Case Report

Colchicine-induced myoneuropathy in a cyclosporine-treated renal transplant recipient

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Abstract

Colchicine is a relatively safe medication that is widely used for both prevention and treatment of gout attack. However, serious adverse events, including myoneuropathy and multiorgan failure, have been reported. We report a case of colchicine-induced myoneuropathy in a female kidney transplant recipient who had been taking cyclosporine. She developed gastrointestinal discomfort and paresthesia 5 days after the initiation of colchicine. She showed signs of myoneuropathy, and hepatic and renal injury. Colchicine toxicity was suspected, and colchicine was discontinued. Her symptoms and laboratory findings improved gradually. Literature was reviewed for previous reports of colchicine-induced myoneuropathy in solid organ transplant recipients.

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Introduction

Gout is common in organ transplant recipients as a consequence of cyclosporine therapy, and impaired renal function acts as another predisposing factor in renal transplant recipients [1]. As nonsteroidal anti-inflammatory drugs (NSAIDs) are potentially nephrotoxic, colchicine is used frequently for both treatment and prevention of acute gout attack. Although colchicine is a relatively safe medication, it has been reported to be toxic. Gastrointestinal symptoms are common symptoms of colchicine toxicity; however, more severe adverse events such as myoneuropathy [2] and multiorgan failure [3] have also been reported. Cyclosporine is used widely as an immunosuppressant in organ transplant recipients. A number of case reports of colchicine toxicity associated with concomitant use of cyclosporine have been published [3–11], but they vary depending on the symptoms, dose, and duration of medication; the affected organs; and outcomes. Here, we report another case of myoneuropathy and multiple organ involvement associated with concomitant use of colchicine and cyclosporine in a renal transplant recipient, and review the previous case reports.

Case report

A 57-year-old female, with diabetes, hypertension, and a history of kidney transplantation 13 years ago from a deceased donor, was admitted due to epigastric pain and poor oral intake. She maintained normal renal function for 10 years, but her estimated glomerular filtration rate started to fluctuate 3 years prior to admission. Her serum creatinine was stabilized at 1.65 mg/dL about 2 years ago and was maintained in the range of 1.4–1.6 mg/dL thereafter. The patient developed the first acute gout attack on her left ankle 2 years ago, and was started on prednisolone 10 mg twice a day and allopurinol 100 mg once a day. After 1 month, prednisolone was tapered off gradually, but the aggravation of gout about 2 months prior to admission
required readministration of prednisolone. For control of hyperglycemia, prednisolone was substituted by colchicine 0.3 mg twice a day about 3 weeks prior to admission. The patient had been taking deflazacort 3 mg once a day, cyclosporine 50 mg twice a day, and mycophenolate 500 mg twice a day. She was also taking rosuvastatin 20 mg once a day, which had been used since January 2009 without any side effects. Five days after starting colchicine, she developed epigastric pain with nausea and vomiting. She began to complain of tingling sensation and numbness on the plantar area of both feet and the radial side of both hands 2 days later. After 21 days on colchicine, she visited the emergency department of our center. On initial presentation, physical examination revealed no abnormal finding, except mild dehydration. Sensory function of affected limbs was normal, and she did not show any signs of motor weakness. The complete blood count showed white blood cell count of 8,770/μL, hemoglobin level of 15.8 g/dL, and platelet count of 198,000/μL. Chemistry profiles were as follows: total bilirubin 1.5 mg/dL, blood urea nitrogen 26.4 mg/dL, creatinine 197 mg/dL, uric acid 7.6 mg/dL, creatine kinase 1,497 IU/L, lactate dehydrogenase 973 IU/L, and myoglobin 2,150.8 ng/mL (Table 1). Serum uric acid has remained at an optimal level.

Discussion

Previous case reports of colchicine myoneuropathy in patients with concomitant administration of cyclosporine were searched on MEDLINE, using the phrase “colchicine AND cyclosporine AND toxicity.” Among 48 results, case reports were selected, whose demographic and clinical characteristics are summarized in Table 2.

