

Fatal reactivation of HBV and HDV during a long-lasting interruption of HAART in a patient co-infected with HIV, HCV, HBV and HDV

Riattivazione letale di HBV/HDV durante un'interruzione non strutturata della HAART in un paziente HIV coinfecto da HCV, HBV e HDV

Ennio Polilli¹, Federica Sozio², Elena Mazzotta², Alessandro Pieri²,
Luciana Alterio², Elena Placido², Adriana Agostinone²,
Francesco Di Masi², Monica Tontodonati², Augusta Consorte²,
Luana Cosentino¹, Giustino Parruti²

¹Clinical Pathology Unit, Ospedale Civile "Spirito Santo", Pescara, Italy;

²Infectious Disease Unit, Ospedale Civile "Spirito Santo", Pescara, Italy

INTRODUCTION

Coinfection by the Human Immunodeficiency Virus (HIV) and Hepatitis Viruses, in particular HCV, is a frequent condition among drug addicts as a consequence of shared transmission routes [1].

The proportion of HIV-HCV coinfecting patients ranges between 8.9% and 33% in reported series; HBV coinfection is less frequently diagnosed, accounting for up to 6-14% of patients [2-5]. Finally, about 5-12% of HIV infected patients may show anti-HDV reactivity in addition to HBV coinfection [6].

In coinfecting patients, liver injury is amplified because of HIV-related immune impairment, with a more rapid progression to the advanced stages of cirrhosis, hepatic carcinoma and hepatic failure.

For this reason, mortality due to HCV-related disease greatly increased in patients with HIV infection over the past decade, while its secondary prevention has become one major priority [1].

Many lines of evidence now indicate that both the use of highly active antiretroviral therapy (HAART) and the treatment of hepatitis virus infections are essential to prevent progression of liver disease [7-9]. Control or clearance of he-

patic viruses may also decrease overall toxicity of HAART and enhance its durability [10, 11]. Treatment of chronic hepatitis C in HIV coinfecting patients is not always feasible, is poorly compatible with several HAART regimens and is effective in less than 40% of treated patients [12-14].

Treatment of HBV in coinfecting patients requires tenofovir-based HAART regimens, as interferon is only marginally effective [15]. It is not yet clear how to de-intensify HAART in these patients and to what extent HAART interruptions may be practiced [16, 17].

In the present study we report on the case of a patient with a history of drug and alcohol abuse in his second and third decades, who got sequentially infected with HIV, HCV, HBV and HDV. This patient was successfully treated with pegylated-interferon (PEG-INF) for HCV in 2004 and died shortly after interferon treatment due an overwhelming reactivation of HBV while practising a long lasting interruption of HAART.

CASE REPORT

A 48-year-old Caucasian patient was followed at our institution from 1993. In 1982, he was di-

agnosed elsewhere with asymptomatic HIV infection, and a year later with NBNA hepatitis. In 1985 he was found to be HBsAg, anti-HBe, anti-HBc positive, with HBV DNA undetectable in ELISA.

In 1993, he was first referred to our institution due to increased ALT levels, asthenia and hyperchromic urine, with an unchanged pattern for chronic HBV infection (HBsAg, anti-HBe, anti-HBc positive with undetectable HBV DNA in ELISA).

At this time, however, he was found to be Hepatitis D Virus antigen positive, with positive anti-Delta IgM immunoglobulins. His CD4 T-cell counts being $353/\text{mm}^3$, the patient began his first line antiretroviral monotherapy with zidovudine (AZT), which he assumed discontinuously until June 1997, when his HIV viral load was 342,000 c/mL and his CD4 T-cell count $527/\text{mm}^3$.

Throughout this observation period, repeated assays for HBV-DNA in ELISA persistently yielded negative results.

In August, 1997, the patient started his first HAART therapy with lamivudine (3TC), stavudine (d4T) and indinavir, with conserved CD4 lymphocyte cell counts ($343/\text{mm}^3$).

