Extrahepatic Manifestation in Hepatitis C

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Abstract: Extrahepatic manifestations in chronic hepatitis C virus (HCV) infection are described. Cryoglobulinemia and vasculitis have been observed as frequent complications of chronic HCV infection. Similarly membranoproliferative glomerulonephritis and autoimmunity have also been reported. Autoimmune hepatitis occasionally develops after HCV infection. Molecular mimicry between auto-antigens and HCV-related antigens has been postulated as the causative factor in some cases. Other clinical manifestations of autoimmunity such as thyroiditis, polymyositis, dermatomyositis, Sjögren's syndrome, and idiopathic thrombocytopenic purpura (ITP) are often reported. One of the causes for the development of autoimmunity in chronic HCV infection might be due to lymphotropism of HCV. Perihepatic lymphoadenopathy and B cell-type non-Hodgkin lymphoma have been reported to have a possible correlation with chronic HCV infection. Since minus-strand HCV RNA has been detected in platelets and cardiomyocytes, it has been postulated that there is extrahepatic HCV infection of these tissues. Malignancies and lichen planus in the oral cavity are also frequently observed in patients with chronic HCV infection. All of these clinical manifestations have been observed through careful detailed medical examinations of all body systems and continuing this approach will facilitate the discovery of new disease entities in the future.

Key words: Hepatitis C virus; Autoimmunity; Cytokine; Infection

Introduction

In acute viral hepatitis, viral infection causes damage mainly to hepatocytes, leading to symptoms specific to hepatitis such as fever, anorexia, nausea, and jaundice. However, other atypical symptoms of hepatitis are sometimes found and these are called extrahepatic manifestations.

Hepatitis C virus (HCV) was discovered by a venture company in 1989, which has been assumed for a long time causing post-transfusion hepatitis. During the decade since that discovery, studies on various liver diseases have
progressed rapidly with the advances in biotechnology. As a result, a molecular biological approach has enabled researchers to find HCV more often in organs other than the liver. However, it is still unclear whether HCV detected by the polymerase chain reaction (PCR) method really causes damage to the organ from which HCV is detected.

Extrahepatic manifestations are caused not only by HCV, but also by other viruses. HAV and HBV induce various dermal symptoms in the early period of the first infection. Among them, Gianotti-Crosti disease combining papular peripheral dermatitis with acute hepatitis B is well known. Extrahepatic manifestations such as membranous nephropathy (reportedly caused by the deposition of immunocomplex of virus and immunoglobulin on the glomerulus), arteritis nodosa, and cryoglobulinemia have been recognized.

Some researchers have recently insisted that those manifestations are caused only by HCV in a mixed infection of HCV and HBV, although proof of this hypothesis has been difficult. On the other hand, a recent report has shown that cryoglobulinemia and nephropathy were cured by disinfection of HBV with Lamivudine, a virucide. Therefore, extrahepatic manifestations may be attributed to either of HBV or HCV.

Cryoglobulinemia

Cryoglobulinemia is most frequently observed among HCV-infected patients. In cryoglobulinemia, immunoglobulins in blood that precipitate out when the serum is stored under 37°C, the average body temperature. This precipitation is redissolved by heating. Among the various types of globulin, type II consisting of polyclonal IgG and monoclonal IgM is most frequently observed.

We detected cryoglobulin in approximately 35% of chronic hepatitis C and cirrhosis patients. Most of them had advanced hepatic diseases. Cryoglobulin requires careful procedures for detection. It is detected most effectively by observing precipitation in a sample kept at 4°C for 3 days after coagulation and centrifugation at 37°C.

HCV RNA can be detected from the precipitate of cryoglobulin collected by this method (called cryoprecipitate) employing RT-PCR analysis. Moreover, concentrations of HCV RNA in the cryoprecipitate, which exceed the levels in serum can be established by a competitive RT-PCR analysis. Namely, this cryoprecipitate is believed to be an immunocomplex of HCV as an antigen and immunoglobulin.

