CASE REPORT

De novo membranous glomerulonephritis in a kidney graft recipient

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In renal transplantation, chronic allograft nephropathy is the leading cause of long term graft losses, transplant glomerulopathy being its glomerular form. Differential diagnosis from recurrent or de novo glomerulonephritis should be enstablished. Whether hepatitis C virus is associated with glomerular damage in renal allograft recipients, as in native kidneys, is not known. The aim of this case report was to show the clinical course of a HCV-positive kidney graft recipient who four and a half years posttransplantation presented de novo allograft glomerulonephritis. He was a 45-year-old male kidney graft recipient who presented to the Outpatient Department of Organ Transplant Unit at Hippokratio General Hospital of Thessaloniki on 1999, for further clinical and laboratory evaluation because of bilateral lower extremity edema, proteinuria (24h urine protein: 1,5 g) and mild hypertension. He was a healthy hepatitis C carrier who had received a kidney allograft from his 42-years-old sister on 1995 and no specific treatment was given to him for the positive HCV test before kidney transplantation. He had repeated episodes of acute tonsillitis while he was six years old and he presented rheumatic fever symptoms at age of eight. Aortic and mitral valve deficiency were added at age of fifteen and proteinuria, microscopic hematuria and mild elevation of serum creatinine (Scr : 1,8 mg/dl) at age thirty two. He had two replacements of aortic valve while he was thirty three and thirty eight years old and one of mitral valve at age of thirty eight. The renal function deteriorated gradually and he commenced hemodialysis treatment at age of forty four. He became HCV-positive during the renal replacement treatment. On 13th post-transplant day he was discharged with normal kidney graft function. One month after renal transplantation he presented acute bronchitis which was treated successfully with antibiotics and concomitant reduction of immunosuppression , while four months later he was admitted to our department with acute cholecystitis due to chololethiasis. Sixteen months after kidney transplantation he underwent laparoscopic cholecystectomy but two months later the clinical and laboratory evaluation at the Outpatient Department revealed mild elevation of blood pressure (BP: 140/95 mmHg), microscopic hematuria of upper urinary system origin and microalbuminuria (24h urine protein: 150 mg). The kidney and the liver function tests remained within normal limits during the 2nd , 3rd and 4th post-transplantation year. Proteinuria of nephrotic type (24h urine protein : 1,5 g) and edema of the lower extremities were added to the clinical syndrome, four and a half years post-transplantation. The circulating immune complexes (CICs) were found above normal limits (CIC:75 ng/ml, normal range : 0,5-15 ng/ml) while at the same period the blood viral load of HCV by polymerase chain reaction (HCV-RNA PCR) was greater than 10^6 copies/ml. Renal graft biopsy demonstrated de novo stage II membranous glomerulonephritis with mild arteriosclerosis. Valsartan was added to the treatment in order to reduce proteinuria and stabilize blood pressure and allograft function. Eight years after kidney transplantation there is no impairment either of kidney or liver function, his 24h urine protein is 750 mg, he has negative HCV-RNA PCR and normal serum concentrations of CICs. In conclusion, we have shown that in renal allograft recipients with a past rheumatic fever history, HCV infection may be rarely associated with de novo membranous glomerulonephritis. In this group of patients the angiotensin II type I receptor antagonists may play a useful role for the treatment of proteinuria and hypertension.

Since hepatitis C virus (HCV) was identified in 1989 by Choo et al.[1] as the main cause of non-A non-B hepatitis, HCV infection has achieved a great relevance in nephrology on the basis of its high prevalence among dialysis patients, renal allograft recipients, as well as in essential mixed cryoglobulinemia with associated membranoproliferative glomerulonephritis[2,3]. Although it is well established that HCV infection is the main cause of chronic liver damage in renal allograft recipients, the role of HCV with regard to graft and patient survival remains controversial[4]. HCV infection at the time of transplantation is associated with an increased risk of death, irrespective of whether patients remain on dialysis or undergo transplantation. However, kidney transplantation has a beneficial rather than adverse effect on long term survival in anti-HCV positive patients[5].

Epidimiologic, clinical, and experimental data suggest that HCV infection may induce glomerular damage[6]. HCV has been implicated in the development of membranoproliferative and membranous glomerulonephritis with or without cryoglobulinemia in renal allograft recipients[7]. Most authors suggest that these are immune complex mediated nephritides, while a few failed to show direct evidence for cryoglobulinemia and circulating immune complexes[8]. Recently, renal thrombotic microangiopathy in renal transplant recipients with HCV infection has been reported and the presence of anticardiolipin antibody was implicated in the pathogenesis of this syndrome[9]. It seems that HCV infection in renal transplant recipients is linked to various autoantibodies, some of which show pathogenic activity, such as cryoglobulins with rheumatoid factor activity and anticardiolipin antibodies. More investigations are warranted to clarify these issues and the posttransplantation setting provides an interesting opportunity to investigate the relationship between HCV and glomerulonephritis[10].

