Repeated spontaneous clearance of hepatitis C virus infection in the setting of long-term non-progression of HIV infection

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Abstract

Hepatitis C Virus (HCV) and human immunodeficiency virus (HIV) are global pandemics that affect 170 million and 35 million individuals, respectively. Up to 45% of individuals infected with HCV clear their infections spontaneously – correlating to factors like aboriginal descent and some host specific immune factors. HIV, however, establishes true latency in infected cells and cannot be cured. In the setting of long-term non-progressors (LTNPs) of HIV, a state of immune preservation and low circulating viral load is established. Regarding HIV/HCV co-infection, little is known about the relationship between spontaneous clearance of HCV infection and long-term control of HIV infection without medical intervention. We describe a case of a HIV-infected female defined as a LTNP in whom spontaneous clearance of HCV was documented on multiple occasions. Similar cases should be documented and identified in an effort to develop novel hypotheses about the natural control of these infections and inform research on immune-based interventions to control them.

Introduction

Hepatitis C Virus (HCV) epidemic accounts for >185 million infections worldwide.[1] An acute infection is usually asymptomatic, and is only very rarely associated with life-threatening disease. Approximately 15-45% of infected individuals clear their infection spontaneously, without any medical intervention.[2] Female sex, being aboriginal descendant, symptomatic acute hepatitis and some host specific immune factors are associated with more frequent spontaneous HCV clearance.[3]

Human immunodeficiency virus (HIV) infection is another global pandemic affecting more than 35 million individuals.[4] In the majority of cases, it is has the characteristics of a chronic, progressive infection. As HIV establishes true latency in infected cells, this infection cannot be cured. However, in a small minority of infected individuals, a status of long-term non-progression (LTNP) can be established, with a preserved immune system and low circulating HIV viral load. Patients in whom this status is achieved are termed long-term non-progressors (LTNPs).[5] Clinically, LTPNs maintain high CD4 counts, and do not develop symptoms of AIDS, exhibiting a detectable, although low, HIV viral load (<1000 copies/mL), while elite controllers maintain an undetectable viral load without antiretroviral therapy.[5]

In Canada, approximately 17% of HIV-infected individuals are co-infected with HCV, the majority of whom are current or recent injection drug users.[6,7] There is limited knowledge about the relationship between spontaneous clearance of HCV infection and long-term control of HIV infection without the benefit of antiretroviral therapy. We describe a case of an HIV-infected female who was an established LTNP in whom spontaneous clearance of HCV was documented on multiple occasions.

Case Report

We report a 52-year-old woman of mixed Caucasian and aboriginal heritage with a 30-year history of injection drug use. Since 1997, she has been injecting heroin and smoking cocaine intermittently until 2004, when she attempted to abstain and was successful until 2005. Unfortunately, she relapsed onto heroin addiction in 2005, and continued to inject until her latest visit on December 5th, 2016. In 1997, she was tested for HIV and HCV and was reported to be negative for both. She lives in the Vancouver Downtown East Side where the most prevalent HCV genotype is 1a. Based on chart review, the patient presented regularly for follow-up regarding HIV infection, and recent injection drug use prompted HCV testing. Antibodies to HCV were first detected in 1999, with a corresponding test for viremia being negative at that time, consistent with acquisition and spontaneous clearance of HCV infection between 1997 and 1999. HIV antibody testing was first reported as positive in 2003, with HIV viral load that was undetectable without the benefit of antiretroviral therapy. For HIV viral load measurements, Roche COBAS Ampliprep/COBAS Taqman quantitative HIV-1 RNA assay was used (F. Hoffmann-La Roche AG, Basel, Switzerland). HIV viral load tests performed between 2003 and 2009 were also below the limit of detection (<40 copies/mL). During this time, the patient is classified as an elite controller, as her viral load is consistently undetectable. For all HCV viral load measurements, Roche's COBAS Amplicor/Taqman quantitative HCV RNA test was used, with a detection range of 12-100,000,000 IU/mL and Qualitative HCV tests with Amplicor PCR was used to confirm the presence/absence of circulating HCV RNA.

