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CASE REPORT

Successful Treatment of Intractable Tuberculous Peritonitis in a Woman with Chronic Kidney Allograft Dysfunction Using Contezolid Containing Regimen

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Abstract: Tuberculosis(TB) is a serious infection that affects transplant recipients, particularly in high TB burden countries. Clinical presentation of these patients is atypical, and the care and management are frequently tricky as multi-drug interaction and intolerable adverse effects. Contezolid, a novel oxazolidinone antibacterial agent, had been demonstrated to be effective for TB in vitro and had been shown in some clinical cases with a more favorable safety profile than linezolid, the first-generation oxazolidinone, which had a commonly seen myelosuppression and neuropathy. Additionally, Contezolid has a unique metabolic mechanism that leads to less drug interaction. Here, we report a case of multi-system TB in a transplant recipient with chronic kidney allograft dysfunction. She was intolerant to most first and second-line anti-TB drugs and repeatedly developed ascites and nocturnal low-grade fever. She finally achieved good efficacy and safety results after enhanced anti-TB treatment with the addition of contezolid. Given the increased risk of TB in patients with organ transplantation and multi-drug interaction in patients with severe comorbidities, further clinical studies are needed to investigate the application and appropriate dosage of contezolid in patients with active TB.

Keywords: tuberculosis, contezolid, kidney dysfunction, kidney transplantation, tuberculous peritonitis

Introduction

The management and care of tuberculosis(TB) in organ transplantation recipients is challenging. Recipients are more likely to develop disseminated TB and experience more atypical clinical symptoms, more significant treatment-related toxicity, and more unfavorable outcomes than the general population.[1]

Contezolid (Youxitai ®) is an orally administered novel oxazolidinone antibiotic developed in China.[2] It has been mainly used to treat complicated gram-positive bacteria infections.[3–5] Several vitro studies also demonstrated bactericidal activity against *Mycobacterium tuberculosis*.[6,7] Recent clinical case reports also indicate it is effective for active tuberculosis, with a lower incidence of toxic adverse effects such as bone marrow suppression and neurotoxicity than the first-generation product linezolid.[8–10] Furthermore, previous studies have indicated that Contezolid does not require dose adjustment in patients with mild to moderate renal impairment,[11,12] but data on its use in patients with severe renal impairment is currently lacking. Only a case demonstrated its safety in short-course anti-bacterial infection in patients with continuous renal replacement therapy via hemodialysis.[13] As a novel agent with a unique metabolism mechanism, it has been proven to have little interaction with other medicines.[14] However, its application and safety evidence in different clinical scenarios still need more clinical data to support it.

Here, we report a case of multi-system TB in a middle-aged woman with chronic kidney allograft dysfunction. The patient presented with recurrent intractable tuberculous ascites and multi-drug intolerance, which was solved by an

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enhanced anti-TB regimen with contezolid later. We hope to provide a reference for future anti-TB treatment and research, particularly for patients with severe comorbidities.

Case Description

A 54-year-old woman was transferred to our hospital on 18 May 2023. She underwent kidney transplantation 8 years ago and had been taking tacrolimus twice daily(2 mg at 8 AM, 1.5 mg at 8 PM), mycophenolate mofetil twice daily (360 mg at 8 o'clock, 180 mg at 20 o'clock), and methylprednisolone 8 mg daily for immune suppression. She started to develop intermittent fever, abdominal distension, and night sweating two months ago and was admitted to the local hospital. Routine blood test showed white blood cell(WBC) 4.23*10^9/L, Hemoglobin (Hb) 76g/L, Platelets (PLT) 161*10^9/L; Blood albumin(ALB) 25g/L, Creatinine(Cr) 167 mmol/L, estimated glomerular filtration rate (eGFR) 25.34mL/min (eGFR was calculated according to CKD-EPI equation). Ascites was detected on ultrasound. Chest tomography (CT) shows scattered path on both lung and left pleural effusion (Figure 1). Left thoracentesis was performed. The lab results of pleural effusion were listed below: total leukocytes 0.677*10^L, monocytes 61%, polymorphonuclear cells 39%; total protein 24g/L, adenosine deaminase 7.6U/L, lactate dehydrogenase 155U/L, glucose 6.45 mmol/L; GeneXpertMTB/RIF for pleural effusion was positive and the detection level was "Very Low" with no rifampicin resistance detected. The culture for *M. tuberculosis* of pleural fluid was positive; further drug susceptibility tests showed that the strain was susceptible to first and second-line drugs for TB. Her peripheral blood was also sent for metagenomic Next-generation sequencing (mNGS), and 2 *M. tuberculosis* complex DNA sequences were detected. She was diagnosed with multi-system TB.

