Case Report:

**Immune-mediated clearance of hepatitis C virus in the occupational setting**

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Abstract:

**Introduction:** Hepatitis C is an important occupational disease that affects healthcare workers. The main method of transmission of hepatitis C in the healthcare setting is via needlestick injuries. Although rare, blood splashes to the eyes and to open wounds have also been reported to occur. Many patients exposed to hepatitis C in the occupational setting who seroconvert will develop chronic hepatitis C infection. A minority of patients exposed to hepatitis C will spontaneously clear the infection without any treatment. We report a case of an individual who spontaneously cleared the infection without the need for medical treatment.

**Case Presentation:** A 20 year old healthcare worker presented to the occupational health clinic after needlestick injury to the index finger. The source patient was known to have chronic hepatitis C infection which was untreated. The healthcare worker was followed for eight months after the exposure and developed no symptoms. Labs were drawn on or about the date of injury which showed no amplification of hepatitis C RNA and normal liver enzymes. Labs were again drawn four months after the injury which revealed positive hepatitis C antibody but negative hepatitis C RNA. This laboratory profile reflects evidence of an immune response to the hepatitis C viremia with subsequent immune-mediated clearance of the virus without medical treatment.

**Conclusion:** In a small minority of patients, hepatitis C viral infection can be cleared spontaneously by the immune system without the need for medical treatment. Patients who appear to have cleared the infection on their own should be monitored for at least 12 months after the initial injury to ensure that no dormant virus is detected in the bloodstream. Patients who spontaneously clear the infection in the occupational setting should also be referred for consultation with a gastroenterologist prior to discharge even if there is no evidence of hepatitis C RNA amplification. In this case report we will review hepatitis C infection, epidemiology, prevalence and risk factors as well as testing, clearance and its prevention.

**Hepatitis C Infection**

Viral hepatitis is an inflammation of the liver caused by any of the five types of the hepatitis virus (A, B, C, D, and E). Ever since Hepatitis C (HCV) official discovery in 1991, its prevention and transmission still poses an enormous challenge for the global public health community [1]. The WHO estimates that around 150 million people are infected with the virus worldwide, and a projected 350,000 of those infected will die every year [2]. In 2014, CDC and the National Health and Nutritional and Examination Survey (NHNES) reported that there were around 3.5 million Americans infected with HCV. In the recent years, the incidence rate of HCV infection in the U.S. has significantly increased [3]. This alarming rise in cases is predominantly seen in younger adult injection drug users, whose risk behaviors are associated with in HCV infection [4, 5].
HCV can be transmitted by exposure to bodily fluids, healthcare providers are at a much higher risk of getting infected in comparison to the general population [6]. Outside of the infected patient’s body, the virus is able to survive and retain its infectious properties up to six weeks, and the risk of transmission to a healthcare provider after needle stick exposure is about 1.8% [7].

With the advent of medications like direct-activating antivirals (DA), HCV infection is very curable. These medications have demonstrated to be more effective in eliminating the infection, while reducing the treatment duration and side effects [8]. Interestingly enough, there is a very small amount of patients who are capable of spontaneously clearing the HCV virus from their system. Studies indicate that these patients can mount a strong HCV-specific T-cell response that protects them from a persistent infection [9, 10].

There is also substantial evidence that humoral immunity contributes to spontaneous clearance by making broadly neutralizing antibodies targeting HCV [11, 12]. At the same time, the patient’s genetic makeup is a crucial determinant of their response to the infection. Several studies have highlighted the role certain polymorphisms of the interleukin 28B gene and its association with an enhanced host viral response and clearance [13-15]. Some ethnic groups, carrying different alleles for the interleukin 28B gene, have a reduced capability to spontaneously clear HCV infection [16, 17]. This case report aims to focus on a patient’s ability to spontaneously clear HCV infection, and whether there are associated immunological factors that may contribute to this phenomenon.

**Epidemiology of Hepatitis C**

Hepatitis C virus (HCV) remains a public health concern across the globe, with total global HCV prevalence and viraemic rate estimated at 2.5% and 70.5%, respectively, with North America at 1.2% prevalence rate, and a viraemic rate of 75.7%. There are 4 most commonly reported HCV genotypes, with the most represented genotype group in the United States being G1 at 66.3% [18]. A 10-year long study in Japan enrolled 1,125 antibody HCV (Anti-HCV) seropositive residents to analyze mortality rates and causes of death in Hepatitis C positive individuals. They found that liver-related mortality, including death due to hepatocellular carcinoma, is associated with the presence of HCV viremia among persons who were anti-HCV positive, and HCV core antigen as well as alanine aminotransferase levels were predictors in HCV carriers [19].

