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Neuromyopathy caused by long term colchicine therapy

*[1]Hyung Jun Park, *[2]Hyung-Soo Lee, [3]Heasoo Koo, [4]Soo Jeong Han, [5]Euno Choi, [6]Chan Young Lee, [6]Seung Ah Lee, [7]Young-Chul Choi, [6]Kee Duk Park
**Hyung Jun Park and Hyung-Soo Lee contributed equally to this work*

[1]Department of Neurology, Gangneung Asan Hospital, University of Ulsan College of Medicine, Gangneung; [2]Department of Neurology, Presbyterian Medical Center, Jeonju; [3]Department of Pathology, Seonam Hospital, Seoul; Departments of [4]Rehabiliation Medicine, [5]Pathology, and [6]Neurology, Mokdong Hospital, Ewha Womans University School of Medicine, Seoul; [7]Department of Neurology, Yonsei University College of Medicine, Seoul, Republic of Korea

Abstract

Colchicine-induced neuromyopathy is an extremely rare complication, and can develop in the setting of acute overdose or chronic administration in therapeutic doses. A 72-year-old man presented with proximal muscle weakness and myalgia. He had angina pectoris and Behçet's disease, leading to the treatment of colchicine (1.2 mg daily for about 6 years), cyclosporine, methylprednisolone, simvastatin, and aspirin. A biceps brachii muscle biopsy was performed and electron microscopic examination revealed scattered autophagic vacuoles. He was initially treated with steroid pulse therapy. However, muscle weakness did not improve. After the discontinuation of colchicine, muscle power and myalgia improved steadily. There should be heightened awareness of colchicine-induced neuromyopathy because that clinical suspicion is the most important diagnostic clue, and termination of colchicine is the only treatment.

Keywords: colchicine, toxicity, muscular disease, polyneuropathies

INTRODUCTION

Colchicine is commonly used for the treatment of gout, familial Mediterranean fever, Behçet's disease and recurring pericarditis with effusion. The use of colchicine is usually safe, but several adverse effects are known. The most prevalent adverse effect is dose-related gastrointestinal intolerance (nausea, vomiting, and abdominal pain), followed by bone marrow suppression, dermatitis, alopecia, and neuromyopathy. Colchicine-induced neuromyopathy is an extremely rare complication, and can develop in the setting of acute overdose or chronic administration in therapeutic doses. One recent study mentioned that the incidence of colchicine induced neuromyopathy is not rare (1.4%).[1] However, it was overestimated because this study defined myopathy as myalgia/muscle weakness and elevated creatine kinase level without confirmation of electrodiagnostic studies and muscle biopsies. Several studies mentioned that colchicine toxicity was influenced by chronic renal failure, abnormally high colchicine doses and the concomitant use of immunosuppressive drugs or statins. Muscle biopsy specimens were characterized by vacuolar changes.[2] The early diagnosis of colchicine induced neuromyopathy is important as the reversal of muscle weakness requires termination of colchicine therapy. We reported here a case of neuromyopathy after long term colchicine therapy.

CASE REPORT

A 72-year-old man was referred to our institution due to proximal muscle weakness and myalgia. He had angina pectoris and Behçet's disease, leading to the treatment of colchicine (1.2mg daily for about 6 years), cyclosporine, methylprednisolone, simvastatin, and aspirin (Fig. 1). He firstly felt gait disturbance and myalgia six months before admission. The Muscle weakness rapidly progressed and he could not walk independently one month before admission. Neurologic examination revealed proximal muscle weakness and muscle tenderness on palpitation. Muscle power was grade 3/5 in the shoulder girdle muscles and grade 2/5 in the pelvic girdle muscles. Hypoesthesia was only present in the

Address correspondence to: Kee Duk Park MD, PhD, Department of Neurology, Ewha Womans University College of Medicine, 1071, Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Korea. Tel: +82-2-2650-6010; E-mail: pkd1165@ewha.ac.kr

