CASE REPORT

Brucellosis in renal transplant recipients: a comparative review of 5 cases

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SUMMARY

Although brucellosis in renal transplant recipients is rare, we studied the clinical characteristics of this infection in this patient population due to the significantly increased number of renal transplantations performed over the past few decades. We report one case from our experience and undertake a review of the previously reported cases retrieved from the PubMed. A total of 5 cases of brucellosis in renal transplant recipients were found to date. The mean time from transplantation to diagnosis of brucellosis was 4.7 years (range, 4 months to 13 years). Blood culture and detection of anti-*Brucella* antibodies were frequently used diagnostic investigations. Treatment with appropriate antibiotic regimen led to a clinical cure and marked improvement in *Brucella* titre in all the patients. This review illustrates that clinicians should remain vigilant for this infectious aetiology following renal transplantation. Further studies are required to delineate the magnitude and scope of this association.

post-transplant diabetes mellitus, ischaemic heart disease status post coronary artery bypass grafting and hepatitis B with sustained virological response achieved using entecavir. Furthermore, he was status post one failed living-unrelated kidney transplant from his wife. After failing the graft secondary to allogenic graft nephropathy, haemodialysis was started until his current renal transplantation. He was on triple immunosuppressive regimen; consisting of tacrolimus, mycophenolate mofetil and prednisolone.

The patient presented to the emergency department with fever and burning micturition for 2 days. He did not have a history of cardiorespiratory, neurological or abdominal problems. Physical examination was remarkable for dry mucous membrane and few small axillary and inguinal lymph nodes. On admission, his vital sign examination revealed blood pressure 95/38 mm Hg and body temperature 39°C.

BACKGROUND

Brucellosis is a common infectious disease that is caused by a bacterium of the genus *Brucella*. Although the exact incidence is unknown, more than half a million new cases are reported worldwide annually.¹ Recently, the rates of brucellosis in developed countries have substantially decreased.¹ However, it remains a serious public health problem in low-income and middle-income countries.² Awareness about this disease is of particular importance as it frequently poses significant diagnostic and therapeutic challenges.³ It is notable that brucellosis following renal transplantation has rarely been documented. To the best of our knowledge, only 5 such cases have been reported to date.^{4–8} In this review, we highlight the need for broad differentials, including brucellosis, in patients following renal transplantation who present with fever and constitutional symptoms. Furthermore, this review outlines our current understanding of the epidemiology of and risk factors for brucellosis following renal transplantation, the pathophysiology of this disorder and currently available approaches to diagnosis and treatment.

CASE PRESENTATION

This study involves a 63-year-old man who received a living-donor renal transplant from his son 8 years ago. He had a history of hypertension,

INVESTIGATIONS

Laboratory evaluation revealed white cell count $6.5 \times 10^9/L$ (normal, $4.5–11.0 \times 10^9/L$), platelet count $392 \times 10^9/L$ (normal, $150–450 \times 10^9/L$), haemoglobin 12.9 g/dL (normal, 12.5–18.0 g/dL), ferritin 41 ng/mL (normal, 30–400 ng/mL), mean corpuscular volume 76 fL (normal, 75–95 fL), C-reactive protein 3 mg/L (normal, <0.8 mg/L), vitamin D 50.8 nmol/L (normal, 50–250 nmol/L), alanine transaminase 35 IU/L (normal, 0–41 IU/L), aspartate transaminase 20 IU/L (normal, 5–40 IU/L), lactate dehydrogenase 117 IU/L (normal, 135–225 IU/L), gamma-glutamyl transpeptidase 62 IU/L (normal, 8–61 IU/L) and urate $354 \mu\text{mol/L}$ (normal, $202–417 \mu\text{mol/L}$). His serum creatinine level was elevated to $292 \mu\text{mol/L}$ ($50–104 \mu\text{mol/L}$). Serum electrolytes, lipid panel and coagulation profile were within normal limits.

