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Neurology 2004;62;451-456

DOI 10.1212/01.WNL.0000106941.51340.A2

This information is current as of February 9, 2004

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.neurology.org/content/62/3/451.full.html>

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Treatment-induced leukoencephalopathy in primary CNS lymphoma

A clinical and autopsy study

Rose Lai, MD; Lauren E. Abrey, MD; Marc K. Rosenblum, MD; and Lisa M. DeAngelis, MD

Abstract—Background: Treatment-related leukoencephalopathy is the leading toxicity after successful treatment of primary CNS lymphoma (PCNSL). Its mechanism is poorly understood and there are no autopsy data available on such patients. **Methods:** From a database of immunocompetent patients with PCNSL diagnosed between 1985 and 2001, the authors identified five autopsied patients who died of leukoencephalopathy. The authors reviewed their clinical records, MRI, and autopsy findings. **Results:** The median age was 74 years (range 41 to 79) at PCNSL diagnosis. Symptoms of neurotoxicity developed a median of 1 month after treatment completion, and median survival was 30 months (range 22 to 68 months) after neurotoxicity onset. All had white matter hyperintensity on T2-weighted MRI, and two developed enhancing lesions 5 and 14 months following completion of treatment. At autopsy no PCNSL was identified. Myelin and axonal loss, gliosis, pallor, spongiosis, and rarefaction of the white matter were found in all; two patients had tissue necrosis that correlated with the enhancement on MRI, and one had fibrinoid necrosis of vessels. Four of the five patients had atherosclerosis of large cerebral vessels in the circle of Willis and all had small vessel disease; two had recent strokes at autopsy. **Conclusions:** Treatment-induced leukoencephalopathy is not a late delayed consequence of neurotoxic treatment but can be seen very early in some patients. Vascular disease may be a component of this white matter injury.

NEUROLOGY 2004;62:451–456

Primary CNS lymphoma (PCNSL) is a rare tumor that is treated with methotrexate-based chemotherapy often in combination with whole brain radiotherapy (WBRT).¹ Over 90% of patients over age 60 successfully treated with the combination of chemotherapy and WBRT will develop treatment-related neurotoxicity² characterized by dementia, gait abnormalities, and urinary incontinence.^{3–5} Neuroimaging shows diffuse leukoencephalopathy, atrophy, and often communicating hydrocephalus.⁴ Few studies have described the pathologic findings and potential mechanisms of brain toxicity from radiation or chemotherapy,^{3,4,6} and no autopsy series have been reported in PCNSL patients who died of neurotoxicity. In this study, we describe the clinical course and autopsy findings of five PCNSL patients who died from treatment-induced neurotoxicity.

Methods. Memorial Sloan Kettering Cancer Center's PCNSL and autopsy databases were reviewed, and 15 immunocompetent patients with a diagnosis of PCNSL who had an autopsy were identified. Ten died from progressive PCNSL and were described elsewhere.⁷ Five died from neurotoxicity and form the basis of this report. Clinical information and autopsy findings were reviewed for all. MR scans were available for review in one patient and neuroimaging reports were used for the other four.

Results. The median patient age at diagnosis of PCNSL was 74 years with a range of 41 to 79; three were women and two were men (table 1). Only one patient was younger than 60 at diagnosis of PCNSL. All patients had WBRT in

doses ranging from 3,000 to 4,140 cGy and three received a boost between 900 and 1,440 cGy. Three patients had pre-RT high-dose methotrexate-based chemotherapy and intrathecal (IT) or intra-Ommaya (IO) methotrexate. Four had post-RT chemotherapy: two high-dose cytarabine (3 g/m²) and one doxorubicin and etoposide. One patient was treated with WBRT and IT cytarabine post-RT; she received no systemic chemotherapy.

Symptoms of neurotoxicity began a median of 1 month from completion of treatment and within 3 months in all patients. The initial symptoms were confusion in two and short-term memory loss in three; a few months later, four had gait impairment, three had urinary incontinence, and one developed seizures. All patients became demented. Symptoms were progressive over months but eventually stabilized; all required custodial care by the time symptoms stopped progressing.

