

Guillain-Barre Syndrome Associated with Non-Hodgkin's Lymphoma

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A 67-year-old man developed swelling of the right leg with inguinal and abdominal pain over a period of 5 days. Excisional biopsy of the left supraclavicular lymph nodes revealed the diffuse, large B cell type of malignant lymphoma. After chemotherapy, he complained of a tingling sensation and weakness in the left upper extremity, and then this progressed to quadriplegia. Electrodiagnostic testing demonstrated the characteristic findings of demyelination, which was consistent with Guillain-Barre syndrome (GBS). Non-Hodgkin's Lymphoma (NHL) leading to GBS, as was observed in the present case, suggests that physicians should be aware of GBS and non-Hodgkin's lymphoma as the full spectrum of these diseases has not been fully defined. (*Korean J Hematol* 2008;43:263-267.)

Key Words: Guillain-Barre syndrome, Non-Hodgkin's lymphoma, Chemotherapy, Quadriplegia

INTRODUCTION

The neurologic complications of lymphoma have been reviewed by a number of authors. It has been estimated that the nervous system is involved in about 10~25% of cases.¹⁾ Its neurologic complications include: local depositions in brain, spinal cord, and cranial and peripheral nerves; disorders of obscure origin, such as, encephalomyelitis, cerebellar degeneration, peripheral neuropathy, and polymyositis; progressive multifocal leukoencephalopathy; and opportunistic infections, such as, herpes zoster and cryptococcosis.²⁾

Guillain-Barre syndrome (GBS) is an inflammatory demyelinating symmetrical sensorimotor polyneuropathy that involves peripheral and cranial nerves and roots. GBS is viewed as a reactive, self-limited, autoimmune disease triggered by a preceding bacterial or viral infection. Immune reactions in GBS against target epitopes in Schwann-cell surface membrane or myelin result in acute inflammatory demyelinating neuropathy (85% of cases). Moreover, reactions against epitopes contained in axonal membranes cause the acute axonal forms of GBS (15% of cases).³⁾

The effects of lymphoma on the peripheral nervous system have been reviewed in some

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article.^{4,5)} At least 10 reports have been issued on GBS in association with Hodgkin's disease, but its association with non-Hodgkin's lymphoma (NHL) is relatively rare. This study stresses the possibility of the occurrence of GBS in a patient with NHL, and suggests that the spectra of these disease entities have not been fully defined.

CASE REPORT

In October 2002, a 67-year-old man developed right leg swelling with inguinal and mild abdominal pain 5 days prior to his presentation at our clinic. A physical examination revealed mild abdominal tenderness and non-tender movable lymph nodes in the left supraclavicular area. There was no evidence of other neurological abnormalities. The only significant medical history was that of a ureter stone, which had been removed 2 weeks before this presentation.

Ultrasonography showed lymphadenopathy of paraaortic and both iliac vessels, and in lumbar areas. Abdominal and chest computerized tomographic (CT) scans showed enlarged multiple lymph nodes on the celiac axis, around the superior mesentery artery, both lower tracheal regions, and in paraaortic, subcarinal and both hilar areas, and revealed splenomegaly and hydronephrosis.

Results of hematological laboratory tests were; white cell count 5,870/ μ L, hemoglobin 12.1g/dL, platelets 201,000/ μ L, atypical lymphocytes 11% (reference 0%), beta 2 microglobulin 7.12 (reference range 1.0~3.0), LDH 650U/L (reference range 101~208), calcium 8.8mg/dL, uric acid 9.9 mg/dL (reference range 2.4~7.0mg/dL), BUN/Cr 18/1.7mg/dL, AST/ALT 42/12U/L. Serum electrophoresis results were compatible with acute inflammation, i.e., increased α 1 and α 2 globulin and normal δ globulin. Bone marrow (BM) aspiration and biopsy indicated malignant B-cell lymphoma, suggesting BM metastasis. Excisional biopsy of the left supraclavicular lymph nodes confirmed malignant lymphoma, of the diffuse, large

B cell type. B cell associated antigens (CD20, CD79a, bcl-2, bcl-6, MIB) were positive.

On day 12 after admission, chemotherapy with cyclophosphamide (1,350mg, day1), adriamycin (40mg, day1), vincristine (2mg, day1) and solondo (100mg, days 1~5) was started. On day 38 post-admission, chemotherapy was repeated.

On day 44 post-admission (6 days after repeat chemotherapy), the patient complained of tingling sensation in the left hand, which later extended to the left foot. On day 64 (26 days after repeat chemotherapy), weakness appeared in his left upper extremity without any definite sensory abnormality.

