Rapidly Evolving Hepatitis C Virus–Related Cirrhosis in a Human Immunodeficiency Virus–Infected Patient Receiving Triple Antiretroviral Therapy

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Triple antiretroviral therapy combining reverse transcriptase and protease inhibitors modifies the prognosis of human immunodeficiency virus (HIV) infection, with dramatic improvement in immune status. The precise impact, if any, of anti-HIV triple therapy on hepatitis C virus (HCV) infection is unknown. We describe an unusual case of rapidly evolving HCV-related cirrhosis that paralleled restoration of immune status in an HIV-infected patient and discuss the possible link between such a severe course of hepatitis C and anti-HIV triple therapy.

Triple combination therapy with reverse transcriptase and protease inhibitors markedly modifies the prognosis of HIV infection, with dramatic increase in immune status [1]. The pathophysiology of hepatitis C virus (HCV) infection is still debated, especially the respective parts of direct viral cytopathic and immune-mediated effects on liver damage [2]. Beneficial enhancement of immunity could be deleterious in diseases involving immune-mediated mechanisms. Severe liver injuries in HCV-infected patients have been reported after discontinuation of chemotherapy, thus underlining a possible link between enhancement of cellular immunity and worsening of HCV-related liver lesions [3]. We have recently shown that anti-HIV triple therapy does not modify HCV replication [4]. Whether anti-HIV triple therapy induces more severe liver lesions in HCV/HIV-coinfected patients is unknown. We describe a case of rapidly evolving HCV-related cirrhosis that paralleled immune restoration and marked decrease in HIV and HCV viremia in an HCV/HIV-coinfected patient receiving triple antiretroviral therapy.

Case Report

A 36-year-old woman was referred to our liver unit in January 1997 because of ascites and liver failure. She was known to be infected by both HCV and HIV since 1987. She had no history of chronic alcohol consumption or of ingestion of herbs or mushrooms. The clinical course and virological and histological aspects of her HCV and HIV infections are summarized in table 1.

Her first liver biopsy was performed in September 1993 for evaluation of HCV-related chronic hepatitis. Liver biopsy samples were embedded in paraffin. Sections were stained with hematoxylin-eosin. Chronic liver disease was classified as chronic hepatitis or cirrhosis. For an accurate evaluation of the activity of liver disease, a semiquantitative scoring system was used according to the classification of Knodell et al. [5]: periportal necrosis, 0 to 10; intralobular necrosis, 0 to 4; inflammation, 0 to 4; and fibrosis, 0 to 4. A score for necrotizing and inflammatory activity was determined by summing the first three of these four numbers making up the Knodell score.

The first liver biopsy showed moderate necrotizing and inflammatory activity and fibrosis (Knodell score, 8 [1-3-3-1]). A second liver biopsy, performed in July 1995 for evaluation of unexplained fever and cholestasis, revealed Mycobacterium avium–related granulomas (treated by chemotherapy with multiple agents including clarithromycin) and mild chronic hepatitis; the Knodell score was 2 (0-0-1-1), indicating spontaneous improvement in the hepatic necrotizing and inflammatory activity.

Triple therapy with lamivudine (150 mg b.i.d.), indinavir (2,400 mg/d), and stavudine (40 mg b.i.d.) was started in May 1996. Nine months later, in January 1997, she was referred to our liver unit because of ascites. At the time of admission, laboratory tests revealed that the prothrombin time and factor V level were 36% of the normal values and that the total and conjugated serum bilirubin levels were 35 and 25 µmol/L, respectively. The alanine aminotransferase level was 60 IU/L (normal range, 5–40 IU/L), the alkaline phosphatase level was 107 IU/L (normal range, 30–90 IU/L), and the γ-glutamyltransferase level was 119 IU/L (normal range, 8–38 IU/L). Serum was negative for DNA from hepatitis B virus as well as for cytomegalovirus antigen, Epstein-Barr virus, and IgM antibodies to herpes simplex virus. Autoantibodies (antinuclear antibodies; antimicrosomal antibodies to liver, kidney, and smooth muscle; and antimitochondrial antibodies) were not detected. Ceruloplasmin, iron, transferrin, and α1-antitrypsin levels were within normal ranges.

Abdominal ultrasonography showed homogenous hepatomegaly and mild ascites. A transjugular liver biopsy was performed to distinguish between viral, drug-related, and intrahe-
Table 1. Summary of data on a case of rapidly progressive HCV-related chronic hepatitis in an HCV/HIV-coinfected patient that paralleled efficient anti-HIV triple therapy: clinical, virological, and histological findings.

