

Multiple Sclerosis Preceding CNS Lymphoma: A Case Report

Jium-Han Yang and Shey-Lin Wu

Abstract- Multiple sclerosis (MS) is an autoimmune disease that targets the myelin of the brain, spinal cord, and optic nerves. The inciting trigger that activates this immune response is unknown. Primary central nervous system (CNS) lymphoma is usually a diffuse large B-cell non-Hodgkin's lymphoma that originates in the brain, spinal cord, leptomeninges, or eyes. We report a 33-year-old patient who was diagnosed to have multiple sclerosis initially and a CNS lymphoma was noted 38 months later. Primary CNS lymphoma is a potential complication of chronic immunosuppression. Due to the uses of steroid, immunosuppressants and beta-interferon for multiple sclerosis, our patient developed an immuno-compromised state. These agents might contribute to the occurrence of a primary CNS lymphoma. On the other hand, a demyelinating disease may have preceded the diagnosis of primary CNS lymphoma. A possibility of neoplastic transformation in CNS inflammatory diseases such as multiple sclerosis may occur. The association of coexistent primary CNS lymphoma and multiple sclerosis may be more than coincidental.

Key Words: Primary CNS lymphoma, PCNSL, Large B-cell non-Hodgkin's lymphoma, Multiple sclerosis, Progressive multifocal leukoencephalopathy

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INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease that targets the myelin of the brain, spinal cord, and optic nerves. This immunological attack results in demyelination and, potentially, axonal injury. The inciting trigger that activates this immune response is unknown. Potential causes may be a combination of genetic abnormalities and environmental exposures to the pathogens, such as viruses. Primary central nervous

system (CNS) lymphoma is usually a diffuse large B-cell non-Hodgkin's lymphoma that originates in the brain, spinal cord, leptomeninges, or eyes. Here we describe a patient whose initial diagnosis was multiple sclerosis, and a CNS lymphoma developed eventually.

CASE REPORT

A 33-years old man presented with blurred vision in the left eye at the age of 30 and the diagnosis was optic

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neuritis on the left eye in July 2002. At that time, his brain MRI showed multiple lesions in the right middle cerebellar peduncle, bilateral cerebral hemispheres. Brain metastasis, granulomatous inflammation (such as tuberculous or cryptococcal infection) or multiple sclerosis were suspected. (Fig. 1) After 3 days of steroid therapy (methylprednisolone 250 mg q6h), the symptoms recovered completely and the patient was discharged on July 11.

In August 2003, he suffered from diplopia, slow response, unsteady gait and depressive mood. Left hemiparesis (muscle power grade 4+ on MRC scale) was noted during neurological examinations. Brain MRI revealed multiple enhanced lesions located in the pons, midbrain, bilateral cerebellar and cerebral hemispheres (Fig. 2). As comparison with previous MRI in July 2002,

the number and size of lesions were increased, especially in the brainstem and cerebellum. However, sizes of lesions apparently decreased in the periventricular area over the right occipital lobe and left lateral ventricle. His brainstem auditory evoked potentials (BAEP) study revealed prolonged wave V latency on the left side. Somatosensory evoked potential (SSEP) study showed prolonged N20 latency on the left side, dampened P27-N33 on the right side via median nerve stimulation; of the left P37 was absent and the right P37 latency was prolonged on stimulation of the posterior tibial nerve. Visual evoked potentials (VEP) study was still within normal limits.

The cerebrospinal fluid (CSF) study on October 29, 2003 revealed no evidence of CNS infection. (WBC count 2, RBC count 0, protein 59.8 mg/dl, glucose 62

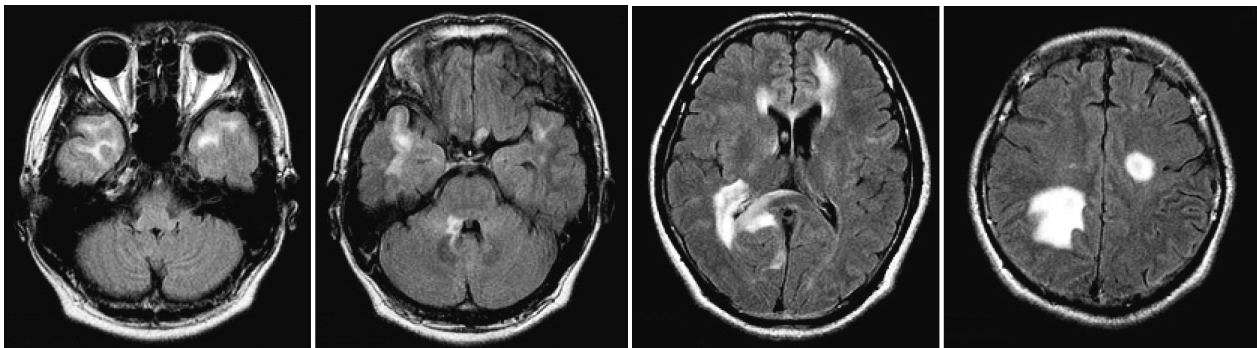


Figure 1. Brain MRI in July 2002
FLAIR series showed multiple lesions in the right cerebellar peduncle and bilateral cerebral hemispheres.

