

[ CASE REPORT ]

## Demyelinating Neuropathy Due to Intravascular Large B-cell Lymphoma

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### Abstract:

We herein report the case of a 67-year-old man who presented with the acute onset of limb weakness. Brain magnetic resonance imaging revealed multiple abnormal-signal-intensity lesions. Steroids were administered, and the patient initially responded. Nerve conduction testing findings were consistent with demyelinating polyneuropathy. A sural nerve biopsy specimen revealed fascicles with extensive onion-bulb formation. Although skin and sural nerve biopsies showed no atypical cellular infiltration, the histopathological diagnosis of intravascular large B-cell lymphoma was obtained by a brain biopsy. The neuropathy in this patient may be attributed to a demyelinating process independent of ischemic damage by lymphoma.

**Key words:** demyelinating neuropathy, intravascular large B-cell lymphoma, sural nerve biopsy, onion-bulb formation

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### Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a subtype of large B-cell lymphoma characterized by selective growth of lymphoma cells within the lumen of small blood vessels. Vascular occlusion may occur and subsequently result in ischemic, hemorrhagic, or necrotic lesions in the organs involved (1). IVLBCL is difficult to diagnose, particularly when neurologic symptoms are the only manifestation. The central nervous system is commonly involved, but the involvement of the peripheral nervous system is rare (2). Neurolymphomatosis, demyelinating neuropathy, and vasculitic neuropathy caused by direct neural invasion or paraneoplastic syndrome may occur in patients with lymphoma (3, 4).

We herein report a rare case of a patient with IVLBCL who harbored peripheral neuropathy with onion-bulb formations observed on a sural nerve biopsy.

### Case Report

A 67-year-old man was admitted to the hospital for the acute onset of bilateral lower limb numbness and weakness that persisted for 10 days. His medical history was unremarkable.

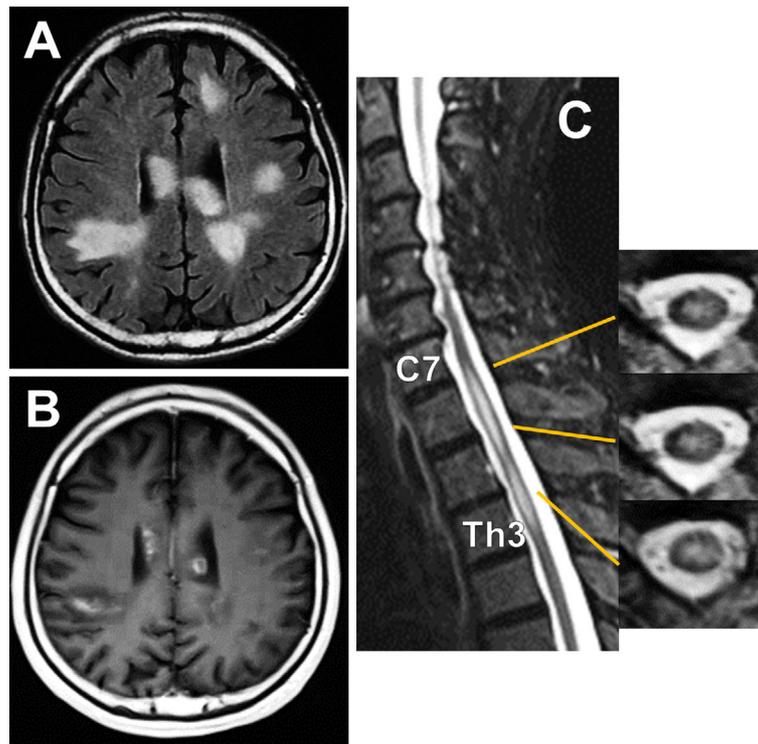
A physical examination did not show skin lesions or lymphadenopathy. A neurological examination revealed mild dysarthria, lower limb weakness predominantly in the left leg, thermal hypoalgesia in the right leg, and a severely impaired vibration sensation in the lower limbs. He had cognitive deficits in memory and calculation, with a Mini-Mental State Examination score of 21/30. The cranial nerve functions were normal, deep tendon reflexes were brisk in the lower extremities, and the plantar reflex was extensor bilaterally.

