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Colchicine and Clarithromycin Induced Rhabdomyolysis in a Hemodialysis Patient with Familial Mediterranean Fever

Ailevi Akdeniz Ateşi Olan Hemodiyaliz Hastasında Kolşisin ve Klaritromisin Kullanımına Bağlı Rabdomiyoliz

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ABSTRACT

Familial Mediterranean fever (FMF) is an autosomal recessive hereditary disease characterized by recurrent attacks of fever, usually accompanied by sterile polyserositis. Although colchicine is the main medical treatment option for FMF, potential adverse effects and drug interactions should be considered during follow-up of these patients. Herein, we presented a case of FMF and hemodialysis patient who developed who developed rhabdomyolysis due to concomitant use of colchicine-clarithromycin for pneumonia treatment.

KEY WORDS: Colchicine, Rhabdomyolysis, Kidney failure

ÖZ

Ailevi Akdeniz Ateşi (AAA), çoğunlukla steril poliserozitin eşlik ettiği tekrarlayan ateş atakları ile karakterize olan otozomal resesif geçişli kalıtsal bir hastalıktır. AAA için ana tıbbi tedavi seçeneği kolşisin olmasına rağmen, bu hastaların takibinde kolşisine bağlı olası yan etkiler ve ilaç etkileşimleri göz önünde bulundurulmalıdır. Bu olgu raporunda, pnömoni tedavisi için verilen klaritromisinin kolşisin ile etkileşimi sonucunda rabdomiyoliz gelişen bir AAA ve hemodiyaliz hastası sunulmuştur.

ANAHTAR SÖZCÜKLER: Kolşisin, Rabdomiyoliz, Böbrek yetmezliği

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease affecting mainly the ethnic groups originating from the Mediterranean basin. FMF is caused by mutations in the MEFV gene coding for pyrin, which is a component of inflammasome functioning in the inflammatory response. The clinical presentation usually consists of recurrent attacks of fever and serosal inflammation. End stage renal disease due to secondary AA type amyloidosis is the major cause of morbidity and mortality in patients with FMF (1). Colchicine is a kind of anti-inflammatory drug that is largely used in the treatment of patients with FMF. Colchicine affects the motility of neutrophils, which is crucial for their extravasation in response to inflammatory stimuli. Colchicine is metabolized via the enzyme CYP3A4 and is transported by P-glycoprotein. At therapeutic dosages, it is well tolerated, except for moderate gastrointestinal disturbances (2). Long-term administration of colchicine reduces FMF attacks and prevents amyloidosis development (3). Rhabdomyolysis is one of the important adverse effects of the colchicine that may occur at toxic doses due to drug interactions and kidney or liver failure (4). We describe the case of rhabdomyolysis in a hemodialysis patient with FMF under colchicine treatment after co-administration of clarithromycin for pneumonia.

CASE REPORT

A 55-year-old male patient with FMF who has been under hemodialysis for 7 years was admitted to our hospital for generalized myalgia and weakness. He had a known history of chronic kidney disease with

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unknown etiology, hypertension, chronic obstructive pulmonary disease, familial Mediterranean fever and ankylosing spondylitis. Kidney biopsy had not been performed due to fibrotic kidneys on the initiation of renal replacement therapy seven years ago. His medication included pregabalin 75 mg once daily (due to neuropathic pain for a year), calcium acetate 1000 mg twice daily, etanercept 25 mg twice weekly, and colchicine 0.5 mg once daily. The patient had recently been diagnosed with pneumonia and was prescribed clarithromycin 500 mg once daily ten days ago. Etanercept had been discontinued due to infection.

He was hemodynamically stable and afebrile. Cardiovascular and abdominal examination was unremarkable. Pulmonary examination revealed basilar wheezes, and ronchi. The neurological examination revealed that the upper and lower extremities had tender muscles with muscle weakness of lower extremities (grade 3/5). Deep tendon reflexes were diminished on the upper extremities and were absent on the lower extremities.

Laboratory studies revealed hemoglobin 11.4 g/dL (14-18 g/dL), leucocyte count 4.97 x 106/L (4.8-10.7/L), platelet count 132 x 109/L (130-400/L), blood urea nitrogen was 56.0 mg/dL (6-20 mg/dL), creatinine 8.79 mg/dL (0.7-1.2 mg/dL), aspartate aminotransferase 603 U/L (0-40 u/L), alanine aminotransferase 268 U/L (0-41 u/L), creatine phosphokinase 8595 U/L (39-308 u/L), creatine kinase-MB 198 U/L (-<25 u/L), and high-sensitive cardiac troponin T 0.194 ng/ml (0-0.014 ng/mL). Urine analysis could not be performed because the patient was anuric. Serum thyroid stimulating hormone level was within normal range. Hepatitis testing was positive for Anti-HCV. The quantitative HCV RNA test was negative. Hepatobiliary ultrasound was normal. Investigations and in particular serologies for HIV, Brucella, CMV, and EBV ruled out an infectious process. Electroneuromyography revealed significant bilaterally sensorimotor neuropathy on the lower extremities. He was diagnosed with colchicine-induced rhabdomyolysis caused by interaction with clarithromycin. Colchicine was discontinued. The patient was followed by routine dialysis and subsequently recovered without treatment in two weeks. During follow-up, the patient's transaminases and CPK returned to normal levels (Figure 1).

