

Clinical Article

Leukoencephalopathy and Disseminated Necrotizing Leukoencephalopathy Following Intrathecal Methotrexate Chemotherapy and Radiation Therapy for Central Nerve System Lymphoma or Leukemia

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Objective : Intrathecal methotrexate (MTX) therapy combined with whole brain radiotherapy (WBRT) is one of the major treatment modalities for leukemia and lymphoma involving the central nervous system (CNS). The purpose of this study was to retrospectively determine the incidences of leukoencephalopathy and disseminated necrotizing leukoencephalopathy (DNL) following intrathecal MTX therapy for CNS lymphoma or leukemia and to assess the potential risk factors.

Methods : Between January 2000 and August 2009, 143 patients with CNS lymphoma or leukemia received intrathecal MTX therapy alone or in combination with WBRT at a single institution. Patients were followed up clinically and radiologically at regular two- or three-month intervals. Medical records were reviewed to obtain information regarding the patients' demographics, medical histories, radiologic characteristics, treatments, and clinical courses.

Results : On follow-up MR images, leukoencephalopathy was found in 95 of 143 patients (66.4%). The median time to develop leukoencephalopathy was 6.6 months. Among those with leukoencephalopathy, four patients showed seven extensive white-matter changes with strongly enhancing lesions demonstrating DNL. Histological confirmation was done in six lesions of three patients and radiological diagnosis alone in one patient. Four lesions spontaneously disappeared on MR images without any treatment, with a mean duration of 14 months before disappearance of DNL.

Conclusion : Leukoencephalopathy is a common phenomenon that occurs following intrathecal MTX therapy; however, DNL occurs at a very low incidence. For newly developed enhancing lesions, consideration for the occurrence of DNL should be taken to avoid unnecessary invasive procedures or therapies.

Key Words : Leukoencephalopathy · Methotrexate · Intrathecal · Lymphoma · Leukemia.

INTRODUCTION

Methotrexate (MTX) is a common anti-cancer agent that acts as a folic acid antagonist by inhibiting dihydrofolate reductase. It is a highly ionized and lipid-insoluble compound that barely penetrates the blood-brain barrier of the central nervous system (CNS), despite its high cytotoxic effect. Therefore, an intrathecal route has been widely used as the primary treatment modality for CNS involvement of leukemia, lymphoma and other neoplasms. Furthermore, combination of intrathecal (IT)

MTX therapy with whole brain radiotherapy (WBRT) can enhance the effect of the treatment^{6,14,22}. However, this sometimes results in injury to the CNS such as leukoencephalopathy or, rarely, disseminated necrotizing leukoencephalopathy (DNL).

Leukoencephalopathy, seen as white matter hyperintensities on T2-weighted MR imaging, is one of the potentially serious complications of chemotherapy and may be either persistent or transient^{24,28}. Diffuse periventricular changes in the hyperintense signal on T2-weighted images are frequently encountered in patients treated with MTX, most of whom have no neurological deficits. Although most signal changes are subclinical and usually transient, some rare patients have extensive signal change and contrast-enhancing lesions accompanying rapid neurological deterioration after treatment with MTX^{15,18}, a condition known as DNL.

Some patients may be at greater risk for developing treatment-related neurotoxicity. However, predisposing factors re-

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main poorly understood, because it is difficult to accurately predict individual risks in a clinical setting²²). Potential risk factors include the specific therapeutic modality and dosage, combination of radiation and chemotherapy, genetic background and idiosyncratic patient predilections^{12,22,23}). It is difficult to assess new contrast-enhancing lesions following chemotherapy and radiation therapy because treatment-related findings may radiologically mimic tumor recurrence.

Here, we evaluated the radiological findings and clinical courses of treatment-related complications such as leukoencephalopathy and DNL in the treatment of CNS lymphoma, leukemia.

MATERIALS AND METHODS

Patient population

We reviewed our CNS lymphoma and leukemia database for all patients who were treated with IT MTX via intraventricular catheter between 2000 and 2009. The diagnosis of CNS lymphoma/leukemia, including primary and secondary lesions, was established by means of morphologic, cytochemical, immunophenotyping, and genetic studies.

