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CASE REPORT

Acute Q Fever after Kidney Transplantation: A Case Report

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Abstract

Aims/Background Patients receiving kidney transplant experience immunosuppression, which increases the risk of bacterial, viral, fungal, and parasitic infections. Q fever is a potentially fatal infectious disease that affects immunocompromised renal transplant recipients and has implications in terms of severe consequences for the donor's kidney.

Case Presentation A patient with acute Q fever infection following kidney transplantation was admitted to the Tsinghua Changgung Hospital in Beijing, China, in March 2021. Next-generation sequencing (NGS) was used to diagnose Q fever in the patient. Based on the patient's blood test, we detected *Rickettsia*, the causative agent of Q fever and a zoonotic disease that can manifest in acute or chronic forms in humans. Comprehensive data on clinical symptoms, blood tests, chest computed tomography (CT), NGS, Immunoglobulin G (IgG) antibody titer, and therapeutic efficacy associated with Q fever infection following renal transplantation in this patient were gathered.

Conclusion This is the first reported case of acute Q fever occurring in a Chinese renal transplant recipient detected using metagenomic NGS. This case underscores the need to consider acute Q fever as a possible differential diagnosis in kidney transplant recipients with fever of unknown origin.

Key words: Q fever; *Coxiella burnetii*; renal transplantation; infection; case report

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Introduction

Post-transplant infections belong to a critical and complex issue (Razonable, 2024). Although kidney transplantation, as a primary treatment for end-stage renal disease, has significantly improved the quality of life and survival rate, its postoperative infection has been a major challenge for clinicians and patients. Following kidney transplantation, most patients generally face the challenges of a suppressed immune system caused by immunosuppressants, which increases the risk of bacterial, viral, fungal, and parasitic infections (Loupy et al, 2019; Tasci, 2023). These infections not only affect the patient's recovery process, but also can be life-threatening in severe cases.

Coxiella burnetii is the zoonotic agent responsible for Q fever (Ahaduzzaman and Reza, 2024; McQuiston and Childs, 2002). Many domesticated animals could fall victim to a pandemic virus (Georgiev et al, 2013). *C. burnetii* is a tiny, obligate intracellular Gram-negative bacterium that resembles *Rickettsia* in appearance.

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Cattle, goats, sheep, and other livestock are the most prevalent vectors contributing to these infections in humans. In recent years, Q fever has become a global pandemic (Kirchgessner et al, 2013). The International Animal Health Organization has declared an epidemic for Q fever, and the disease has been listed as one of the zoonotic infectious disorders in China. The first case of the disease was documented in 1999 in the United States, and by 2001, *C. burnetii* was classified as a possible biohazard agent (Morroy et al, 2016). The annual incidence of the disease in the United States is reported to range from 0 to 2.4 per 1,000,000 people, depending on the state (McQuiston and Childs, 2002).

In healthy individuals, the symptoms of acute Q fever are modest and often resolve on their own. They can collectively manifest as either an acute or a chronic illness in patients (Morroy et al, 2016). The causative agent of Q fever has an incubation period of 9 to 30 days. Acute Q fever is associated with self-limiting fever and pneumonia, with the former manifesting symptoms for a short duration of 2–14 days. Acute Q fever most commonly manifests as one of three flu-like illnesses, pneumonia or hepatitis (Melenotte et al, 2018). Most cases of Q fever are caused by influenza, and the symptoms are similar to those of the flu, such as sudden onset of high fever, headache, weakness, and systemic myalgia. Complications from persistent Q fever are severe and can even be fatal (Wegdam-Blans et al, 2012). These consequences include endocarditis and chronic nephritis. Endocarditis is a common complication of chronic Q fever, especially in the elderly and individuals with compromised immune systems (Barten et al, 2013).

This report documents a case of Q fever, which is, to the best of our knowledge, the first reported case of acute Q fever occurring in a Chinese renal transplant recipient detected using metagenomic next-generation sequencing (NGS).

Case Report

We present the case of a 41-year-old man on immunosuppressive therapy with tacrolimus (2 mg/d), mycophenolate mofetil (1000 mg/d), and prednisolone (10 mg/d) after undergoing kidney transplantation at Tsinghua Changgung Hospital in Beijing, China, on 17 March 2021.

