Hepatitis-B Associated Nephropathy

Vandana Baraskar

Abstract:

Glomerulonephritis is an important extrahepatic manifestation of chronic hepatitis B virus (HBV) infection. The uncommon occurrence, variability in renal histopathology, and heterogeneity in clinical course present challenges in clinical studies and have resulted in a relative paucity of data and uncertainty with regard to the optimal management of HBV-related glomerular diseases. The advent of nucleos(t)ide analogue medications that effectively suppress HBV replication has markedly altered the clinical outcomes of kidney transplant recipients with HBV infection, but the emergence of drug resistance is an escalating problem. This article reviews the recent knowledge of the pathogenesis and treatment of HBV-related membranous nephropathy.

Introduction:

The hepatitis B virus (HBV) has a complex relationship to kidney diseases. Chronic HBV infection is an etiologic factor in secondary glomerular diseases. HBV is not directly cytopathic to hepatocytes. The host immune response, especially via virus-specific cytotoxic T lymphocytes, is the basis for hepatocellular damage as well as viral clearance. Neonatal exposure to HBV when the immune system is immature results in minimal acute hepatitis, but this is followed by chronic infection in 90% of subjects, and contributes to the bulk of chronic HBV carriers. After entering hepatocytes by endocytosis, the partially double-stranded viral genomic DNA is transported into the nucleus, where it is converted to covalently closed circular DNA, which serves as a template for transcription of viral mRNAs, which in turn are used for viral replication through reverse transcription and the production of viral DNA polymerase and other viral proteins. Intrahepatic covalently closed circular DNA thus accounts for the persistence of infection. About 350 million people worldwide have chronic HBV infection. The importance of HBV in clinical nephrology increases markedly in areas with endemic infection such as South East Asia, where the proportion of chronic HBV carriers can exceed 10% in the general population. In this regard, data from a recent series that included 390 patients with membranous nephropathy showed that HBV was the underlying cause in 12% of patients [1]. This article reviews the clinical and therapeutic aspects of HBV-related glomerulonephritis focusing on membranous nephropathy.

Address for correspondence

Vandana Baraskar MD DNB
Consultant Nephrologist
Baraskar Hospital, Ramdaspeth, Nagpur.

HBV-related Glomerulonephritis:

Extrahepatic manifestations of HBV infection can present as glomerulonephritis, vasculitis, or reactive arthritis. Glomerular disease is more

common in children than adults, and in men than women [2]. The more common renal histopathologies include membranous nephropathy and membranoproliferative glomerulonephritis. An association with IgA nephropathy has been reported, and recent reports also suggest a possible link with focal segmental glomerulosclerosis [3].

Pathogenic Mechanisms:

Both viral and host factors are involved in pathogenesis. An association with HLA genes has been reported, indicating the impact of genetic predisposition [4]. The main pathogenic mechanism in HBV-related glomerular diseases is through the deposition of immune complexes in the glomerulus. The immune complexes are comprised of viral antigens and the antibodies that these antigens invoke from the host. Whether these immune complexes are formed in situ or are derived from circulating immune complexes being trapped in the glomerulus remains controversial. Various HBV antigens including hepatitis B surface antigen (HBsAg), hepatitis B envelop antigen (HBeAg), and hepatitis B core antigen (HBcAg) have been demonstrated in the glomeruli of patients with HBV-related glomerulonephritis, and the detection of covalently closed circular DNA in renal tissue has also been reported [5]. Immune deposition occurs predominantly in the subepithelial region but can also involve the mesangial and occasionally subendothelial areas, depending on the size of the antigens and immune complexes. It has been speculated that the low molecular weight of HBeAg ($3x10^5$ Da) might account for its ability to traverse the glomerular basement membrane and thus the formation of subepithelial immune deposits [6]. The observed association between remission of proteinuria and clearance of HBeAg also provides indirect evidence that the antigen is involved in pathogenesis. The immune complexes then activate complements and glomerular injury occurs via the formation of membrane attack complex and other downstream events such as the induction of proteases, oxidation injury, and disruption of cytoskeleton [7, 8]. Investigations on renal gene expression profile with microarrays, in transgenic mice that expressed HBsAg and HBcAg in the cytoplasm of renal tubular epithelial cells but without replication of the whole virus, have revealed upregulation of complement and coagulation pathways and acute phase response genes, and reduced circulating C3 levels [9].

It has been reported that the sera of patients with chronic HBV infection could induce apoptosis in cultured HK-2 cells, a cell line for the study of human proximal renal tubular epithelial cells, via up-regulation of Fas gene expression [10]. Furthermore, the induction of apoptosis correlated with the level of circulating HBV DNA, and HBV carriers also showed a higher circulating level of transforming growth factor-beta, a growth factor implicated in the potentiation of apoptosis and renal fibrosis. These preliminary data suggest the presence of serum factor(s) in HBV carriers which could alter renal tubular cell function, and should be confirmed using samples from patients with documented nephritis and in podocytes.

