울혈반모양 혈관병증 환자에서 발생한 다발성 단신경병증: 증례 보고

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Multiple Mononeuropathy Associated with Livedoid Vasculopathy: A Case Report and Review

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This report describes a rare case of livedoid vasculopathy (LV) with sensory and motor neurologic deficits. A 46-year-old woman who had been diagnosed with LV developed acute left-foot drop. An electrodiagnostic study showed multiple mononeuropathy involving both the common peroneal and sural nerves, primarily on the left side. Nerve biopsy findings showed intravascular thrombosis in the perineurium and extensive infarct of the peripheral nerve. The patient was prescribed continuous anticoagulants, which resulted in a good clinical outcome. LV associated with multiple mononeuropathy is a rare condition, and the exact pathophysiologic mechanism of nerve involvement and treatment for neurologic deficits remain unclear. The histologic findings in the present case support the possibility that the peripheral neuropathy related to LV was primarily derived from an ischemic injury rather than inflammation. Continuous anticoagulant use could be helpful in the neurologic recovery of LV patients with multiple mononeuropathy.

Keywords: Livedoid vasculopathy; Mononeuropathies; Case reports

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Introduction

Livedoid vasculopathy (LV) is a chronic, painful, thrombo-occlusive cutaneous vasculopathy. It affects the lower extremities, and clinical symptoms are primarily confined to the skin [1]. In rare cases, there is involvement of the peripheral nervous system, which the most common form is multiple mononeuropathy [2].

The exact pathophysiologic mechanism of the nerve involvement in LV and treatment for neurologic deficits remain unclear.

Case reports have suggested that multiple mononeuropathy in LV can result from ischemic injury [3,4]; however, perivascular lymphocytes have been observed in microscopic findings of nerve biopsies, suggesting that inflammation could also be the cause [2,4-8]. A systematic review of LV suggests that patients' ulcerations, pain, or purpura can be treated with anticoagulants, anabolic steroids, antiplatelets, intravenous immunoglobulins, thrombolytics [9]; a fully successful treatment for peripheral nerve involvement, however, has not yet been established, and

only a few reports have suggested specific therapies [3-7].

We report on an LV patient presenting with multiple mononeuropathy, which helps identify the mechanism and has been successfully treated. In addition, we review 6 previous LV cases with multiple mononeuropathy in which nerve biopsies were performed. Written informed consent was obtained from the patient for publication of this case report.

Case Report

The patient was a 46-year-old woman who came to the neuromuscular disease clinic of our institution mainly complaining of a left-foot drop. Although the patient had no history of trauma, she had suffered from radiating pain in the left lower extremity 3 months previously; 4 days before visiting our clinic, she suddenly had trouble moving her left foot.

The patient had been diagnosed with LV in 1996 and suffered painful ulcerations during the summer on all extremities. She denied other medical histories except surgery for an ectopic pregnant in 2008. There was no familial history. She took pentoxifylline and rivaroxaban prescribed by another clinic only in the summer but did not take them in the autumn voluntarily when she visited the clinic.

A clinical examination revealed skin lesions with livedo reticularis and multiple hyperpigmented patches on all extremities, and lower extremities had fibrosclerotic white scars. Muscle strength in her left leg was graded using the Medical Research Council (MRC) scale: ankle dorsiflexion, grade 1; great toe extension, grade 3; ankle plantarflexion, grade 4; and ankle eversion and inversion, grade 4 for each. No muscle weakness was observed in other muscles. There was a decrease in light touch and pin-prick sensation in the left lateral, posterior calf, foot dorsum, and sole. Both knees and ankles had decreased deep muscle reflexes, and there was no Babinski's sign or ankle clonus on either side. A step-page gait pattern was observed in the left leg during gait.

Laboratory tests were within normal limits for complete blood count, liver function test, electrolytes, prothrombin time, activated partial thromboplastin time. Her rheumatoid factor was elevated (36 IU/mL [normal < 14 IU/mL]). However, she was negative for antinuclear antibody Ab, direct and indirect Coombs test, anti-cyclic citrullinated peptide Ab, anti-Sjögren's-syndrome-related antigen A, B Ab, anticardiolipin immunoglobulin (Ig) G, M, anti-double-stranded DNA Ig G, and antineutrophil cytoplasmic Abs. She had negative serologic tests for syphilis, human immunodeficiency virus, and hepatitis B and C.

