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A case of rhabdomyolysis after atorvastatin therapy of a liver transplant recipient receiving immunosuppressive therapy with cyclosporine

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Abstract

Rationale. *To date, liver transplantation is the most effective method of treating end-stage liver failure, and therefore this treatment has become widespread throughout the world. However, due to the improvement in the quality of transplant care and an increase in the long-term survival of patients, the development of concomitant pathology, which often requires medical treatment, is inevitably associated with a higher life expectancy of liver transplant recipients. Thus, in patients who underwent liver transplantation, there is. a significant increase in the incidence of dyslipidemia. However, a long-term immunosuppressive therapy in organ transplant patients can adversely modify the effect of the prescribed*

drugs, which requires careful monitoring and consideration of drug interactions.

Purpose. *Using a clinical example to demonstrate the importance of taking drug interactions into account in the treatment of patients after organ transplantation receiving immunosuppressive drugs.*

Material and methods. *In the presented clinical case, a patient after orthotopic liver transplantation performed in 2005 underwent a staged treatment of cicatricial stricture of choledochal anastomosis in the City Clinical Hospital n.a. S.P. Botkin. During the following hospitalization, the patient complained of minor muscle pain when walking. At doctor's visit 3 weeks before hospitalization, a local physician prescribed therapy with atorvastatin 10 mg per day due to an increase in blood plasma cholesterol levels. The patient underwent removal of the self-expanding nitinol stent. During the follow-up examination, the patient had no evidence of an impaired bile outflow, however, muscle pain and weakness progressively increased, the rate of diuresis decreased, and in the biochemical analysis of blood there was an abrupt increase in the concentration of creatinine, aspartate aminotransferase, alanine aminotransferase. Atorvastatin was canceled, a diagnosis of acute non-traumatic rhabdomyolysis was established, treatment with hemodialysis and plasma exchange was started on 03/05/2020. The last session of renal replacement therapy was 03/30/20.*

Results. *With the restoration of the diuresis rate, there was a spontaneous decrease in the level of creatinine to 170 μmol/L. The patient was discharged with satisfactory renal and hepatic function. The pain syndrome completely resolved.*

Conclusion. *Drug interactions between atorvastatin and cyclosporine have resulted in acute rhabdomyolysis with life-threatening consequences. This once again confirms the importance of taking drug*

interactions into account when managing patients after solid organ transplantation.

Keywords: liver transplantation, rhabdomyolysis, atorvastatine, cyclosporin

Conflict of interests Authors declare no conflict of interest

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ALT, alanine aminotransferase

AST, aspartate aminotransferase

CPK, creatine phosphokinase

RRT, renal replacement therapy

Introduction

At the current stage of medicine development, the problem of irreversible liver damage in patients with chronic liver failure might be solved by performing donor liver transplantation in such patients [1, 2]. In patients undergoing liver transplantation, postoperative monitoring demonstrates a significant increase in the incidence of dyslipidemia [3, 4]. With elevated cholesterol and triglyceride levels, statins are the first-line therapy ensuring a good tolerability and having a proven efficacy in patients after liver transplantation [5]. According to the Guidelines of the European Society of Cardiology, the first-line treatment for hyperlipidemia in patients undergoing organ transplantation is the

administration of low-dose statins with constant monitoring of possible drug interactions. The likelihood of developing a potentially significant drug interaction is the highest when statins and cyclosporine are used simultaneously; tacrolimus is also metabolized with the CYP3A4 involvement, but this drug is less likely apt than cyclosporine to dangerous drug interactions with statins. The risk of drug interactions is also lower when using fluvastatin, pravastatin, pitavastatin, and rosuvastatin [6]. Complications of statin therapy include: statin-associated muscle symptoms, new cases of diabetes melitus, insulin resistance, the impact on liver function, hemorrhagic strokes, and cancer. Muscle symptoms include myalgia, myopathy, myositis, myonecrosis, and rhabdomyolysis [7]. The incidence of rhabdomyolysis ranges from 0.44 to 0.54 cases per 10,000 people per year [8]. The pathogenesis of rhabdomyolysis has not been studied well enough. The role of a decreased level of the ubiquinone coenzyme in muscle tissue and the vitamin D deficiency, which lead to a decreased activity of mitochondrial respiratory chains, and consequently to an impaired energy production, and muscle protein degradation, is under discussion [9]. Mortality in rhabdomyolysis reaches 10% and significantly increases if the renal failure is added [10]. The most common cause of death is cardiac arrhythmia due to hyperkalemia.

Most of the statins are metabolized in the liver through the cytochrome P450 pathway with the involvement the CYP3A4 isoenzyme. Therefore, the simultaneous use of statins with CYP3A4 inhibitors may increase the plasma concentration of statins and raise the risk of side effects.

About 97% of liver transplant recipients are discharged from the hospital with recommendations for taking calcineurin inhibitors [11]. Cyclosporine and tacrolimus inhibit CYP3A4, so their simultaneous use

with statins can provoke the development of side effects. There have been isolated cases of rhabdomyolysis reported after liver and kidney transplantation in foreign and home literature [12, 13].