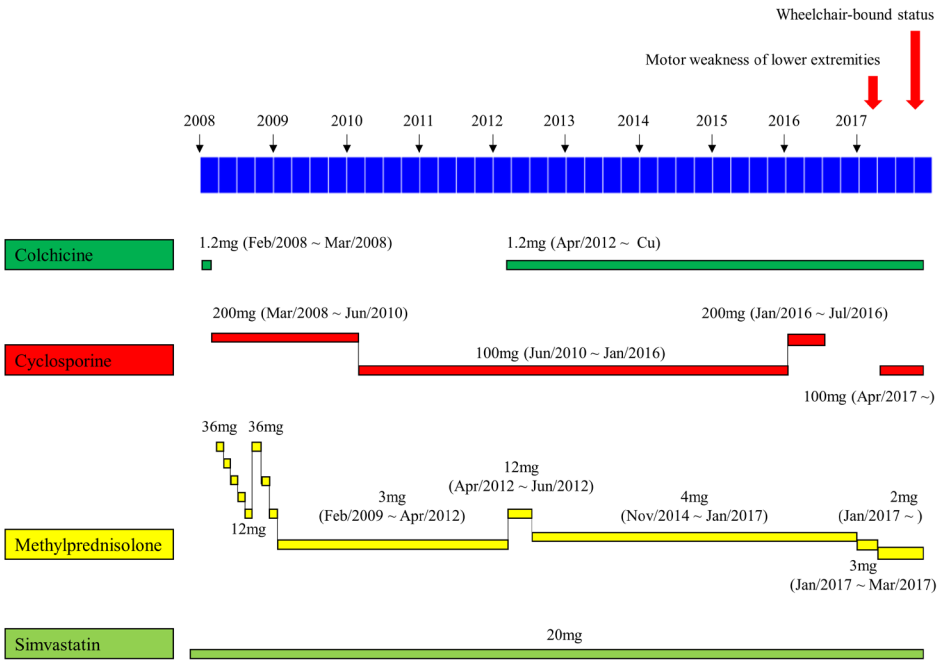

Figure 1. Previous drugs used in the patient with colchicine-induced neuromyopathy