HBV can be classified into eight major genotypes based on genome sequence divergence. The impact of viral genetics was recently investigated in a study that included two pediatric and four adult Japanese patients, five of whom had membranous nephropathy, and one with membranoproliferative glomerulonephritis [11]. All the patients were HBeAg-positive and had high circulating HBV DNA levels. The investigators did not find any association between nephropathy and mutations in the HBV genome. However, the genotyping results were interesting. Previous studies showed that genotype C was predominant among local subjects with chronic hepatitis B,

whereas genotype A accounted for only 1.7% [12]. Yet complete viral genome sequencing showed that among the patients with nephropathy four had HBV genotype A1/A2, whereas two were infected with genotype C2. A high prevalence of genotype A in patients with HBV-related nephropathy had been reported by other investigators [13, 14]. Whether HBV genotype A may indeed be more likely to lead to renal manifestations compared with other genotypes, and the mechanisms accounting for such difference, require further investigations.

Clinicopathologic Features of HBV-related Membranous Nephropathy and Membranoproliferative Glomerulonephritis:

Patients with HBV-related membranous nephropathy typically present with proteinuria, which could be in the nephrotic range, and microscopic hematuria. Impaired renal function is more common in patients with membranoproliferative glomerulonephritis. The natural history of HBV-related membranous nephropathy appears different between children and adults. In contrast to pediatric subjects, in whom spontaneous remission of proteinuria is common and the renal function is often well preserved, adult patients are more likely to have progressive disease and up to one third of patients might eventually develop renal failure [13, 15, 16]. A temporal relationship between increased hepatitic activity and deterioration of proteinuria has been observed in some patients [17], and could be associated with cryoglobulinemia.

HBV-related membranous nephropathy is characterized by thickened capillary wall and glomerular basement membrane on light microscopy. Although this feature could be subtle in the early stage, the capillary wall can assume a rigid appearance in advanced disease. Immunofluorescent staining and electron microscopy demonstrate granular IgG, C3, and some IgM staining in the subepithelial region along the glomerular basement membrane accompanied by extensive effacement of the podocyte foot processes, and in some cases viral particles in various locations within the glomerulus. Mesangial abnormalities are more common in secondary membranous nephropathy compared with the idiopathic form. Mesangial expansion and capillary wall thickening resulting in a lobular appearance of the glomerular tuft characterize the light microscopic findings in membranoproliferative glomerulonephritis. The capillary wall also demonstrates a double-contour appearance and hypercellularity with interpositioning of cells. The latter may include infiltrating monocytes and neutrophils. Immune deposits containing IgG, complement components, and IgM appear granular on immunofluorescent staining, and are located in the subendothelial, mesangial, and paramesangial areas. In addition to these electron-dense deposits, which could also be present in the subepithelial region, albeit in smaller amounts, electron microscopy also shows subendothelial expansion and the formation of new basement membrane material, which accounts for the double-contour appearance on light microscopy. The subendothelial and mesangial immune deposits trigger complement activation and increased local expression of inflammatory and chemotactic mediators, leading to the infiltration of inflammatory cells.

Treatment of HBV-related Membranous Nephropathy:

Much of the data on the treatment of HBV-related glomerular diseases came from patients with membranous nephropathy, the most common histologic presentation, whereas the data on membranoproliferative glomerulonephritis or focal segmental glomerulosclerosis remain largely anecdotal. Treatment with interferon [14, 18–25] or lamivudine [17, 26–28] has been reported to lead to a reduction of proteinuria in patients,

mostly children, with HBV-related membranous nephropathy.

Conventional and pegylated interferon-α possess both immunoregulatory and antiviral effects [29]. Interferon-α activates cellular pathways that lead to breakdown of viral RNA and enhances cell-mediated immune response toward hepatocytes infected with HBV. Interferon treatment given for 4–12 months was associated with sustained remission of proteinuria in 20% to 100% of patients, clearance of HBeAg in 20% to 80%, and a drop-out rate of 10% to 15%. Resolution of proteinuria was often associated with clearance of HBeAg and/or HBsAg, and usually occurred within 6 months of seroconversion [13, 23, 24]. However, most of the reported data were anecdotal reports or data from small series. Bias from selective publication of positive results remains possible. There is also a general impression that the results in adults may be less favorable compared with children.

