OMCR

Oxford Medical Case Reports, 2016;10, 248–251

doi: 10.1093/omcr/omw073
Case Report

CASE REPORT

Induction treatment of previously undiagnosed ANCA-associated vasculitis in a renal transplant patient with Rituximab

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Abstract

We report the case of a 40-year-old female transplant patient with undiagnosed ANCA-associated vasculitis (AAV) and renal allograft dysfunction who achieved disease remission with restoration of transplant function following induction therapy with rituximab. There are currently no trial data looking at the use of rituximab for induction of remission of renal transplant patients with AAV. Although recurrence of AAV following renal transplantation is rare, such patients have invariably had multiple previous exposures to induction and maintenance immunosuppressive regimens, often limiting treatment options post-transplantation. In this case, rituximab was well tolerated with no side effects, and was successful in salvaging transplant function. Optimal treatment regimens for relapsed AAV in the transplant population are not known, and clinical trials are needed to evaluate the efficacy and safety of rituximab at inducing and maintaining disease remission in relapsed AAV following transplantation.

INTRODUCTION

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a group of autoimmune diseases that cause necrotizing inflammation of small blood vessels, and include granulomatosis with polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis. Up to 85% of patients with AAV will have renal involvement at some point and 50% have renal involvement at presentation [1]. Despite advances in induction and maintenance therapies 25% of patients with AAV progress to end-stage renal failure (ESRF), (median time of 1.9 months, range: 0–129.6 months), requiring dialysis or transplantation [2]. Renal transplantation offers the best survival outcomes for patients who develop ESRF secondary to AAV and relapse rates are lower in transplanted patients compared to those on dialysis or with preserved native renal function. AAV recurrence is associated with increased morbidity and mortality and maintaining transplant renal function is crucial due to the survival benefit for patients with a functioning renal transplant compared to patients on dialysis. Relapses of AAV following renal transplantation are traditionally treated

Received: July 12, 2016. **Revised:** July 25, 2016. **Accepted:** July 27, 2016

with glucocorticoids and cyclophosphamide in the same way as vasculitis relapses in patients with native renal function, but treatment side effects of this regimen are high with over 40% of patients experiencing treatment-related morbidity.

Rituximab (an anti-CD20 B-cell depleting monoclonal antibody) is non-inferior in randomized control trials (RCT) as induction therapy for patients with newly diagnosed AAV with renal involvement compared to cyclophosphamide [3], and may be superior at inducing remission in patients experiencing relapse [4]. There are no trial data on the use of rituximab to treat relapses of AAV following renal transplant, with experiences limited to case reports [5]. We present the case of a renal transplant patient found to have previously undiagnosed AAV and renal allograft dysfunction who achieved disease remission with restoration of transplant function following induction therapy with rituximab.

CASE REPORT

A 40-year-old female transplant patient presented with unexplained constitutional symptoms, shortness of breath, atypical chest pain and fatigue. Pulmonary function tests, electrocardiogram, transplant-drug levels, CMV, EBV titres and parvovirus B19 were normal. A decline in transplant function was noted, with the development of moderate proteinuria (urine Polymerase chain reaction (PCR) 108 mg/mmol, sub-nephrotic range).

She initially presented in 1997 (aged 17) with nephrotic syndrome, invisible haematuria, preserved renal function and biopsy findings of focal segmental proliferative glomerulonephritis with tuft necrosis but no crescents (Fig. 1A,C). Serological tests in 1997 for vasculitis (including ANCA (immunofluorescence testing), anti-glomerular basement membrane, dsDNA, ANA and complement) were negative. She was treated unsuccessfully with oral cyclophosphamide and intravenous methylprednisolone when she developed progressive decline in native renal function and received her first living-related renal transplant when she reached ESRF in 1998. Her first living-related transplant failed after 15 years due to chronic allograft nephropathy and she received a second pre-emptive living-related transplant 3 years prior to the episode we describe with a baseline serum creatinine of 140 mmol/L.

