Ann Hematol (2011) 90:607–609
DOI 10.1007/s00277-010-1061-7

LETTER TO THE EDITOR

Epidural leukemic involvement and intracranial hemorrhage as initial manifestations in a newly diagnosed chronic myeloid leukemia patient

Shih-Feng Cho · Ta-Chih Liu · Chi-Yu Lu · Chao-Sung Chang

Received: 5 July 2010 / Accepted: 18 August 2010 / Published online: 9 September 2010

Dear Editor,

Intracranial leukemic involvement is an extremely rare initial manifestation in the chronic phase of chronic myeloid leukemia (CML) patients. We present the case of a 33-year-old Taiwanese man who was admitted to the hematology ward in December 2007 because of abnormal findings in the white blood cell count in the hemogram (total, 186,260 cells/μl; blast cells, 2%; promyelocytes, 5.5%; myelocytes, 16%; metamyelocytes, 12%; band cells, 14%; segmented cells, 43.5%; monocytes, 2%; and lymphocytes, 5%) since October 2007. The findings of the cytogenetic study and molecular examination revealed that the patient was positive for Philadelphia (Ph') chromosome and Bcr-Abl, respectively. The patient was diagnosed with CML in the chronic phase.

This patient had severe headache, vomiting, and drowsiness 3 days after admission. Computed tomography (CT) revealed a right parietal epidural hemorrhage (Fig. 1, panel a). An emergent craniotomy was performed, and an epidural hematoma with intact dura mater and some brain tissue-like substance were observed. The excised tissue was mixed with hematoma and some friable yellowish specimen. Microscopic examination of this mixed tissue (Fig. 1, panels d–f) revealed a tumor composed of hemorrhage mixed with focally increased large blast-like cells. Immunohistochemical analysis showed positive myeloperoxidase and positive lysozyme staining. On the day after the operation, we observed dilation of the right pupil and weakness in the left-side muscles of the patient. Repeated CT showed right parietal epidural, subdural, and putaminal hemorrhage. A second craniotomy was performed to remove the hematoma and for drainage. After the operation, the patient was initially administered hydroxyurea (1 g/day) and then switched to imatinib mesylate (IM; 400 mg/day) from January 2008 with the approval of the National Health Insurance program. The postoperative brain CT scan showed resolved hematoma (Fig. 1, panel b). This patient had mild weakness in the left side at discharge. Complete hematologic remission was achieved by March 2008. The brain CT and cerebrospinal fluid (CSF) analysis yielded a completely normal result (Fig. 1, panel c). Since the patient showed a suboptimal response, wherein the 3-log reduction

S.-F. Cho · T.-C. Liu · C.-S. Chang
Division of Hematology and Oncology,
Department of Internal Medicine,
Kaohsiung Medical University Hospital,
Kaohsiung, Taiwan

T.-C. Liu
Graduate Institute of Medicine, College of Medicine,
Kaohsiung Medical University,
Kaohsiung, Taiwan

C.-Y. Lu
Department of Biochemistry, College of Medicine,
Kaohsiung Medical University,
Kaohsiung, Taiwan

C.-S. Chang
Graduate Institute of Healthcare Administration,
College of Health Science, Kaohsiung Medical University,
Kaohsiung, Taiwan

C.-S. Chang (✉)
No.100, Tzyou 1st Road,
Kaohsiung 807, Taiwan, Republic of China
e-mail: albert@kmu.edu.tw