Nucleos(t)ide analogues such as lamivudine, telbivudine, adefovir, entecavir, or tenofovir suppress HBV replication through their inhibitory effect on viral DNA polymerase. Because the deposition of immune complexes within the glomerulus is perceived to play a pivotal role in the pathogenesis of HBV-related nephropathy, reducing the quantity of viral antigens and thereby reducing immune complex deposition in the kidneys should (in theory) ameliorate kidney damage. Compared with interferon, nucleos(t)ide analogues offer the advantages of convenient administration and high tolerability, but often require long-term administration and could result in the selection of drug-resistant HBV strains. Adefovir should be used with caution in patients with renal impairment in view of its nephrotoxicity, which is mediated through inhibitioin of mitochondrial DNA replication resulting in disruption of normal mitochondrial respiratory function in proximal renal tubular epithelial cells. There are also uncommon reports of renal tubular toxicity with tenofovir [30]. Even fewer data exist regarding nucleos(t)ide analogues than interferon on HBV-related nephropathy. The factors predictive of treatment efficacy and the selection criteria for treatment also remain undefined. Data from a recent report on 10 patients with HBV-related membranous nephropathy showed that lamivudine treatment was associated with complete resolution of proteinuria in six patients [28]. However, the concomitant use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and antihypertensive medications precluded definitive conclusions on the renal effect of antiviral treatment. Future studies on the effect of antiviral therapy on proteinuria or renal survival should thus include concurrent controls with comparable exposure to these potential confounders.

The renal prognosis is distinctly different between pediatric and adult patients, with the incidence of chronic kidney disease reported as less than 3% in children and up to 30% in adult patients [13, 15]. The overall data suggest that a favorable renal response to antiviral treatment seems more likely in pediatric patients than adults, and in patients when renal manifestations are accompanied by increased viral replication, a high HBV DNA level, and hepatitic flare.

Conclusions:

Although the incidence of new infection is decreasing with the increasing practice of hepatitis B vaccination, HBV infection is still a profound global problem and an important cause of secondary glomerular diseases. The data suggest that patients presenting with proteinuria accompanied by active viral replication, a high viral load, and active hepatitis are more likely to show renal benefit following antiviral treatment. More data from adults, and on nucleos(t)ide analogues, are awaited. By contrast, data are accumulating

to confirm the efficacy of nucleos(t)ide analogue treatment in improving the survival of HBsAg-positive kidney transplant recipients, given either preemptively when HBV DNA level is increasing or prophylactically from the time of transplantation. Quantitation of circulating HBV DNA level facilitates the early diagnosis of hepatitic flare and the emergence of resistance. The management of drug resistance, and the threshold HBV DNA level for treatment, continue to evolve with increasing clinical experience.

References:

1. Zeng CH, Chen HM, Wang RS, et al. Etiology and clinical characteristics of membranous nephropathy in Chinese patients. Am J Kidney Dis. 2008;52:691–698. doi: 10.1053/j.ajkd.2008.06.006.
2. Levy M, Chen N: Worldwide perspective of hepatitis B-associated glomerulonephritis in the 80s. Kidney Int 1991, Suppl 35:S24–S33.
3. Khaira A, Upadhyay BK, Sharma A, et al. Hepatitis B virus associated focal and segmental glomerular sclerosis: report of two cases and review of literature. Clin Exp Nephrol. 2009;13:373–377. doi: 10.1007/s10157-008-0124-8.
4. Park MH, Song EY, Ahn C, et al. Two Subtypes of hepatitis B virus-associated glomerulonephritis are associated with different HLA-DR2 alleles in Koreans. Tissue Antigens. 2003;62:505–511. doi: 10.1046/j.1399-0039.2003.00141.x.
5. Chen L, Wu C, Fan X, et al. Replication and infectivity of hepatitis B virus in HBV-related glomerulonephritis. Int J Infect Dis. 2009;13:394–398. doi: 10.1016/j.ijid.2008.08.014.
6. Takekoshi Y, Tochimaru H, Nagata Y, Itami N: Immunopathogenetic mechanisms of hepatitis B virus-related glomerulopathy. Kidney Int 1991, Suppl 35:S34–S39.
7. Nangaku M, Couser MG. Mechanisms of immune-deposit formation and the mediation of immune renal injury. Clin Exp Nephrol. 2005;9:183–191. doi: 10.1007/s10157-005-0357-8.]
8. Topham PS, Haydar SA, Kuphal R, et al. Complement-mediated injury reversibly disrupts glomerular epithelial cell actin microfilaments and focal adhesions. Kidney Int. 1999;55:1763–75. doi: 10.1046/j.1523-1755.1999.00407.x.
9. Ren J, Wang L, Chen Z, et al. Gene expression profile of transgenic mouse kidney reveals pathogenesis of hepatitis B virus associated nephropathy. J Med Virol. 2006;78:551–560. doi: 10.1002/jmv.20575.
10. Deng CL, Song XW, Liang HJ, et al. Chronic hepatitis B serum promotes apoptotic damage in human renal tubular cells. World J Gastroenterol. 2006;12:1752–1756.
11. Kusakabe A, Tanaka Y, Kurbanov F, et al. Virological features of hepatitis B virus-associated nephropathy in Japan. J Med Virol. 2007;79:1305–1311. doi: 10.1002/jmv.20941.
12. Orito E, Ichida T, Sakugawa H, et al. Geographic distribution of hepatitis B virus (HBV) genotype in patients with chronic HBV infection in Japan. Hepatology. 2001;34:590–594. doi: 10.1053/jhep.2001.27221.
13. Gilbert RD, Wiggelinkhuizen J. The clinical course of hepatitis B virus-associated nephropathy. Pediatr Nephrol. 1994;8:11–14. doi: 10.1007/BF00868249.
14. Bhimma R, Coovadia HM, Adhikari M. Hepatitis B virus-associated nephropathy in black South African children. Pediatr Nephrol. 1998;12:479–484. doi: 10.1007/s004670050492.
15. Lai KN, Li PK, Lui SF, et al. Membranous

