Lack of Seroconversion in a Health Care Worker after Polymerase Chain Reaction–Documented Acute Hepatitis C Resulting from a Needlestick Injury

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We present a case of documented acute hepatitis C that occurred in a health care worker who sustained a needlestick injury while caring for an individual who was infected with both hepatitis C virus (HCV) and human immunodeficiency virus (HIV). According to the findings of third-generation serological assays performed during a follow-up of >1 year, the health care worker, who was treated with interferon-α (during weeks 2–6) and ribavirin (during weeks 5–9), did not develop antibodies against HCV, in spite of documentation of an HCV-specific T cell response.

The rate of occurrence of acute infection due to hepatitis C virus (HCV) among health care workers who sustain a needlestick injury while caring for an individual with acute hepatitis C is estimated to be <5%. Complete recovery from acute hepatitis C, which is defined by sustained clearance of HCV RNA and normalization of the transaminase level, seems to occur spontaneously in 30%–50% of cases of non–transfusion-associated acute hepatitis; however, antiviral therapy is still recommended to decrease the risk of progression toward chronicity [1, 2]. Nevertheless, absence of HCV seroconversion in patients with acute hepatitis C has rarely been detected, particularly by use of sensitive third-generation serological assays. We describe a total and durable lack of HCV-antibody seroconversion in a health care worker who developed definite acute hepatitis C after a needlestick injury and who received early treatment with IFN-α and ribavirin.

Case report. An HIV-HCV–negative 35-year-old male nurse was followed after he sustained a needlestick injury during hemoculture of an HIV-HCV–coinfected donor at week 0. The HIV and HCV loads in plasma and serum samples obtained from the donor were 4.34 log10 copies/mL and 6.00 log10 copies/mL, respectively (HIV and HCV Amplicor Monitor; Roche Diagnostic System). Nevertheless, the donor’s alanine aminotransferase (ALT) level was repeatedly found to be normal (<40 IU/L). The health care worker began receiving postexposure anti-HIV triple therapy (zidovudine, lamivudine, and indinavir) within 5 h of the time when the needlestick injury occurred, and treatment was continued for 1 month.

Two weeks after exposure (week 2), the health care worker presented with malaise, fatigue, and mild jaundice, in addition to an increase in the ALT level. Results of qualitative and quantitative HCV PCR (Cobas Amplicor 2.0 and Cobas Amplicor HCV Monitor 2.0; Roche Diagnostic System) were repeatedly positive (table 1). Both the health care worker and the health care worker harbored the same genotype (1b), as was determined by sequencing of the 5′ noncoding and nonstructural 5B regions of the genome (TruGene HCV Genotyping assay; Visible Genetics Europe). IFN-α therapy, 3 × 106 IU t.i.d., was initiated at week 2, and treatment with ribavirin, 1200 mg/day, was initiated at week 5.

After a rapid decrease in ALT and HCV RNA levels occurred, the ALT level increased again at week 6, in association with myalgia, asthenia, and cephalgia; however, this increase was not accompanied by reappearance of HCV RNA. IFN toxicity was suspected, and IFN-α therapy was discontinued; treatment with ribavirin was continued until week 9. Since that time, the ALT level has remained normal. In addition, results of tests for the detection of HCV RNA were continuously negative for >1 year. Nested in-house HCV reverse-transcriptase PCR done on peripheral blood mononuclear cells produced positive results at week 2 and negative results at weeks 8, 12, and 52.

For the health care worker, results of serological tests for HCV, as assessed by 2 third-generation EIAs (AXSYM HCV, version 3.0 [Abbott Laboratories], and ELISA-3 [Ortho Diag-
Table 1. Clinical and biological findings for a male health care worker with acute hepatitis C.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Finding or therapy status, according to no. of weeks after exposure</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>ALT level, IU/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Qualitative HCV RT-PCR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>Serum</td>
<td>ND</td>
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<tr>
<td>PBMCs</td>
<td>ND</td>
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<tr>
<td>Quantitative HCV RT-PCR&lt;sup&gt;c&lt;/sup&gt; (serum)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>ND</td>
</tr>
<tr>
<td>HCV serological finding</td>
<td>By third-generation EIA</td>
</tr>
<tr>
<td>By third-generation SIA</td>
<td>-</td>
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<tr>
<td>Antiviral therapy</td>
<td>IFN-α</td>
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<tr>
<td>HIV prophylaxis</td>
<td>Ribavirin</td>
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</tbody>
</table>

**NOTE.** ALT, alanine aminotransferase; HCV, hepatitis C virus; Ind, indeterminate; ND, not done; PBMCs, peripheral blood mononuclear cells; RT, reverse transcriptase; SIA, strip immunoblot assay; X, administration of therapy; +, positive; −, negative.

<sup>a</sup> Normal value, <40 IU/L.

<sup>b</sup> Sensitivity of qualitative RT-PCR: for serum, 2.0 log<sub>10</sub> copies/mL; for PBMC, 2.0 log<sub>10</sub> copies/μg DNA.

<sup>c</sup> Sensitivity, 3.0 log<sub>10</sub> copies/mL.

