Colchicine-Induced Myopathy in Renal Failure

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Abstract

A 60 year-old woman with chronic renal failure developed acute proximal muscle weakness after receiving a regular dosage of colchicine. Elevation of muscle enzymes and electromyography were compatible with myopathy. Muscle biopsy revealed variation in muscle fiber size and few vacuolated fibers which were features of colchicine-induced myopathy. The clinical improvement and decreasing in muscle enzyme level occurred after colchicine withdrawal. Other potential causes of myopathy such as chronic renal failure and other drugs were ruled out. We suggested that colchicine should be used with caution in the presence of renal failure especially when other drugs which affect the metabolism of colchicine are also prescribed.

Many drugs and subtance abuse such as alcohol, corticosteroids, chloroquine etc are well known causes of myopathy(1). Isolated case reports or case series of colchicine-induced myopathy are speckled(1,2). Recently, myopathy was observed even in regular dosage of colchicine in individuals with underlying renal insufficiency(3-7). Since colchicine-induced myopathy is potentially reversible, prompt recognition of this complication is essential in medical practice. We report a rare case of acute colchicine-induced myopathy who had renal failure and developed rapidly progressive proximal muscle weakness after a regular dosage of this drug.

CASE REPORT

A 60 year-old woman was admitted on 5th August 1994 due to generalized myalgia and progressive weakness. She had a history of controlled diabetes mellitus for 10 years. Four years later, she developed diabetic retinopathy and renal insufficiency with a serum creatinine of 2.3 mg/dl. Five years before admission, she had hyperlipoproteinemia which was controlled by fenofibrate 300 mg once daily. She also had a history of coronary heart disease with congestive heart failure for one year and received hydralazine, hydrochlorothiazide and clonidine. She was regularly followed-up and her clinical status was stable.

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On 7th July 1994, she was admitted because of acute renal failure and unstable angina. Apart from the diabetic retinopathy, her general physical examination and neurological examination were unremarkable. The serum creatinine was 7.0 mg/dl. The cardiac muscle enzymes including serum glutamic oxaloacetic (SGOT), lactic dehydrogenese (LDH) and creatine kinase (CK) were within normal limits. Diltiazem, isosorbide dinitrate and aspirin were given to her. On 10th July 1994, during the hospitalization, she developed an acute gouty attack at her right knee. Colchicine 0.6 mg twice daily and allopurinol 100 mg once daily were given. The diabetic, cardiac and renal conditions were unchanged.

She was discharged on 12th July 1994, and began to observe proximal muscle weakness of the extremities and myalgia. She needed some support while standing and walking. Her sensation, bowel and bladder functions were normal. At home, the weakness was progressive. Finally she could not walk and was readmitted on 5th August 1994. The neurological examination revealed symmetrical proximal muscle weakness of both legs (MRC grade 3/5) and the arms (MRC grade 4/5). Truncal weakness was also observed. No muscular atrophy or fasiculation was detected. Normal pinprick sensation was noted but vibration sensation was slightly decreased in both feet. All deep tendon reflexes were absent.

The laboratory findings included blood urea nitrogen of 57 mg/dl, creatinine level of 6.8 mg/dl, CK 864 IU/liter (0-195), SGOT 94 IU/liter (0-38) and LDH 542 IU/liter (230-460). Blood electrolytes, calcium, phosphate, magnesium, plasma glucose, complete blood counts and urinalysis were normal. The erythrocyte sedimentation rate was 100 mm/h. The electromyography demonstrated partial denervation and myopathic pattern as evidence by increased polyphasic action potentials, fibrillations, positive sharp waves, short duration and low amplitude of motor units in biceps and gastrocnemius muscles. The sensory and motor nerve conduction velocity of both median and peroneal nerves showed mild degree of axonopathy. Left vastus medius muscle was biopsied. Hematoxylin and eosin (H & E) stain revealed variation of muscles fiber size, with atrophic fibers and mild increased in endomysial connective tissue but without inflammation. There were a few vacuolated fibers (Fig. 1). Adenosine triphosphatase (ATP_{ase}) (PH 9.5) stain demonstrated numerous type II fiber atrophy.

Colchicine and fenofibric acid were stopped. The motor weakness was marked improved. Two weeks later she was able to sit up and walk by herself. The repeated muscle enzymes were normal (CPK 138 IU/liter, LDH 327 IU/liter). During two years of follow-up, no recurrent attack of myopathy recurred.

DISCUSSION

Clinical features of colchicine myoneuropathy include gradual onset of progressive proximal muscle weakness with occasional myalgia and mild distal symmetrical sensory symptoms and distal areflexia[3,5]. However, acute onset of myopathy within 1-2 weeks after starting the administration of colchicine was also observed[6,7]. The elevation of CK is the most sensitive indicator for colchicine-induced myopathy which may be elevated as high as 44-folds but some patients may remain asymptomatic[3]. The muscle strength usually becomes normal within 4 weeks of either discontinuation of colchicine or reduction of the dosage to 0.6 mg per day[3]. The clinical improvement was paralleled to the decreasing level of CK enzyme [3-7]. The electrodiagnostic studies of this condition reveal mild sensory and motor axonopathy as well as a myopatic pattern which sometimes contain frequent positive sharp waves, fibrillation potentials and complex repetitive potentials which

