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A case of drug-induced myopathy in alcoholic cirrhosis caused by voriconazole

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Abstract – BACKGROUND: Voriconazole is a new generation of broad-spectrum antifungal agents commonly used in the treatment of invasive aspergillus infections.

CASE REPORT: We reported a rare case of myopathy induced by voriconazole, which showed severe muscle pain and significantly elevated myocardial enzymes. Enzymes eventually achieved good efficacy by switching voriconazole to micafungin and the use of L-carnitine.

CONCLUSIONS: This reminded us it was necessary to be vigilant for rare adverse reactions of voriconazole in the population with liver dysfunction, the elderly population, and people with multiple underlying diseases in clinical practice. During medication of voriconazole, close attention should be paid to the occurrence of adverse reactions to avoid life-threatening complications.

Key Words:
Voriconazole, Drug induced myopathy, Alcoholic cirrhosis, Counteraction.

Introduction

Voriconazole belonged to a new generation of triazole broad-spectrum antifungal agents and it was mostly used for the treatment of severe infections caused by invasive *Aspergillus, Fusarium,* and *Scedosporium*, as well as severe invasive infections caused by fluconazole-resistant *Candida* species, and candidemia without neutropenia reduction[1-3]. In clinical practice, voriconazole is a drug with good safety and tolerance. Common related adverse reactions of voriconazole include respiratory dysfunction, visual disturbance, abdominal pain, liver dysfunction, peripheral edema, drug-induced rash, vomiting, fever, headache, nausea, and diarrhea, which were generally considered mild and did not lead to discontinuation[4,5]. We reported that patients with cirrhosis developed severe voriconazole-related myopathy. Therefore, it was necessary to be vigilant for rare adverse reactions of voriconazole in the population with liver dysfunction, the elderly population, and people with multiple underlying diseases in clinical practice. During medication of voriconazole, close attention should be paid to the occurrence of adverse reactions to avoid life-threatening complications.

Case Report

A 46-year-old male was admitted to our hospital on February 9, 2022, complaining of fatigue with yellow urine for more than 1 year, aggravation with icteric sclera for 2 days, and fever for 1 day. After drinking heavily in September 2020, this patient was admitted to another hospital and developed fatigue, anorexia, and yellow urine. Liver function examination showed that γ-glutamyltransferase (GGT) was 1717U/L, alanine aminotransferase (ALT) was 80.4 U/L, aspartate aminotransferase (AST) was 243.2U/L, and total bilirubin (TBIL) was 107 μmol/L. Abdominal ultrasound findings showed splenomegaly and fatty liver. The patient was diagnosed with "alcoholic cirrhosis" and treatment of liver protection and jaundice reduction with unknown details was given. After treatment, the patient was discharged after amelioration of symptoms. Later, the patient visited the above hospital intermittently due to bilirubin elevation and was given liver protection, jaundice reduction and hormone pulse. The details are unknown. On January 19th, 2022, the patient went out of the hospital again for abnormal liver function. Magnetic resonance imaging (MRI) and diffusion-weighted imaging (DWI) of the upper abdomen were performed, and the diagnosis was "sclerosing cholangitis" combined with clinical symptoms. The patient got better after receiving methylprednisolone pulse therapy and was discharged after taking oral steroids. On February 7, 2022, the patient

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felt that scleral jaundice was aggravated, accompanied by cough and yellow purulent sputum. The body temperature gradually increased with a maximum temperature of 38.1°C. Outside laboratory results showed albumin (ALB) 35 g/L, ALT 41 U/L, AST 48 U/L, TBIL 384.52 μmol/L, direct bilirubin (DBIL) 317 μmol/L, prothrombin time activity (PTA) 51%, ammonia 2.7 μmol/L, platelet (PLT) 81×10^9/L, white blood cell (WBC) 13.11×10^9/L, white blood cell (HGB) 101 g/L and neutrophil (NE)% 84%. Computed Tomography (CT) showed micronodules in bilateral lower lung, multiple patchy consolidation shadows in bilateral lung, abdominal effusion, gallbladder wall thickening and cholecystitis. The patient was given piperacillin tazobactam sodium and moxifloxacin hydrochloride for anti-infection treatment for 3 days in outside hospital, but the effect was poor. So, the patient presented to our hospital with a diagnosis of alcoholic cirrhosis, decompensated cirrhosis, sclerosing cholangitis, lung infection, portal hypertensive gastropathy, and abdominal effusion.

