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Liver Fibrosis during an Outbreak of Acute Hepatitis C Virus Infection in HIV-Infected Men: A Prospective Cohort Study

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Abstract

Outbreaks of acute hepatitis C virus (HCV) infection are occurring in HIV-infected men who have sex with men. We evaluated risk factors and liver histopathology in 11 consecutively enrolled men with newly acquired HCV infection that was diagnosed on the basis of antibody seroconversion, new elevations in alanine aminotransferase level, and wide fluctuations in HCV RNA level. Ten patients reported unprotected anal intercourse, and 7 reported “club-drug” use, including methamphetamine. Liver biopsy showed moderately advanced fibrosis (Scheuer stage 2) in 9 patients (82%). No cause of liver damage other than acute HCV infection was identified. The specific pathways leading to periportal fibrosis in HIV-infected men with newly acquired HCV infection require investigation.

Immunosuppression accelerates the progression of fibrosis in hepatitis C virus (HCV)–infected patients. The magnitude of the acceleration is relatively modest if immunosuppression occurs *after* the chronic phase of HCV infection has been established. Thus, although the fibrosis progression rate (FPR) of patients with chronic HCV infection and end-stage renal disease is ~0.11 fibrosis units per year, if these patients undergo kidney transplantation and begin receiving immunosuppressive drugs, the FPR increases to ~0.14 U per year [1]. Injection drug users (IDUs), who typically acquire HCV infection before HIV infection [2], provide another example. Classic studies [3] indicate that the FPR of patients with chronic HCV monoinfection is ~0.11 U per year and that the FPR of patients with chronic HIV/HCV-coinfection is <2-fold greater, ~0.15 U per year. The majority of HIV/HCV-coinfected IDUs are not expected to develop cirrhosis (stage 4 fibrosis) for 20 years or more.

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In contrast, patients who acquire HCV infection when they already have defects in cellular immunity are reported to progress to cirrhosis, end-stage liver disease, and death in as few as 3 years. This dire outcome has been observed in transplant recipients [4, 5], patients with hematological disorders and immunodeficiencies [6, 7], and patients with preexisting HIV infection [8, 9]. Fortunately, HCV infection of immunocompromised patients has been rare, especially since the advent of blood screening tests. Recently, however, outbreaks of acute HCV infection in HIV-infected men who have sex with men (MSM) have been reported in Europe and the United States (see Danta et al. [10] and references therein). The rapid progression of fibrosis in other groups of immunocompromised patients with newly acquired HCV infection suggests that these men may be at a high risk for greatly accelerated liver damage. To explore this possibility and to determine risk factors for HCV transmission, we performed a prospective study of HIV-infected MSM who had recently acquired HCV infection. Liver biopsy of 9 of 11 consecutively enrolled patients showed moderately advanced fibrosis (Scheuer stage 2, scale of 0–4 [11]). Ten patients reported unprotected anal intercourse, and 7 reported “club-drug” use, including methamphetamine.

Methods

Written informed consent was obtained with approval of the Mount Sinai Institutional Review Board, in accordance with the Helsinki Declaration of 1975, as revised in 2000. Patients were interviewed and completed a detailed questionnaire about sexual practices and drug use during the prior 12 months (modified from Danta et al. [10]). Medical records were reviewed. The HCV antibody test used was a third-generation HCV EIA (Abbott HCV EIA 2.0). The HCV RNA test used was HCV Cobas Amplicor (version 2.0; Roche Diagnostics; cutoff, 2.8 $\log_{10}$ IU/mL). HCV was genotyped by INNO-LiPAssay (Bayer Diagnostics). The hepatitis B virus (HBV) load test used was real-time polymerase chain reaction (Quest Diagnostics Nichols Institute; cutoff, 100 IU/mL). The test used for HIV load was Amplicor (version 1.5; Roche Diagnostics; cutoff, 1.7 $\log_{10}$ copies/mL).

