KAWASAKI MED. J. VOL. 9 : NO. 3, 157-166 (1983)

A Neuropathologic Study of Disseminated Necrotizing Leukoencephalopathy Following Intrathecal Methotrexate Therapy

Teruo SHIRABE, Takashi FUKUYA and Hideki ASAKI*

Division of Human Pathology (Neuropathology),
Department of Pathology,
**Department of Pediatrics,*
Kawasaki Medical School, Kurashiki 701-01, Japan
Accepted for Publication on May 23, 1983

ABSTRACT. Neuropathologic findings of a case of disseminated necrotizing leukoencephalopathy following intrathecal methotrexate therapy are described.

A five-year-old boy with acute lymphocytic leukemia was seen over a twenty-two month course and was administered methotrexate intrathecally for meningeal leukemia. After the seventh intrathecal administration he developed akinetic mutism and decorticated rigidity which persisted until the patient's death seventeen months later.

Neuropathologically, there were widespread necrotic lesions with scattered lipid-laden macrophages and extensive astrocytic gliosis mainly in the white matter of the cerebrum and cerebellum in addition to meningeal and perivascular infiltration by leukemia cells. Nerve cell loss was considerable in the thalamus, cerebellar cortex, dentate nucleus, pontine nucleus and inferior olivary nucleus.

The disseminated necrotizing leukoencephalopathy in this case was thought to be caused mainly by the direct toxic effect of intrathecally administered methotrexate and not by irradiation or leukemia cell infiltration.

Key words : methotrexate encephalopathy — disseminated necrotizing leukoencephalopathy — intrathecal methotrexate therapy — meningeal leukemia

Direct and indirect nervous system complications of leukemia include hemorrhages due to hemorrhagic diathesis, infarctions due to hyperviscosity or thrombosis, infiltrations of leukemia cells or meningeal leukemia, opportunistic infections of virus, bacteria or fungi, progressive multifocal leukoencephalopathy, compression necrosis of the spinal cord due to epidural leukemic infiltration, toxic neuropathy due to therapeutic agents and so-called carcinomatous neuromyopathy of various types.[1-6] The incidence of meningeal leukemia has been increasing as a result of the extended survival of leukemia patients due to improved methods of chemotherapy. Presently, a combination of intrathecal administration of methotrexate and irradiation of the brain is used as a standard therapy for the treatment or prevention of meningeal leukemia.[7] Recently as a consequence of this combination therapy a disseminated necrotizing

調 輝男, 福屋 崇, 浅木秀樹

leukoencephalopathy has been recognized.[8]

The purpose of this paper is to describe the neuropathologic findings of a patient with acute lymphocytic leukemia who received this combination therapy and developed disseminated necrotizing leukoencephalopathy. The possible pathogenetic mechanisms underlying this condition are discussed.

CASE REPORT

Clinical Course (A 57810)

The patient was admitted to Kawasaki Medical School Hospital for evaluation of facial pallor and petechiae around the eyelids of one week's duration on May 12, 1978, at the age of three years. On examination, the white-cell count of the peripheral blood was 72,400, with 68 per cent lymphoblasts. A bone marrow aspiration disclosed 80 per cent lymphoblasts.

He was diagnosed as having acute lymphocytic leukemia and was given vincristine sulfate and prednisolone. In July, methotrexate, 8.16 mg each time, combined with hydrocortisone and prednisolone, was administered intrathecally three times every two weeks and 2,400 rads of radiation was irradiated to the brain over 24 days to prevent an infiltration of leukemia cells into the central nervous system. He improved and was discharged on August 30.