Admission physical examination results showed that the proximal and distal muscle strength of both upper and lower limbs was grade 5, muscle tension of the limbs was normal, sensation of shallow and deep was normal, tendon reflex of the limbs was symmetrical, bilateral Babinski sign (-). After admission, the results of laboratory examination showed that white blood cells were 14.25×10^9/L, platelets were 54×10^9/L, norepinephrine was 88.5%, HGB was 86 g/L, lymphocyte (LYM) was 4.8%, albumin was 27.87 g/L, aspartate aminotransferase was 29 U/L and alanine aminotransferase was 25 U/L. Butyl imide 330.08 μmol/L, TBIL 377.45 μmol/L, and glutamyltransferase (GGT) 36 UCT results showed that bilateral lung changes, whole heart and abdominal effusion were the result of (1-3) -β-D glucan test (G test) was >600 pg/mL and the result of galactomannan test (GM test) was 0.415 ug/L. Sputum culture showed Gram-negative bacilli. CT findings showed double pneumonic changes not excluded, full heart, and abdominal effusion. Considering the previous history of heavy glucocorticoid use combined with the laboratory results, the patient was diagnosed with invasive fungal pneumonia.

Patient was treated with hepatoprotective therapy (specific drugs: acetylcysteine, adenosylmethionine succinate, compound glycyrrhizin), anti-infection therapy (specific drugs: voriconazole, moxifloxacin, piperacillin) and ambroxol expectorant symptomatic therapy. Beginning on February 11, 2022, voriconazole was administered at 200 mg intravenously every 0.5 days. After the above treatment, the symptoms of cough and expectoration were significantly relieved than before, and the results of blood routine showed that the infection was controlled (Table I).

On February 23, 2022, the patient gradually developed muscle weakness and progressive aggravated pain in the lower back, neck, shoulder, and limbs. On February 25, 2022, the patient showed a further obvious decrease in muscle strength, increased pain and was unable to stand. Patients can't cooperate with head-down test, head-turning test or head-front rotation test. Physical examination results showed that the proximal and distal muscle strength of both upper limbs were grade 3, the proximal and distal muscle strength of both lower limbs were grade 3-, and the muscle tone of the limbs was normal. Bone and joint related diseases were excluded by no abnormalities on CT examination. The patient refused muscle biopsy. The laboratory parameters were reexamined on February 25, 2022, and the results showed that ALB was 33.64 g/L, ALT was 55 U/L, AST was 197 U/L, ALP was 83 U/L, GGT was 29 U/L, TBIL was 357.95 μ mol/L, DBIL was 322.09 μ mol/L, CK was 1661.5U. LDH 383.24 U/L, HBDH 377. Considering the slight increase of transaminase and myocardial enzyme series in patients, drug-induced myopathy is not excluded. voriconazole for injection was discontinued and changed to micafungin for continued antifungal therapy. L-carnitine was used to improve myalgia and muscle weakness and prevent myocardial injury, and the specific usage was 2 g intravenously once daily. Additio-

Table I. Changes in percentage of WBC, NEUT, LYM.

	Day 0	Day 10	Day 15	Day 22	Day 27	Day 32
WBC×10^9/L	14.25	7.39	5.59	5.37	5.17	5.55
NEUT %	88.5	68.9	68.9	65.4	61.7	63.1
LYM %	4.8	19.6	19.6	19.4	24.7	21.1

White blood cell (WBC); Neutrophil (NEUT); Lymphocytes (LYM).

nally, the patient was given intravenous drip of sodium bicarbonate to correct acidosis, and the remaining treatment regimen was the same as before. Two days later, the patient's muscle soreness gradually resolved. During the subsequent treatment, the patient's indicators of infection and myocardial enzyme series gradually returned to normal levels (Tables I-II), and re-examination of lung CT on March 14, 2022, showed significant absorption of inflammation. The muscle strength of the patient's limbs gradually returned to normal (Table III).