Because there is no single definitive test for acute HCV infection, we considered 3 criteria in combination: seroconversion, elevation in alanine aminotransferase (ALT) level, and changes in the serum level of HCV RNA. Large and abrupt fluctuations in HCV RNA level are a hallmark of acute HCV infection and are rare during chronic infection [12]. We classified the subjects as having either a definite case of acute HCV infection (seroconversion within 12 months and a new ALT elevation to >10-times the upper limit of normal [ULN]), a probable case (seroconversion >1 year, a new ALT elevation to >5-times the ULN, and a fluctuation in HCV load of >1 $\log_{10}$ IU/mL within 4 months), or a possible case (either seroconversion >1 year and a new ALT elevation to >5-times the ULN or no known prior negative HCV test results, a new ALT elevation to >5-times the ULN, and a fluctuation in HCV load of >1 $\log_{10}$ IU/mL within 4 months).

Percutaneous liver biopsies were performed using 18-gauge, 100-mm Jamshidi Menghini needles (Allegiance Healthcare). Specimens were fixed in formalin, embedded in paraffin, and treated with hematoxylin-eosin and Masson trichrome stains. The Scheuer criteria for chronic HCV infection were applied, although the patients were in the acute phase of HCV

infection. Immunostains for HBV surface antigen (HBsAg) and HBV core antigen (HBcAg) were performed.

FPRs were determined by dividing the fibrosis stage in units (according to the Scheuer system [11]) by the interval between the estimated date of infection and the date of the biopsy (in years). Infection was estimated to have occurred 8 weeks before the first new ALT elevation.

Results

Eleven MSM with asymptomatic, sexually acquired HIV infection of 11 months' to 16 years' duration were found at routine medical visits to have elevated transaminase levels, which led to further testing and the clinical diagnosis of acute HCV infection. The cases are summarized in table 1. In all patients, acute hepatitis A virus infection was excluded serologically and acute and chronic HBV infections were included both serologically and by HBV DNA testing. Eight patients were completely asymptomatic for liver disease throughout the acute course of infection; patients 3, 8, and 11 became jaundiced transiently. Ten patients had recently engaged in unprotected receptive anal intercourse, some with many partners. None had had an ulcerative sexually transmitted infection within the prior year. Patients 1, 3, and 6 reported a single recent episode of injecting methamphetamine; one remembered sharing the injection equipment, but the others had no recollection of sharing injection equipment. Patients 2, 6, and 11 had shared paraphernalia used for the snorting of drugs on multiple occasions with other MSM. Patient 4 had a possible percutaneous exposure, given that he had received multiple intravenous infusions of vitamins from a nonmedical practitioner. Five men denied any parenteral risk factors or club-drug use.

No patient was obese (all had a body mass index of ≤29), none had abnormal fasting glucose levels, none drank >30 *g* of alcohol per day, and most drank <30 g of alcohol per week (table 1). Ten patients had received antiretroviral therapy (ART) for periods ranging from 11 months to 16 years; patient 6 had never received ART, and patients 1, 2, 8, and 10 had received stavudine or didanosine in the past.

The acute phase is the initial 6-month period of a newly acquired HCV infection [12]. As described in Methods, we based the diagnosis of acute HCV infection on seroconversion to HCV antibody positivity, a marked elevation in serum ALT level, and a wide fluctuation in HCV RNA level, a hallmark of the acute phase [12]. The diagnosis of acute HCV infection was considered to be definite for patients 3, 5, 6, and 10; probable for patients 1, 2, 7, and 9; and possible for patients 4, 8, and 11. The diagnosis of acute HCV infection was supported by HCV RNA fluctuations in all patients except 4 and 10. Patient 10 had confirmatory seroconversion data, with a negative HCV antibody test result 6 months before presentation (table 1). Patient 4 had a negative test result for HCV RNA level 2.5 years before presentation; we acknowledge that he could have become infected anytime after.

Percutaneous liver biopsy was performed 3–21 weeks after the onset of hepatitis (first new ALT elevation) in 9 patients and 14 and 16 months after onset in 2 additional patients. All patients underwent biopsy before the initiation of interferon/ribavirin except patient 3, who

had received <1 week of therapy. The Scheuer system was applied to determine the fibrosis stage (scale of 0–4) [11]. Nine biopsy specimens had stage 2 fibrosis, 1 had stage 1 fibrosis, and 1 had stage 0 fibrosis (table 1). The biopsy specimens also showed portal inflammation, interface hepatitis, and necroinflammatory changes in the lobules. A representative biopsy specimen is shown in figure 1. Immunostaining results for HBsAg and HBcAg were negative for all patients.