On September 14 of the same year, the patient developed fever, malaise, appetite loss and vomiting. He was readmitted four days later. An examination of the cerebrospinal fluid revealed 136/3 mononuclear cells per cubic millimeter, 98 per cent of which were lymphoblasts, despite the fact that the leukemia of the bone marrow and peripheral blood was in a state of complete remission. He was diagnosed as having meningeal leukemia. Methotrexate, 10 mg each time, was administered intrathecally every four days together with cytarabine and prednisolone from September 22. On October 4, after the fourth intrathecal injection, he became stuporous ; he scarcely moved his extremities spontaneously and reacted only to painful stimuli. The extremities were extended and rigido-spastic. Bilateral Babinski signs were elicited. In a few days the patient rapidly developed akinetic mutism and decorticated rigidity which remained until his death. An electroencephalogram showed irregular high voltage slow waves. A computed tomographic (CT) scan of the brain demonstrated widened sulci and ventricular dilatation with periventricular lucency. Lymphoblasts in the cerebrospinal fluid soon disappeared, and the intrathecal injection of methotrexate was discontinued.

In January 1979, he had generalized seizures, for which anticonvulsants were prescribed. In March, the patient had a relapse of acute lymphocytic leukemia. The white-cell count of the peripheral blood was 16,100, with 24 per cent lymphoblasts. He was discharged on May 2 after remission.

On May 14 of the same year, he developed fever and vomiting. Four days later he was readmitted because of the recurrence of both acute lymphocytic leukemia and meningeal leukemia. The white-cell count of the peripheral blood was 15,500, with 44 per cent lymphoblasts. The cerebrospinal fluid contained 164/3 mononuclear cells per cubic millimeter, 86 per cent of which were lymphoblasts. He was discharged on July 20 after complete remission.

He was readmitted a fourth time on July 23 for aspiration pneumonia and discharged on September 22.

He was hospitalized a fifth time from November 20, 1979, to February 6, 1980, because of the exacerbation of the leukemia. The white-cell count of the peripheral blood was 4,900, with 3 per cent lymphoblasts.

On February 14, 1980, petechiae were noted over the whole body. He was readmitted two days later. The white-cell count of the peripheral blood was 3,400, with 21 per cent lymphoblasts. On March 19, the cell count of the cerebrospinal fluid was 5,300/3 per cubic millimeter, with 90 per cent lymphoblasts. He received 9.36 mg of methotrexate intrathecally with hydrocortisone two times. The cell count of the cerebrospinal fluid on the day before the patient's death was 200/3 per cubic millimeter, with 94 per cent lymphoblasts. He died at the age of five years of pulmonary edema on March 27, twenty-two months after the diagnosis of acute lymphocytic leukemia and seventeen months after the onset of encephalopathy. He had received a total of nine intrathecal injections of methotrexate. The clinical course of the patient is schematically illustrated in Fig. 1.

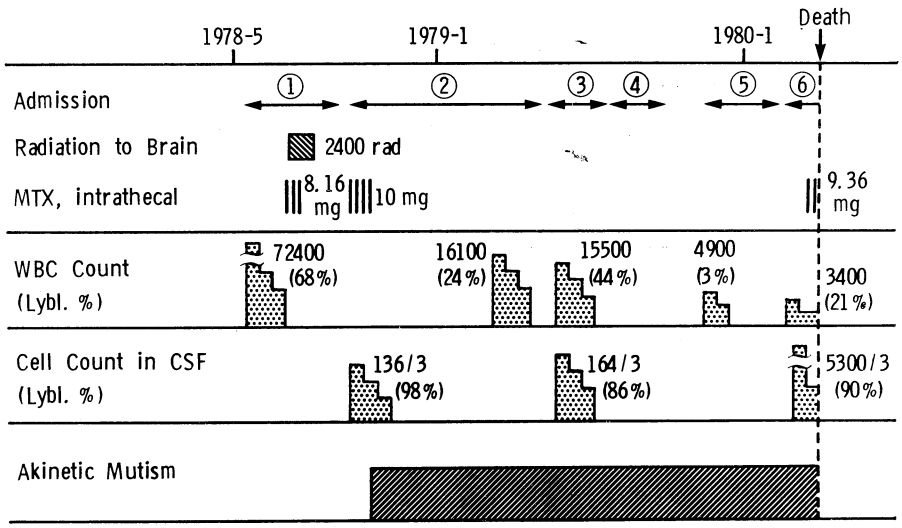

Fig. 1. Clinical course of the patient.

