Glomerular Diseases Associated With Hepatitis B and C

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Infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are prevalent worldwide. In this review, we discuss the epidemiology, pathogenesis, clinical manifestations, and treatment of HBV- and HCV-related glomerulonephritis (GN). The most common histopathologic presentation of HBV-GN is HBV-associated membranous nephropathy, which usually manifests clinically with varying grades of proteinuria and microscopic hematuria. The pathogenesis is likely to be immune complex mediated; however, other host and viral factors have been implicated. The treatment of HBV-GN revolves around antiviral therapy. Various histologic types of glomerular diseases are reported in association with HCV infection, the most frequent being Type 1 membranoproliferative glomerulonephritis, usually in the context of Type 2 mixed cryoglobulinemia. The pathogenesis of HCV-GN can be attributed to glomerular deposition of cryoglobulins or noncryoglobulin-immune complexes. Cryoglobulins typically comprised immunoglobulin Mκ with rheumatoid factor activity. Clinically, patients may present with proteinuria, microscopic hematuria, hypertension, and acute nephritic and/or nephrotic syndrome. The treatment of HCV-GN, especially cryoglobulinemic membranoproliferative glomerulonephritis, encompasses various options including contemporary antiviral therapy with or without conventional and novel immunomodulatory agents.

Key Words: Hepatitis B, Hepatitis C, Cryoglobulinemia, Glomerulonephritis

HEPATITIS B VIRUS-ASSOCIATED GLOMERULAR DISEASES

In 1971, Combes and coworkers described the association between chronic hepatitis B virus (HBV) infection and glomerular diseases. Their patient had hepatitis from transfusion-related HBV infection, following which he became a chronic HBV surface antigen (HBsAg) carrier. One year later, he presented with nephrotic syndrome because of membranous nephropathy (MN) in which HBsAg could be localized in the glomerular capillary wall by immunofluorescence microscopy.[1] Since then, several histologic patterns of glomerulopathies/glomerulonephritis associated with HBV infection (HBV-GN) have been reported. These include MN, membranoproliferative glomerulonephritis (MPGN), immunoglobulin (Ig) A nephropathy, and focal segmental glomerulosclerosis (FSGS). Although not a glomerular disease per se, polyarteritis nodosa, which is an antineutrophil cytoplasmic antigen-negative necrotizing small- and medium-vessel vasculitis, has historically had a strong association with HBV.

Serological evidence of past or present HBV is present in one third of the world's population—a staggering 2 billion people. Of these, 20% (400 million) are chronic HBV antigen (Ag) carriers.[2] The prevalence of chronic HBV infection is highly variable, ranging from 0.1% in the United States to 20% to 30% in some Pacific Islands.[3]

The prevalence of HBV-GN can only be estimated. The reported prevalence of glomerular involvement closely parallels geographic prevalence of HBV. Thus, the introduction of nationwide HBV vaccination in China in 1992 led to significant decreases in childhood glomerular disease.[4] Of 190 French patients who were HBsAg positive for at least 6 months, 16% developed extrahepatic manifestations, but only 3% developed kidney disease.[5] In a retrospective analysis of 11,618 kidney biopsies performed from 1987 to 2012 at a single center in Beijing, China, 3% (352) were reported to have HBV-associated nephritis.[6] Nephrotic syndrome occurring in black patients in South Africa's Kwa/Zulu Natal region was most commonly associated with HBV, with MN present in 75%.[7] Overall, glomerular disease occurs in a minority of HBV carriers, with MN representing the most common clinically apparent disease.

PATHOGENESIS

Glomerular HBV Antigen-Containing Immune Complexes

The host humoral immune response is directed towards HBV surface (s), core (c) and extracellular (e) antigens (Ag) (Fig 1); while this is necessary to clear the virus, it can also lead to formation of pathogenic immune complexes relevant in HBV-GN. Glomerular immune complexes can deposit from circulating immune complexes and/or form in situ. This may be related to the size and charge properties of HBV antigen and antibodies. There are also studies reporting the coexistence of HBV DNA and presence of HBV antigens in the kidney tissue, implying that HBV antigens, particularly HB core antigen (HBcAg) and its immune complex, could result from local expression.[8]

All 3 major HBV antigens are anionic. HBsAg and HBcAg are large ($>10^6$ Da). Thus, given the size and net charges of HBsAg- or HbcAg-containing immune complexes, they are unlikely to directly deposit within the subepithelial space to lead to characteristic immune deposits in HBV-MN. Instead, these characteristics would promote their deposition within the mesangium and subendothelial spaces. To this end, there is evidence that immune

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complexes containing HBsAg are pathologic in HBV-MPGN. Circulating immune complexes have been shown to contain anti-HBsAg/HBsAg, and anti-HBsAg has been eluted from the kidney tissue of 1 patient with HBV-MPGN.[9]