Discussion

Among 11 consecutive HIV-infected MSM who underwent liver biopsy during the early periods of HCV infection, nine (82%) had stage 2 fibrosis. The mean ± SD FPR of these 11 patients was 4.3±2.7 U per year. In contrast, biopsy specimens from immunocompetent patients obtained during the early periods of HCV infection contained no or minimal fibrosis. Kamal et al. [13] performed biopsies on 87 patients 8–10 months after the onset of hepatitis. All had stage 0 fibrosis according to the Ishak scoring system. Larghi et al. [14] performed biopsies on 9 patients 6 months after a diagnosis of hepatitis. Five patients had stage 0 fibrosis and the remaining 4 had stage 1 fibrosis, for a mean FPR of ~0.9 U per year. Finally, Tanaka et al. [15] performed biopsies on 33 patients within 1 year of the onset of hepatitis and reported a mean FPR of 0.9 U per year. Thus, the FPR of the HIV-infected MSM with newly acquired HCV infection in our study was far higher than that of immunocompetent patients with acute HCV infection.

Our findings of moderately advanced fibrosis during the initial period of HCV infection are consistent with the rapid clinical progression to end-stage liver disease reported in previous studies of individuals who acquired HCV infection while already infected with HIV or who acquired HIV and HCV infection simultaneously. In a case series, Martin et al. [8] found that all 3 HIV-infected patients referred for evaluation of non-A, non-B hepatitis progressed to decompensated cirrhosis within 3 years of acquiring HCV infection. Similarly, a woman who acquired both HIV and HCV infection simultaneously developed hepatic failure and died within 2.5 years [9].

The major strengths of our study are the prospective design (we enrolled 11 consecutive patients) and the consistency of our findings (we found periportal fibrosis in 9 [82%] of 11 patients). Our study, however, also has a number of limitations. We do not know whether our results are specific to HIV-infected MSM with acute HCV infection or whether similar liver disease is present in other groups of immunocompromised patients with newly acquired HCV infection. Prospective trials are needed to explore this question.

We cannot rule out the possibility that 1 or more of our patients had either occult chronic HCV infection or an additional liver disease; however, 9 patients had documented antibody seroconversion and 9 had marked fluctuations in HCV RNA level. Each patient’s presentation was indistinguishable from what would be diagnosed as acute HCV infection in clinical practice. False-negative HCV antibody test results occur only in ~3% of HIV/HCV-coinfected patients. Occult chronic HCV infection is an unlikely explanation for the liver disease we observed. It is possible that the stage 2 periportal fibrosis we observed is a manifestation of an unknown, nearly universal disease process in HIV-infected MSM and is

not the result of acute HCV infection; however, the near uniformity of our findings and the rapid fibrosis progression observed in several other groups of patients who acquired HCV infection while immunocompromised [4–9] argue against this explanation.

In summary, our study indicates that high-risk sexual practices and noninjection-drug use may play a role in the transmission of HCV to HIV-infected MSM. Our findings also demonstrate that HIV-infected men with acute HCV infection have moderately advanced liver disease. The FPR of this population is ~5 times greater than that for people who are not immunocompromised at the time when they become HCV infected. Our findings are of particular importance with regard to the recent outbreaks of acute HCV infection in HIV-infected MSM in Europe and the United States [10]. Regular screening of MSM for HCV antibodies is not currently recommended by US or international HIV-care guidelines, and ALT elevations during acute HCV infection are relatively transient and therefore could be easily missed during routine clinical care. It is likely that, even in areas in which the outbreaks have been recognized, many or most cases of acute HCV infection remain undiagnosed. More-intensive screening of HIV-infected MSM is therefore warranted, given that, in light of our findings, the implications of missing the diagnosis of acute HCV infection in these patients are grave. Further research is needed to identify the mechanism(s) of liver injury in this population.

