CASE REPORT

Hepatitis C and leptospirosis: simultaneous acute infections or recurrence of occult hepatitis C

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SUMMARY

People who inject drugs are vulnerable to several infections. To the best of our knowledge, this is the first case report of a simultaneous diagnosis of leptospirosis and acute infection or recurrence of occult hepatitis C in an HIV-infected drug user. We report a case of a 47-year-old Caucasian man with HIV infection, on antiretroviral therapy, and with a history of hepatitis C (positive anti-hepatitis C virus (HCV) and HCV RNA persistently negative) who was admitted with febrile acute hepatitis. He was a former injecting drug user, on opioid substitution therapy, who relapsed to injection drug use 3 weeks prior to admission. Work up revealed positive HCV RNA and *Leptospira* DNA in his urine. Four weeks later he had an undetectable HCV load, and also at 6 months of follow-up. This case highlights the presence of two concomitant infectious aetiologies of acute hepatitis in an HIV-infected drug user.

BACKGROUND

People who inject drugs are vulnerable to several infections, the majority of them acquired by sharing needles or related paraphernalia. The high burden of HIV and hepatitis C virus (HCV) infection among this population is well documented.¹

Because HCV is approximately 10 times more infectious through percutaneous blood exposures than HIV, intravenous drug users (IDUs) who acquire HIV infection are commonly HCV infected. As a result, the prevalence of HCV infection among persons who acquired HIV from injection drug use can approach 90%.¹

The majority of patients with acute hepatitis C progress to chronic infection (although symptomatic infection is related to higher rates of cure) that is associated with an increased risk of developing cirrhosis and hepatocellular carcinoma. HIV-infected people are at higher risk, not only due to the lower spontaneous clearance rates of HCV but also because HIV accelerates liver disease progression.²

Leptospirosis is a zoonotic infection caused by *Leptospira*, which can present with a wide variety of symptoms, from a self-limited febrile disease to pulmonary haemorrhage, renal or liver failure. It is a biphasic illness: the first is a septicæmic or leptospiraemic phase, in which bacteria are present in the blood and cerebral spinal fluid. In the second phase, referred to as the immune or leptospiruric phase, circulating IgM antibodies are produced and *Leptospira* is excreted in the urine.³

We report a case of an HIV-infected adult who relapsed to injecting drug use and presented with

icteric febrile hepatitis. Simultaneously, a positive PCR for *Leptospira* DNA and an acute infection or recurrence of an occult hepatitis C were elicited.

CASE PRESENTATION

We report a case of a 47-year-old man, an injecting drug user, with HIV infection diagnosed in 2003 and negative HCV baseline screening. He recalled a history suggestive of symptomatic hepatitis in 2005, months before starting opioid substitution therapy (methadone) with regular clinical follow-up. His work up at the time revealed anti-HCV positivity with undetectable HCV RNA. Posterior measurements of HCV RNA were persistently undetectable and hepatic liver enzymes were normal. He was immune to hepatitis A (IgG HAV positive) and had positive anti-HBs and anti-HBc with negative AgHBs. He was followed in our ambulatory clinic and was on antiretroviral therapy including emtricitabine, tenofovir and boosted lopinavir/ritonavir, with immune recovery and virological suppression (CD4+ count of 495/mm³ and non-detectable HIV load in August 2013). He denied injecting drug use after 2005.

The patient was asymptomatic until 20 November 2013, when he presented at our hospital with a history of fever, asthenia, anorexia, choluria, jaundice, nausea, vomiting and upper abdominal pain for 5 days. He admitted a relapse to intravenous cocaine use on a single occasion, 3 weeks prior to admission, under non-sterile conditions in an abandoned building.

Physical examination revealed a temperature of 37.2°C, blood pressure 135/73 mm Hg, pulse 53/min and respiratory rate 16/min with room air oxygen saturation of 99%. The patient's scleras and skin were icteric. The abdomen was diffusely tender and a liver edge was palpable 7 cm below the costal margin. There were no other significant findings.

The patient was admitted to the infectious diseases department with febrile acute hepatitis for further investigation.

INVESTIGATIONS

Laboratory tests revealed a normal red blood and white cell count, a platelet count of 121×10⁹/L, sedimentation rate 21/mm³, aspartate aminotransferase 169 UI/L and alanine aminotransferase 1942 UI/L (greater than 50 times the upper limit of normal), γ-glutamyl transferase of 301 UI/L, alkaline phosphatase 228 UI/L, total bilirubin 10.05 mg/dL and direct bilirubin 6.28 mg/dL, and lactate dehydrogenase 227 mg/dL. Albumin was

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35.1 mg/dL and coagulation tests were normal. Renal function was impaired with creatinine of 2.97 mg/dL and urea 76 mg/dL. The urine analysis demonstrated proteinuria and microscopic haematuria.

Abdominal ultrasonography revealed hepatomegaly (18.5 cm) with no focal lesions, gallbladder dilation with slightly thickened walls and intrahepatic biliary canaliculus dilation with no evident obstruction.

