Case Report

Rapid Development of Advanced Liver Fibrosis after Acquisition of Hepatitis C Infection during Primary HIV Infection

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Abstract

We report the first reported case of a 61-year-old MSM who was diagnosed with syphilis, primary HIV infection, and acute hepatitis C (HCV) within the same time period who rapidly developed significant liver fibrosis within 6 months of acquisition of both infections. It has been well described that individuals with primary HIV infection have an increase in activated CD8⁺ T cells, which causes a state of immune activation as was evident in this patient. Acquisition of HCV during this time could have further skewed this response resulting in massive hepatocyte destruction, inflammation, and subsequent liver fibrosis. Recent literature suggest that MSM with primary HIV infection have higher rates of acquisition of HCV than other HIV-positive cohorts and HCV acquisition can occur very soon after acquiring HIV. This case of rapid hepatic fibrosis progression coupled with the increasing incidence of HCV in individuals with primary HIV infection demonstrates a need for this phenomenon to be studied more extensively.

Introduction

APPROXIMATELY 40,000 CASES of acute hepatitis C infection (HCV) occur annually in the United States and are responsible for approximately 20% of cases of acute hepatitis in the United States.¹ Because of shared routes of transmission, HCV infects approximately 15%–30% of HIV-infected individuals.¹ While advanced age, male gender, alcohol consumption, and HIV coinfection are all known to be associated with a faster fibrosis rate, we report the first reported case of acute hepatitis C infection associated with advanced fibrosis within 6 months of acquisition in an elderly man with recently acquired HIV infection. The probable risk factor for HIV, HCV, and syphilis in this case was high-risk men who have sex with men (MSM) sexual behavior.² To the best of our knowledge there have been no reported cases of such rapid progression described in patients with recent acquisition of both HIV and HCV infections. Recent literature suggest that

MSM with primary HIV infection have higher rates of acquisition of HCV than other HIV positive cohorts and HCV acquisition can occur very soon after acquiring HIV.³ This case of rapid hepatic fibrosis progression coupled with the increasing incidence of HCV in individuals with primary HIV infection demonstrates a need for this phenomenon to be studied more extensively.

Case Report

A 61-year-old Caucasian MSM male with a history of hypertension and hyperlipidemia developed symptoms suggestive of acute HIV seroconversion with low-grade fevers, swollen lymph nodes, fatigue, and myalgias lasting for a 1-week period in July 2007. He had undergone his annual examination by his physician a week earlier with normal laboratory results including liver function tests (LFTs). In August 2007, he tested positive for syphilis and HIV (oral

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swab test with confirmatory test) at a local health clinic and was referred to an infectious disease clinic where he was treated with 3 doses of intramuscular benzathine penicillin for secondary syphilis. He had been regularly tested for sexually transmitted diseases every 3 months based on his high-risk MSM sexual behavior with his last negative HIV and syphilis tests in May 2007. His initial evaluation for HIV infection revealed a CD4⁺ T cell count was 493 cells per microliter with a viral load of 240,000 copies per milliliter. He was tested for hepatitis A, B, and C with negative serologies.

A month later in September 2007, he presented with a 6-day history of arthralgias, fatigue, jaundice, dark urine, and pale stools. His alanine aminotransferase (ALT) was 1926 U/L (normal, <60 U/L); aspartate aminotransferase (AST), 2097 U/L (normal, <35 U/L); bilirubin, 7.1 mg/dL (normal, <1.2 mg/dL); and alkaline phosphatase, 382 U/L (normal, <115 U/L). His initial test for HCV antibody was nonreactive but a repeat test a week later was reactive. His HCV serologies turned positive in the following order: low positive HCV antibody by chemiluminescent immunoassay; indeterminate HCV antibody by recombinant immunoblot assay, and finally, reactive HCV immunoglobulin G (IgG). He was observed in the hospital for a 2-day period but his clinical condition improved significantly upon discharge and was back to his baseline approximately 4 weeks later.

He was referred to the National Institutes of Health (NIH) Clinical Center for a clinical trial for treatment of hepatitis C in HIV coinfecting individuals. He signed Institutional Review Board (IRB)-approved informed consent to commence treatment of his HCV as part of a clinical research protocol at the National Institute of Allergy and Infectious Diseases (NIAID). Detailed workup of his HCV infection at the time of screening revealed a HCV genotype of 1a/1b with HCV viral load of 280 million IU/mL (Abbott real-time PCR assay, Abbott Laboratories, Abbott Park, IL). His ALT and AST were 154 U/L and 182 U/L, respectively, and have stayed in that range with normalization of other liver chemistry laboratory values. His CD4⁺ T cell count was 422 cells per microliter with a viral load of 189,274 copies per milliliter. His body mass index (BMI) was 21.3 and he had a previous history of social drinking of 1–2 beers per week, which he had discontinued upon HCV diagnosis.