All patients underwent a standardized MRI protocol with contrast agent at diagnosis and during follow-up every three to five months. MR imaging was checked whenever neurologic deterioration occurred in order to identify the brain lesions. Medical records including tissue biopsy result, symptom, locations and morphologies of the enhancing lesions were reviewed after the diagnosis of DNL in order to characterize the clinical syndrome. Patients with mild leukoencephalopathy and DNL were assessed for potential risk factors and outcomes, retrospectively. Potential risk factors included age, gender, cranial radiotherapy, radiotherapy dose, chemotherapy dose and etiology of the CNS lymphoma/leukemia.

Chemotherapy and radiotherapy protocols

For primary CNS lymphoma, chemotherapy consisted of intravenous (IV) MTX 3.5 g/m² diluted in 500 mL D5W infused over 6 hours and IV leucovorin 15 mg/m² per 6 hours, for a total of 12 doses, 24 hours after the onset of IV MTX infusion on weeks 1, 3, 5, 7, and 9; IT MTX at a dose of 12 mg and PO leucovorin at 10 mg every 12 hours, for a total of 8 doses, after 24 hours of IT MTX infusion on weeks 2, 4, 6, 8, and 10; vincristine 1.4 mg/m² IV bolus on weeks 1, 3, 5, 7, and 9; and procarbazine 100 mg/m²/day from days 1 to 7 on weeks 1, 5, and 9, or as clinically indicated. The chemotherapy protocol consisted of IV MTX and IT MTX without vincristine or procarbazine.

Systemic lymphoma with CNS involvement was treated with 1) IT MTX 15 mg, IT AraC 30 mg/m², IT hydrocortisone 15 mg/m² infusion three times/week. 2) IV ifosfamide 1,000 mg/m² diluted in 200 mL D5W infused over 1 hour and mesna 200 mg/m² diluted in 50 mL D5W infused over 15 minutes on days 1 to 5; methotrexate 30 mg/m² IV bolus; IV VP-16 100 mg/m² diluted in 500 mL NS over 90 minutes; PO prednisolone 100

mg q 8 hrs on days 1 to 5. 3) The same protocol was followed for primary CNS lymphoma.

Patients with acute lymphoblastic leukemia and acute myeloid leukemia with CNS recurrence after IV chemotherapy received IT MTX 15 mg, IT AraC 30 mg/m², IT hydrocortisone 15 mg/m² infusion three times/week until the CSF cytology cleared.

Cranial radiotherapy was given with whole brain radiotherapy following completion of chemotherapy and was administered at a dose of 4,500 cGy delivered in 25 treatments of 180 cGy each or 3,600 cGy delivered in 20 fractions. Ten patients received an additional 1,260 cGy or 1,440 cGy radiation treatment to the tumor bed area.

MR data acquisition and relative cerebral blood volume (rCBV) analysis

MR imaging studies were performed with 3.0-T system (Achieva, Philips Medical Systems, Best, Netherlands). Imaging sequences of the brain included spin-echo T1-weighted images, fast spin-echo T2-weighted images, fluid attenuated inversion recovery (FLAIR) images, and enhanced T1-weighted images with gadobutrol (Gadovist, Schering, Berlin, Germany). The MR imaging parameters were as follows: 500 ms/10 ms/90/256 × 190 (TR/TE/FA/matrix) for spin-echo T1-weighted images; 3,000 ms/80 ms/90/240 × 190/416 × 264 (TR/TE/FA/matrix) for fast spin-echo T2-weighted images; and 11,000 ms/125 ms/90/240 × 190/368 × 210 (TR/TE/FA/matrix) for FLAIR images. The other parameters were the following: section thickness, 5 mm with a 1.5 mm gap; FOV, 240 × 190 mm. DSC perfusion-weighted MR images were acquired during the intravenous injection of a bolus gadobutrol at a dose of 0.1 mmol per kilogram of body weight and a rate of 4 mL/sec by using a single-shot gradient-echo echo-planar imaging sequence (repetition time msec/echo time msec, 1,500/35; flip angle, 40°; field of view, 24 cm; matrix, 256 × 256; section thickness, 5 mm; intersection gap, 2 mm).