MRI and CSF cytology were negative for recurrent lymphoma at symptom onset. The MRI showed cerebral atrophy, ventricular dilatation, and white matter hyperintensity on FLAIR and T2 images that progressed for months and then stabilized. Two patients developed enhancing lesions in the right parietal lobe at 5 and 14 months following the completion of treatment. In both patients this was thought initially to be tumor recurrence, but their neurologic condition was so poor that no further treatment was given; they died 27 and 22 months from onset of neurotoxicity. Four patients had placement of a ventriculoperitoneal (VP) shunt; one regained continence and had improved personality and gait for 4.5 months but

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Received July 29, 2003. Accepted in final form September 18, 2003.

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Table 1 Clinical findings of five PCNSL patients who died from neurotoxicity (NT)

Patient number/sex/age at diagnosis, y	Symptoms and signs of toxicity	Latency to NT after completion of treatment, mo	Pre-RT chemo	Total RT dose, cGy	Post RT chemo	CSF shunt; result	Time to death after onset of NT, mo	MRI findings
1/F/60	Confusion, memory difficulties, gait abnormalities, urinary incontinence	1	MTX (3.5 g/m ²)-PCB-VCR ×5; IO MTX ×5	5,040 (4,140 WBRT; 900 boost)	Ara-C 3 g/m ² ×2	Yes; no benefit	27	Cerebral atrophy, ventricular dilatation, PVWM hyperintensity, pachymeningeal enhancement, R parietal enhancing lesion
2/F/77	Confusion, memory impairment, gait difficulties, seizures	2	None	4,050 (WBRT)	DOXO; VP-16 doses unknown	No	68	Cerebral atrophy, ventricular dilatation, PVWM hyperintensity
3/M/79	Dementia, ataxia of gait	3	MTX (1 g/m ²) ×2; IT MTX ×6	5,580 (4,140 WBRT; 1,440 boost)	Ara-C 3 g/m ² ×2	Yes; no benefit	30	Cerebral atrophy, PVWM hyperintensity, ventricular dilatation
4/M/41	Dementia, personality changes, depression, gait abnormalities, urinary incontinence	1	MTX (3.5 g/m ²)-Thiotepa-PCB ×5; IO MTX ×5	5,040 (4,140 WBRT; 900 boost)	None	Yes; improved for 4.5 mo	50	Cerebral atrophy, ventricular dilatation, PVWM hyperintensity, bilateral subdural fluid collections
5/F/74	Dementia, confusion, urinary incontinence	1	None	3,000 (WBRT)	IT Ara-C doses unknown	Yes; no benefit	22	PVWM hyperintensity, ventricular dilatation, R parietal enhancing lesion

PCNSL = primary CNS lymphoma; RT = radiotherapy; MTX = methotrexate; PCB-VCR = procarbazine-vincristine; IO = intra-Ommaya; WBRT = whole brain RT; Ara-C = cytarabine; PVWM = periventricular white matter; DOXO = doxorubicin; VP-16 = etoposide; IT = intrathecal.

the other three did not improve. MRI in three of these patients showed chronic subdural fluid collections post-shunt.

Median survival after onset of neurotoxicity was 30 months, ranging from 22 to 68 months. At autopsy, no patient had residual tumor (table 2). All patients had axonal and myelin loss, pallor, rarefaction, spongiosis, and gliosis of the cerebral hemispheric white matter (figure 1). Two patients had evidence of tissue necrosis. One of the two had focal fibrinoid necrosis in the vasculature of cerebral white matter, brainstem, and cervical spinal cord in areas that had not received the radiation boost. The other patient had necrosis limited to the area of radiation boost. Both of these patients had contrast enhancement on MRI but necrosis extended beyond the area of enhancing lesions. Four of the five patients had atherosclerosis of the large cerebral blood vessels in the circle of Willis: one mild, one moderate, and two severe. Three of the five patients had evidence of systemic atherosclerosis. All patients had fibrotic thickening of small blood vessels in the deep white matter without luminal clot. Three patients had cerebral infarcts: two recent and one remote. The two patients with recent infarcts had no stroke risk factors except advanced age; neither had systemic atherosclerosis. Stroke was the cause of death in one of these patients. The clinical courses of Patients 1 and 2 are illustrated below.