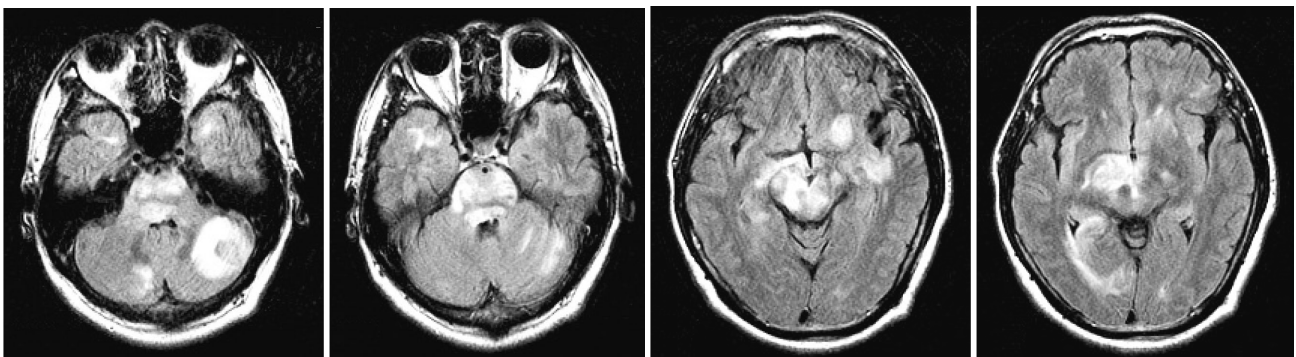


Figure 2. Brain MRI in October 2003
FLAIR series revealed multiple hyperintense lesions distributed in the pons, midbrain, bilateral cerebellar and cerebral hemispheres. As comparison with previous MRI in July 2002, the size and number of lesions were increased, particularly in the brainstem and cerebellum.

mg/dl). The cryptococcus antigen, acid fast stain, and culture for tuberculosis bacilli were negative. The VDRL was non reactive. The CSF IgG index was 0.636. The cytology revealed no malignant cell. The serum study did not show response to HIV antigen and antinuclear antibodies were negative. The patient accepted the pulse therapy (methylprednisolone 500mg q12h) for 5 days and got clinical improvement. According to the McDonald criteria, he fulfilled the diagnosis of relapsing-remitting multiple sclerosis (RRMS).

Interferon beta-1a (Rebif) treatment started in March 2004. From March 26 to July 8, 2005, he experienced several attacks in which presented with generalized seizure, dysphagia, tachypnea, and left hemiplegia. He received multiple pulse therapies after each attack and the symptoms improved after the treatment.

Follow-up brain MRI on March 29, 2005 revealed multiple lesions involving the white matter of bilateral cerebral hemispheres and brainstem with strong enhancement. Magnetic resonance spectroscopy (MRS), a study with single voxel placed in the right corona radiata, showed increased choline, decreased creatine and decreased N-acetylaspartate levels, consistent with inflammation, demyelination and neuronal loss.

The patient has been taking immunosuppressant (azathioprine 50mg bid) since April 2005. Due to frequent attacks under the interferon therapy, the medication was shifted to mycophenolate mofetil 250mg bid on August 6.

On August 8, he was transferred to neurological intensive care unit and intubated with respiratory support due to seizure with respiratory failure. Low grade fever persisted and consciousness level deteriorated. We discontinued mycophenolate mofetil. Due to the poor response with interferon, steroid and immunosuppressants, plasma exchange was performed for 5 times. But the clinical conditions did not improve.

