Clinicopathological features of rapidly progressive hepatitis C virus infection in HCV antibody negative renal transplant recipients

Ercan Ok¹, Abdulkadir Unsal¹, Ali Celik³, Aysun Zeytinoglu², Galip Ersöz³, Yaman Tokat⁴, Selda Erensoy², Ulus S. Akarca³, Ali Basçi¹ and Gül Yuce⁵

Departments of ¹Nephrology, ²Microbiology, ³Gastroenterology, ⁴Surgery and ⁵Pathology, Ege University Medical School, Bornova, Izmir, Turkey

Abstract

Background. Hepatitis C virus (HCV) infection acquired during dialysis treatment generally shows a relatively benign course after renal transplantation (RTx). However, less is known about the course of HCV infection acquired during or after RTx.

Methods. Clinical and histopathological assessment of 15 renal transplant recipients who acquired HCV infection during or after RTx.

Results. Alanine aminotransferase levels rose for the first time 1–19 weeks after RTx. HCV RNA was found positive in all patients, but anti-HCV became positive in only nine of them. During a mean follow-up of 21 ± 12 months, jaundice appeared in 12 patients while ascites and/or hepatic encephalopathy occurred in six. Azathioprine was stopped in all patients. Cyclosporin was also stopped in four patients and in two of them prednisolone was also interrupted for a period of 3–7 weeks. Following this, ascites, hepatic encephalopathy and biochemical disturbances improved, while no deterioration was seen in graft function. Nine of the 15 patients had undergone two consecutive liver biopsies (LB). The first LB revealed cirrhosis in three and chronic hepatitis in six patients; the second LB showed cirrhosis in seven patients. The histological activity index (Knodell's score) progressed from 11.8 ± 3.5 to 13.8 ± 3.8.

Conclusions. The results suggest that HCV infection acquired during or after RTx may run an unusual and rapidly progressive clinical and histopathological course at least in some of these patients. Decrease or withdrawal of immunosuppressive drugs may improve early hepatic failure without detrimental effect on graft function during that period.

Key words: cirrhosis; HCV antibody; Hepatitis C virus; hepatic failure; renal transplantation

Introduction

Chronic liver disease is an important cause of late morbidity and mortality in renal transplant recipients (RTR) [1] and its major cause is hepatitis C virus (HCV) infection. The prevalence of HCV infection ranges from 10 to 65% [2,3] and is mainly determined by the rate of infection in the dialysis population. Transmission via the graft, or blood/blood product transfusion after renal transplantation (RTx), is also possible.

There are controversial data about the association between HCV markers, liver disease and graft/patient survival in RTR. Many authors accept that HCV infection does not show any detrimental effect on patient and graft survival [4–6], but one report noticed an increase in the prevalence of liver disease, overall mortality and death especially due to sepsis [7]. In addition to this, there have been isolated case reports of progressive liver failure due to HCV in solid-organ transplant recipients [8–11]. These discrepancies may be related to differences in the follow-up period, relative lower sensitivity of the antibody-detection tests in this population, the fact that biochemical parameters do not correlate well with histopathology in chronic hepatitis, and the time of acquisition of infection (before and during/after RTx).

Here, we present a series of RTR who acquired HCV infection during or after RTx and exhibited clinical and histopathological signs of severe liver disease.

Patients and methods

In Ege University Organ Transplantation and Research Center, 271 patients underwent RTx between 10.5.1988 and 19.4.1996. As part of the pretransplant evaluation, recipients and donors are routinely screened for aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltranspeptidase (GGT), bilirubin and serological tests of HAV, HBV, HCV and HDV. We do not routinely study HCV RNA before RTx in anti-HCV negative patients.
whose ALT levels are normal. AST, ALT, GGT and bilirubin levels are assessed monthly during dialysis and after RTx.

Patients

Among the patients whose ALT levels had always been normal during dialysis and whose hepatitis B surface antigen (HBsAg)/anti-HCV tests were negative at the time of RTx, persistent ALT elevation was observed in 17 patients after RTx. In two of them, HBsAg and anti-hepatitis B core (anti-HBc) IgM were detected after RTx (post-transplant acute HBV infection). In the other 15 patients, HCV RNA was found to be positive following ALT elevation. We assumed that they acquired HCV infection during or after RTx. We will refer to these cases as ‘post-transplant acute HCV infection’, defined as ALT elevation with positive HCV RNA occurring firstly in the post-transplant period, while normal ALT levels and negative HCV antibody had been documented during dialysis.

All patients had clinical and biochemical signs of severe liver disease. In nine patients with HCV infection who gave consent, two consecutive LB were performed to assess the progression of liver histopathology. In this paper, we describe the clinical course of 15 patients with post-transplant acute HCV infection and the histopathological features of nine patients.