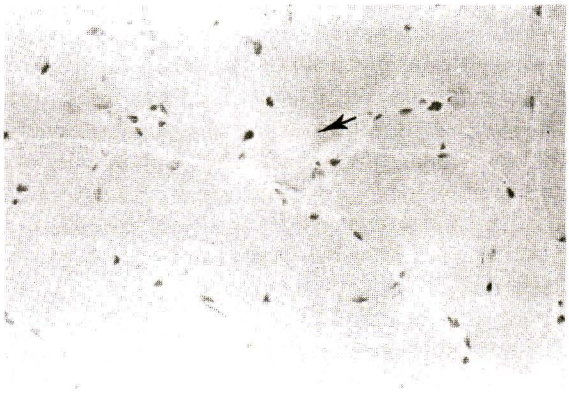

Fig. 1. Hematoxylin and eosin stain of muscle biopsy revealed variation in muscle fiber size and few vacuolated fiber (arrow).

may be misdiagnosed as polymyositis[3-7]. The histologic and electron microscopic pictures show vacuolar myopathy due to the presence of accumulation of lysosomes and heterogenous membrane debris and mild loss of large myelinated axon and the presence of degenerating and regenerating axon[3,5].

Our patient had received colchicine 0.6 mg twice daily and developed rapid onset of myopathy with elevation of muscle enzymes. She regained her muscle strength and muscle enzymes returned to normal level after discontinuation of the drug. The clinical course paralleled with the administration and discontinuation of colchicine. The electrodiagnostic tests demonstrated definite evidence of myopathy and partial denervation. The clinical and electrophysiological evidence of neuropathy may be due to diabetic neuropathy or myoneuropathy related to colchicine. Muscle biopsy showed prominent muscle fiber type II atrophy which indicating the underlying muscle changes in chronic renal insufficiency[8]. The "vacuole" in muscle fiber which is a prominent feature in chronic colchicine myopathy were occasionally observed in our case and may be explained by short duration of colchicine exposure.

Our patient had other possible causes of myopathy. The first one was the myopathy in renal insufficiency. Myopathy with elevated muscle enzymes had been observed in acute renal failure with rhabdomyolysis and in chronic dialysis patients[9,10]. However, during the peak of acute renal failure, our patient did not develop myopathy and had normal muscle enzymes and dialysis was not performed. Chronic uremic myopathy had a normal muscle enzyme and is not compatible with our case presentation[8]. Another possible drug that can cause myopathy was fenofibrate[11]. Fenofibrate can cause myalgia and elevated CK level[12]. Only 2 reports of fenofibrate induced myopathy have been documented, one was a case of slow progressive necrotic myopathy[13] and another was a case of polymyositis during the high dose therapy[14,15]. Our patient developed acute onset and received a regular dose of 300 mg once daily. The muscle biopsy was neither necrotic myopathy nor polymyositis. Thus, it is unlikely that our patient's condition was caused by fenofibrate.

In colchicine-induced neuropathy, the mechanism is postulated to be a defective axonal transport resulting from dysfunction of microtubule[3,5]. In myopathic form, disruption of cytoskeleton is a possible mechanism[3,16]. Colchicine binds with tubulin, the subunit protein of microtubule, causes muscle cell to round up, fragment and form a vacuole or myosac[13,5,17]. The acute onset of myopathy in our case may be due to the combination of acute renal failure ontop of the chronic renal insufficiency. In addition, inhibition of cytochrome P 450 system by calcium channel blocker (diltizaem) will further promote the rapid increase in colchicine level and cause colchicine toxicity by the impairment of the hepatic and renal metabolism[2,3,7,17].

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โรคกล้ามเนื้อเหตุยาโคชิซีนในผู้ป่วยไตวาย

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รายงานผู้ป่วยหนึ่งรายเป็นหญิง ไตวายเรื้อรัง อายุ 60 ปี มีอาการอ่อนแรงกล้ามเนื้อส่วนต้นแขนและขา ภายหลังได้รับโคชิซีนขนาดปกติ. การตรวจเอ็นไซม์กล้ามเนื้อ และการตรวจทางไฟฟ้าของกล้ามเนื้อเข้าได้กับรอยโรคในกล้ามเนื้อ การตรวจทางพยาธิวิทยาของกล้ามเนื้อพบใยกล้ามเนื้อมีขนาดแตกต่างกัน และใยกล้ามเนื้อที่มีแวคคูโอล. ซึ่งเข้าได้กับลักษณะของโรคกล้ามเนื้อเหตุยาโคชิซีน. อาการของผู้ป่วยดีขึ้นและระดับเอ็นไซม์ของกล้ามเนื้อลดลงภายหลังถอนยา. ในผู้ป่วยรายนี้ได้วินิจฉัยแยกภาวะและโรคที่อาจทำให้เกิดโรคกล้ามเนื้ออ่อนแรงอื่น ๆ. เช่น ไตวายเรื้อรังและยาอื่น ๆ ผู้รายงานเสนอแนะให้แพทย์ใช้ยาโคชิซีนด้วยความระมัดระวัง ในผู้ป่วยที่มีไตวาย และผู้ป่วยมีการใช้ยาอื่น ๆ ที่อาจทำให้เมตาโบลิสมของโคชิซีนเปลี่ยนแปลง.

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