Definitions of leukoencephalopathy and DNL

In this database, leukoencephalopathy was defined radiologically as a hyperintense signal change in the white matter on T2-weighted or FLAIR MR images after therapy, involving at least 25% of signal change in the white matter by square measure. DNL was defined based on a newly developed contrast enhancement and a more extensive change in white matter on MR images, except the pathologic specimen revealed recurrence. Those lesions characteristically involve the area around the chemoport catheter or an area distant from the primary origin. In cases with difficulty in differentiating DNL from tumor recurrence, stereotactic biopsy was performed for histological confirmation, which contributed to decisions regarding further treatment strategies.

Statistical analysis

Time to the development of leukoencephalopathy was calculated using the Kaplan-Meier method. The estimates of the inci-

dences of leukoencephalopathy for various groups were compared using a modified χ^2 test²⁷. The univariate analyses for the cumulative incidences of leukoencephalopathy and DNL were performed using a log-rank test for various parameters, including age (<60 years vs. \geq 60 years), gender (male vs. female), cranial radiotherapy (yes or no), radiotherapy dose (360-4,100 cGy vs. \geq 4,140 cGy), chemotherapy dose (<60 mg vs. \geq 60 mg), and etiology of the CNS lymphoma/leukemia (primary vs. secondary).

RESULTS

Patient population

One-hundred-forty-three patients with CNS lymphoma or leukemia were treated with intrathecal MTX therapy alone or

in combination with whole brain radiotherapy in our institution from January 2000 to August 2009. The median age was 52 years; there were 86 men and 57 women. CNS lymphoma was regarded as primary origin in 92 patients (64%) or as secondary involvement in 51 patients (36%) (Table 1, 2). Eighty patients (56%) with CNS lymphoma or leukemia received WBRT after intrathecal MTX treatment. The median overall follow-up period was 1.3 years (range, 0.1-9.0 years).

Incidence of leukoencephalopathy

Leukoencephalopathy developed in 95 of 143 patients (66%). The cumulative incidence of leukoencephalopathy was 28% (95% CI, 21-37%) at three months, 54% (95% CI, 45-63%) at six months, 76% (95% CI, 67-84%) at two years, and 88% (95% CI, 78-94%) at five years (Fig. 1). Combination of intrathecal MTX with WBRT was not closely associated with the development of leukoencephalopathy. No other potential risks were found to be significantly related to leukoencephalopathy (Table 2).

Incidence of DNL

We screened 29 patients with newly developed enhancing lesions on MR.

Table 1. Characteristics of all 143 patients with CNS lymphoma/leukemia

Characteristic	Finding
Age at diagnosis of CNS lymphoma/leukemia, median (range), y	52 (17-80)
Follow-up after LE onset, median (range), y	1.2 (0.1-7.9)
Follow-up after disease diagnosis, median (range), y	1.3 (0.1-9.0)
Patients who developed LE, No. (%)	95 (66.4%)
Patients who developed new enhancing mass and DNL, No. (%)	29 (19.4%), 4 (2.8%)
Patients who diagnosed to lymphoma and leukemia, No. (Primary/Secondary)	138 (91/47), 5 (1/4)

CNS : central nervous system, LE : leukoencephalopathy, DNL : disseminated necrotizing leukoencephalopathy

Table 2. Univariate analysis of risk factors (n=143)

Variable	Total No.(%) of patients	No.(%) of patients with LE	No. of patients with DNL	3-month Incidence, LE, % (95% CI)	6-month Incidence, LE, % (95% CI)	2-year Incidence, LE, % (95% CI)	5-year Incidence, LE, % (95% CI)	p-value
Age, y								
<60	100	71	3	25 (17-34)	52 (42-63)	75 (65-84)	86 (75-94)	0.24
\geq 60	43	24	1	39 (25-58)	59 (43-76)	81 (59-95)	-	
p-value				0.34	1.00	1.00	-	
Sex								
Male	86	57	2	26 (18-37)	51 (40-63)	78 (67-88)	85 (72-93)	0.57
Female	57	38	2	32 (21-46)	58 (45-73)	77 (63-89)	-	
p-value				1.00	1.00	1.00	-	
Radiotherapy								
Yes	80	60	4	25 (17-36)	54 (43-66)	76 (65-86)	90 (79-97)	0.85
No	63	35	0	34 (23-48)	53 (40-68)	77 (61-90)	77 (61-90)	
p-value				1.00	1.00	1.00	1.00	
Radiotherapy dose, cGy								
360-4100	57	39	2	28 (18-42)	55 (42-69)	76 (62-88)	89 (74-97)	1.00
\geq 4140	23	21	2	17 (6-39)	54 (35-75)	77 (58-91)	90 (74-98)	
p-value				1.00	1.00	1.00	1.0	
Chemotherapy alone, dose, mg								
<60	15	6	0	29 (15-52)	60 (39-80)	80 (58-94)	-	0.61
\geq 60	48	29	4	28 (21-38)	53 (44-63)	76 (66-84)	86 (76-94)	
p-value				1.00	1.00	1.00	-	
Etiology								
Primary	92	64	4	27 (19-37)	54 (44-65)	72 (61-82)	87 (75-95)	0.43
Secondary	51	31	0	32 (20-48)	54 (39-70)	89 (72-97)	89 (72-97)	
p-value				1.00	1.00	0.20	1.00	