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References

1. Alric L, Di-Martino V, Selves J, et al. Long-term impact of renal transplantation on liver fibrosis during hepatitis C virus infection. Gastroenterology. 2002; 123:1494–1499. [PubMed: 12404224]
2. Thomas DL, Vlahov D, Solomon L, et al. Correlates of hepatitis C virus infections among injection drug users. Medicine (Baltimore). 1995; 74:212–220. [PubMed: 7623656]
3. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. Hepatology. 1999; 30:1054–1058. [PubMed: 10498659]
4. Ok E, Unsal A, Celik A, et al. Clinicopathological features of rapidly progressive hepatitis C virus infection in HCV antibody negative renal transplant recipients. Nephrol Dial Transplant. 1998; 13:3103–3107. [PubMed: 9870473]
5. Delladetsima I, Psichogiou M, Sypsa V, et al. The course of hepatitis C virus infection in pretransplantation anti-hepatitis C virus-negative renal transplant recipients: a retrospective follow-up study. Am J Kidney Dis. 2006; 47:309–316. [PubMed: 16431260]
6. Rossi G, Tucci A, Cariani E, Ravaggi A, Rossini A, Radaeli E. Outbreak of hepatitis C virus infection in patients with hematologic disorders treated with intravenous immunoglobulins: different prognosis according to the immune status. Blood. 1997; 90:1309–1314. [PubMed: 9242566]
7. Chapel HM, Christie JM, Peach V, Chapman RW. Five-year follow-up of patients with primary antibody deficiencies following an outbreak of acute hepatitis C. Clin Immunol. 2001; 99:320–324. [PubMed: 11358426]

8. Martin P, Di Bisceglie AM, Kassianides C, Lisker-Melman M, Hoofnagle JH. Rapidly progressive non-A, non-B hepatitis in patients with human immunodeficiency virus infection. Gastroenterology. 1989; 97:1559–1561. [PubMed: 2511056]

9. Ridzon R, Gallagher K, Ciesielski C, et al. Simultaneous transmission of human immunodeficiency virus and hepatitis C virus from a needle-stick injury. N Engl J Med. 1997; 336:919–922. [PubMed: 9070472]

10. Danta M, Brown D, Bhagani S, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. AIDS. 2007; 21:983–991. [PubMed: 17457092]

11. Scheuer PJ, Standish RA, Dhillon AP. Scoring of chronic hepatitis. Clin Liver Dis. 2002; 6:335–347. v–vi. [PubMed: 12122859]

12. Heller T, Rehermann B. Acute hepatitis C: a multifaceted disease. Semin Liver Dis. 2005; 25:7–17. [PubMed: 15731994]

13. Kamal SM, Turner B, He Q, et al. Progression of fibrosis in hepatitis C with and without schistosomiasis: correlation with serum markers of fibrosis. Hepatology. 2006; 43:771–779. [PubMed: 16557547]

14. Larghi A, Zuin M, Crosignani A, et al. Outcome of an outbreak of acute hepatitis C among healthy volunteers participating in pharmacokinetics studies. Hepatology. 2002; 36:993–1000. [PubMed: 12297849]

15. Tanaka E, Kiyosawa K. Natural history of acute hepatitis C. J Gastroenterol Hepatol. 2000; 15(Suppl):E97–E104. [PubMed: 10921390]