Clinical and biochemical assessments

All patients were seen regularly by one of us (E.O.). Biochemical parameters were obtained from patients’ cards.

Serological evaluation

HAV, HBV and HDV markers (Organon Teknika) and anti-HCV (Second generation enzyme-linked immunosorbent assay, EIA UBI HCV-EIA) were determined by micro EIA. HCV RNA was studied by qualitative reverse transcriptase polymerase chain reaction (RT–PCR) (Amplitrac, HCV Amplification Kit, Roche Diagnostic System). HCV genotype could be determined in only four patients (University of Edinburgh, Medical School, Department of Medical Microbiology).

Histopathological evaluation

About 6 months after the first ALT elevation, which we considered to be the acute phase of new-onset hepatitis, the first liver biopsy (LB) was performed. At least 6 months after the first biopsy, a second biopsy was carried out. LB specimens, fixed in 10% formalin solution, were cut at 4 μm and stained with haematoxylin–eosin, reticulin and Van Gieson or Masson-trichrome stains. Specimens were examined blindly by the same pathologist using the scoring system of Knodell et al. [12]. In this semi-quantitative classification of chronic hepatitis, piecemeal necrosis, lobular degeneration, portal inflammation and portal fibrosis were scored on a histological activity index (HAI) scale (maximum 22).

Results

Patients characteristics

The mean age of the 15 patients was 37 ± 8 years (four female, 11 male), mean dialysis duration was 9.1 ± 4.3 months (one on CAPD, 14 on haemodialysis), and mean pre-transplant blood transfusion was 3.0 ± 1.4 units. The patients had received no blood transfusion intra- or postoperatively. All donors had normal ALT levels and were negative for anti-HCV. There were no anti-HCV positive persons in the surgical team.

All but two patients received organs from living related donors. Immunosuppressive therapy consisted of prednisolone (Pred; 30 mg/day during first month, 10 mg/day at 6 months), azathioprine (Azt; 1.5 mg/kg/day), and cyclosporin (CsA; 8 mg/kg/day on the first day, and then tapered according to Cs trough level; 150–250 ng/ml during 6 months, 100–200 ng/ml after the sixth month). Anti-thymocyte globulin (ATG) was used in one patient who had undergone cadaveric RTx (Patient 5).

Clinical and biochemical evaluation

The first ALT elevation was noticed 1–19 weeks after RTx and reached peak levels at a mean of 6.7 ± 2.4 months, GGT reached peak levels at a mean of 8.3 ± 2.1 months and bilirubin at a mean of 8.4 ± 3.3 months after the beginning of ALT elevation. The mean peak levels of ALT, GGT and total bilirubin were 225 ± 114 U/l, 1016 ± 1087 U/l and 8.0 ± 7.6 mg/dl, respectively. Twelve patients developed jaundice. Five patients also showed hypoalbuminaemia (less than 35 g/l) when biochemical disturbances were at their maximum.

During a mean follow-up of 21 ± 12 months after first ALT elevation, one patient died with peritonitis due to duodenal perforation as a complication of endoscopic retrograde cholangiopancreatography (Patient 2). Ascites occurred in two of the patients (Patients 2, 7), hepatic encephalopathy in two (Patients 3, 5), and ascerts and hepatic encephalopathy in the another two (Patients 1, 6). Thus six of the 15 patients developed signs of hepatic failure within 11.3 ± 5.0 months of first ALT elevation, but none of them died from this. Hypophosphataemia was also seen in three of four patients with hepatic encephalopathy. After treatment consisting of decreasing or stopping immunosuppressive medications, correction of hypophosphataemia and lactulose administration, flapping tremor and mental disturbances disappeared.

When liver function deteriorated and jaundice occurred, the first step was to stop Azt, and then CsA dosage was reduced. In four patients who developed ascites and/or hepatic encephalopathy, CsA was stopped completely for a period of 3–7 weeks (Patients 2, 3, 5, 6); two of them continued with Pred only at a dose of 10 mg/day, while in the other two patients steroids were also stopped. This partial or complete interruption of immunosuppression did not cause graft dysfunction in any patient during that period. After disappearance of encephalopathy, ascites and jaundice, immunosuppressive therapy was resumed with CsA (generally 2–3 mg/kg/day), alone or with Pred. The surviving 14 patients have well-functioning grafts up to the time of writing.
Rapidly progressive Hepatitis C virus infection in renal transplant recipients

Serological evaluation

None of the 15 patients had anti-HAV IgM, HBsAg, anti-HBc IgM, HDVAg, anti-HDV or anti-HIV during the follow-up. After ALT elevation, HCV RNA was studied, found to be positive in all cases, and remains positive at the time of writing. In six of the 15 patients, anti-HCV remained negative during the follow-up of 9–41 months after first ALT elevation. In the other nine patients, anti-HCV became positive at a mean of 9.6 ± 8.8 months after first ALT elevation. Genotype determination could be obtained in only four patients; three of them were type 1b, and one was type 1a.

