

Intravascular Lymphomatosis Mimicks a Cerebral Demyelinating Disorder

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Abstract- Intravascular lymphomatosis is a rare extra-nodal form of diffuse, large B-cell non-Hodgkin's lymphoma that causes a myriad of neurological symptoms, including focal neurological deficits, cognitive decline, and seizure. Intravascular lymphomatosis is difficult to make ante-mortem diagnosis because of its variable clinical presentation and non-specific laboratory findings. Neuroimaging findings also vary widely in patients of intravascular lymphomatosis. We present, herein, a patient with rapidly deteriorating neurological deficit whose brain MRI revealed rapidly progressing white matter diseases. This patient was diagnosed and treated as having a cerebral demyelinating disorder. Intravascular lymphomatosis involving multiple organs was finally diagnosed after autopsy.

Key Words: Intravascular lymphomatosis, Leukoencephalopathy, Cerebral demyelinating disorders

Acta Neurol Taiwan 2006;15:264-268

INTRODUCTION

Intravascular B-cell lymphoma is a rare extra-nodal form of diffuse, large B-cell non-Hodgkin's lymphoma that occurs within the lumen of small-to-medium-sized vessels. It most commonly affects the vessels of the skin and the central nervous system, resulting in occlusions and subsequent ischemias⁽¹⁻³⁾. The signs and symptoms of the disorder are attributed to vascular occlusion. Some case series reports suggest that 80% of patients have CNS involvement, of which more than 90% develop multifocal cerebrovascular events, dementia, suba-

cute encephalopathy, and myelopathy⁽⁴⁾. Neuropathies, polyradiculopathies and myopathies have also been reported⁽⁵⁾. The malignant population usually originate from B-cell roots, although there have been cases of intravascular T-cell lymphoma reported. Most cases of intravascular lymphomatosis are not diagnosed until postmortem because of variable clinical presentation and non-specific laboratory findings⁽¹⁻²⁾. But many ante-mortem diagnoses of this lymphoma are made incidentally in biopsies conducted for unrelated reasons. The disease is clinically aggressive and usually fatal, even with early detection and treatment⁽⁴⁾. Here, we present a

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Received February 24, 2006. Revised March 27, 2006.
Accepted May 10, 2006.

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case of rapidly progressive neurological deficit within three months. The brain MRI of this case revealed rapidly progressing white matter disease, which mimicked demyelinating disorders such as multiple sclerosis or acute disseminated encephalomyelopathy (ADEM). Intravascular lymphomatosis involving multiple organs was finally diagnosed after autopsy.

PRESENTATION OF CASE

A 49-year-old woman was admitted to the neurology ward on April 7, 2003, due to rapid progression of left limbs weakness that started on March 20, 2003. She was generally in good health. The patient was an international businesswoman who was frequently traveling around the world. She initially noticed clumsiness in her left limbs that rapidly worsened until she was unable to grasp objects firmly. On admission, she walked unsteadily and had dysarthria but no choking. She had no fever, no loss of weight nor night sweating. In fact, she had neither ocular blindness nor sphincter incontinence before this event. She had no relevant family history such as stroke, migraine, CADASIL or leukodystrophy. And neither were there prior antineoplastic drugs, heavy metals or chemical exposure history. There were no prior URI symptoms before this admission. She had experienced a transient skin rash a few weeks before admission. Upon admission, her temperature was 36.8 °C, pulse rate 86/min, respiration rate 20/min and blood pressure 120/80 mmHg. On examination the patient was alert and fully oriented. Her physical examination was largely normal; there was no skin lesion or rash, the liver and spleen spans were within normal limits. Her speech was fluent without paraphasic errors, but mild dysarthria was noted. Her neck was supple, eye movement was full, pupillary diameter was symmetric and showed symmetric light reflex, the visual fields were normal by confrontation test. A left side central type facial palsy was noted. Other cranial nerves were unremarkable. Her muscle tone was normal. Muscle power was grade 4+ on right side and 4 on left side. The plantar responses were up going bilaterally. The deep tendon reflexes were hyperreflexic on both sides. No patellar or ankle clonus

