CLINICAL CASE

Sexually transmitted HCV infection and reinfection in HIV-infected homosexual men

Infections et réinfections d’origine sexuelle par le VHC chez des patients homosexuels infectés par le VIH

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Summary Multiple, concomitant or successive hepatitis C virus (HCV) infections have been described in injection drug users and following organ transplantation and blood transfusion. However, data on sexual HCV reinfection is scarce. We report sexual HCV reinfection following viral eradication of a first HCV infection in two homosexual HIV-infected men. The first patient acquired HCV genotype 4 infection after resolution of an initial acute HCV genotype 1a infection. The second patient was infected with genotype 1a HCV following remission of an initial acute HCV genotype 4c/d infection. The two subjects were successfully treated with peginterferon alpha-2a and ribavirin for their first and second infection and achieved a sustained virological response on both occasions. Unprotected anal intercourse with multiple partners known to be HIV-positive (serosorting) was the only risk factor for HCV transmission reported by both patients. Therefore, sexual HCV reinfection can occur in homosexual men having unprotected sex and “serosorting” should be considered a risk factor for the sexual transmission of HCV.

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Résumé Les infections multiples, concomitantes ou successives, par le virus de l’hépatite C (VHC) ont été décrites chez les patients utilisateurs de drogues par voie veineuse, et après transplantation d’organe ou transfusion sanguine. Peu de cas de réinfections par le VHC d’origine sexuelle ont été rapportés à ce jour. Nous décrivons le cas de deux patients homosexuels infectés par le VIH, ayant eu une réinfection par le VHC d’origine sexuelle, après guérison d’une première infection par le VHC également d’origine sexuelle. Le premier patient a été réinfecté par un VHC de génotype 4 après guérison d’une infection aiguë par un VHC de génotype 4c/d. Les deux sujets ont été traités avec peginterferon alpha-2a et ribavirine pour leurs premières et secondes infections et ont atteint une réponse virologique durable à chaque occasion. L’intercours anal sans protection avec de multiples partenaires connus HIV positifs ("serosorting") était le seul facteur de risque pour la transmission de l'HCV rapporté par les deux patients. Par conséquent, les réinfections HCV peuvent se produire chez les hommes homosexuels ayant des relations sexuelles sans protection et le "serosorting" devrait être considéré comme un facteur de risque pour la transmission sexuelle de l'HCV.

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1a. The second patient a été réinfecté par un VHC de génotype 1a après guérison d’une infection aiguë par un VHC de génotype 4. Les deux patients avaient été traités pour leur première infection par l’association peginterferon alpha-2a et ribavirine et avaient une réponse virologique sustenue au moment de leur réinfection. Les deux patients ont été re-traités par la même association pour leur seconde infection et ont également eu une réponse virologique soutenue. Les deux patients rapportaient comme seul facteur de risque d’infection par le VHC, des rapports anaux non protégés avec des partenaires multiples dont ils connaissaient le statut sérologique positif vis-à-vis du VIH (« sérotriage »). Le VHC peut faire l’objet de réinfections d’origine sexuelle chez les patients homosexuels ayant des rapports non protégés. La pratique du sérotriage devrait être considérée comme un facteur de risque vis-à-vis de la transmission sexuelle du VHC.

The sexual transmission of hepatitis C virus (HCV) remains a controversial aspect of hepatitis C epidemiology. Evidence of sexual exposure as a risk factor of HCV infection can be found in American and European studies which identified multiple sexual partners as being an independent risk factor associated with sporadic acute hepatitis C [1,2]. On the other hand, no association has been found between male homosexual or heterosexual activity in long-term monogamous relationships and sexual transmission of HCV [1]. Several explanations have been proposed to explain this apparent discrepancy, one which states that high-risk sexual practices might promote transmission of HCV. Here, we report successive infection and reinfection with different HCV genotypes in two homosexual men with none of the classic risk factors for HCV transmission except for unprotected intercourse with multiple partners and a history of multiple sexually transmitted diseases.

The first patient presented in August 2003 with asymptomatic acute cytolitic hepatitis (aspartate aminotransferase [AST] 189 IU/L, alanine aminotransferase [ALT] 534 IU/L). Human immunodeficiency virus (HIV) infection was known since 1987 and the patient had been taking antiretroviral therapy since 1989. Nadir CD4 cells count was 106/mm³ in 1995. On presentation, he had been taking nevirapine, zidovudine, lamivudine and abacavir for more than 2 years with a good tolerance. CD4 cells count was 569/mm³ and HIV viral load was 1088 copies/mL. His past medical history included secondary syphilis in 1987 and acute hepatitis A virus infection in 1991. Hepatitis B virus (HBV) serology was suggestive of a past infection (positive HBs antibody and HBe antibody). HCV antibodies were positive as well as serum HCV-RNA (6 136 470 IU/mL) and HCV genotype was identified as being 1a (Bayer Visible Gen. Trugene 5’NC and Beckman HCV 5’NC). Retrospective analysis of frozen plasma confirmed that HCV antibodies were still negative in January 2003 and became positive in March 2003. Peginterferon alpha-2a 180 µg/week and ribavirin 1000 mg/day were begun in October 2003 and resulted in a rapid and sustained virological response since HCV-RNA remained undetectable from December 2003 to August 2006. In August 2006, an increase in transaminases (AST 187 IU/L, ALT 190 IU/L) was again associated with positive HCV-RNA (12 088 034 IU/mL). HCV genotype was determined as being type 4 (Beckman 5’NC) this time. Antiretroviral treatment at that time consisted of nevirapine, abacavir and boosted fosamprenavir which was begun on October 2004. CD4 cells count was 1158/mm³ and HIV viral load was <50 copies/mL. Peginterferon alpha-2a 180 µg/week and ribavirin 1000 mg/day were started again in February 2007 but had to be stopped in August 2007 because of psychiatric symptoms. HCV-RNA became undetectable after 4 weeks of therapy and remained undetectable so far. A detailed questionnaire revealed no other risk factors for HCV infection in this patient except for unprotected anal intercourse with multiple HIV-infected partners. Fig. 1 presents the evolution of ALT, AST and HCV-RNA in this patient.

