Gram-negative sepsis following biopsy of a transplant recipient with asymptomatic allograft pyelonephritis

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Abstract Pyelonephritis post-renal transplantation is common and in up to 50% of cases can be asymptomatic. Transplant pyelonephritis shares a lot of histopathological features with acute cellular rejection. We present a case of asymptomatic acute graft pyelonephritis where a renal biopsy was complicated by sepsis, and discuss the difficulties in interpretation of renal histology in the setting of transplant pyelonephritis where rejection may also be a possibility, but differentiation is challenging.

Keywords Acute graft pyelonephritis · Urinary tract infections · Transplantation

Introduction

The incidence of pyelonephritis in recipients post-renal transplantation is reported to be between 10 and 25%, with nearly half of these cases are asymptomatic. Transplant pyelonephritis shares many histopathological features with acute cellular rejection (ACR), such as an interstitial infiltrate and tubulitis, and may potentially mask detection of ACR.

We present a case of a renal transplant recipient with asymptomatic acute graft pyelonephritis who underwent a diagnostic transplant biopsy for investigation of graft dysfunction. Post-biopsy course was complicated by

haematuria and sepsis requiring inotropic support. Histopathological examination showed features of acute graft pyelonephritis, although rejection could not be excluded.

We also review the literature outlining the clinical features and diagnosis of acute graft pyelonephritis, and difficulties in differentiation from ACR, as well as reported long-term outcomes.

Case report

A 41-year-old male presented for a renal transplant biopsy for investigation of graft dysfunction.

He had a history of end-stage kidney disease secondary to IgA nephropathy (initially diagnosed in 1989) and had commenced haemodialysis in 1998. He underwent a cadaveric renal transplantation at The Royal Melbourne Hospital (RMH) in 2004, with a post-transplant period that was initially uncomplicated. His serum creatinine plateaued with a level between 120 and 150 $\mu\text{mol/L}$, and his immunosuppression consisted of cyclosporine 25 mg bd, mycophenolate mofetil 500 mg bd, and prednisolone 5 mg daily. Other medications included diltiazem, atenolol, frusemide, simvastatin, folic acid, omeprazole, and co-trimoxazole.

From 2005 until late 2013, he was managed locally in a rural area and not been seen at RMH until he was referred back with deteriorating graft function. His serum creatinine had increased to 230 $\mu\text{mol/L}$ in the early 2014 from a baseline of 180 $\mu\text{mol/L}$ several months prior (Fig. 1). A graft biopsy was planned in the early Feb 2014 to investigate the cause of his gradually worsening graft function.

Given the patient was being administered warfarin, which was commenced 2 years earlier for a cardiovascular

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Fig. 1 Change in serum creatinine level (μmol/L) since transplantation

event, this medication was ceased and he was started on enoxaparin. Admission to RMH was arranged the night before the biopsy for convenience given geographical issues. On admission, the patient was asymptomatic with unremarkable vital signs. Blood results revealed serum creatinine 219 μmol/L, urea 15.4 mmol/L, hemoglobin 138 g/L, and white cell count $11.5 \times 10^9/L$ (neutrophils 9.5). Urine had been sent for microscopy, but results were pending at the time of biopsy. He underwent a transplant biopsy with one pass (one core) and no immediate complications.

Two hours following the biopsy, the patient developed tachycardia, with a heart rate of 140 bpm in atrial fibrillation. He became hypotensive, with a systolic blood pressure falling from 140 to 90 mmHg, and his temperature was 38.5 with associated rigors and sweats. He subsequently developed haematuria, associated with clots, and his urine output reduced over the next few hours. Management involved intravenous fluid and antibiotics and insertion of a urinary catheter. With ongoing hypotension, he was admitted to the Intensive Care Unit (ICU) for inotropic support. A CT of his abdomen showed no active bleeding, no obvious haematoma, good perfusion of the graft, and no hydronephrosis.

