Case Report

Nephrotic range proteinuria in a renal transplant associated with oncocyotoma of the native kidney

Michael Lian1, William Mulley1, Kathleen Kan1, Duncan MacGregor2, Andrew Tosolini1 and Francesco Ierino1

1Department of Nephrology and 2Department of Anatomical Pathology, Austin Health, Victoria, Australia

Keywords: membranous glomerulonephritis; oncocyotoma; proteinuria; renal transplant

Introduction

Membranous glomerulonephritis (MGN) is known to cause post-transplant nephrotic syndrome and may be recurrent or de novo [1,2]. Focal glomerulosclerosis (FGS) may also present with nephrotic range proteinuria and has a high incidence of recurrence post-transplantation (20–40%) and approximately half of these recurrences may lead to allograft failure. The risk of recurrent MGN has been reported to be 29% at 3 years and it appears to be more common than de novo MGN in transplant recipients [2,3]. Schwartz et al. [2] have reported that de novo MGN may occur in 5.3% of patients at 8 years. Although nephrotic syndrome is known to complicate underlying malignancies in the non-transplant setting, the association between nephrotic range proteinuria and tumours following renal transplantation is less well defined. This case report addresses the possible mechanisms of proteinuria in a patient with simultaneous recurrent FGS and de novo MGN in a renal transplant. The report describes the association between the removal of an oncocyotoma and the complete reversal of nephrotic range proteinuria, likely to relate to MGN, suggesting that this tumour was the underlying immunological stimulus for the proteinuria.

Case

A 48-year-old female with chronic renal failure secondary to idiopathic FGS received a cadaveric renal transplant 7 months after commencing peritoneal dialysis. Induction immunosuppression included prednisolone, azathioprine and cyclosporine. The patient had an uncomplicated initial clinical course with no evidence of significant proteinuria measured by dipstick urine analysis and no rejection episodes. Prednisolone was slowly reduced and stopped 3 years and 10 months after transplantation. Her other medical problems included hypertension, hyperlipidaemia, cerebrovascular disease, migraine and squamous cell carcinomas of the skin.

The patient presented ~4.5 years post-transplantation with stable renal function (serum creatinine 0.06 mmol/l), persistent hypoalbuminaemia (26 g/l), minimal peripheral oedema and nephrotic range proteinuria (13 g/day). She was on azathioprine 50 mg, cyclosporine 125 mg bd, diltiazem 180 mg, atorvastatin 80 mg, ticlopidine 250 mg bd, atenolol 50 mg, irbesartan 150 mg, pizotifen malate 1 mg and doxepin hydrochloride 10 mg. A renal transplant biopsy was performed to investigate the proteinuria, which showed de novo membranous nephropathy (Figure 1) and FGS (Figure 2). The biopsy included 27 glomeruli of which eight were globally sclerosed. Well developed segmental sclerosis was seen in four of the remaining glomeruli with focally vacuolated hyalinosis in one of these. There was diffuse, global eosinophilic peripheral capillary wall thickening with fine supraperithelial spikes seen in most segments on silver staining. There was mild focal interstitial scarring with focal tubular atrophy. No isometric vacuolation was seen in tubular epithelial cells and there were no arteriolar changes to suggest cyclosporin toxicity. Distinction between recurrent primary FGS or secondary FGS related to the MGN was not possible.

A clinical assessment did not reveal specific symptoms or signs of secondary causes for MGN. Hepatitis serology, autoimmune markers and protein electrophoresis were either normal or negative. At this time the relative contribution of the MGN and FGS to the proteinuria was uncertain. Irbesartan was increased to a maximum dose of 300 mg daily, resulting in some reduction in proteinuria, to a level of ~8 g/day.

Correspondence and offprint requests to: Dr Francesco Ierino, Department of Nephrology, Austin Health, Studley Road, Heidelberg 3084, Victoria, Australia. Email: frank.ierino@armc.org.au

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Fig. 1. Transplant kidney (periodic acid–silver methenamine stain) showing membranous change with silver positive spikes protruding from the basement membrane.

Fig. 2. Transplant kidney (haematoxylin and eosin stain) showing segmental collapse and focal hyalinosis.
The peripheral oedema remained minimal and asymptomatic without the addition of a diuretic. While ongoing review and management was in progress, the patient presented with incidental acute abdominal pain and a diagnostic CT scan revealed a dilated appendiceal tip consistent with acute appendicitis and a mass on her left native kidney (Figure 3). She underwent urgent surgery which confirmed acute appendicitis.

One month following the appendicectomy, the patient proceeded to have a left native nephrectomy and the histology of the left kidney mass demonstrated an oncocytoma. There was no evidence of metastatic disease. Following resection of the oncocytoma, the serum albumin markedly increased from 21 to 31–34 g/l within 21 days post-nephrectomy and the degree of proteinuria profoundly dropped from 4+ to 1+ on testing with urine dipstick analysis during the same time period. Following this, the urine protein was measured at 1.1 g/day and serum albumin normalized to 37 g/l. The fall in proteinuria and normal serum albumin has been sustained since the resection of the oncocytoma. Currently, the patient has 0.35 g/day of proteinuria and a normal serum albumin, 1 year after the native nephrectomy.

