NEPHROLOGY 2006; **11**, 147–150 doi:10.1111/j.1440-1797.2006.00542.x

Case Report

Colchicine myoneuropathy in chronic renal failure patients with gout

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SUMMARY: Colchicine myoneuropathy is a rare and often underdiagnosed disease. It often presents as painless subacute muscle weakness. We present a case of painful colchicine myoneuropathy in a 76-year-old man with chronic renal failure and gout. Published work about clinical presentations of colchicine myoneuropathy in gouty arthritis patients are reviewed. During the previous year, the patient had a drug regimen of colchicine 0.5 mg three times per day for a 3 day course each month. He developed bilateral lower leg weakness and severe myalgia. His serum creatinine level was 680.7 μmol/L and creatinine kinase was 959 IU/L on admission. Laboratory findings included decreasing amplitude of motor and sensory nerve conduction velocity and an electromyogram showed small amplitude, short duration polyphasic waves over the right biceps. A muscle biopsy disclosed vacuolar changes in the cytoplasm. These results all supported a diagnosis of colchicine myoneuropathy. After cessation of colchicine, the creatinine kinase level decreased approximately 50% in 6 days, myalgia subsided and his muscle weakness improved gradually over the next 2 weeks.

KEY WORDS: **chronic renal failure, colchicine myoneuropathy, gout.**

Colchicine is widely used in the treatment of gouty arthritis. Acute toxic side-effects of colchicine other than gastrointestinal upset are rare; however, chronic side-effects, including myopathy, neuropathy, bone marrow suppression should be emphasised especially in renal or hepatic dysfunction. The first case of colchicine myoneuropathy was reported in 1962,[1] but was associated with ingestion of a toxic dose. Colchicine myoneuropathy typically presents as painless muscle weakness. This report describes a case of colchicine myoneuropathy with significant myalgia as the predominant feature and reviews current published work on clinical presentation of colchicine myoneuropathy

CASE PRESENTATION

A 76-year-old man was admitted to the hospital on 8 September 2003 because of progressive bilateral lower leg weakness for 1 week.

The patient was married and unemployed. He had a history of chronic renal failure (serum creatinine was 565.8 μmol/L 3 weeks before admission) and gouty arthritis. Because of recurrent gouty arthritis in the left knee, he had taken 0.5 mg colchicine three times per day and 2.5 mg dexamethasone three times per day for a 3 day course each month during the past year as prescribed at another clinic. Three weeks before admission, he was prescribed the following medications in our outpatient department: 0.5 mg colchicine twice daily, 40 mg furosemide daily, 500 mg $CaCO_3$ twice daily, and 100 mg nimesulide twice daily. Approximately 1 week prior to this admission, the patient started to have difficulty rising from chairs, he could no longer walk without support and he noticed severe bilateral leg myalgia with slight numbness in his lower legs and feet. Because these symptoms were increasing in severity, he was admitted.

Physical examination on admission revealed that he looked acutely ill. His body temperature was 36.1°C, heart rate 84 per minute, respiratory rate 20 per minute, and blood pressure 130/80 mmHg. The proximal and distal muscles were tender bilaterally. Motor strength was normal over the arms. Proximal muscle weakness of the legs was found with iliopsoas strength right 3/5 and left 2/5; and tibialis anterior strength right 2/5 and left 2/5. The decrease in muscle strength in the distal limbs may have been related to the myalgia because distal limb muscle power improved after the myalgia subsided. The deep tendon reflex was absent in the legs. The sensation of light touch decreased symmetrically from knee to foot.

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Accepted for publication 31 October 2005.