Lumbar spine magnetic resonance imaging showed no definite

Table 1. Nerve Conduction Study Findings 4 Days after the Patient First Experienced Foot Drop

Nerve	Record site	Segment	Latency (ms)	Amplitude	NCV (m/s)
Motor					
Median (R/L)	APB	DL	2.86/3.07	12.8/12.5	
		W-E		12.7/11.9	58.4/60.2
		F-wave	24.01/24.22		
Ulnar (R/L)	ADM	DL	3.07/2.70	10.7/10.3	
		W-E		9.8/10.1	65.1/61.9
Peroneal (R/L)	EDB	DL	3.02/2.45	3.3/3.6	
		A-BK		2.5/1.8	48.3/43.9
	TA	DL	3.02/2.45	3/2.5	
Tibial (R/L)	AH	BK-AK		2.7/2	49.2/46.8
		DL	3.39/3.44	11.5/10.4	
		A-PF		7.9/7.7	45.3/48
		F-wave	46.35/46.25		
Sensory		H-reflex	28.44/28.39		
Median (R/L)	Digit III	F-W		50.1/53.4	42.0/41.3
Ulnar (R/L)	Digit V	F-W		30.6/44	42.0/40.1
Superficial peroneal (R/L)	Ankle	A-C		NE/NE	
Sural (R/L)	Ankle	A-C		NE/NE	

Amplitudes are measured in millivolt (mV, motor) and microvolt (μ V, sensory).

NCV, nerve conduction velocity; R, right; L, left; APB, abductor pollicis brevis; DL, distal latency; W, wrist; E, elbow; F, finger; ADM, abductor digiti minimi; EDB, extensor digitorum brevis; A, ankle; BK, below knee; TA, tibialis anterior; AK, above knee; AH, abductor hallucis; PF, popliteal fossa; C, calf; NE, not evoked.

abnormal findings. Computed tomography angiography in lower extremities was normal.

A nerve conduction study (NCS) was performed 4 days after the patient first complained of left-foot drop. She did not exhibit evoked sensory nerve action potentials (SNAPs) in either superficial peroneal or sural nerves. There were decreased amplitudes of the compound motor nerve action potentials (CMAPs) of both peroneal nerves recorded from the tibialis anterior muscles

(Table 1). Needle electromyography showed no motor unit action potential (MUAP) in the left tibialis anterior muscle, but other sampled muscles had no abnormal findings (Table 2). The electrodiagnostic study showed multiple mononeuropathy involving both the common peroneal and sural nerves.

Follow-up NCS and needle electromyography were conducted 20 days after complaining foot drop. The SNAPs were not evoked in both superficial peroneal nerves; however, a SNAP in

Table 2. Needle Electromyography Findings 4 Days after the Patient First Experienced Foot Drop

Muscle	IA	ASA	MUAP	Recruitment pattern	Interferential pattern
B. L2–L5 PSP	N	None			
B. BB	N	None	N	N	N
B. FCR	N	None	N	N	N
B. FDI	N	None	N	N	N
B. Gmax	N	None	N	N	N
B. Gmed	N	None	N	N	N
L. BF (short)	N	None	N	N	N
L. BF (long)	N	None	N	N	N
L. ST	N	None	N	N	N
B. VM	N	None	N	N	N
R. TA	N	None	N	N	N
L. TA	N	None	No MUAP		
L. PL	N	None	N	N	N
L. TP	N	None	N	N	N
B. GCM (medial)	N	None	N	N	N

IA, insertional activity; ASA, abnormal spontaneous activity; MUAP, motor unit action potential; B, both; PSP, paraspinalis; N, normal; BB, biceps brachii; FCR, flexor carpi radialis; FDI, first dorsal interosseous; Gmax, gluteus maximus; Gmed, gluteus medius; L, left; BF, biceps femoris; ST, semitendinosus; VM, vastus medialis; R, right; TA, tibialis anterior; PL, peroneus longus; TP, tibialis posterior; GCM, gastrocnemius.

