Fibrosing Cholestatic Hepatitis in Hepatitis C Virus-Infected Renal Transplant Recipients

EDUARDO MUÑOZ DE BUSTILLO,* CAROLINA IBARROLA,* FRANCISCO COLINA,† GREGORIO CASTELLANO,‡ ANTONIO FUERTES,§ AMADO ANDRES,* JOSE M. AGUADO,‖ JOSE L. RODICIO,* and JOSE M. MORALES*

Departments of *Nephrology, †Pathology, ‡Gastroenterology, §Microbiology, and ‖Infectious Diseases, Renal Transplant Unit, Hospital 12 de Octubre, Madrid, Spain.

Abstract. Severe hepatitis C virus (HCV)-related fibrosing cholestatic hepatitis leading to early liver failure has been reported only exceptionally. Of 259 HCV-infected renal transplant (RT) patients in one hospital unit, four (1.5%) are described, representing the first series of this particular post-RT disease. Patient mean age was 55.7 yr. Three were men. All had pretransplant, hepatitis B surface antigen-negative and were anti-HCV antibodies positive. Three of them showed pretransplant mild liver enzyme abnormalities, and all received kidneys from HCV-negative donors. All were on steroids, cyclosporine, and azathioprine (AZA). The clinical pattern appeared early after RT (mean, 11.5 mo). In three patients, hyperbilirubinemia (6.5 to 20 mg/dl) and high alkaline phosphatase levels (428 to 859 IU/L) were observed. Also, in all subjects, high gamma glutamyl transpeptidase levels (639 to 4270 IU/L), mild aspartate aminotransferase and alanine aminotransferase abnormalities, and serum HCV RNA were observed. Liver biopsy revealed diffuse fibrosis, leukocyte infiltrates, and different degrees of cholestasis, with typical signs of HCV hepatitis in only one patient. Two patients developed subfulminant liver failure and died 2 and 3 mo after biopsy, respectively. One patient also suffered hepatic failure, receiving a liver transplant. The fourth is alive on dialysis awaiting a combined kidney and liver transplant. It is concluded that fibrosing cholestatic hepatitis is a new, early, and severe complication after RT in HCV(+) patients, which appears in patients with ongoing HCV infection under AZA therapy, despite a nonaggressive immunosuppressive protocol. Both HCV and AZA could play a concurrent role in the pathogenesis of this severe complication after RT. (J Am Soc Nephrol 9: 1109–1113, 1998)

Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease in renal transplant (RT) recipients. The prevalence rate of HCV in this context reaches 10 to 30% with second-generation tests (enzyme-linked immunosorbent assay [ELISA-2]/recombinant immunoblot assay-2), and most patients acquire the infection while on dialysis (1,2). Although there is some controversy regarding prognosis of HCV infection after RT (3–6), most studies hold that its course is relatively benign. In fact, in almost all published series, graft and patient survival is not different from HCV(−) patients (4–6). Active chronic hepatitis and/or cirrhosis are well known long-term complications of HCV infection in this setting (7). However, early liver failure in HCV(+) RT patients is exceptional.

In this study, we report four HCV(+) RT recipients who developed early deterioration of liver function, leading to short-term hepatic failure and a common pathologic pattern defined by diffuse fibrosis and different degrees of cholestasis, accompanied in only one of them by typical features of HCV hepatitis. This clinicopathologic pattern is similar to fibrosing cholestatic hepatitis (FCH), an aggressive form of hepatitis B virus (HBV) infection described in immunosuppressed subjects (8). The extreme severity of these unusual cases of HCV infection has led us to report our experience of this particular pattern of liver damage to identify its risk factors and alert the scientific community to this potential complication.

Materials and Methods

Patients

Of 259 HCV(+) RT patients in our unit, we have retrospectively analyzed four of them (1.5%) with a common clinicopathologic pattern of FCH.

HCV Serology

Anti-HCV antibodies were tested using a second-generation ELISA test system (Ortho HCV ELISA 2.0 Test System, Ortho Diagnostic Systems, Raritan, NJ) and a second-generation strip immunoblot assay system (Recombinant Immunoblot Assay HCV Test System, Chiron Corp., Emeryville, CA). HCV RNA was detected by PCR according to a nested PCR protocol (Ravaggi, Sawgjia, Italy; PCR Meth. App. 1992). HCV genotype was determined by reverse hybridization (INNO-LIPA HCV, Innogenetics, Antwerp, Belgium) (9). Frozen sera from patients receiving RT before these tests were available were analyzed retrospectively.
Pathology

Histologic classification was performed according to the following criteria. (1) Signs consistent with hepatitis due to HCV: portal/peripoportal/lobular hepatitis, portal lymphoid aggregates, steatosis. (2) Cholestasis-associated changes: ductal lesions, ductular proliferation, biliary pigment, hepatocytic hydropic swelling with “feathery” degeneration; (3) Fibrosis: portal/peripoportal/portal septal/diffuse. (4) Other: sinusoidal dilation, veno-occlusive lesions, nodular regeneration.

