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Case Report

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Histological findings in two renal transplants accomplishing operational tolerance criteria

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Abstract
Operational tolerance is defined as stable renal function in transplants without immunosuppression for at least 1 year. We present histological assessments of two patients with operational tolerance. The first withdrew immunosuppression in 2005 and presents stable renal function (creatinine 1.5 mg/dL) without proteinuria. The biopsy showed mild chronic tubulointerstitial changes without inflammation. The second withdrew immunosuppression in 2009 and maintains stable renal function (creatinine 1.6 mg/dL) with mild proteinuria. Histology showed chronic humoural rejection and Class II anti-human leukocyte antigen antibodies were detected. These cases suggest that a renal biopsy may be useful to rule out subclinical pathology in patients with operational tolerance.

Keywords: chronic humoural rejection; operational tolerance; renal biopsy

Introduction

Renal transplantation requires life-long immunosuppression and despite the fact that new immunosuppressants have allowed the acute rejection rate to be reduced, long-term results have not clearly improved [1]. Thus, in order to achieve tolerance, important resources have been focussed on finding a strategy to overcome treatment complications and chronic allograft dysfunction. Tolerance in renal transplantation constitutes a very unusual circumstance described in recipients of simultaneous renal and haematopoietic cell transplantation or in a few treatment non-compliant patients [2–9]. The very rare cases of tolerant renal transplants are actively sought to evaluate biomarkers that can be employed to recognize cases that might benefit from immunosuppression withdrawal [7, 9].

The term 'operational tolerance' has been coined as stable graft function in the absence of immunosuppression, without markers of chronic rejection for >1 year. It has been accepted that a serum creatinine <1.7 mg/dL and a proteinuria of <1 g/24 h constitute a reasonable threshold for the absence of chronic rejection [6]. However, this definition is imprecise and does not specify how to rule out signs of chronic rejection. Accordingly, it is open to discussion whether patients who have accomplished operational tolerance criteria should be biopsied to rule out subclinical pathology. In January 2009, we decided to biopsy patients who had accomplished operational tolerance criteria after obtaining informed consent. We report two cases with clinical operational tolerance who were biopsied.

Patient 1

A male, born in 1934, with chronic renal failure of unknown origin and on haemodialysis since 1980 received a deceased, three human leukocyte antigen (HLA) mismatched and 60-year-old kidney in 1984. He received azathioprine and prednisone and the clinical course was uneventful. In 1992, an intestinal B-cell lymphoproliferative disorder was diagnosed. Resection of a jejunal lesion was performed and six cycles of chemotherapy (cyclophophamide, doxorubicin, vincristine and prednisone) were administered. Azathioprine was withdrawn and immunosuppression consisted of prednisone 10 mg/day. In 2001, an inguinal lymphadenopathy revealed a relapse of the B-cell lymphoproliferative disorder. The patient declined chemotherapy and local radiotherapy was performed. In 2004, he slowly reduced and spaced prednisone until complete withdrawal in 2005. Serum creatinine remained stable and proteinuria was consistently <0.5 g/day. In June 2010, the attending physician realized that the patient was free of immunosuppression for 5 years. Serum creatinine was 1.56 mg/dL and proteinuria 100 mg/24 h. Anti-HLA antibodies were negative by solid-phase Luminex assay. A surveillance biopsy was performed after receiving informed consent. It contained six normal and two sclerosed glomeruli. There was mild interstitial fibrosis and tubular atrophy without interstitial infiltrating cells (Figure 1). The arteries showed mild fibrous intimal thickening and the arterioles showed mild hyaline changes. There was no glomerulitis or peritubular capillaritis and C4d staining was negative.

Patient 2

A male, born in 1974, with chronic renal failure due to posterior urethral valves initiated haemodialysis in 1991.

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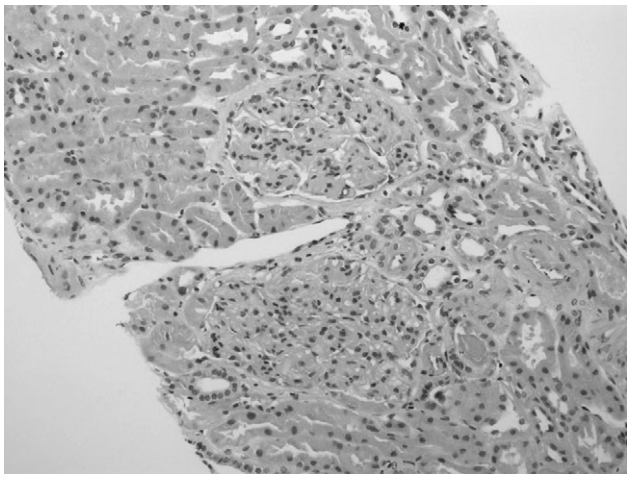

Fig. 1. Renal biopsy showing two normal glomerular sections: absence of interstitial infiltrate and very mild interstitial expansion (haematoxylin and eosin stain, ×200).