CI : confidence interval, LE : leukoencephalopathy, DNL : disseminated necrotizing encephalopathy

Diffusion-weighted images of the enhancing lesions showed restricted diffusion, and a CBV map did not show increased perfusion in the same position (Fig. 2). In 13 of 29 patients, stereotactic biopsy was performed for the histological confirmation of DNL because MR findings were not sufficient for differentiating DNL from tumor recurrence. The neuroradiologist (Kim, ST) at our institution assayed the MRI and biopsy results for the four patients with DNL. Three patients then underwent tissue confirmation of DNL, while the remaining patient was diagnosed with DNL according to MR imaging alone. Tumor recurrence was confirmed by tissue biopsy in ten patients. Three patients developed two recurrent DNLs at different sites, and biopsies were

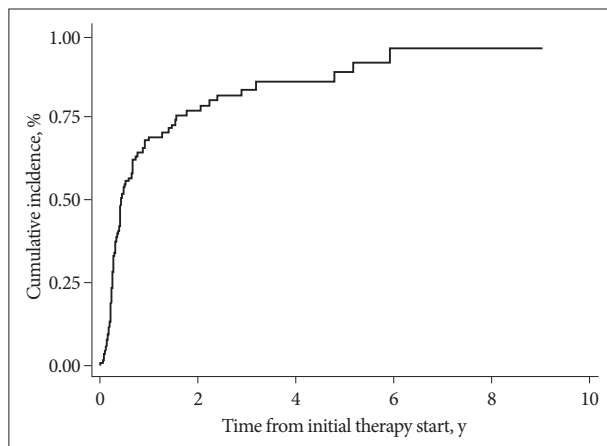


Fig. 1. Cumulative incidence of leukoencephalopathy from initial therapy, showing that 54% (95% CI, 45-63%) at 6 months.

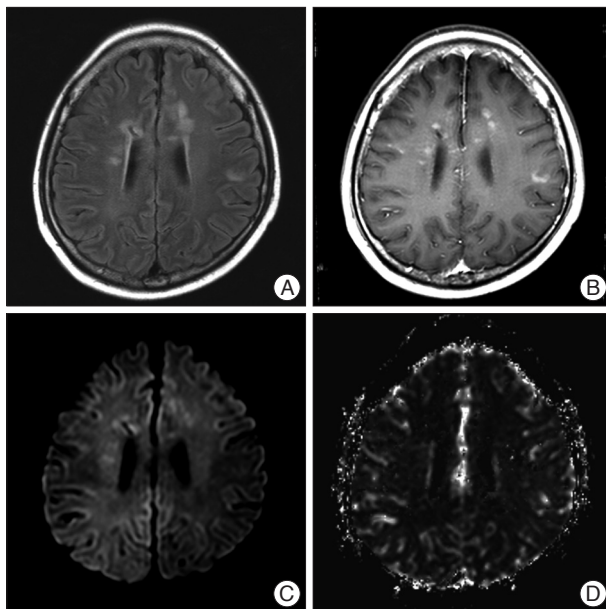


Fig. 2. MRI brain during acute symptomatic period. A : Axial T2 FLAIR shows hyperintense lesions in the both centrum semiovale, periventricular white matter and corpus callosum. B : Axial enhanced T1WI at the same level shows multiple nodular enhancing lesions. C : Diffusion-weight image in the same position with enhancing lesions shows restricted diffusion. D : CBV map shows not increased perfusion in the same position.

performed on each (Table 3). Histopathological examinations revealed necrosis compatible with DNL. In only one patient, MR findings were compatible with DNL and those lesions spontaneously disappeared without further treatment. In three other patients, stereotactic biopsy revealed multifocal ischemic necrosis with reactive gliosis and macrophage infiltration, diffuse microglial cell proliferation and astrogliosis with fibrin deposit, which indicated DNL (Fig. 3, Table 3).