Vasculitis

Many patients with cryoglobulinemia (40–95%) present with purpura. Although it is pathologically dermal vasculitis, other symptoms such as crus ulcer, papule, pustule, pigmentation are also found, and arthralgia and Raynaud’s phenomenon are sometimes observed. Since these symptoms appear more frequently during the cold season, we persuade cryoglobulin-positive patients to protect themselves from the cold. Those symptoms are caused by precipitation of cryoglobulin on the vascular wall. Its precipitation on the glomerulus sometimes causes membranoproliferative glomerulonephritis. The decrease in the levels of not C3 but C4 and CH50 are observed in serum complement activity.

Those vascular manifestations can also be partly attributed to autoimmunity. Some researchers insist that hepatitis C induces autoimmune phenomena, is the leading cause of frequent episodes of cutaneous vasculitis and periarthritis. Many of the patients with hepatitis C seem to present with dermal symptoms such as urticaria, which may be related to vascular symptoms.

Autoimmunity

In chronic hepatitis, the leakage of cellular components due to persistent destruction of cells may be one of the causes of production of
autoantibodies. About 20% of patients with hepatitis C are ANA-positive (Fig. 1), which can result from persistent destruction of cells. Furthermore, some researchers insist that viral infection induces autoimmunity. One of the possible reasons is that viral infection induces the appearance of autoantibodies because of the molecular mimicry between HCV and autoantigens. LKM-1 antibody, observed in autoimmune hepatitis, is sometimes observed in chronic hepatitis C. This can be attributed to the mechanism of molecular mimicry, in which the immune response to HCV induces cross-reactivity against autoantigens.

In our study, among a group of patients with chronic hepatitis C, high titers of ANA and significantly high levels of immunoglobulin were observed (Fig. 2). According to autoimmune hepatitis score (AIH score), not small cases can be diagnosed as definite autoimmune hepatitis. These patients are often females and having high staging (fibrotic) scores. They are characterized by their poor response to interferon treatment irrespective of the genotype, despite a low viral load (Fig. 3). Therefore, this phenomenon is one of the reasons why HCV-positive patients are included in the Japanese diagnostic criteria of autoimmune hepatitis. It is still possible that those patients initially suffer from autoimmune hepatitis and then, they receive HCV infection afterwards.

Similarly, it has been reported that autoimmune thyroiditis, polymyositis, dermatomyositis, Sjögren’s syndrome, and idiopathic thrombocytopenic purpura (ITP) are frequently seen, or are exacerbated, following interferon treatment in patients with chronic hepatitis C. Sjögren’s syndrome is considered to be clearly linked with HCV infection because sialadenitis...
was observed in an animal model produced by Koike et al. (transgenic mice with the outermost envelope of HCV). 8) Although the relationship of other types of autoimmunity with HCV infection is unclear, various evidences are accumulating.

Abnormality of Lymphocytic Cells

Another potential cause of autoimmunity is HCV infection in immunocytes. HCV infection in lymphocytes and HCV proliferation within lymphocytes have been demonstrated in vitro, and functional alteration of lymphocyte is possibly induced. Production of excessive autoantibodies and cryoglobulin can be induced by abnormal lymphocytic function caused by HCV infection in immunocytes.

Infection of HCV in lymphocytes may cause other extrahepatic manifestations. Abdominal ultrasonography of a patient with chronic hepatitis C often shows swelling of lymph nodes near the hepato-duodenal ligament. 9) An Italian study reported that approximately 60–70% of patients with swelling of lymph nodes were HCV-positive. The study concluded that HCV infection induced lymphocyte proliferation.