Nerve conduction studies (NCS), i.e., needle electrode examination (NEE), and somatosensory evoked potential (SEP), were performed. Skin temperature was maintained at 34°C. No motor responses were obtained. Sensory studies of the left median, ulnar and superficial radial nerves revealed low response amplitudes, except for the left lateral antebrachial cutaneous nerve, which had a normal latency and amplitude. Motor and sensory conduction studies in the left upper limb are shown in Table 1. SEPs of both median nerves were normal. On NEE, no evidence of denervation was obtained for all muscles investigated in the left upper extremity. This electrodiagnostic testing was regarded as an incomplete

Table 1. Results of nerve conduction studies

Motor nerve	Amplitude (mV) Right/Left	DML (msec) Right/Left	NCV (m/s) Right/Left
Median	NA/NR	NA/NR	NA/NR
Ulnar	NA/NR	NA/NR	NA/NR
Sensory nerve	Amplitude (μ V) Right/Left	Latency (msec) Right/Left	NA/NR
Median	NA/5.2	NA/3.85	
Ulnar	NA/2.8	NA/3.65	
Superficial radial	NA/4.3	NA/2.15	
LAC	NA/21.0	NA/2.20	

NCS, nerve conduction study; DML, distal motor latency; NCV, nerve conduction velocity; NR, no response; NA, not assessed; LAC, lateral antebrachial cutaneous.

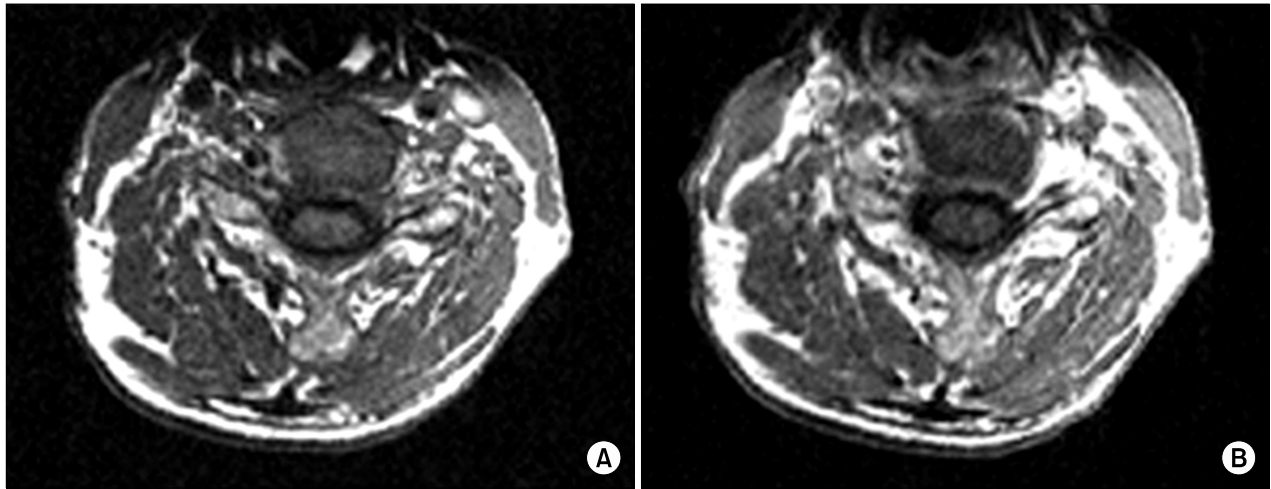


Fig. 1. Magnetic resonance imaging findings demonstrating a swelling and enhancement in the 6th and 7th cervical nerve roots. (A) T1 weighted axial imaging. (B) Gadolinium enhanced T1 weighted axial imaging.

Table 2. Follow-up nerve conduction studies

Motor nerve	Amplitude (mV)	DML (msec)	NCV (m/s)
	Right/Left	Right/Left	Right/Left
Median	NR/0.2	NR/3.85	NA/NA
Ulnar	NR/NR	NR/NR	NA/NA
Common peroneal	NA/0.2	NA/3.3	NA/35.3
Tibial	1.0/0.6	6.40/6.30	31.1/36.5
Sensory nerve	Amplitude (μ V)	Latency (msec)	
	Right/Left	Right/Left	
Median	0.9/1.2	3.5/3.55	
Ulnar	1.2/NR	3.6/NR	
Superficial radial	NR/8.5	NR/1.95	
Superficial peroneal	NR/NR	NR/NR	
Sural	NR/NR	NR/NR	

evaluation due to the patient's clinical status, i.e., prominent left hand swelling.

On day 65 post-admission (27 days after repeat chemotherapy), brain MRI (magnetic resonance imaging) revealed no brain involvement. However, cervical MRI revealed swelling and enhancement at the 6th and 7th cervical spinal nerve roots (Fig. 1). Accordingly, a compression lesion at the cervical root was regarded as the reason for the initial tingling sensation and weakness in his left upper extremity.