Clinical manifestations that appeared with the onset of DNL were categorized from just after the completion of therapy to many months later and include urinary incontinence, gait disturbance, memory difficulty, decreased attention and slowness, hemiparesis, facial palsy, dysarthria, aphasia, decreased vision, decreased mentality and seizure.

Risk factors and outcomes of DNL

Four patients with DNL had lymphoma, were 60 years of age or younger, and had WBRT; the IT MTX doses of three patients were 60 mg or more. The average doses of the IT MTX, IV MTX

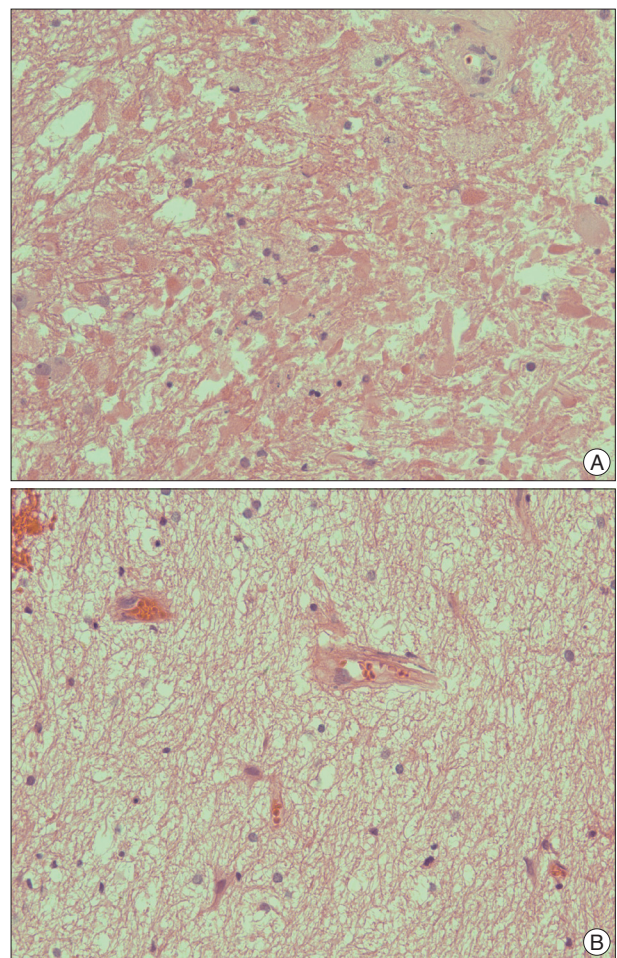


Fig. 3. A : Histopathology (Hematoxylin-eosin stain \times 400) from the affected white matter shows abundant macrophage infiltration with reactive astrogliosis and microglial cell proliferation. B : In a severely affected area, the brain architecture has been lost, being replaced by foamy macrophages and residual blood vessels.

Table 3. Characteristics of four patients with DNL

Sex/Age	Disease	MTX dose, mg (IT/IV)	Radiotherapy dose, cGy; total	Duration (initial therapy to DNL/DNL therapy to death), month	Location of the DNL	Pathology	Symptoms at DNL appearing	Treatment and MRI follow-up of DNL (Time from initial therapy, month)
M/60	Lym (2)	105/30000	3000	10/6	Lt. parietal, Rt. corpus callosum (white)		No symptom	No biopsy, IT+IV MTX, steroid (10)→PR (15)
F/51	Lym (1)	60/30000	4500	12/15	1st : Lt. cerebellum, 2nd : Lt. temporal (white)	1st : necrotic brain tissue, 2nd : hemorrhagic infarct with macrophage infiltration	1st : gait disturbance, 2nd : decreased vision, gait disturbance, memory difficulty	1st : biopsy, no treatment (12) → CR (23) 2nd : biopsy, steroid (20)→PR(23)
F/59	Lym (2)	48/15190	3000	23/79	1st : Rt. frontal (white to gray), 2nd : Rt. frontal (white)	1st : focal fibrin deposit, 2nd : necrotic brain tissue	1st : no symptom, 2nd : urinary incontinence, gait disturbance, decreased attention, slowness, apathy, memory disturbance	1st : biopsy, no treatment (12)→CR (23), 2nd : biopsy, steroid (14)→PR (25)
M/49	Lym (1)	60/33000	4600	38/72	1st : Lt. cerebellum (white), 2nd : Lt. basal ganglia	1st : multifocal ischemic necrosis with reactive gliosis, 2nd : diffuse microglial cell proliferation and astrogliosis,	1st : facial palsy, 2nd : hemiparesis, dysarthria,	1st : biopsy, no treatment (38)→CR (60), 2nd : biopsy, no treatment (60)→CR (72)