**Prevalence and Risk Factors for Infection**

The National Center on Health Statistics came out with a data brief in 2010 on prevalence of hepatitis C infection. From 1988-1994, persons aged 30-39 years had the highest prevalence of HCV infection (3.9%), but from 1999-2002, highest prevalence, at 4.3%, shifted to persons aged 40-49 years, and remained in that age range from 2003-2008. In regards to race/ethnicity or sex, overall prevalence has decreased in three subgroups from 1999-2002 to 2007-2008, including males (2.1%-1.6%), non-Hispanic black (3.2% to 2.6%), and Mexican-American individuals (1.7% to 1.1%). There were minimal to no changes among non-Hispanic white persons or among females [20].

In regards to the individual discussed in this case report, healthcare workers face a daily risk of coming into contact with infected patients and their body fluids. Injuries to medical staff from sharp or pointed objects are among the most frequently reported occupational accidents in healthcare [21]. A systematic review and meta-analysis conducted in
2015 on the prevalence of hepatitis C among healthcare workers found that Europe and the United States, countries with relatively low HCV prevalence, showed an increased prevalence of HCV infection in healthcare workers compared to controls (OR 2.1; 95% CI 1.31 to 3.42), with the most affected individuals being laboratory personnel and staff members who perform exposure prone procedures [6]. No prophylaxis exists for HCV, and immediate testing after suspected exposure is imperative in order to consider early treatment should transmission occur [22].

Testing and Clearance of Hepatitis C Virus
As mentioned earlier, HCV increases the risk for liver related disease and infection, as well as increased mortality, but there is currently no vaccine for HCV due to the high viral replication rate and the existence of several HCV genotypes. To determine if an individual has been infected, testing includes a blood exam looking for both anti-HCV antibodies or HCV-RNA [23]. Another marker for exposure to HCV is detecting HCV-specific CMI. Individuals who were exposed to Hepatitis C but tested negative for anti-HCV were found to have T-cell responses directed toward the virus, an indication of cell mediated immunity [24]. These findings define what is known as HCV spontaneous clearance. This is reported to happen in 15-50% of infected subjects [25]. Several factors play a role in determining the natural course of HCV, including medication, genetics, immune responses, viral load and infectivity, viral genotype, and co-infections [23].

T cell responses play a major role in clearing hepatitis C infection during the adaptive immune response. Upon exposure, activated dendritic cells can present the HCV antigens to specific T-helper cells, with subsequent proliferation of cytokines, such as IL-2, IFN-gamma, or IL-4. These steps are necessary in order for CD8 T lymphocytes to perform their role in lysing HCV-infected cells [26]. Although individuals with chronic infection can have a larger amount of HCV-specific T-cells, they have a reduced proliferative response, lower cytotoxicity, and defective IFN-gamma production and proliferation compared to those who were able to clear the virus [27]. In addition, a longitudinal study on hepatitis C found that subjects with a chronic infection failed to sustain a T-cell specific response, with cell mediated immunity actions dropping to undetectable levels, and displayed a faster decline in IFN-gamma production during the acute stages of HCV-infection. In comparison, those who spontaneously cleared were able to maintain a broader HCV-specific T cell response up to 12 months after diagnosis of an acute infection [28]. The cell-mediated response offers a strong protective mechanism against developing chronic hepatitis.

A study in 2009 measured the levels of interferon (IFN)-gamma-positive T cells in healthcare workers with HCV-RNA and anti-HCV negative blood tests, compared to histologically proven chronic hepatitis, and a control group of healthy blood donors. They found that levels of HCV-specific INF-gamma positive cells were higher in the healthcare worker group compared with both the infected patients and the control group. This could suggest how persistent exposure may stimulate host defenses with no evidence of hepatitis by way of inducing a virus specific IFN-gamma-producing CD8 T cell response [29]. Another study in Egypt looked at healthcare workers exposed to a high-risk HCV infected population. They found that more than half of the anti-HCV negative and aviremic healthcare workers at high risk for infection had broad HCV-specific...
IFN-gamma responses without detectable viremia or seroconversion. It is an important observation to make among healthcare workers, as the immune response could have resulted from a transient previous infection without seroconversion. The authors of the study suggested the repeated exposure to low viral doses could induce cell-mediated immunity as a protective mechanism against acquiring the infection [30]. Having a T cell immune response against HCV may explain the low prevalence of hepatitis C in medical healthcare workers.

**Prevention**

Further investigation into the role of cell mediated immunity in the clearance of hepatitis C is warranted in understanding how some individuals exposed to hepatitis C test negative for the virus. It is a promising aspect of disease prevention and could be used to guide making a vaccination and other treatment options for hepatitis C. Though there are current treatment options for Hepatitis C, prevention, especially in the healthcare setting, is of utmost importance. A study in 1998 found that surgeons in their survey underestimated the seroconversion rates of HIV, Hepatitis B, and Hepatitis C. Many surgeons did not believe that using double gloves would protect against puncture wounds, and should a needle stick occur, their survey suggested many of these incidents go unreported [31]. Recent changes in the design and distribution of equipment are improving the incidence of needlestick injuries, spurred by the Needlestick Safety and Prevention Act of 2000 and regulations set by OSHA. These include engineering controls, additions to the exposure control plan, personal protective equipment, and improved record keeping [32].

**References**


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