was elicited. There was no significant objective sensory disturbance including pinprick and light touch testing. There was no dysmetria, dyssynergia or truncal ataxia. The laboratory data including hematogram (WBC $8.5 \times 10^3/\mu\text{L}$, segment 62.5%, lymphocyte 23.3%, Hb 11.9g/dl, platelet $216 \times 10^3/\mu\text{L}$), inflammatory profiles, biochemistry and urinalysis were unremarkable except for a high LDH level (738 IU/L). The brain MRI with contrast study conducted on April 17, 2003 revealed diffuse subcortical plaque-like lesions especially in the periventricular area (Fig. 1A). The white matter lesions were hyperintense on diffusion-weighted, T2-weighted and T2-FLAIR images. T1-weighted image revealed hypointense signal without enhancement. In addition, no meningeal enhancement was noted. We arranged toxicology screening, COHb level, autoimmune test, thyroid function test, Vitamin B12, folic acid, serologic test for syphilis, HIV and *Borrelia burgdorferi* to check for acquired leukoencephalopathy. All the results were unremarkable. Cerebrospinal fluid (CSF) was studied for IgG

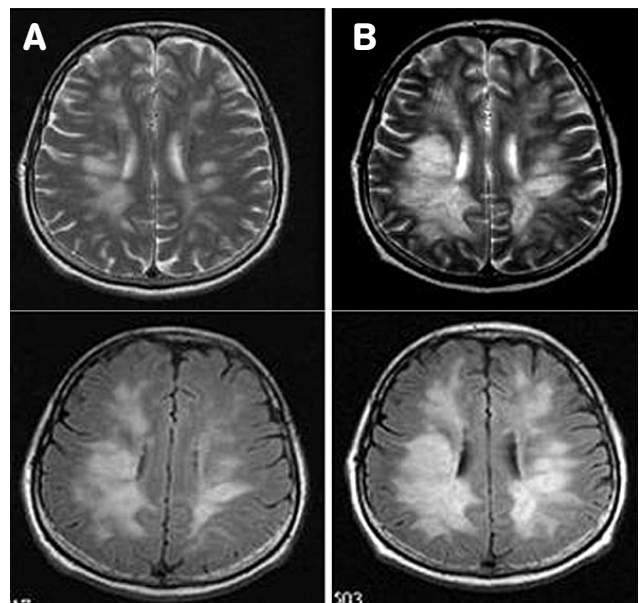


Figure 1. A(Left). Brain MRI in April, 2003 showed diffuse hyperintense plaque-like lesion in the subcortical white matter on T2-weighted (upper panel) and T2-FLAIR image (lower panel). B(Right). Brain MRI in May 2003 revealed extended bilateral subcortical white matter changes on T2-weighted (upper panel) and T2-FLAIR images (lower panel).

index, oligoclonal IgG bands, viral titers, cytology and polymerase chain reaction (PCR) for JC virus but none revealed abnormalities. The BAEP study was normal. But VEP study showed delayed P100 responses following stimulation of both eyes separately. There was also prolonged latency of the thalamocortical component (N20 and P37) in the SSEP study. Resting ECG showed sinus rhythm and cardiac sonography revealed neither valvular abnormality nor thrombus formation. A Gallium-67 scan was unremarkable. Abdomen and pelvis CT studies revealed no lymph node, nor liver or spleen enlargement. After hospitalization, the patient's neurological deficit rapidly deteriorated over two weeks. We initially prescribed methylprednisolone (500mg, q12h for 5 consecutive days) therapy and IVIG under the impression of multiple sclerosis or ADEM. The patient entered a stupor and took on a decorticate posture after one month. We arranged for a second brain image study on May 3, 2003 due to rapid neurological deterioration; this second brain image showed further extended bilateral subcortical white matter lesions (Fig. 1B). The patient was admitted to the intensive care unit on May 9, 2003 due to respiratory failure and septic shock. She patient died on June 21, 2003 due to septic shock and multi-organ failure.