The second patient presented in October 2006 with primary HIV infection. His past medical history included rectal gonorrhoea in June 2005 and acute HAV hepatitis in 2004 which was presumed to be sexually transmitted in the absence of other usual risk factors for HAV infection. The patient had been referred to the unit in January 2000, April 2002 and August 2003 for HIV postexposure prophylaxis following unprotected intercourse with anonymous partners. At the time of HIV primary infection, transaminases were normal. HCV antibodies were negative, total HAV antibodies were positive and HBs antibodies were positive following HBV vaccination. No antiretroviral treatment was administered. On the next visit, 4 weeks later, the patient presented with acute hepatitis (AST 233 IU/L, ALT 468 IU/L). HCV-RNA was positive (581 787 IU/L), as was the first sample drawn in October. HCV genotype was determined as 4c/d (Inolipa 2.0). CD4 cells count was 543/mm³ and HIV viral load was 37 000 copies/mL. Peginterferon alpha-2a 180 µg/week and ribavirin 1200 mg/day were given from December 2006 to July 2007 with a good overall tolerance. HCV-RNA became undetectable from January 2007 to January 2008 and met the criteria for a sustained viral response. Despite counselling and psychotherapy, the patient continued to have unprotected sex and was diagnosed with acute syphilis in June 2007, rectal gonorrhoea in December 2007 and rectal lymphogranuloma venereum in March 2008. In April 2008, a systematic blood test revealed asymptomatic acute hepatitis (AST 1438 IU/L, ALT 2395 IU/L). HCV-RNA was again positive in serum (6638 IU/mL) and the genotype was determined as 1a (Inolipa 2.0). CD4 cells count was 889/mm³ and HIV viral load was 74 000 copies/mL in the absence of antiretroviral treatment. Peginterferon alpha-2a 180 µg/week and ribavirin 1200 mg/day were given this time from May 2008 to November 2008. HCV viral load became
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undetectable at week 2 and is still negative so far. Like the former patient, no other risk factors for HCV infection were found except for unprotected anal intercourse with multiple HIV-infected partners. Fig. 2 presents the evolution of ALT, AST and HCV-RNA in this patient.

Several clusters of acute HCV infections have been described in homosexual, mostly HIV-infected, men [3—6]. High-risk sexual practices, including unprotected anal intercourse as well as unprotected active and passive fisting and group sex, have been associated with acute HCV infections, along with sharing drugs via the nasal or anal route and being involved in multiple high-risk activities [3—6]. "Serosorting", meaning that people with "known" HIV status voluntarily decide to have unprotected sex with persons of the same status, has been associated with an increase in syphilis and other sexually transmitted diseases [7,8] and with HIV transmission from patients during the primo-infection stage [9]. Multiple, concomitant or successive HCV infections have been well-described in patient populations where multiple exposures are common such as intravenous drug users or following organ transplantation or blood transfusion [10]. A recent cross-sectional study in HIV-infected

Figure 1  Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and HCV-RNA evolution for patient 1 (non proportional time scale). Peg-IFN: pegylated interferon; RBV: ribavirin.

Figure 2  Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and HCV-RNA evolution for patient 2 (non proportional time scale). Peg-IFN: pegylated interferon; RBV: ribavirin.
patients showed that patients who were presumed to be infected by injection drug use spontaneously cleared HCV infection less frequently (11.6%) than patients in whom sexual transmission of HCV was suspected (21.9%) [11]. However, this difference was mainly due to a higher clearance rate in heterosexual patients (26%) than in homosexual patients (13.5%). The authors hypothesized that smaller viral inoculums in case of sexual transmission might explain the ability of the immune system to clear HCV. An editorial in the same issue of the *Journal of Hepatology* suggested that this phenomenon could be related to less frequent HCV reinfections in case of sexual transmission [12]. Regarding the high frequency and the severity of chronic HCV infection in HIV-infected patients, HCV treatment is systematically started in our unit as soon as HCV acute infection is confirmed, which precludes analysis of spontaneous clearance in such cases. However, our observation, in addition to two other similar cases recently reported in the literature [13], further suggest that HCV reinfections following viral eradication of an acute infection with a different HCV genotype may be quite frequent in homosexual men who engage in unprotected anal intercourse. Other patterns of multiple HCV infections in homosexual HIV-infected men have been recently reported by Ghosn et al. [13], who described the case of a HCV type 3 superinfection in a patient with chronic HCV type 4d infection, and the case of a HCV type 1a reinfection with a different HCV type 1 strain following eradication of the first strain in another patient. As no immune protection can be expected from a previous HCV infection, HCV should be added to the list of sexually transmitted infections that may repeatedly occur, as long as high-risk practices continue. Serosorting and associated unprotected intercourse alone should be considered a major risk factor for transmission of HCV and other sexually transmitted diseases. Regular screening of transaminases and HCV-RNA should be considered in this high-risk population. In case of unexpected recurrence of HCV-RNA following virological response, HCV genotype should be determined to distinguish relapse of HCV infection from reinfection.

**Conflicts of interest**

None.

**References**