The initial anti-tuberculosis treatment regimen was isoniazid 300mg, rifabutin 150mg, moxifloxacin 400mg, and linezolid 600mg once daily, ethambutol 750mg every other day. Her body temperature returned to normal after 3 days of treatment. But 10 days later, she developed fatigue, and a routine blood test showed WBC 0.67*10^9/L, Hb 62g/L, and PLT 21*10^9/L. Severe myelosuppression was observed, and all anti-TB drugs were temporarily stopped. She received therapy for elevating WBC and PLT, and a repeated blood routine test a week later showed blood cells elevated: WBC 3.24*10^9/L, Hb 82g/L, PLT 157*10^9/L. Anti-TB drugs were restarted one by one. Pyrazinamide 1000mg every other day was tried but stopped soon as she appeared to have nausea, vomiting, and stomach upset. Moxifloxacin 400mg every day was tried, but she reported insomnia, and moxifloxacin was temporarily stopped. Cycloserine was also intolerable because of psychiatric symptoms. Her abdominal distension worsened, and repeated ultrasound showed an increased volume of ascites. She was then transferred to our hospital for further care.

On admission in our hospital, body examination showed her height was 155 cm and weight 40 kg. There is no obvious abnormality in the heart and lungs. There was abdominal tenderness, rebound pain in the whole abdomen, and positive ascites sign. A routine blood test showed WBC 8.03*10^9/L, Hb 89g/L, PLT 164*10^9/L; ALB 34.2g/L, Cr 215 umol/L, eGFR 21.79mL/min, and the concentration of tacrolimus drug 13.7ng/mL; Ascites drainage was performed and ascites test were showed as: WBC 203*10^6/L, and the percentage of single nucleated cells 96.6%, total protein 26.5g/L, ADA 3U/L, LDH 86U/L; TB-DNA and tuberculosis culture of ascites were all negative. The drainage volume of ascites was recorded. Isoniazid 300mg once daily, rifapentine 450mg twice a week, and moxifloxacin 400mg were given for

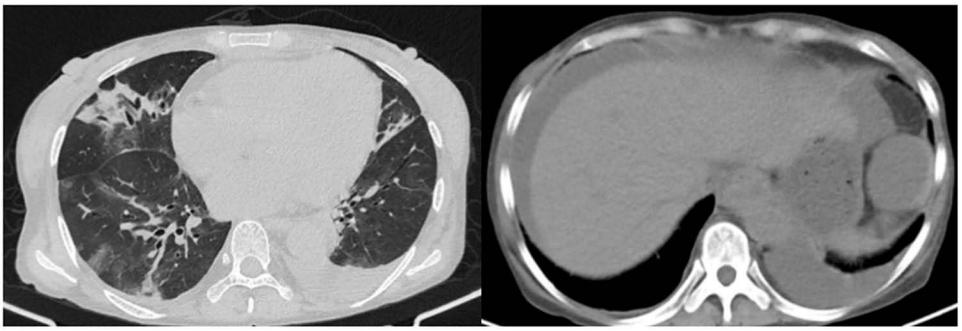

Figure 1 Chest CT showed scattered patchy in both lungs, enlarged heart, pleural effusion and ascites.

anti-tuberculosis treatment, with intravenous albumin supplementation and strengthening of enteral nutrition. She was well tolerant of these three anti-TB drugs. Chest CT showed that the lung and pleural effusion path were gradually absorbed. However, the patient repeatedly developed a nocturnal low-grade fever and ascites (Figure 2). The drainage of ascites was repeatedly performed to relieve the symptoms. After five weeks of three-drug regimen treatment, we attempted to add Linezolid(Lzd) 300 mg once daily to enhance anti-TB treatment. But she developed thrombocytopenia again, and Lzd was permanently stopped. Lzd 300 mg once daily was only used for two weeks. Her ascites and intermittent nocturnal low-grade fever persisted. On July 25, contezolid(Czd) 400mg twice daily (every 12 hours) was added to strengthen anti-tuberculosis treatment. We found that her body temperature returned to normal, and her ascites gradually decreased and completely disappeared after 3 months of treatment (Figure 2). Her abdominal distension was significantly relieved, and she could perform general work and life. During the treatment with Czd, the routine blood test returned to normal, with no myelosuppression observed (Figure 3). The creatine was stable, and tacrolimus concentrations did not fluctuate (Figure 4). As of press time, her anti-TB treatment is completed and she is now living a normal life.