Three days earlier, he presented fever, Tmax 39.0 °C, exhaustion, and myalgias, without chills, rigors, palpitations, rash, cough, flank pain, vomiting, diarrhea, dysuria, urgency, and frequency. He denied having traveled outside Beijing and close contacts with animals. In the hospital's fever clinic, the patient's temperature was 38.2 °C. Auscultation of both lungs was clear. The sounds of his heart were normal, and there was no murmur. The stomach was tender. As shown in Table 1, standard tests were executed. The white cell count was normal (reference range: 3.5–9.5 $\times$ 10^9 g/L), with 78.10% polymorphonuclear leukocytes (reference range: 40–75%), 11% lymphocytes (reference range: 20–50%), and 19.2 mg/L of C-reactive protein (reference range: 0–5.0 mg/L). The serum creatinine level was 107.0 µmol/L (reference range: 57–97 µmol/L), while the lactate dehydrogenase (LDH) level was 269 U/L (reference range: 120–250 U/L). Other indicators reflecting kidney and liver functions were within the normal ranges. The urinalysis test

results were also normal. Computed tomography (CT) of the chest revealed tiny bilateral pulmonary nodules, consistent with previous findings. Ceftriaxone was administered to the patient, but no improvement was observed. During hospitalization, the patient also reported new onset abdominal pain and was found to have mild liver function abnormalities, including elevated liver enzymes.

For further assessment, he was hospitalized in the kidney transplantation department. On physical examination, the patient's body temperature once again reached 38.3 °C, and no other positive signs were noticed. The same array of lab tests were implemented again (Table 1). Repeat lab tests showed an increase in polymorphonuclear leukocytes to 81.1%, and a C-reactive protein level of 68.5 mg/L, higher than initial levels. Procalcitonin (PCT) levels were slightly elevated at 0.65 ng/mL (reference range: 0.05 ng/mL). β-D-glucan test, Galactomannan test, and CMV-DNA test findings were likewise normal. Blood and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) cultures were negative. Considering the patient's immunocompromised status and lack of improvement, a combination of ganciclovir, oseltamivir, and piperacillin-tazobactam was initially administered, but no clinical improvement was observed. On the second day, further diagnostic testing, including pathogen metagenomic sequencing (PM seq), identified *C. burnetii* as the causative agent (Fig. 1 and Table 2), confirmed by quantitative polymerase chain reaction (qPCR). Although serological tests for phase I Immunoglobulin G (IgG) and Immunoglobulin M (IgM) were negative, phase II IgG was critically elevated, indicating acute Q fever.

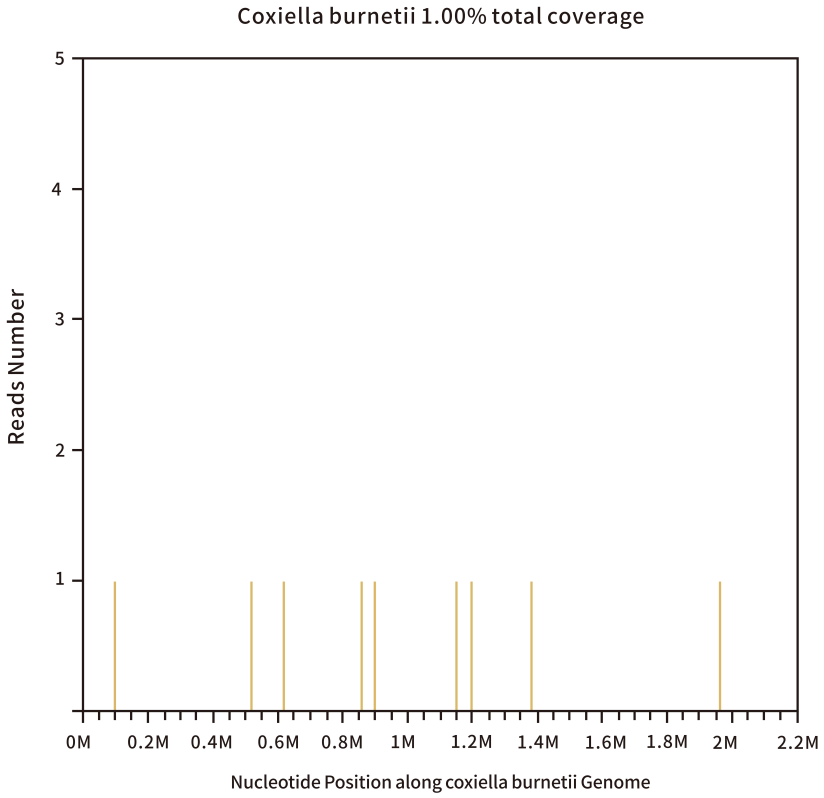

Fig. 1. Pathogen metagenomic sequencing result.

