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Abstract

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AN ADULT CASE OF CHRONIC MYELOGENOUS LEUKEMIA WITH MYELOBLASTIC INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM

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Abstract. A 31-year-old female with chronic myelogenous leukemia, who developed myeloblastic involvement of the central nervous system during acute myeloblastic transformation of the disease, was treated with methotrexate intrathecally. The therapy produced prompt clinical response and complete reversal of abnomal cerebrospinal fluid findings. However, the patient expired 10 months following the acute blastic crisis.

Key words : chronic myelogenous leukemia, central nervous system leukemia, methotrexate, blastic crisis.

Central nervous system (CNS) leukemia is a common complication of acute leukemia of childhood, and its clinical and pathologic characteristics have been described in detail (1, 2). However, few reports have been published on CNS leukemia in adults with chronic myelogenous leukemia (CML) (3). We have recently experienced an adult patient with CML who developed myeloblastic involvement of the CNS during acute blastic crisis. Intrathecal methotrexate therapy resulted in prompt clinical response and corrected abnormalities of the cerebrospinal fluid (CSF). This report describes the diagnosis and treatment of meningeal leukemia in adult cases of CML.

CASE REPORT

The patient, Y.H., was a 31-year-old woman who had been healthy until May 1977, when difficulty of hemostasis following tooth extraction was experienced. Her white blood cell count was found to be 135,000/mm^3. She was admitted to Okayama University Hospital, and examinations of peripheral blood and bone marrow established a diagnosis of CML in July 1977. Busulfan therapy (2-4 mg/day) was initiated from October 1977, and abnormalities of the peripheral blood and bone marrow were corrected. The patient was discharged in November 1977, and followed in the outpatient clinic. The patient did well at home. On January 1980, peripheral blood examinations revealed findings identical to acute blastic crisis of CML, and splenomegaly was observed again. She

was readmitted and treated with antileukemic agents such as vincristine, 6-mercaptopurine, cytosine arabinoside and prednisolone. Complete remission was obtained in May 1980.

However, at the end of July, high fever and general dullness appeared, and she was again admitted in August 1980. She was weak but alert, with a blood pressure of 110/50, pulse of 96/min and temperature of 37.5 ℃. The conjunctiva was anemic but not icteric. There was abdominal distension, with the liver and spleen palpable 1.5 and 6.0 finger-breadths below the respective costal margins. Neither ascites nor edema was detected. Neurological examination showed no abnomality.

Initial laboratory data included hematocrit 25 %, hemoglobin 9.0 g/dl and red cell count 2,320,000/mm³. The white cell differentiation indicated 24 % myeloblasts, 16 % progranulocytes, 2 % myelocytes, 2 % metamyelocytes, 3 % neutrophils (bands), 20 % neutrophils (segmented), 1 % lymphocytes, 2 % eosinophils and 30 % basophils. Bone marrow was compatible with that of acute blastic crisis. Liver function tests yielded normal results, and the urine showed no abnormal findings. Occult blood of feces was slightly positive. The erythrocyte sedimentation rate (ESR) was 97 mm/h. C-Reactive protein (CRP) was 4-

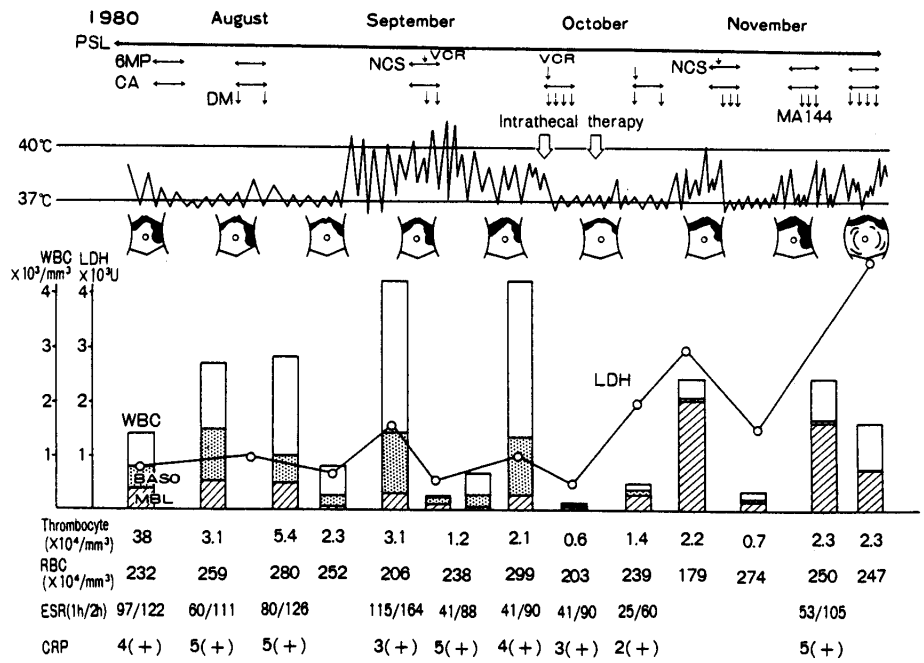

Fig. 1. Clinical course. Prednisolone (PSL), 6-mercaptopurine (6-MP), cytosine arabinoside (CA), daunomycin (DM), neocarzinostatin (NCS), vincristine (VCR), and aclarubicin (MA 144) were administered at the times indicated by arrows. Intrathecal therapy is indicated by large arrows.

