

Glomerular disease during HCV infection in renal transplantation

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Abstract. In general nephrology, HCV infection has been associated with type I membranoproliferative glomerulonephritis (MPGN type I) associated with cryoglobulinaemia. In a cohort of 399 renal transplantation (RT) recipients, 117 of whom (29%) were HCV-positive, we selected all patients diagnosed as having membranous GN or type I MPGN by graft biopsy. The prevalence of MGN was 16/399 (4%) with three recurrences, and 13 *de novo* cases. Only 5/16 (31%) were HCV+, not different from the general RT population. Five patients had an outcome of graft failure after 43 months. Conversely, there were 15 cases of type I MPGN (two recurrences, 13 *de novo*) but with eight HCV+ recipients (53%, $P=0.02$). Considering only the French patients, prevalence was 44% vs 12% in the French RT population ($P=0.006$). Eight patients had graft rejection after 59 months (five HCV+). In this type I MPGN subgroup, there were two positive cryoglobulins, two rheumatoid factors and four hypocomplementaemias. In conclusion, there is a clear association between HCV infection and the occurrence of type I MPGN in the allograft in renal transplantation, with terminal renal failure as an outcome.

Introduction

HCV infection in renal transplantation (RT) has several consequences:

- Hepatic consequences, both clinical and histological, making up HCV liver disease.
- Extra-hepatic consequences. They have been little studied in relation to renal transplantation. In this study, we investigated: a link between HCV infection and the *de novo* or recurrent glomerulonephritis (GN) in renal allografts; the presence of a circulating immune complex disease signalled by serum complement activation and by the presence of rheumatoid factor and/or cryoglobulins.

Materials and methods

Population studied

The population comprised all RT performed from August 1984 to December 1991, totalling 415 RT performed in 399 recipients. All patients were treated with cyclosporin A as part of a triple therapy with azathioprine and prednisone.

The population comprised of 133 women and 266 men (66.6%) whose mean age at the time of RT was 41.7 years (range 8–65). The mean follow-up duration was 75 months (range 24–145).

From that population, we selected patients who had been histologically diagnosed as having membranous GN or membranoproliferative type I GN on the graft.

We found a prevalence of HCV infection in that population of 117/399 (29.3%) [1].

Methods

HCV infection was detected by antibody screening using the ELISA II technique and confirmed by the RIBA II technique (structural antigen C22.3 and non structural antigens C100.3, C33c, 5.1.1).

HCV RNA screening was performed by RT-PCR technique (after total RNA extraction) and by using primers selected from the highly conserved 5' non coding region of the genome.

The immune complex systemic disease was investigated by titration of the serum complement (CH50) and its fractions (C3, C4) and by cryoglobulin, rheumatoid factor and anti-nuclear antibody screening.

Results

Membranous GN (MGN) [2]

We found 16 cases of MGN with the following characteristics: 11 men and five women, seven non-French (five Italians, one Turk, one Yugoslav) and nine French; mean age was 37.1 years (range 8–62) at the time of RT. There were 15 first RT and one third time RT. The initial renal failure was chronic GN in 12 cases and congenital uropathy with pyelonephritis in four cases.

The diagnosis was based on renal graft biopsy performed with a mean interval of 44.1 months following transplantation (range 6–98). There were three genuine MGN recurrences and 13 *de novo* MGN (non recurrent).

Twelve patients were seropositive and four were seronegative for cytomegalovirus (CMV) immediately after transplantation. There were three primary and a single secondary CMV infections. These infections were not time-related to the occurrence of nephritis.

Five cases of MGN (four *de novo*, one recurrent) (31.3%) were HCV+ from the time of RT, an equal proportion to that of the RT population studied ($\chi^2 =$

0.03; $P=NS$). There was only one case of isolated HBV infection. The five HCV+ patients were all non-French persons (four Italians, one Yugoslav).

At the time of renal biopsy (RB), eight patients presented with massive proteinuria (three HCV+, five HCV-). We recorded five failures (two HCV+ and three HCV-) after a mean follow-up of 43 months (four patients returned to dialysis and one died). Eight patients exhibited creatinine $\leq 200 \mu\text{mol/l}$ and three had poor renal function at the last visit.