<sup>d</sup> Positive results detected were as follows: at week 2, 5.8 log<sub>10</sub> copies/mL; at week 3, 5.9 log<sub>10</sub> copies/mL; and at week 4, 3.2 log<sub>10</sub> copies/mL.

Diagnostic System]) and by 1 third-generation strip immunoblot assay (CHIRON RIBA HCV 3.0; SIA), were negative from week 0 through week 58. At weeks 6 and 8, results of the third-generation recombinant immunoblot assay were considered indeterminate because serum samples displayed a weak reactivity to recombinant antigen c33c (derived from the nonstructural 3 protein [NS3]). At weeks 6 and 8, results of 1 of 2 EIAs showed a slight increase in optical density values, which remained below the positive cutoff level. The health care worker had no apparent immunodeficiency (e.g., absence of lymphopenia or hypogammaglobulinemia, and a normal CD4:CD8 ratio). Neither cryoglobulinemia nor autoantibodies were present. Furthermore, he was known to have responded well to hepatitis B and BCG vaccines. The results of serological tests for ubiquitous viruses (i.e., Epstein-Barr virus, cytomegalovirus, and hepatitis A virus) were positive, as was expected.

**Discussion.** Among health care workers who have acute hepatitis C, anti-HCV antibodies are usually detected with the use of a third-generation assay within 7–24 weeks after contamination. In rare cases, the window for serological detection can be wider. Ridzon et al. [5] reported acute hepatitis C and HCV seroconversion at 8 and 13 months, respectively, after a needlestick injury had occurred during the care of an HIV-HCV–coinfected patient. In their report, HCV serological testing was done by use of second-generation assays that are known to be less sensitive, and no HCV RNA testing was available. Delayed seroconversion was also detected, by use of a third-generation assay, among patients who had undergone hemodialysis or multiple transfusions or who were injection drug users. However, the exact dates of contamination were often ignored in these studies [6].

In the case report presented here, delayed seroconversion in the health care worker seemed unlikely because of the clear clinical picture of self-limited acute hepatitis C, the long follow-up, and the absence of preexisting detectable immunodeficiency. The lack of detectable antibodies does not mean that there was an absence of humoral immune response, as was suggested by the observation, made by use of immunoblot assay, of a transient and weak presence of antibodies against the recombinant NS3 protein. The possibility that the results of future, more sensitive serologic assays would be positive for all cases of acute hepatitis C cannot by excluded.

To our knowledge, this is the first report of absence of seroconversion long after the onset of acute hepatitis C, as detected with the currently used, most sensitive third-generation serological assays. In a study by Sodeyama et al. [7], a health care worker developed acute hepatitis 1 month after sustaining a needlestick injury while caring for a carrier of HCV. Spontaneous resolution without anti-HCV treatment occurred within 5 months. The results of second-generation HCV serological testing were negative for 1 year after the accident, but all results of HCV RNA testing were also negative, thereby casting doubt on a diagnosis of acute hepatitis C. Genesca et al. [8] described 2 patients who had resolution of PCR-documented acute hepatitis C after receiving 3 months of treatment with IFN-α-2b and who had absence of seroconversion after a
follow-up of 31 months. Again, only second-generation assays were used, and the epidemiological characteristics of the disease and the patients were not specified.

The immunological correlates of HCV clearance during acute hepatitis C are still being debated. Some studies have shown that health care workers or healthy individuals who are repeatedly exposed to small amounts of HCV might develop a protective T cell response in the absence of detectable anti-HCV antibodies [9–11]. Recently, Takaki et al. [12] demonstrated that 10 patients who had recovered from accidental acute hepatitis C had clear seroconversion, as determined by use of third-generation immunoassays, followed by a decrease in HCV antibody titers 10–18 years after the accident. Five of the patients were HCV seronegative 18 years after the accident, although HCV-specific T cell responses were maintained. Unfortunately, we could not analyze the cellular immune response against HCV during the acute phase of hepatitis. Nevertheless, we demonstrated, by use of a T cell proliferation assay performed on peripheral blood mononuclear cells obtained at week 54, that the health care worker displayed a strong proliferative response against a pool of recombinant HCV proteins (i.e., core protein, NS3 protein, nonstructural 4 protein [NS4], and nonstructural 5 protein [NS5]), a response as great as that against the recall antigen tetanus toxoid (data not shown). This finding suggests at least an HCV-specific CD4+ T cellular response in the health care worker. Finally, we do not know whether early, albeit short and incomplete, anti-HCV treatment played a role in producing this lack of antibodies.

This observation may be relevant for the counseling and follow-up of patients with acute hepatitis C. In addition to showing long-term seroreversion after acute hepatitis C, findings for this health care worker demonstrated that antibodies may never appear in patients who have recovered from a bout with acute hepatitis C. The case in this health care worker may not be representative of the natural history of acute hepatitis C in immunocompetent persons. It would be interesting to search for virological, immunological, or genetic differences between patients who have recovered from acute hepatitis C with detectable antibodies versus those who have recovered without detectable antibodies. Because of undetectable antibodies against HCV, the incidence of self-limited HCV infection may be underestimated in the general population.

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References