The aim of our case report was to show the clinical course of a HCV-positive kidney graft recipient who four and a half years posttransplantation presented de novo membranous allograft glomerulonephritis.

Case report

A 45-year-old male kidney graft recipient presented to the Outpatient Department of Organ Transplant Unit at Hippokratio General Hospital of Thessaloniki on December 12th 1999, with bilateral lower extremity edema to the knees and proteinuria (24h urine protein:1,5gr). He was subsequently found to have mild hypertension (BP: 145/95 mmHg) with normal serum creatinine (Scr: 1,2 mg/dl).

Past medical history revealed a patient with chronic glomerulonephritis and simultaneous chronic hepatitis C healthy carrier who had received a kidney graft from his 42-years-old sister on June 7th, 1995. No specific treatment was given for the positive HCV test before kidney transplantation.

He had repeated episodes of acute tonsillitis while he was six years old and he presented with symptoms of rheumatic fever (multiple arthritis syndrome) two years later. Aortic and mitral valve deficiency were added to the clinical syndrome at age fifteen and proteinuria, microscopic hematuria, hypertension and mild elevation of serum creatinine (Scr: 1,8 mg/dl) at age thirty two. He had two replacements of aortic valve while he was thirty three and thirty eight years old and one of mitral valve at age of thirty eight. The renal function deteriorated gradually and he started hemodialysis treatment one year before kidney transplantation. He became HCV-positive during the renal replacement treatment period (2 blood transfusions). The donor and recipient characteristics are shown on Table 1. On 13th post-trans-

Table 1. Kidney donor and recipient characteristics

	DONOR	**RECIPIENT**
Age	42 y	45 y
Sex	female	male
Blood group	O(IV)Rh(+)	O(IV)Rh(+)
Common HLA-B-DR	A11,B51,DR11,DR16	A11,B51,DR11,DR16
Viral tests	HBsAg,HCV,CMV,EBV,HIV:neg	HBsAg,CMV,EBV,HIV:neg, HCV : pos
Primary renal disease	-	Chronic glomerulonephritis
Duration of dialysis	-	18 months
Pannel test	-	0%
Immunosuppression	-	Mpz+AZA+CsA

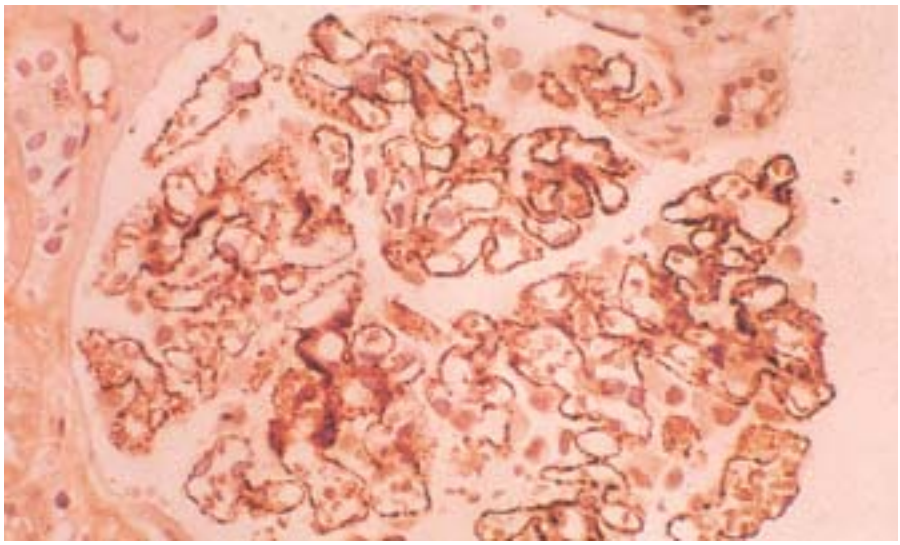

Fig. 1. De novo membranous allograft nephropathy with argyrophylic basement membrane spikes. Silver stain

