Colchicine Myopathy in a Patient With Familial Mediterranean Fever and Normal Renal Function

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Introduction

Patients with familial Mediterranean fever (FMF) routinely take large daily doses of colchicine to both prevent and abort acute attacks (1,2) and to reduce the risk of developing amyloidosis (3). Unfortunately, colchicine can also cause a number of toxic side effects, including neuromyopathy. Almost all cases of colchicine neuromyopathy previously described have been associated with renal insufficiency (4). We report the first case of biopsy-confirmed myopathy due to chronic colchicine administration in an adult with FMF and normal renal function.

Case report

A 38-year-old woman with FMF and Crohn’s disease presented in October 2001 for evaluation of worsening muscle weakness over the previous 3 years. She had difficulty walking up stairs or doing overhead work. She reported no muscle pain, rash, fevers, Raynaud’s phenomenon, joint pain, paresthesias, or numbness.

The patient has carried the diagnosis of FMF (homozygous for mutation V726A) since childhood. She had recurrent attacks every 3–4 weeks lasting 24–48 hours accompanied by fevers to 40°C and abdominal or chest pains. Her symptoms had responded to treatment with 1.8–2.4 mg of colchicine daily and she has been maintained on this dosage since her teenage years. She had not had any attacks of FMF for 20 years.

In 1997 the patient developed diarrhea and was diagnosed with Crohn’s disease for which she was treated with combinations of mesalamine, oral glucocorticoids, methotrexate, and infliximab. At the time of her presentation with weakness, the Crohn’s disease was under good control with balsalazide alone. Other medical conditions included gastroesophageal reflux disease and irritable bowel syndrome. In October 2001 her medications included omeprazole (20 mg/day), balsalazide (2.25 gm 3 times per day), colchicine (1.8 mg/day), calcium carbonate (500 mg 3 times per day), and amitriptyline (50 mg/day).

Physical examination revealed a weight of 48 kg, blood pressure of 100/70 mm Hg and pulse of 80 beats/minute. Neurologic examination revealed 5–/5 strength in the proximal upper extremity muscle groups and 4+/5 strength in the proximal lower extremity muscle groups bilaterally. She had great difficulty performing 1 deep knee bend (squat). Distal muscle groups had normal strength. Deep tendon reflexes were absent in the biceps, triceps, knees, and ankles bilaterally. Sensation to light touch, gait, and cranial nerve examination were normal. The results of the remainder of her physical examination were normal.

The patient’s laboratory studies were notable for the following values: creatine phosphokinase (CPK) enzyme level 889 U/liter (normal 30–250 U/liter), aldolase 9.5 U/liter (normal 1.2–7.6 U/liter), white cell count 4,200/mm3, hematocrit 31%, platelet count 161,000/µl, blood urea nitrogen 6 mg/dl, creatinine 0.3 mg/dl, albumin 4.0 gm/dl (normal 3.5–4.8 gm/dl), urinalysis results were normal. Abdominal fat aspirate was negative for amyloid.

Nerve conduction and electromyography studies revealed moderately severe denervation in the proximal muscles of the upper and lower extremities, as well as absent superficial peroneal sensory responses and low amplitude sural sensory responses.

Muscle biopsy of the right quadriceps revealed central rimmed vacuoles and endomysial fibrosis (Figure 1). There was marked variability of fiber size with atrophic fibers and few basophilic regenerating fibers. There was a noted absence of necrotic fibers and a paucity of inflammatory infiltrate. Electron microscopy showed central longitudinal autophagic vacuoles containing aggregates of cellular degradation products and exhibiting areas of myofibrillar disarray (Figure 2).

Colchicine was discontinued following the muscle biopsy in early November 2001 and no other medication changes occurred. By March 2002 her strength gradually improved, but her CPK enzyme level had only decreased...
Within the muscle disarray. There are numerous autophagic vacuoles centrally located a, electron microscopy of muscle biopsy from right thigh. Figure 2.

to patients with renal or hepatic insufficiency, it can cause bone marrow failure and death (5). Myopathy and neuropathy are well recognized but rare toxicities of treatment with oral colchicine. Colchicine may lead to myopathy by causing a toxic accumulation of lysosomal and autophagic vacuoles in myocytes through disruption of the cytoskeletal network by which these vacuoles are excreted (6).

Colchicine is bound by tissues in the extravascular space because its volume of distribution is greater than total body water (7). Studies in mice have determined that, 4 hours after intravenous administration, significant amounts of colchicine accumulate in the intestines, kidneys, and spleen but not in blood, the brain, or muscles (8). However, colchicine concentrations in these tissues were not evaluated at later time points. Others have found leukocytes to contain significant concentrations of colchicine 10 days following intravenous administration (9). Colchicine and its metabolites are cleared through the bile (10) and urine (11), thus renal or hepatic dysfunction may lead to elevation of plasma colchicine levels and increase the risk of toxicity (12). Interestingly, the mean elimination half-life for colchicine in patients with FMF is more than twice as long as in healthy individuals, despite normal renal function and no evidence of amyloidosis (13).

Kuncl et al described the characteristic features of colchicine neuromyopathy in 12 patients (4). These features include proximal weakness, an elevation of creatine kinase, proximal myopathic changes on electromyography, axonal polyneuropathy on nerve conduction velocities, and vacuolar myopathy on muscle biopsy, all of which our patient exhibited. However, unlike the patients presented by Kuncl et al, our patient had persistently normal renal function. Furthermore, our patient’s CPK levels did not return to normal for 8 months following discontinuation of colchicine, while normalization typically occurs within 4 weeks.

Three prior cases of colchicine-associated neuromyopathy in patients with normal renal function have been reported (14,15). Two of these cases occurred in children with FMF. However, neither of these cases had evidence of muscle involvement, with symptoms consisting only of neuropathy. The third case occurred in a patient on chronic suppressive therapy for gout who, similar to our patient, also required a prolonged, 4-month period for resolution of myopathic toxicity (14).

Treatment of patients with FMF after the development of colchicine myopathy is problematic. Over 9 years, 49% of patients with FMF will develop proteinuria due to renal amyloidosis if colchicine is not used, compared with just 1.7% in patients compliant with colchicine therapy (3). One report of 10 patients describes interferon alfa being used in an effort to abort attacks of FMF instead of colchicine (16). However, it is unknown whether interferon alfa will prevent the development of amyloidosis. As there is some evidence that colchicine can reverse or stabilize renal amyloidosis, the risks of colchicine could potentially be avoided until proteinuria first develops. Patients with previous myopathy could be then rechallenged with a lower dose of colchicine (0.6 mg/day). This case illustrates the importance of continued clinical monitoring for col-

Discussion

Our patient presented with an insidious onset of muscle weakness, CPK elevation, peripheral neuropathy, and a vacuolar myopathy on muscle biopsy. The resolution of her symptoms with normalization of CPK enzymes following discontinuation of colchicine further implicates colchicine as the cause of her myopathy. Colchicine is well known for its toxic side effects. Even at low doses it can commonly cause gastrointestinal distress. When given via the intravenous route in doses greater than 2 mg, especially to patients with renal or hepatic insufficiency, it can not be avoided until proteinuria first develops. Patients with previous myopathy could be then rechallenged with a lower dose of colchicine (0.6 mg/day). This case illustrates the importance of continued clinical monitoring for col-

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REFERENCES