We present our case report of acute rhabdomyolysis that developed in a liver transplant recipient who had been on a long-term immunosuppressive therapy with cyclosporine.

Clinical case report

Patient A., 44 years old, underwent orthotopic liver transplantation in 2005. In the postoperative period, the patient developed a cicatricial stricture of biliary, for which he received a step-by-step treatment in the City Clinical Hospital named after S.P. Botkin. The following planned hospitalization was scheduled on 26.02.2020; at the time of admission, the patient complained of minor muscle pain when walking. When questioning the patient, we found out that 3 weeks before hospitalization, the therapist in the local clinic at the place of residence had prescribed therapy with atorvastatin, 10 mg per day, for increased plasma cholesterol. The patient underwent removal of a self-expanding nitinol stent. The postoperative course was uneventful. During the control examination (abdominal ultrasonography, magnetic resonance cholangiopancreatic imaging), there were no findings of bile flow impairments in the patient. However, muscle pain and weakness progressively increased, and the diuresis rate decreased. A control blood test showed an acute increase in the creatinine concentration, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine phosphokinase (CPK) activities, and myoglobin content (Table 1).

Table 1. Patient's laboratory data

Date	27.02	4.03	5.03	6.03	6.03	7.03	7.03	8.03	8.03	9.03	10.03	10.03	11.03	12.03	14.03
Creatinine, mcmol/L	114	360	Hemodialysis	557	Hemodialysis, plasma exchange	587	Hemodialysis	539	Hemodialysis, plasma exchange	587	323	Hemodialysis, plasma exchange	587	Hemodialysis, plasma exchange	516
AST, U/L	35	1 489		1 425		1165		1194		956	674		357		62
ALT, U/L	55	237		286		251		307		285	168		124		83
CPK, U/L	—	114 931		137 229		—		129 400		97 700	52 000		2 943		205
Myoglobin, mcg/L	—	12 800		157 562		163 800		216 140		145 236	60 330		9 572		265

Atorvastatin was discontinued, a conservative therapy was initiated, which was ineffective due to occurred anuria and increased blood K^+ levels (6.7 mmol/L). On the basis of medical history, clinical symptoms (progressive muscle weakness), and laboratory study results (an acute increase in the blood levels of CPK and myoglobin), the diagnosis of acute non-traumatic rhabdomyolysis and acute renal failure was made; the renal replacement therapy (RRT) was initiated, plasmapheresis with albumin and plasma replacement in a ratio of 1/3 with the replacement of 1 volume of circulating plasma at a session. In the first 4 days of treatment for acute rhabdomyolysis, daily 6-hour hemodialysis sessions were required due to a rapidly increasing plasma K^+ concentrations. Plasma exchange sessions were performed every other day, but despite that, there was an increase both in the concentration of blood plasma myoglobin (from 12,800 mcg/L to 216,140 mcg/L) and in CPK activity (from 114,931 U/L to 137,229 U/L). From the 5th day of treatment, a gradual decrease in these parameters was recorded with a simultaneous decrease in pain syndrome in the patient (Table 1). In total, 4 plasma exchange sessions were performed. The last RRT session was held on 30.03.2020, then, on restoring the rate of diuresis, a spontaneous decrease in creatinine level to 170 mcmol/L was recorded.

The patient was discharged home with satisfactory renal and hepatic functions. The pain syndrome was completely stopped. The length of hospital stay was 49 days.

Discussion

Orthotopic liver transplantation is the only method of treating the liver cirrhosis of various etiologies with an impaired organ function and the development of chronic or acute liver failure [14]. By 2018, 2,632

liver transplants had been performed in the Russian Federation. Over the recent 5 years, the number of operations has increased more than twice (from 1,150 in 2013 to 2,632 by 2018). This figure is expected to grow in the future [15]. With constantly increasing life expectancy of liver transplant recipients, there may arise the risk of a concomitant pathology development in them, which often requires medical treatment. However, the administration of an additional drug in a standard dosage in patients undergoing immunosuppressive therapy may lead to undesirable drug interactions and result in the development of severe side effects, which in some cases can threaten patient's life [16]. Reviewing the literature data, one can assume that in the described case, the cyclosporine inhibition of CYP3A4 led to a decrease in atorvastatin metabolism and an increase in its plasma concentration, which, in turn, led to a decreased level of ubiquinone in muscle tissue and acute rhabdomyolysis. Having agreed upon the administration an additional drug therapy with the transplant center will help to reduce the number of undesirable drug interactions.

The patient's stay at the time of acute rhabdomyolysis in a transplant center, where all the necessary resources are available to treat this complication, made it possible to immediately start treatment and achieve the patient recovery.

Conclusion

Reduced atorvastatin metabolism against cyclosporine therapy resulted in acute rhabdomyolysis with life-threatening consequences. This once again confirms the importance of careful consideration of possible drug interactions in patients after solid organ transplantation.

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