Pathologic findings (A 80-34)

A general autopsy disclosed microscopic infiltration by lymphoblasts in the bone marrow, lymph nodes, liver and spleen; aspergillosis in the tonsils, larynx, esophagus, stomach and small intestine; bilateral pulmonary edema and ascites of 100 ml.

The brain weighed 1,000 g. The leptomeninges were thickened and brownly pigmented. The cerebral gyri were slightly narrowed, and the sulci were slightly widened. In coronal sections, the white matter of both cerebral hemispheres was diffusely diminished in volume and scattered with brownish, irregular and confluent necrotic lesions. Similar necrotic lesions were found also in the white matter of the cerebellum. The lateral and third ventricles were markedly dilated.

The gray matter of the cerebral cortex and the basal ganglia were intact. The optic chiasm and brainstem were slightly atrophic and elastic hard in consistency.

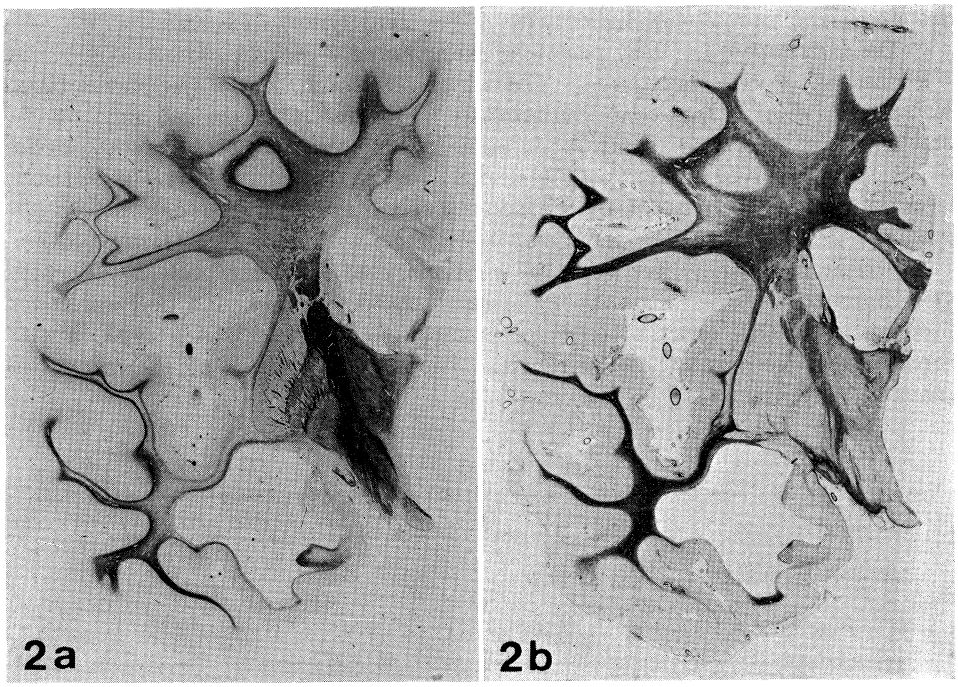

Fig. 2. Photograph of the coronal section of the cerebral hemisphere through the mammillary body showing widespread demyelinated lesions with prominent gliosis. 2a ; Klüver-Barrera, × 0.9, 2b ; Holzer, × 0.9.

Microscopically, the leptomeninges were fibrously thickened and infiltrated by numerous leukemia cells (Fig. 3), in addition to old and fresh subarachnoid hemorrhages of a mild degree. Leukemia cells also infiltrated the Virchow-Robin spaces of the cerebral cortex continuously from the subarachnoid space (Fig. 4). Architecture of the cerebral cortex was well preserved, except that the stroma of the second layer was occasionally loose and nerve cells in these regions were pyknotic.

