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Diagnosis and treatment of Whipple disease after kidney transplantation: A case report

Qian Chen, Yu-Lin Niu, Tao Zhang

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Abstract

BACKGROUND

Kidney transplantation is the standard treatment for end-stage renal disease. Particularly, rare and specific pathogenic infections which are asymptomatic are often difficult to diagnose, causing delayed and ineffective treatment and thus seriously affecting prognosis. *Tropheryma whipplei* (*T. whipplei*) is a Gram-positive actinomycete widely found in soil, sewage, and other external environments and is present in the population as an asymptomatic pathogen. There is relatively little documented research on *T. whipplei* in renal transplant patients, and there are no uniform criteria for treating this group of post-transplant patients. This article describes the treatment of a 42-year-old individual with post-transplant *T. whipplei* infection following kidney transplantation.

CASE SUMMARY

To analyze clinical features of Whipple's disease and summarize its diagnosis and treatment effects after renal transplantation. Clinical data of a Whipple's disease patient treated in the affiliated hospital of Guizhou Medical University were collected and assessed retrospectively. The treatment outcomes and clinical experience were then summarized *via* literature review. The patient was admitted to the hospital due to recurrent diarrhea for 1 mo, shortness of breath, and 1 wk of fever, after 3 years of renal transplantation. The symptoms of the digestive and respiratory systems were not significantly improved after adjusting immunosuppressive regimen and anti-diarrheal, empirical antibiotic treatments. Broncho-scopic alveolar fluid was collected for meta-genomic next-generation sequencing (mNGS). The deoxyribonucleic acid sequence of *Tropheryma whipplei* was detected, and Whipple's disease was diagnosed. Meropenem, ceftriaxone, and other symptomatic treatments were given, and water-electrolyte balance was maintained. Symptoms resolved quickly, and the patient was discharged after 20 d of hospitalization. The compound sulfamethoxazole tablet was continued for 3 mo after discharge. No diarrhea, fever, and other symptoms occurred during the 6-month follow-up.

CONCLUSION

Whipple's disease is rare, with no specific symptoms, which makes diagnosis difficult. Polymerase chain reaction or mNGS should be immediately performed when the disease is suspected to confirm the diagnosis.

Key Words: Kidney transplantation; Immunosuppression; Whipple disease; Whipple's nutrient barrier; Macrogenomics second-generation sequencing technology; Case report

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Core Tip: Whipple disease is rare and has no specific symptoms, which makes diagnosis difficult. When the disease is suspected, polymerase chain reaction or meta-genomic next-generation sequencing should be performed immediately to confirm the diagnosis.

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INTRODUCTION

Kidney transplantation is standard treatment for end-stage renal disease[1,2]. Human and kidney survival rates have improved significantly after kidney transplantation with the development of immunosuppressive drugs, advancements in surgical techniques, and improved perioperative management protocols[3,4]. However, infectious diseases are significantly more frequent in post-transplant recipients than in general population due to prolonged immunosuppressive medication, and infection has become one of the main causes of death after kidney transplantation[5]. Particularly, rare and specific pathogenic infections which are asymptomatic are often difficult to diagnose, causing delayed and ineffective treatment and thus seriously affecting prognosis[6]. *Tropheryma whipplei* (*T. whipplei*), a Gram-positive actinomycete, is widely found in soil, sewage, and other external environments and is present in the population as an asymptomatic pathogen[7,8]. Historically, the symptoms of Whipple's disease included intermittent and recurrent arthralgia or arthritis with chronic diarrhea, abdominal pain, weight loss, and central nervous and cardiovascular systems effects[9,10]. The occurrence of Whipple's disease after renal transplantation has not been reported yet. A patient with Whipple's disease was admitted with respiratory and digestive systems infections after renal transplantation and the treatment outcomes were good. This case aimed to report clinical data and treatment outcomes. Furthermore, the relevant domestic and international literature was also included to provide a reference for the timely diagnosis and treatment of this rare disease.

CASE PRESENTATION

Chief complaints

Diarrhea for 1 mo, shortness of breath with fever for 1 wk.