Histopathological evaluation

LB, performed in nine patients 12.2 ± 8.4 months after the beginning of ALT elevation, revealed chronic active hepatitis in six and cirrhosis in three cases. Cirrhosis developed as early as 6 months after the beginning of ALT elevation in Patient 5 who had received ATG therapy. In the second biopsies, performed 10.3 ± 7.4 months after the first (22 ± 11 months after first ALT elevation), cirrhosis was found in seven and chronic active hepatitis in two cases. The mean interval between the diagnosis of cirrhosis and the beginning of ALT elevation was 20.0 ± 15.6 months. The mean HAI was 11.8 ± 3.5 on the first biopsy, and 13.8 ± 3.8 on the second (Table 1).

Discussion

The course of HCV infection in immunocompetent individuals is generally asymptomatic; although a chronic course is frequent, progression is rather slow. The outcome of HCV infection in RTR is less clear. None of the 15 patients had anti-HAV IgM, HBsAg, anti-HBc IgM, HDVAg, anti-HDV or anti-HIV during the follow-up. After ALT elevation, HCV RNA was studied, found to be positive in all cases, and remains positive at the time of writing. In six of the 15 patients, anti-HCV remained negative during the follow-up of 9–41 months after first ALT elevation. In the other nine patients, anti-HCV became positive at a mean of 9.6 ± 8.8 months after first ALT elevation. Genotype determination could be obtained in only four patients; three of them were type 1b, and one was type 1a.

Histopathological evaluation

LB, performed in nine patients 12.2 ± 8.4 months after the beginning of ALT elevation, revealed chronic active hepatitis in six and cirrhosis in three cases. Cirrhosis developed as early as 6 months after the beginning of ALT elevation in Patient 5 who had received ATG therapy. In the second biopsies, performed 10.3 ± 7.4 months after the first (22 ± 11 months after first ALT elevation), cirrhosis was found in seven and chronic active hepatitis in two cases. The mean interval between the diagnosis of cirrhosis and the beginning of ALT elevation was 20.0 ± 15.6 months. The mean HAI was 11.8 ± 3.5 on the first biopsy, and 13.8 ± 3.8 on the second (Table 1).

Table 1. The histopathological data of nine patients with post-transplant acute HCV infection

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>First liver biopsies</th>
<th>Diagnosis and HAI (a + b + c + d)</th>
<th>Second liver biopsies</th>
<th>Diagnosis and HAI (a + b + c + d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Biopsy time* (months)</td>
<td></td>
<td>Biopsy time* (months)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>32</td>
<td>CH-16 6 + 4 + 3 + 3</td>
<td>40</td>
<td>Ci-17 6 + 4 + 3 + 4</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>Ci-13 5 + 3 + 1 + 4</td>
<td>14</td>
<td>Ci-17 6 + 3 + 4 + 4</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>CH-10 3 + 3 + 3 + 1</td>
<td>14</td>
<td>Ci-16 5 + 3 + 4 + 4</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>CH-8 1 + 1 + 3 + 3</td>
<td>43</td>
<td>Ci-13 5 + 1 + 3 + 4</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>Ci-12 6 + 1 + 1 + 4</td>
<td>12</td>
<td>Ci-16 6 + 3 + 3 + 4</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>CH-16 6 + 3 + 4 + 3</td>
<td>21</td>
<td>CI-13 5 + 3 + 1 + 4</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>Ci-16 6 + 3 + 3 + 4</td>
<td>16</td>
<td>Ci-17 6 + 4 + 3 + 4</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>CH-10 3 + 1 + 3 + 3</td>
<td>15</td>
<td>CH-10 3 + 1 + 3 + 3</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>CH-8 3 + 1 + 3 + 1</td>
<td>26</td>
<td>CH-8 1 + 1 + 3 + 1</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>12 ± 8</td>
<td>11.8 ± 3.5</td>
<td>22 ± 11</td>
<td>13.8 ± 3.8</td>
</tr>
</tbody>
</table>

Since first ALT elevation; CH: Chronic hepatitis; CI: Cirrhosis; a: Piecemeal necrosis/bridging necrosis; b: Lobular degeneration/focal necrosis; c: Portal inflammation; d: Portal fibrosis.
hepatitis, and a rapid progression to hepatic failure and eventual death. Krogs et al. [9] reported a patient who died 5 years after cardiac transplantation with complications of cirrhosis. Dussel et al. [10] reported a case of severe hepatitis occurring 1 month after RTx who contracted HCV infection just before RTx, and progressed early to chronic liver disease. Chan et al. [11] described rapidly progressive and ultimately fatal liver disease due to chronic active hepatitis C in a RTR. In these cases, anti-HCV was negative before RTx and remained negative after the onset of liver disease, but HCV RNA became positive [9–11].

