Case Report

A case report of oral sulfamethoxazole in the treatment of posttransplant *Listeria monocytogenes* meningitis

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Background: Renal transplant recipients are prone to *Listeria monocytogenes* (Lm) infection due to immunosuppressive therapies. Ampicillin or penicillin G is regarded as the first-line treatment of Lm meningitis. For patients with allergy to penicillin, convention to trimethoprim-sulfamethoxazole (TMP-SMX) iv should ideally be performed since TMP-SMX remarkable bactericidal activity. But there's still scarcity of reports indicating oral TMP-SMX regimen on Lm meningitis.

Case Description: A 30-year-old male who received a renal transplant 4 months ago was admitted to the hospital with generalized pain and headache for 3 days accompanied by diarrhea and fever for 1 day. The patient had been treated with regular oral immunosuppressants post-transplantation. After admission, the patient poorly responded to cefoperazone sulbactam and progressed rapidly with increasing headache, persistent diarrhea, diplopia, and dyspnea and was subsequently transferred to the intensive care unit (ICU) for ventilatory support. Later, as Lm was detected successively in the patient's blood culture and cerebrospinal fluid culture, the patient was diagnosed with Lm infection. Due to the patient's allergy to penicillins, the TMP-SMX was selected for oral treatment, and the patient well tolerated to TMP-SMX oral regimen without significant adverse effects and recovered after 2 weeks. After discharge, follow-up has shown that the patient has generally remained in good condition with stable graft function to date.

Conclusions: The case of our study demonstrated Lm infection post renal transplantation can be cured by oral TMP-SMX. Furthermore, the recent research and clinical progress of Lm microbiological characteristics, clinical manifestations, diagnosis, and treatment of listeriosis were summarized.

Keywords: Kidney transplant; *Listeria monocytogenes* (Lm); meningitis; sulfamethoxazole; case report

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Introduction

Listeria monocytogenes (Lm) is a gram-positive facultative anaerobic bacterium that is widely distributed in soil, water, and decaying vegetation, and it can also colonize the human digestive tract. Lm can adapt to a wide range of temperatures and grow well at −0.4 to 45 ℃ (1). Individuals-particularly pregnant women, the elderly and immunocompromised individuals can become infected by ingesting food heavily contaminated by this bacterium (2). The incidence of listeriosis in renal transplant patients is 0.06%, whereas patients with diabetes mellitus, a history of cytomegalovirus (CMV) infection within 6 months, and a history of high-dose glucocorticoid use are at greater risk (3). Patients can become infected by taking contaminated food (raw bean sprouts, unpasteurized milk, cheese, cold meat, and smoked seafood), or develop localized infections of eyes

and skin by direct contact with Lm infected patients (4). Listeriosis can cause gastroenteritis, bacteremia, and meningitis. The median incubation period of Lm infection is 8 days (range, 1–67 days), and the incubation period can vary significantly depending on the morbidity crowd and the site of infection: 9 days (range, 1–14 days) in central nervous system (CNS) infections, and 2 days (range, 1–12 days) in bacteremia (5).

The primary therapy is preferred to ampicillin iv or penicillin iv plus gentamicin iv. The therapy may be hampered for patients with allergy to penicillin and contraindications for gentamicin due to advanced kidney diseases, and trimethoprim-sulfamethoxazole (TMP-SMX) is a reasonable alternative as monotherapy iv (6,7). There are only case reports on the clinical efficacy of oral TMP-SMX in the treatment of Lm infection (8-10). This article reports a case of Lm infection after renal transplant, and summarizes the features of listeriosis by reviewing available literature. We present the following article in accordance with the CARE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-83/rc).

Case presentation

A 30-year-old man with end-stage renal disease due to hypertensive nephropathy received a deceased-donor kidney transplant 4 months ago. The patient attended the urology department for treatment with generalized pain, headache, fever, and palpitation, which lasted for 3 days, and he had experienced 4 times of watery diarrhea 1 day before admission. He received triple immunosuppression consisting of tacrolimus capsules (FK-506; 1.5 mg every 12 hours), mycophenolate mofetil capsules (MMF; 0.75 g every 12 hours), and prednisone acetate tablets (Pred; 25 mg at 8:00 a.m. daily), and antihypertension medicine (metoprolol succinate sustained-release tablets 47.5 mg daily).