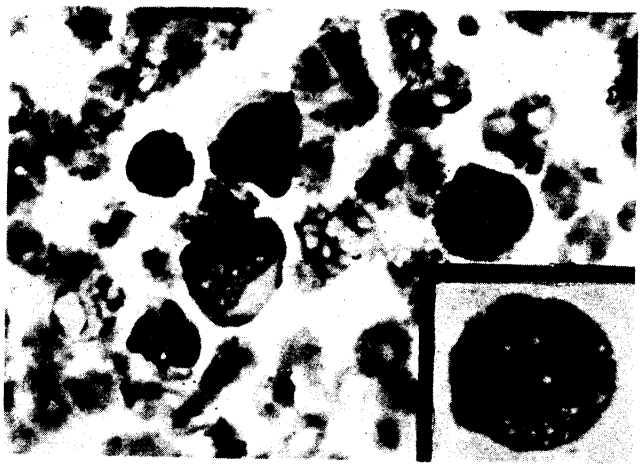

Fig. 2. Wright's stained films of cerebrospinal fluid cellular sediment (× 1000). Cells possess a fine nuclear chromatin pattern and multiple prominent nucleoli characteristic of myeloblasts. The inset shows an enlarged myeloblast in the cerebrospinal fluid (× 1700).

positive. Cultures of blood, urine and bone marrow were repeatedly negative. After admission, she was treated with antibiotics and antileukemic agents such as daunomycin and neocarzinostatin in addition to the agents used before (Fig. 1). Although the peripheral blood did not significantly change, fever and spleen enlargement were improved by these treatments.

The administrations of daunomycin, neocarzinostatin, vincristine, cytosine arabinoside and prednisolone in the middle of September resulted in an abrupt decrease of peripheral white cell numbers. However, in the beginning of October 1980, peripheral white cell counts rapidly increased again, and the patient complained of severe headache, vomiting and pain of the eyeballs. A second lumbar puncture performed on October 6, 1980 revealed a clear fluid under an opening pressure of 320 mm H_2O. The protein concentration was 96 mg/dl and sugar 47 mg/dl. There were 38 cells/mm^3, all of which appeared to be mononuclear cells; bacterial and fungal studies were negative. All the mononuclear cells were identified as myeloblasts by Wright's stain of the cell sediment (Fig. 2). The patient was treated with methotrexate, cytosine arabinoside and prednisolone intrathecally at the time of the second CSF examination. Systemic therapy with the antileukemic agents was simultaneously initiated (Fig. 3). Severe headache, vomiting and pain of eyeballs disappeared the day following the intrathecal therapy. A third lumbar puncture performed 8 days after the first intrathecal administration showed a marked decrease in the opening pressure and cell numbers; a second intrathecal treatment was performed.

In November 1980, she was repeatedly treated with a combination of chemotherapeutic agents including aclarubicin. However, high fever continued despite

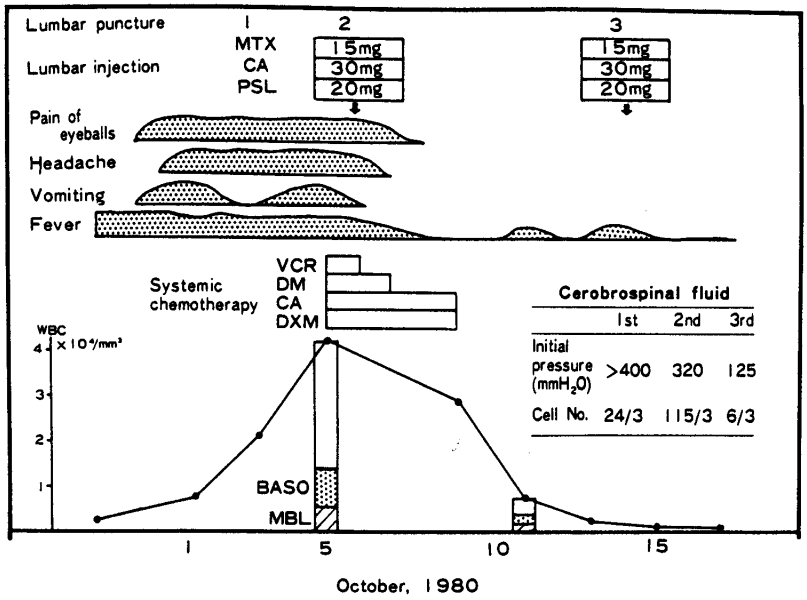

Fig. 3. Changes in clinical manifestations, peripheral white blood cell counts and initial pressure and cell counts of CSF during the intrathecal and systemic treatments with antileukemic agents. MTX, methotrexate; DXM, dexamethasone; MBL, myeloblasts, and BASO, basophils. The two longitudinal bars indicate the white cell differentials.

the intensive chemotherapy. She developed ascites. Candidial stomatitis and a bleeding tendency, such as nasal bleeding, due to remarkable thrombocytopenia were observed. Cachexia did not improved. She died on December 6, 1980. The patient survived 3 years and 7 months after the diagnosis of CML and 10 months following the acute blastic crisis.