Patient 1. A 60-year-old woman presented with lethargy, aphasia, and right hemiparesis that progressed over 3 months. MRI revealed two enhancing lesions, one in the deep left frontal lobe compressing the frontal horn of the lateral ventricle, and a second smaller one in the left basal ganglia. She was diagnosed with PCNSL, B-cell immunoblastic subtype by stereotactic biopsy. CSF, chest, abdomen, and pelvic CT scans and bone marrow biopsy were all negative for systemic lymphoma. HIV serology was negative. An Ommaya reservoir was inserted, and she completed five courses of systemic methotrexate (3.5 g/m²) and procarbazine and vincristine and five courses of IO methotrexate, followed by WBRT at 4,140 cGy, with a 900 cGy boost for a tumor dose of 5,040 cGy, and then two cycles of high-dose cytarabine. During her methotrexate therapy, she developed a transient episode of right hemiparesis that resolved within 12 hours and was immediately followed by a brief episode of left hemiparesis that also resolved completely. This was attributed to acute methotrexate toxicity,^{8,9} and she tolerated subsequent cycles without difficulty. She had a complete response to treatment.

One month after her last cytarabine dose and 3 months after cranial irradiation, she developed memory difficulty and periods of confusion. Three months later, her gait became unsteady and she required increasing assistance.

Table 2 Autopsy findings of five PCNSL patients who died from neurotoxicity (NT)

Patient no.	Findings of NT	Intracranial atherosclerosis	Systemic atherosclerosis
1	Tissue necrosis in the R temporal-occipital regions, L BG and CC	Marked atheroma of large vessels	30% occlusion of coronary arteries; other vessels normal
2	Gliosis, pallor, and rarefaction of CHWM	Massive recent bilateral cerebral hemispheric infarction, older cavitated infarcts, severe atherosclerosis of large cerebral vessels	None
3	Gliosis, pallor, and rarefaction of CHWM	Multiple recent infarcts in L insula, R BG; R occipital and medial temporal lobes; large intracranial vessels normal	None
4	Severe axonal and myelin loss, gliosis, and macrophage infiltrates	Focal mild atherosclerosis of large cerebral vessels	90% stenosis in mid left anterior descending coronary artery; other vessels normal
5	Fibrinoid necrosis of PVWM and cervical myelopathy	Arteriolar sclerosis cerebri was present; moderate atheromatous changes in large cerebral vessels; old L parietal infarct	Severe atherosclerosis of aorta and coronary arteries with interstitial myocardial fibrosis

No patient had PCNSL present on autopsy.

PCNSL = primary CNS lymphoma; BG = basal ganglia; CC = corpus callosum; CHWM = cerebral hemisphere white matter; PVWM = periventricular white matter.

Her balance and cognitive problems progressed. MRI performed 3 months after completion of treatment showed no evidence of PCNSL; however, atrophy, ventricular dilatation, and prominent diffuse bilateral white matter abnormalities were evident. Two months following this MRI, her Ommaya reservoir was converted into a shunt, but she did not improve symptomatically. She was bedbound, required a percutaneous gastrostomy and Foley catheter, and was sent to a nursing home.

Fourteen months following the completion of treatment, her clinical condition deteriorated severely; she could not speak or understand others, and was unable to recognize

her husband. She could not stand, even with support, and had no bladder control. There was increased tone in all four limbs, with brisk reflexes in the arms and Babinski signs bilaterally. MRI showed progressive diffuse white matter changes on T2-weighted images; a new right parietal enhancing mass appeared as well as subdural collections secondary to the VP shunt (figure 2, A and B). No further treatment was instituted; her neurologic condition deteriorated and she died 28 months after completion of therapy.