On September 7, 2005, four limbs cyanosis, CO₂ retention and dysconjugate gaze occurred. The CSF study revealed WBC count 1 (lymphocyte), RBC count 20, protein 53 mg/dl, glucose 87 mg/dl, lactate: 5.65 mmole/L. Repeated brain MRI showed multiple lesions involving the white matter of bilateral cerebral hemi-

spheres and brainstem with strong enhancement; especially in right cerebellar hemisphere, bilateral frontal lobes, right corona radiata, right parietal lobe and right temporal lobe. A round, enhanced mass over the right temporal lobe was noted. (Fig. 3)

Due to rapid downhill of clinical conditions and poor responses to the above therapy, brain biopsy was performed on the right temporal lesion. The pathology revealed large B-cell malignant lymphoma. Microscopically, sections showed focal aggregation of large lymphoma cells with vesicular nuclei and prominent nucleoli. Immunohistochemical study reveals these large lymphoma cells were CD20(+) and CD3(-). (Fig. 4)

Bone marrow aspiration for lymphoma staging showed negative for malignancy. Microscopically, sections showed hypercellular marrows with hyperplasia of

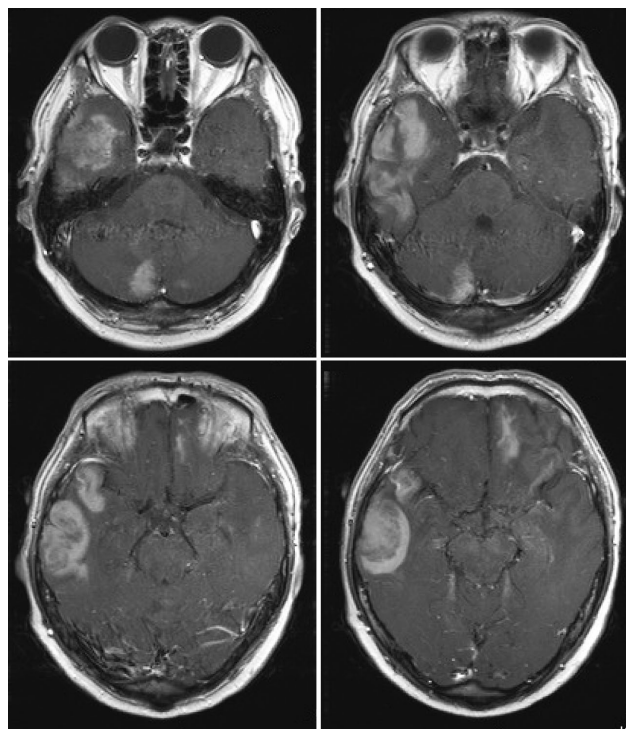


Figure 3. Brain MRI in September 2005

T1 with contrast series revealed multiple lesions involving the white matter of bilateral cerebral hemispheres and brainstem with strong enhancement, in the right cerebellar hemisphere, bilateral frontal lobes, right corona radiata, right parietal lobe and right temporal lobe. A round lesion over the right temporal lobe was noted.

trilinear elements. No atypical aggregation were found. Immunohistochemical study for CD20 demonstrated scanty and dispersed small lymphocytes, likely reactive.

The patient died on December 7, 2005 due to sepsis.

DISCUSSION

The usual interval from the initial presentation to the final diagnosis of primary CNS lymphoma was about 3 months⁽¹⁾. Schaumberg et al.⁽²⁾, Williams et al.⁽³⁾ and Ruff et al.⁽⁴⁾ reported some cases in which relapsing and remitting signs and symptoms resembling multiple sclerosis were followed up to 8 years later by a fulminant terminal course of primary CNS lymphoma. Our patient was diagnosed having multiple sclerosis initially and then developed with primary CNS lymphoma approximately 38 months later.

A possible epidemiological association between multiple sclerosis and lymphoma has been reported⁽⁵⁾. Cases of coincident primary CNS lymphoma and multi-

ple sclerosis have been documented in the literature^(6,7). Hjalgrim et al.⁽⁸⁾ reported familial clustering of multiple sclerosis and Hodgkin lymphoma in Denmark and, that supported Newwell's hypothesis of a shared etiology⁽⁹⁾. Their studies and another report by Vineis et al. indicated a familial association between multiple sclerosis and non-Hodgkin lymphoma⁽¹⁰⁾.

The Epstein-Barr virus has been suspected as a risk factor for multiple sclerosis, non-Hodgkin's lymphoma or Hodgkin's disease. Ascherio and Munch and other authors invoked a late onset of infectious mononucleosis or other infectious diseases that had lead to a strong association with multiple sclerosis⁽¹¹⁾. Epidemiological studies suggested that persons with infected Epstein-Barr virus asymptomatically in childhood, or infection in the adolescence or early adulthood can cause clinical infectious mononucleosis. A subset of these subjects can develop MS⁽¹²⁾.