The patient's examination results included poor mental status, the highest temperature of 38.4 ℃, and a blood pressure reading of 80/60 mmHg on day of hospital admission. It was found that his vital signs and system tests were normal, and he had no history of interprovincial travel or exposure to confirmed or suspected coronavirus disease of 2019 (COVID-19). Laboratory tests showed that the patient had a leukocyte count of 10.38×10^9/L, a neutrophil percentage of 90%, and a hemoglobin of 63 g/L. His serum creatinine (SCr) level was 344 μmol/L. The hemoglobin had been further reduced to 43 g/L due to external hemorrhoid. The patient experienced infusions of suspended red blood cells at last.

CMV and BK virus infections and graft rejection were ruled out on day 3, after which the patient received intravenous cefoperazone sulbactam (3 g every 12 hours) for empirical antimicrobial therapy from day 4 to day 7. However, the patient's symptoms were not ameliorated in the following 3 days.

From the 8th to 12th day since admission, the patient experienced frequent convulsions, headaches, and diplopia. Physical examination showed that the patient was conscious and clear-headed, but his general condition was poor. His meningeal irritation sign was negative. The patient had a maximum body temperature of 40.0 ℃, a pulse rate of 64–120 beats/min, a respiratory rate of 16–39 breaths/min, a white blood cell count of 5.34×10^9/L, a neutrophil percentage of 92%, and a procalcitonin (PCT) of 3.2 mg/L. The patient's biochemical examination of cerebrospinal fluid revealed a total protein (TP-CSF) of 2.37 g/L, chloride (Cl) of 125.3 mmol/L, and glucose of 4.36 mmol/L (*Table 1*), and no cryptococcus was detected by ink staining on day 12. Lm was detected successively in his blood culture (day 8) and cerebrospinal fluid (CSF) culture (day 12). The patient's cranial magnetic resonance imaging (MRI) scan was performed on day 10, and the MRI revealed lesions in the posterior horn of the left lateral ventricle, adjacent temple, and occipital lobes with irregular shape and blurred borders (*Figure 1*). Finally, he was definitively diagnosed with Lm sepsis and Lm meningitis, and was subsequently transferred to the intensive care unit (ICU) with assisted breathing via

Highlight box

Key findings

- The case of our study demonstrated Lm infection post renal transplantation can be cured by oral TMP-SMX.

What is known and what is new?

- Lm is a gram-positive facultative anaerobe, widely distributed in soil, water, and decayed vegetation, and can also be planted in the human digestive tract.
- This study reported the diagnosis and treatment of a case of Lm infection, and summarized the features of listeriosis by reviewing available literature.

What is the implication, and what should change now?

- Through a retrospective analysis of a case of Lm cured by oral TMP-SMX, the microbiological characteristics, clinical manifestations, diagnosis, and treatment of listeriosis were described in this paper.

Table 1 Comparison of the routine and biochemical indexes of the cerebrospinal fluids before and after treatment

Indexes	Before treatment	After 35 days of treatment
pH	6.5	6.5
Color	Yellow	Pale yellow
Transparency	Transparent	Transparent
Protein	+++	–
White blood cell	$1,706\times10^6$/L	32×10^6/L
Percentage of polykaryocytes (body fluid)	82.2%	3.1%
Percentage of monocytes (body fluids)	17.8%	96.6%
Absolute value of polykaryocytes (body fluids)	$1,403\times10^6$/L	1×10^6/L
Absolute value of monocytes (body fluids)	303×10^6/L	31×10^6/L
Red blood cell count (body fluid)	0	0
Total protein (CSF)	2.37 g/L	0.29 g/L
Chlorine	125.3 mmol/L	123.6 mmol/L
Glucose measurement (CSF)	4.36 mol/L	4.28 mol/L

CSF, cerebrospinal fluid.