At autopsy, widespread treatment effect was found in the right temporal-occipital regions, left basal ganglia, splenium, corpus callosum, and deep white matter. Tissue necrosis was found at the site of the enhancing lesion but extended beyond it. The circle of Willis revealed marked atherosclerosis, but no strokes were identified. There was moderate atherosclerosis of the coronary arteries and aorta. There was no lymphoma in the CNS, eyes, or extra-neural tissues.

Patient 2. A 77-year-old woman without prior medical illness presented with a 5-month history of reduced vision and floaters in the right eye. She was diagnosed elsewhere with ocular lymphoma; it was unclear whether she received ocular treatment but she did not receive systemic chemotherapy or radiotherapy. Her visual symptoms resolved in a few months. For 1 year, she had progressive intermittent nausea and lightheadedness, and her examination was notable for mild confusion and an unsteady gait but no lateralizing signs. Cranial MRI revealed multiple enhancing lesions in the periventricular area, particularly around the occipital horns and the vermis. Some of these lesions resolved after she was started on dexametha-

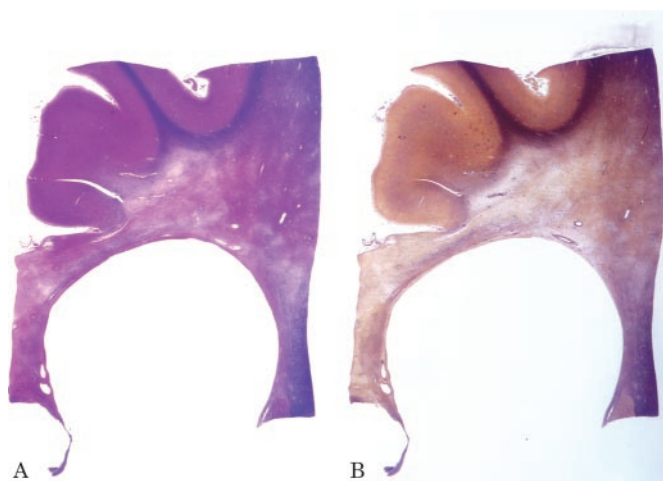


Figure 1. Whole mount of cortex demonstrating patchy demyelination of white matter (A, Luxol fast blue) and axonal loss in same areas (B, Bielschowsky). Note the relative preservation of “U” fibers.