Following her presentation with constitutional symptoms and unexplained graft dysfunction she underwent renal transplant biopsy. This showed focal segmental proliferative glomerulonephritis in a similar pattern to her original native renal biopsy, with no evidence of crescents or fibrinoid necrosis (Fig. 1B,D). Given these findings, serological tests for vasculitis were repeated, this time showing a strongly positive pANCA titre (1:640) (immunofluorescence testing), with MPO titre >134 IU/ml and PR3 titre <5 IU/ml (ELISA testing) (normal ranges <5 IU/ml). A new diagnosis of AAV was made. Given her previous exposure to cyclophosphamide she received induction treatment with rituximab. She had two doses of intravenous rituximab (1 g) 2 weeks apart, with a reducing dose of oral prednisolone (from 60 mg). Over the subsequent 3 months her renal function stabilized to its previous levels and proteinuria resolved (Fig. 2). Constitutional symptoms abated and ANCA titres reduced within 6 months from >134 IU/ml to 58 IU/ml. Her immunosuppressive regimen was unchanged during the treatment of her vasculitis flare (Prograf (Tacrolimus) 1.5 mg/1 mg BD) and she continued on 5 mg oral prednisolone following her reducing dose of oral prednisolone.

DISCUSSION

It is most likely that the patient we describe had vasculitis at presentation as a 17-year old that was serologically negative

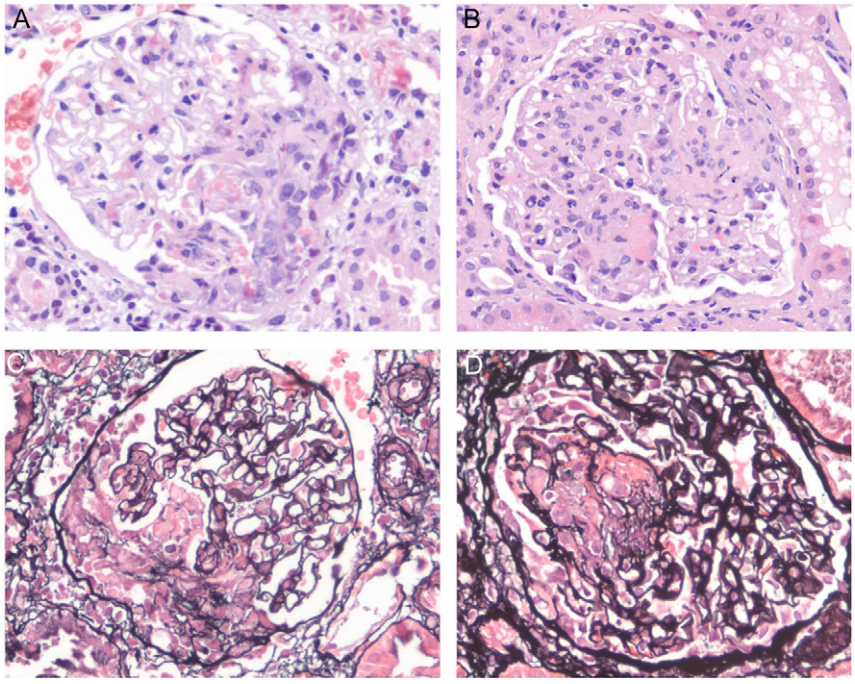

Figure 1: (**A**) Hematoxylin and eosin stain (H&E) from original native renal biopsy in 1992. Glomerulus shows significant segmental increase in cellularity of glomerular tuft, with tuft necrosis. (**B**) H&E from transplant renal biopsy 2015. Glomerulus pictured shows very solid glomerular tuft. In places there is hypereosinophillic material suggestive of early fibrinoid necrosis. (**C**) Silver stain of native renal biopsy from 1992, confirms presence of tuft necrosis but shows no other structural abnormality. (**D**) Silver stain of transplant renal biopsy from 2015, confirms the presence of tuft necrosis. The pattern of glomerular injury in the transplant biopsy from 2012 is similar to that seen in the original biopsy from 1992 and suggest a recurrence of the primarily underlying glomerulonephirits.