In 10 out of 13 cases, patients were male, which is in accordance with the male-to-female incidence ratio of gout. Mean age of the affected patients was 56.9 ± 10.0 years. Doses of colchicine were 1 mg/d or lower in most of the cases, but doses higher than 1 mg/d were administered in three cases. Development of colchicine toxicity after its chronic use was reported in one case, after 8 years [7]. However, serum concentration of cyclosporine was also found to be at a toxic level in this case, so possibility of cyclosporine toxicity cannot be ruled out. Excluding this extreme, the mean duration of colchicine use was 12.6 ± 9.7 days. Side effects have been reported after 2 days or 3 days of colchicine administration [4,6,10]. Serum colchicine concentration was measured only in one case, which was within the therapeutic range. Serum concentrations of cyclosporine were above 400 ng/mL in three cases, and above 1,000 ng/mL in two of them. High serum cyclosporine level in these patients raises suspicion of cyclosporine toxicity, but it might be secondary to acute kidney injury due to colchicine toxicity. Signs of myopathy and hepatic involvement were universal in reported cases. Serum creatinine was above the normal range in all cases in which creatinine level was reported, but the degree of kidney injury was difficult to estimate due to a lack of data on baseline serum creatinine level. Neutrophil count was below the normal range in two cases, which was also seen in our patient. All patients recovered after cessation of colchicine. Laboratory abnormalities were usually normalized within 2 weeks, but complete recovery from weakness and paresthesia took longer than a month in most of the cases reviewed.

Colchicine binds to tubulin in a poorly reversible manner [12], preventing its polymerization, which is required for the formation of a microtubule. Microtubules are involved in cell division, signal transduction, regulation of gene expression, and migration of cell. Concomitant administration of cyclosporine increases the risk of colchicine toxicity. It is suggested that this might be due to strong inhibition of the membrane P glycoprotein by cyclosporine [8,13]. A drug–drug interaction

Table 1. Laboratory findings of the patient

| Serum concentration | Day* |
|---------------------|------|
|  | −20 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 22 |
| CK (IU/L) | 1,497 | 1,239 | 2,316 | 1,177 | 499 | 87 |
| LD (IU/L) | 973 | 761 | 227 | 176 | 124 | 492 |
| AST (IU/L) | 23 | 166 | 168 | 227 | 176 | 124 | 106 | 91 | 75 | 25 |
| ALT (IU/L) | 28 | 118 | 151 | 153 | 162 | 149 | 106 | 91 | 75 | 25 |
| BUN (mg/dL) | 30.8 | 26.4 | 23.8 | 16.7 | 12.5 | 14.6 | 18.7 | 14.7 | 14.3 | 16.1 |
| Creatinine (mg/dL) | 1.97 | 1.71 | 1.42 | 1.27 | 1.09 | 0.98 | 0.99 | 0.83 | 1 |
| ANC (10*/μL) | 4.67 | 4.569 | 1.7 | 1.71 | 1.58 | 1 | 1.64 | 2.41 | 5.25 | 568 |
| Cyclosporine (ng/mL) | 63.5 | 66.3 | 1.7 | 1.71 | 1.58 | 1 | 1.64 | 2.41 | 5.25 | 568 |

* Day −20 denotes the day colchicine was prescribed. On Day 0, the patient visited the emergency department and colchicine was discontinued. The patient was discharged on Day 8. On Day 22, the patient visited the outpatient clinic.

ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; BUN, blood urea nitrogen; CK, creatine kinase; LD, lactate dehydrogenase.
Table 2. Clinical characteristics of 13 previous case reports

| No | Refs | Sex | Age (y) | Transplanted organ(s) | Colchicine dose (mg/d) | Duration of colchicine use | Serum concentration (colchicine; ng/mL) | Cyclosporine dose (mg/d) | Serum concentration (cyclosporine; ng/mL) | Symptoms | CK (IU/L) | LD (IU/L) | Myoglobin (ng/mL) | BUN (mg/dL) | Cr (mg/dL) | AST (IU/L) | ALT (IU/L) | Neutrophil (cells/mm³) |
|----|------|-----|---------|-----------------------|------------------------|---------------------------|--------------------------------------|-------------------------|------------------------------------------|----------|-----------|-----------|-------------------|-----------|-----------|-----------|-----------|----------------------|
| 1  | [6]  | M   | 49      | Kidney                | 2.4                    | 3 d                       | 250                                  | 267                     | Pain, weakness                           | 14,958   | 1,102     | ≥300      | 2.7               | 561       | 403       |
| 2  | [4]  | M   | 70      | Kidney                | 1                      | 16 d                      |                                      |                          | Weakness                                 | 425      |           |           |                   |           |           |
| 3  | [4]  | M   | 55      | Kidney                | 1                      | 2 d                       |                                      |                          | Pain                                     | 1,840    |           |           |                   |           |           |
| 4  | [4]  | F   | 49      | Kidney                | 1                      | 26 d                      |                                      |                          | Pain                                     | 1,234    |           |           |                   |           |           |
| 5  | [4]  | M   | 56      | Kidney                | 1                      | 11 d                      |                                      |                          | Pain                                     | 251      |           |           |                   |           |           |
| 6  | [4]  | M   | 67      | Kidney                | 1                      | 10 d                      |                                      |                          | Pain, weakness                           | 1,135    |           |           |                   |           |           |
| 7  | [7]  | M   | 53      | Heart                 | 0.6                    | 8 y                       | 350                                  | 1,450                   | Weakness, pain, fatigue                   | ≥3,000   | 36        | 2.9       | 449               |           |           |
| 8  | [7]  | M   | 56      | Heart                 | 0.6                    | 6 d                       | 450                                  | ≥2,000                   | Weakness, fatigue                         | 700      | 43        | 1.9       |                   |           |           |
| 9  | [7]  | F   | 57      | Heart                 | 0.6                    |                            |                                      |                          | Weakness                                 | 700      |           |           |                   |           |           |
| 10 | [9]  | M   | 72      | Kidney                | 1                      | 30 d                      | 150                                  | 134                     | Pain, weakness                           | 766      | 1,102     | 1.2       | 170               |           |           |
| 11 | [3]  | M   | 62      | Kidney                | 2 for 3 d, 1 mg qod for 5 d, then 1 for 9 d | 17 d                   | 250                                  |                          | Constipation, nausea, abdominal pain, fatigue, confusion, arrhythmia | 2,671    | 898       | 2.27      | 341               | 321       | 1,300     |
| 12 | [10] | M   | 60      | Heart                 | 1                      | 3 d                       | 350                                  | 475                     | Fever, dyspnea, tachycardia, arrhythmia   | 1,553    | 2,188     | 23.1      | 7.9                | 2,061     | 3,074     |
| 13 | [11] | M   | 34      | Heart, lung           | 1 mg tid for 1 d, 1 mg bid for 1 d, then 1 for 6 d | 8 d                      | 13                                  | 340                     | Cough, dyspnea, diarrhea, general weakness | 3,206    | 573       | 52.7      | 2.44               | 122       | 136       |