plant day he was discharged with serum creatinine 1,2 mg/dl, normal blood pressure and triple immunosuppressive treatment protocol [Medrol: 44mg/d, azathioprine (AZA): 100mg/d and cyclosporine A (CsA): 400mg/d].One month after renal transplantation he presented acute bronchitis which was treated successfully with amikacin and ceftazidime, while four months later he was admitted to our department with acute cholecystitis due to chololethiasis. Sixteen months after kidney transplantation he underwent laparoscopic cholecystectomy but two months later (1,5 year after KdTn) his clinical and laboratory evaluation at the Outpatient Department showed mild elevation of blood pressure (BP: 140/95 mmHg), microscopic hematuria and microalbuminuria (24h urine protein: 150 mg). Microscopic examination of urine revealed that 50% of red blood cells were of upper urinary system origin. The kidney and liver function tests were within normal limits during the 2nd, 3rd and 4th post-transplantation year [range of Scr: 1,2-1,4 mg/dl, normal aminotransferases (SGOT, SGPT: 20-45 IU/L, 25-40 IU/L) and mild prolongation of prothrombin time due to asenokoumarol consumption]. He had a normal echocardiogram (EF: 65%, without pathological valve lesions), normal immunoglobulin and cryoglobulin titles (Table 2) and on 4th post-transplantation year he was under triple drug immunosuppressive treatment with prednizolon: 7,5mg/d, AZA: 75mg/d and CsA: 150mg/d (CsA blood trough levels: 110 ng/ml). Proteinuria of nephrotic type (24h urine protein: 1,5 g), hypertension (BP: 150/95mmHg) and edema of the lower extremities were added to the above clinical syndrome, four and a half years post-transplantation.

The kidney graft function on admission was normal again (Scr: 1,3 mg/dl, normal renal graft scintigram with Tc^{99m} DTPA) and there were not any changes of total cholesterol, triglycerides and HDL-cholesterol at the same period of time. The circulating immune complexes (CICs) were measured at 75 ng/ml (normal range: 0,5-15 ng/ml), the blood viral load of HCV by polymerase chain reaction (HCV-RNA PCR) was greater than 10^6 copies/ml and there was a slight increase of SGPT (SGPT:65 IU/L). Renal graft biopsy demonstrated de novo stage II membranous GN with mild arteriosclerosis (Figure 1). Valsartan (80 mg/d) was added to the treatment in

Table 2. Laboratory evaluation of the kidney graft recipient before renal graft biopsy

CIC	75 ng/ml (range : 0,5-1,5 ng/ml)
Serum immunoglobulins	IgA : 375 mg/dl
	IgM :310 mg/dl
	IgG : 2000 mg/dl
Cryoglobulins	10mg/100ml (range : 2-10mg/100ml)
HCV-RNA PCR	Positive
24h urine protein	1,5 g

order to control and stabilize both proteinuria and arterial BP. Eight years after kidney transplantation there is no impairment either of kidney graft or liver function, his 24h urine protein is 750 mg, he has negative HCV-RNA PCR and normal serum concentrations of CICs [CIC-C1q: 12 μg/ml (normal range: 0,1-45 μg/ml) and CIC-RAJI: 19 μg/ml (normal range: 0,1-60 μg/ml)].

DISCUSSION

We have described a renal allograft recipient with membranous glomerulonephritis (MGN) and circulating immune complexes with concomitant HCV-seropositivity. In contrast to HCV membranoploriferative glomerulonephritis (MPGN) reported in native kidneys[11] in this case cryoglobulins were detected in very low plasma concentrations, as their detection and characterization is difficult. It is possible that both the type of glomerulonephritis (de novo MGN) and the immunosuppressive therapy could modify and alter the cryoglobulin serum levels and account for the absence of extrarenal manifestations of cryoglobulinemia[10,11].

The most common de novo glomerulonephritis after kidney transplantation in HCV-positive patients is type I MPGN with or without cryoglobulinemia[12]. HCV infection may be, less frequently, associated with membranous GN[13]. These immune- mediated disorders may appear in HCV-RNA-positive renal allograft recipients without severe liver disease. Our patient had normal liver function tests in all period of disease follow-up, except a period of three months before kidney graft biopsy. During that period of time a mild elevation of SGPT and HCV-RNA seropositivity were detected.

Histology of de novo MGN in kidney allograft recipients resample idiopathic MGN except for the presence of interstitial and vascular lesions due either to chronic allograft nephropathy or to other causes such as donor factors (age and hypertension of the donor)[12]. Our patient had on histology, stage II MGN, but also grade II arteriosclerosis possibly due to chronic allograft nephropathy.