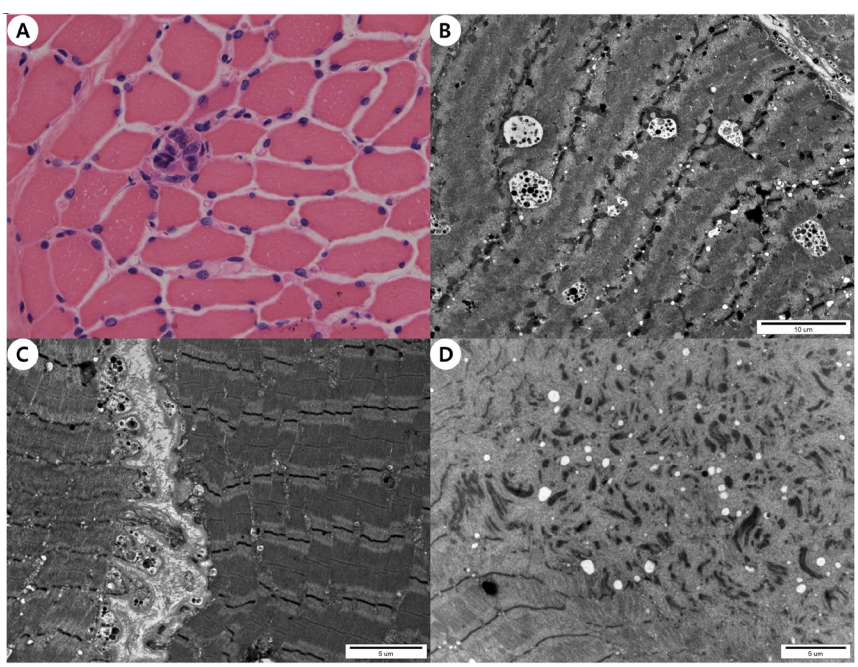

Figure 2. Histopathological findings of biceps brachii muscle biopsy. (A) Hematoxylin and eosin staining revealed mild variation of the fiber size and shape with scattered necrotic myofibers. On electron microscopic examination, the markedly necrotic myofibers (B) show poorly defined sarcomeres mixed with degenerated organelles and diffusely scattered autophagic vacuoles. The relatively preserved myofibers (C) show diffuse or localized disruption of normal intermyofibrillar pattern with empty vacuoles or autophagic vacuoles of lysosomal origin as well as prominent subsarcolemmal accumulation of autophagic vacuoles. There are myofibers with smeared Z line material and myofibrillar disruption (D).
(A: x40; B and C: x7000; D: x10000)

Table 1: Electrophysiological features of the patient with colchicine-induced neuromyopathy

	Day*						Normal value
	-18		-1		18		
Side	Rt	Lt	Rt	Lt	Rt	Lt	
Median nerve							
TL (ms)	**4.5**	**5.2**	**4.8**	**5.1**	3.9	3.9	≤ 3.9
CMAP (mV)	**5.0**	**4.3**	**3.6**	**2.9**	**4.7**	**3.5**	≥ 6.0
MNCV (m/s)	50.0	**48.0**	55..0	53.0	51.0	54.0	≥ 50.5
Ulnar nerve							
TL (ms)	**3.1**	**3.3**	**3.1**	3.0	3.0	3.0	≤ 3.0
CMAP (mV)	7.3	7.9	**4.5**	**3.3**	**4.6**	**4.9**	≥ 8.0
MNCV (m/s)	51.0	51.0	52.0	54.0	51.1	53.0	≥ 51.1
Peroneal nerve							
TL (ms)	4.5	4.0	4.1	4.6	**A**	3.6	≤ 5.3
CMAP (mV)	**1.2**	**1.2**	**0.4**	**0.1**	**A**	**0.5**	≥ 1.6
MNCV (m/s)	41.0	**38.0**	**37.0**	**38.0**	**A**	43.0	≥ 41.2
Tibial nerve							
TL (ms)	4.0	4.3	4.8	4.8	3.7	4.1	≤ 5.4
CMAP (mV)	**2.1**	**1.9**	**0.6**	**1.2**	**1.8**	**1.6**	≥ 6.0
MNCV (m/s)	39.0	40.0	37.0	39.0	**44.0**	**43.0**	≥ 41.1
Median sensory nerve							
SNAP (μV)	**6.1**	**3.8**	**8.3**	**7.2**	**5.9**	**4.4**	≥ 8.8
SNCV (m/s)	35.0	35.1	**41.0**	**40.0**	37.0	35.0	≥ 39.3
Ulnar sensory nerve							
SNAP (μV)	**5.4**	**7.3**	**5.5**	**5.6**	**3.0**	8.0	≥ 7.9
SNCV (m/s)	**34.0**	**37.0**	41.0	41.0	**34.0**	38.0	≥ 37.5
Sural nerve							
SNAP (μV)	**5.2**	**2.8**	**3.4**	**3.8**	**A**	**A**	≥ 6.0
SNCV (m/s)	39.0	39.0	**28.0**	**29.0**	**A**	**A**	≥ 32.1
H-reflex (ms)	**A**	**A**	**A**	**A**	**A**	**A**	≤ 30.2

Bold characters indicate abnormal values.
*Day 0 denotes the day colchicine was discontinued.
Rt, right; Lt, left; A, absent potentials; TL, terminal latency; CMAP, compound muscle action potential; MNCV, motor nerve conduction velocity; SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity

tip of the toes. Deep tendon reflexes were absent. Laboratory studies showed that complete blood count, electrolyte level, blood urea nitrogen and serum creatinine were normal. The serum cyclosporine level was low (45.10 ng/ml). The following serum markers were elevated: creatine kinase (CK) 332 IU/l (normal: ≤185 IU/l), lactate dehydrogenase 472 IU/l (normal: ≤211 IU/l), aspartate aminotransferase 92 IU/l (normal: ≤40 IU/l), and alkaline phosphatase 72 IU/l (normal: ≤40 IU/l). Chest and abdominopelvic CT scans did not show any malignant lesions. Nerve conduction studies showed axonal sensorimotor polyneuropathy (Table 1). Needle electromyography revealed a myopathic pattern. A biceps brachii muscle biopsy was performed (Figure 2). The biopsy material consisted of myofibers with mild variation of size and shape and occasionally noted scattered degenerated or necrotic myofibers with faint basophilic tinge in sarcoplasm. Necrotic myofibers with mononuclear cells are also noted as well as internalization of sarcolemmal nuclei. There was no evidence of endomysial edema, fibrosis, or mononuclear inflammatory cell infiltration. Periodic acid-Schiff stain and oil-red-O stains do not show abnormal positive reaction (accumulation of glycogen or lipid). The ATPase reaction with different pH preincubation and immunostaining with Myosin Heavy Chain (fast), Myosin Heavy Chain (slow), and Myosin IIa shows no abnormal fiber type proportion. On electron microscopic examination, the myofibers showed varying degrees of degenerative changes. The markedly

necrotic fibers show poorly defined sarcomeres mixed with degenerated organelles, granular amorphous material, and scattered autophagic vacuoles. The relatively preserved myofibers show diffuse or localized disruption of normal intermyofibrillar pattern with scattered empty vacuoles or autophagic vacuoles of lysosomal origin, associated with whorled membranous myeloid or spheromembranous bodies, derived from the sarcoplasmic reticulum. Myofibers with prominent subsarcolemmal accumulation of autophagic vacuoles containing heterogeneous granular and membranous bodies, glycogen, and lysosomes were also noted. In addition, there were myofibers with smeared Z line material and myofilament disruption.

The patient had adult-onset progressive muscle weakness, elevated serum CK level and electromyographic findings without family history of neuromuscular diseases. He had taken simvastatin, colchicine, and cyclosporine about 10 years ago. Based on these evidences, he was initially diagnosed with inflammatory myopathy and was treated with steroid pulse therapy. However, the muscle weakness did not improve. Then, we considered colchicine-induced neuromyopathy and stopped the colchicines, based on the presence of both myopathy and neuropathy, and muscle biopsy showing vacuolar changes without inflammatory cell infiltration. After the discontinuation of colchicine, muscle power and myalgia improved steadily. One and a half months later, muscle power was grade 4/5 in the pelvic girdle muscles and he could walk using a cane.

DISCUSSION

We believed that long term colchicine therapy was the cause neuromyopathy in our patient based on the following evidences: (i) His muscle weakness improved after colchicine discontinuation, and (ii) muscle biopsy demonstrated autophagic vacuoles without inflammatory cell infiltration. We thought that the myopathy was not due to cyclosporine or simvastatin, based on the followings: Firstly, these drugs was not commonly associated with neuropathy; Secondly, the serum cyclosporine level was low; Thirdly, muscle power improved despite of continuous use of these drugs. However, colchicine, cyclosporine, and simvastatin were metabolized by cytochrome P450 3A4.[3,4] Therefore, the concomitant use of these drugs could increase the toxicity of colchicine.

Colchicine is a known tubulotoxin and inhibits microtubule polymerization by binding to the α and β monomers of tubulin. However, the pathogenic mechanism of colchicine induced neuromyopathy is unclear. It has been postulated that impaired microtubule assembly and network cause defective axonal transport in axons and altered extrusion of lysosomes and autophagosomes in skeletal muscles.[3]

In conclusion, we present a case that demonstrates typical clinical and pathological presentation of colchicine induced neuromyopathy. Colchicine induced neuromyopathy is an extremely rare toxic complication. However, clinician should be aware the diagnosis, as clinical suspicion is the most important diagnostic clue, and the only effective treatment is termination of the colchicine.

ACKNOWLEDGEMENTS

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DISCLOSURE

Conflicts of interest: None

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