DISCUSSION

After development of end stage renal disease due to amyloidosis secondary to FMF, most patients still need to continue colchicine to prevent FMF attacks and also halt the progression of amyloid deposition in the tissues (2). However, the daily colchicine dose should be reduced in patients with renal insufficiency and they should also be carefully followed-up in terms of potential drug interactions and colchicine toxicity (5).

Colchicine is mainly metabolized in the liver by CYP3A4 enzymes and eliminated by p-glycoprotein through bile excretion. In addition, 10-20% of the colchicine metabolites are eliminated by kidney (2,3). Inhibition of both CYP3A4 enzyme and P-glycoprotein such as with cyclosporine or clarithromycin can increase the colchicine dose excessively due to dual blockade and adverse effects are seen more commonly with drug-drug pharmacokinetic interactions (6). Rhabdomyolysis is one of the important adverse effects of colchicine toxicity and typically presents with fever, fatigue and muscle weakness and tenderness (7). Colchicine-induced rhabdomyolysis has also been observed in patients with preexisting in renal or liver failure (8). In addition, colchicine-induced problems have been well documented in

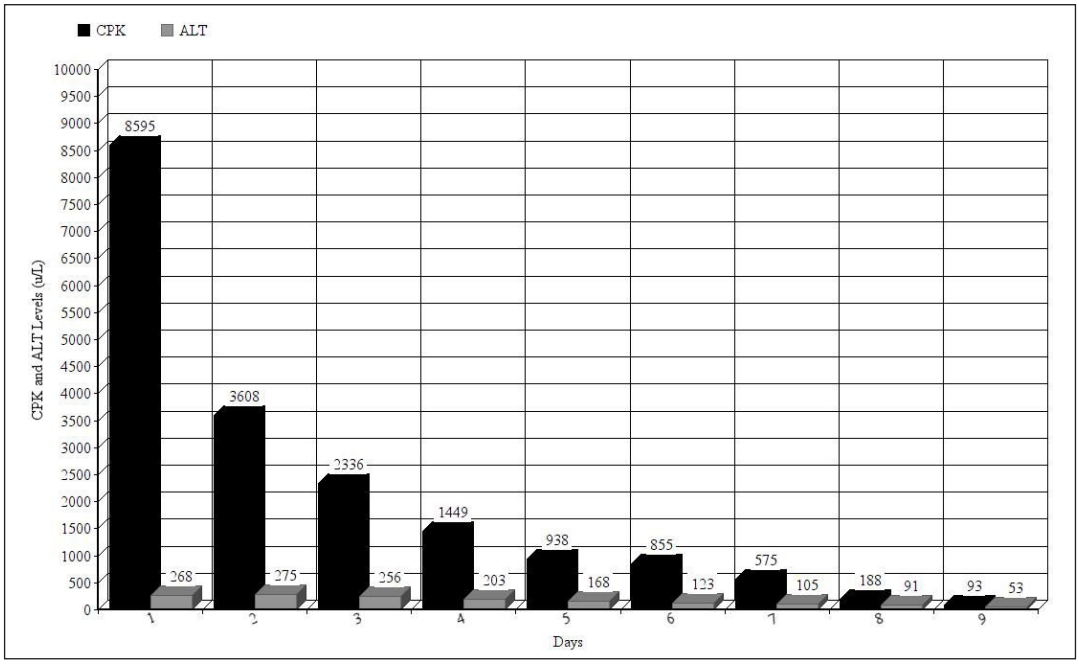

Figure 1: *CPK and ALT concentrations during follow-up of the patient with rhabdomyolysis due to colchicine-clarithromycin interaction.*
CPK: *creatine phosphokinase,* ***ALT:*** *alanine aminotransferase.*

several case reports specifically with concomitant use of fibrate, gemfibrozil, statins, cyclosporine and clarithromycin (9). Hung et al. retrospectively analyzed 116 patients who were prescribed clarithromycin and colchicine during the same clinical admission in terms of toxicity. They concluded that, clarithromycin increases the risk of fatal colchicine toxicity, especially for patients with renal insufficiency and presenting with severe pancytopenia. Cessation of colchicine and clarithromycin resulted in recovery in many patients (10). Kato et al. reported a case of pregabalin- and azithromycin-induced rhabdomyolysis with purpura. In that case, patient was also using fenofibrate, hence the drug interaction between fenofibrate and azithromycin might be responsible for the clinical scenario. It was reported that azithromycin increases the bioavailability of ivermectin, for which the transporter is CYP34A. This report is suggestive of a drug interaction between azithromycin and statins. Pregabalin does not inhibit hepatic metabolism or cytochrome P450 metabolism. It is not known whether the combination of pregabalin and azithromycin increases the risk of rhabdomyolysis. Morevoer, rhabdomyolysis associated with azithromycin or pregabalin monotherapy is very rare. (11). However, it has been reported that the pregabalin and statin interaction may induce rhabdomyolysis (12). In our case, the patient recovered by cessation of colchicine and clarithromycin. In addition, neither pancytopenia nor purpura was observed during follow-up. The patient has continued the pregabalin medication for neuropathic pain. Pregabalin-induced rhabdomyolysis may be included in the differential diagnosis of the patient, if clinical improvement has not been achieved.

Colchicine is an important drug in the treatment of patients with FMF; physicians should be alert prescribing medications to these patients especially if they have renal dysfunction, since results could be fatal.

Compliance with Ethical Standards

- The authors have declared that no conflict of interest exists.
- This article does not contain any studies with human participants or animals performed by any of the authors.
- Informed consent was obtained from the patient in this case report.

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