Table 1. Laboratory values.

	Reference range	Disease course					
		Baseline	Day 1 (May 13)	Day 4 (May 16)	Day 6 (May 18)	Day 9 (May 21)	Day 36 (June 17)
White blood cells (10^9/L)	3.5–9.5	6.7	8.2	6.0	5.7	4.3	7.0
Hemoglobin (g/L)	130–175	128	143	131	115	121	126
Platelets (10^9/L)	125–350	258	231	174	214	298	285
Polymorphonuclear leukocytes (%)	40–75	68.0	78.1	81.1	73.3	61.9	65.1
Lymphocytes (%)	20–50	19.6	11.6	8.9	15.1	32.6	22.8
CRP (mg/L)	<5	0.3	19.2	68.5	45.3	8.6	0.6
Aspartate aminotransferase (U/L)	15–40	17.3	35.5	42.7	27	27.5	23.8
Alanine aminotransferase (U/L)	9–50	22.2	39.8	52.2	37.3	25.1	15.8
Lactate dehydrogenase (U/L)	120–250	221	269	297	252	254	225
Creatinine (μmol/L)	57–97	95.5	107.0	116.8	92.7	94.9	96.8

CRP, C-reactive protein.

Table 2. High-throughput microbial gene detection report from pathogen metagenomic sequencing.

Type	Genus		Species	
	Name	Number of detected sequences	Name	Number of detected sequences
Gram-negative bacteria	*Coxiella*	77	*Coxilla burnetii*	77

Given the confirmed diagnosis and the patient's immunosuppressed state, we initiated a targeted therapy with moxifloxacin and minocycline. These antibiotics were chosen based on their efficacy against *C. burnetii* and their safety profile in patients with compromised renal function. The dosage was carefully adjusted, and the patient was closely monitored for any potential side effects, particularly hepatotoxicity, given his mild liver enzyme elevations. Remarkably, the patient's fever and systemic symptoms, including abdominal pain and liver function abnormalities, resolved within 48 hours. During the 12-day course of moxifloxacin and minocycline (Fig. 2), the patient experienced a gradual normalization of liver enzyme levels and made no further complaints of abdominal pain. One month later, follow-up serological tests still showed negative phase I IgG and IgM, but phase II IgG remained critically elevated, and phase II IgM was now positive. Also, the patient reported no relevant symptoms or complications, including recurrence of abdominal pain or other systemic symptoms, during the follow-up visits, and his kidney function maintained at stable levels (Table 3).