The immunosuppressive regimen was held, and he was empirically started on piperacillin/tazobactam therapy. Urinalysis, microscopy and urine culture came out negative. Acute rejection panel was unremarkable. Renal Doppler ultrasound showed good vascularity with preserved corticomedullary differentiation of left transplanted kidney (figure 1). On spectral Doppler analysis, main renal artery was patent with a slightly raised resistive index; however, resistive indices of arcuate and interlobar arteries were within normal limits (figure 2). Chest radiography did not show any

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Figure 1 Doppler ultrasonography of left transplanted kidney showing good vascularity and preserved corticomedullary differentiation.

abnormalities. Furthermore, transthoracic echocardiography was inconclusive. Therein, an extensive workup was conducted for probable infectious aetiologies. After 3 days, blood culture showed gram-negative *Coccobacillus* suggestive of brucellosis. *Brucella* agglutination testing was performed using immunocapture assay, which came out positive at 1:10240. It was negative before renal transplantation. Although the patient received piperacillin/tazobactam for 4 days by that time, there was no improvement in his condition.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses were malaria, urinary tract infection, pneumonia, endocarditis, typhoid fever, dengue fever, fever of unknown origin, HIV infection, systemic lupus erythematosus and tuberculosis. On the basis of diagnostic workup findings and exclusion of probable aetiologies, the patient was diagnosed with brucellosis in the setting of renal transplantation.

TREATMENT

After consultation with the infectious disease team, mycophenolate mofetil was held for 3 days. The patient was initiated on oral doxycycline 100 mg and ciprofloxacin 500 mg twice a day.

Figure 2 Spectral Doppler ultrasonography showing patent main renal artery with peak systolic velocity (PSV) of 47.0 cm/s, end-diastolic velocity (EDV) of 10.5 cm/s and a raised resistive index (RI) at 0.78. The resistive indices of arcuate arteries are ranging from 0.60 to 0.74. In interlobar artery, the resistive indices are ranging from 0.68 to 0.71.

OUTCOME AND FOLLOW-UP

On day 5 of treatment, he became haemodynamically stable and his fever subsided. He recovered well, and the rest of his clinical course was uneventful. He was discharged from the hospital in a stable condition with clear instructions to follow the complete course of doxycycline for 6 weeks and ciprofloxacin for 2 weeks. After successfully completing the therapy, his repeat *Brucella* titre and blood culture came out negative. Furthermore, his serum creatinine normalised to 71 $\mu\text{mol/L}$ (50–104 $\mu\text{mol/L}$).

DISCUSSION

Brucellosis is a common zoonotic disease in low-income and middle-income countries.¹ Four of the six defined *Brucella* species in animals are pathogenic to humans. *Brucella melitensis* is the most common and the most virulent bacterium that causes human disease.¹ Brucellosis spreads to humans either through direct contact with the animal hosts, including cattle, goats, pigs and sheep or due to the consumption of contaminated dairy products derived from them. In the Western world and most of the Americas, the disease has been controlled appreciably. However, it is endemic in many countries of Persian Gulf, Central Asia and Mediterranean basin with Syria, Turkey, Kingdom of Saudi Arabia (KSA), Iran, Iraq, Mongolia, Kyrgyzstan, Tajikistan and Kazakhstan representing the major disease burden and incidence. India and Pakistan in South Asia, some areas of Mexico in North America and Argentina, Peru and Guatemala in Central and South America have a substantial presence of this disease.²

People of KSA are inherently at a higher risk of brucellosis as the country is a major importer of live animals and hosts pilgrimage for millions of Muslims every year. Many of these animals are slaughtered as a part of Hajj proceedings leading to a more frequent human contact with the infected animal's blood, saliva, urine or placenta. Practices of drinking unpasteurised milk are also prevalent in the KSA. Although brucellosis has been a notifiable disease in KSA for a very long time, multiple precautionary steps resulted in a decreasing trend. The reported incidence rate in 2012 was still 12.5/100 000 (95% CI 12.1 to 13).³ The patient in this case is a Muslim male and a citizen of KSA; the attributes that reportedly increase the risk of contracting brucellosis significantly.