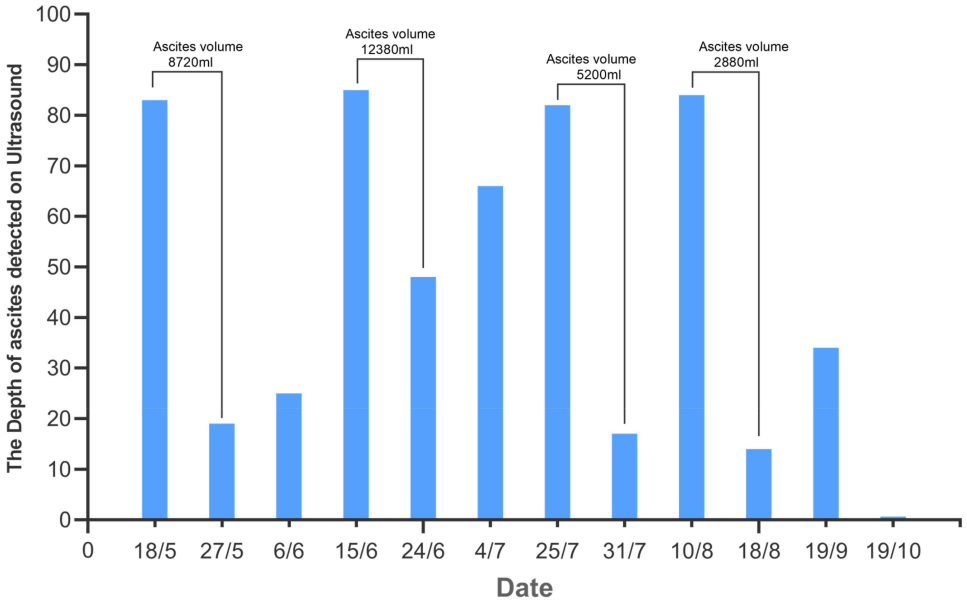

Figure 2 The change of ascites volume detected on Ultrasound during the treatment.

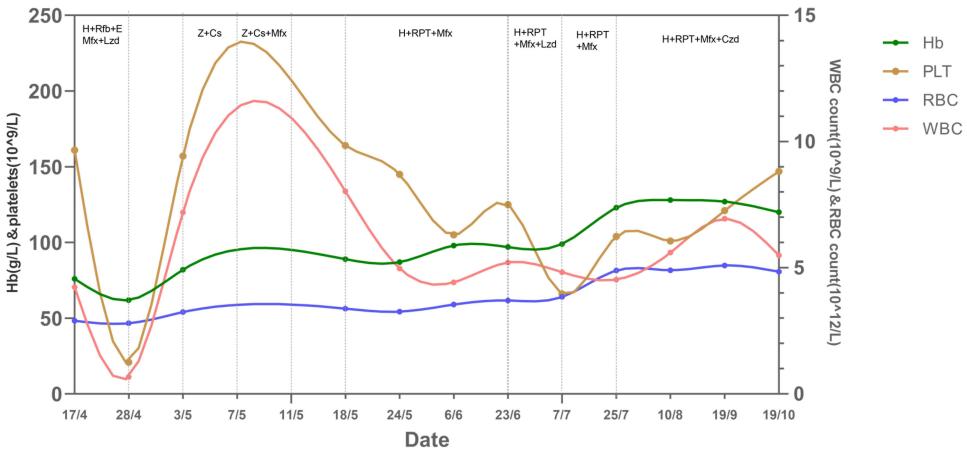

Figure 3 The change of hematologic parameters during treatment.

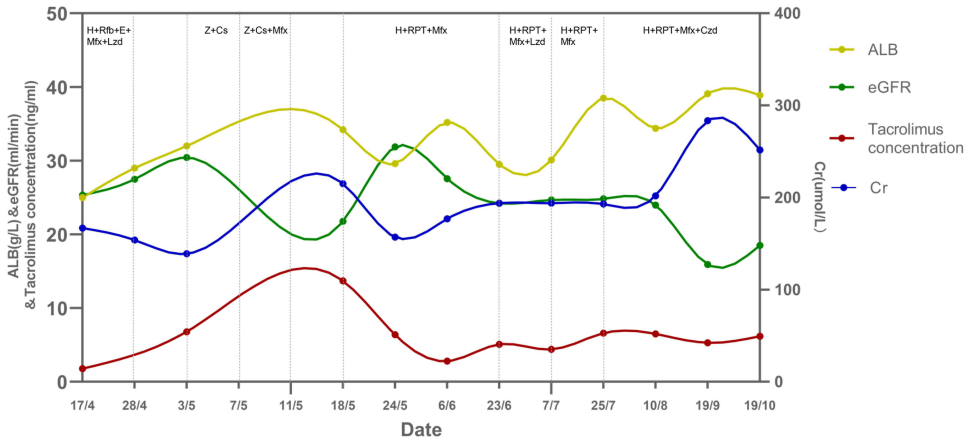

Figure 4 A timeline of treatment and clinical events with laboratory parameters.
Abbreviations: H, Isoniazid; R, Rifampicin; Z, Pyrazinamide; E, Ethambutol; Lzd, Linezolid; Mx, Moxifloxacin.Cs, Cycloserine; RPT, Rifapentine; Czd, Contezolid.