In the white matter of the cerebral hemispheres, there were widespread demyelinated lesions with scattered lipid-laden macrophages, mainly around blood vessels, and prominent astrocytic gliosis (Fig. 2 and 5). The center of these lesions was occasionally cystic (Fig. 6). Small amounts of pseudocalcium were deposited in some places. These lesions were more prominent in the deeper portions of the white matter around the lateral ventricles, while subcortical white matter tended to be free of such lesions. Many of the ependymal cells of the lateral ventricles were absent. Fibrous thickening or hyaline degeneration of the walls or hypertrophy or proliferation of the endothelial cells of blood vessels within these lesions were not found, and only mild perivascular infiltration by leukemia cells was seen in some places. There was

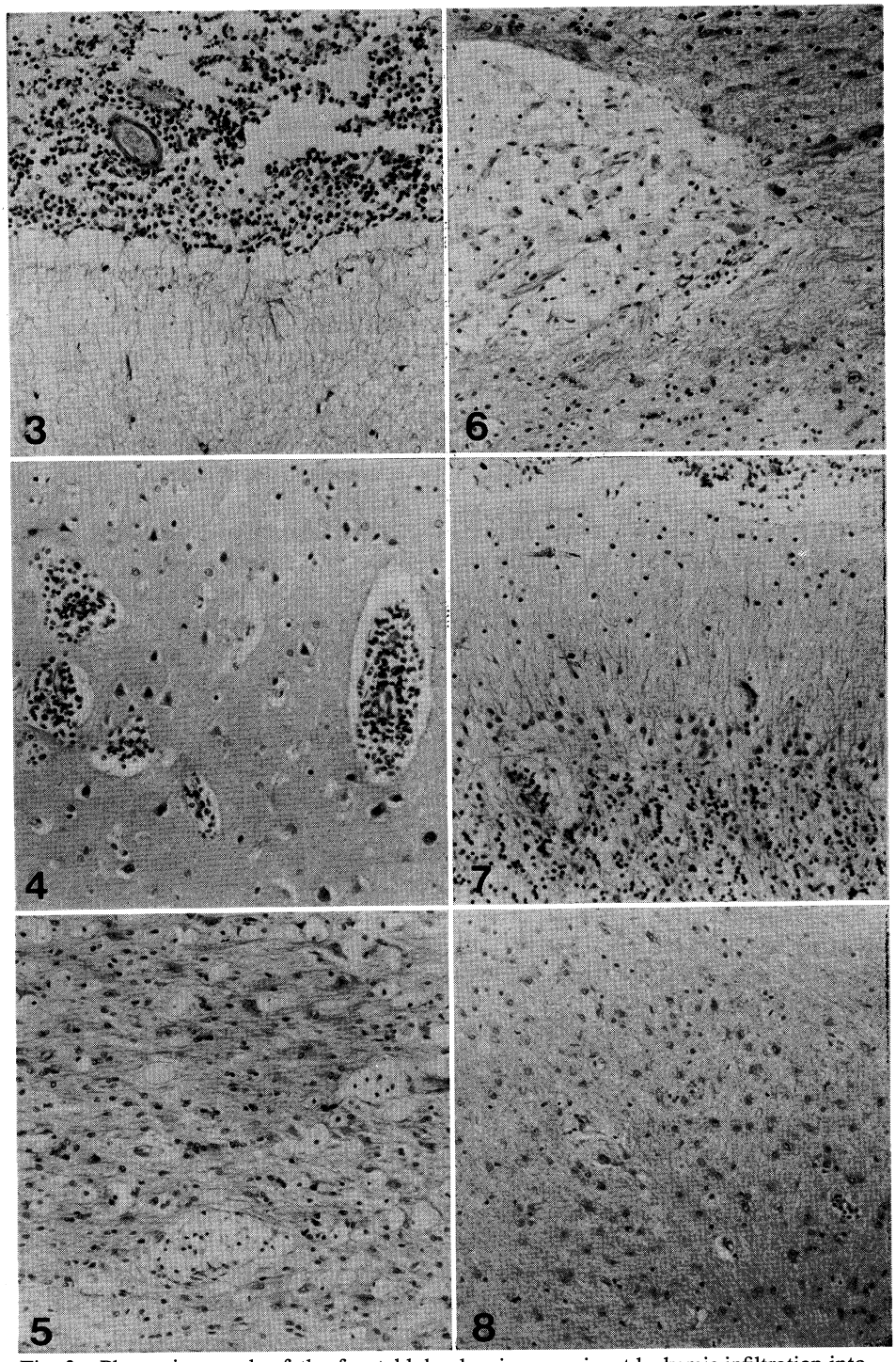

Fig. 3. Photomicrograph of the frontal lobe showing prominent leukemic infiltration into the subarachnoid space. HE, ×136.

Fig. 4. Photomicrograph of the cerebral cortex of the frontal lobe showing leukemic infiltration into the Virchow-Robin spaces. Architecture of the cerebral cortex is well preserved, although the nerve cells are pyknotic. HE, ×136.
Fig. 5. Photomicrograph of the cerebral white matter showing lipid-laden macrophages around the blood vessels and prominent astrocytic gliosis. HE, ×136.
Fig. 6. Photomicrograph of the cerebral white matter showing cystic lesions surrounded by astrocytic gliosis. HE, ×136.
Fig. 7. Photomicrograph of the cerebellar cortex showing nerve cell loss of the Purkinje cell and granule cell layers. The Bergmann glia proliferate in the Purkinje cell layer. HE, ×136.
Fig. 8. Photomicrograph of the inferior olivary nucleus showing prominent nerve cell loss and astrocytic gliosis. HE, ×136.

no relation between the severity of the demyelinated lesions and the severity of the perivascular infiltration by leukemia cells. Leukemia cell infiltration was almost absent in the severely involved areas.

In the basal ganglia, mild perivascular infiltration by leukemia cells was seen, while the nerve cells were well preserved. In the thalamus, there was quite a loss of nerve cells, especially in the anterior nucleus, with astrocytic gliosis.