Brucellosis in the renal transplant recipients has rarely been recognised. We conducted a structured literature search of PubMed (National Library of Medicine, Bethesda, MD) using a combination of terms, including 'brucellosis', 'renal transplant', '*Brucella*' and 'posttransplant'. After carefully reviewing the relevant literature consisting of but not limited to original articles, case series and case reports, a total of 5 cases of brucellosis in renal transplant recipients were found to date.^{4–8} A comprehensive review of the cases showed clear gender predominance (males, 4; females, 1). The mean post-transplantation time to diagnosis of brucellosis was 4.7 years (range, 4 months to 13 years). The clinical presentation dominated by fever while weakness, cough and malaise were other notable presenting symptoms. Patients were diagnosed based on the findings of blood culture and/or *Brucella* titre. The data of individual cases on epidemiology, clinical presentation, diagnosis and management of patients with brucellosis following renal transplantation are summarised in table 1. It is important to mention here that a thorough history, including family history and physical examination can be of vital importance for a timely diagnosis and identification of other contacts with the exposure.⁹

The pathogenesis of brucellosis has extensively been studied. In such patients, polymorphonuclear cells are infected with

Table 1 Literature review of brucellosis in patients with renal transplantation

Authors	Publication year	Age/gender	Country	Time post-transplant	Clinical presentation	Creatinine, mg/dL	Diagnostic modality	Complication	Treatment	Clinical outcome
Bishara <i>et al</i> ⁴	2010	41/M	Israel	3 years	Fever, weakness	1.6	Blood culture (<i>Brucella melitensis</i>)	Infective endocarditis	Doxycycline, rifampin, TMP/SMX for 6 weeks	Recovered
Yousif and Nelson ⁵	2001	88/M	Saudi Arabia	13 years	Fever, confusion	6.0 (admission), 2.71 (discharge)	<i>Brucella</i> titre (1:320)	Neurobrucellosis	Doxycycline and rifampin for 6 weeks	Recovered
Einollahi <i>et al</i> ⁶	2003	44/F	Iran	17 months	Fever, right knee swelling	3.8 (admission), 1.71 (discharge)	Synovial fluid, blood culture	Brucellosis arthritis	Doxycycline, rifampin and ciprofloxacin	Recovered
Ting <i>et al</i> ⁷	2013	58/M	Taiwan	3 years	Fever, sweating, malaise	1.25	Blood culture (<i>B. melitensis</i>)	Haematologic, hepatobiliary	Tigecycline for 2 weeks; minocycline and TMP/SMX for 3 months	Recovered
Ay <i>et al</i> ⁸	2016	20/M	Turkey	4 months	Cough, fever, right flank pain, weakness	1.4 (admission), 1.08 (discharge)	<i>Brucella</i> titre (1:320)	Brucellosis pneumonia	Doxycycline and rifampin for 6 weeks	Recovered
The present report	2017	61/M	Saudi Arabia	8 years	Fever, burning micturition, dizziness, headache	3.3 (admission), 0.8 (discharge)	<i>Brucella</i> titre (1:10240)	Haemodynamic compromise	Doxycycline and ciprofloxacin	Recovered

F, female; M, male; TMP/SMX, trimethoprim/sulfamethoxazole.

