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Case Report

Spontaneous Clearance of Chronic HCV: The Key Ending Left in the Dark

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Abstract

BACKGROUND: Hepatitis C is the second leading cause of liver cirrhosis and hepatocellular carcinoma. Although the discovery of direct-acting agents made the disease curable, HCV elimination can be achieved solely by the host's immunologic arsenal.

CASE REPORT: We report the case of a 29-year-old woman with chronic hepatitis C infection - elevated transaminases, positive serology. HCV was detectable on two occasions, and histology showed mild disease - A1F1. Upon follow up and without any treatment, the patient achieved spontaneous clearance confirmed by two consecutive undetectable HCV RNA tests. Spontaneous HCV clearance rarely occurs – 0.5% per person-year. This is sometimes accompanied by special circumstances like additional disease or medical interventions. Host factors like gender and interleukin-28B polymorphisms have been known to contribute to clearance. Viral factors like HCV RNA levels are also a factor. The characteristics of host-viral interplay – age of acquisition and fibrosis stage – cannot be overlooked.

CONCLUSION: All of the abovementioned factors contribute to the complex immunological interaction between virus and host and the result, although rarely can be spontaneous clearance.

Introduction

Hepatitis C (HCV) is an enveloped, single-stranded RNA virus capable of causing acute and subsequent chronic infection [1] affecting mainly but not only the liver [2]. Although 20-40% of the acutely infected clear the virus spontaneously, about 75% of the individuals develop chronic infection [3]. Chronic HCV has a 170 million worldwide burden and is the second leading cause of liver cirrhosis and hepatocellular carcinoma [4].

The discovery of direct-acting agents, an undisputed breakthrough of modern medicine, has changed the course of the disease. The natural progression has given way to treatment with a near-to-100% success and a WHO Program for the worldwide elimination of HCV as a public health threat by 2030 [5]. Nevertheless, recovery can be achieved by the host's immunologic arsenal [6]. There's more to be found, as the mechanisms and predictors of spontaneous clearance in the chronic setting remain as blurred as the rarity of the event itself.

Case Report

We report the case of a 29-year-old woman who presented to our clinic with an anti-HCV (+) positive test done 2 months earlier. The patient was unaware of her HCV infection. She has a history of intravenous drug use, currently on Methadone therapy and a sexual partner (also currently on Methadone therapy) with an HCV infection that was diagnosed at the same time as her diagnosis. She has no concomitant diseases or therapy and is a smoker.

Further laboratory testing verified elevated transaminases (ASAT 386 IU/ml ALAT 740 IU/ml) and a low total bilirubin elevation 21.4 µmol/l. No concomitant HBV or HIV infection was discovered. HCV RNA was 7 247 IU/ml, genotype 3. After four months she presented with normal transaminases and still detectable HCV RNA. This time the genotype was 1b. As per the national consensus for treating chronic viral hepatitis, a percutaneous liver biopsy was performed with an 18G true cut needle showing slight activity and fibrosis-METAVIR A1F1.

The unusual change in genotype arose some concerns, and before any treatment, a third HCV RNA test was done (nine months after the first one) with an undetectable result. Spontaneous clearance of chronic HCV RNA was discussed, and a last HCV RNA test was performed after 3 months (1 year after the initial) confirming the elimination.

Discussion

Spontaneous elimination of chronic hepatitis C occurs rarely: a Scottish cohort demonstrating incidence of 0.19-0.36 per 100person-years [7]; a Japanese study demonstrated a clearance rate of one 0.5%/year/person [8], and a third study placed the number at 0.75% per person-year (1.15 per 100person-years) in Alaska natives [9]. In most published cases loss of HCV RNA is associated with special circumstances like pregnancy and parturition [10], [11], [12], HBV superinfection [13], alcoholic hepatitis [14] or hepatocellular carcinoma [15]. Medical interventions can also alter the natural course of the disease – HCV clearance has been reported after surgery [16] including transplantation indicated for HCV cirrhosis [17] or the initiation of HAART for HIV co-infection [18]. Checkpoint inhibitors used in oncology show a promising effect when used in the setting of a concurrent chronic viral infection [19].

As in the presented case, perhaps more often than reported, HCV RNA is eliminated without any of the abovementioned events. Host (genetic) and virologic factors have been distinguished, influencing an interplay with several characteristics found to be clinically important. Female gender contributes to better prognosis in HCV infection, with HCV RNA rates higher for males than females [20]. Polymorphism on chromosome 19 - the interleukin-28B gene (IL28B) in particular the IL28B-CC genotype is associated with spontaneous clearance in the chronic setting. The latter is especially important in the setting of pregnancy/parturition [10] or HIV coinfection [18]. A genome-wide study detected an important polymorphism on chromosome 6-the HLA class II region near DQB1*03:01 [21]. Although the study did not distinguish between chronic and acute spontaneous resolution, the gene has a role in chronic disease. It has a higher incidence in patients who are asymptomatic carriers compared to those with HCV associated cirrhosis [22]. Younger age of infection is associated with a higher chance of spontaneous HCV clearance [7], [9]. Same can be said for the absence of significant fibrosis (evaluated by ultrasound) [8], although spontaneous elimination has been observed in the cirrhotic setting [14], [15]. There is a connection between the age of infection and fibrosis-younger age of HCV acquisition (< 40 years) is predictive of a slower progression to fibrosis [23]. As far as viral factors go, neither of the known genotypes has been associated with a higher rate of spontaneous clearance in the chronic setting, but low baseline HCV RNA is often discussed [6], [9].

The abovementioned “criteria”, in which chronic HCV spontaneous elimination takes place, have their logical connection when looking into the immunology behind the events. Usually, an acute viral infection triggers a robust T-cell response. With antigenic clearance, immunological reactivity declines (protecting potential autoimmunity) and memory T-cells form [24]. In chronic infections, such as HCV, memory T-cells enter a state of exhaustion, unable to repeat the initial rapid response while antigens persist [25]. Up-regulation of PD-1 (programmed-death-1 receptor) on virus-specific T-cells marks and explains the state of exhaustion. The same receptor is influenced by the innovative checkpoint inhibitors used in cancer therapy [26]. PD-1 blockade improves T-cell proliferation, altering the state of exhaustion, and induces a significant reduction in HCV viremia [27], [28] even to a level below quantitation [28]. But T-cell exhaustion is not only medically reversible. Heterologous viral infections can also trigger the immune system [29]. Both alcohol consumption and parturition have been shown to induce a switch of responses [12], [14]. Humoral immune responses play a role in the decline of HCV RNA-neutralizing antibodies appears [30]. Despite the lack of clearance due to neutralising antibodies alone, there is a connection between them and the natural resolution of HCV [31].

The presented case and discussion perhaps only scratch the surface on the topic of spontaneous clearance in chronic HCV. Further work is required to uncover its true complex mechanisms. Nevertheless, the search continues. Despite the therapeutic success, true elimination will require more – a vaccine development [32].

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