On day 72 (34 days after repeat chemotherapy), he complained of weaknesses of the lower extremities, facial palsy, and respiratory difficulties, and electrodiagnostic testing was re-performed. Compound motor action potentials (CMAPs) of the right median and both ulnar nerves were not detectable while the CMAPs of both tibial, left common peroneal and left median nerves showed reduced amplitudes, conduction block, and low conduction velocities. Sensory nerve action potentials (SNAPs) of the right superficial radial, both superficial peroneal and sural nerves were not measurable, while the SNAPs of both median, right ulnar, and left superficial peroneal nerves showed reduced amplitudes and prolonged latencies. Motor and sensory conduction studies in both upper and lower limbs are shown in Table 2. NEE showed denervation potentials in the left flexor carpi radialis and tibialis anterior muscles. Based on his clinical course and neurologic test findings, a diagnosis of GBS was made.

Although treatment with high-dose steroids was started immediately after the diagnosis was made, he experienced respiratory difficulties and finally required intubation and assisted ventilation.

DISCUSSION

Patients with lymphoma frequently develop neurologic abnormalities. The differential diagnosis of peripheral neuropathies depends on the clinical setting, but mainly includes nervous system infiltration with lymphoma and drug toxicity, both of which have been well described.⁶⁾ Central nervous system infiltration can usually be diagnosed easily using imaging techniques, and in certain circumstances, by subsequent stereotactic biopsy. The occurrence of lymphoma causing peripheral nerve infiltration has been described, but is uncommon and difficult to diagnose.⁵⁾ Peripheral nerve involvement in lymphoma can present with several different syndromes. Patients may present with plexopathy or individual cranial or peripheral nerve deficits, or with generalized sensory, sensorimotor or motor neuropathies.²⁾

As discussed above, many factors have been implicated as precipitating causes of GBS, but although a number of causes are possible, it is assumed that immune response in the central and peripheral nervous systems is responsible. It seems likely that malignant tumors act as sources of the antigenic factors that are responsible for initiating an immune response in the nervous system, which may then manifest as GBS.⁷⁾

Drug toxicity is the other major cause of neurological abnormalities. High-dose cytarabine may cause cerebellar dysfunction,⁸⁾ vinca alkaloids typically induce sensorimotor polyneuropathy.⁵⁾ Furthermore, intrathecal chemotherapy with methotrexate and cytarabine may be responsible for myelopathy.⁹⁾

Chemotherapy, especially with vinca alkaloids, is probably the commonest cause of peripheral neuropathy in patients with lymphoma. Moreover, all currently proven combinations of chemotherapeutic regimens used for advanced lymphoma treatment use at least one of the vinca alkaloids, which makes it difficult to detect whether

other drugs are also neurotoxic. Evidence incriminating vinca alkaloids as a cause of peripheral neuropathy relates mostly to vincristine, but vindesine and vinblastine almost certainly possess similar neurotoxicities.⁵⁾

Pal PK studied clinical and electrophysiological characteristics in vincristine induced neuropathy.¹⁰⁾ Conduction studies showed prolonged mean distal latencies, decreased mean amplitudes of compound muscle action potentials, with almost unchanged conduction velocities. They concluded that vincristine produces a distal symmetrical sensorimotor neuropathy, predominantly involving large diameter fibers during the early stages. Furthermore, electrophysiological studies characterized this neuropathy as a distal axonopathy.

In the described case, the compression lesion at the 6th and 7th cervical root was regarded as the reason for the initial tingling sensation and weakness in his left upper extremity. Rapid progression of proximal symmetrical motor weakness over a 27~29 day period after repeat chemotherapy, together with areflexia, lead to a suspicion of GBS. He also displayed most of the diagnostic features of GBS, including progression of symptoms over days to four weeks, mild sensory symptoms or signs, weakness of facial muscles, and swallowing difficulty.

Electrodiagnostic testing was used to differentiate GBS and toxic polyneuropathy because our patient had finished repeat chemotherapy containing vincristine within the preceding 6 days. This was in-line with the characteristic findings of demyelination, which is consistent with GBS.

In summary, we describe a rare association between NHL and GBS in an elderly man administered chemotherapy containing vincristine. Toxic polyneuropathy was excluded based on clinical features and electrodiagnostic testing. We conclude that although the occurrence of GBS in a patient with NHL is rare, it should be considered in the differential diagnosis of neurologic

symptoms in chemotherapy-treated lymphoma patients.

요 약

미만성 거대 B세포 림프종에서 부종양 증후군으로 길리안 바레 증후군이 발생하는 경우는 드물며 기전도 확실하지 않다. 저자들은 미만성 거대 B세포 림프종이 있는 환자에서 항암치료를 하던 중 부종양 증후군으로 길리안 바레 증후군을 전기진단 검사로 진단하였고 그 예를 경험하였기에 보고하는 바이다.

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