nephropathy related to hepatitis B virus in adults. N Engl J Med. 1991;324:1457–1463.

16. Lin CY. Hepatitis B virus-associated membranous nephropathy: clinical features, immunologic profiles and outcomes. Nephron. 1990;55:37–44. doi: 10.1159/000185916.
17. Okuse C, Yotsuyanagi H, Yamada N, et al. Successful treatment of hepatitis B virus-associated membranous nephropathy with lamivudine. Clin Nephrol. 2006;65:53–56.
18. Garcia G, Scullard G, Smith C, et al. Preliminary observation of hepatitis B-associated membranous glomerulonephritis treated with leukocyte interferon. Hepatology. 1985;5:317–320. doi: 10.1002/hep.1840050228.
19. Mizushima N, Kanai K, Matsuda H, et al. Improvement of proteinuria in a case of hepaittis B-associated glomerulonephritis after treatment with interferon. Gastroenterology. 1987;92:524–526.
20. Man RA, Schalm SW, Heijden AJ, et al. Improvement of hepatitis B-associated glomerulonephritis after antiviral combination therapy. J Hepatol. 1989;8:367–372. doi: 10.1016/0168-8278(89)90036-6.
21. Lisker-Melman M, Webb D, Bisceglie AM, et al. Glomerulonephritis caused by chronic hepatitis B virus infection: treatment with recombinant human alpha-interferon. Ann Intern Med. 1989;111:479–483.
22. Wong SN, Yu EC, Lok AS, et al. Interferon treatment for hepatitis B-associated membranous glomerulonephritis in two Chinese children. Pediatr Nephrol. 1992;6:417–420. doi: 10.1007/BF00873997.
23. Conjeevaram HS, Hoofnagle JH, Austin HA, et al. Long-term outcome of hepatitis B virus-related glomerulonephritis after therapy with interferon alfa. Gastroenterology. 1995;109:540–546. doi: 10.1016/0016-5085(95)90343-7.
24. Lin CY. Treatment of hepatitis B virus-associated membranous nephropathy with recombinant alpha-interferon. Kidney Int. 1995;47:225–230. doi: 10.1038/ki.1995.27.
25. Chung DR, Yang WS, Kim SB, et al. Treatment of hepatitis B virus associated glomerulonephritis with recombinant human alpha interferon. Am J Nephrol. 1997;17:112–117. doi: 10.1159/000169083.
26. Connor FL, Rosenberg AR, Kennedy SE, Bohane TD. HBV associated nephrotic syndrome: Resolution with oral lamivudine. Arch Dis Child. 2003;88:446–449. doi: 10.1136/adc.88.5.446.
27. Filler G, Feber J, Weiler G, Saux N. Another case of HBV associated membranous glomerulonephritis resolving on lamivudine. Arch Dis Child. 2003;88:460. doi: 10.1136/adc.88.5.460.
28. Tang S, Lai FM, Lui YH, et al. Lamivudine in hepatitis B-associated membranous nephropathy. Kidney Int. 2005;68:1750–1758. doi: 10.1111/j.1523-1755.2005.00591.x.
29. Cooksley WG, Piratvisuth T, Lee SD, et al. Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. J Viral Hepat. 2003;10:298–305. doi: 10.1046/j.1365-2893.2003.00450.x.
30. Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. Clin Infect Dis. 2003;36:1070–1073. doi: 10.1086/368314.