Over the next 24 h, he developed anuria and required hemofiltration. Noradrenaline was continued in ICU. Blood cultures were positive for both *Escherichia coli* and *Enterobacter aerogenes*, which were also cultured from the urine collected prior to the biopsy. A diagnosis was made of urosepsis with biopsy-induced bacteremia. The following day, inotropic support was withdrawn and he was discharged from ICU. His renal function improved and he remained stable in hospital until discharge 7 days later, with a serum creatinine of 177 μmol/L. Oral antibiotics were continued for a further week and immunosuppression remained unchanged.

Histology from the biopsy revealed active pyelonephritis on a background of severe tubular atrophy and interstitial fibrosis with moderate arteriolar hyalinosis (although acute cellular rejection could not be excluded as a cause of graft dysfunction) (Fig. 2). Immunofluorescence was unremarkable. Five months following discharge from this, admission graft function was stable with a creatinine level between 180 and 210 μmol/L (Fig. 1).

Discussion

We present a case of a renal transplant recipient who underwent a diagnostic renal biopsy to investigate graft dysfunction but had concurrent asymptomatic allograft pyelonephritis. The post-biopsy course was complicated by haematuria, acute kidney injury, and septic shock requiring admission to ICU for inotropic support. Graft function recovered to baseline prior to the biopsy. The diagnosis of graft pyelonephritis was a clinical one based on the urine microscopy and clinical presentation, given the difficulty in interpretation of the graft histology.

Urinary tract infections (UTIs) are common in recipients post-renal transplantation, with reported incidence between 10 and 85%. The incidence of acute graft pyelonephritis (AGPN) is reported to range between 10 and 25% in those with documented UTIs. Both UTIs and AGPN can progress and lead to bacteremia with an increased risk of morbidity and mortality, especially during the first 6-month post-transplant. This time coincides with the highest risk of acute rejection and when immunosuppressive therapy is at its maximum [1, 2, 6–8].

In renal transplantation, with administration of immunosuppression, many of the classical features of acute pyelonephritis are subdued or not present (for example flank pain, dysuria, fevers, and raised inflammatory markers) with published reports, indicating about 50% of cases of AGPN are asymptomatic. Urine microbiology is also often unhelpful in the diagnosis of UTIs in transplantation with more than 50% of cases of allograft biopsies showing features of AGPN despite negative urine microbiology. AGPN is, therefore, commonly determined coincidentally from histology of an allograft biopsy [3]. Interstitial inflammation with a predominance of polymorphonuclear leukocytes (PMNs) and intra-tubular PMNs forming micro-abscesses are the hallmark histological features of AGPN. However, infiltration of PMNs can occur in ACR and, given the patchy nature of AGPN in addition to sampling issues, intra-tubular PMNs, and micro-abscesses may not always be seen on the biopsy sample, therefore, differentiating between AGPN and ACR can often be difficult [4, 5].

Fig. 2 Renal histology

Reports of the effect of AGPN on long-term graft and patient survival are conflicting with some showing a deleterious effect and others no difference. Pelle et al. reported that AGPN was associated with poorer long-term renal graft function and Giral et al. reported that the early AGPN (within the first 3 months) was significantly detrimental for graft outcome, independent of acute rejection [6, 7]. Fiorante et al. however, reported no association between AGPN and long-term graft survival [8]. The underlying pathogenesis of interstitial inflammation, either from AGPN or ACR, is important to determine because of differences in management. Treatment of AGPN is primarily antibiotics and reduction in immunosuppression, whereas ACR is generally treated with increased corticosteroids and often an increase in other immunosuppressive therapy, which may potentially further potentiate the risk of infection. Given the importance of determination of new methods to differentiate between AGPN and ACR, investigators have researched the potential use of micro-RNAs to differentiate AGPN from ACR on biopsy samples, but studies to date are small in number and results will require extensive validation and optimization before these techniques are clinically established [9].

In conclusion, we highlight a case of a renal transplant recipient with asymptomatic allograft pyelonephritis who

developed septic shock following an indication renal biopsy for worsening renal function. ACR as a cause of graft dysfunction could not be excluded as there are similarities in histology with the features of transplant pyelonephritis.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of interest The author declares no conflict of interest.

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