<table>
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<tbody>
<tr>
<td>HIV viremia* ([Eq·Gen/mL])</td>
<td>ND</td>
<td>ND</td>
<td>1,318,261</td>
<td>ND</td>
<td>21,038</td>
<td>19,965</td>
<td>24,271</td>
</tr>
<tr>
<td>CD4 cell count in /µL (%)</td>
<td>319 (23)</td>
<td>31 (3)</td>
<td>25 (0.3)</td>
<td>10 (2)</td>
<td>43 (3)</td>
<td>96 (6)</td>
<td>150 (9)</td>
</tr>
<tr>
<td>CD8 cell count in /µL (%)</td>
<td>873 (69)</td>
<td>378 (36)</td>
<td>301 (35)</td>
<td>461 (41)</td>
<td>828 (58)</td>
<td>909 (57)</td>
<td>648 (54)</td>
</tr>
<tr>
<td>HCV viremia* ([Eq·Gen/mL × 10^3])</td>
<td>ND</td>
<td>ND</td>
<td>1,200</td>
<td></td>
<td>503</td>
<td>&lt;2</td>
<td>39</td>
</tr>
<tr>
<td>Knodell score²</td>
<td>1-3-3-1</td>
<td>0-0-1-1</td>
<td>1,200</td>
<td></td>
<td>503</td>
<td>&lt;2</td>
<td>39</td>
</tr>
<tr>
<td>ALT level³</td>
<td>4</td>
<td>2.5</td>
<td>3</td>
<td>6.5</td>
<td>3</td>
<td>3</td>
<td>3.5</td>
</tr>
<tr>
<td>Bilirubinemia (µmol/L; normal value, &lt;17 µmol/L)</td>
<td>5</td>
<td>12</td>
<td>20</td>
<td>50</td>
<td>25</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time§</td>
<td>100</td>
<td>92</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>ND</td>
<td>36</td>
</tr>
</tbody>
</table>

NOTE. ALT = alanine aminotransferase; HCV = hepatitis C virus; ND = not determined. Triple antiretroviral therapy with lamivudine, indinavir, and stavudine was started in May 1996. Liver failure occurred in January 1997.

*p Assessed by quantitative PCR analysis according to a commercially available method (Roche Diagnostic Systems, Neuilly, France).

¹ Evaluation of liver biopsy specimens [5].

² Percentage of normal value.

Since we suspected that triple therapy played a role in liver deterioration, protease inhibitor therapy was stopped in March 1997, resulting in improvement in liver function. The patient died 7 months after the first episode of ascites and the death was related to progressive liver failure.

Discussion

We describe an unusual case of rapidly evolving HCV-related cirrhosis that paralleled restoration of immune status in an HIV-infected patient. Spontaneous improvement in the hepatic necrotizing and inflammatory activity was observed...
while the CD4 cell count was decreasing; this occurrence was followed by liver deterioration when immune restoration was achieved with triple therapy with a protease inhibitor and two other antiretroviral drugs. Such an observation questions the mechanisms of HCV-related chronic hepatitis and the future follow-up of HCV/HIV-coinfected patients treated with triple antiretroviral therapy.

The pathophysiology of chronic HCV infection is still debated, especially the respective parts of direct viral cytopathic and immune-mediated effects on liver damage [2]. More severe liver disease associated with immunosuppression suggests a direct cytopathic effect of HCV: it may be related to a marked increase in the HCV viral load, which has been associated with the so-called fibrosing cholestatic hepatitis syndrome during immunosuppression [6, 7]. On the other hand, immunopathogenic mechanisms may be involved in HCV infection as suggested by the identification in the liver of CD8 T lymphocytes directed against specific HCV antigens in correlation with disease activity [8, 9].

Although we cannot completely exclude a sampling phenomenon, we assume that triple antiretroviral therapy, in the absence of other overt causes of liver deterioration, favored the occurrence of cirrhosis by promotion of immune-mediated mechanisms. Indeed, impairment of liver lesions chronologically paralleled a marked increase in CD4 and CD8 cell counts and a decrease in HCV viral load (evidence of immune-mediated liver injury). Recent data showed that protease inhibitor therapy gave rise to a substantial and sustained increase in the number of activated CD8 lymphocytes [10], as was observed in our case; these CD8 T lymphocytes could be specific for pathogens such as HCV. Moreover, there was an increase in the number of CD8+ T lymphocytes in the liver (as shown by immunohistochemical analysis) that paralleled immune restoration (figure 2). Finally, low HCV viremia and absence of a histological picture consistent with hepatic fibrosing cholestasis argues against a direct viral cytopathic effect. Furthermore, severe liver injuries have been reported after discontinuation of chemotherapy for HCV-infected patients [3], underlining the probable link between enhancement of cellular immunity and worsening of HCV-related liver lesions.

Our case suggests but does not definitively conclude that there is a link between protease inhibitor–related immune restoration and hepatic deterioration, since a twofold higher incidence of cirrhosis [11] and a rapidly evolving course of HCV-related hepatitis [12, 13] have been described for HCV/HIV-coinfected patients. Nevertheless, our observations suggest that dramatic improvement in immune status in HIV-infected patients may have a deleterious impact on the course of HCV coinfection, underlining the need to carefully assess these coinfected patients receiving triple antiretroviral therapy. Such an observation should be confirmed by prospective study.

References