Lym : lymphoma, (1) : primary brain lesion, (2) : secondary brain lesion, white : white matter, gray : gray matter, CR : complete resolution, PR : partial resolution, DNL : disseminated necrotizing encephalopathy, IT : intrathecal, IV : intravenous, MTX : methotrexate

and radiation dose in the four patients with DNL were 87 mg, 21,840 mg and 3,593 cGy vs. 68 mg, 27,040 mg and 3,775 cGy, compared with those in the overall group of 143 patients, indicating that chemotherapy dose and radiation dose were not significantly related to the appearance of DNL. Four patients had a total of seven DNL lesions, four of which disappeared completely without any treatment after an average of 14 months.

DISCUSSION

Although a few reports focusing on the incidence of leukoencephalopathy are available, interpretation of results has been limited by small sample size, short follow-up period, and variations in definition³⁰. The present study provides the most comprehensive description, to our knowledge, of the radiologic and pathological consequences associated with successful combination modality treatment for CNS lymphoma/leukemia.

Chemotherapy and radiotherapy induced brain injury

Leukoencephalopathy is a potentially serious complication of chemotherapy. This is particularly true for regimens that include methotrexate, although other drugs, such as BCNU, melphalan, fludarabine, cytarabine, 5-fluorouracil, levamisole and cisplatin, have also been implicated^{5,17}. In many cases, a mild and reversible form of injury is seen acutely, whereas others show permanent deficits or fatal progression. Vascular injury is a well-described feature of radiation-induced central nervous system damage. Studies in humans and animal models have demonstrated that radiation induces vessel wall thickening, vessel dilation, nuclear enlargement in endothelial cells, and necrosis. These are features of radionecrosis that recently have been recognized as important in treatment-related leukoencephalopathy. The risk of serious or permanent damage appears to be greatest when methotrexate is combined with radiation therapy, and therefore, it may be difficult to determine the relative contributions of each modality to this type of pathology^{4,7}. Nevertheless, methotrexate has occasionally been shown to cause the same type of leukoencephalopathy, even in the absence of radiation, particularly in cases with intrathecal or intraventricular administration. In our series, 80 patients were treated with intrathecal methotrexate in addition to cranial radiotherapy, and 63 patients were treated with chemotherapy alone; leukoencephalopathy developed in 60 (75%) and 35 of these patients (55%), respectively, and DNL developed in four and 0 of these patients, respectively. But, the univariate analyses showed that the combined therapy was not a statistically significant risk factor.

Risk factors and outcomes of leukoencephalopathy

The mechanisms of chemotherapy-induced neurotoxicity are enigmatic, but may include direct toxic effects on axons, oligodendrocytes, and progenitor cells, as well as secondary immunologic reactions, oxidative stress, and microvascular inju-

ry^{14,20,26}). Risk factors for toxicity are also incompletely understood, but relate to dosages of methotrexate and radiation, modes of administration, types of diluent, preexisting folate deficiency, and idiosyncratic predispositions. In our series, potential risk factors were assayed, including age (<60 years vs. ≥60 years), gender (male vs. female), cranial radiotherapy (yes or no), radiotherapy dose (360–4,100 cGy vs. ≥4,140 cGy), chemotherapy dose (<60 mg vs. ≥60 mg), and type of the CNS lymphoma/leukemia (primary vs. secondary). Leukoencephalopathy developed more often in patients who were younger than 60 years and who had cranial radiotherapy, higher radiation dose, higher chemotherapy dose and primary etiology. However, univariate analysis revealed that there were no statistically significant risk factors for the development of leukoencephalopathy (Table 2). Because the present study is limited by its retrospective nature, the interval of MRI follow up was not exactly same, several patients lost of the taking MRI during overall follow up period. Leukoencephalopathy was defined radiologically as a hyperintense signal change in the white matter at least 25% of in the white matter by square measure. Excluded patients with less than 25% of signal change and these limitations may affect the no statistical significance.