In the optic chiasm, there were diffuse demyelination and astrocytic gliosis, in addition to moderate perivascular infiltration by leukemia cells.

In the cerebellum, the molecular layer had become loose and thin. Purkinje cells and granule cells were moderately to severely decreased in number (Fig. 7). The Bergmann glia proliferated in the Purkinje cell layer. The remaining nerve cells of the cerebellar cortex were reduced in size. The white matter of the cerebellum had widespread demyelinated lesions scattered with lipid-laden macrophages, and prominent astrocytic gliosis with occasional cyst formation, similar to the cerebral white matter. Nerve cells of the dentate nucleus were reduced greatly in size and decreased in number. Astrocytic gliosis was observed in the dentate nucleus as well.

In the brainstem, similar but milder lesions were seen in the cerebral peduncles of the midbrain, pontine basis, and the inferior olivary nucleus, medial lemniscus and pyramids of the medulla oblongata. Pseudocalcium was deposited in these lesions. Nerve cells of the pontine nucleus and inferior olivary nucleus (Fig. 8) were markedly reduced in number with prominent astrocytic gliosis.

DISCUSSION

The case presented here was of a five-year-old boy with acute lymphocytic leukemia complicated by meningeal leukemia, for which he was given methotrexate intrathecally. During this intrathecal administration of methotrexate the patient became stuporous and soon thereafter developed akinetic mutism and decorticated rigidity. Neuropathologic examinations upon the patient's death seventeen months later revealed widespread demyelinated lesions with scattered lipid-laden macrophages and prominent astrocyic gliosis in the white matter of the cerebrum and cerebellum. Although mild perivascular infiltration by leukemia cells were seen in these demyelinated lesions, a thickening of the walls of blood vessels was not found. Nerve cell loss was detected

mainly in the thalamus, cerebellar cortex, dentate nucleus, pontine nucleus and inferior olivary nucleus.

