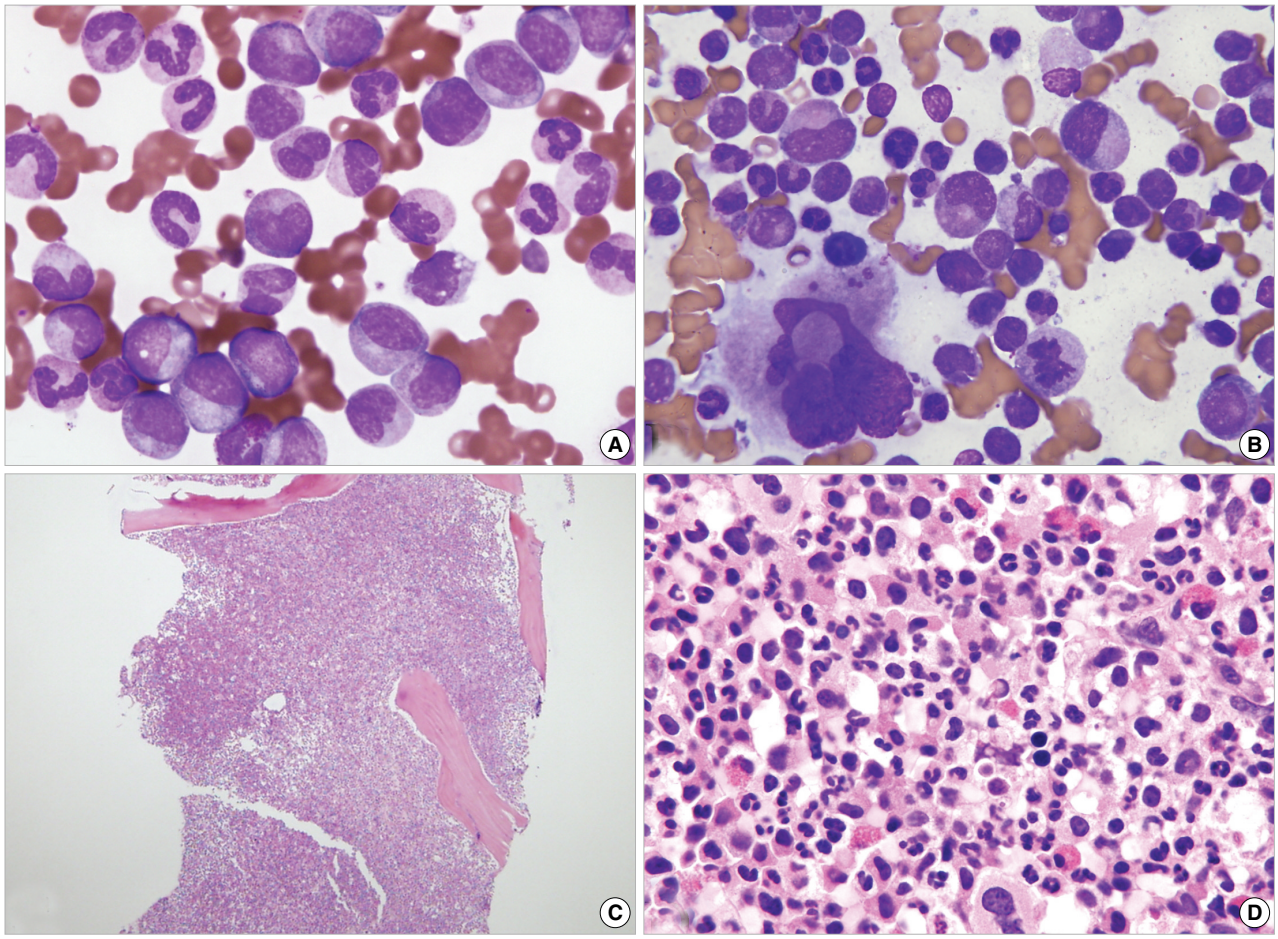

Fig. 4. The peripheral blood (A) and bone marrow aspirate (B) smears show increased myeloid cells at various maturation stages. Bone marrow biopsy shows packed marrow (C) with immature myeloid cells, and small, dwarf megakaryocytes (D).