Table 3. Nerve Conduction Study and Needle Electromyography Findings 20 Days after the Patient First Experienced Foot Drop

	Record site	Segment	Latency (ms)	Amplitude	NCV (m/s)	IA	ASA	MUAP	Recruitment pattern	Interferential pattern					
Motor nerve															
Peroneal (R/L)	EDB	DL	3.23/5.83	3.7/0.4	47.2/28.8										
		A-BK		3.2/0.3											
	TA	DL	2.03/2.50	3.6/0.8	50.1/34.9										
		BK-AK		3.6/0.7											
Tibial (R/L)	AH	DL	3.85/5.10	10.1/9.9	48.7/60.4										
		A-PF		9.7/8.7											
		F-wave	41.30/46.15												
Sensory nerve															
Superficial peroneal (R/L)	Ankle	A-C		NE/NE											
Sural (R)	Ankle	A-C		5.6	33.4										
Muscle															
L TA						Decreased	Fib/PSW	N	Reduced	Discrete					

Amplitudes are measured in millivolt (mV, motor) and microvolt (μ V, sensory).

NCV, nerve conduction velocity; IA, insertional activity; ASA, abnormal spontaneous activity; MUAP, motor unit action potential; R, right; L, left; EDB, extensor digitorum brevis; DL, distal latency; A, ankle; BK, below knee; TA, tibialis anterior; AK, above knee; AH, abductor hallucis; PF, popliteal fossa; C, calf; NE, not evoked; N, normal.

the right sural nerve was newly evoked with low amplitude. Amplitudes of the CMAPs in both peroneal nerves recorded on tibialis anterior muscles were decreased, more on the left side. In needle electromyography, fibrillation and positive sharp wave were observed in the left tibialis anterior muscle and MUAPs were newly observed with reduced recruitment patterns (Table 3).

A nerve biopsy was performed on the left sural nerve, and microscopic pathological examination showed asymmetric loss of myelinated fibers within and between the fascicles. There were hyalinized dermal blood vessels with intravascular thrombosis in the perineurium and extensive infarct of the peripheral nerve and Schwann cells. Only a few perivascular mononuclear cells infiltrates were observed (Fig. 1).

A day before the nerve biopsy, we prescribed her oral prednisolone 50 mg per day and enoxaparin 50 mg via subcutaneous injection twice per day first. Prednisolone had been given due to the possibility of secondary neuropathy derived from systemic inflammation of the LV. Five days after the start of treatment, oral rivaroxaban 10mg per day was substituted for enoxaparin. After confirming that the pathologic finding showed little inflammation, oral prednisolone was gradually stopped.

After 2 weeks, her left ankle dorsiflexion muscle strength improved to MRC grades 2. The patient continued to take oral rivaroxaban for 1 year. After a follow-up period of 1 year, her left ankle dorsiflexion gradually rose to MRC grade 5. The patient's gait pattern was normal, but numbness on the dorsum area of the left-foot persisted.

Discussion

LV pathogenesis is related to occlusion of the cutaneous capillary circulation leading to thrombosis, ischemia, and infarction [1]. However, LV can be secondary to rheumatoid arthritis, scleroderma, systemic lupus erythematosus, connective tissue

disease, polyarteritis nodosa, Sjögren's syndrome, and solid organ or hematologic malignancies [1].

There have been 6 previously reported LV cases with multiple mononeuropathy in which nerve biopsies were performed (Table 4) [2-4,6-8]. Nerve biopsies in 3 cases (Pai and Pai [6], Toth et al. [7], and Tubone et al. [8]) showed chronic histologic findings; a nerve biopsy performed by Malaguti et al. [4] showed pleomorphic mononuclear cell infiltration in the endoneurium, perineurium, and epineurium. Four histologic findings from nerve biopsies could not distinguish whether multiple mononeuropathy in LV was derived from inflammation or infarction.

The peripheral nerve involvement in our patient was derived from ischemic injury rather than inflammation. In our case, the laboratory results showed no evidence of connective tissue disease or vasculitis. The sural nerve biopsy showed intravascular thrombosis in the perineurium and extensive infarct of the peripheral nerve and Schwann cells but few perivascular mononuclear cells infiltrates. Prednisolone, which was administered before the biopsy, had the potential to suppress inflammation; however, the biopsy was conducted the day after the treatment, which was unlikely to have a significant effect on the pathology result.

Similarly, the report by Kim et al. [3] described a patient who had occasional perivascular lymphocytes infiltrating the arterioles in the epineurium; moreover, the patient's nerve biopsy showed endoneurial capillary congestion with hemorrhage and infarct in the peripheral nerve and Schwann cells. The histologic findings from both our case and Kim et al. [3]'s case demonstrate that the neuropathy of LV was primarily caused by capillary occlusion leading to ischemic injury rather than inflammation.