Type I membranoproliferative glomerulonephritis (MPGN)

We found 15 MPGN cases in grafts. These were seven women and eight men (four Italians, one North-African and 10 French). Mean age at RT was 42.3 (range 15–57). Diagnostic renal biopsy was performed 57 months on average after RT (range 6–110). The initial renal disease was chronic GN in 10 cases, congenital uropathy in four cases and renal polycystic kidney disease in one case. Type I MPGN was authentically recurrent in two cases (only one HCV+) and in the other 13 cases MPGN had occurred *de novo*. In 13 cases it was the first RT and the second in two cases.

Four patients were CMV-seronegative at RT, three developed primary infection, and there were three secondary infections.

Eight patients out of 15 (53.3%) were HCV-positive (including six at RT). This prevalence, compared with that of HCV infection in the transplanted population, was at the fringe of statistical significance ($\chi^2=5.40$; $P=0.02$). These eight HCV+ patients were three Italians, one North-African and four French. Statistical analysis in the sub-group of French patients revealed an incidence of 44.4% vs 12.1% of HCV infection, hence the existence of MPGN ($\chi^2=7.70$; $P=0.006$).

Proteinuria was massive at the time of RB in seven cases. The outcome in that group was very pejorative. At the last follow-up, eight patients had returned to dialysis after a mean period of 58.8 months (range 7–115) and seven remained functional; four patients exhibited serum creatinine $\leq 200 \mu\text{mol/l}$ and three others had poor renal function. Among the patients who returned to dialysis, five out of eight were HCV+ (71%) and three out of seven were HCV-. Two HBV infections were noted (including one co-infection with HCV).

Screening for systemic immune complex disease

Among the 15 MPGN cases, we found two patients with positive cryoglobulins (two HCV+), four complement activations (three HCV+). That activation included a decrease in CH50 ($n=4$) and in C3 ($n=3$). Rheumatoid factor was positive in two cases (one HCV+) and antinuclear antibodies were all negative.

It is worth pointing out the case of an Italian (man, 54) whose initial renal disease was type I MPGN associated with mixed cryoglobulinaemia (HCV+), who had an early recurrence in his graft with cryoglobulinaemia, complement activation, massive nephrotic

syndrome and graft loss at 7 months, despite aggressive therapy (steroid bolus and plasma exchanges).

Among the 16 MGN, none was positive for cryoglobulin. CH50 was diminished in two cases (two patients with type I MPGN as their original renal disease, including one HCV+); C3 was low in two cases (one HCV+); no rheumatoid factor was detected; antinuclear antibody screening remained always negative in both groups.

Discussion

The prevalences of MGN (16/399=4%) and MPGN (15/399=3.1%) in the grafts are low. In HMGN, there is no relationship with HCV infection in our experience, contrary to other authors [3]. Conversely, in type I MPGN the frequency of concomitant HCV infection is high (54%) and suggests the existence of a causal relationship, as was demonstrated in general nephrology for the initial renal disease [4–6]. Indeed, Johnson's team [4] and other authors have clearly demonstrated the link between MPGN and HCV infection.

Above all, when hypocomplementaemia and/or rheumatoid factor and/or cryoglobulinaemia are present, it is a strong argument for immune complex systemic disease, which may result in type I MPGN in a HCV-infected recipient.

Another problem with MPGN type I is to discriminate between MPGN induced by a virus like HBV or HCV and MPGN as a specific allograft nephritis associated with chronic rejection. The latter exhibits few or no glomerular deposits by immunofluorescence microscopy.

Conclusion

Extrahepatic damage linked to HCV is infrequent. However, the virus appears to play a role in the onset, most often delayed, of progressive type I MPGN occurring on allograft. The characteristic but non specific biological pattern clearly suggests a causal link between HCV and MPGN (*de novo* or recurrent on the graft), although it has not been formally demonstrated.

References

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