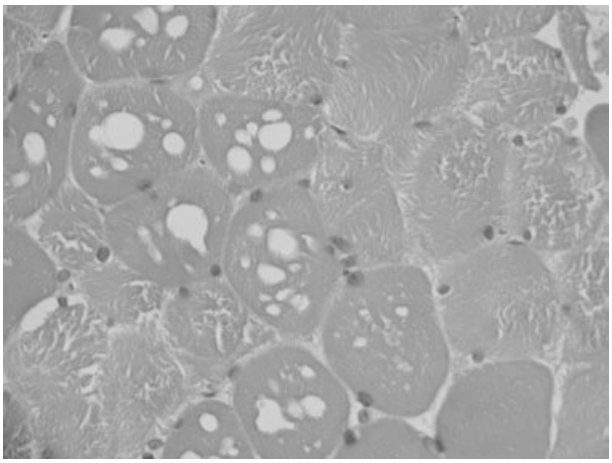

Fig. 1 Muscle biopsy specimen. There are empty vacuoles in the cytoplasm without obvious lymphocyte infiltration (HE stain; original magnification, ×400).

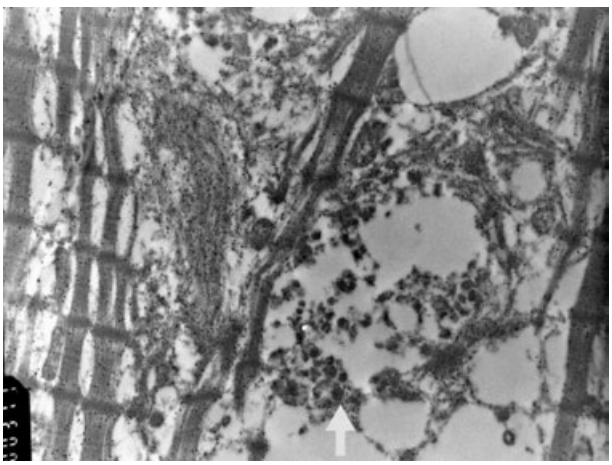

Fig. 2 Muscle biopsy specimen. The muscle cells contain subsacrolemmal and intermyofibrillar vacuoles with electron dense granules (arrow) (original magnification, ×8000).

The initial laboratory findings included a creatinine level of 680.7 μmol/L (7.7 mg/dL) and a creatinine kinase level of 959 IU/L.

Nerve conduction studies (NCV) showed sensorimotor neuropathy of the axonal type. An electromyogram revealed small amplitude, short duration, polyphasic waves over the right biceps, which indicated myopathic changes.

A muscle biopsy of the left quadriceps was performed. Light microscopic examination of the muscle fibres showed large empty vacuoles in the cytoplasm without obvious lymphocyte infiltration (Fig. 1). The empty vacuoles were negative for glycogen and lipid in periodic acid-Schiff (PAS), diastase-periodic acid-Schiff (DPAS) and oil red stains. They were more commonly seen in type I muscle fibres in the nicotinamide dinucleotide tetrazolium reductase (NADH-Tr) stain. Electron microscopy studies (Fig. 2) revealed subsacrolemmal and intermyofibrillar vacuoles with electron dense granules content. These findings were consistent with colchicine myopathy.

Meperidine and tramadol were given for pain control initially but were both ineffective. On the fourth day of hospitalisation, local heat and tenderness developed over the left knee and 5 mg prednisolone three times per day was given under the impression of gouty arthritis. We chose prednisolone rather than non-steroid anti-inflammatory drugs to avoid further aggravating his renal failure. Colchicine was not given because of suspected colchicine myoneuropathy. The left knee pain subsided gradually. Colchicine treatment was discontinued 4 days after admission. Serum creatinine kinase decreased approximately 50% (472 IU/L) 6 days after cessation of colchicine. Myalgia subsided at the same time. The patient's muscle power gradually improved over the next 2 weeks. His hip flexion reached a score of 4/5 (right) and 3/5 (left) and he was able to walk with a walker.