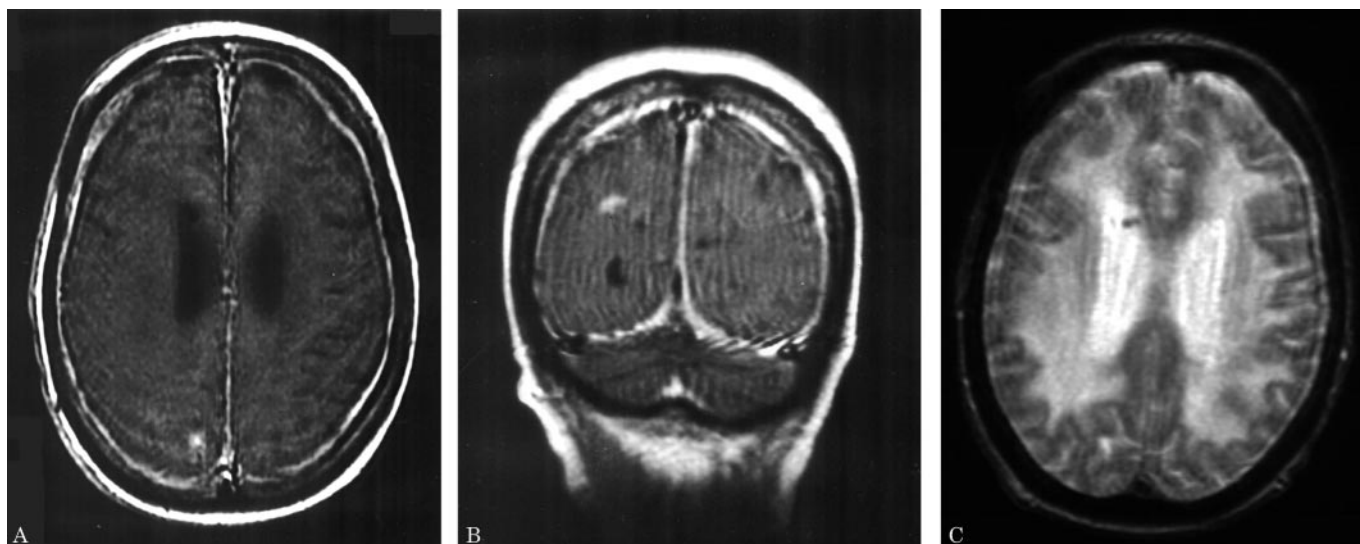


Figure 2. Gadolinium enhanced T1 (A) axial and (B) coronal MRI showing a small right parietal enhancing lesion that was found to be radionecrosis at autopsy (Patient 1). (C) T2 MRI demonstrating severe diffuse leukoencephalopathy.

sone. Chest, abdominal, and pelvic CT scans, mammography, and upper endoscopy showed no evidence of tumor. CSF revealed a negative cytologic examination. Given her diagnosis of ocular lymphoma and the multiple enhancing lesions responsive to steroids, she was treated for PCNSL with 4,050 cGy WBRT in 21 fractions. After RT, she received etoposide and doxorubicin, and 1 month after treatment, contrast enhanced CT showed no evidence of tumor, but atrophy and diffuse white matter hypodensity were evident.

Two months after completing treatment, she was readmitted to the hospital for confusion and general deterioration. An MRI showed atrophy and white matter changes with no enhancement after gadolinium; CSF had no lymphoma cells. She was given a course of doxorubicin and etoposide for presumed recurrence and was discharged. However, she was readmitted in 1 month with failure to thrive, confusion, serum sodium of 124 mg/L, and a possible seizure. Neurologic examination revealed disorientation and memory impairment but no lateralizing signs. An MRI showed no tumor, but atrophy, ventricular dilatation, and periventricular white matter hyperintensity on T2 images had worsened compared to her MR scans 1 month previously. She was started on dexamethasone and phenobarbital, but the medications made her more agitated and confused. Dexamethasone was eventually tapered and phenobarbital was stopped. The patient was discharged home and her family transferred her care to Memorial Sloan-Kettering Cancer Center.

On examination she was oriented to place and self but not date. She had poor short-term memory, and could not remember her relationship to family members. Initially her mental status improved at home, attributed to the reduction in medications. Despite her temporary improvement, her short-term memory and orientation deteriorated over the next 2 years. She also had progressive gait difficulty with instability and frequent falls, but no incontinence. Her course was complicated by frequent complex partial seizures. MR scans performed during those 2 years

showed progressive bilaterally symmetric hemispheric white matter changes consistent with a diffuse leukoencephalopathy; these findings stabilized after 1 year. The patient died in a long-term care facility 68 months after onset of neurotoxicity.

At autopsy, no residual lymphoma was found in the CNS, eyes, or systemically. The cerebral hemispheric white matter had extensive myelin and axonal loss, gliosis, spongiosis, and rarefaction, consistent with post-treatment leukoencephalopathy. Severe atherosclerosis of large intracerebral arteries and recent bilateral cerebral hemispheric infarction, which was the cause of death, were found (figure 3). Older cavitated infarcts of the right putamen, occipital lobe, anterior frontal lobe, medial frontoparietal lobe, and cerebellum were also seen. There was no systemic atherosclerosis, and she had no vascular risk factors except her age.