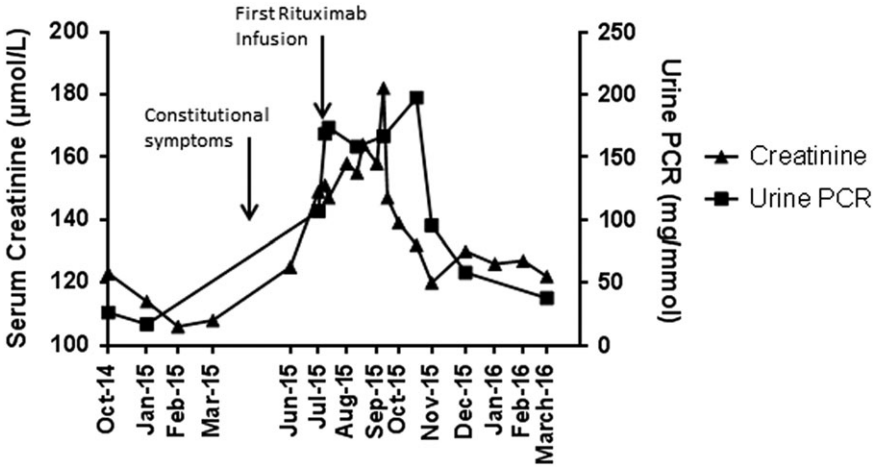

Figure 2: Change in serum creatinine and urine PCR during vasculitis flare and following induction therapy with Rituximab. Second Rituximab infusion was given 2 weeks following the first.

(a phenomenon thought to occur in 10% of patients with AAV [6]), and this recurred in her second transplant in association with a positive ANCA. Relapses of AAV following renal transplantation usually manifest as pauci-immune necrotizing glomerulonephritis and although recurrence following transplantation is rare, they may develop at any time. Data suggest that with modern immunosuppressive regimens, AAV relapse following transplantation is less common than in patients with native renal function, occurring in just 9% of patients [7].

The use of rituximab in renal transplantation is not new. It has been used with varying degrees of success to treat antibody-mediated rejection, post-transplant lymphoproliferative disease and to manage ABO-incompatible transplants. Outcome data suggest that it is safe making it an attractive therapeutic option given that induction regimens with cyclophosphamide and glucocorticoids increase rates of lymphoma, leukaemia and bladder cancer, and cause drug-induced cystits, cytopaenias, infection and infertility. Long-term safety concerns about the use of rituximab as maintenance therapy for AAV after remission induction with rituximab have been reported in the MAINRITSAN trial [8] and are being addressed in an ongoing international, multi-centre, open label, RCT comparing outcomes for patients with relapsing AAV treated with rituximab or azathioprine as maintenance (RITAZAREM; NCT01697267).

There is good RCT evidence from the RAVE trial that rituximab is non-inferior to cyclophosphamide for induction remission in patients with native renal function and severe AAV, and is superior to cyclophosphamide in patients who present with severe disease relapse at baseline [4]. The RAVE trial suggested that the effects of one induction course of rituximab (dose of 375 mg/m^2) once weekly for 4 weeks was equivalent to 18 months conventional therapy of daily cyclophosphamide (3–6 months) followed by azathioprine [9]. The RITUXVAS trial showed no differences in efficacy or safety outcomes between patient who underwent induction therapy with cyclophosphamide vs patients who underwent induction therapy with rituximab plus cyclophosphamide in patients with newly diagnosed AAV [10]. Overall, the RAVE and RITUXVAS trials suggest that in patients with major renal disease, rituximab is at least equivalent to cyclophosphamide for remission induction, even if initial eGFR is <30 mL/min/1.73 m^2. Based on the efficacy data from these two trials, the use of rituximab for remission induction may be justified in any patient with severe AAV and for treatment of severe disease relapses due to potentially superior efficacy [11].

There are case reports of renal transplant patients being successfully treated with rituximab for AAV relapse [5], but no trial data. Extrapolating data from treatment of AAV in patients with native renal function is the best we can do, but clinical trial work is needed in this population to assess efficacy of rituximab vs standard therapy. Such trials must address safety concerns about the long-term effects of rituximab in a patient group who are already immunosuppressed and in whom the medium-to-long-term risk of malignancy is significantly elevated. This case highlights the importance of revisiting a diagnosis in the light of new clinical features, even if the patient has been under follow-up for nearly 20 years!.

ACKNOWLEDGEMENT

Not applicable.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

There was no funding for this report.

ETHICAL APPROVAL

No ethical approval required.

CONSENT

Not applicable.

GUARANTOR

Dr Matthew Graham-Brown.

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