Magnetic resonance imaging (MRI) revealed multiple hyperintense white matter lesions in the brain on T2 fluid-attenuated inversion recovery sequences (Fig. 1A, B) and a spinal cord lesion that involved more than three vertebral

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**Figure 1.** Magnetic resonance imaging (MRI) findings on admission. (A) Axial fluid-attenuated inversion recovery sequence MRI of the brain showing multiple hyperintense white matter lesions. (B) Axial T1-weighted post-contrast sequence showing multiple enhancing lesions. (C) Sagittal cervical and thoracic spine T2-weighted MRI showing a high signal extending from C7 to Th3.

levels (Fig. 1C). Nerve roots were not enlarged on spinal MRI. Levels of serum-soluble interleukin-2 receptor (1,790 U/mL, normal range <591 U/mL), lactate dehydrogenase (308 U/L, 119-229 U/L), and C reactive protein (1.16 mg/dL, <0.3 mg/dL) were elevated, but other routine laboratory investigation showed no marked abnormalities. Tests for serum angiotensin-converting enzyme, anti-neutrophil cytoplasmic, anti-SS-A/B, anti-double stranded DNA, anti-aquaporin 4, anti-nuclear, anti-ganglioside, and anti-neurofascin 155 antibodies were all negative. A cerebrospinal fluid analysis showed an increased protein level (84 mg/dL) with a normal glucose level and cell count; no malignant cells were observed on a cytological examination, and the results of a microbiological analysis were negative. Whole-body computed tomography revealed no marked abnormalities. The patient was treated with intravenous methylprednisolone 1 g/day for 3 days, followed by oral prednisolone, as he was suspected of having autoimmune encephalomyelitis. Initial clinical improvement was observed following treatment, and the patient was transferred to the recovery phase rehabilitation ward.

However, he manifested progressive worsening of bilateral lower limb weakness following the transfer and subsequently was readmitted three weeks later. During his stay in the rehabilitation ward, his deep tendon reflexes disappeared. Therefore, we performed a nerve conduction study on day 74 after the first hospitalization, which showed prolonged distal motor latencies in the median and ulnar nerves

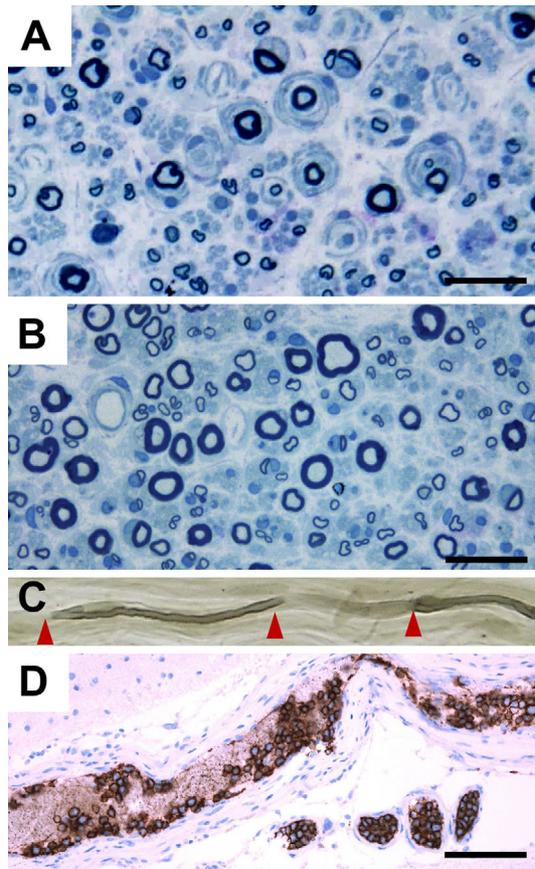
as well as decreased motor and sensory nerve conduction velocities in the median, ulnar, and tibial nerves, which was consistent with demyelinating sensorimotor polyneuropathy (Table) (5). Sensory nerve action potentials in bilateral sural nerves were not elicited. A sural nerve biopsy specimen revealed onion bulbs in some fascicles (Fig. 2A). The extent of onion-bulb formation differed among individual fascicles, ranging from fascicles with abundant onion bulbs to those with almost normal findings (Fig. 2B). Atypical cellular infiltration was not observed (Fig. 2A, B). Segmental demyelination was observed in the teased-fiber study (Fig. 2C). After readmission, the patient's consciousness level and lower limb weakness gradually worsened. He was treated with intravenous immunoglobulin (IVIg, 400 mg/kg/day for 5 days), which did not result in any improvement. The retested serum-soluble interleukin-2 receptor level was markedly elevated (8,350 U/mL). Random skin and bone marrow biopsies revealed no evidence of lymphomatous cells. A brain biopsy revealed several round CD20-positive tumor cells within the lumen of small blood vessels, leading to the diagnosis of IVLBCL (Fig. 2D). Despite intravenous cyclophosphamide pulse therapy to treat lymphoma, the patient continued to deteriorate and ultimately died of pneumonia on day 141 after the first hospitalization. No autopsy was performed.