Histopathologic findings after autopsy: (Fig. 2)

Postmortem pathology showed multiple acute and subacute infarcts involving the white matter of the brain,

cerebellum, brainstem and spinal cord. The small and middle-sized cerebral and leptomeningeal blood vessels were plugged by numerous neoplastic mononuclear cells. These cells were noncohesive and free in the lumina. The neoplastic cells had a high nucleus to cytoplasm ratio; the nuclei were large with moderate chromatin density and these cells contained one or more distinct nuclei. The malignant cells did not extend into the adjacent brain parenchyma (Figs. 2A-B). Vessel involvement was best seen in the area adjacent to the area of infarct and necrosis. Similar pathological pictures were also found in the other organs including lungs, myocardium, kidneys (Fig. 2C), adrenal glands, uterus and skin. Immunohistochemical staining of the tumor cells were positive for the B-cell antigen CD20 (Figs. 2B-C).

DISCUSSION

Intravascular lymphoma is an uncommon malignancy. It is shown pathologically by neoplastic proliferation of lymphoid cells within the lumens of capillaries, small veins, and arteries, with little or no adjacent parenchymal involvement. The neoplastic lymphomatous cell proliferates within small vessels, leading to occlusions and hemorrhage. In intravascular lymphomatosis, almost all patients have neurologic manifestations. But there was no abnormality in bone marrow biopsy. Chest and abdominal tomographic examinations did not show adenopathy. And CSF analysis was also normal^(2-4,6).

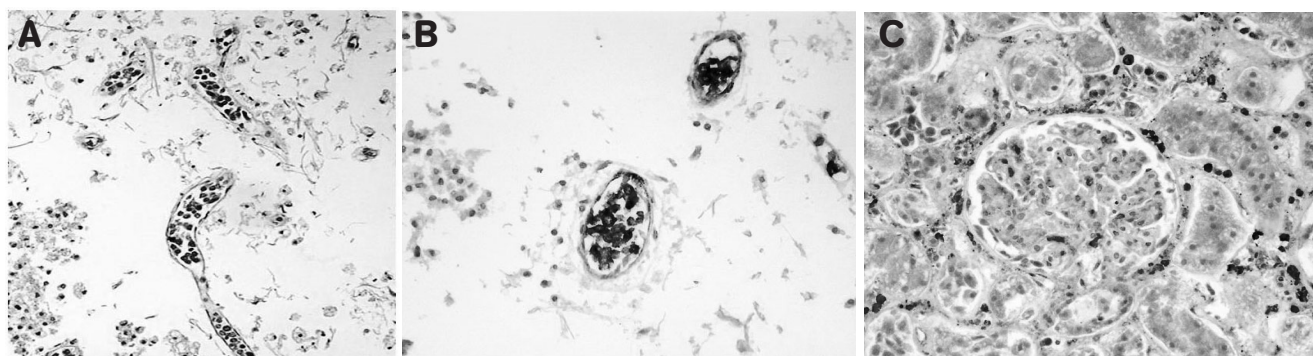


Figure 2. A. Histopathologic findings within necrotic brain parenchyma showed large atypical mononuclear cells occluding the small vessels. (H&E, $\times 100$). B. Immunohistochemical staining of the tumor cells were positive for the B-cell-associated antigen CD20 (H&E and AEC stain, $\times 200$). C. The immunohistochemical staining of the intravascular lymphoma cells were also positive for the CD 20 antigen in kidney tissue. (H&E and AEC stain, $\times 200$)

In our patient, the neurological deficit progressed rapidly and the brain image showed diffuse white matter change mimicking demyelinating disorders such as multiple sclerosis, progressive multifocal leukoencephalopathy or ADEM. There were no identified causes for acquired leukoencephalopathy even with extended workup studies in the ante-mortem period. Besides, acquired leukoencephalopathy differential diagnoses include vascular, toxic, metabolic, autoimmune, inflammation, hereditary, tumor and infectious causes⁽⁷⁻⁸⁾.

Infectious diseases that may be manifested as a leukoencephalopathy, such as Lyme neuroborreliosis, neurosyphilis, HIV and tuberculosis were also excluded by serology test. Progressive multifocal leukoencephalopathy (PML) was considered as the differential diagnosis due to rapidly progressive multifocal white matter lesions, but PML was not favored for our patient due to normal immune status and negative cerebrospinal fluid PCR assay for JC virus. During the past decade, detection of JC virus DNA in the CSF by the PCR assay was found to have a high sensitivity and specificity rate for the diagnosis of progressive multifocal leukoencephalopathy in either HIV-positive and or negative subjects⁽⁹⁻¹⁰⁾.

