



Case report

Chronic alcohol abuse and spontaneous clearance of hepatitis C virus

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ABSTRACT

Spontaneous clearance of hepatitis C virus (HCV) is an uncommon occurrence in the course of chronic infection. We reported a rare case of a 41-year-old male patient infected with HCV genotype 3a who presented spontaneous viral elimination after increasing his daily consumption of alcoholic beverage. In this short review, we overview how modulation of the hepatic inflammatory response could have a role in the viral elimination process.

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Introduction

Approximately 25% of cases of acute hepatitis C virus infection progress to spontaneous elimination, defined as the absence of plasma viremia detectable after 6 months of infection, in the absence of specific treatment [1]. However, in chronic infection, the spontaneous elimination of the virus is especially rare and estimated at 0.5% /year/person [2].

Although the mechanisms are not totally explained, some factors of the host have been described as responsible for increasing the probability of spontaneous elimination of HCV, such as: female sex [3]; younger than 30 years old [4]; nonblack race [5]; CC genotype of rs12979860 gene of interferon lambda 4 [6]; increased production of IL-12 [7]; and, B27 and B57 variants of the HLA gene [8].

In this study, we reported the case of a patient who presented spontaneous viral elimination after increasing their daily consumption of alcohol, and reviewed the cases previously reported in the literature.

Case report

A 41-year-old man was referred to the NUPAIG Viral Hepatitis Outpatient Clinic with a positive HCV serology. He had a history of abusive use of alcohol (daily use of about 400 g of ethanol in the last 5 years) and recurring use of inhaled and intravenous drugs.

He did not have other previous laboratory tests for comparison. Initial laboratory tests confirmed HCV 3a genotype infection, with the viral load of 5 log IU/mL. He had also elevated total bilirubin (1.99 mg/dL, 47% direct), slightly prolonged prothrombin time (international normalized ratio 1.28), high level of aspartate aminotransferases (AST 170 U/L, with AST / alanine transaminase = 4.3) and thrombocytopenia (platelets = 102,000/mm³). The clinical serology tests revealed susceptibility to hepatitis B virus; IgG reactive for hepatitis A virus; IgG reactive for hepatitis E virus (HEV) with a non-detectable quantitative viral load of RNA HEV; non-reactive serology for HIV-1 virus.

The initial clinical assessment revealed advanced liver fibrosis with a APRI (AST to Platelet Ratio Index) score of 4.08, Child-Turcotte-Pugh score of 5 (class A), and MELD (Model for End-Stage Liver Disease) score of 12. Initially, treatment with the combination of pegylated interferon plus ribavirin was contraindicated, given the abusive use of alcohol, and the patient was lost to follow-up for two years.

The patient continued his alcohol habits and, in mid-2015s, returned to the outpatient clinic, reporting a history of asthenia, abdominal pain, increased abdominal volume, lower limb swelling, and eventual gingivorrhagia while brushing his teeth. According to his report, despite having stopped using drugs, he had significantly increased alcohol consumption in recent years to about 800 g of ethanol/day.

During the exam, he was alert, cooperative, without asterixis but with a fine tremor of extremities and moderate ascites. In new laboratory tests, the HCV genotype 3a was maintained, with a viral load of 4.07 log IU/mL, reduced albumin (3.0 g/dL), high total bilirubin (2.36 mg/dL, 51% direct) prolonged prothrombin time (international normalized ratio 1.34), high aspartate

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aminotransferases and thrombocytopenia (platelets=88,000/mm³). The transient hepatic elastography confirmed hepatic cirrhosis (48.8 kPa); the upper digestive endoscopy evidenced medium-sized esophageal varices; and the upper abdominal ultrasound revealed a 15 mm-diameter portal vein, a 11 mm-diameter splenic vein, splenomegaly and collateral circulation of the portal system. At the moment and facing the incorporation of direct-acting antivirals for the treatment of HCV into the Public Health System, it was indicated the treatment with the combination of sofosbuvir plus daclatasvir and ribavirin.