He substantially adhered to this HAART regimen until 1999, when he was hospitalized due to severe pulmonary interstitial disease, molecularly diagnosed as *Pneumocystis jiroveci* pneumonia; HAART was resumed shortly after treatment of the opportunistic infection. In 2001, he experienced a relapse of interstitial pneumonia, complicated by acute myocardial infarction (AMI).

HIV viremia was 3,230 c/mL at that time, with a CD4 T-cell count of $412/\text{mm}^3$. HAART was changed to d4T, 3TC and nelfinavir and 3 months later, at his first scheduled check after discharge, his HIV viremia was undetectable.

In the next 3 years, his clinical and immunological status was stable, but HIV viremia presented a low-level relapse (median: 12,200 c/mL, r. 780-27,400 c/mL), with slowly increasing CD4 T-cell counts (Zenith $736/\text{mm}^3$).

For 4% type II cryoglobulinemia, persistently high ALT levels (3-7 fold ULN) and a severe Knödel score at liver biopsy (23/25, F5), in March 2004 the patient was prescribed PEG-INF alpha-1b (1.4 micrograms/kg) and ribavirin (RBV) (12 mg/kg) for his genotype 3a chronic HCV hepatitis.

His HAART regimen was not changed. HCV RNA was undetectable after 4 weeks of thera-

py, and Early Virologic Response was complete at 12 weeks. Treatment was stopped after 6 months; at that time, HBV DNA was undetectable by PCR.

In 2005, the patient was hospitalized due to peripheral paralysis of the VI and VII right cranial nerves. At that time, he was diagnosed with a moderate to severe protein-losing nephropathy, with HIV persistently detectable and $<10,000$ c/mL.

To the benefit of his renal function, HAART was stopped and the patient was put on lamivudine monotherapy for approximately 6 months, until October 2005, when a new HAART regimen was based on saquinavir (SAQ/r), didanosine (ddI), 3TC according to the HIV drug resistance profile obtained by GRT.

HCV viremia relapsed 12 months after treatment discontinuation, in parallel with a new rise in ALT (Zenith 150 U/L). HBV DNA was undetectable at 2 consecutive checks by PCR.

In September 2006, the patient deliberately discontinued his current and successful HAART regimen due to fatigue and persistent elevations of serum CK and LDH, diffuse myalgia, as well as appearance of several subcutaneous nodules at his trunk and limbs. At the first check after interruption of HAART, HIV viremia was 1,200 c/mL and CD4 T-cell counts $598/\text{mm}^3$.

Six months after HAART discontinuation, the patient was hospitalized due to acute liver failure, with deep asthenia, acholic faeces, in-gravescent jaundice (total serum bilirubin rose up to 49 mg/dL), considerable weight loss, reduction of lean mass, ascites.

This was quickly complicated by renal failure, with ensuing generalized oedema (pleural and peritoneal effusions), causing respiratory and haemodynamic failures. The previous episode of AMI and severe impairments of renal function precluded evaluation for liver transplantation.

Virological investigations showed - for the first time in his twenty-year period of clinical and laboratory observation - the presence of high level replication of HBV (123,000,000 c/mL) and low reactivity of Delta antigen in the absence of anti-HDV IgM (March 2007).

Adefovir and lamivudine were administered without further deterioration of renal function. The haemodynamic instability precluded any possible palliative treatment with plasmapheresis.

Despite a rapid decrease of HBV DNA to 650 c/mL within 2 weeks, the patient entered hepatic coma, dying on April 12th, 2007.

■ DISCUSSION

The remarkable finding of this case is that the reactivation of HBV and HDV ensued after a very long period of latency, likely begun soon after primary infection, and persisted for over 20 years, with a relatively preserved immune system (lymphocyte CD4 T-cell counts never dropped below of 350/mm³ in our patient) and in spite of a course of immune stimulatory treatment with PEG-INF and RBV just 2 years in advance.