Table 3. Differential count of bone marrow aspirate

Blast	1.9%
Promyelocyte	2.3%
Myelocyte	17.8%
Metamyelocyte	31.9%
Bandform neutrophil	15.9%
Segmented neutrophil	25.2%
Eosinophil	1.7%
Basophil	0%
Pronormoblast	0%
Basophilic normoblast	0%
Polychromic normoblast	0.4%
Orthochromic normoblast	0.8%
Lymphocytes	1.1%
Monocytes	0.8%
Plasmocyte	0.2%
M:E ratio	80.6:1

blast crisis-state and he was treated with imatinib mesylate (Gleevec®) at 400 mg/day. Three months later, he presented DOA (dead on arrival) to the emergency room. Any postmortem examination was not done.

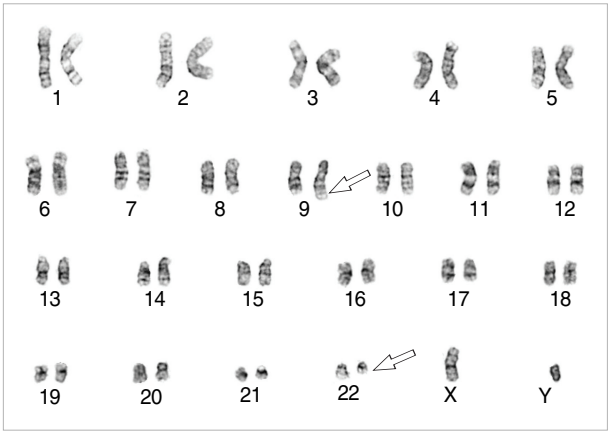

Fig. 5. The karyotyping of bone marrow shows 46, XY, t(9;22)(q34;q11.2) (arrow).

DISCUSSION

A blast crisis as an initial presentation of CML is rare, and this

accounts for 10% of all the cases of CML.[5] An extramedullary blast crisis at presentation is even rarer with this phenomenon being cited in individual case reports.[6] Various signs and symptoms may occur as a result of the specific effect of an extramedullary blastic tumor. In this current case, the tumor involved the leptomeninges and the patient developed neurologic symptoms. Based on the clinical history of an acute onset of neurologic symptoms, a previous history of hypertension and the radiologic findings, he was clinically diagnosed as suffering with a subdural hematoma. Several recent case reports have described a central nervous system (CNS) blast crisis in a patient with CML during imatinib mesylate therapy or after complete remission with therapy.[7-9] However, the isolated CNS involvement of a blast crisis as an initial manifestation of CML has not yet been reported. Approximately 70% of the patients with a blast crisis have the myeloid phenotype, and the remaining 30% have the precursor lymphoblast phenotype. The present case displayed an extramedullary B lymphoblastic crisis in the leptomeninges as an initial presentation of CML.

When an extramedullary blast crisis occurs as an isolated event without a previous history of CML, then de novo non-Hodgkin's lymphoma, granulocytic sarcoma or other tumors with small round cell morphology can be considered in the differential diagnosis. Fortunately, the peripheral portion of the present lesion showed infiltration of myeloid cells in various stages of maturation, which was considered as being typical CML, and we suspected the lesion to be a blast transformation of CML. Based on the immunohistochemical and histochemical staining, we could exclude granulocytic sarcoma and other non-hematologic malignancies. Using the double-color FISH method on the paraffin-embedded tissue, we detected *bcr/abl* gene fusion signals in both the lymphoblastic and CML components, and we confirmed that the blasts were derived from the clone that was responsible for Philadelphia chromosome positive CML rather than from an independent lymphoid malignancy. The double-color FISH method is a rapid, accurate cytogenetic technique in detecting *bcr/abl* fusion, which is valuable for making the diagnosis of an extramedullary blast crisis of CML. However, the interpretation of FISH in the paraffin-embedded tissue sections may be troublesome. Apart from the truncation artifact, the piling up of blast cells in the tissue sections in the present case made the accurate quantitative analysis very difficult, although we used 2 μm-thick sections.