ALT, alanine transaminase; AST, aspartate transaminase; bid, twice daily; BUN, blood urea nitrogen; CK, creatine kinase; Cr, creatinine; LD, lactate dehydrogenase; q.o.d, four times daily; tid, three times daily.
study performed in vivo revealed that cyclosporine increases total exposure, half-life, and peak concentration of colchicines significantly [14].

Regarding diagnosis, temporal relations and distinctive syndrome of muscle injury and symptoms suggesting peripheral neuropathy should raise suspicion of colchicine toxicity. No specific test provides a definitive diagnosis, but muscle biopsy and electromyography/nerve conduction studies were performed frequently in previous cases. The characteristic histological features of colchicine myopathy are vacuolar myopathy—the presence of lysosomes and autophagic vacuoles [2,5,9]. Absence of inflammatory finding is useful to exclude polymyositis.

Electromyography and nerve conduction studies may also demonstrate distinctive features. Myopathic motor unit potentials and early recruitment in proximal limb and truncal muscles, positive sharp waves, or complex repetitive discharges are seen. Reduced amplitude of motor and sensory responses, but normal or borderline-slow conduction velocities, which suggests mild axonal neuropathy, can be seen in nerve conduction studies [9].

It is questionable whether muscle biopsy or electrodiagnostic studies are always necessary for the diagnosis. They are often helpful in ruling out other diseases of polymyositis and Guillain–Barré syndrome, respectively. However, polymyositis usually takes an insidious course over several months, and antinuclear antibodies are detected in up to 80% of patients with dermatomyositis or polymyositis. Guillain–Barré syndrome does not cause prominent muscle injury as observed in cases of colchicine toxicity. Therefore, those invasive tests can be reserved for atypical presentation or delayed recovery after cessation of colchicine.

The mainstay of treatment is a prompt cessation of colchicine and supportive care. Colchicine is not removed by dialysis [15], and there is no proven treatment to reduce the serum concentration of colchicine. Thus, currently, the highly qualified intensive care with organ support is the only option in severe cases. Artificial liver or organ transplantation could be theoretically possible options, but have never been practiced in this condition.

Treatment of gout is complicated in those patients who have experienced colchicine toxicity. Corticosteroid and NSAIDs remain as alternative options for the management of acute exacerbation. A short course of oral corticosteroid is a safe and effective treatment option, especially considering nephrotoxicity of NSAIDs. Control of hyperuricemia and avoidance of risk behaviors cannot be overemphasized, as colchicine cannot be taken for the prevention of acute gout attack.

Colchicine can cause severe myoneuropathy with multi-organ involvement, and its risk is increased in patients with concomitant use of cyclosporine. Withdrawal of colchicine usually results in rapid clinical improvement, but associated mortality has also been reported. Thus, clinical suspicion and prompt cessation of colchicine are very important. In addition, invasive and costly diagnostic tests can be avoided by a timely diagnosis. Therefore, all physicians who are involved in the care of renal transplant recipients should be familiar with colchicine-induced myoneuropathy.

Conflict of interest

All authors declare no conflict of interest.

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