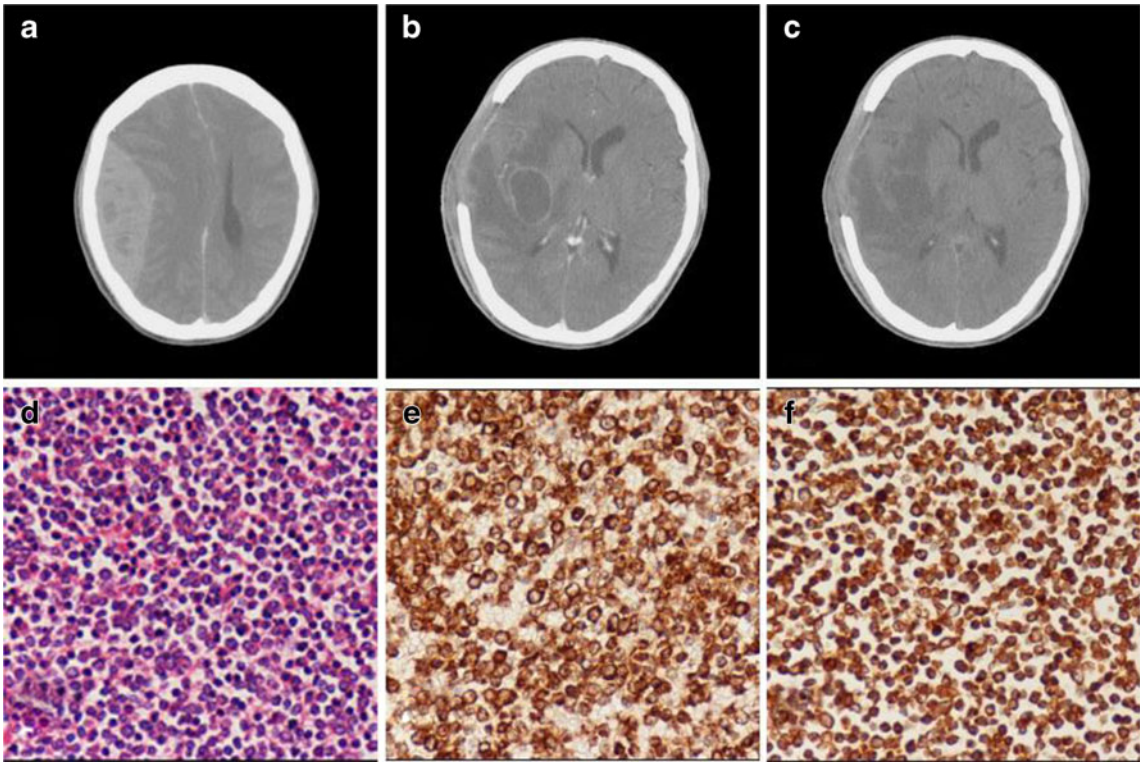

Fig. 1 Series of brain image examinations (*panels* **a** to **c**). Non-contrast brain CT revealed epidural hemorrhage (*panel* **a**) on the third day of hospitalization. Approximately 1 month after the operation, enhanced brain CT scan showed resolved hematoma (*panel* **b**). Three months after the operation, the brain CT (*panel* **c**) scan showed minimal encephalomalacia and no recurrence of CNS malignancy. Microscopic examination of the brain tumor (*panels* **d** to **f**). The specimen from the hematoma was composed of hemorrhage admixed with large blast-like cells, which have a slight to moderate rim of cytoplasm, fine chromatin, and nucleoli. The different degrees of differentiation, including immature cells and mature cells, were present. (*panel* **d**, HE stain, ×100). Immunohistochemical study showed that these cells were positive for myeloperoxidase (*panel* **e**) and lysozyme (*panel* **f**), but negative for CD20, CD3, and GFAP. *HE stain*, hematoxylin & eosin stain, *GFAP* glial fibrillary acidic protein, *CNS* central nervous system, *CT* computed tomography

in the Bcr-Abl transcript levels was not achieved after 2 years of IM therapy, imatinib was substituted with dasatinib in December 2009. Currently, the patient is in hematologic remission and has follow-ups in our hematology outpatient clinic regularly.

Pharmacokinetic analyses have shown that IM penetrates poorly into the central nervous system (CNS); the ratio of the IM concentration in the serum to that in CSF was 40–155 [1–5]. The poor IM penetration rate in the CNS may be a potential cause for the CNS relapse in approximately 20% of the CML patients, especially in patients in the advanced CML stages [6–8]. Our patient has been in hematologic remission without CNS relapse for approximately 2 years after craniotomy and IM therapy. We analyzed the IM concentrations in the CSF and the serum during stable remission by using liquid chromatography and spectrophotometric assay. The results of these analyses showed that the ratio of the IM concentration in the serum to that in the CSF was 25, which was lower than that reported in previous studies.

In conclusion, initial leukemic involvement of the CNS is quite unusual in the chronic phase of CML. Interestingly, in this case, we observed that even partial penetration of IM through the blood–brain barrier due to operative damage could lead to disease recovery and durable remission of leukemia in the CNS.

Authors' disclosures of potential conflicts of interest The author(s) have no potential conflicts of interest.

References

1. Takayama N, Sato N, O'Brien SG, Ikeda Y, Okamoto S (2002) Imatinib mesylate has limited activity against the central nervous system involvement of Philadelphia chromosome-positive acute lymphoblastic leukaemia due to poor penetration into cerebrospinal fluid. Br J Haematol 119(1):106–108. doi:3881
2. Petzer AL, Gunsilius E, Hayes M, Stockhammer G, Duba HC, Schneller F, Grunewald K, Poewe W, Gastl G (2002) Low

concentrations of sti571 in the cerebrospinal fluid: a case report. Br J Haematol 117(3):623–625. doi:3523
3. Senior K (2003) Gleevec does not cross blood–brain barrier. Lancet Oncol 4(4):198. doi:S1470204503010507
4. Wolff NC, Richardson JA, Egorin M, Ilaria RL Jr (2003) The CNS is a sanctuary for leukemic cells in mice receiving imatinib mesylate for Bcr/Abl-induced leukemia. Blood 101(12):5010–5013. doi:10.1182/blood-2002-10-30592002-10-3059
5. Bornhauser M, Jenke A, Freiberg-Richter J, Radke J, Schuler US, Mohr B, Ehninger G, Schleyer E (2004) CNS blast crisis of chronic myelogenous leukemia in a patient with a major cytogenetic response in bone marrow associated with low levels of imatinib mesylate and its N-desmethylated metabolite in cerebral spinal fluid. Ann Hematol 83 (6):401–402. doi:10.1007/s00277-003-0829-4
6. Rytting ME, Wierda WG (2004) Central nervous system relapse in two patients with chronic myelogenous leukemia in myeloid blastic phase on imatinib mesylate therapy. Leuk Lymphoma 45(8):1623–1626. doi:10.1080/10428190410001667703 6DWB2RT2HEFWNKGT
7. Leis JF, Stepan DE, Curtin PT, Ford JM, Peng B, Schubach S, Druker BJ, Maziarz RT (2004) Central nervous system failure in patients with chronic myelogenous leukemia lymphoid blast crisis and Philadelphia chromosome positive acute lymphoblastic leukemia treated with imatinib (STI-571). Leuk Lymphoma 45(4):695–698
8. Altintas A, Cil T, Kilinc I, Kaplan MA, Ayyildiz O (2007) Central nervous system blastic crisis in chronic myeloid leukemia on imatinib mesylate therapy: a case report. J Neurooncol 84(1):103–105. doi:10.1007/s11060-007-9352-0