History of present illness

A 46 years old male patient was enrolled at the affiliated hospital of Guizhou Medical University for the uremic stage of chronic renal failure (primary nephropathy unknown) and underwent a living donor kidney transplant in July 2019. The patient received left kidney of his father. The donor-recipient blood type is A. The human leukocyte antigen mismatch was 2. The recipient had a negative preoperative penicillin reactive antibody and a complement-dependent cytotoxicity test of 3%. The donor underwent laparoscopic kidney resection, and the recipient underwent conventional kidney transplantation at the right iliac fossa. The rabbit anti-human thymocyte immunoglobulin (r-ATG) was administered intra- and post-operatively at 50 and 25 mg from D1 to D4, respectively. There were no postoperative complications, and the patient was discharged 14 days after the surgery. With regular follow-up after discharge, a triple immunosuppressive regimen of tacrolimus + mycophenolate + glucocorticoids was used to prolong anti-rejection and tacrolimus trough maintained between 5 and 10 ng/mL was prescribed. The patient with 1 mo of diarrhea visited the hospital; he had 5-6 stools per day, diluted and watery, without mucus, pus, and blood. Outpatient treatment with symptomatic anti-diarrhea and intestinal flora regulation did not significantly relieve diarrhea symptoms. Subsequently, the immunosuppressive regimen was adjusted, and diarrhea frequency decreased to 2 to 3 times daily. After one week, the patient developed shortness of breath with fever after activity with no apparent cause, with a maximum temperature of 38.5 °C. He was diagnosed with "diarrhea and fever to be investigated" and was admitted to the hospital without cough, sputum, nausea, vomiting, and frequent and urgent urination. On the day of admission, he relieved loose stools twice and urinated 1200

mL. He had lost about 2.5 kg of weight in the past month.

History of past illness

Denied unclean diet, cold and close contact with febrile patients before the disease onset, hypertension, diabetes, coronary heart disease, tuberculosis, hepatitis B, *etc.* There was no history of trauma, blood transfusion, drug or food allergy, living in infected areas, contact with infected water or sources, or exposure to radiation, toxins, or drugs. Furthermore, there was no residence history in areas with medium to high risk of neoconiosis or close contact.

Personal and family history

Born and raised in Guizhou Province, no history of extended travel outside the country, no smoking or drinking. Parents, children and spouse are all healthy.

Physical examination

The initial checkup indicated a temperature of 37.8 °C, pulse 106/min, respiration 28/min, blood pressure 123/85 mmHg, and finger pulse oxygen 91%. After a physical examination, he was clear and had shortness of breath, with a medium body shape, general nutrition, and cooperation. The pupils were equally large and rounded bilaterally, and the light reflex was sensitive. There was no yellowing of the skin and sclera, and no petechiae were observed on the skin mucosa. No enlargement of superficial lymph nodes was detected throughout the body. Breath sounds were coarse in both lungs, and a few wet rales could be heard in the middle and lower lungs. He had a uniform heart rhythm with no murmur in the valves. Abdominal and neurological investigations were negative; no abnormal external genitalia development or external urethral discharge was identified. Furthermore, there was no abnormal joint movement of the limbs.

Laboratory examinations

The blood profile revealed the following: Leukocytes = 8.94×10^9 /L, lymphocyte = 4.3%, absolute lymphocyte value = 0.38×10^9 /L, neutrophil = 90.5%, absolute neutrophil value = 8.09×10^9 /L, calcitoninogen = 0.45 µg/L, creatinine = 131.0 µmol/L, blood sodium = 132.1 mmol/L, blood chloride = 79.9, blood glucose = 8.43 mmol/L, albumin = 32.5 g/L, and ultrasensitive C-reactive protein = 24.94 mg/L. The routine stool test and *Vibrio cholera*, *Salmonella*, and *Shigella* culture were negative. Tacrolimus blood concentration was 4.76 ng/mL.

Imaging examinations

Chest computed tomography (CT) showed multiple exudates in both lungs, and infection was considered.

FINAL DIAGNOSIS

Whipple disease.

TREATMENT

After the admission, the cardiac profile was monitored, nasal catheter oxygenation was administered, the empirical anti-infection regime of moxifloxacin was initiated, mortification with mortification, symptomatic anti-diarrhea medication was started, the water-electrolyte acid-base balance was carefully maintained for active infection improvement and pathogenesis-related tests were performed.

Blood and urine BK and human cytomegalovirus virus deoxyribonucleic acid were negative, fungal (1,3)-β-D glucan ≤ 37.5 pg/mL, *Aspergillus galactomannan* = 0.205 S/CO, and antibodies to 12 common respiratory pathogens were also negative. After 3 d of empirical anti-infective treatment, the patient's shortness of breath and fever did not improve; the fever peak rose to 38.9 °C and was mainly experienced from 2 pm to 10 pm daily. Therefore, the anti-infective regimen was adjusted to moxifloxacin + cefoperazone-sulbactam sodium with micafungin (antifungal). Furthermore, blood bacterial and fungal cultures and fiberoptic bronchoscopy were performed, which were negative. Fibronectomy indicated abnormal trachea and bronchi. On brush examination of the posterior segment of the right lung's upper lobe, ciliated columnar cells, a few erythrocytes, and phagocytes were seen microscopically, and no acid-resistant bacilli were found on antacid staining. Bronchoalveolar lavage fluid (BALF) was obtained for metagenomics next-generation sequencing (mNGS), which Whipple's nutrient barrier sequence was detected after 2 days. Since this was a rare pathogen and our department has no previous experience with this disease, literatures were reviewed, and multidisciplinary consultation (MDT) with the Department of Infection, Clinical Pharmacy, Respiratory Medicine, and Gastroenterology was requested to change the anti-infective regimen to meropenem alone. After 48 h of this new regime, the patient's temperature dropped to 36.8 °C and fluctuated within the normal range after that. After 9 d, the regimen was changed to ceftriaxone; post- 5 days of ceftriaxone, it was changed to oral cotrimoxazole.