Results

The most important clinical characteristics of the patients are summarized in Table 1. All had pretransplant (pre-Tx) hepatitis B surface antigen-negative and anti-HCV antibodies positive. Three of them exhibited pre-Tx mild liver abnormalities (alanine aminotransferase [ALT] levels <2.5 times normal values) and, notably, all received kidneys from HCV-negative (ELISA2) donors. All were on steroids, cyclosporine (CsA) and azathioprine (AZA). AZA was administrated at a dose of 1 to 2 mg/kg per d for a mean time of 18.3 mo (range, 1 wk to 48 mo). Also, three patients received low-dose cyclophosphamide (0.5 to 1 mg/kg per d) after AZA withdrawal. One patient received high-dose steroids because of acute rejection.

Remarkably, the first signs of worsening of liver function appeared early after RT: three patients in the first 6 mo, mean 11.5 mo (range, 2 to 36). In three patients, hyperbilirubinemia (6.5 to 20 mg/dl; normal range, 0.2 to 1.2 mg/dl) and high alkaline phosphatase levels (428 to 859 IU/L; normal range, 40 to 280 IU/L) were observed. Also, in all subjects very high gamma glutamyl transpeptidase (GGT) levels (639 to 4270 IU/L; normal range, 6 to 50 IU/L) and mildly elevated aspartate aminotransferase (AST) and ALT levels were detected. An obstructive biliary cause of cholestasis and cytomegalovirus infection were excluded.

Liver biopsy was performed at a mean of 21.7 mo after RT (range, 5 to 48), revealing a similar pathologic pattern characterized by periportal fibrosis associated with neutrophilic interstitial infiltrates, slight sinusoidal diffuse fibrosis, and different degrees of histologic cholestasis, accompanied in only one of them by typical features of HCV infection as portal and periportal lymphocytic infiltrates with lymphoid aggregates and piecemeal necrosis (Table 2 and Figure 1).

Serum HCV RNA was positive in all patients at the time of liver biopsy, corresponding in three patients to genotype 1b. The outcome after biopsy was ominous; two patients went on to subfulminant liver failure and died 2 and 3 mo after biopsy, respectively. One patient also suffered hepatic failure, receiving a liver transplant 15 mo after biopsy. The fourth is alive on dialysis 8 yr after biopsy, awaiting a combined kidney and liver transplant. None received interferon or antiviral therapy.

Discussion

HCV infection is an important cause of liver disease after RT, but its influence on long-term graft and patient survival is still unclear. Currently, it is accepted that patients with HCV infection develop biochemical liver abnormalities more frequently than HCV(-) patients (1). Furthermore, some HCV(+) RT recipients develop chronic hepatitis and cirrhosis after a longer period, but earlier than individuals with community-acquired or posttransfusion C virus hepatitis (1). Early liver failure due to HCV infection after RT is extremely rare.

Among our population of 259 RT recipients infected by HCV, we have described four of them who presented a common clinicopathologic pattern of FCH with an early and extremely unfavorable outcome, corresponding to an incidence of 1.5%. Only one similar observation has been recently published in this setting as a case report (10). Moreover, to our knowledge, only one series of HCV-related FCH after liver transplantation has been reported, although recurrence of HCV infection under these circumstances is almost universal (11). In this single report of FCH after liver transplantation, the incidence rate rose to 4 of 30 (13.3%) (11). However, the real incidence of this disease is still unknown; several studies of

Table 1. Clinical picture

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender/Age</td>
<td>Male/58 yr</td>
<td>Male/55 yr</td>
<td>Male/68 yr</td>
<td>Female/42 yr</td>
</tr>
<tr>
<td>Pre-Tx ALT abnormalities</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>AZA therapy</td>
<td>48 mo</td>
<td>21 mo</td>
<td>5 mo</td>
<td>1 wk</td>
</tr>
<tr>
<td>Onset after RT</td>
<td>36 mo</td>
<td>5 mo</td>
<td>2 mo</td>
<td>5 mo</td>
</tr>
<tr>
<td>HBsAg/anti-HCV</td>
<td>(-)/(+)</td>
<td>(-)/(+)</td>
<td>(-)/(+)</td>
<td>(-)/(+)</td>
</tr>
<tr>
<td>HCV RNA/genotype</td>
<td>(+)/ND</td>
<td>(+)/1b</td>
<td>(+)/1b</td>
<td>(+)/1b</td>
</tr>
<tr>
<td>ALT(σ)/γGTσ</td>
<td>80/2318</td>
<td>239/639</td>
<td>85/4270</td>
<td>159/780</td>
</tr>
<tr>
<td>Bilirubin(σ)/APσ</td>
<td>14/859</td>
<td>20/428</td>
<td>6.5/542</td>
<td>1.3/69</td>
</tr>
<tr>
<td>Outcome</td>
<td>Died 49 mo after RT</td>
<td>Liver Tx 30 mo after RT</td>
<td>Died 22 mo after RT</td>
<td>Awaiting liver Tx 101 mo after RT</td>
</tr>
</tbody>
</table>

Pre-Tx, pretransplantation; ALT, alanine aminotransferase; AZA, azathioprine; RT, renal transplantation; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; ND, not determined; γGT, gamma glutamyltransferase; AP, alkaline phosphatase.

