

Severe Respiratory Muscle Weakness Related to Long-Term Colchicine Therapy

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We report a case of colchicine-induced myopathy, in which the initial presenting and predominant clinical feature was respiratory muscle dysfunction; there was also chronic renal failure and electromyographically-measured myopathy. Discontinuation of colchicine led to marked improvement. Colchicine discontinuation was the only therapy performed (other medications were unchanged), and within 3 weeks the patient had regained motor function and resumed daily activities. Myopathy from primary biliary cirrhosis was ruled out. In contrast to acute colchicine intoxication, chronic colchicine toxicity is related to prolonged use rather than colchicine serum level, so colchicine serum level was not measured and did not affect the decision to discontinue colchicine. Although the diagnosis was not confirmed by muscle biopsy, we believe the typical presentation and the rapid improvement after withdrawing colchicine confirm the diagnosis. We conclude that long-term colchicine therapy, especially in the setting of chronic renal failure, can produce symptomatic respiratory muscle weakness. Key words: colchicine, myopathy, respiratory, biliary cirrhosis. [Respir Care 2004;49(2):189–191. © 2004 Daedalus Enterprises]

Introduction

Neuromuscular toxicity related to colchicine therapy is well recognized. However, severe respiratory muscle dysfunction leading to substantial respiratory symptoms has not been reported as a complication of long-term colchicine use. We present a case of colchicine-induced myopathy in a patient who had respiratory muscle dysfunction as the initial presenting and predominant clinical feature.

Case Summary

We saw a 54-year-old woman with a long history of primary biliary cirrhosis complicated by portal hyperten-

sion and esophageal varices, which were well controlled with ursodiol 300 mg twice daily and colchicine 0.6 mg twice daily. Her medications also included omeprazole, nadolol, isosorbide dinitrate, multivitamins, and calcium supplements.

Four months before presentation she felt progressively dyspneic and her exercise tolerance gradually deteriorated. Her New York Heart Association (NYHA) classification was estimated to be class II. Review of systems revealed no chest pain, paroxysmal nocturnal dyspnea, or worsening pedal edema. Her abdominal girth was unchanged. She denied previous pulmonary complaint or difficulty in carrying out her usual daily activities. She did not have signs of congestive heart failure on physical examination and her motor strength was well preserved. The initial workup revealed normal hematocrit and serum electrolytes. A chest radiograph revealed normal lung volumes, with clear lung fields bilaterally. The electrocardiogram was normal.

The patient's dyspnea worsened and she became progressively weaker, as evidenced by difficulty in lifting objects and rising from a sitting position. She could no longer walk unsupported. She was then referred to our pulmonary clinic for evaluation for progressive dyspnea. Her vital signs were normal and her blood oxygen saturation (measured via pulse oximetry, while breathing room

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air) was 97%. She had no sign of respiratory distress at rest in the sitting position, but developed orthopnea within minutes in the recumbent position. A rapid shallow breathing pattern with thoracoabdominal paradox was evident on examination. There was no jugular venous distention. The chest was clear to auscultation bilaterally and there was some abdominal distension, which suggested minimal ascites. There was trace pedal edema. The neurologic examination showed weakness of the proximal muscles, which was symmetrically distributed but more prominent in the legs (Medical Research Council [MRC] grade 4/5 in the proximal muscles of the upper extremity and 4-/5 in the lower extremities). Sensory and cerebellar functions were normal. Deep tendon reflexes were diminished in all extremities.

Initial blood values were normal, including hemoglobin level, white blood cell count, platelet count, and liver and thyroid function tests. Her blood urea nitrogen (25 mg/dL) and serum creatinine (1.7 mg/dL) were unchanged from baseline values obtained approximately 5 years earlier (19 mg/dL and 1.7 mg/dL). Her serum albumin was 2.6 g/dL and prothrombin time was 9.8 s (international normalized ratio [INR] = 1.0). Her creatinine kinase was 157 international units/L (normal 20–165 international units/L), but aldolase was elevated at 6.3 units/L (normal 1.7–4.9 units/L).

A repeat chest radiograph revealed bilateral elevation of hemidiaphragms, small lung volumes, and basilar atelectasis. Echocardiography showed a normal ejection fraction, normal chamber sizes, normal pulmonary artery pressure, and no pericardial effusion. Pulmonary function tests performed in the upright position showed low diffusing capacity for carbon monoxide and severely low maximum inspiratory and expiratory pressures (Table 1). The maximum inspiratory and expiratory pressures were low before substantial lung volume reduction was evident.