The nonrandom secondary chromosomal aberrations during a blast crisis have been previously described. The patterns of cytogenetic evolution vary in relation to the treatment, and as for the lineage of crisis, i17q and TP53 mutations are more common in myeloid crisis, and monosomy 7, hypodiploidy, and CDKN2A deletions are more frequent in lymphoid crisis.[10] Among them, genetic or functional inactivation of p53 seems the most common abnormality in the CML blast phase.[11] The p53 gene was shown to be mutated in 25% to 30% of the patients with the myeloid type of CML blast crisis. The homozygous deletion of the p16INK4A/ARF locus, which indirectly affects the p53 function, was detected in approximately 50% of the patients with the lymphoid type of CML blast crisis.[12] In this present case, the expression of p53 was extremely high in the lymphoblast component (60-70%), compared to the p53 expression in the CML component (<5%). We can infer that the p53 tumor suppressor gene is involved in the progression of CML, and this may suggest that CML progression is similar to the progression of a premalignant or low grade tumor to a frankly malignant or higher grade malignant state of in solid tumor.

REFERENCES

1. Eric D, Hsi M. Hematopathology-A volume in foundations in diagnostic pathology series. 1st ed. Philadelphia Churchill Livingstone, 2006; 455-68.
2. Vardiman JW PR, Thiele J, Imbert M, Brunning BD, Flandrin G. Chronic myelogenous leukemia. In: Taffe ES HN, Stein H, Vardiman JW, eds. World Health Organization classification of tumours pathology and genetics of tumours of the haematopoietic and lymphoid tissues. Lyon. Washington IARC Press, 2002; 20-6.
3. Ichinohasama R, Miura I, Takahashi N, *et al*. Ph-negative non-Hodgkin's lymphoma occurring in chronic phase of Ph-positive chronic myelogenous leukemia is defined as a genetically different neoplasm from extramedullary localized blast crisis: report of two cases and review of the literature. Leukemia 2000; 14: 169-82.
4. Yashima-Abo A, Satoh T, Abo T, *et al*. Distinguishing between proliferating nodal lymphoid blasts in chronic myelogenous leukemia and non-Hodgkin lymphoma: report of three cases and detection of a bcr/abl fusion signal by single-cell analysis. Pathol Int 2005; 55: 273-9.
5. Sun T, Susin M, Koduru P, *et al*. Extramedullary blast crisis in chronic myelogenous leukemia. Demonstration of T-cell lineage and Philadelphia chromosome in a paraspinal tumor. Cancer 1991; 68: 605-10.
6. Ganessan K, Goel R, Kumar K, Bakhshi S. Biphenotypic extramedullary blast crisis as a presenting manifestation of Philadelphia chromosome-positive CML in a child. Pediatr Hematol Oncol 2007; 24: 195-8.

7. Altintas A, Cil T, Kilinc I, Kaplan MA, Ayyildiz O. Central nervous system blastic crisis in chronic myeloid leukemia on imatinib mesylate therapy: a case report. J Neurooncol 2007; 84: 103-5.
8. Rajappa S, Uppin SG, Raghunadharao D, Rao IS, Surath A. Isolated central nervous system blast crisis in chronic myeloid leukemia. Hematol Oncol 2004; 22: 179-81.
9. Rytting ME, Wierda WG. Central nervous system relapse in two patients with chronic myelogenous leukemia in myeloid blastic phase on imatinib mesylate therapy. Leuk Lymphoma 2004; 45: 1623-6.
10. Johansson B, Fioretos T, Mitelman F. Cytogenetic and molecular genetic evolution of chronic myeloid leukemia. Acta Haematol 2002; 107: 76-94.
11. Calabretta B, Perrotti D. The biology of CML blast crisis. Blood 2004; 103: 4010-22.
12. Trotta R, Vignudelli T, Candini O, *et al*. BCR/ABL activates mdm2 mRNA translation via the La antigen. Cancer Cell 2003; 3: 145-60.