DISCUSSION

Colchicine myoneuropathy typically presents as subacute proximal muscle weakness with numbness. Associated symptoms include distal hyporeflexia, areflexia and decreases sensations of vibration, position and light touch. Myalgia is not a characteristic symptom according to previous reports. However, in the present case, both myalgia and muscle weakness were predominant features. Colchicine myoneuropathy is usually misdiagnosed as polymyositis initially due to similar clinical features. However, polymyositis per se is not accompanied by polyneuropathy. A muscle biopsy would demonstrate lymphocyte infiltration. Polymyositis can be controlled by steroids, but steroids are ineffective in treating colchicine myoneuropathy. In the present case, steroids were used temporarily to control gouty arthritis. A high dose of steroids could result in steroid myopathy as well. Steroid myopathy may occur gradually or abruptly, and is heralded by weakness and muscle aches. The serum creatinine kinase is normal. Muscle histology reveals extensive type II muscle fibre atrophy and loss of thick filaments on electron microscopic examination.

In the published work review,[1–9] we found that dose and duration of colchicine administration leading to myoneuropathy varies, ranging from 0.6 mg three times per day for 2 weeks to 0.5 mg three times per day for 15 years (Table 1). Most patients who develop colchicine myoneuropathy have renal dysfunction. However, normal renal function dose not prevent colchicine myoneuropathy even when recommended oral dosages are used.

The characteristic symptoms of colchicine myoneuropathy are muscle weakness and numbness (Table 1). Muscle weakness is seen in approximately 95% of cases and sensory symptoms (mainly presenting as numbness) occur in approximately 44%. According to previous published work,[10] myalgia is not the typical symptom in colchicine myoneuropathy. However, our patient complained of severe myalgia despite narcotic administration. In the 19 cases we

Table 1 Summary of reported cased of colchicine myoneuropathy

Reference	Age/Sex	Cr (μmol/L)	Dose/Duration to induce colchicine myoneuropathy	After discontinuing colchicine, muscle power improved in	Symptoms			Neurological examination			
					Muscle weakness	Sensory symptoms	Myalgia	Distal areflexia or hyporeflexia	Limb weakness		Distal sensory abnormality
									Proximal	Distal	
Kontos.[1]	48/M	NA	1 mg t.i.d. × 5+ year	6 weeks	1/1	0/1	0/1	0/1	1/1	1/1	0/1
Kuncl *et al.*[2]	59/M	≥141.4	0.6 mg b.i.d. × 2 years	3 weeks							
	86/M	≥141.4	0.6 mg b.i.d. × 3 years	2 weeks							
	60/M	≥141.4	0.6 mg b.i.d. × 3+ year	NA							
	85/M	≥141.4	0.6 mg b.i.d., several year	2 months							
	—	—	—	—	10/11‡	4/11‡	1/11‡	10/11‡	8/10‡	1/10‡	7/10‡
Riggs *et al.*[3]	43/F†	NA	1.2 mg hourly × 4 h, more than 1–2 times per week, for 5 years	1 years	1/1	1/1	NA	1/1	1/1	1/1	1/1
Younger *et al.*[4]	60/F	176.8	1.2 mg q.d. × 6 months	2 months	1/1	1/1	NA	1/1	1/1	NA	1/1
Fernandez *et al.*[5]	75/M	79	1 mg q.d. × 3 weeks	NA	1/1	NA	1/1	NA	1/1	NA	NA
Altiparmak *et al.*[6]	69/M	H/D	0.5 mg t.i.d. × 15 years	3 weeks	1/1	NA	NA	1/1	1/1	NA	1/1
Choi *et al.*[7]	84/F	176.8	0.5 mg b.i.d. × 4 weeks	3 weeks	1/1	1/1	NA	1/1	1/1	0/1	1/1
Rutkove *et al.*[8]	48/F	256.4	0.6 mg q.d. × 9 months	10 weeks	1/1	0/1	0/1	1/1	1/1	1/1	1/1
Schiff *et al.*[9]	71/F	176.8	0.6 mg t.i.d. × 2 weeks	Several days	1/1	0/1	0/1	1/1	1/1	1/1	1/1
Present case	76/M	353.6	0.5 mg t.i.d. × 3 days per month, for 1 year	2 weeks	1/1	1/1	1/1	1/1	1/1	0/1	1/1
Rate	—	—	—	—	19/20 (95%)	8/18 (44%)	3/16 (18%)	17/19 (89%)	17/19 (89%)	5/16 (31%)	4/18 (78%)