Discussion. Leukoencephalopathy is a severe and potentially fatal complication of effective PCNSL therapy, particularly in those who have received

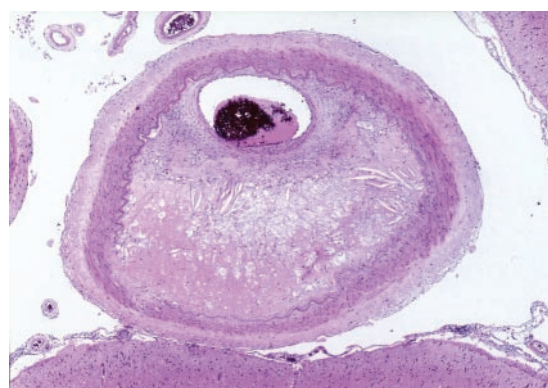


Figure 3. Middle cerebral artery from Patient 2. Prominent atherosclerosis can be seen with a recent thrombus in the compromised lumen.

WBRT combined with chemotherapy. It is usually classified as a late delayed complication occurring years after completion of treatment,¹⁰ and consequently, only long-term survivors are considered vulnerable. However, the most striking feature of our five patients is the short latency between completion of therapy and the onset of neurotoxicity. Three patients developed symptoms within 1 month and all within 3 months of completing treatment. This rapid onset was even observed in our one relatively young patient (age 41) and in the patient (no. 5) who did not receive any systemic chemotherapy or methotrexate. The early appearance of treatment-induced leukoencephalopathy has not been previously reported, and means that all treated patients are potentially at risk for this complication. Even focal radionecrosis, long considered a delayed complication, appeared within 5 months of therapy completion in one patient. Known factors critical to the development of leukoencephalopathy were prevalent in our population, but they did not describe every patient: older age (4/5 >60 years), higher doses of RT (3/5 received >50 Gy), higher daily fractions of RT (only 1/5 received 3 Gy fractions), and chemotherapy with known neurotoxicity, especially methotrexate (3/5).^{10,11}

Methotrexate and WBRT have synergistic neurotoxicity, but only three patients received methotrexate prior to cranial radiotherapy. Patient 2 received etoposide and doxorubicin, agents thought to have limited penetration of the blood-brain barrier (BBB); however, this patient's chemotherapy was administered after WBRT. The effect of cranial irradiation on the BBB is variable and may be time dependent. Most experimental studies demonstrate an increase in the BBB permeability after RT regardless of whether large single fractions or multiple standard daily fractions were used¹²⁻¹⁶; rarely, reduced permeability has been observed.¹⁷ This enhanced permeability may persist for weeks to months and can reverse to normal.¹⁴ These findings have been confirmed in human studies that show an initial disruption of the BBB following RT that can reverse over several months.^{18,19} We do not know the exact timing of the chemotherapy administered to Patient 2, but radiation-induced increased permeability of the BBB may have allowed these agents to penetrate into the CNS. Thus, enhanced toxicity may be seen with chemotherapeutic agents that usually have minimal neurotoxicity under ordinary circumstances. Cytarabine is also a neurotoxin and three of our patients received it post-RT, two systemically and one intrathecally. The IT cytarabine may have contributed to the leukoencephalopathy that developed in Patient 5 who had WBRT but no systemic chemotherapy.

Similar to previous studies, neuroimaging features in our patients were characterized by a diffuse leukoencephalopathy. Two developed foci of enhancing radionecrosis in addition to white matter changes: one corresponded to the radiation boost but the