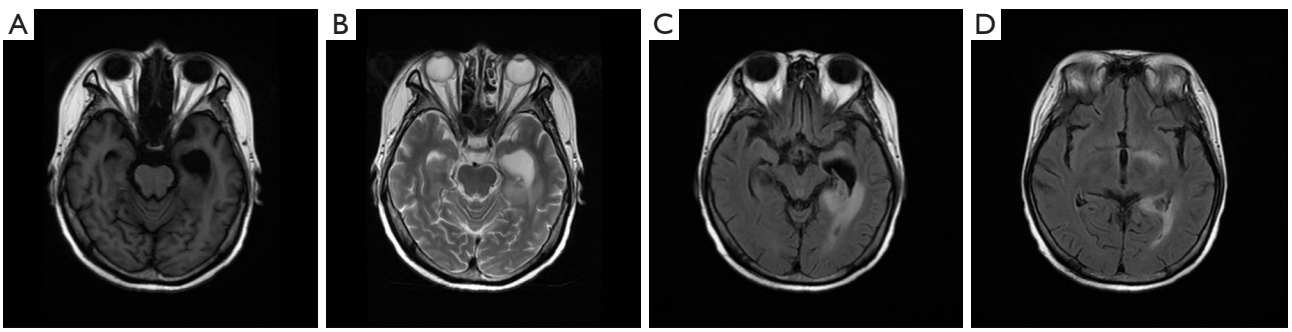

Figure 1 The patient's cranial MRI. (A-D) Cranial MRI of the patient on the 10th day after admission: there are lesions in the posterior horn of the left lateral ventricle, adjacent temple, and occipital lobes with irregular shape and blurred borders. The T1WI shows low signal, and T2 FLAIR showed high signal with the enlargement of the inferior horn of the left lateral ventricle, whereas the posterior horn of the lateral ventricle shows a heterogeneous signal. The midline structure is not displaced. The remaining ventricular system is normal in size and morphology with no abnormal signal shadows. MRI, magnetic resonance imaging; T1WI, T1 weighted imaging; T2WI, T2 weighted imaging; FLAIR, fluid-attenuated inversion recovery.

tracheal intubation on day 12. The patient took a sodium penicillin infusion pump of 4 million units every 4 hours and 0.5 g of levetiracetam tablets every 12 hours to control epilepsy from day 12. To prevent rejection, the patient was administered 40 μg of methylprednisolone daily, and FK-506 and MMF were discontinued.

On the 15th day of admission (the 4th day of treatment with penicillin), the penicillin was withdrawn due to an allergic reaction (The patients experienced unexpected rashes on lower back and four limbs). Considering that there was no intravenous formulation of sulfamethoxazole in the market of the mainland of China, the treatment regimen had to be adjusted to compound sulfamethoxazole [trimethoprim-sulfamethoxazole (TMP-SMX) 1:5] tablets 960 mg every 6 hours through a nasogastric tube to continue anti-infective therapy from day 16.

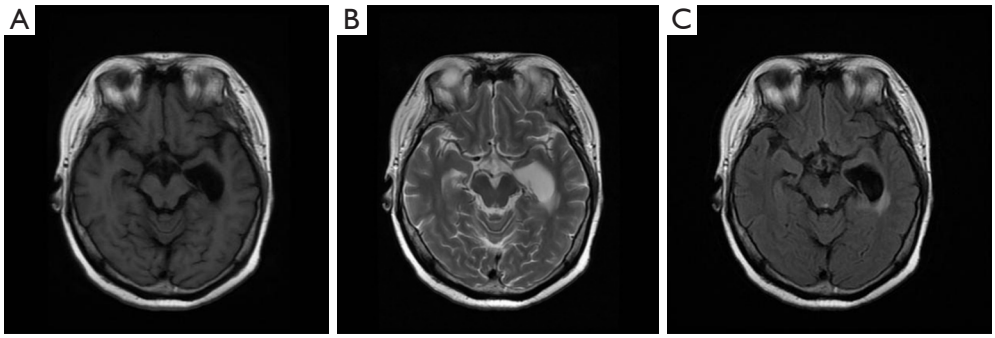

Figure 2 The patient still had a T2 hyperdense shadow in the brain. (A-C) The patient underwent cranial MRI 6 months after discharge: slightly longer schistose T1 lateral ventricles and the thalamus, and a high signal can be seen in the T2 FLAIR. There is no diffusion signal and a long T2 signal can be seen in the left hippocampus, the temporal and occipital horns of the restriction on DWI, and the temporal horn of the left lateral ventricle is enlarged. Compared with 6 months ago, the area of gliosis is smaller, and the absorption of mastoiditis is smaller. MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion weighted imaging; T1WI, T1 weighted imaging; T2WI, T2 weighted imaging.

After 21 days of treatment with TMP-SMX (for day 16 to day 37), the patient's symptoms and indicators of infection improved significantly, and the tracheal intubation was removed. After transferring out of the ICU, the oral treatment with TMP-SMX 960 mg every 12 hours was maintained for 2 weeks, and the immunosuppressant therapy was resumed. Another 2 weeks later, the patient's recheck showed a temperature of 36.7 ℃, a hemoglobin level of 83 g/L, a white blood cell count of 4.51×10^9/L, and a neutrophil percentage of 72.4% on day 65. The patient's CSF was yellowish and protein-negative, with 123.6 mmol/L chlorine, 123.6 mmol/L glucose (*Table 1*), and 269.8 μmol/L SCr. Although the patient still had a T2 hyperdense shadow in the brain (*Figure 2*), there was no recurrence of meningitis and no deterioration of the transplanted kidney after discharge from the hospital. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Clinical manifestations and diagnosis of Lm meningitis