These observations of the white matter are indicative of disseminated necrotizing leukoencephalopathy[8] resulting from combination therapy of intrathecal administration of methotrexate and irradiation of the brain. Neurologic manifestations such as akinetic mutism and decorticated rigidity seen in this patient reflect the widespread lesions in the white matter. A causal relationship between the intrathecal administration of methotrexate and the disseminated necrotizing leukoencephalopathy is suggested by the rapid development of neurologic manifestations after the methotrexate therapy. Irradiation was not considered to be the cause of the disseminated necrotizing leukoencephalopathy, because pathologic changes of the walls of blood vessels as seen in cases of delayed radiation necrosis were not found.

Leukemia cell infiltration may have had something to do with producing these lesions which occurred seventeen months before the patient's death. However, the widespread occurrence of demyelinated lesions can not be explained only by leukemia cell infiltration since the cerebral cortex, in which leukemia cell infiltration was most intense, was almost intact, while the severely involved areas of the white matter had very little leukemia cell infiltration. The fact that neurologic manifestations developed when the meningeal leukemia had almost completely improved is also contrary to this possibility. Only the nerve cell loss of the cerebellar cortex may be explained by the direct compression or secondary circulatory disturbance due to meningeal and perivascular infiltration by leukemia cells.

In 1958, Whiteside et al.[9] introduced the intrathecal administration of methotrexate as a treatment for meningeal leukemia. After that a combination therapy of intrathecal administration of methotrexate with irradiation of the brain was established.[7] Although at first this combination therapy was thought to be harmless, side effects began to be reported from the latter half of the 1960's.[10] Common among these side effects are transient meningeal irritation or chemical meningitis producing nuchal rigidity, headache and vomiting.[11] Rarer but more severe complications include paraplegia due to myelopathy[12–14] or radiculopathy,[15] and personality change, disturbance of consciousness and convulsion due to encephalopathy.[16] At times an acute hypersensitivity reaction to methotrexate develops.[17]

In 1972, Kay et al.[16] reported for the first time pathologic findings of disseminated necrotizing leukoencephalopathy in a patient treated with this combination therapy. Several similar cases have been reported thereafter.[8,18–27] Some authors[20,25,28] stress that marked calcification and axonal swelling are characteristically seen in lesions of such cases, but in our case only a small amount of pseudocalcium was deposited and axonal swelling was not apparent.

Although it has been pointed out that there may be an interaction[23,25] between methotrexate and other chemical agents, steroids and irradiation given simultaneously and, further, that leukemic infiltration may be a cause of the encephalopathy, the most possible etiologic factor seems to be methotrexate. In our case, also, there was an intimate relation between the period of administration of methotrexate and the onset of neurologic manifestations. Considering

the time lag between the time of irradiation and the time of onset of the patient's encephalopathy, it is unlikely that the irradiation of the brain destroyed the cerebrospinal fluid-brain barrier and let methotrexate easily diffuse into the cerebral parenchyma. Furthermore, the fact that the same type of lesions were found in cases treated only by intrathecal methotrexate and not in combination with irradiation[26] lends support to this conception. The direct toxic effect of methotrexate in the central nervous system through the cerebrospinal fluid-brain barrier or, as pointed out by Kay et al.[16] and Norrell et al.[19] the secondary disturbance of folic acid metabolism within the brain produced by methotrexate may be the cause of the disseminated necrotizing leukoencephalopathy. Either of these two possible causes may be reinforced by elevated cerebrospinal fluid methotrexate concentration related to abnormal cerebrospinal dynamics due to meningeal infiltration by leukemia cells as suggested by Gagliano et al.[12] and Bleyer et al.[29] Intravenous administration of methotrexate does not seem to cause leukoencephalopathy through the blood brain barrier because the cerebrospinal fluid concentration of methotrexate is not elevated much in the case of intravenous administration.[30]

In our case, when methotrexate was given three times every two weeks for the prevention of meningeal leukemia, neurologic complications did not occur. But when methotrexate was given every four days three months later for the treatment of meningeal leukemia, neurologic complications occurred after the use of a total amount of 64.48 mg. In the literature, the amount of methotrexate which produced this type of encephalopathy ranged from 35[28] to 600 mg,[19] and the term until the occurrence of this disorder ranged from one week[29] to four years.[28] The variation of the amount and the term is probably attributable to the difference in the sensitivity of individuals to this medicine.