σ Highest reached levels.
**Table 2. Histologic picture**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Architecture and fibrosis</strong></td>
<td>Architectural disarray</td>
<td>Mild periportal and perisinusoidal fibrosis</td>
<td>Fibrous septa; mild periseptal and perisinusoidal fibrosis</td>
<td>Mild periportal hepatitis;<em>a</em> fibrous septa; moderate periportal and perisinusoidal fibrosis</td>
</tr>
<tr>
<td><strong>Hepatocellular regeneration</strong></td>
<td>Mild, sometimes nodular</td>
<td>Interstitial neutrophilic infiltrates</td>
<td>Interstitial neutrophilic infiltrates</td>
<td>Interstitial neutrophilic infiltrates</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>Cholestatic signs without biliary pigment</td>
<td>Biliary pigment and other cholestatic signs, bile duct injury</td>
<td>Biliary pigment and other cholestatic signs, bile duct injury</td>
<td>Biliary pigment and other cholestatic signs, bile duct injury</td>
</tr>
</tbody>
</table>

*a* Periportal fibrosis with lymphoid aggregates as in “classical” piecemeal necrosis.

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**Figure 1.** Periportal interface shows perihapatocytic fibrosis spreading into the lobule. Mesenchymal and pericellular inflammatory infiltrates are scarce. Note clear cytoplasm (arrowheads) of the hepatocytes (cholate stasis) and some ductular proliferation (white arrows). Hematoxylin and eosin, ×240.

Recurrent HCV hepatitis after liver transplantation do not mention this pattern of liver damage (12–14).

It is worth noting that the subjects we report here shared similar characteristics. Indeed, three of them exhibited pre-Tx mild liver enzyme abnormalities. Our group demonstrated previously that this may influence the development of chronic liver disease after transplantation (15). Also, their main clinical manifestations were similar, with most showing a cholestatic pattern of serum liver enzymes, which is atypical for HCV infection. Furthermore, this complication appeared early after kidney transplant. It is interesting that all donors were HCV(−) (ELISA2), and all patients received a nonaggressive immunosuppressive treatment regimen.

Some of the pathologic features observed, mainly cholestasis and diffuse fibrosis, are reminiscent of those appearing after AZA toxicity (16–20). However, these patients lacked other typical histologic signs of AZA toxicity, such as veno-occlusive lesions, peliosis, and central lobular hemorrhage (19–21). Moreover, although aggravation of liver disease due to AZA toxicity has been observed despite drug withdrawal (19,20),
most reported cases have shown remission of clinical cholestasis and regression of histologic damage after therapy is stopped (17,18,21). Although it has been recently proposed that AZA hepatotoxicity might be potentiated by ongoing viral hepatic infection (17), the extremely unfavorable outcome despite AZA withdrawal and the absence of these histologic signs that usually characterize AZA hepatotoxicity suggest a particular type of liver injury in which other factors may be involved. Hence, it is tempting to speculate that HCV infection could have acted in conjunction with AZA toxicity to induce this particular pattern of hepatic injury. In fact, most reported cases of AZA toxicity showing unfavorable prognosis were described before HCV serologic status could be determined (19,20). Therefore, it is possible that HCV infection could have played a concurrent or even fundamental role in the pathogenesis and outcome of this disease. Along these lines, Zylberberg et al. suggest that HCV could exert a direct hepatocytotoxic injury linked to high intrahepatic viral antigen expression in this syndrome (10). Unfortunately, we could not determine the quantitative viremia levels in our patients. Finally, other unknown factors could also be involved. Although it is now accepted that HBV infection can induce FCH after RT (8), HCV has only been related to a similar clinicopathologic pattern in two reports outside the liver transplant context (10,22). Interestingly, both cases were also receiving AZA, although the potential pathogenic concurrent role of this drug has not previously been taken into account.

The information concerning therapy for HCV-related FCH is limited. AZA withdrawal seems mandatory, although in our experience, it only seemed useful in patient 4, who is alive on dialysis 101 mo after RT after complete and immediate immunosuppression withdrawal. On the other hand, liver transplantation was successfully performed in patient 2, with no evidence of recurrent FCH after a follow-up of 6 mo. Interferon therapy seems not to modify the clinical course of HCV-related disease, and could potentially induce graft failure (23). Finally, promising results have been obtained in HBV-related FCH with nucleoside analogues that inhibit viral replication (24,25). Ganciclovir has been reported to induce sustained clinical remission in a single case report (24). More recently, a course of at least 20 wk of lamivudine has been shown to constitute a beneficial and well tolerated therapy for these patients (25). However, the effect of these newer therapies over a longer period has yet to be established.

In summary, some RT patients with active HCV infection could develop an extremely aggressive form of FCH often quickly leading to liver failure. Perhaps HCV itself, AZA administration, and possibly other unknown factors play a pathogenic role in this often fatal complication, which appears without aggressive immunosuppression. This new complication must be considered among the differential diagnoses of cholestasis in HCV-infected RT recipients.

References