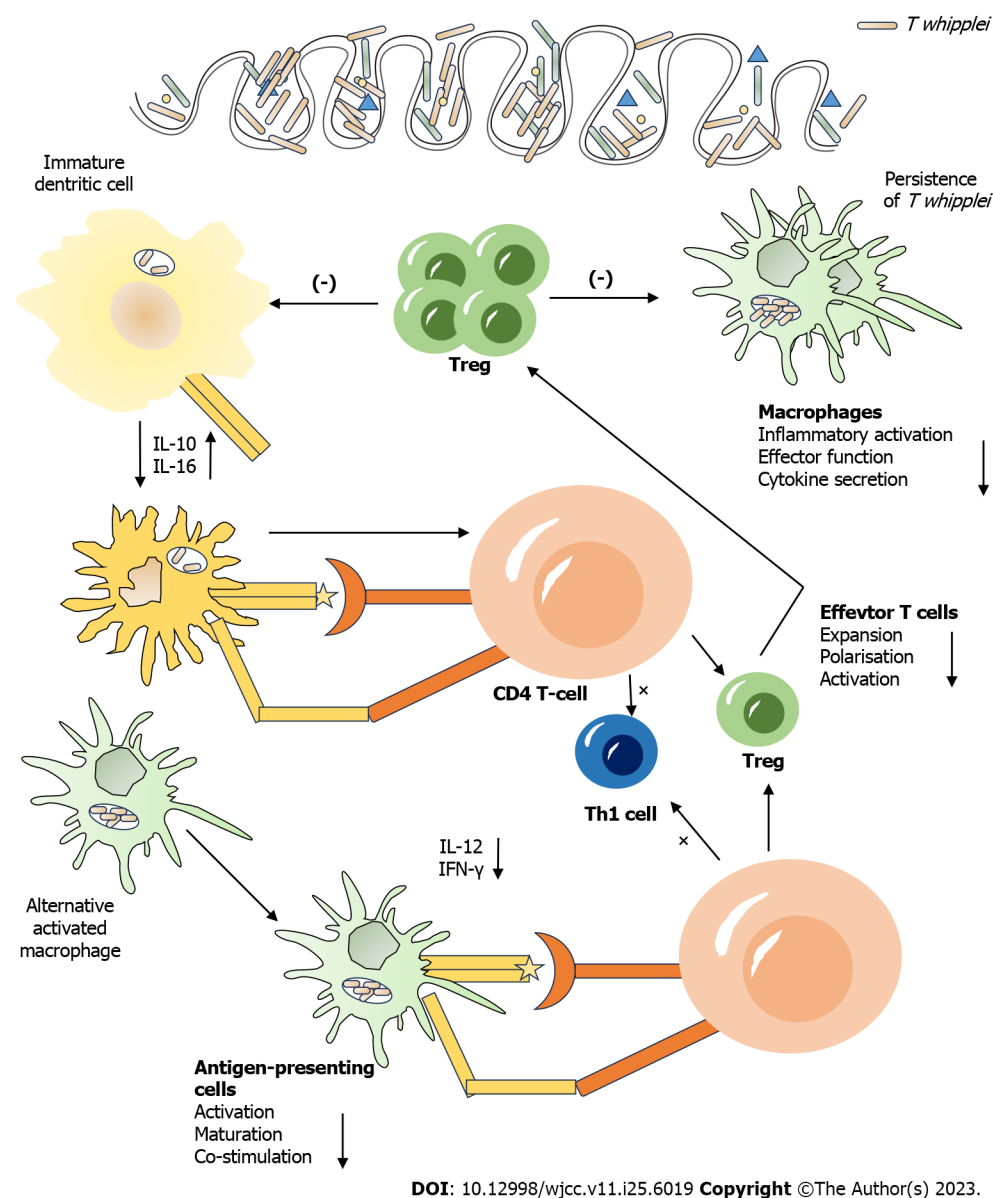


Figure 1 Pathogenesis of Whipple's disease. IL: Interleukin; IFN: Interferons; *T. whipplei*: *Tropheryma whipplei*.

OUTCOME AND FOLLOW-UP

The patient was discharged after 20 d of hospitalization and continued on oral cotrimoxazole for 3 mo after discharge. At 6 mo post-discharge follow-up, the patient's transplanted renal function was stable, no significant abnormalities were observed in the relevant biochemical indices, and no extended symptoms such as diarrhea or fever occurred.

