Recurrence idiopathic membranous nephropathy in the renal allograft: successful treatment with the anti-CD20 monoclonal antibody rituximab

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Abstract

Idiopathic membranous glomerulonephritis (IMGN) is one of the most common causes of nephrotic syndrome in adults. Disease progression is associated with the magnitude and duration of proteinuria [Reichert LJ, Koene RA, Wetzels JF. Prognostic factors in idiopathic membranous nephropathy. Am J Kidney Dis 1998; 31: 1–11]. Membranous nephropathy is also one of the glomerular diseases that is well described to recur in the transplanted kidney [Kotanko P, Pusey CD, Levy JB. Recurrent glomerulonephritis following renal transplantation. Transplantation 1997; 63: 1045]. There is no definitive therapy for primary membranous glomerulonephritis or recurrent disease in the graft. Cyclophosphamide plus steroids or cyclosporine [Cattran DC, Greenwood C, Ritchie S et al. Canadian Glomerulonephritis Study Group. A controlled trial of cyclosporine in patients with progressive membranous nephropathy. Kidney Int 1995; 47: 1130–1135] have been the preferred agents for the treatment of MGN involving the native kidneys. More recently, several reports have described the use of the anti-CD20 monoclonal antibody rituximab in patients with IMGN. In the current report, we present a patient with ESRD secondary to IMGN who developed nephrotic range proteinuria 5 months after receiving a kidney transplant from a deceased donor. A biopsy of the allograft demonstrated changes compatible with recurrent membranous glomerulonephritis. The patient was treated with four weekly infusions of rituximab over a 1-month period with a significant decrease in proteinuria and an improvement in renal function.

Keywords: proteinuria; recurrent membranous nephropathy; renal allograft; rituximab

Introduction

Worldwide, membranous nephropathy is the most common cause of nephrotic syndrome in adults with a predominance in Caucasian men. The disease is usually idiopathic although it has been associated with certain infections such as hepatitis B and C virus, syphilis and schistosomiasis as well as treatment with gold and penicillamine. The disease can resolve spontaneously, remain relatively stable for long periods of time or progress to end-stage renal disease over a period of years.

Membranous nephropathy has characteristic findings on histology. On light microscopy, there is thickening of the glomerular basement membrane without mesangial or epithelial expansion. The silver stain classically demonstrates ‘spikes’, and immunofluorescence shows a diffuse granular pattern of IgG and C3 staining along the glomerular basement membranes. On electron microscopy, there are subepithelial deposits with effacement of the epithelial cell foot processes. It is unclear which antigen(s) are present in the glomeruli that trigger the immune complex deposition; however, recent studies suggest that NEP (neutral endopeptidase) is one of the target antigens in membranous glomerulonephritis (MGN) [5].

The pathogenesis of MGN is related to an antigen–antibody reaction. Experimentally, the Heymann nephritis model has been used to study the pathophysiology of membranous glomerulonephritis in animals. In this model, there are antibodies against megalin (not presented in humans), a receptor present on epithelial cell foot processes. The interaction between the antibody and megalin leads to subsequent complement activation and insertion of the C5b-9 membrane-attack complex. As a consequence of this process, there is podocyte injury with loss of slit diaphragm functionality, inflammation and glomerular basement membrane expansion with the subsequent development of clinical proteinuria. The corresponding human antigen is still not known, and the development of new, more focused therapies will be dependent on progress in this area of research.

The clinical presentation of MGN is well described. Most patients present with nephrotic syndrome and its attendant complications (hyperlipidaemia, increased risk of venous thrombosis, hypoalbuminaemia and increase risk of infections). A kidney biopsy remains the gold standard
for diagnosis, and secondary causes of MGN should be excluded.

There is no widely accepted standard treatment for MGN, and the most common approach at this time is usually the combination of cyclophosphamide and steroids. Cyclosporine has also been used with or without steroids with some success [3].

Recurrence of membranous nephropathy in the transplanted kidney is not common compared to other glomerular diseases such as focal segmental glomerulosclerosis and membranoproliferative glomerulonephritis [6]. The rates of recurrence with MGN vary from 10 to 30%, and interestingly, the disease is often more clinically aggressive in the allograft [7]. Currently available therapies for immunosuppression including cyclosporine, rapamycin, tacrolimus and mycophenolate mofetil have not been found to be very effective in cases of recurrent disease [8]. There are some reports in the literature that describe the use of the monoclonal antibody against CD-20 (rituximab) with good response [6,9,10]. The theory behind the use of this product is that it depletes the B-cell population with a subsequent decrease in the production of the antibody of interest. The patient described in this current report had a recurrence of MGN while on maintenance doses of tacrolimus and mycophenolate mofetil.

**Case**

The patient is a 43-year-old gentleman with end-stage renal failure secondary to IMGN. He was originally diagnosed in 1998 and received treatment with cyclosporine, mycophenolate mofetil and corticosteroids. Despite this therapy, he had progressive chronic kidney disease over an 8-year period and required the initiation of renal replacement therapy in December 2006.

The patient received a one A-, two B- and one DR-mismatched renal transplant from a deceased organ donor on 1 April 2008. Induction therapy with thymoglobulin (1.5 mg/kg daily, seven doses daily after transplant) and Zenapax [daclizumab, (1 mg/kg daily on day 0 and another dose 14 days after transplant)] was administered, and he was discharged on day 4 post-transplant on tacrolimus and mycophenolate mofetil without maintenance steroids.

The patient’s protein/creatinine ratio after discharge was stable at ~1; however, by 2 months post-transplant the protein/creatinine ratio increased to 2.9. Workup for other causes of proteinuria was negative including serum and urine protein electrophoresis. An allograft biopsy was performed (Figures 1 and 2) at that time which showed changes consistent with stage 1 MGN. The immunofluorescent stain demonstrated coarse, diffuse granular staining with IgG, C3, IgM and lambda. Intratubular staining for albumin was positive and C4d was negative.

The patient was continued on maintenance immunosuppressive therapy with tacrolimus and mycophenolate mofetil. Four weekly infusions of rituximab (375 mg/m²) were administered over the next month. The CD19/20 positive lymphocyte count became undetectable, and there was mild improvement of the renal function (creatinine decreased from 1.9 to 1.3 mg/dl). A dramatic improvement of the proteinuria was observed following completion of
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the rituximab course of therapy with a decrease in the protein/creatinine ratio to 0.5 (Figure 3). Two months after receiving rituximab, the protein/creatinine ratio has decreased to 0.25. Blood pressure has been controlled with the use of an angiotensin receptor blocker.

Discussion

Our patient presented with recurrent membranous nephropathy in the allograft although the biopsy was atypical because of the immunofluorescence staining demonstrating the presence of lambda protein, a finding not typical in idiopathic membranous glomerulonephritis. Serum and urine protein electrophoresis were negative, and no light chains were identified.

The anti-CD20 monoclonal antibody rituximab has been used for the treatment of lymphomas and many autoimmune conditions (SLE, rheumatoid arthritis, vasculitis). There are several reports describing the use of this product in patients with idiopathic membranous glomerulonephritis. Serum and urine protein electrophoresis were negative, and no light chains were identified.

The current case adds another report to this limited literature and suggests that rituximab may be beneficial in the treatment of recurrent MGN and should be considered as an alternative therapy.

Conflict of interest statement. None declared.

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