All patients had gout except †purported history of gout; ‡total 12 cases, but only included patients that were examined by the author.

reviewed, only two other cases (for a total three cases including ours) presented with severe myalgia. The aetiology of myalgia remains to be determined. Although myalgia is not the characteristic symptom of colchicine myoneuropathy, its diagnosis can not be excluded by myalgia alone.

On neurological examination (Table 1), approximately 89% patients have distal areflexia. Proximal muscle weakness occurs in approximately 89% and distal muscle weakness in 31%. Distal sensory abnormality has been noted in 78% of cases and decreases in the sensation of vibration, position and light tough have all been described.

Recovery time from colchicine myoneuropathy varies from 2 weeks to 1 year after discontinuing the drug (Table 1). It seems that there is no obvious correlation between the duration/dose of colchicine use and the recovery time from colchicine myoneuropathy. In addition, renal dysfunction does not significantly interfere with the recovery time. However, because the above 19 cases were examined by different authors, it is difficult to define the degree of recovery of muscle strength and normal sensation.

Serum creatinine kinase activity may elevate in colchicine myoneuropathy. However, the range varies. It may have a 44-fold increase.[2] Some authors have suggested that muscle strength is correlated with creatinine kinase activity. The creatinine kinase level in our patient increased 10-fold. Six days after discontinuing colchicine, the creatinine kinase level dropped approximately 50% and myalgia also subsided. Muscle power improved 2 weeks later.

Electromyographic (EMG) assessment in colchicine myopathy reveals pure myopathic changes in the proximal limb muscles, whereas in the distal limb muscles these changes are associated with neurogenic features due to the coexisting neuropathy.[10,11] Nerve conduction velocity studies show sensorimotor polyneuropathy of the axonal type. In our patient, fibrillation potential, positive sharp waves and polyphasic waves were found on EMG and decreasing amplitudes were noted in motor and sensory nerves on NCV. These findings are compatible with colchicine myoneuropathy.

Pathologically, the characteristic feature of colchicine myopathy is the accumulation of membranous material in cytoplasmic vacuoles in the muscle on both light and electron microscopy examination. These vacuoles are believed to be derived from lysosomes because staining for acid phosphatase is positive. Colchicine myopathy involves mainly type I muscle fibers.[5] Muscle fibre necrosis may be seen which is correlated with the serum creatinine kinase level.

The mechanism of colchicine myoneuropathy remains uncertain. Colchicine binds to tubulin reversibly at a high affinity site and prevents the polymerisation of tubulin into microtubules, thereby impairing axoplasmic transport in peripheral nerves.[12] Colchicine also alters the microtubular network that localises, moves or allows the normal extrusion of lysosomes and autophagosomes in skeletal muscle cells. Colchicine myoneuropathy may result from disruption of axonal transport and organelle trafficking in both nerve and muscle cells with autophagic vacuole overdevelopment.

Colchicine has many side-effects and should be used carefully in patients with chronic renal failure. Chronic side-effects include myopathy, neuropathy and bone marrow suppression. To prevent colchicine myoneuropathy, dose adjustment according to renal function and age is necessary.[13,14] In order to diagnose colchicine myoneuropathy as early as possible, it is important to monitor muscle power and peripheral sensation in chronic colchicine users. Measurement of the serum creatinine kinase level is suggested in patients with suspected disease. The best way to diagnose colchicine myoneuropathy is to be aware of the possibility of this condition.

ACKNOWLEDGEMENTS

The authors are grateful to colleagues in the Department of Nephrology and Department of Pathology, Taipei Medical University Hospital for their support.

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