Clinical Features of Vascular Disorders Associated with Chronic Hepatitis Virus Infection

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Introduction

Chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is a life-threatening disease that causes progressive liver damage including liver cirrhosis and hepatocellular carcinoma [1, 2]. In addition, several extrahepatic manifestations may develop during the clinical course of chronic hepatitis [3, 4]. Among them, vasculitis is a significant complication of chronic HBV and HCV infection [5]. The onset of this condition is generally attributed to host immune response triggered by hepatitis virus infection [6]. However, the presence of the virus in immune and endothelial cells might also be associated with the pathogenesis of hepatitis virus-related vasculitis. Interestingly, the profile and condition of vasculitis differs between HBV- and HCV-related disease. For example, polyarteritis nodosa (PAN) is more frequently reported in patients with chronic hepatitis B than those with chronic hepatitis C. Similarly, membranous nephropathy is a notable manifestation among hepatitis B virus-positive patients. In contrast, patients infected with hepatitis C virus are at risk for cryoglobulinemia and membranoproliferative glomerulonephritis. Antiviral therapy is necessary to control these kinds of vasculitis related to hepatitis virus infections; however, immunosuppressive agents may be required to treat severe cases. New antiviral drugs for viral hepatitis could improve the prognosis of vascular and renal involvement.
Cryoglobulinemia Associated with Hepatitis Virus Infection

Cryoglobulins are abnormal proteins, generally immunoglobulins, which precipitate from plasma at temperatures below 37°C and dissolve again if the blood is heated. These abnormal blood proteins are observed in several pathological conditions such as infection, autoimmune disease and malignant tumors. Cryoglobulins can cause organ damage through coagulation within peripheral vessels, which leads to vascular damage through immune reactions [9]. Cryoglobulinemia is classified by the types of immunoglobulin involved and the clonality. Type I is most commonly encountered in patients with plasma cell dyscrasia. The abnormal proteins involved are monoclonal IgM or IgG. Type II cryoglobulinemia is associated with monoclonal IgM and polyclonal IgG. The monoclonal IgM protein has rheumatoid factor activity and may react with the Fc region of IgG. Type III involves polyclonal IgM and IgG and is strongly associated with autoimmune disease such as systemic lupus erythematosus and rheumatoid arthritis. Types II and III carry both IgG and IgM components and are called mixed cryoglobulinemia (MC). The latter two types of cryoglobulinemia are associated with HCV infection, particularly with type II cryoglobulinemia [6]. However, HBV infection may also be involved in the pathogenesis of this complication [10], although the prevalence of HBV in MC patients is not as high [11]. A case of cryoglobulinemia onset after HBV vaccination has also been reported [12].

Onset of cryoglobulinemia may be asymptomatic or may lead to a MC syndrome or to a more severe vasculitis [13]. The frequency of cryoglobulinemia in HCV-positive patients is varied among the reports, which might be attributed to the duration of HCV infection and the stage of liver fibrosis [14]. The proportion of HCV-positive cases in MC patients ranges from 30 to 100% among studies. However, the occurrence of MC among HCV-positive patients was reported to be approximately 3% [9]. It has also been reported that the association of HCV envelope glycoprotein E2 with B cell CD81 receptors could trigger the monoclonal expansion of B cells and induce the production of monoclonal IgM [15]. This type of monoclonal protein could react with the HCV core protein and associate with IgG antibodies against several HCV-derived proteins [16]. These immune complexes may lead to vasculitis through the activation of the complement system.

Treatment of Hepatitis Virus-Related Cryoglobulinemia

Although the treatment of HCV-related MC depends on the severity of the disease, antiviral therapy against HCV is essential. Corticosteroids are used to control the acute phase of moderate to severe vasculitis [9]. Immunosuppressant therapy and plasma exchange might be required to remove cryoglobulins in life-threatening cases. Rituximab is also administered to suppress the expansion of B cells that could be a source of cryoglobulins. A combination therapy involving rituximab and antiviral agents against HCV has been reported to be more effective than antiviral therapy alone, and has shown a shorter mean time to clinical remission, better renal response rates and higher rates of cryoglobulin clearance [17].

In contrast to B cell proliferation, patients with HCV-related vasculitis reportedly present with reduction of regulatory T cells, and resolution of the HCV infection correlates with vasculitis resolution and recovery of regulatory T cell levels. Interestingly, administration of low-dose interleukin-2 led to restoration of regulatory T cells, reduction of cryoglobulinemia and concomitant clinical improvement in patients with HCV-induced vasculitis [6].

HBV Infection and PAN

The association between HBV infection and onset of PAN was first reported in the early 1970s [7]. This rare complication is reported more frequently in North America and Europe than in Asia [8]. According to previous reports, PAN was preceded by HBV infection [18]. Although the carrier rate of HBV among patients with all types of vasculitis was <1%, almost one-third of PAN cases yielded positive results for HBV markers [18]. However, the prevalence of PAN decreased with increased vaccination against HBV [19].

Generally, since the immune reaction responsible for PAN occurs within 6 months of infection by HBV, vasculitis may be symptomatic before the onset of hepatitis. Although the detailed mechanisms of HBV-related PAN are still controversial, the majority of HBV-related PAN cases carried wild-type HBV characterized by hepatitis B envelope (HBe) antigenemia and high HBV replication. This supports the theory that the deposition of viral antigen-antibody complexes, possibly involving HBeAg, might be responsible for the onset of PAN [18]. However, some HBV-related PAN cases showed a precocious mutation, which abrogates the formation of HBeAg [20].
Therefore, it is also possible that an undefined circulating HBV-related protein is involved in the pathogenesis of PAN.