In February 2008, 6 months after his HIV and hepatitis C diagnoses, he underwent a per protocol liver biopsy procedure, which revealed moderate to marked portal chronic inflammatory infiltrate with marked piecemeal and bridging necrosis (Fig. 1A and 1B) perivenular hepatocyte dropout and minimal steatosis with bands of bridging and perisinusoidal fibrosis (Fig. 1C). His hepatic inflammation score (HAI) was 13 of 18 with a fibrosis score of 4 of 6 based on modified Ishak scoring system described in detail by Ghany et al.⁴ As part of the protocol screening, which excludes other causes of chronic liver diseases, he was ruled out for hereditary causes like Wilson's disease, hemochromatosis, other viral hepatitis, autoimmune hepatitis, and hepatitis due to other drugs and toxins.

His repeat CD4⁺ T cell count and HIV viral load were 325 cells per microliter (28%) and 94,212 copies per milliliter, respectively, and he was started on ATRIPLA[®] (efavirenz, emtricitabine, and tenofovir; Bristol-Myers Squibb, New York, NY/Gilead Sciences, Foster City, CA) in March 2008. He responded well to therapy with viral suppression below

FIG. 1. Photomicrographs of liver biopsy specimens. **A:** Hematoxylin-eosin staining of the patient's liver biopsy showing moderate to marked portal inflammation with marked interface hepatitis (original magnification 200 $\times$). **B:** Hematoxylin-eosin staining of the patient's liver biopsy. Focally, bridging necrosis was present, here extending between a portal area (P) and a central vein (V) (original magnification 200 $\times$). **C:** Masson staining showing fibrotic bands (blue) and focal bridging fibrosis of the liver (original magnification 40 $\times$).

TABLE 1. IMMUNE MARKERS

Values [mean]	Our patient	Acute HIV n = 7 [range] Mean values	HIV and HCV n = 10 [range] Mean values
CD3%	85	80 [75–83]	72 [49–80]
Total CD3	969	1789 [1138–2643]	1539 [640–2616]
CD4%	37	25 [12–37]	29 [12–51]
Total CD4	422	546 [334–1178]	609 [240–1333]
CD8%	46	52 [36–65]	43 [22–63]
Total CD8	524	1192 [659–1744]	894 [231–1613]
CD4 ₈	1	1 [0–1]	1 [0–2]
CD19	7	12 [5–14]	18 [9–36]
CD16 ₅₆	7	7 [3–13]	9 [3–17]
Cd3 ₃₈ DR*	42	38 [23–64]	20 [6–55]
CD3 _{DR}	44	47 [27–65]	29 [12–71]
CD3 ₃₈ *	84	68 [41–92]	59 [42–74]
CD4 ₃₈ DR*	16	11 [6–20]	9 [3–28]
CD4 _{DR}	19	15 [9–20]	15 [6–21]
CD4 ₃₈ *	74	62 [33–80]	51 [41–64]
CD8 ₃₈ DR*	63	51 [31–76]	30 [11–64]
CD8 _{DR} *	63	58 [39–75]	35 [16–74]
CD8 ₃₈ *	91	70 [41–95]	65 [36–83]

Important immune markers involved in inflammatory process.

the level of detection (less than 50 copies per milliliter by week 16. He was enrolled in an NIH0sponsored clinical trial for treatment of hepatitis C in HIV coinfecting individuals and was started on treatment with Albuferon® (alb interferon alfa-2b; Human Genome Sciences, Rockville, MD/Novartis, Basel, Switzerland) with ribavirin in May 2008 and has had good early virologic response (less than 10 IU/mL by week 12) and is currently at week 28 of 48 week therapy.

Discussion

The incidence of acute HCV infection has declined over the last 20 years as a result of blood screening, needle exchange programs, and aseptic techniques, however, there have been recent reports of increasing incidence of acute HCV in MSM.³ Although sexual transmission of hepatitis C is extremely low, it is well established that high-risk sexual behaviors with multiple partners and coexisting sexually transmitted diseases such as syphilis and HIV infection can increase that risk significantly.⁵

While advanced age (older than 50 years), male gender, and HIV coinfection^{2,6} are all known to be associated with a faster progression rate of liver fibrosis in chronic hepatitis C infection,^{7–10} there have been no reports of documented advanced liver fibrosis within 6 months of disease acquisition. The fact that our patient was biopsied early in his disease might account for necrosis and inflammation seen, however, the degree of fibrosis observed was unexpected.