In addition, Lyme disease and progressive multifocal leukoencephalopathy have been reported in association

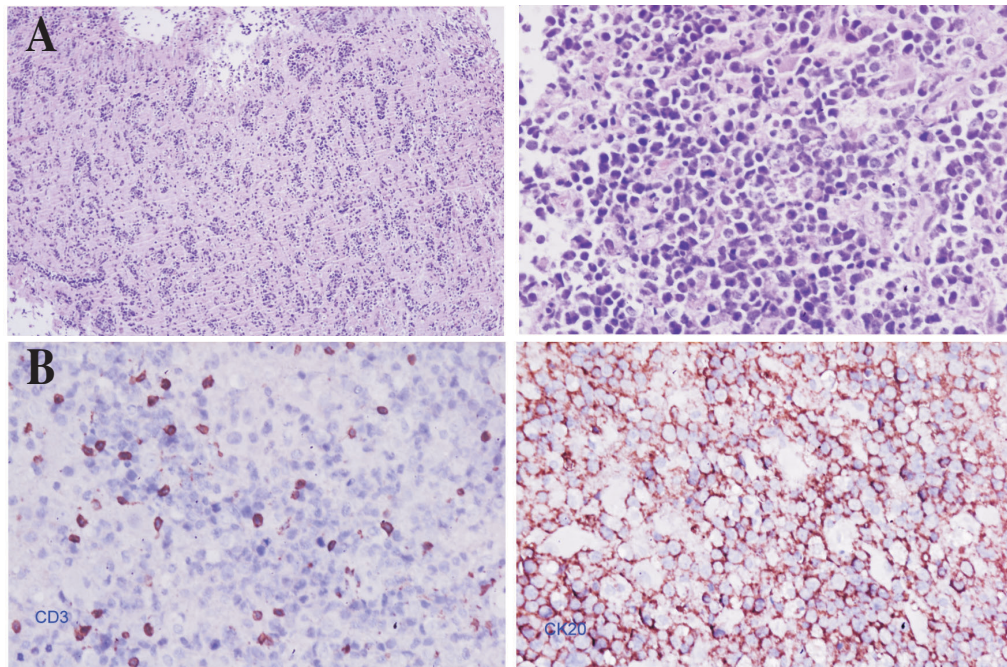


Figure 4. Pathology of brain biopsy(A) H&E stain

The sections showed focal aggregation of large lymphoma cells (left) with vesicular nuclei and prominent nucleoli (right, × 400); (B)Immunohistochemical stain (left: CD3; right: CD20). These large lymphoma cells are highlighted by positive staining for CD20 and negative staining for CD3.

with primary CNS lymphoma⁽¹³⁾.

Markus et al. suggested that the central nervous system produced B-cell activating factor of the tumor necrosis factor family (BAFF) may support B-cell survival both in inflammatory disease (such as multiple sclerosis) and primary B-cell lymphoma⁽¹⁴⁾. Carolyn et al. stated that monoclonal B-cell population mimicking lymphoma may occur in patients with multiple sclerosis⁽¹⁵⁾.

Chronic suppression of cell-mediated immunity may be associated with a substantially increased risk of malignancy. Primary CNS lymphoma is a rare malignant tumor comprising less than 1% of all primary brain tumors⁽¹⁶⁾. It is rare in immunocompetent patients, but as many as 24% of posttransplant lymphomas are primary CNS lymphomas^(17,18). The association of primary CNS lymphoma with chronic immunosuppression in patients with idiopathic autoimmune diseases remains unclear. The dysimmune state may play a role because there have been cases of primary CNS lymphoma complicating autoimmune diseases in immunosuppression-naïve patients. There was a report of an elderly patient who had developed immunosuppression-related primary CNS lymphoma after 3-year treatment of myasthenia gravis with mycophenolate mofetil⁽¹⁹⁾.

Brecher et al. suggested that demyelinating disease may have preceded the diagnosis of primary CNS lymphoma. Possible neoplastic transformation may occur in inflammatory disease such as multiple sclerosis⁽⁷⁾.

This 33-year-old patient may develop immunocompromised state because of his steroid usage, immunosuppressants (azathioprine, mycophenolate mofetil) and interferon beta-1a. We favored that the immunocompromised state in this patient contributed to the occurrence of primary CNS lymphoma.

The above findings suggested that the association of coexistent primary CNS lymphoma and multiple sclerosis may be more than coincidental. We suggest that in patients with multiple sclerosis, if there are unusual clinical progression, poor response to steroid, interferon and immunosuppressants treatment or atypical brain image, further survey for other diagnostic alternatives should be performed.

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