Most cases of methotrexate encephalopathy are seen in childhood as in ours. This does not mean that the brains of children are more sensitive to methotrexate, but merely means that meningeal leukemia is apt to occur in childhood leukemia and consequently children are apt to receive intrathecal administration of methotrexate.

Nerve cell loss of the thalamus, dentate nucleus, pontine nucleus and inferior olivary nucleus in our case may have been due to the direct toxic effect of methotrexate. Descriptions of such changes in the gray matter are rarely found in the literature of disseminated necrotizing leukoencephalopathy. In this respect our case is somewhat unusual. In the final analysis, it is necessary to consider the possibility of the occurrence of disseminated necrotizing leukoencephalopathy when treating meningeal leukemia with methotrexate by intrathecal administration.

REFERENCES

1) Shirabe, T., Mitsuyasu, Y. and Hamada, T. : Three autopsy cases of leukemia with spinal cord involvement. J. Kyushu Hematol. Soc. (Fukuoka) **17** : 421–434, 1967 (in Japanese)
2) Shirabe, T. : A pathologic study of the central nervous system in leukemia. J. Kyushu Hematol. Soc. (Fukuoka) **18** : 177–218, 1968 (in Japanese)
3) Shirabe, T., Nagamatsu, K., Kuroiwa, Y., Kikuchi., M. and Yoshida, H. : An autopsy case of progressive multifocal leukoencephalopathy. Adv. Neurol. Med. (Tokyo) **16** :