Discussion

The aetiology of MGN is often unknown but is likely to relate to various antigenic stimuli and has an immunological basis. There are a variety of identifiable associations with MGN, which include malignancy, systemic lupus erythematosus, rheumatoid disease, drugs, hepatitis B and/or C and MGN may be associated with other renal diseases. The clinical course in de novo MGN in a renal transplant tends to be later in onset when compared with recurrent disease. This is reflected in the onset of proteinuria in de novo MGN, usually occurring 18–21 months after transplantation, compared with a mean onset of 10 months for recurrent MGN [4]. The use of cyclosporine does not change the incidence of de novo and recurrent MGN. This is consistent with our case report, with a late onset following transplantation and presentation despite significant immunosuppression.

MGN can occur with other glomerular diseases, such as FGS, diabetic nephropathy, IgA nephropathy and crescentic glomerulonephritis [5,6]. It is unclear whether these are related or have developed concurrently. In the present case, two possible explanations may account for the presence of the FGS with the MGN. The FGS may represent recurrence of the patient’s primary disease (idiopathic FGS), or secondary FGS, and the histological features in the present case were consistent with either primary or secondary FGS. The late onset of the nephrotic range proteinuria years after transplantation and the resolution of the severe proteinuria are not typical features of recurrent primary FGS, which would generally be progressive once nephrotic range proteinuria is present. Sclerotic glomerular lesions may be observed in association with glomerulonephritis or any cause of renal damage resulting in nephron loss. In the absence of other causes of chronic renal damage such as chronic rejection or clear changes of calcineurin inhibitor nephrotoxicity, secondary FGS in association with the MGN would be a possible clinical relationship. Recurrent primary FGS cannot be excluded as the underlying cause for the sclerotic glomerular lesions.

Underlying malignancy may be associated with ~10% of cases of primary MGN [7] and the risk tends to be highest amongst those over the age of 60. The frequency of malignancy in recurrent or de novo MGN post-transplantation remains less well defined, however, the higher overall incidence of tumours in transplant recipients would support the search for an underlying associated malignancy in these cases.

Removal of underlying tumours in MGN may result in a gradual remission in proteinuria and associations between tumour antigens and MGN have been suggested [8]. Prior to removal of the oncocytoma in our case, it was not known if the proteinuria related to the de novo MGN with secondary FGS, recurrent primary FGS or both. Since primary FGS is more likely to be progressive compared with MGN, the resolution of the nephrotic range proteinuria would support MGN as the underlying cause of the proteinuria. Since there appears to be a strong correlation between the removal of the native kidney oncocytoma and resolution of the nephrotic range proteinuria, the proteinuria was more likely to be associated with the de novo MGN, rather than FGS. Whilst the patient remains in clinical remission, a repeat biopsy to demonstrate resolution of the MGN changes has not been performed. Spontaneous remission of proteinuria secondary to recurrent primary FGS without a change in therapy would be unlikely. Although spontaneous
remission is well described in MGN, it would be difficult to ignore the clinical correlation demonstrated in our case between the removal of the renal oncocytoma and the remission of the proteinuria. This would support the putative association between the resolution of the nephrotic range proteinuria and the removal of tumour antigen, rather than spontaneous remission of the MGN.

Renal oncocytomas are distinct tumours to renal cell carcinomas. Oncocytomas have large, well differentiated neoplastic cells with eosinophilic granular cytoplasm. They are uncommon and typically behave in a benign fashion. Oncocytomas are usually well encapsulated, are rarely invasive and are seldom associated with metastases. They may be difficult to distinguish histologically from low grade renal cell carcinoma or chromophobe renal cell carcinoma [9]. Since MGN is often associated with malignant tumours, it will be important to monitor our patient closely to determine whether the oncocytoma will clinically follow a malignant course.

There is only one case report by Forland and Bannayan [10] of an association between renal oncocytoma and minimal change disease. Similar to the case described by Forland and Bannayan, the proteinuria was seemingly uninfluenced by immunosuppression. However, following resection of the oncocytoma, there was a significant drop in the degree of proteinuria, similar to the present case. Importantly, the remission of the proteinuria has been maintained in our case, at least a year after removing the oncocytoma. This suggests that the mechanism of the proteinuria in our case was related to the presence of the oncocytoma and its unique antigens.

In summary, this report suggests that nephrotic range proteinuria may be associated with a unique renal tumour and that MGN was the likely causative renal lesion. Further studies are required to determine whether specific oncocytoma antigens and antibodies can be identified in MGN lesions and it is important that all cases are reported to determine if this association can be confirmed by others.

Conflict of interest statement. None declared.

References


Received for publication: 22.3.03
Accepted in revised form: 5.9.03