Postmortem examination confirmed leukemic infiltration of the meninges, liver, spleen, kidneys, lungs, pleura and lymphnodes. Severe candidiasis of the esophagus, stomach and small and large intestines with multiple ulcer formations were observed.

COMMENTS

This is a rare case of meningeal leukemia observed in an adult with CML. Intracranial complications in the present case were observed during acute blastic crisis. However, there are several reports that meningeal leukemia is a clinical feature of an acute blastic phase of CML which occurs before other clinical or histological manifestations of blastic transformation are clearly evident. Kwaan *et al.* (3) reported a 55-year-old male with the Philadelphia (Ph^1) chromosome in the cells of the CSF and suggested that these cells were derived from CML cells outside the CNS. In Japan, Sakata *et al.* (4) reported a similar adult case of

CML in which intrathecal therapy resulted in a 4-month remission before general systemic involvement by acute myeloblastic leukemia occurred.

Wolk *et al.* (5) reported one case of clinically diagnosed CNS leukemia among 28 with acute blastic crisis of CML, and 7 cases among 18 in which the CNS leukmia was confirmed by autopsies showing the presence of leukemic infiltration to the dura, arachinoid, parenchyma or Virchow-Robin spaces. The histological examinations were important in the diagnosis of CNS leukemia. The higher incidence of CNS leukemia as revealed by autopsy might be attributed to the low clinical suspicion of meningeal involvement in CML.

A positive relationship between prolonged survival and the cummulative incidence of CNS leukemia suggests that as adults with leukemia survive longer, clinically evident CNS leukemia will become more prevalent (1, 2, 4, 5). CNS leukemia may develop from insufficient induction therapy and incomplete consolidation and maintenance therapy during partial or complete hematological remission. Remaining leukemic cells can grow in CSF into which chemotherapeutic agents can not penetrate. In the treatment of CML, rather conservative and passive procedures to diminish white blood cell numbers, splenic enlargement and subjective complaints were taken, and no aggressive therapy was performed until acute blastic transformation was manifested systematically. Therefore, CNS leukemia might have developed making treatment very difficult. Such conservative treatment may be another reason for increased numbers of CNS leukemia cases. Therefore, recently, even during remission treatments such as immunotherapy with BCG-CWS are carried out (6).

In the present case, in sufficient induction therapy permitted the migration of leukemia cells into the CNS. Intrathecal methotrexate was highly successful in treating meningeal leukemia of the present case and completely reversed abnormalities of CSF for several days. However, the patient eventually died of acute blastic crisis. Intensive efforts have been directed toward the development of compounds that will pass the blood-brain barrier and permit treatment of meningeal leukemia. Methods for prolonging therapy-induced remission of CNS leukemia have also been investigated, since standard and conventional chemotherapy for meningeal leukemia cause relapse for only about 3 months. Prophylactic effects of various treatments of meningeal leukemia have been reported (7, 8), but none of the treatments have been very successful. Further studies are necessary for establishment of treatment and prevention of CNS leukemia stemming from CML.

REFERENCES

1. Evans, A.E., Gilbert, E.S. and Zandstra, R.: The increasing incidence of central nervous system leukemia in children. *Cancer* **26**, 404-409, 1970.
2. Melhorn, D.K., Gross, S., Fischer, B.J. and Newman, A.J.: Studies on the use of "prophylactic" intracranial amethopterin in childhood leukemia. *Blood* **36**, 55-60, 1970.

3. Kwaan, H.C., Piere, R.V. and Long, D.C.: Meningeal involvement as first manifestation of acute myeloblastic transformation in chronic granulocytic leukemia. *Blood* **33**, 348-352, 1969.
4. Sakata, Y., Sugawara, K., Iwaki, Y., Sato, A., Yoshida, A., Kawamura, S., Chiba, Y. and Yoshida, Y.: A case of chronic myelogenous leukemia with meningeal leukemia. *Sogo Rinsyo* **31**, 537-540, 1982 (in Japanease).
5. Wolk, R.W., Masse, S.R., Conklin, R. and Freireich, E.J.: The incidence of central nervous system leukemia in adults with acute leukemia. *Cancer* **33**, 863-869, 1974.
6. Sokal, J.E.: Immunotherapy for chronic granulocytic leukemia. *Clin. Hematol.* **6**, 129-139, 1977.
7. Pinkel, D., Hernandez, K., Borella, L., Holton, C., Aur, R., Samoy, G. and Pratt, C.: Drug dosage and remission duration in childhood lymphocytic leukemia. *Cancer* **27**, 247-256, 1971.
8. Simone, J.V.: Preventive central-nervous-system therapy in acute leukemia. *N. Engl. J. Med.* **289**, 1248-1249, 1973.