Discussion

Invasive aspergillosis was a critical opportunistic deep fungal infection, and voriconazole was the drug of choice for the treatment of invasive aspergillus infections[6,7]. The patient had decompensated liver cirrhosis and decreased immune function due to long-term steroid use. He was diagnosed with aspergillus lung infection and was treated with voriconazole. On the day 13, the patient, who was suspected "drug-related myopathy", gradually became more and more painful in the muscles of the back, neck, shoulders, and limbs, and on the 15th day, the series of myocardial enzymes increased significantly. After stopping voriconazole for 2 days, the symptoms of muscle soreness were gradually relieved, and all muscle enzyme parameters decreased to normal on the 17th day. The patient had no previous history of myopathy, and myopathy was considered to be related to the use of voriconazole in combination with the course of the disease. Drug-induced myopathy is a known type of adverse reaction to voriconazole, and related cases have previously been reported in the literature[8,9]. After the patient developed symptoms such as myalgia, decreased muscle strength, and increased muscle enzyme series, we stopped voriconazole and switched to the treatment of micafungin + L-carnitine. After 2 days of treatment, the symptoms of myalgia began to resolve, and myocardial enzymes gradually returned to normal. Repeated chest CT on Day 32 showed lung inflammation was significantly absorbed than before.

Other hepatoprotective drugs and ambroxol are chronic drugs, and the transaminase parameters are slightly increased, which excludes the possibility of myopathy and disease progression caused by other drugs. According to Karch-Lasagna method[10], the causality assessment of adverse drug reaction should meet the following requirements: (1) there is a reasonable temporal relationship; (2) it meets the known adverse reaction type; (3) adverse reaction is relieved after drug withdrawal; (4) there is no other explanation. We evaluate this presence as likely due to the use of voriconazole in this case.

Table II. Changes in cardiac enzymes series.

	Day 0	Day 10	Day 15	Day 22	Day 27	Day 32
CK	40.5	93.5	1661.5	549.5	66.8	26
CKMB	38.21	18.36	46.94	22.14	7.68	15.36
LDH	175.67	181.7	383.24	346.33	261.39	202.8
HBDH	145.56	151.53	377.98	352.01	262.56	182.47

Creatine kinase (CK); Creatine kinase MB (CKMB); Lactate dehydrogenase (LDH); Hydroxybutyrate dehydrogenase (HBDH).

Table III. Changes in symptoms.

	February 11	February 23	February 25	February 27	March 14
Treatment plan	Start using voriconazole	Voriconazole	Voriconazole was replaced by micafennet and start using L-carnitine	Voriconazole + L-carnitine + sodium bicarbonate	Stop using L-carnitine
Symptoms	No symptoms of myalgia or muscle weakness	Muscle pain of lumbar back, neck, shoulder, limb aggravated	The patient is unable to stand and has significantly reduced muscle strength in his extremities Bow test, turn to look at the object test, head bending rotation test cannot cooperate.	The muscle pain gradually decreased	Myalgia disappeared completely, and muscle strength and tension of the limbs returned to normal

However, due to the unrepeatability of the cases, we could not verify them again.

Conclusions

In this case report, patient with suspected voriconazole-related myopathy who presented with muscle soreness and elevated myocardial enzymes eventually achieved good efficacy by stopping treatment of voriconazole and the use of micafungin and L-carnitine. This reminded us that drug-induced myopathy is a non-negligible adverse effect of voriconazole. In the application of voriconazole, we should monitor plasma concentrations, pay attention to whether the patient has the symptoms of myalgia and decreased muscle strength, and pay attention to the changes in myocardial enzymes and liver function to guard against the occurrence of serious adverse reactions of myopathy. Timely replacement of the treatment regimen could effectively control the development of voriconazole-related myopathy.

Informed Consent

Patient signed an informed consent for the publication.

Conflict of Interest

All authors have no conflict of interest.

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