Increasing rates of HCV acquisition in primary HIV infection is an emerging public health problem.³ As demonstrated in our case, acquisition of syphilis, hepatitis C, and HIV infection in the same period might result in a robust immune response, which may result in rapid progression of liver disease. As shown in Table 1 our patient's immune markers were higher compared to a random selection of study patients with either primary HIV infection or established HIV-HCV coinfection, thereby suggesting an exaggerated immune response. These were patients involved in other NIAID protocols. Pri-

mary HIV cohort was defined as HIV acquisition in the 4 months prior to enrollment, while established HIV-HCV patients were randomly selected from our research protocols for chronic HCV in coinfecting individuals. It has been clearly established that individuals with primary HIV infection have an increase in activated CD8⁺ T cells, which could result in a state of immune activation as evident in this patient.^{11,12} Acquisition of HCV during this time could result in skewing the immune response in a way that could result in destruction of hepatocytes, resulting in massive hepatic inflammation and subsequent liver fibrosis. Since the pathogenesis of hepatic inflammation and liver fibrosis are a result of host immune-mediated effects and not due to direct viral cytopathicity,¹³ our hypothesis seems reasonable in explaining rapid liver disease progression in this patient. There also remains a possibility that the aggressive hepatic inflammation observed might be due to a yet unidentified factor(s) that renders him a rapid progressor of HCV infection.

Our case demonstrates clinico-pathologic confirmation of the deleterious effects of acquiring both HIV and HCV within a short time. This report underscores the importance of improved surveillance and education in high-risk groups especially in MSM about the consequences of possible worse outcomes of one or both infections especially if acquired concurrently. Furthermore this report warrants a prospective study of the role that acquisition of hepatitis C and HIV within the same time frame plays in the development and progression of hepatic fibrosis. Larger trials of patients who concurrently acquire HCV and HIV are required to confirm this finding.

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Author Disclosure Statement

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References

1. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 1999;341:556–562.
2. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfecting patients. The Multivirc Group. *Hepatology* 1999;30:1054–1058.
3. Fox J, Nastouli E, Thomson E, et al. Increasing incidence of acute hepatitis C in individuals diagnosed with primary HIV in the United Kingdom. *AIDS* 2008;22:666–668.
4. Ghany MG, Kleiner DE, Alter H, et al. Progression of fibrosis in chronic hepatitis C. *Gastroenterology* 2003;124:97–104.
5. Filippini R, Coppola N, Scolastico C, et al. Does HIV infection favor the sexual transmission of hepatitis C? *Sex Transm Dis* 2001;28:725–729.

6. Schiavini M, Angeli E, Mainini A, et al. Risk factors for fibrosis progression in HIV/HCV coinfecting patients from a retrospective analysis of liver biopsies in 1985–2002. *HIV Med* 2006;7:331–337.
7. Martinez-Sierra C, Arizcorreta A, Díaz F, et al. Progression of chronic hepatitis C to liver fibrosis and cirrhosis in patients co-infected with hepatitis C virus and HIV. *Clin Infect Dis* 2003;36:491–498.
8. Martin-Carbonero M, Benhamou Y, Puoti M, et al. Incidence and predictors of severe liver fibrosis in HIV-infected patients with chronic hepatitis C: A European collaborative study. *Clin Infect Dis* 2004;38:128–133.
9. Mendes-Correa MC, Widman A, Brussi ML, et al. Incidence and predictors of severe liver fibrosis in HIV-infected patients with chronic hepatitis C in Brazil. *AIDS Patient Care STDs* 2008;9:701–707.
10. Sánchez-Conde M, Berenguer J, Miralles P, et al. Liver biopsy findings for HIV-infected patients with chronic hepatitis C and persistently normal levels of alanine aminotransferase. *Clin Infect Dis* 2006;43:640–644.
11. Cossarizza A, Ortolani C, Mussini C, et al. Massive activation of immune cells with an intact T cell repertoire in acute human immunodeficiency virus syndrome. *J Infect Dis* 1995;172:105–112.
12. Kim H.N, Harrington R.D, Shuhart MC, et al. Case report: Hepatitis C virus activation in HIV-infected patients initiating highly active antiretroviral therapy. *AIDS Patient Care STDs* 2007;21:718–723.
13. Powell EE, Edwards-Smith CJ, Hay JL, et al. Host genetic factors influence disease progression in chronic hepatitis C. *Hepatology* 2000;31:828–833.

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