Typically, HBeAg-containing circulating immune complexes are relatively small (~2.5×10^5 Da).[10] Moreover, anti-HBeAg IgG antibodies tend to be cationic, which also raises the net charge of HBeAg-containing immune complexes.[11] These properties facilitate the accumulation of immune complexes in the subepithelial space, both from the circulation and formed in situ. Experimentally, subepithelial immune complex deposits form when cationic antibodies directed against various anionic antigens were passively administered.[12] The potential importance of HBeAg in HBV-MN is further supported by the observations that circulating HBeAg-containing immune complexes correlate with disease severity, and HBeAg often is the predominant antigen in glomerular immune deposits.[12,13]

Direct Viral Effects

HBV virus may directly infect glomerular cells contributing to the pathogenesis of HBV-GN. This is supported by the expression of HBV DNA in glomeruli.[14] These findings were confounded by the finding of HBV-related antigens, particularly HBcAg, in the same kidney tissue. To overcome this confounding factor, Diao and colleagues[15] purified HBV from the sera of HBV-infected patients and co-cultured human mesangial cells with purified HBV. They found a significant increase in human mesangial cell proliferation and also increased expression levels of type IV collagen and fibronectin, thus suggesting that HBV directly induces mesangial cell proliferation and expression of extracellular matrix proteins. The exact mechanism, however, remains unknown. HBV x protein (HBx) has been shown to act as an indirect transcriptional transactivator to regulate cell proliferation, transdifferentiation, and apoptosis and has been implied in pathogenesis of hepatocarcinogenesis related to HBV.[16]

Host and Viral Genetic Factors

There is some evidence that HBV-associated glomerular diseases are linked to particular major histocompatibility complex Class II alleles. In HBV-MN, relatively small, yet significant increases have been noted in the frequency of DQB1*0603 in black children,[17] DQB1*0301 in Polish children,[18] and DRB1*1501 in Korean adults.[19] In the latter population, DRB1*1502 was strongly associated with HBV-MPGN, being present in 23% of patients, compared with 9% of HBV-MN and 2% of controls.

There are significant differences in the epidemiology of HBV infection between continents and regions. There are 8 recognized genotypes of HBV (A through H); genotype A is predominant in North America, Europe, and Africa. Relevant to HBV-GN is the relative responsiveness of HBV/A to interferon (IFN)-α therapy (see Treatment of HBV-GN below). Whether different genotypes influence clinical presentation of HBV-associated glomerular diseases is not entirely clear. Lei and colleagues[20] suggested that the HBV/C could play a role in HBV-GN among Northwest Chinese children. Yet, because HBV/C is predominant in Asia (~85% in Japan), that 4 of 5 Japanese patients with HBV-MN had HBV/A (2 each HBV/A1 and/A2) implicates HBV/A in the pathogenesis of HBV-MN.[21] In a recent study from Shandong Peninsula, China, 42 of 50 patients (84%) with HBV-GN, compared with 5 of 60 (8%) asymptomatic HBV carriers had 1 or more single-point mutations in the HBV *x* gene; these result in amino acid substitutions within key regulatory regions within the HBx protein affecting viral replication.[22]

CLINICAL SUMMARY

- Chronic hepatitis B and hepatitis C virus infections remain a major global health problem and can be associated with a spectrum of glomerular diseases.
- Membranous nephropathy is the commonest hepatitis B virus-induced glomerulopathy comprising up to 15% of all membranous nephropathy cases in endemic areas.
- Type 1 membranoproliferative glomerulonephritis associated with mixed Type 2 or 3 cryoglobulinemias is the most common glomerular pathology seen in chronic hepatitis C virus infection and involves deposition of cryoglobulins containing immunoglobulin Mκ in glomeruli.
- The pathogenesis of hepatitis B virus- and hepatitis C virus-related glomerular diseases is directly related to the virus. With the marked improvement in antiviral regimens occurring regularly, the outlook for patients who develop hepatitis-related glomerulopathies is considerably better than in the past.

CLINICAL PRESENTATION AND NATURAL HISTORY

Children with HBV-MN typically present between the ages of 2 and 12 years (mean 6 years) with proteinuria that often is within the nephrotic range and microscopic or rarely macroscopic hematuria. Hypertension is present in less than 25% of cases. Typically kidney function, as judged by serum creatinine and the derived estimated glomerular filtration rate, is preserved. Although idiopathic MN is associated with a slight male predominance, as many as 80% to 100% of children with HBV-MN are males.[23] The disease generally has a benign course in children. The cumulative probability of remission at 4 years is 64%,[24] which is more likely in younger patients and those with a smaller burden of subepithelial immune deposits.[25] In the United States, a predominance in the African-American population has been noted. The natural history in adults may not be as benign. One study of adults infected in an endemic area indicated that spontaneous remission was uncommon in this population in which progressively declining kidney function was seen in 29%, including 10% developing ESRD in an average follow-up period of 60 months.[26]

Antiphospholipase A2 receptor antibody (anti-PLA2R), described in seminal studies by Beck and coworkers,[27] can help differentiate idiopathic MN and HBV-MN. In a study from China, only 1 in 16 with HBV-MN was positive for