Acute HCV infection seen after RTx is most frequently acquired with the transplanted organ. Pereira et al. [16] assessed a series of 14 cases who developed liver disease as a result of RTx from HCV RNA positive donors. Two patients suffered from subfulminant hepatic failure; six patients died. Cirrhosis was seen in two and chronic active hepatitis in six of eight patients in whom a LB was performed. Hepatic failure seems to be more frequent in our patients than in Pereira et al.’s series. While the first LB of our patients was similar to those of Pereira et al. subsequent LB revealed a high rate of progression to cirrhosis. This difference may be related to the quantity of inoculated virus or to virus genotype. Unfortunately, genotype determination could only be performed in four of our cases. Therefore it is not possible to comment on this issue.

The fact that none of our patients expired from hepatic failure, unlike in Pereira et al.’s series, may be due to early interruption of the immunosuppressive drugs when signs of hepatic failure appeared. While ascites and jaundice disappeared by decreasing/stopping immunosuppression, graft function was preserved during this period. As reported earlier [17,18], this may indicate that HCV produces additional immunosuppression. To our knowledge, the present study is the first to systematically describe the course of HCV infection acquired during or after RTx, with consecutive LB. Our peri- or postoperatively infected RTR progressed rapidly to cirrhosis (mean 20.0 ± 15.6 months) and this interval was only 6 months in the patient who had been treated with ATG. It thus appears that the progression to cirrhosis is very rapid in RTR with HCV infection acquired during immunosuppressive therapy. Nine of our cases showed seroconversion of HCV antibody in a very late period; the remaining six are still negative 9–41 months after the first ALT elevation. Thus, the sensitivity of second generation EIA anti-HCV assay seems to be very low (60%) in HCV infection acquired peri-operatively or after RTx. In such patients, a negative anti-HCV does not exclude HCV infection, and HCV RNA is mandatory for the accurate diagnosis.

We cannot claim that the course of HCV infection acquired during or after RTx is always as severe as in our patients. Because we assessed only the patients whose ALT levels were permanently elevated after RTx, and did not routinely study HCV RNA in all patients after RTx. There may be some patients with acute post-transplant HCV infection without persistently elevated ALT levels. However, this does not change the fact that at least some of patients with acute post-transplant HCV infection show an unusually severe course with early hepatic failure. It is our experience, in accordance with the literature that such a course is not seen in patients with pretransplantation HCV infection (data not shown).

Unfortunately, we do not know how these patients acquired the infection, because no blood transfusion was given peri-operatively or after RTx, and all of the donors and transplantation team were anti-HCV antibody negative. It cannot be excluded that some dialysis patients may have been infected despite negative anti-HCV tests since HCV RNA results before RTx are not available. But this probability is rather low (2.5%) [19]. We did not find any anti-HCV negative individual among HCV RNA positive patients in our dialysis unit (anti-HCV was positive in all of 17 HCV RNA positive dialysis patients); the prevalence of anti-HCV is 34% in our hemodialysis patients, 0.5–1.0% in blood donors in our country. Therefore, there must have been a breakdown of the infection control chain in our transplantation unit. The source of infection could not be determined. We suspect the operation room as the site of contamination but we do not have any objective evidence.

In summary, this clinicopathological study shows that HCV infection acquired during or after RTx runs, at least in some patients, an aggressive course and progresses rapidly to cirrhosis. Hepatic failure may improve by decreasing or stopping immunosuppression. During this period graft function is preserved, probably due to an additional immunosuppressive effect of HCV.

Acknowledgements. We thank Dr Peter Simmonds and Catherine Blake for HCV genotype determination (University of Edinburgh, Medical School, Department of Medical Microbiology), Dr Anna S.F. Lok and Dr Evert J. Dorhout Mees for their critical comments on reviewing the manuscript.

References

Rapidly progressive Hepatitis C virus infection in renal transplant recipients

8. Lim HL, Lau GKK, Davis Gl, Dolson DJ, Lau JY. Cholestatic hepatitis leading to hepatic failure in a patient with organ transmitted hepatitis C virus infection. Gastroenterology 1994; 106: 248–251


19. Chan TM, Lok ASF, Cheng IKP, Chan RT. Prevalence of hepatitis C virus infection in hemodialysis patients: a longitudinal study comparing the results of RNA and antibody assays. Hepatology 1993; 17: 5–8

Received for publication: 25.6.97
Accepted in revised form: 3.8.98