She was found to be viremic for HCV genotype 1a/1b in April 2009. In June 2009, HCV RNA was once again undetectable without the benefit of antiviral intervention. During this time, HBV antibody testing for HBs and HBc was also preformed, and found to be positive.

Elevated transaminase were detected in July 2014 (AST:50 U/L, ALT: 76 U/L), suggesting a new episode of HCV infection but HCV RNA testing remaining negative when last tested in March 2016. Once again, no treatment directed against HCV infection had ever been administered to this patient. Relevant laboratory results are summarized in Table 1. With respect to her HIV infection, she never received antiretroviral therapy. Plasma viral load results have been consistently below 200 copies/mL, with a single value of 1527 copies/mL in April 2009. CD4 cell counts, with a single exception in April 2009 (associated with detectable HCV RNA) have been within the normal range. HIV-related laboratory parameters are also summarized in Table 1.

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Discussion

HCV and HIV infections are recognized world-wide pandemics, with co-infection particularly affecting injection drug users. HCV affects more than 240,000 Canadians, including approximately 15,000 co-infected with HIV, such as our patient.[7] HCV/HIV co-infection is generally associated with a lower likelihood of spontaneous HCV clearance, more rapid HCV-related disease progression and higher rates of clinical complications.[8] In our HIV LTNP patient, we have documented repeated instances of spontaneous clearance of HCV viremia, one of which preceded the acquisition of HIV infection. A review of the literature reveals a number of instances of HIV/HCV co-infected individuals on antiretroviral therapy with spontaneous clearance of HCV infection.[8-11] There are a few reports of single episodes of spontaneous clearance of HCV infection in the setting of HIV-related LTNP, including some patients defined as elite controllers , defined as individuals with HIV plasma viral load measures that are consistently undetectable without the benefit of antiretroviral therapy.[12,13] To our knowledge, this case report represents the first documentation of repeated instances of clearance of HCV infection in the setting of HIV-related LTNP.

Although pre-existing HIV infection has been identified as a negative predictor of spontaneous clearance of HCV infection, it does not preclude its occurrence. A number of factors may help predict spontaneous clearance, such as treatment-associated immune reconstitution and the presence of certain genetic polymorphisms (IL28B-CC and HLA-B57 among them).[9,14-16] In a Spanish study of HIV/HCV co-infected individuals, 75 HIV controllers, (including 33 LTNP and 42 elite controllers) were compared to 261 other subjects with a broad range of HIV plasma viral load measures above 1000 copies/mL. All HIV controllers, including elite controllers, had lower circulating HCV viral load measures, and the presence of the HLA-B57 allele was predictive of lower values across all groups.[12] In another cross-sectional study, co-infection with HIV (in the condition of either LTNP or elite controller) was associated with an increased likelihood of spontaneous HCV clearance where 23.3% of such individuals, as compared to 9.1% of 350 HCV mono-infected and only 6.5% of 350 non-LTNP HIV co-infected individuals, spontaneously cleared their HCV infection.[13] While the 9.1% rate of spontaneous clearance quoted in this study is lower than the WHO's estimated 20% value,[2,13] this is likely due to a relatively small sample size. However, the significant conclusion that HCV mono-infected individuals demonstrate a lower rate of spontaneous clearance when compared to HIV co-infected LTNPs remains.

It is also interesting to speculate as to any contribution the patient's environment or exposure history may have had in the outcome of her HIV and HCV infections. Researchers in Montreal have identified some degree of natural immunity to HIV infection in highly exposed uninfected African female sex workers due to polymorphisms in the *IRF-1* gene.[5] Furthermore, one study showed that HCV reinfection occurred in 50% of injection drug users who previously spontaneously controlled their primary HCV infection. Although viral clearance occurs in approximately 25% of patients with primary infections, spontaneous viral clearance was observed in 83% of re-infected patients.[17] In our patient, we may speculate that specific host factors present in the context of repeated low-level exposure to HIV and HCV, could have produced a state of natural immunity that, if identified, could help us learn more about natural immunity to these chronic viral infections. Her continual re-infection with HCV could have also had a role in providing baseline protection against future persistent HCV infections.