Two weeks after her evaluation her generalized weakness and dyspnea deteriorated and arterial blood gas values showed hypercapnia and respiratory acidosis. She was admitted to the hospital for concern about acute respiratory failure. Electromyography (EMG) revealed abundant, widespread myotonic discharges in all muscles examined. Diaphragmatic EMG was not performed. Motor unit potentials were generally of small amplitude and short duration, showing increased polyphasia and early recruitment. These findings were consistent with myopathy.¹ She refused muscle biopsy. Immediately upon admission, colchicine therapy was discontinued, on the assumption that it might have contributed to the muscle weakness and myopathic EMG pattern. She was treated conservatively, with supplemental oxygen and bronchodilator therapy.

Within 3 days her clinical symptoms dramatically improved and she was discharged home. No other therapeutic measures were performed and the rest of her medications were unchanged. At a visit 3 weeks later she had regained her motor function and had resumed her daily activities.

Table 1. Pulmonary Function Test Results

Variable	PFT 1 (% of Predicted)	PFT 2 (% of Predicted)
FEV ₁ (L)	1.82 (81)	1.99 (88)
VC (L)	2.68 (98)	2.73 (99)
FEV ₁ /VC	68 (83)	73 (89)
Flow at 50% of VC (L/s)	0.90 (35)	1.46 (56)
MVV (L/min)	63 (65)	74 (76)
TLC (L)	3.68 (83)	4.45 (100)
RV (L)	1.09 (65)	1.68 (115)
D _{LCO} (mL/min/mm Hg)	8.9 (39)	7.9 (34.6)
MIP (cm H ₂ O)	25 (33)	64 (84)
MEP (cm H ₂ O)	32 (23)	61 (44)

PFT = pulmonary function test

FEV₁ = forced expiratory volume in the first second

VC = vital capacity

MVV = maximum voluntary ventilation

TLC = total lung capacity

RV = residual volume

D_{LCO} = diffusing capacity of the lung for carbon monoxide

MIP = maximum inspiratory pressure

MEP = maximum expiratory pressure

The repeated pulmonary function test, after discontinuation of colchicine, found substantially improved inspiratory and expiratory pressure and modest improvements in lung capacity and forced expiratory volume in the first second (FEV₁), consistent with improved respiratory muscle strength (see Table 1).

Discussion

Colchicine is used in the treatment of primary biliary cirrhosis, acute gout, amyloidosis, and familial Mediterranean fever.^{2–4} In one prospective study colchicine improved survival among primary biliary cirrhosis patients.³ Colchicine-induced myopathy has been well described in the literature, especially with long-term therapy in the presence of chronic renal failure.^{5,6} Since colchicine is partially metabolized in the liver, by deacetylation,⁷ toxicity may also occur when liver function is impaired.⁸ However, a greater fraction of the drug is excreted in the urine of patients with reduced hepatic uptake and elimination.^{7–9} Evidence from human and animal studies suggests that colchicine causes myopathy by disrupting the microtubular network involved in lysosome processing.^{4,6,10} However, the exact mechanism is not known. There is no evidence in the literature to indicate that colchicine has any negative effect on the respiratory muscles.¹¹ Colchicine myopathy was strongly suspected in this case because of the presence of chronic renal failure and the typical myopathic findings on the EMG.¹ Furthermore, the clinical and radiological presentations were consistent with respiratory muscle weakness.^{11–13}

The diagnosis of colchicine-induced respiratory muscle weakness in this case was further confirmed by the rapid, dramatic improvement in the patient's respiratory status and the improvement of maximum inspiratory and expiratory pressures, total lung capacity, and maximum voluntary ventilation after discontinuation of colchicine therapy. Because of the rapid improvement, primary-biliary-cirrhosis-related myopathy¹⁴ was excluded. Since chronic colchicine toxicity is related to prolonged use rather than drug serum level (in contrast to acute colchicine intoxication), colchicine serum level was not obtained or included in the decision to discontinue colchicine therapy.

Although the diagnosis was not confirmed by muscle biopsy, the typical presentation and the rapid improvement after withdrawing the offending agent suffice to confirm the diagnosis. We conclude that long-term colchicine therapy, especially in the setting of chronic renal failure, can produce symptomatic respiratory muscle weakness. EMG, pulmonary function test, maximum inspiratory and expiratory pressures, and lung volumes in the upright and supine positions help establish the diagnosis. Discontinuation of colchicine therapy should lead to rapid improvement in respiratory symptoms and respiratory muscle strength.

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