LV cases with peripheral nerve involvement are much rarer, and treatment for a neurologic deficit remains unknown. Our patient was initially treated with both anabolic steroids and anticoagulants before her histologic findings. After confirming the nerve biopsy findings, anabolic steroids were gradually discontinued. The patient had taken an anticoagulant, rivaroxaban, for over a year as maintenance therapy. After we added oral rivaroxaban to her drug regimen, the patient showed improved motor capability in her left ankle dorsiflexion with no complications.

Among the 6 previously reported cases of LV with multiple mononeuropathy, 4 were initially treated with anticoagulants, antiplatelets, anabolic steroids, or immunosuppressants (Table 4) [2-4,6-8].

In the case reported by Toth et al. [7], the patient had an improvement in skin lesions after treatment with anabolic steroids, but numbness appeared in a new location after steroid administration was discontinued. The sensory deficit improved after

Fig. 1. Sural nerve biopsy, lateral malleolus, left. (A) Hyalinized dermal blood vessels with an intravascular thrombosis (arrow) (paraffin section; H&E, ×100). (B) Severe loss of myelinated fibers and some axonal degeneration due to ischemic necrosis (circle with dotted line) (paraffin section; H&E, ×100).

Table 4. Nerve Biopsies in Previous Cases of Patients with Livedoid Vasculopathy and Multiple Mononeuropathy

Study (year)	Type of study	Biopsy site (n)	Histologic findings	Motor symptom	Initial treatment	Maintenance treatment	Outcome
Toth et al. [7], 2003	Case report	Peroneal nerve (2)	Decreased large myelinated fibers with chronic axonal loss. Occasional lymphocytes near vessels.	None	Methylprednisolone, prednisone	Warfarin	Subjective improved sensation and skin lesion
Kim et al. [3], 2011	Case report	Sural nerve (1)	Endoneurial capillary ectasia and hemorrhagic congestion. Extensive infarct in the peripheral nerve. Occasional perivascular lymphocytes infiltrating the arterioles in the epineurium. Intravascular thrombosis with mild lymphocytic infiltration in the epineurium.	None	Pentoxifylline, clopidogrel		Not aggravated
Pai and Pai [6], 2013	Case report	Sural nerve (1)	Chronic vasculitis with marked sectorial fiber loss and chronic axonopathy	Both distal upper limbs weakness	Prednisolone, azathioprine, pentoxifylline	Prednisolone, azathioprine	Complete healing in skin lesions
Tubone et al. [8], 2013	Case report	Sural nerve (1)	Chronic neuropathy, degenerative alterations, and predominantly perivascular inflammatory infiltrate	None	Not mentioned		
Malaguti et al. [4], 2015	Case report	Sural nerve (1)	Symmetric loss of myelinated fibers. High proportion of fibers at different stages of Wallerian degeneration with regenerating small myelinated fibers. Some pleomorphic mononuclear cell infiltrates in the endoneurium, perineurium, and epineurium.	Left ulnar innervated hand muscles weakness	Acetylsalicylate		Improved neurological symptoms
Gardette et al. [2], 2018	Observational study	Undescribed (1)	Severe loss of myelinated axons associated with vasculopathy. Alterations of the endoneurium with endothelial cell damage and necrosis of capillaries.	None	Not mentioned		
Current case	Case report	Sural nerve (1)	Asymmetric loss of myelinated fibers. Hyalinized dermal blood vessels with intravascular thrombosis in the perineurium. Extensive infarct of the peripheral nerve. Few perivascular mononuclear cell infiltrates.	Left foot drop	Enoxaparin, prednisolone	Rivaroxaban	Complete motor recovery

treatment with an appropriate dose of warfarin. In the case described by Kim et al. [3], the patient received antithrombotic and antifibrinolytic agents and had no further attacks, but improvement in neurological symptoms was not described.

Two cases of LV with multiple mononeuropathy showed motor impairment. In the case reported by Pai and Pai [6], there was no motor improvement after treatment with antiplatelets, an anabolic steroid, and an immunosuppressant agent. Malaguti et al. [4] described neurological improvement after treatment with acetylsalicylate, but the motor improvement was not communicated.

Rarely, multiple mononeuropathy can occur in LV. According to histologic findings of our case, multiple mononeuropathy in LV was induced by ischemic injury rather than inflammation. In this case, multiple mononeuropathy in LV with motor deficits showed good clinical outcomes after anticoagulant treatment; therefore, it is thought that early anticoagulation treatment may be helpful in LV with peripheral nerve involvement.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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