Anti-HCV antibodies before renal transplantation are apparently a risk factor for the appearance of proteinuria with poor outcome, suggesting that HCV infection may cause glomerular lesions with a variety of mechanisms[14]. HCV-positive patients with MGN after kidney transplantation show both nephrotic proteinuria and hypertension. The clinical course is similar to idiopathic de novo MGN posttransplantation but the prevalence of MGN is higher in HCV-positive than in HCV-negative kidney graft recipients (3,6% Vs 0,36%, $p < 0,001$)[15]. Our patient had a mild elevation of blood pressure, microscopic hematuria and microalbuminuria since one and a half year posttransplantation but he showed nephrotic type proteinuria, hypertension and edema of lower extremities four and a half years after kidney transplantation. At that period of time there were high plasma concentrations of circulating immune complexes (CIC), increased blood viral load of HCV measured by polymerase chain reaction as well as a mild elevation of SGPT. The above findings led us to perform the graft biopsy.

The pathogenesis of MPGN and MGN in HCV-positive kidney graft recipients involves deposition of HCV-containing immune complexes and cryopecipitates that may seem paradoxical in immunosuppressed patients. A potential relation between HCV associated glomerulonephritis and transplant glomerulopathy has also been reported[3,12]. Our patient had a typical course both of rheumatic fever associated nephritis and extrarenal manifestations of this immune mediated disease (multiple arthritis syndrome, aortic and mitral valve deficiency). In the great majority of rheumatic fever cases that there is continuous immune mediated stimulus the coexistent glomerulonephritis is type I or II MPGN. After a successful kidney transplantation the percentage of relapse is about 25-30% and the fact that renal allograft histology revealed stage II membranous glomerulonephritis shows that this type of de novo glomerulonephritis posttransplantation in a HCV-positive patient with rheumatic fever history and artificial cardiac valves is at least very unusual[16].

There is no specific therapy for HCV-related glomerulonephritis after kidney transplantation[3]. Interferon in nontransplanted patients can reduce proteinuria, suppress viremia and improve renal function tests, but interferon induces acute rejection or renal failure in kidney graft recipients. It can also exacerbate proteinuria and glomerulonephritis in HCV-positive renal transplant recipients[17]. Experience with ribavirin in this indication is not available. Four liver graft recipients were effectively treated with ribavirin for an HCV-associated nephrotic syndrome. Though the drug may cause a dose depended red blood cell hemolysis it could be useful in renal patients as well[10,18].

Angiotensin II type I receptor blockers have been used successfully for the treatment of hypertension and retardation of glomerular and interstitial damage in proteinuric hypertensive kidney graft recipients.We and others have shown that these drugs

may reduce or even stabilize the amount of 24h urine protein and ameliorate both systolic and diastolic blood pressure[19]. Our patient showed significant reduction of 24h urine protein and blood pressure only six months after initiation of valsartan treatment and this is consistent the last three years.

In conclusion, we have shown that in renal allograft recipients with a past rheumatic fever history, HCV infection may be rarely associated with membranous glomerulonephritis and the angiotensin II type I receptor antagonists could be useful for the treatment of proteinuria and hypertension in this group of patients.

ΠΕΡΙΛΗΨΗ

Γρ. Μυσερλής, Γ. Βέργουλας, Μ. Λεοντσίνη, Α. Παπαγιάννης, Β. Παπανικολάου, Δ. Γάκης, Δ. Τακούδας, Α. Αντωνιάδης. **De novo μεμβρανώδης σπειραματονεφρίτιδα σε ασθενή με μεταμόσχευση νεφρού.** Ιπποκράτεια 2002, 6 (4) : 171-176.