Discussion

Our patient underwent kidney transplantation and received long-term immunosuppressive therapy. The kidney allograft showed a functional decline over time. Her estimated glomerular filtration rate (eGFR) was less than 30 mL/min when multi-system TB, including pulmonary TB and tuberculous pleurisy and peritonitis onset. The recommendations for treating TB in transplant recipients are similar to those in the general population.[15,16] For our patient, even drug susceptibility testing showed that the strain was not drug-resistant, she was intolerant to several first and second-line drugs. Moreover, she suffered severe bone marrow suppression when the physician tried linezolid 600mg once daily. It is difficult to tailor an effective and safe anti-TB regimen for patients with organ transplantation and severe comorbidities.

In our hospital, we tried to combine isoniazid, rifapentine, and moxifloxacin to balance the efficacy and safety of the anti-TB regimen. At the same time, we monitor the serum concentration of tacrolimus for drug interaction between rifapentine and tacrolimus. We found the serum through centenarian of tacrolimus was stable in the normal range (5~15ng/mL), which means the immune suppression is acceptable for preventing allograft rejection.[17] Moreover, she had a relatively good tolerance to moxifloxacin this time and reported no insomnia. We thus assumed that the regimen was effective for her TB. But unfortunately, her TB symptoms and ascites persisted for several months, and even repeated drainage was performed. After the tumor, hypoproteinemia, portal hypertension, and other possible pathological conditions were excluded, we attributed the refractory ascites and intermittent night fever to the uncontrolled tuberculous peritonitis. It has been proved that TB patients post-transplantation are more likely to suffer from severe TB and more challenging for clinical care.[1] The dose of linezolid should be reduced in patients with eGFR < 40 mL/min, as these patients had significantly higher trough concentrations of linezolid, which was associated with the onset of adverse events.[18] We then tried to use half-dose, 300mg once daily, to enhance the anti-TB effect and decrease the risk of bone marrow suppression. Unfortunately, our patient developed thrombocytopenia again, and linezolid was permanently stopped. Additionally, she had psychiatric symptoms when we tried cycloserine, which was then ceased.

Contezolid is approved by the National Medical Products Administration of China in 2021 for treating complicated Gram-positive cocci infection. Compared with linezolid, contezolid demonstrated a significantly decreased myelosuppression.[19] Some clinical cases reported that contizolid has a satisfactory anti-tuberculosis effect and fewer toxicities than linezolid.[8,20,21] Considering the short half-life of contizolid and the significant decrease in eGFR of our patient, we prescribed 400mg twice daily for her treatment. At the same time, we monitored the concentration of tacrolimus to see if there was any interaction between tacrolimus and contezolid. We found that the concentration of tacrolimus was stable, suggesting that contizolid did not affect the absorption and metabolism of tacrolimus. After the initiation of contezolid, the drainage volume of ascites gradually decreased, and the ascites completely disappeared after 3 months of treatment. Notably, no myelosppressional toxicity or neuropathy occurred during the treatment, indicating that contezolid had better safety than linezolid.

There are two limitations in our study. Firstly, we only used half of the standard dose of contezolid in our patient, the plasma pharmacokinetics of contezolid had not been performed, so we could not determine the optimal dosage of contezolid for patients with severe kidney dysfunction. Secondly, though our patient has been improving since enhanced anti-TB treatment with contezolid, the favorable outcomes cannot be directly attributed to contezolid alone as the multi-drug anti-TB regimen was continued.

In conclusion, contezolid may be a very promising and safe drug for the treatment of TB in patients with organ transplantation and severe kidney dysfunction. Further clinical studies are needed to verify this new drug and determine its optimal dosage for TB treatment, particularly in patients with comorbidities.

Abbreviations

TB, tuberculosis; WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; PLT, platelets; CT, computed tomography.

Consent

Written informed consent for the publication of this report was obtained from the patient. And institutional approval wasn't required to publish the case details.

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Disclosure

The authors report no conflicts of interest in this work.

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