DISCUSSION

Whipple's disease is a rare systemic infection caused by *T. whipplei*, most frequently observed in patients with diabetes, chronic kidney disease, liver disease, and immunodeficiency[11,12]. Its Pathogenesis of Whipple's disease is shown in Figure 1. It is also detected in the general population as an asymptomatic pathogen. A study reported its incidence to be 3 in a million, and no relevant epidemiological report from China exists[13]. It is primarily manifested with intermittent and recurrent arthralgia or arthritis with chronic diarrhea, abdominal pain, and weight loss. It can affect multiple systems such as cardiovascular, central nervous, respiratory, and skin systems. If left untreated, many serious complications can occur, with poor prognosis[14]. Because of the rarity, non-specific clinical manifestations, and absence of classical diagnostic techniques (smear microscopy, microbial culture, antigenic antibody testing, etc.) to identify *T. whipplei* nurturing bodies, the disease is difficult to diagnose and is mainly confirmed using tissue biopsy and pathogenetic genetic testing[15]. Upon suspicion, despite gastrointestinal symptoms, small intestinal mucosal specimens should be obtained *via* microscopy for periodic acid Schiff staining, polymerase chain reaction (PCR), and mNGS testing[16]. If the results of small intestinal tissue examination are not diagnostic, the above tests should be performed by sampling the

corresponding lesion sites (synovial membrane, lymph nodes, alveolar lavage fluid, cerebrospinal fluid, blood, *etc.*) according to the patient's clinical manifestations. With the rapid development of molecular biology techniques, the application of mNGS for pathogenic detection has been increasing, especially for clinically rare, atypical, or caustic microorganisms with important diagnostic value[17,18]. mNGS also allow the detection of multiple pathogens simultaneously in a single specimen, dismissing repeated sampling, and multiple testing[19].

In review, the patient received long-term maintenance therapy with immunosuppressive drugs after renal transplantation and had recurrent diarrhea with weight loss as the first symptom. Diarrhea is frequent in most post-transplant patients and is mostly considered non-infectious and caused by *macrolides*. The diarrhea was slightly relieved after routine adjustment of immunosuppressants and symptomatic anti-diarrhea medications. Subsequently, the patient developed respiratory symptoms, including chest tightness, shortness of breath with fever, and inflammatory exudate in both lungs, evident by chest CT. Although monism was applied to explain the digestive and respiratory symptoms, we could not find a disease or pathogen linked with the incidence of all the clinical symptoms simultaneously, and conventional pathogenic tests were not positive. Therefore, only a preliminary diagnosis of non-infectious diarrhea combined with community-acquired pneumonia was made, and the two systems were treated separately, which was ineffective. The patient's diagnosis was confirmed when BALF was examined by fiberoptic bronchoscopy for mNGS, and a sequence of *T. whipplei* nutrient blockers was detected. This case highlighted that in the future, if a patient with diarrhea and combined motor, cardiovascular, respiratory, or other systemic symptoms is admitted after renal transplantation and the conventional treatment is ineffective, the possibility of Whipple's disease should be considered, and specimen from the appropriate site should be collected for PCR or mNGS testing.

Currently, there are no guidelines or expert consensus on treating Whipple's disease. The primary treatment includes anti-infective therapy against the pathogen and supportive symptomatic therapy against the corresponding systemic symptoms. Effective anti-infective drugs reported in the literature include meropenem, ceftriaxone, cotrimoxazole, doxycycline, and hydroxychloroquine[20,21]. In this case, meropenem was selected as an anti-infection after MDT consultation because of severe respiratory symptoms, which quickly improved the patient's fever and was subsequently stepped down to ceftriaxone. Furthermore, A research reported that a recurrence rate of this disease was 30% to 40%[22]; therefore, an oral combination of sulfamethoxazole or doxycycline + hydroxychloroquine for 3 mo to 1 year was proposed. The patient continued using sulfamethoxazole for 3 mo after discharge. The followed up of > 6 mo reported no further symptoms of diarrhea and fever, as well as had stable transplant renal function[23].

CONCLUSION

In summary, prolonged immunosuppressive medication in organ transplant patients can cause opportunistic infections, especially some relatively rare pathogens in the normal population, and often causes difficulties in clinical management. Whipple's disease after renal transplantation is rarely reported. Therefore, if a patient enrolls with diarrhea and symptoms of motor, respiratory, cardiovascular, or other systems after renal transplantation and indicates poor outcomes after conventional management, Whipple's disease should be considered. PCR or mNGS testing can be performed on the appropriate specimens for early detection of pathogens for targeted anti-infective treatment.

FOOTNOTES

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