Work up revealed positive HCV RNA of 13 270 UI/mL, genotype 1a (HCV RNA detected using Cobas Ampliprep/Cobas TaqMan, HCV quantitative test, V.2.0, Roche). *Leptospira* DNA was negative in the blood and positive in the urine.

Leptospira DNA was detected using our routine laboratory test for this target. We used published primers for the first and nested amplification.⁴ The first 50 µL PCR reaction 25 µL of 2X Quantitect Sybergreen PCR master mix (Qiagen), 0.5 µM of each primer, 0.5 U of uracil-*N*-glycosylase (UNG) and 10 µL of extracted sample, positive control (*Leptospira interrogans*, serovar *copenhageni*, strain M20) or negative control (water). The reaction consisted of UNG, Taq activation step and 45 cycles (15 s of 95°C, 30 s with annealing temperature starting at 65°C and 1°C decrease for 10 cycles, and finally 30 s at 72°C with fluorescence acquisition) using the real time thermocycler RG-3000 (Corbett research). For the nested PCR, the sample consisted of 5 µL of the first amplification product and a melting curve analysis of the amplicon was added. This product was also analysed after electrophoretic separation on agarose gel (Elitech Molecular Diagnostics). The presence of *Leptospira* DNA was considered positive as the sample melting temperature was the same as the positive control and a 379 pb band was detected on the agarose gel.

DIFFERENTIAL DIAGNOSIS

Treponema pallidum particle agglutination assay and hepatitis E RNA were negative. Serological studies revealed positive IgG and negative IgM for herpes simplex, Varicella-Zoster and Epstein-Barr viruses, IgG and IgM were negative for cytomegalovirus.

TREATMENT

Antiretroviral therapy was temporarily withheld, methadone maintained and the patient was started on supportive treatment with fluids.

OUTCOME AND FOLLOW-UP

The patient's clinical condition improved rapidly and he was discharged home 4 days later.

Antibiotic treatment for leptospirosis was not prescribed, as the patient was already asymptomatic at the time of diagnosis. Antiretroviral treatment was restarted and he was referred to our ambulatory clinic. During follow-up, clinical and analytic recovery were documented (figure 1).

One month later, HCV RNA was undetectable. Six months later HCV load remained undetectable, confirming high probability of spontaneous clearance.

Leptospira's serology was not performed as the patient was temporarily lost to follow-up.

DISCUSSION

Despite being frequent in people who inject drugs, acute hepatitis C is not easily diagnosed given its common asymptomatic behaviour. Only one-third to one-half of individuals with acute HCV infection show signs of an acute illness⁵ and, furthermore, people infected with HIV hardly ever present with clinical symptoms of acute HCV infection.⁶

Figure 1 Analytical evolution (ALT, alanine aminotransferase; HCV, hepatitis C virus; ND, undetectable).

In this case, our patient developed symptomatic hepatitis, with evidence of simultaneous HCV and *Leptospira* infections. Leptospirosis suspicion was based on the epidemiological context, namely, intravenous drug use under non-sterile conditions in an abandoned building.

Given the fact that the patient recalled a single relapse of injecting drug use 3 weeks prior to admission, we have considered that possibly he had acute hepatitis C simultaneously with the *Leptospira* infection. *Leptospira* PCR positivity in urine at admission also supports this time frame.

We cannot be certain that the symptoms were related to the HCV acute infection, or whether they were due to the leptospirosis, or both (most likely). If the patient had not had the *Leptospira* infection he could possibly have had an asymptomatic course of acute HCV infection that we would not be able to diagnose.

A spontaneous viral clearance was observed and 1 month later the patient's HCV RNA was undetectable.

It is known that most acute infections with HCV will become chronic in the absence of antiviral therapy, with an average spontaneous viral clearance rate of only 25% at least 6 months after diagnosis. Risk factors for progression to chronic HCV infection are: asymptomatic acute infection, male sex, African-American ethnicity, co-infection with HIV and lower HCV loads.²

On the contrary, high spontaneous clearance rates are more frequent in people with symptomatic infection and in genotypes 2 and 3.⁷

Given all these facts and considering we do not know the previous infection HCV genotypes, we cannot be sure whether this was an acute HCV infection or reactivation of HCV infection. Indeed, a recurrence of occult previous chronic hepatitis C with a persistently undetectable viraemia (and also persistently

Learning points

- ▶ This case highlights the importance of considering the multiple infections associated with intravenous drug use under non-sterile conditions.
- ▶ To the best of our knowledge, this is the first simultaneous diagnosis of leptospirosis and hepatitis C in an HIV-infected patient. Promotion of harm reduction strategies, namely, needle/syringe exchange and opioid substitution therapy programmes, is crucial to reduce the burden of infectious diseases among injecting drug users.

normal liver enzymes) that became detectable^{8 9} in the context of the leptospirosis is another possible explanation.

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Competing interests None declared.

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