Recurrent tubulointerstitial nephritis and uveitis syndrome in a renal transplant recipient

Isioma Onyekpe¹, Mohan Shenoy¹, Helen Denley², Hany Riad³ and Nicholas J.A. Webb¹

¹Department of Paediatric Nephrology, Royal Manchester Children’s Hospital, Manchester, UK, ²Department of Histopathology, Manchester Royal Infirmary, Manchester, UK and ³Renal Transplant Unit, Manchester Royal Infirmary, Manchester, UK

Abstract
We report for the time a patient with recurrence of tubulointerstitial nephritis and uveitis (TINU) following renal transplantation. Our patient was diagnosed at the age of 8 years and, despite treatment with systemic steroids, developed established renal failure. At the age of 17 years, he underwent a live-related donor renal transplant. Immunosuppression included tacrolimus, mycophenolate mofetil and prednisolone. Having had normal renal function for 3 years after transplantation, he developed uveitis and decline in the graft function. A biopsy of the allograft demonstrated recurrent granulomatous interstitial nephritis. The recurrence of TINU following transplantation suggests a role for circulating autoantibodies in the disease pathology.

Keywords: corticosteroids; disease recurrence; kidney transplant; TINU syndrome

Introduction
Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare oculorenal disorder characterized by the development of acute tubulointerstitial nephritis (TIN) and uveitis. It was first described in two adolescent girls who developed acute renal failure associated with eosinophilic TIN, anterior uveitis and bone marrow granulomas [1]. The median age of onset is 15 years and there appears to be a female predominance. Presenting symptoms are typically non-specific, including anorexia, nausea, vomiting, abdominal pain, fever, lethargy, myalgia, arthralgia and weight loss. The timing of the ocular symptoms of eye pain and redness, photophobia and reduced acuity is variable and symptoms can be absent at presentation. Laboratory findings include renal impairment with normo- or hypokalaemia, anaemia and elevated ESR and IgG. Urinary findings are consistent with tubulopathy (glycosuria, non-nephrotic proteinuria, sterile leucocyturia, microscopic haematuria). In the majority of cases in children, TIN resolves completely, either spontaneously or following the administration of systemic steroids and/or other immunosuppressive agents in those with severe functional impairment. The uveitis, while often initially treatment responsive, has a tendency to relapse, requiring multiple courses of topical steroids and long-term ocular complications occur in ~20% [2].

The cause of TINU is unknown and the pathogenesis remains unclear. There is evidence from reports that cell-mediated as well as humoral immune responses are implicated [3, 4]. An autoimmune pathogenesis has been suggested in reports with evidence of T-cell-mediated reaction against renal tubular epithelial and retinal antigens [5–7]. TINU has been reported in a mother and her son and in two sets of twins, where identical haplotypes have been proven, suggesting a genetic predisposition to TINU [8–12].

We report for the first time a case of recurrent TINU following renal transplantation (RT).

Case
An 8-year-old boy presented with an 18-month history of weight loss, pallor, poor appetite, nausea and intermittent abdominal pain. He also complained of a painful red left eye for 5 months. There was no history of vomiting, diarrhoea, fever, polyuria or urinary symptoms. General examination revealed pallor, hypertension (138/83 mmHg), bilateral red eyes and unequal and poorly reacting pupils. There were no known allergies and he was receiving no medications. There was no significant family history. Investigations revealed a reduced eGFR at 26 mL/min/1.73m² with otherwise normal biochemistry and normocytic normochromic anaemia. There was proteinuria (U₇PCR 108 mg/mmol) and glycosuria. Ultrasound demonstrated normal-sized kidneys with increased echogenicity. Ophthalmological assessment confirmed bilateral anterior uveitis, more severe on the left.

Further investigations are shown in Table 1. Appearancees on renal biopsy (Figure 1a) were in keeping with granulomatous interstitial nephritis.

He was treated with oral prednisolone 2 mg/kg for 4 weeks followed by a slow reduction to a maintenance dose of 0.5 mg/kg on alternate days. Topical eye treatment
(steroid and cycloplegic drops) was also administered. Hypertension was controlled with calcium channel blockers and beta-blockers. Prednisolone was discontinued after 9 months because of lack of major clinical improvement (eGFR 41 mL/min/1.73m²) and the development of cushingoid features and multiple viral warts. He remained symptom free for 6 months following discontinuation of steroids and renal function improved (eGFR 52 mL/min/1.73m²). He then had a relapsing course of uveitis and nephritis over the following 3 years which was again treated with topical eye drops and oral prednisolone plus azathioprine 100 mg/day. Despite this, renal function showed a steady decline and he developed established renal failure (ERF) 9 years following the initial presentation.

At 17 years of age, he received a pre-dialysis renal transplant from his father (44 years, mismatch 0:1:1). Maintenance immunosuppression included tacrolimus (trough levels 5–8 mcg/L), prednisolone 10 mg alternate days and mycophenolate mofetil (MMF) 300 mg/m² twice daily. His renal function remained normal 36 months post-RT (eGFR 94 mL/min/1.73m²), after which a gradual decline was observed (eGFR 52 mL/min/1.73m²). This was associated with mild anaemia. Urine culture and transplant ultrasound were normal. Transplant biopsy at 41 months revealed granulomatous interstitial nephritis.

His immunosuppression was increased (MMF to 600 mg/m² and prednisolone to 10 mg daily). Renal function remained impaired at 52 months (eGFR 32 mL/min/1.73m²). Repeat allograft kidney biopsy at this stage (Figure 1b) again showed granulomatous interstitial nephritis in keeping with recurrent primary disease with no evidence of rejection. By this stage, he had also developed recurrent bilateral anterior uveitis. A repeat immunology screen, angiotensin-converting enzyme level, Mantoux test and chest X-ray were all normal.

Following three doses of intravenous methylprednisolone 1 g, graft function improved. He remains well with an eGFR of 40 mL/min/1.73m² 66 months post-transplant.

### Discussion

We report the first case of TINU recurring 3.5 years after renal transplantation in a 20-year-old male. The presenting episode of TINU at 8 years of age stabilized following the introduction of prednisolone, though his renal function remained abnormal and following a relapsing course progressed to ERF. While unusual in that the renal outcome in the majority of patients with TINU is good, there are a number of other reports of individuals developing ERF [4]. The episode of histologically proven recurrent disease, which occurred at 41 months post-transplantation, was initially unresponsive to intensification of his maintenance immunosuppression, though there was sustained improvement in renal function following three doses of intravenous methylprednisolone. Our patient remains well with reasonable graft function >2 years after the first histological confirmation of recurrent disease.
Despite >200 reports of TINU in the medical literature, the disease pathogenesis remains poorly understood and many different mechanisms have been postulated. The development of recurrent renal and ocular disease following transplantation as reported here is strongly supportive of the presence of a circulating autoantibody with cross-reactivity against a shared tubular and uveal epitope. It is interesting to speculate whether differences in antigenic load between the kidney and eye might explain the frequently reported delay in presentation of the uveitis in relation to the interstitial nephritis. A number of different candidate antigens have previously been reported and further characterization of these is required [5–7]. The identification of an autoantibody as the cause of TINU might also be of potential therapeutic importance.

Conflict of interest statement. None declared.

References

Received for publication: 3.5.11; Accepted in revised form: 20.5.11