Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 49, No. 4, August 15, 2003, pp 614–616
DOI 10.1002/art.11185

TRAINEE ROUNDS

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

EUGENE Y. KISSIN,[1] JOSEPH C. CORBO,[2] FRANCIS A. FARRAYE,[1] AND PETER A. MERKEL[1]

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/mm^3, 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

Dr. Merkel is supported in part by a Mid-Career Development Award in Clinical Investigation (NIH-NIAMS: K24 AR-2224-01A1).

[1]Eugene Y. Kissin, MD, Francis A. Farraye, MD, MSc, Peter A. Merkel, MD, MPH: Boston University School of Medicine, Boston, Massachusetts; [2]Joseph C. Corbo, MD, PhD: Children's Hospital and Harvard Medical School, Boston, Massachusetts.

Address correspondence to Peter A. Merkel, MD, MPH, Arthritis Center E5, Boston University School of Medicine, 715 Albany Street, Boston, MA 02118. E-mail: pmerkel@bu.edu.

Submitted for publication August 8, 2002; accepted in revised form December 6, 2002.

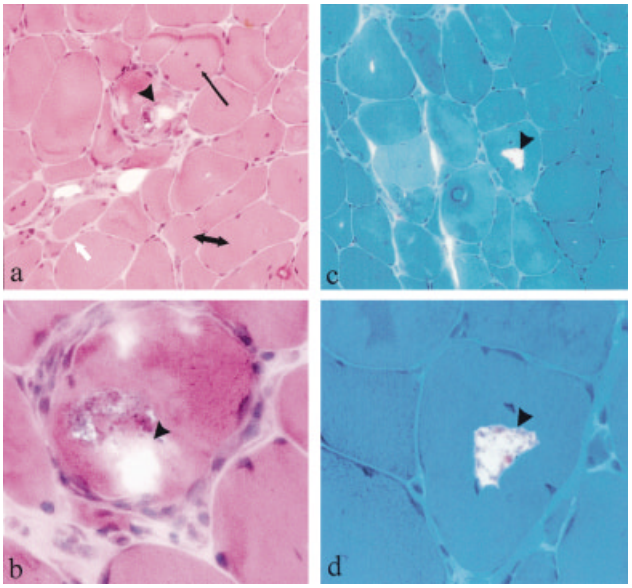

Figure 1. Conventional histology of muscle biopsy from right thigh. Hematoxylin-eosin stain **a**,**b** and trichrome stain **c**,**d** demonstrate variation in muscle fiber size (**double arrow**), centralization of nuclei (**small arrow**), endomysial fibrosis (**white arrow**), and central vacuoles (**arrowhead**) in several myofibers. There is a paucity of inflammatory cells and no necrosis of myofibrils.

to 482 U/liter. Normalization of CPK (138 U/liter) and return of normal strength occurred by June 2002, 8 months after discontinuation of colchicine. The patient has not had any attacks of FMF over these 8 months.

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 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).

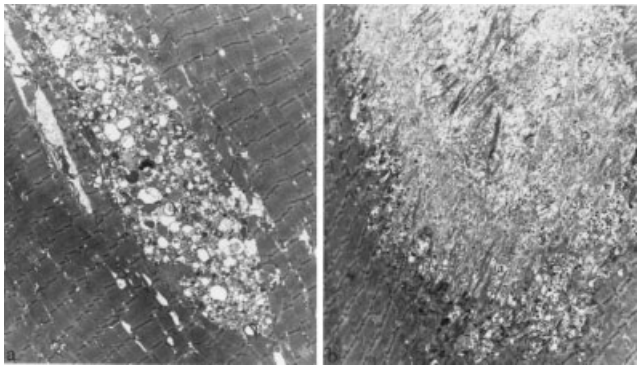

Figure 2. Electron microscopy of muscle biopsy from right thigh. **a,** There are numerous autophagic vacuoles centrally located within the muscle fibers and containing heterogeneous material. **b,** Numerous autophagic vacuoles produce extensive myofibrillar disarray.

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 the offending drug, 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 proteinurea 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-

chicine toxicity in patients on long-term treatment, even when renal and hepatic function is normal.

REFERENCES

1. Zemer D, Revach M, Pras M, Modan B, Schor S, Sohar E, et al. A controlled trial of colchicine in preventing attacks of familial Mediterranean fever. N Engl J Med 1974;291:932–4.
2. Dinarello CA, Wolff SM, Goldfinger SE, Dale DC, Alling DW. Colchicine therapy for familial Mediterranean fever: a double-blind trial. N Engl J Med 1974;291:934–7.
3. Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. N Engl J Med 1986;314:1001–5.
4. Kuncl RW, Duncan G, Watson D, Alderson K, Rogawski MA, Peper M. Colchicine myopathy and neuropathy. N Engl J Med 1987;316:1562–8.
5. Bonnel RA, Villalba ML. Deaths associated with the intravenous administration of colchicine [abstract]. Arthritis Rheum 2001;44 Suppl 9:S129.
6. Shinde A, Nakano S, Abe M, Kohara N, Akiguchi I, Shibasaki H. Accumulation of microtubule-based motor protein in a patient with colchicine myopathy. Neurology 2000;55: 1414–5.
7. Putterman C, Ben-Chetrit E, Caraco Y, Levy M. Colchicine intoxication: clinical pharmacology, risk factors, features, and management. Semin Arthritis Rheum 1991;21:143–55.
8. Back A, Walaszek E, Uyeki E. Distribution of radioactive colchicine in some organs of normal and tumor-bearing mice. Proc Soc Exp Biol Med 1951;77:667–9.
9. Ertel NH, Mittler JC, Akgun S, Wallace SL. Radioimmunoassay for colchicine in plasma and urine. Science 1976;193: 233–5.
10. Hunter AL, Klaassen CD. Biliary excretion of colchicine. J Pharmacol Exp Ther 1975;192:605–17.
11. Wallace SL, Omokoku B, Ertel NH. Colchicine plasma levels: implications as to pharmacology and mechanism of action. Am J Med 1970;48:443–8.
12. Achtert G, Scherrmann JM, Christen MO. Pharmacokinetics/bioavailability of colchicine in healthy male volunteers. Eur J Drug Metab Pharmacokinet 1989;14:317–22.
13. Halkin H, Dany S, Greenwald M, Shnaps Y, Tirosh M. Colchicine kinetics in patients with familial Mediterranean fever. Clin Pharmacol Ther 1980;28:82–7.
14. Pirzada NA, Medell M, I. AI. Colchicine induced neuromyopathy in a patient with normal renal function. J Clin Rheumatol 2001;7:374–6.
15. Harel L, Mukamel M, Amir J, Straussberg R, Cohen AH, Varsano I. Colchicine-induced myoneuropathy in childhood. Eur J Pediatr 1998;157:853–5.
16. Tunca M, Tankurt E, Akbaylar Akpinar H, Akar S, Hizli N, Gonen O. The efficacy of interferon alpha on colchicine-resistant familial Mediterranean fever attacks: a pilot study. Br J Rheumatol 1997;36:1005–8.