MRI features of DNL

Rubinstein and colleagues coined the term “disseminated necrotizing leukoencephalopathy” for this more severe, typically progressive and fatal form of disease that they originally described in children with metastatic meningeal acute lymphoblastic lymphoma (ALL) treated with high-dose methotrexate-based chemotherapy and whole brain irradiation²⁵. MRI may be helpful to differentiate mild leukoencephalopathy from DNL. The presence of multiple low signal foci within the T2WI abnormalities and contrast enhancement are proposed to be more suggestive of DNL¹⁹. In the retrospective review, the presence of intense contrast enhancement on the initial MR images in our patients could be viewed as a feature indicating a more fulminant disease process. MR images performed at the time of rapid deterioration showed extensive involvement of white matter or white to gray matter, with intense tumor-like solid enhancement and mass effect. Various patterns including tumor-like forms have been described in DNL¹³.

Histopathologic features of DNL

The histopathology from the contrast-enhancing portion of the lesion at the initial presentation was characterized by demyelination, macrophagic infiltration, pericapillary lymphomononuclear infiltrate and fibrinoid changes in the tunica intima¹⁵. The presence of prominent vascular changes leading to disseminated coagulative necrosis and consequent contrast enhancement on MRI are striking features in DNL compared with the less severe and more commonly observed pattern of reversible leukoencephalopathy¹⁹. In this study, the capillary changes on histopathology and contrast enhancement on MRI in this series

were suggestive of endothelial damage and blood brain barrier disruption, presumably because of direct toxic effect of MTX on the vascular endothelium. These results demonstrate that chemotherapy also plays a pathogenic role.

Clinical features of DNL

Clinically, DNL is characterized by a rapidly progressive subcortical dementia, with manifestations similar to those of arteriosclerotic encephalopathy (Binswanger’s disease), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and normal pressure hydrocephalus^{4,20}. Over time, cognitive deficits progress to frank dementia, with motor and autonomic deficits becoming increasingly apparent. In this series, symptoms that appear with the onset of DNL are categorized from just after the completion of therapy to many months later and include urinary incontinence, gait disturbance, memory difficulty, decreased attention and slowness, hemiparesis, facial palsy, dysarthria, aphasia, decreased vision, decreased mentality and seizure. However, one patient in our study had no symptoms with the onset of DNL. The symptoms were based on clinically significant cognitive dysfunction, and mild cases may have been missed.

Incidence of DNL

In this study, only four patients were diagnosed with DNL, and a five-year cumulative incidence of DNL could not be estimated, although the overall incidence of DNL was 2.8%.

The present study was limited by its retrospective nature. The diagnosis of leukoencephalopathy was based on radiological findings such as hyperintense signal in the white-matter on T2-weighted or FLAIR MR images, not on the clinical manifestations. Another limitation was the limited protocol for MR examinations. Diffusion-weighted images and perfusion images were not included in the follow-up MRI protocol for any patient. The diagnosis of disseminated necrotizing leukoencephalopathy was also limited. Therefore, a prospective study is needed to ascertain whether these radiological changes on MRI are part of the spectrum of delayed neurotoxicity or whether they represent a nonprogressive consequence of direct tumor damage or treatment-related acute toxicity.

CONCLUSION

The more leukoencephalopathy can be developed in patients with younger than 60 years, cranial radiotherapy, higher radiation dose, higher chemotherapy dose and primary etiology, although these were not statistically significant risk factors.

Diagnosis of MTX-induced DNL requires a high index of suspicion, and it may not be possible to differentiate DNL from a recurrent mass, even on advanced images such as diffusion-weighted images and perfusion images. However, a correct diagnosis of DNL can spare the patient from unnecessary invasive biopsy or therapies.

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