

Primary Lymphoma of the Central Nervous System in an Immunocompetent Patient

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Primarily central nervous system lymphoma (PCNSL) is a non-Hodgkin's lymphoma confined to the craniospinal axis.¹ The occurrence of PCNSL has been increasing in frequency in both immunocompromised and immunocompetent patients in the United States during recent decades. The overall incidence of this nonsystemic disease rose from 2.5 cases per 10 million persons in 1973 to 30 cases per 10 million persons in 1992 and was projected to rise again to at least 51 cases per 10 million persons by the end of 2000.^{2,3}

We report the case of a 77-year-old woman with cognitive decline in whom a tentative diagnosis of PCNSL was made. The epidemiological features, possible etiology, diagnosis, and current management of the disorder will be discussed briefly.

CASE PRESENTATION

A 77-year-old right-handed woman was admitted to the neurology service because of a 1-month history of rapidly progressive memory loss and confusion. There was no history of an antecedent febrile illness, head trauma, recent diagnosis of cancer, or other illnesses. She was taking a mild diuretic to control her high blood pressure but no other medications. The patient was retired from her work as a salesperson, drank alcohol occasionally, and smoked half a pack of cigarettes daily.

Initial physical examination was unremarkable; blood pressure was 136/82 mm Hg, and pulse was 86 bpm and regular. Guaiac-based testing of her stool was negative for occult blood. Neurologic examination was slightly more revelatory. The patient scored 24 (of a total 30) on a Folstein Mini-Mental State Examination, exhibiting selective loss of short-term memory. Examination of the optic fundi did not reveal increased intracranial pressure. The cranial nerves were intact, and there were no sensorimotor deficits. There were no abnormal movements. Her stance, gait, and coordination were within normal limits.

A cranial computed tomography (CT) scan without

contrast obtained at the time of admission was unremarkable and appropriate for her age; electroencephalography (EEG) similarly showed no abnormalities. Results of routine hematologic and biochemical profiles also were within normal limits. However, cranial magnetic resonance imaging (MRI) with gadolinium showed multiple periventricular enhancing lesions (**Figure 1**). Results of initial laboratory analysis of cerebrospinal fluid (CSF) were leukocyte count, 45/mm³ (lymphocytes, 39/mm³; monocytes, 6/mm³); erythrocytes, none; protein, 143 mg/dL; and glucose, 50 mg/dL. Further tests on the CSF, including serology for Lyme disease and cytomegalovirus, VDRL test for syphilis, and polymerase chain reaction for herpes simplex virus, were negative; no malignant cells were detected. Serum angiotensin-converting enzyme level was within normal limits, and tests to detect vasculitis and paraneoplastic disorder were also negative. A tuberculin skin test using mumps and candidiasis as controls was negative for tuberculosis after 72 hours. A brain biopsy was considered but refused by her family, and the patient was discharged.

The patient returned to the emergency department with new onset diplopia after 1 month; her cognitive state had continued to worsen. Repeat MRI with gadolinium showed worsening of the periventricular lesions and a new area of enhancement in the right caudate nucleus (**Figure 2**). Repeat CSF analysis was inconclusive. Results of a brain biopsy showed no abnormalities. However, CSF obtained from the lateral ventricle at the time of the biopsy contained cells that were positive for leukocyte-common-antigen and L26 immunostaining, suggesting the presence of a B-cell lymphoma of a large cell type.

An extensive search for an extracranial tumor site, including CT scans of the thorax, abdomen, and pelvis

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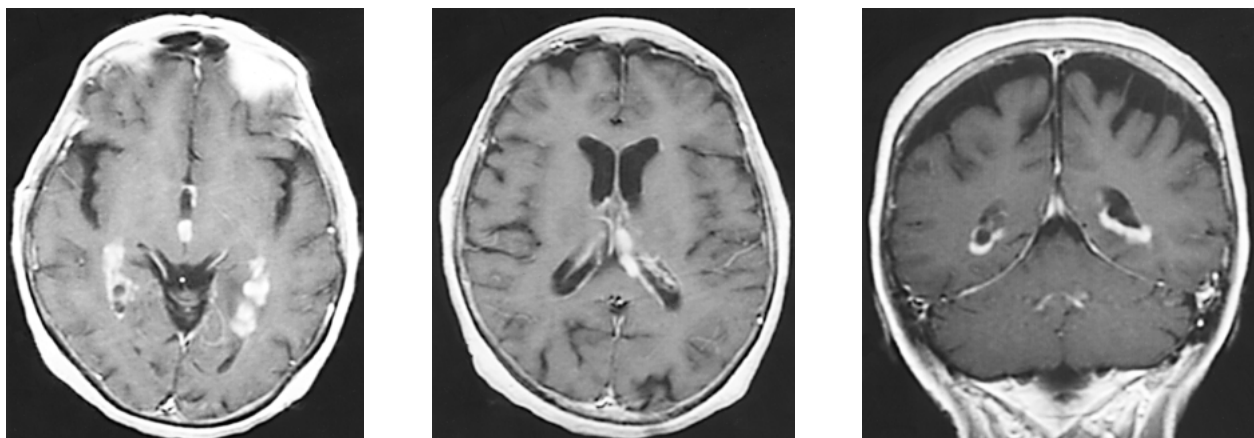


Figure 1. T1-weighted, gadolinium-enhanced magnetic resonance images of the brain in the axial and coronal planes obtained in the case patient show multifocal enhancing nodules surrounding the ventricles.

and biopsy of the bone marrow, yielded no results. The patient was transferred to the oncology service, where she was treated with intrathecal injection of high-dose cytosine arabinoside (1 g/m²) and whole brain radiation (40 Gy). Subsequent MRI with gadolinium showed complete disappearance of the periventricular lesions (**Figure 3**).