Σε αυτή τη μελέτη παρουσιάζεται η κλινική πορεία ενός λήπτη νεφρικού μοσχεύματος, φορέα της ηπατίτιδας C, ο οποίος τεσσεράμισι χρόνια μετά τη νεφρική μεταμόσχευση εμφάνισε de novo μεμβρανώδη σπειραματονεφρίτιδα μοσχεύματος. Ο ασθενής ηλικίας 45 ετών προσήλθε στο Εξωτερικό Ιατρείο του Κέντρου Μεταμοσχεύσεων του Ιπποκράτειου Νοσοκομείου Θεσσαλονίκης με οίδημα σφυρών, λευκωματουρία και ήπια υπέρταση. Είχε πάρει νεφρικό μόσχευμα από την αδελφή του, ηλικίας 42 ετών στις 7 Ιουνίου 1995 και δεν είχε αντιμετωπισθεί θεραπευτικά για την ηπατίτιδα C πριν την νεφρική μεταμόσχευση. Σε ηλικία 6 ετών παρουσίασε επανειλημμένα επεισόδια οξείας αμυγδαλίτιδας και σε ηλικία 8 ετών συμπτωματολογία ρευματικού πυρετού. Σε ηλικία 15 ετών εμφάνισε ανεπάρκεια αορτικής και μιτροειδούς βαλβίδας ενώ σε ηλικία 32 ετών προστέθηκαν λευκωματουρία, μικροσκοπική αιματουρία, υπέρταση και αρχόμενη νεφρική ανεπάρκεια (Scr: 1,8 mg/dl). Δύο φορές υποβλήθηκε σε αντικατάσταση της αορτικής βαλβίδας σε ηλικία 33 και 38 ετών και μία φορά σε αντικατάσταση της μιτροειδούς βαλβίδας σε ηλικία 38 ετών. Η νεφρική λειτουργία επιδεινώθηκε σταδιακά και σε ηλικία 44 ετών εντάχθηκε σε πρόγραμμα χρόνιας αιμοκάθαρσης. Έγινε φορέας της ηπατίτιδας C ενώ βρισκόταν σε θεραπεία υποκατάστασης με τεχνητό νεφρό. Μετά τη νεφρική μεταμόσχευση εξήλθε τη 13η μετεγχειρητική ημέρα με φυσιολογική νεφρική λειτουργία. Ένα μήνα αργότερα παρουσίασε λοίμωξη αναπνευστικού η οποία αντιμετωπίστηκε επιτυχώς ενώ τέσσερις μήνες μετά προσήλθε με οξεία χολοκυστίτιδα λόγω χολολιθίασης. Δεκαέξι μήνες μετά τη νεφρική μεταμόσχευση υποβλήθηκε σε λαπαροσκοπική χολοκυστεκτομή ενώ δύο μήνες αργότερα η κλινικοεργαστηριακή εξέταση στο εξωτερικό ιατρείο έδειξε ήπια υπέρταση (ΑΠ : 140/95 mmHg), μικροσκοπική αιματουρία από το ανώτερο ουροποιητικό και μικρολευκωματινουρία (λεύκωμα ούρων 24ώρου : 150 mg). Η λειτουργία του νεφρικού μοσχεύματος και η ηπατική λειτουργία παρέμειναν φυσιολογικές στη διάρκεια του δεύτερου, τρίτου και τέταρτου χρόνου μετά τη νεφρική μεταμόσχευση. Λευκωματουρία νεφρωσικού τύπου (λεύκωμα ούρων 24ώρου : 1,5g) και οιδήματα κάτω άκρων προστέθηκαν στην κλινική εικόνα του ασθενή τεσσεράμισι χρόνια μετά τη νεφρική μεταμόσχευση. Παράλληλα η εργαστηριακή διερεύνηση έδειξε άνοδο των κυκλοφορούντων ανοσοσυμπλεγμάτων (CIC : 75 ng/ml, φ.τ. : 0,5 – 15 ng/ml) και θετική HCV-RNA PCR. Η βιοψία του νεφρικού μοσχεύματος έδειξε μεμβρανώδη σπειραματονεφρίτιδα με ήπια αρτηριοσκλήρυνση. Για τον έλεγχο της λευκωματουρίας και της υπέρτασης στο θεραπευτικό σχήμα προστέθηκε βαλσαρτάνη σε δόση 80 mg/H. Οκτώ χρόνια μετά τη νεφρική μεταμόσχευση ο ασθενής παρουσιάζει φυσιολογική νεφρική και ηπατική λειτουργία, είναι αρνητικός σε HCV-RNA PCR, έχει 750 mg λεύκωμα ούρων 24ώρου και φυσιολογικά επίπεδα κυκλοφορούντων ανοσοσυμπλεγμάτων. Συμπερασματικά, σε λήπτες νεφρικού μοσχεύματος με προηγούμενο ιστορικό ρευματικού πυρετού, η λοίμωξη με τον ιό της ηπατίτιδας C μπορεί σπάνια να σχετίζεται με εμφάνιση de novo μεμβρανώδους σπειραματονεφρίτιδας στο μόσχευμα και η θεραπεία με ανταγωνιστές των υποδοχέων τύπου Ι της αγγειοτενσίνης ΙΙ μπορεί να αποδειχθεί χρήσιμη στη αντιμετώπιση τόσο της λευκωματουρίας όσο και της υπέρτασης σε αυτή την ομάδα των ασθενών.

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