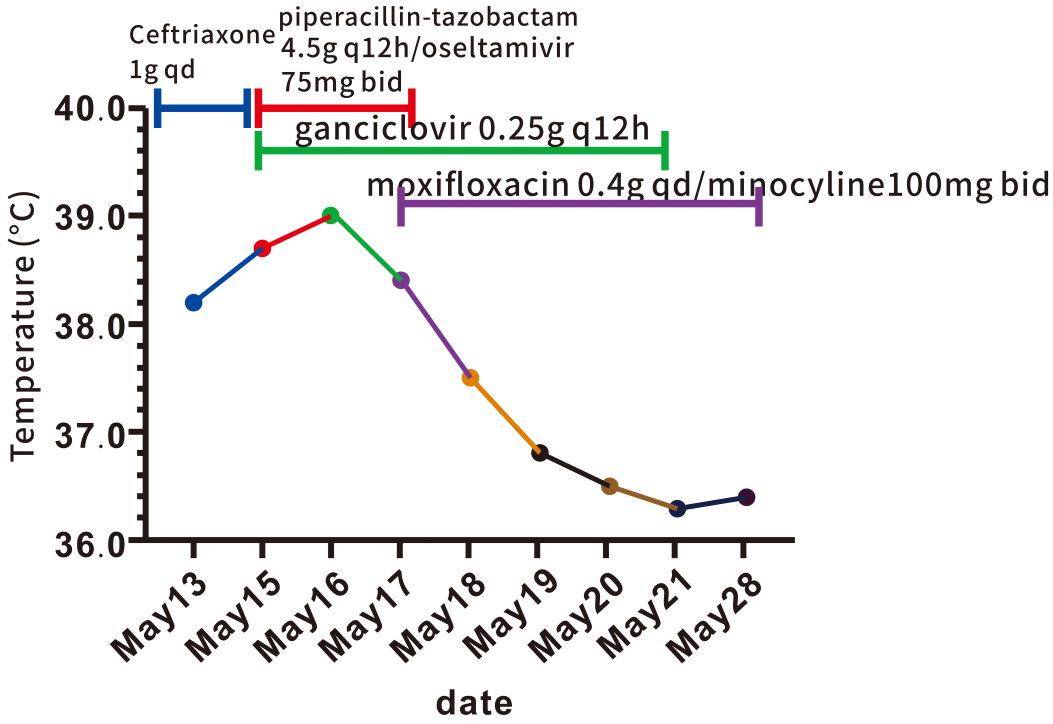

Fig. 2. Changes in body temperature and therapy regimen for the patient over the disease course from May 13 to 28.

Discussion

We present the case of an adult with severe renal failure who underwent a kidney transplant and has been on immunosuppressants for some time. His first manifestations of Q fever are similar to those of a flu (Godinho et al, 2015). During hospitalization, the patient also reported new onset abdominal pain and was found to have mild liver function abnormalities, including elevated liver enzymes. These

Table 3. Result of Bernakshi serotests for IgG and IgM.

		First test (May 16)	Day 36 (June 17)	Day 50 (July 2)
Phase I	IgG	Negative	Negative	Negative
Phase I	IgM	Negative	Negative	Negative
Phase II	IgG	Threshold	Threshold	Threshold
Phase II	IgM	Threshold	Positive	Positive

IgG, Immunoglobulin G; IgM, Immunoglobulin M.

findings suggested that Q fever might be affecting multiple organ systems, which is not uncommon given the systemic nature of the infection. The abdominal pain and liver enzyme elevations suggested a potential hepatic involvement, which has been documented in Q fever cases, particularly in immunocompromised patients.

With the aid of metagenomic NGS, we successfully identified that *C. burnetii* was the pathogen responsible for the Q fever in this case on day 2 after admission; the sequencing results were verified by qPCR. According to the epidemiological survey, several people in the neighbourhood where the patient lived had pets like cats and dogs. Upon the timely identification of the offending agent, we started administering targeted anti-infection therapy to the patient immediately, as previously described (Million et al, 2009). The patient's body temperature normalized on day 2 of doxycycline treatment. Moxifloxacin and doxycycline were continued for 12 days while the patient was hospitalized. At one month, Bernakshi serotests were negative for IgG and IgM at stage I, IgG and IgM at stage II, IgG at stage II as cutoff, and IgM at stage II. After being monitored for over a year, the patient's kidney function was restored to healthy level and he showed no signs of chronic Q fever.

Given the patient's immunosuppressed state, a mix moxifloxacin and minocycline were utilized to counteract *C. burnetii* infection to minimize potential drug toxicity arising from each antibiotic. Previous study has shown that moxifloxacin is particularly effective in treating Q fever due to its ability to penetrate intracellular compartments where *C. burnetii* resides. Minocycline, often used in conjunction, enhances this effect and provides broad coverage (Rolain et al, 2001).

Both drugs are less nephrotoxic, making them suitable for patients with renal impairment. Throughout the treatment, the patient's liver and kidney functions were closely monitored, given the potential for adverse effects in immunosuppressed individuals. The rapid resolution of symptoms and normalization of laboratory values support the effectiveness of this regimen in treating acute Q fever in an immunocompromised host.

The use of proprietary serology, as reported by Kampschreur (Kampschreur et al, 2012), for diagnosing Q fever has been validated in clinical practice. Treatment should begin as soon as the clinician detects signs of the disease, but significant titration changes will not occur until 3–4 weeks after infection (Raoult et al, 2005). Of 100 patients diagnosed with Q fever, only 39 showed improvement on the first test (Sarrell et al, 2021; Wegdam-Blans et al, 2012). A patient whose second serum test is negative and who shows health improvement may be hesitant to get tested

again (Million et al, 2010). This is especially more common in people residing in remote regions where transports to inspection facilities are limited. Second-generation high-throughput gene sequencing technology combined with enzyme-linked immunosorbent assays (ELISAs) reportedly allows for rapid diagnosis of Q fever, enabling early detection and treatment (Anderson et al, 2013).