**Table.** Nerve Conduction Study.

	DML (ms)	CMAP (mV)	MCV (m/s)	SNAP ( $\mu$ V)	SCV (m/s)	F latency (ms)	FWCV (m/s)
Median nerve (R/L)	4.2/5.4	9.3/6.8	42.6/23.5	9.6/7.2	40.0/37.0	N.E./N.E.	
(Control)	3.4 $\pm$ 0.4	10.7 $\pm$ 3.5	57.8 $\pm$ 3.7	23.5 $\pm$ 8.4	57.8 $\pm$ 4.7		
Ulnar nerve (R/L)	3.6/3.8	7.5/6.7	33.3/38.0	12.3/4.2	33.6/32.5		
(Control)	2.7 $\pm$ 0.3	8.4 $\pm$ 2.5	58.6 $\pm$ 4.3	23.8 $\pm$ 10.3	54.5 $\pm$ 5.5		
Tibial nerve (R/L)	4.9/N.E.	3.0/N.E.	32.6/N.E.			72.8/N.D.	28.5/N.D.
(Control)	4.5 $\pm$ 0.8	10.9 $\pm$ 3.8	46.9 $\pm$ 3.5				
Sural nerve (R/L)				N.E./N.E.			

\*Control values were based on previously published reports (5).

CMAP: compound muscle action potential, DML: distal motor latency, FWCV: F-wave conduction velocity, MCV: motor nerve conduction velocity, N.D.: not done, N.E.: not evoked, SCV: sensory nerve conduction velocity, SNAP: sensory nerve action potential



**Figure 2.** Pathological findings of the sural nerve biopsy (A to C) and brain biopsy (D). (A) A transverse section stained with toluidine blue revealed onion-bulb formation in some of the fascicles. (B) Fascicles with no onion bulbs were also found on the same section of (A). (C) Segmental demyelination was observed in the teased-fiber study (as indicated by arrowheads). (D) Round CD20-positive tumor cells filled the small blood vessel lumens in the brain (immunohistochemical staining for CD20). Scale bar indicates 50  $\mu$ m in (A) and (B) and 100  $\mu$ m in (D).

## Discussion

IVLBCL is a rare form of extranodal non-Hodgkin's lymphoma characterized by the occlusion of small blood vessels

by lymphoma cells. Glass et al. previously reported that 63% of patients with intravascular lymphoma had neurologic manifestations, and disorders in the peripheral nervous system were found in 5% of those cases (6). In the current case, the neurological symptoms progressed acutely and responded initially to steroid therapy. Therefore, the possibility of immune-mediated demyelinating diseases, such as combined central and peripheral demyelination, was considered prior to the diagnosis of IVLBCL.

Although a histopathological diagnosis was not obtained using skin, peripheral nerve, or bone marrow biopsies, a brain biopsy revealed CD20-positive B cells in the lumen of small blood vessels, which is consistent with the diagnosis of IVLBCL. However, in the sural nerve biopsy specimen, onion-bulb formation was observed despite the absence of lymphoma cell infiltration. Onion bulbs are commonly found in demyelinating neuropathies, such as chronic inflammatory demyelinating polyneuropathy (CIDP) and Charcot-Marie-Tooth disease (7, 8). Charcot-Marie-Tooth disease is an inherited disorder characterized by diffuse abnormalities in sural nerve biopsy specimens (7), whereas CIDP is an acquired neuropathy, in which regional differences are occasionally observed (8, 9). As the extent of onion-bulb formation differed among individual fascicles in this patient, we suspected that the demyelinating process was acquired. The known mechanisms underlying peripheral neuropathy associated with lymphoma are as follows: 1) direct neural invasion, 2) ischemic or vasculitic, and 3) paraneoplastic or autoimmune (3). Acute sensorimotor neuropathy, such as Guillain-Barré syndrome, may occur as a paraneoplastic syndrome usually in association with lymphoma (10). Peripheral neuropathy due to IVLBCL is usually believed to be multiple mononeuropathies with axonal degeneration due to ischemia, resulting from intravascular occlusion of small blood vessels by lymphoma cells (11). However, the sural nerve biopsy findings in our case indicated the presence of a demyelinating process that was unrelated to ischemic damage (8). As onion-bulb formation suggests the presence of a long-standing demyelinating process, mechanisms that lead to demyelination may have been subclinically present before the onset of neurological symptoms in our patient. Putative mechanisms leading to demyelina-

tion in patients with lymphoma include direct invasion of lymphoma and paraneoplastic immune processes (3), although the former was not found at the time of the nerve biopsy. Therefore, this case report expands the spectrum of neuropathy associated with IVLBCL.

Further studies will be required to clarify the mechanisms underlying the involvement of the peripheral nervous system in patients with IVLBCL.

**The authors state that they have no Conflict of Interest (COI).**

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