504–513, 1972 (in Japanese)
4) Campbell, R.H.A., Marshall, W.C. and Chessells, J.M. : Neurological complications of childhood leukaemia. Arch. Dis. Child. **52** : 850–858, 1977
5) Crosley, C.J., Rorke, L.B., Evans, A. and Nigro, M. : Central nervous system lesions in childhood leukemia. Neurology **28** : 678–685, 1978
6) Davies-Jones, G.A.B., Preston, F.E. and Timperley, W.R. : Neurological complications in clinical haematology. Oxford, Blackwell Scientific Publications. 1980, pp. 36–60
7) Sullivan, M.P., Vietti, T.J., Fernback, D.J., Griffith, K.M., Haddy, T.B. and Watkins, W.L. : Clinical investigations in the treatment of meningeal leukemia. Radiation therapy regimens vs. conventional intrathecal methotrexate. Blood **34** : 301–319, 1969
8) Rubinstein, L.J., Herman, M.M., Long, T.F. and Wilbur, J.R. : Disseminated necrotizing leukoencephalopathy. A complication of treated central nervous system leukemia and lymphoma. Cancer **35** : 291–305, 1975
9) Whiteside, J.A., Philips, F.S., Dargeon, H.W. and Burchenal, J.H. : Intrathecal amethopterin in neurological manifestations of leukemia. Arch. Intern. Med. **101** : 279–285, 1958
10) Weiss, H.D., Walker, M.D. and Wiernik, P.H. : Neurotoxicity of commonly used antineoplastic agents (First of two parts). N. Engl. J. Med. **291** : 75–81, 1974
11) Kobayashi, Y., Ishigame, Y., Hara, M., Nitta, Y., Higaki, T., Usui, T., Nishio, T., Akaishi, K. and Kobayashi, Y. : Complications of intrathecal methotrexate prophylaxis and treatment of central nervous system leukemia in children. Hiroshima J. Med. Sci. **25** : 107–113, 1976
12) Gagliano, R.G. and Costanzi, J.J. : Paraplegia following intrathecal methotrexate. Cancer **37** : 1663–1668, 1976
13) Tomonaga, M., Takeno, Y., Ishii, N. and Okayama, M. : Paraplegia following intrathecal methotrexate. Adv. Neurol. Sci. (Tokyo) **22** : 1204–1211, 1978 (in Japanese)
14) Grisold, W., Lutz, D. and Wolf, D. : Necrotizing myelopathy associated with acute lymphoblastic leukemia. Case report and review of literature. Acta Neuropathol. (Berl.) 49 : 231–235, 1980
15) Saiki, J.H., Thompson, S., Smith, F. and Atkinson, R. : Paraplegia following intrathecal chemotherapy. Cancer **29** : 370–374, 1972
16) Kay, H.E.M., Knapton, P.J., O'Sullivan, J.P., Wells, D.G., Harris, R.F., Innes, E.M., Stuart, J., Schwartz, F.C.M. and Thompton, E.N. : Encephalopathy in acute leukemia associated with methotrexate therapy. Arch. Dis. Child. **47** : 344–354, 1972
17) Back, E.H. : Death after intrathecal methotrexate. Lancet **2** : 1005, 1969
18) Hendin, B.,Deviro, D.C., Torack, R., Lell, M.E., Ragab, A.H. and Vietti, T.J. : Parenchymatous degeneration of the central nervous system in childhood leukemia. Cancer **33** : 468–482, 1974
19) Norrell, H., Wilson, C.B., Slagel, D.E. and Clark, D.B. : Leukoencephalopathy following the administration of methotrexate into the cerebrospinal fluid in the treatment of primary brain tumors. Cancer **33** : 923–932, 1974
20) Flament-Durand, J., Ketelbant-Balasse, P., Maurus, R., Regnier, R. and Spehl, M. : Intracerebral calcifications appearing during the course of acute lymphocytic leukemia treated with methotrexate and x rays. Cancer **35** : 319–325, 1975
21) Price, R.A. and Jamieson, P.A. : The central nervous system in childhood leukemia. II. Subacute leukoencephalopathy. Cancer **35** : 306–318, 1975
22) Koga, S., Fujimoto, T., Hasegawa, K. and Sueishi K. : Disseminated necrotizing leukoencephalopathy following intrathecal methotrexate in childhood leukemia. Fukuoka Acta Medica **67** : 24–31, 1976 (in Japanese)
23) Devivo, D.C., Malas, D., Nelson, J.S. and Land, V.J. : Leukoencephalopathy in childhood leukemia. Neurology **27** : 609–613, 1977
24) Iinuma, K., Hayashi, T. and Ikuta, F. : Disseminated necrotizing leukoencephalopathy accompanied with calcium deposits following antineoplastic therapy in a case with acute lymphoblastic leukemia. Adv. Neurol. Sci. **21** : 386–393, 1977 (in Japanese)
25) Liu, H.M., Maurer, H.S., Vongsvivut, S. and Conway, J.J. : Methotrexate encephalopathy. A neuropathologic study. Human Pathol. **9** : 635–648, 1978
26) Morimatsu, M., Hirai, S., Ogawa, S., Motegi, M. and Nakazato, Y. : A case of disseminated necrotizing leukoencephalopathy associated with intrathecal methotrexate therapy. Neurol. Med. (Tokyo) **9** : 54–62, 1978 (in Japanese)
27) Ebels, E.J. : Iatrogenic damage to the central nervous system in malignant systemic disease. Acta Neuropathol. (Berl.) Suppl. VII : 352–355, 1981

28) Mueller, S., Bell, W. and Seibert, J. : Cerebral calcifications associated with intrathecal methotrexate therapy in acute lymphocytic leukemia. J. Pediatr. 88 : 650–653, 1976
29) Bleyer, W.A., Drake, J.C. and Cahbner, B.A. : Neurotoxicity and elevated cerebrospinal-fluid methotrexate concentration in meningeal leukemia. N. Engl. J. Med. 289 : 770–773, 1973
30) Shapiro, W.R., Young, D.F. and Mehta, B.M. : Methotrexate. Distribution in cerebrospinal fluid after intravenous, ventricular and lumbar injections. N. Engl. J. Med. 293 : 161-166, 1975