Approximately 43% of patients with Lm meningitis may experience the classic triad of fever, neck stiffness, and altered mental status, 16–37% may experience focal neurological symptoms, and 4–17% may experience seizure symptoms (11-13). If the infection invades the brain parenchyma, the patient may have either consciousness or mental disturbance, cerebellar signs, hemiplegia or hemiparesthesia, and other long tract signs. The patient in this study had fever (the highest body temperature reached 40 ℃), headache before admission, and convulsions after admission, indicating cerebral parenchymal involvement with signs of meningeal irritation, which is consistent with the clinical manifestations of Lm meningitis.

Most cases of Lm meningitis have no specificity in peripheral blood cell count, which may be manifested by elevated C-reactive protein (CRP) levels, hypoproteinemia, anemia, and increased level of leukocytes and neutrophils (14). These laboratory test indexes make it more difficult to distinguish Lm meningitis from other CNS infections, therefore its diagnosis mainly relies on cranial MRI and CSF culture. As the CSF culture of Lm is a time-consuming process with low positive rates ranging from 46% to 68% and false-negatives, it is likely to result in misdiagnosis, missed diagnosis, or delayed treatment, ultimately leading to inadequate treatment and higher morbidity and mortality (up to 26% in China) (15). In this case, the patient's routine examination of CSF suggested a white blood cell count of $1{,}706\times10^6$/L, positive CSF protein (3 plus), 4.36 mol/L CSF glucose and 125.3 mmol/L chloride, and Lm was detected from CSF culture. The patient's cranial MRI is shown in *Figure 1*. Based on the patient's history of unclean

diet, immunocompromise, and failure to use TMP-SMX for prophylaxis of *Pneumocystis jirovecii* pneumonia and other risk factors, it can be concluded that these factors are consistent with the clinical diagnosis of Lm meningitis.

The therapeutic schedule for the Lm meningitis

Antibiotic therapy should be applied early for Lm bacteremia and meningitis. Since Lm is an intracellular parasitic bacterium, antimicrobial drugs can exert their bactericidal effect only by free diffusion (β-lactam antibiotics such as penicillin G) or endocytic uptake (aminoglycoside antibiotics) into the host cell to reach a certain concentration (6). For adult patients with Lm meningitis and normal renal function, the antimicrobial therapy is intravenous ampicillin 2 g every 4–6 hours or intravenous penicillin G 4 million units every 4 hours, combined with intravenous gentamicin 1.7 mg/kg every 8 hours with synergistic effects (2,6). As gentamicin has disadvantages such as nephrotoxicity and poor ability to cross the blood-brain barrier, and the gentamicin combination regimens can increase early mortality (death occurring between 3 and 14 days after admission) (16), patients with poor renal function may be treated initially with β-lactam monotherapy. For patients with suspected IgE-mediated penicillin allergy include desensitization, the alternative therapy is intravenous TMP-SMX 3–5 mg/kg every 6 hours, or intravenous meropenem 2 g every 8 hours (11). Since the bioavailability of TMP-SMX for gastrointestinal administration is similar to that of intravenous administration in critically ill patients, oral administration can be used as an equivalent alternative to intravenous administration (17). As TMP-SMX also has good blood-brain barrier permeability (10,16,17), it could be an effective option for penicillin-allergic patients. TMP-SMX is the combination of sulfamethoxazole and trimethoprim. Sulfamethoxazole exerts bactericide effect by inhibiting the enzyme dihydropteroate synthase to interrupt the synthesis of folate inside microbial organisms. Trimethoprim is a competitive inhibitor of the enzyme dihydrofolate reductase which arrests the production of tetrahydrofolate. Some case reports have elaborated the efficacy of TMP-SMX in Lm infection, but high-quality evidence-based medical evidence still lacks.

Conclusions

Lm meningitis is a relatively rare clinical food-borne infectious disease that commonly occurs in immunocompromised individuals. The absence of atypical clinical manifestations may lead to being misdiagnosed as other infection types, and it has a poor prognosis and high resistance to the third-generation cephalosporins. Through a retrospective analysis of a case of Lm cured by oral TMP-SMX, the microbiological characteristics, clinical manifestations, diagnosis, and treatment of listeriosis were described in this paper.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-83/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-83/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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