DISCUSSION

Epidemiology

PCNSL occurs in all age groups. The average age of presentation in immunocompetent patients is 55 years^{1,4} and in patients with AIDS is 31 years.^{1,5} Specific neurologic deficits are present in more than 50% of affected patients and include altered mental status, seizure, cranial nerve palsies, and headache. Altered mental status and symptoms such as fever, weight loss, and night sweats are more frequent among patients with AIDS.⁶

Etiology

The etiology of PCNSL is still unclear but most likely involves multiple causes, including use of immunosuppressive drugs, immunodeficiency diseases, infections, and exposure to pesticides and solvents. There are virtually no experimental data on whether PCNSL develops outside the brain or arises from polyclonal lymphoproliferations within the brain.⁷

Of note is the consistent finding of Epstein-Barr genomic DNA within PCNSLs in 95% of patients with AIDS but in less than 5% of immunocompetent patients.⁸ The genomes of other herpesviruses, such as human herpesvirus 6 and human herpesvirus 8, have been found in a few cases of PCNSL,^{9,10} suggesting that these or other herpesviruses also might play a role in

this type of lymphoma in immunodeficient and possibly also in immunocompetent patients. Recent studies have additionally implicated the activation of the *c-myc* oncogene and mutations of the tumor suppressors *p53* and *bcl-6* in the development of PCNSL.^{11,12}

Approximately 98% of PCNSLs are B-cell, non-Hodgkin's lymphomas, while only approximately 2% are T-cell lymphomas. The non-AIDS-related cases of PCNSL often involve intermediate- to high-grade histologic subtypes, whereas AIDS-related cases usually involve an aggressive histologic subtype comprising either large immunoblastic or small noncleaved cells.^{6,13}

Diagnosis

The differential diagnosis in a patient with mental status changes and gadolinium-enhanced lesions on MRI includes infectious and neoplastic processes. A primary or metastatic brain tumor was a strong diagnostic consideration in the case patient.

The diagnosis of PCNSL is often suggested by radiographic evidence. On a gadolinium-enhanced MRI, PCNSL appears as relatively well-circumscribed focal masses or as poorly delineated, diffuse infiltrating lesions. Multiple centrally located lesions are frequent. The deep basal ganglia, periventricular region, and corpus callosum are the most common sites of these masses,¹⁴ as illustrated by the gadolinium-enhanced lesions in the caudate nucleus and periventricular areas of the case patient. All masses that are suggestive of PCNSL are enhanced by gadolinium; the enhancement is mostly homogenous in immunocompetent patients and markedly heterogeneous in patients with AIDS.¹⁵ Recent studies have investigated the utility of using thallium-201 single-photon emission computed

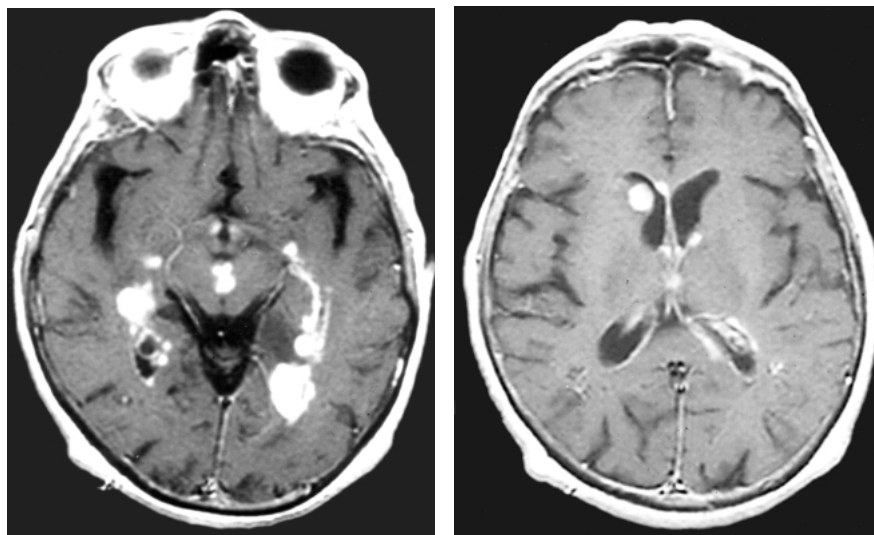


Figure 2. T1-weighted, gadolinium-enhanced magnetic resonance images obtained 1 month after the case patient was discharged from the hospital show enlargement of the previous lesions and a new nodule in the right caudate nucleus.

tomography (SPECT), technetium-99m–sestamibi SPECT, thallium-201 retention, and perfusion MRI in the diagnosis of PCNSL and toxoplasmosis.^{16–18} Despite such advances in imaging techniques, however, tissue biopsy is required to confirm the diagnosis of PCNSL.