Furthermore, it has long been suspected that HCV infection is a causative factor in B cell-type non-Hodgkin’s lymphoma; 10) 20–30% of patients with this type of lymphoma are HCV-positive, and their rate is significantly higher than that in volunteer blood donors. However, because HCV RNA has been detected in not all lymphoma cells, the role of HCV in the development of lymphoma is not definitive. Some researchers postulate that proliferation of lymphocytes is caused by abnormal production of cytokines after viral infection. 11)

HCV Infection of Cells Other Than Hepatocytes

There are other groups of extrahepatic manifestations caused by infection of HCV into certain kinds of cells. The cause of idiopathic thrombocytopenic purpura (ITP) is considered to be an autoimmune response against plate-
lets, while it may be a result of platelet damage triggered by direct HCV infection into platelets. However, reports in the first half of 1990s were based on the results showing that separated platelets were found to be HCV RNA-positive by PCR analysis. It is possible that HCV adhering to the platelets was detected in just those studies, because the results cannot be duplicated. A large proportion of researchers consider the cause to be autoimmunity induced by HCV infection.

Similarly, some recent reports have proposed that myocarditis, in particular dilated cardiomyopathy and hypertrophic cardiomyopathy is caused by infection of HCV into myocytes. The reports showed existence of the minus-strand HCV RNA, indicating the proliferation of HCV in myocytes. However, because the frequency of myocarditis in chronic hepatitis patients reported by hepatologists seems low, its classification as an extra-hepatic manifestation remains unclarified, and some researchers have suggested that there is a virus subgroup with a high affinity for myocytes. The influence of cytokine production by the chronic viral infection in cardiac muscle rather than the direct effects of viral infection is postulated to be the main mechanism involved.

**Intraoral Manifestations**

The relationship of cancer in the oral cavity and oral lichen planus with HCV infection has recently been discussed. It is reported that the HCV antibody-positive rate among patients with cancer in the oral cavity is as high as 25%, and is considered to be due to the continuous excretion of HCV through saliva and blood.

Oral lichen planus is an inflammatory manifestation with abnormal keratinization, and is sometimes confused with stomatitis. There are reports that approximately 60% of patients with this disease are HCV antibody-positive. However, even if the virus is eradicated by interferon treatment the condition persists. Therefore rather than direct viral infestation, an immunomechanism is considered to play a leading role in the manifestation of the disease.

A recent case report stated that oral lichen planus developed after interferon treatment against hepatitis C. Since half of treated patients presented with the disease after the eradication of HCV with interferon therapy, the author concluded that oral lichen planus was caused by the interferon therapy and not by viral infection.

**Other Extrahepatic Manifestations**

In addition to the aforementioned diseases, porphyria cutanea tarda and interstitial pneumonia are reported as potential extrahepatic manifestations. Porphyria is caused by lowered activity of hepatic uroporphyrinogen decarboxylase. The mechanism of HCV attack on this enzyme has not been totally clarified. For interstitial pneumonia, the involvement of fibrosis in the lung, that is the similar condition observed in the liver of chronic hepatitis, is suspected. The facts are still unclear since this hypothesis is based only on a small epidemiological study.

**Conclusion**

Various extrahepatic manifestations of hepatitis C have been reported as described in this paper. However, the direct relationship between HCV and the onset has not been clarified in most cases. For cryoglobulinemia, accompanying nephritis, sialadenitis observed in animal model, and Sjögren’s syndrome, the causal relationship with HCV infection is almost certain. For other diseases, however, the discussion starts from the epidemiological reference point that the HCV antibody-positive rate of the patients was higher than that of control groups. Further well designed, comprehensive studies are required from a broad range of aspects. However, based on a review using the key words “vascular manifestations,” “HCV infection in cells other than hepatocytes,”
“immuno-transition towards autoimmunity,” and “cytokine,” most of the extrahepatic manifestations seem to present under a similar mechanism, suggesting a relation with HCV. Therefore, successful investigations can be anticipated.

Until now, emphasis for gathering information has been focused on specialists because of the hierarchy of medical practice, but now the participation of general physicians is definitely required. It is recognized that, in dealing with extrahepatic symptoms and manifestation, the careful treatment and diagnosis of patients with a wide range of backgrounds in daily medical practice can yield a vast amount of valuable epidemiological data.

REFERENCES