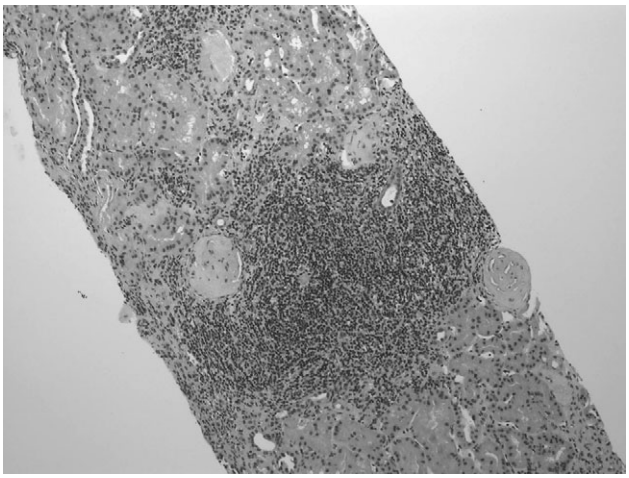

Fig. 2. Severe interstitial infiltrate with mild tubulitis and three sclerosed glomerular sections (haematoxylin and eosin stain, ×100).

He received a deceased, three HLA mismatched and 17-year-old donor kidney in 1993. He was treated with cyclosporine, azathioprine and prednisone. In 1998, azathioprine was replaced by mycophenolate mofetil. In July 2008, he was admitted due to an acute rise in serum creatinine from 1.5 to 4 mg/dL. He was empirically treated with methylprednisolone boluses and serum creatinine returned to 1.6 mg/dL. Before admittance for suspected acute rejection, serum creatinine had been continuously below 1.5 mg/dL with proteinuria <300 mg/day. The patient was attended to until February 2009 when he was lost to follow-up. In May 2010, he returned to the outpatient clinic and serum creatinine was 1.6 mg/dL with proteinuria 500 mg/day. He admitted to irregular compliance with immunosuppression before and after admittance for rejection and complete withdrawal of immunosuppressants on April 2009. Anti-HLA Class I antibodies were negative, while anti-HLA Class II antibodies were positive by solid-phase Luminex assay.

The renal biopsy contained 23 glomeruli, of which 14 were sclerosed and 9 showed mesangial expansion. There was a severe interstitial infiltrate with mild tubulitis (Figure 2). Severe interstitial fibrosis and tubular atrophy were observed. The arteries showed moderate intimal thickening and there was moderate arteriolar hyalinosis. Transplant glomerulopathy, moderate peritubular capillaritis and positive diffuse C4d staining were observed.

Discussion

We describe two patients who accomplished clinical operational tolerance criteria in whom a surveillance biopsy was performed. In the first case, the biopsy was nearly normal and the most remarkable finding was the absence of inflammation. C4d staining and anti-HLA antibodies were negative. Lack of inflammation and signs of chronic humoural rejection suggested true tolerance and immunosuppression was not reintroduced. The second patient had been without immunosuppression for 14 months. The biopsy showed advanced chronic humoural rejection with C4d deposition and anti-HLA Class II antibodies were detected. Despite the fact that the presence of a late episode of acute rejection may herald chronic rejection, this patient also accomplished operational tolerance criteria, and it should be taken into consideration that a tolerant state has also been described after acute rejection [6]. Thus, this case constitutes an example, suggesting that clinical criteria may be insufficient to distinguish between tolerant and rejecting patients.

Since surveillance biopsies have shown that histological lesions may precede renal functional deterioration [10], it seems reasonable that a proportion of patients who have accomplished operational tolerance criteria may suffer from subclinical pathology. However, mistaking chronic humoural rejection for operational tolerance could imply a significant risk for graft failure. In a study describing 10 patients with operational tolerance, two cases were biopsied for renal function deterioration [6]. In one patient, there were no lesions of rejection, but the other one showed C4d-negative transplant glomerulopathy after 7 years without immunosuppression, raising the question whether a surveillance biopsy would have allowed an earlier diagnosis.

European and US Immune Tolerance Networks are looking for patients with operational tolerance to characterize biomarkers of this condition [9]. The few studied patients who have accomplished these criteria have not been biopsied, and misclassification of even a few of them could introduce a significant upheaval in the quest for a tolerant signature.

In summary, we describe the biopsies of two patients with clinical operational tolerance, showing normal histology in the first one and chronic humoural rejection in the second, suggesting that renal biopsy may be useful to rule out subclinical conditions associated with shortened graft survival.

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Conflicts of interest statement. None declared.

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