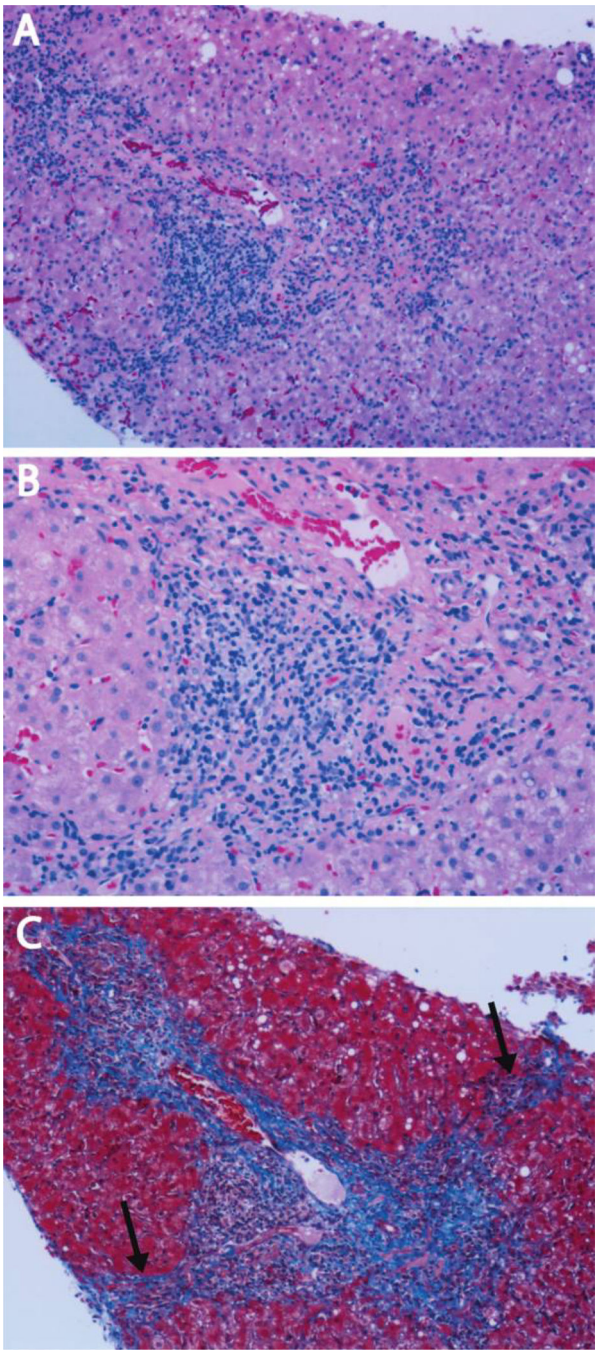

Figure 1.

Needle liver biopsy specimen from patient 6, who had a diagnosis of definite acute hepatitis C virus (HCV) infection supported by seroconversion 3 months after a prior negative test result, a peak alanine aminotransferase level of 1096 U/L, and a fluctuation in HCV RNA level of 2.0 $\log_{10}$ IU/mL in 3 weeks. He had never received antiretroviral therapy. The biopsy was performed 8 weeks after the onset of hepatitis. It showed stage 2 fibrosis and grade 3 necroinflammatory changes. The micrograph in panel A shows marked expansion of portal tracts caused by inflammation (hematoxylin-eosin stain; original magnification,

×100). The magnified view in panel B shows a lymphoid aggregate and severe interface hepatitis (hematoxylin-eosin stain; original magnification, ×200). The micrograph in panel C shows periportal fibrosis with fibrous septum formation *(arrows)* (Masson trichrome stain; original magnification, ×100).

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Table 1

Baseline characteristics and fibrosis scores for 11 HIV-infected men who have sex with men (MSM) with acute hepatitis C virus (HCV) infection.

Patient	Age, years	Duration of HIV infection, years	Duration of ART, years	CD4 cell count, cells/μL	HIV load, $\log_{10}$ copies/mL	Ethanol intake, g/day	HCV seroconversion interval, months[a]	Peak ALT level, U/L	HCV RNA fluctuation, $\log_{10}$ IU/mL	ALT rise to biopsy, weeks[b]	Fibrosis stage, 0–4
1	40	16	16	241	2.9	<20	22	567	1.8 in 4 weeks	7	2
2	47	12	<5[c]	303	5.2	<20	27	1620	2.5 in 16 weeks	19	2
3	47	0.9	0.9	614	<1.7	<20	11	1880	3.7 in 2 weeks	13	0
4	56	5	5	200	<1.7	<20	30	622	<1.0 in 16 weeks	16	2
5	40	4	3	720	<1.7	<20	4.5	1164	1.1 in 2 weeks	3	2
6	46	1	Never	528	4.2	<20	3	1096	2.0 in 3 weeks	8	2
7	31	6	6	842	<1.7	<20	21	807	3.5 in 4 weeks	62	2
8	49	16	14	170	2.7	<20	Unknown[d]	1608	4.1 in 4 weeks	21	2
9	44	12	5	617	<1.7	<20	40	268	1.2 in 7 weeks	14	2
10	44	16	10	502	<1.7	30	6	1105	<1.0 in 16 weeks	3	1
11	36	9	8	525	<1.9	<20	Unknown[d]	>2000	>3.4 in 3 weeks	68	2

[a] Time between the most recent documented negative HCV test result and the positive test result at diagnosis of acute HCV infection. This interval, which represents the maximum possible duration of HCV infection, overestimates the actual duration of infection because long periods of time often separate sequential tests for HCV because of the lack of routine testing of MSM for HCV.

[b] Time from the first elevation in alanine aminotransferase (ALT) level to the liver biopsy.

[c] This patient had not been receiving antiretroviral therapy (ART) for 2 years before presentation.

[d] No HCV testing was performed before the diagnosis of acute HCV infection.