Stereotactic brain biopsy performed by an experienced neurosurgeon yields a diagnosis of PCNSL in more than 95% of cases¹⁹; the case patient was unusual in this respect because biopsy failed to reveal any abnormality, although CSF obtained during the biopsy was positive for lymphomatous cells. CSF cytology is diagnostic in only 10% to 30% of patients with PCNSL unrelated to AIDS and even less diagnostic in cases of AIDS-related PCNSL.^{6,20} An elevated CSF protein level and pleocytosis are not uncommon but are nonspecific for the disease.

Once the diagnosis of PCNSL has been established, the extent of the disease in the nervous system must be assessed.²¹ Active systemic lymphoma can be identified in only 2% to 3% of patients with PCNSL after an extensive systemic evaluation, including chest, abdominal, and pelvic CT scans or a bone marrow biopsy. Cranial MRI with gadolinium, ophthalmologic evaluation (including slit-lamp examination), and lumbar puncture must be part of the evaluation to assess the extent of nervous system involvement. Spinal MRI with gadolinium is performed if the patient has signs and symptoms of spinal cord or cauda equina involvement.²¹

Management

Whole brain radiation therapy offers rapid resolution of the lesions associated with PCNSL but achieves only a transient remission of the disease.^{4,22} The use of chemo-

therapy as an adjunct to the radiation is successful in inducing prolonged remission,²³ especially in many younger (< 60 years) immunocompetent patients. Overall prognosis remains poor, and the median survival after diagnosis is 13.5 months.²⁴

Subacute onset of progressively deteriorating cognitive functions associated with PCNSL (as well as with brain tumor, CNS vasculitis, angiocentric lymphoma, paraneoplastic [limbic] encephalitis, infections, chronic subdural hematoma, prion disease, and preexisting dementia of the Alzheimer's type) in an immunocompetent person can present acutely and involve an intercurrent illness. In the case patient, there was no prior history of head trauma, and normal results on cranial CT ruled out subdural hematoma. CSF cultures for bacteria and fungi, polymerase chain reaction for herpes simplex virus, and cytomegalovirus serology were negative. Negative serology for syphilis in both serum and CSF argues against tertiary syphilis. The patient had no myoclonus or abnormalities on EEG to suggest subacute spongiform encephalopathy. A careful history obtained from the patient's family about her premonitory intellectual function ruled out any preexisting dementing illness. Her clinical course did not suggest CNS vasculitis, and a paraneoplastic screen showed no abnormalities. The gadolinium-enhanced lesions in the periventricular region seen on MRI strongly suggested PCNSL, which was confirmed by demonstration of lymphoma cells in CSF on immunostaining.

SUMMARY

PCNSL is a disease that has been increasing in incidence among patients of all ages. Progress in

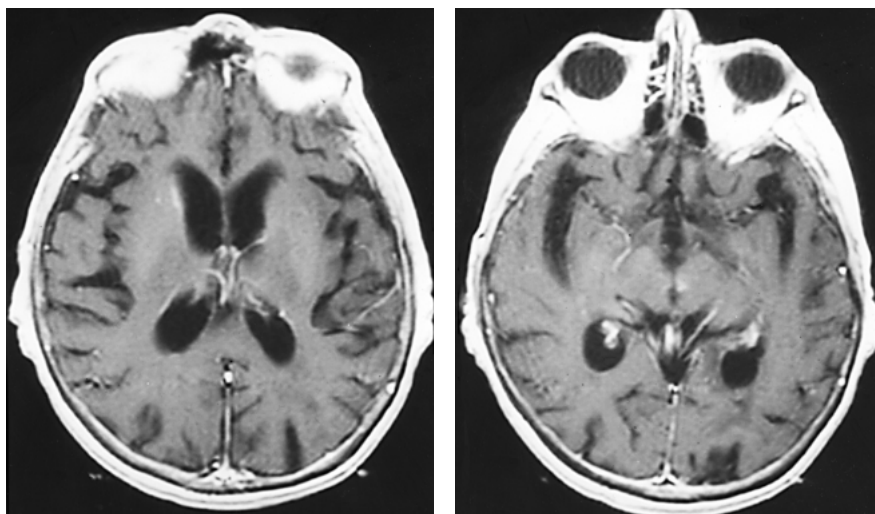


Figure 3. T1-weighted, gadolinium-enhanced magnetic resonance images show resolution of the previous multifocal nodules after the case patient underwent chemotherapy and whole brain radiation treatment.

overcoming this disease will depend on further clinical trials in which more patients respond to treatment and experience prolonged disease-free survival without incurring significant neurotoxicity.

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