The detection of Q fever cases through next-generation sequencing (NGS) technology has become an indispensable part of modern clinical diagnostics. Q fever is a zoonotic disease caused by *C. burnetii*, characterized by diverse clinical manifestations that often lead to misdiagnosis or missed diagnosis. Traditional diagnostic methods such as serology and culture techniques can be time-consuming and have limited accuracy, whereas NGS offers a reliable strategy for pathogen detection by virtue of high throughput, speed, and precision. For suspected cases, initial routine testing should be conducted, and if results are inconclusive, NGS technology should be employed for confirmation. Furthermore, a comprehensive diagnosis should integrate the patient's clinical presentation, epidemiological history, and laboratory test results to ensure a thorough clinical assessment and effective treatment plan (refer to the latest diagnosis and treatment guidelines from Virginia Department of Health: Q fever clinical guidance, http://www.nasphv.org/Documents/Q_Fever_2013.pdf).

Sarrell et al (2021) reported a case with a rare presentation of an uncommon infection: hepatic and splenic abscesses and granulomatous inflammation leading to diagnosis of Q fever. He responded well to therapy. This case highlights the importance of monitoring uncommon conditions in patients, especially those under the immunosuppressed state, as these signs and symptoms can lead to more timely diagnosis and treatment for improving patient outcomes. Furthermore, the relationship between Q fever and immunosuppression provides potential directions for future study (Sarrell et al, 2021).

Manifestations of Q fever may include maculopapular rash, pericarditis/ myocarditis, and aseptic meningitis/encephalitis, with neurological involvement and bone marrow necrosis being some of the rare presentations. Q fever hepatitis tends to occur in a younger age group. Its clinical presentations include hepatomegaly, elevated serum transaminase levels, and prolonged fever of unknown origin. In the classic liver biopsy findings, ring-like granulomas containing a central lipid vacuole surrounded by fibrinoid material are occasionally featured (Raoult et al, 2005).

Kidney transplant recipients rarely acquire Q fever (Godinho et al, 2015). Undiagnosed fever is a common complication among kidney transplant recipients, and the outcome of the condition depends on prompt diagnosis and treatment. To the best of our knowledge, this is the first documented case of acute Q fever following kidney transplantation in China. While probing the history and health profile of an immunocompromised person, it is critical to discern and gauge the patient's likelihood of contracting Q fever, regardless of whether he/she had had any previous contact with livestock. A delayed treatment for acute Q fever can precipitate the formation of chronic Q fever, which takes longer time to resolve.

Conclusion

To our knowledge, this is the first reported case of acute Q fever occurring in a Chinese renal transplant recipient detected by metagenomic NGS. Acute Q fever is associated with high morbidity and mortality if left untreated. This case underscores the need to consider acute Q fever as a possible differential diagnosis in kidney transplant recipients with fever of unknown origin. Furthermore, the intricate relationship between Q fever and immunosuppression provides potential directions for future study.

Learning Points

- The kidney transplant recipients are at increased risk of bacterial, viral, fungal, and parasitic infections due to immunosuppression.
- Despite the rarity of Q fever in kidney transplant recipients, it should be considered for differential diagnosis when the patient experiences a fever of unknown origin.
- Second-generation high-throughput gene sequencing technology (next-generation sequencing) combined with enzyme-linked immunosorbent assays (ELISAs) reportedly provides an efficient strategy for the rapid diagnosis of Q fever.
- Treatment should begin as soon as the clinician suspects signs of Q fever because the outcome of the condition depends on prompt diagnosis and treatment.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding authors upon request.

Author Contributions

JJX, JSY and RHY made contribution to the conception and design, and were responsible for collecting data and conducting analysis, as well as preliminary writing and revision of the article. GL and FWL were responsible for writing, revising, and collaborating, as well as conducting an in-depth analysis of the experimental data cited in the article. ZJB and DJZ were responsible for assisting in data collection and analysis, providing strong support for the discussion section of the article, and also responsible for the revision of the article. BLZ and LXY were responsible for data collection and analysis, also responsible for article revision and proofreading, and strictly monitoring the content of the article to ensure the logical, scientific, and rigorous nature of the paper. JSY and RHY were also responsible for article submission and contacting editors. All authors contributed to the important editorial changes in the manuscript. All authors have read and approved the final manuscript. All authors have fully participated in this work and are responsible for it.

Ethics Approval and Consent to Participate

The case report was approved by the Ethics Committee of Beijing Tsinghua Changgung Hospital (NO.23318-6-01). The informed consent also has been acquired from the patient involved in this case report. The study followed the guidelines of the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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