other received only 3,000 cGy WBRT. Progressive nonenhancing lesions on T2 or FLAIR MR images usually indicate leukoencephalopathy in the treated patient, but recurrent PCNSL can occasionally be diffusely infiltrative and appear on MRI as increased signal on T2 or FLAIR sequences without enhancement.²⁰ Indeed, 2 months after completion of treatment, Patient 2 presented with confusion and was thought to have recurrent lymphoma because of the short latency between the end of therapy and recurrence of symptoms; despite the absence of an enhancing lesion she was given additional chemotherapy. In a recent study of autopsied patients who died from progressive PCNSL, extensive tumor was found throughout the brain, even in areas that were normal on MRI.⁷ These patients had periventricular white matter abnormalities on T2 MR images, but none had progressive leukoencephalopathy on MRI and none had a progressive dementing illness clinically. Neurologic impairment from toxicity is more stereotyped, with onset of short-term memory loss that progresses to dementia and eventually akinetic mutism; gait abnormalities and urinary incontinence develop as the patient deteriorates.³ In contrast, patients with recurrent PCNSL usually have neurologic deficits and symptoms that correspond to contrast enhancement or focal T2 hyperintensity.⁷ In addition, patients with post-treatment neurotoxicity have a more protracted course of illness and can live several years after treatment; long-term survival after onset of neurotoxicity has been observed in three other series.^{3,5,21} This is in contrast to patients who died from widespread progressive PCNSL; their median survival was only 11 months.⁷

At autopsy, treatment-induced neurotoxicity was characterized by gliosis, spongiosis, and rarefaction of the cerebral hemispheric white matter, as well as widespread myelin and axonal loss in all patients. All patients had thickening of small vessels in the deep white matter, including our patient who was only 41 years old and had no vascular risk factors. Four had mild to severe atherosclerosis of large cerebral blood vessels, and three had evidence of stroke on autopsy. Prior autopsy studies of leukoencephalopathy described diffuse chronic edema of the white matter with axonal and myelin loss and widespread spongiosis of the white matter with vacuoles but none described vasculopathy.³⁻⁶ Brain irradiation is well known to cause vascular injury; this is the fundamental mechanism in the development of radionecrosis. However, the spectrum of RT-induced vascular damage is increasing. Vasculopathy following brain irradiation has been observed in children with medulloblastoma, optic nerve glioma, acute lymphoblastic leukemia, and pituitary neoplasm.²²⁻²⁵ Rarely, moyamoya-like vascular changes are seen following brain irradiation during childhood.²⁶ A large study of 421 children with brain tumors treated with chemotherapy or radiation or both found that 25 had developed silent lacunes, indicat-

ing small vessel infarcts; none of the 103 patients observed or treated with surgery alone developed lacunes.²⁷ The most predictive factor for the development of lacunes was age less than 5 years at the time of radiotherapy, probably reflecting the effect of radiation on the developing vascular system. Similarly, in a retrospective study, large vessel vasculopathy was found in 6 of 32 pediatric brain tumor patients 2 to 13 years after radiation.²⁸ However, in adult brain tumor patients, cerebrovascular disease was rarely reported.²⁹ Our study suggests that treatment-induced vasculopathy is more common than previously appreciated and it may play a critical role in CNS damage after effective treatment for PCNSL. Patients with PCNSL may be particularly vulnerable to vascular damage because of the tumor's perivascular location and potential release of cytokines that may lead to vascular injury.³⁰

Vasculopathy may also be an acute toxic effect of methotrexate.³¹ Methotrexate can raise the plasma homocysteine that in turn can damage cerebrovascular endothelium; hyperhomocystinemia is a risk factor for stroke.³¹ A study measuring the concentration of homocysteine and its metabolites in the CSF found that patients treated with methotrexate had a significantly greater concentration of homocysteine and its metabolites in the CSF compared to control patients, and patients with neurologic toxicity had the highest concentrations.³² These data suggest that methotrexate may contribute to cranial vasculopathy by elevating levels of homocysteine and its metabolites. This may be the mechanism of the transient stroke-like events described as a rare subacute neurologic toxicity of methotrexate, as seen in Patient 1.³³ However, these transient events are not known to predispose to permanent methotrexate-related CNS damage.

As therapies for PCNSL are becoming more effective, toxicity from treatment, especially for those over age 60, is being recognized with increasing frequency. Our data demonstrate that leukoencephalopathy can emerge early, and vascular disease may be part of the spectrum of global treatment-related neurotoxicity.

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