Acute disseminated encephalo-myelitis is difficult to differentiate from a first attack of multiple sclerosis especially in primary progressive multiple sclerosis⁽¹¹⁾. The non-contrast enhancement lesions and absence of inflammatory component in CSF study did not support the diagnosis of an acute inflammatory event. We treated this patient as multiple sclerosis or ADEM because of the rapidly progressive course and diffuse predominantly white matter involvement.

Laboratory studies in intravascular lymphomatosis usually reveal an elevated ESR, and CSF studies are typically not diagnostic. Some studies have reported that the most common laboratory abnormality, though neither specific nor highly sensitive, is the elevation of the LDH level, which is abnormal in up to 85% of patients^(1-6,12). Our patient also had significant and persistent elevated LDH level in her clinical course which may be correlated with cell and organ damage. However, the elevated LDH level is not diagnostic or specific for intravascular

lymphomatosis.

Neuroimaging findings vary widely in patients with intravascular lymphomatosis and range from diffuse involvement of the deep white matter to infarct-like lesions. Cerebral magnetic resonance imaging (MRI) may show parenchymal and meningeal gadolinium enhancement⁽¹³⁾. The MR appearance of intravascular lymphomatosis may also manifest as enhancing mass lesions, possibly predicting the extraluminal spread of disease⁽¹⁴⁾. In our patient, the brain MRI showed diffuse patchy hyperintense white matter lesions on diffusion-weighted, T2-weighted and T2-FLAIR images but no contrast enhancement or meningeal enhancement (Figs. 1A-B). The microinfarcts of the parenchyma or sluggish flow within the lumens of capillaries, small veins, and arteries may be responsible for their predilection to involve the periventricular white matter that was not attributed to any vascular territory. Intravascular lymphomatosis should be taken into account in the differential diagnosis of repeated cerebral ischaemia of unusual etiology or acquired leukoencephalopathy⁽¹⁵⁾.

To diagnose intravascular lymphomatosis is challenging because the signs and symptoms are nonspecific and there is no diagnostic test other than a pathological examination. This lack of reliable ancillary tests delays the diagnosis and limits the efficacy of potentially curative chemotherapy. For this reason, an examination should include a biopsy of the affected viscera, especially skin and brain. Brain and meningeal biopsy for those cases in which there is no other more accessible source of affected tissues must be considered in the suspected cases⁽⁴⁾. Non-specific cutaneous features of intravascular lymphomatosis are easily overlooked. However, the involvement of intravascular lymphomatosis in clinically unaffected skin has been described through autopsy findings by other case reports. A random skin biopsy is a quick and minimally invasive procedure that may be highly informative in a patient with suspected intravascular lymphomatosis⁽¹⁶⁻¹⁷⁾. The skin involvement was also noted in our patient after autopsy even there was no characteristic skin manifestations.

The characteristic microscopic findings are distention and occlusion of small cerebral and meningeal

blood vessels by neoplastic mononuclear cells. The neoplastic cells within the vascular lumina are frequently associated with thrombosis, resulting in ischemic infarcts of neural tissue. The reasons for the intravascular localization of the neoplastic cells and their predilection to involve the CNS are not completely understood. An alteration in the normal interaction of endothelial cells and lymphocyte homing surface receptors on the neoplastic cells may be responsible for the intravascular location of the tumor⁽¹⁸⁾.

In conclusion, based on published literature of cases of definitively diagnosed intravascular lymphomatosis, two-thirds of patients had neurologic manifestations, without abnormalities on bone marrow biopsy, chest and abdominal adenopathy on tomographic examinations and CSF analysis^(2-4,6). All intravascular lymphomatosis patients had one or more neurological manifestations: progressive multifocal cerebrovascular events; a subacute encephalopathy; and peripheral or cranial neuropathies. The unexplained presence of any one or more of these neurologic syndromes should alert the physician to the possible presence of this disease⁽¹⁹⁾.

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