Brucella species where most of the organisms get phagocytosed and the remaining microbes replicate intracellularly in the endoplasmic reticuli.¹⁰ *Brucella* uses multiple mechanisms to evade the immune system that contribute to the development of chronicity. Lipopolysaccharides (LPS) of *Brucella* species are different from the endotoxic LPS. It induces a weaker innate immune response that is helpful in immune system evasion.¹¹ LPS play a major role in cell entry, survival and systemic propagation of the infection by cell elimination and apoptosis.¹² Cell-mediated immunity plays the principal role in immunity against the bacteria. Humoral mechanisms are also activated early in the course of the disease. Although these are of high diagnostic importance, their immune significance is limited. Cell-mediated type 1 helper T-cell response is the most important component for brucellosis control in the body that involves coordination of multiple cytokines and markers. Interleukin (IL)-2, IL-12, interferon (IFN)-gamma and tumour necrosis factor (TNF)-alpha are the major constituents.^{13–14} Long-term glucocorticoids administered in renal transplant patients have been speculated to increase the risk of brucellosis by immunosuppression and cytokine modulation, especially TNF-alpha and IFN-gamma.⁵ Additionally, renal function deterioration is a stand-alone factor decreasing the level of immunity on multiple levels that may also predispose such patients to brucellosis.¹⁵ In-depth studies are warranted to ascertain the mechanisms involved in renal transplant recipients contracting *Brucella*.

The diagnosis of brucellosis is based mainly on the culture of the organisms, which is considered as the gold standard. Specimens for culture can be obtained from blood, bone marrow or liver. ELISA and tube agglutination are helpful initially to define the titres. Serum agglutination test showing a fourfold or greater rise in total anti-*Brucella* antibodies, on specimens taken two or more weeks apart with similar laboratory conditions, is a valid definition of the disease in ideal conditions. However, a general consensus of 1:80 in non-endemic areas and 1:160 in endemic regions is followed to avoid treatment delay.^{16–17} ELISA and PCR for *Brucella* markers are preferred investigations. Furthermore,

imaging modalities and synovial fluid analysis may also be required for focal infections.

In the management of patients with brucellosis, two regimens have frequently been employed. Doxycycline and streptomycin regimen with 100 mg oral doxycycline twice a day and 1 g intramuscular streptomycin once a day is recommended as the most common, and the most effective treatment that reportedly cured 92% of the cases in a meta-analysis with a highly significant p value of 0.0004.¹⁸ Doxycycline is continued for 6 weeks while streptomycin can be continued for 2–3 weeks. The other regimen uses oral rifampicin in combination with doxycycline. Although oral therapy with rifampicin in combination with doxycycline is cheap and easier to administer, doxycycline and streptomycin regimen has been identified to be therapeutically superior. Ciprofloxacin can be used as an alternative agent with doxycycline and has comparable efficacy, especially in cases of resistance and relapse.¹⁹ Tigecycline has also been presented as an efficacious drug for brucellosis in a case of renal transplant recipient.⁷ Other regimens that comprised triple drug therapies are used in focal disease, such as neurobrucellosis and spondylitis.¹⁹ As our patient had showed a deranged renal function (serum creatinine, 292 μ mol/L), we used ciprofloxacin instead of streptomycin keeping in view the nephrotoxic nature of streptomycin. The clinical response was remarkable with resolution of the disease.

Physicians should maintain a high index of clinical suspicion for this disease in patients who undergo renal transplantation. A timely aetiology establishment will help to save any inadvertent events in the care of these patients and it will also save the healthcare costs incurred due to the missed diagnoses. Identification of the characteristics of brucellosis, including the monitoring of immunosuppressive agents and therapy dosages among renal transplant recipients are strongly warranted. This article prompts to conduct population-based studies to evaluate the actual incidence of this infection with related clinical implications. In future, cases of brucellosis in renal transplant recipients need to be documented. It will contribute to build surveillance

data and help to frame standard guidelines for the diagnosis and management of these patients.

Learning points

- ▶ While brucellosis is a common infectious disease, it is rarely encountered following renal transplantation.
- ▶ This study highlights that physicians should be vigilant, and a thorough workup should be performed for brucellosis in renal transplant recipients presenting with constitutional symptoms.
- ▶ Complete recovery with combination antibiotic therapy can be achieved; however, prompt diagnosis carries a paramount importance in the management of such patients.
- ▶ Population-based studies are warranted to further investigate this association.

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