The activity of HBV-related PAN has been associated with the proliferation of HBV. On the other hand, serum levels of hepatitis B surface antigen (HBsAg) were not related to the activity of vasculitis, and remission of PAN was noted even in cases with high HBsAg titer.

The frequent complications reported in HBV-related PAN are gastrointestinal involvement followed by malignant hypertension, renal infarction, orchitis and epididymitis. The frequencies of these complications are similar to those of non-HBV PAN [18]. Generally, hepatic manifestations, such as elevated alanine and aspartate transaminase levels and icterus, are mild.

**Treatment of HBV-Related PAN**

PAN has generally been treated with corticosteroids and immunosuppressive agents [18]. This treatment combination might be effective in the active phase of PAN [21]; however, immunosuppression therapy may induce reactivation of HBV and lead to de novo HBV-related fulminant hepatitis, which is a serious condition with high mortality rates [22]. It is also known that the activity of HBV-related PAN decreases after seroconversion of HBeAg and reduction of serum HBV levels [21]. From this point of view, antiviral therapy using nucleotide analogs is necessary to treat HBV-related PAN. For severe cases of vasculitis, immunosuppression and removal of immune complexes using corticosteroids and plasma exchange are applied, followed by long-term suppression of HBV using nucleotide analogs [21].

Rare cases of PAN with HCV have also been reported; however, the association between HCV and PAN remains controversial [18].

**Nephropathy Associated with Hepatitis Virus Infection**

**HBV-Related Nephropathy**

Combes et al. [23] first reported nephropathy associated with HBV in 1971. Deposition of anti-HBV antibodies in immune complexes and complement in the glomerulus was observed in cases with HBV-related nephropathy.

MN is the most common condition with renal involvement among HBV-related nephropathy and more frequent in children than adults. However, MPGN and IgA nephropathy are sometimes observed in adults [8]. Plasma complement C3 and C4 in HBV-related MN patients were significantly lower than in idiopathic MN patients. In addition, segmental glomerular damage, mesangial cell proliferation and tubulointerstitial damage were more common in HBV-related MN than in idiopathic cases. Immunofluorescence staining of polyclonal immunoglobulin and polytypic complement immunoglobulin was frequently noted in HBV-related MN cases; however, no differences in prognosis between HBV-related MN and idiopathic cases were reported [24]. Deposits of IgG, complement 3 and HBeAg were observed in the glomerular capillary walls in the MN cases [25]. However, deposits of HBsAg were observed in the intraglomerular mesangial cell in cases of adult MPGN [8].

As described above, deposition of several HBV-related proteins and immunoglobulins is detected at the basement membrane of the capillary wall of the glomerulus in HBV-positive cases with renal involvement. The immune complex, with a molecular weight of <1,000 kDa, could reportedly trigger nephropathy; a positively charged immune complex of this size could pass through the capillary wall's basement membrane and deposit under the negatively charged glomerular epithelial cells. From this point of view, HBeAg could be a pivotal antigen responsible for HBV-related nephropathy [25]. The deposition of such an immune complex could lead to damage to the glomerulus through the activation of the complement system, platelet aggregation, infiltration of leucocytes, intraglomerular coagulation and fibrin deposition [26]. HBV DNA is also observed in renal tubules and mesangial cells and is associated with disease activity of nephropathy.

**Treatment of HBV-Related Nephropathy**

Corticosteroid and immunosuppressant therapy has been used for the treatment of MN. However, in HBV-related disease, immunosuppression should induce reactivation of HBV and cause severe hepatitis. In addition, since the response to corticosteroids might be insufficient in cases with HBV-related MN, they are not recommended for the treatment of this type of renal complication [26]. Reduction of viral protein using antiviral therapies, such as nucleotide analogs, is required for clinical remission. Lamivudine treatment has been reported to improve renal outcome in HBV carriers with MN [27]. However, dose adjustment of nucleotide analogs is required for cases with renal dysfunction [28].

Generally, HBV-related nephropathy could be improved after seroconversion and reduction of HBeAg levels. The prognosis of HBV-related nephropathy varies among geographic regions, probably due to the differ-
ences of the immune response and clinical course caused by different HBV genotypes. Renal failure should be possible, particularly in adult patients [8].

**HCV-Related Nephropathy**

MPGN is the most common nephropathy among HCV-positive cases [29]. One report noted that MPGN was present in 12 of 963 renal biopsies; 4 of these cases (4/12; 33%) were also positive for HCVAg [30]. HCV-related nephropathy is frequently accompanied by cryoglobulinemia, where IgG, IgM and complements are observed in mesangial cells and capillary walls [8]. A decrease in serum complement, particularly component 4, has been observed, and cryoglobulin-like structures are seen in glomerular epithelial cells using electron microscopy [8]. Antiviral therapy for HCV is administered to treat nephropathy and is effective for proteinuria. However, in cases with limited response, recurrence after antiviral therapy is possible. Recent advancement of antiviral therapy with or without interferon administration would lead to the complete elimination of HCV, which should also improve the extrahepatic manifestation of chronic hepatitis C, including nephropathy.

**Conclusion**

In this review, we describe several types of vascular involvement that may be triggered by hepatitis virus infection, and present accumulating evidence that antiviral therapy is critical to control this complication. Recent advances in antiviral therapy for hepatitis B and C have achieved considerable response rates for both HBV and HCV. These new therapeutic agents could improve the prognosis of vascular and renal involvement in cases with chronic viral hepatitis.

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**Disclosure Statement**

The authors declare that there is no conflict of interest regarding the publication of this article.

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