Three months later, when new pretreatment laboratory tests were performed, unexpectedly, no RNA HCV viral load was detected (lower limit of detection of 12 IU/mL). Therefore, the option was to do not initiate antiviral treatment and return every 12 weeks for clinical evaluation and new laboratory tests. Among 2016 and 2017 the patient was evaluated five times, and, in all occasions, no RNA HCV viral load was detected in the laboratory tests. He still kept the abusive consumption of alcohol and poor adherence to medications prescribed for the management of complications of liver cirrhosis.

Discussion

In this manuscript, we reported a rare case in which a 41-year-old male patient infected with HCV genotype 3a presented spontaneous viral elimination after increasing his daily consumption of alcohol. As far as we know, only one case of spontaneous viral elimination after alcohol consumption has been described in the literature [9]. In this context, permeating the existent relationship between a hepatocellular lesion and viral infection, the role of hepatic inflammatory response on spontaneous viral elimination becomes an important element for the understanding of the case to be discussed here.

During the course of chronic infection, the continuous hepatocellular damage maintains a cycle of destruction and regeneration of hepatocytes that often ends in cirrhosis and hepatocellular carcinoma. As the HCV is a hepatotropic but not a cytopathic virus, it is assumed that its cellular damage results from the recognition and destruction of hepatocytes infected by the adaptive immune response. However, the factors that determine a successful host immune response against hepatitis C virus are still not well defined. In this sense, studies with lymphocytic choriomeningitis virus infection have helped to understand how the virus uses different strategies to escape or sufficiently modify the immune response in order to avoid its elimination [10,11].

The secretion of immunoregulatory cytokines is one of the strategies to manipulate the immune response to promote viral persistence. In this context, the IL-10 cytokine has proved to be a great modulator of the immune response. During the acute course of an infection, it inhibits the activity of T cells, NK cells and macrophages, all of them necessary for viral elimination, but also contributing to tissue damage. Therefore, while limiting collateral tissue damage, it may also prevent successful viral elimination [12].

Actually, studies have shown that patients who could control HCV infection exhibit T lymphocyte-mediated immune response with greater functional avidity and cross-recognition ability than those who had persistent infection [13]. In this regard, the association between chronic HCV infection and the presence of elevated serum levels of IL-10 cytokine has been previously demonstrated [14,15]. Among the reasons for that, it is indicated the monocyte production of cytokine IL-10 in response to the stimulation of its toll-like 2 (TLR2) receptor by the viral core protein [16].

Nonetheless, despite the fact that HCV uses high levels of IL-10 as a viral escape mechanism, we suggested the hypothesis that, by intensifying the hepatocellular damage by increasing the daily

consumption of alcohol, there has been a reconfiguration of the pattern of the secreted cytokines.

In this regard, Crews et al. demonstrated that the regulation of the production of pro and anti-inflammatory cytokines by alcohol depends on the time of exposure to alcohol (that is, acute or chronic) as much as the complexity of costimulatory signals and monocyte activation [17]. In the presence of a single stimulatory signal of the TLR4 receptor, acute alcohol exposure has anti-inflammatory properties that relieve the proinflammatory pathways and increase the production of IL-10. In contrast, prolonged exposure will increase the production of proinflammatory cytokines induced by activation of the NF- κ B signaling pathway. Also, under the circumstances of high-activation of monocytes, such as the combined stimulation of TLR2 and TLR4, the production of proinflammatory cytokines could be increased even in acute exposure situations, suggesting that, in the presence of complex proinflammatory signals or already activated monocytes, acute exposure to alcohol could promote additional inflammation [17].

In conclusion, it is possible that, in this case, the spontaneous viral elimination after the increase of daily consumption of alcohol occurred as a result of the intensification of the stimulation the TLR2 and TLR4 receptors, and the activation of the NF- κ B patchway, in an environment permeated by proinflammatory complex signals and full of monocytic hyperactivation induced by the viral core.

Conflict of interest

The author declares that there is no competing interest.

Ethical approval

The study describes clinical and diagnostic procedure of a specific case. All procedures performed were in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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The authors declare no financial support.

Authors' contribution

HP conceived of the presented idea, designed the concept and drafted the manuscript. GB arranged the ethical approval. GB, JFS, and AC gathered data.

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