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 hypocoomplementaemias. 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 membrano-proliferative 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 (χ²=...
ulinaemia, complement activation, massive nephrotic
who had an early recurrence in his graft with cryoglob-
Rheumatoid factor was positive in two cases (one
with positive cryoglobulins (two HCV +), four comple-
Among the 15 MPGN cases, we found two patients
ment activations (three HCV+). That activation
associated with mixed cryoglobulinaemia (HCV+),
54) whose initial renal disease was type I MPGN
infections were noted (including one co-infection with
others had poor renal function. Among the patients
7-115) and seven remained functional; four patients
25 cases. The outcome in that group was very pejorative.
(71%) and three out of seven were HCV- Two HBV
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
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).

Type I membranoproliferative glomerulonephritis
(MPGN)
We found 15 MPGN cases in grafts. These were seven
women and eight men (four Italian, 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 authen-
tically 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
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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 comple-
ment 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 cryoglob-
ulinaemia, 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 cryoglob-
ulinaemia. 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; antinuc-
lear 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 experi-
ence, 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 nephro-
logy 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 pre-
ent, 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 discrimin-
ate between MPGN induced by a virus like HBV or
HCV and MPGN as a specific allograft nephritis
associated with in 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
graft), although it has not been formally demonstrated.

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