In one large study of HIV,[12] loss of control of HIV infection was observed during subsequent acute HCV infection. This was not clearly observed in our patient, except for a single instance of decreasing CD4 cell count and increasing HIV viremia at the

Table 1. Hepatitis C virus and HIV-related laboratory data (1997-2016).

Date of testing	HCV antibody	Qualitative HCV RNA	Quantitative HCV RNA (copies/mL)	HCV genotype	HIV viral load (copies/mL)	CD4 count (cells/mm^3)
1997	Negative	Negative	NA	1a/1b	NA	NA
February 1999	Positive	Positive	ND	ND	NA	NA
November 2006	Positive	Negative	NA	1a/1b	62	ND
September 2007	Positive	Negative	NA	NA	68	ND
July 2008	Positive	Negative	NA	NA	79	770
April 2009	Positive	Positive	ND	1a/1b	1527	260
June 2009	Positive	Negative	NA	NA	NA	NA
September 2009	Positive	Positive	ND	1a/1b	44	640
November 2009	Positive	Positive	ND	1a/1b	75	730
July 2010	Positive	Positive	ND	1a/1b	129	480
October 2011	Positive	Negative	NA	NA	56	560
September 2012	Positive	Negative	NA	NA	<40	590
September 2013	Positive	Negative	NA	NA	<40	650
April 2013	Positive	Positive	ND	1a/1b	40	650
June 2014	Positive	Positive	<15	1a/1b	<40	450
July 2014	Positive	Positive	<15	1a/1b	ND	ND
July 2014	Positive	Negative	NA	NA	ND	ND
October 2014	Positive	Negative	NA	NA	<40	500
January 2015	Positive	Negative	NA	NA	240	530
December 2016	Positive	Negative	NA	NA	<40	650

NA, not available; ND, not done

time of HCV viremia in April 2009. Her HIV-related LTNP status was quickly restored when this repeated occurrence of hepatitis C viremia was cleared spontaneously. It is further interesting to note that she developed natural (not vaccine-induced) protective immunity to HBV following acquisition of this infection in nature in 2009, as HIV infected individuals are far less likely to develop natural immunity to HBV compared to non-HIV infected individuals (17% compared to >90%).[18]

The patient's HCV genotype was consistently 1a/1b when testing was performed. There are two possible explanations for this persistence – the patient was either repeatedly infected from the same source (such as consistently needle-sharing with a chronically infected individual) or the patient maintained the same infection, despite lab results demonstrating an undetectable plasma viral load. Therefore, one further important point of speculation in this case is the possibility that the patient's repeated suppressions of HCV viral load did not, in fact, represent instances of spontaneous clearance, but rather chronic persistence of the same HCV infection with cyclic viral suppression. For example, numerous studies have identified low-level intra-hepatic viral replication in chronic HCV infection.[18-20] While a viral reservoir within the liver associated with clearance from the circulation is uncommon, it is a possibility that must be considered in this setting. Differentiating between these possibilities will remain a limitation of this case, as samples are not available to determine if different HCV genotypes or isolates are involved, or if we are observing near-complete clearance of the same virus on multiple occasions, and low-level recrudescence of a single pre-existing infection on multiple occasions.

It is important to point out limitations of this report. Laboratory data remain incomplete. The pattern of acquisition and repeated clearance of HCV cannot be precisely defined as specifically timed longitudinal blood samples have not been collected. Samples were not available to determine if different HCV genotypes or isolates were involved, or if we were observing near-complete clearance of the same virus on multiple occasions, and low-level recrudescence of a single pre-existing infection on multiple occasions

Conclusions

We describe an HIV-infected woman, an established LTNP (progressing to elite controller status), with repeated documented episodes of spontaneous clearance of hepatitis C-related viremia. Databases of HIV LTNPs should be examined to identify similar cases who may be exposed repeatedly to HCV and fail to establish persistent infection. This may help develop novel hypotheses about natural control of both HIV and HCV, and provide new insight on various host-mediated factors that result in a continually controlled HIV infection and continuous spontaneous clearance of HCV infection.

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