In the 12 years from HBV infection until the start of a lamivudine containing HAART regimen, HBV-DNA was below the limit of detectability even in the absence of any anti-HBV therapy.

Although the phenomenon of viral interference in mixed infections has been previously described, the interplay between hepatitis viruses and the regulatory mechanisms involved are still not well defined in terms of mutual replicative suppression.

It has been suggested that this may be attributed to a peculiar role of HDV in multiply coinfected patients [18, 19]. In the triple infection with HCV, HBV and HDV, the dominant role of HDV has been described in recent works from Mathurin et al., and Jardi et al., who reported that replicative activity of HDV negatively affected HBV and HCV replication [18, 20]. Conversely, it has been shown that the progressive course of HCV, HBV and HDV triple infection is usually dominated by HCV replication [21, 22]. The reason for these discrepant results may be related to the fact that these studies were

conducted on different populations in terms of geographic areas and with different infection durations. Indeed, the dominant role of HDV was postulated in studies conducted in Europe alone, with a high prevalence of HDV-genotype 1 patients [20].

In 1997 our patient started lamivudine in his first line HAART, which was discontinued only in 2006. A few months later, HBV-HDV reactivation was observed.

In 2004 treatment of HCV coinfection was successfully attempted in stable clinical conditions. Under such conditions, clearance of HDV has been reported.

Complete resolution of a chronic hepatitis B and D indeed occurred in a patient co-infected with HCV and HIV. Cure was observed after 24 weeks of combination therapy with PEG-INFN and RBV given to treat HCV and discontinued, as in our patient, after 6 months [23].

In HIV-HBV-HDV and HIV-HCV-HBV-HDV coinfecting patients, however, an unfavorable effect of HIV on the severity of liver disease has been suggested by Housset et al. and by Buti et al. and HDV infection has been indicated as the main cause of death in HIV-coinfecting patients, independently of the development of full-blown AIDS [24-27].

The unstructured HAART interruption was likely detrimental. HBV reactivation was associated with reactivation of HDV and acute liver failure ensued, in spite of a prompt viral response to rescue therapy.

Our observation adds further evidence to the knowledge that reactivation of HBV and HDV in multiply coinfected patients is possible even after a long latency and in spite of mild immune depletion and recent immune therapy.

Key words: HIV, HBV, HDV, viral reactivation, HAART interruption.

SUMMARY

Coinfection by the Human Immunodeficiency Virus (HIV) and hepatitis viruses is a frequent condition in drug addicts. In the present study we report on the case of a patient with a history of drug and alcohol abuse who was sequentially infected with HIV, HCV, HBV and HDV. He died of an overwhelming reactivation of HBV and HDV in spite of a recent interferon treatment.

HBV and HDV resumed their active replication after over 20 years of complete latency, that is after long-lasting viral undetectability, when the patient deliberately discontinued his last HAART regimen. HBV and HDV reactivated in spite of a relatively preserved immune system and a recent immune stimulatory treatment with pegylated interferon.

RIASSUNTO

La coinfezione da HIV e virus epatitici è una condizione frequente tra i tossicodipendenti. Gli autori descrivono il caso di un paziente con lunga storia di tossicodipendenza e abuso di alcol, infettatosi in sequenza con HIV, HCV, HBV e HDV, il quale, nonostante un trattamento recente con interferone, è deceduto per una grave riattivazione di HBV e HDV. La riattivazione è avvenuta dopo oltre 20 anni di completa latenza, cioè dopo una

costante non rilevabilità dell'HBV DNA e dell'antigene Delta sin dalla fine delle relative infezioni acute. La riattivazione è coincisa con una completa interruzione della terapia HAART. La persistenza dell'infezione da HBV e HDV è esitata in riattivazione nonostante il buono stato del sistema immunitario, solo parzialmente compromesso da HIV, e il trattamento con interferone peghilato.

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