Hepatitis B Virus Infection and Extra-Hepatic Manifestations: A Systemic Disease

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People living with hepatitis B virus (HBV) chronic infection are exposed to high rates of liver complications including end-stage liver disease and hepatocellular carcinoma. Extrahepatic manifestations of HBV infection have long been underestimated. Several of these extrahepatic syndromes have been well described, including systemic vasculitides, glomerulonephritis, and cutaneous manifestations. Other manifestations have been more recently described such as hematological malignancies and neurological diseases. These extrahepatic manifestations are associated with significant morbidity and mortality. Although not completely understood, underlying mechanisms include HBV-induced local and systemic inflammation. Suppression of HBV replication usually improves extrahepatic manifestations. This review will discuss how HBV induces inflammation and the extrahepatic manifestations of HBV infection to guide clinical management.

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INTRODUCTION

Approximately 257 million people are living with hepatitis B virus (HBV) infection [defined as hepatitis B surface antigen (HBsAg) positive]. In 2015, HBV infection resulted in 887,000 deaths, mainly from complications including end-stage liver disease and hepatocellular carcinoma (HCC) (1). Although a protective vaccine has excellent efficacy and safety, the completeness vaccination campaigns vary worldwide.

Extrahepatic manifestations may be observed in the context of acute or chronic HBV infection, and some of them have long been underestimated (Figure 1). Several of these extrahepatic syndromes have been well described, including polyarteritis nodosa (PAN) and other vasculitides, glomerulonephritis (GN), and cutaneous manifestations. Other manifestations have been more recently described such as hematological complications and neurological diseases. These extrahepatic manifestations can be associated with significant morbidity and mortality. Ongoing chronic inflammation associated with HBV infection might drive most extrahepatic manifestations. The crucial pathogenic mechanism in most extrahepatic manifestations is believed to be driven by immune responses against HBV, with the deposition of immune complexes (IC) in targeted tissues and a generalized inflammation.

An awareness and recognition of these manifestations are important to allow early diagnosis and treatment.

Current treatments include pegylated interferon-alpha (PEG-IFN-a) or nucleoside analogs (NA). NA often require lifelong administration because they do not lead to viral eradication (2). However, suppression of HBV replication usually improves extrahepatic manifestations (3–11). Several guidelines have been published for the management of patients with HBV infection (3–5). There is hope for a HBV cure increasing the number of candidates for therapy, beyond the present guidelines (12).

This review will discuss how HBV induces inflammation and the associated systemic extrahepatic manifestations of HBV infection to guide clinical management.

HBV replication

HBV belongs to the hepadnaviridae family of viruses. HBV genome consists of a 3.2 kb partially double-stranded DNA, known as relaxed circular DNA (13). HBV genome codes for the core protein, hepatitis B core antigen (HBcAg), which forms the viral nucleocapsid, the precore protein (hepatitis B e antigen, HBeAg), and HBsAg.

HBV infects hepatocytes through human sodium taurocholate cotransporting polypeptide receptor (14). On fusion with the host membrane, the rcDNA-containing nucleocapsid is released into the cytoplasm and travels to the nucleus (15). Then, relaxed circular DNA is converted to covalently closed circular DNA (cccDNA) via the host DNA repair machinery. Chronicity is believed to be because of persistent of cccDNA inside the nucleus (16). cccDNA is the transcriptional template for virus gene expression and generation of pregenomic RNA. HBV DNA is also found integrated into the host chromosome (17). Once all viral proteins are synthesized and the rcDNA-containing nucleocapsid is formed, it can travel through the cellular secretion pathway and be released as an enveloped and infectious virion (16). HBsAg proteins are accumulated to excrete enveloped virus from infected hepatocytes by the secretion pathway. It has also been reported recently that integrated viral genomes may serve as a template for HBsAg transcription (18).

HBV and inflammation

Several arguments favor a major role of HBV infection in inducing inflammation: the inflammatory infiltrate in the liver, the induction of IFN pathways, interactions with several cellular or

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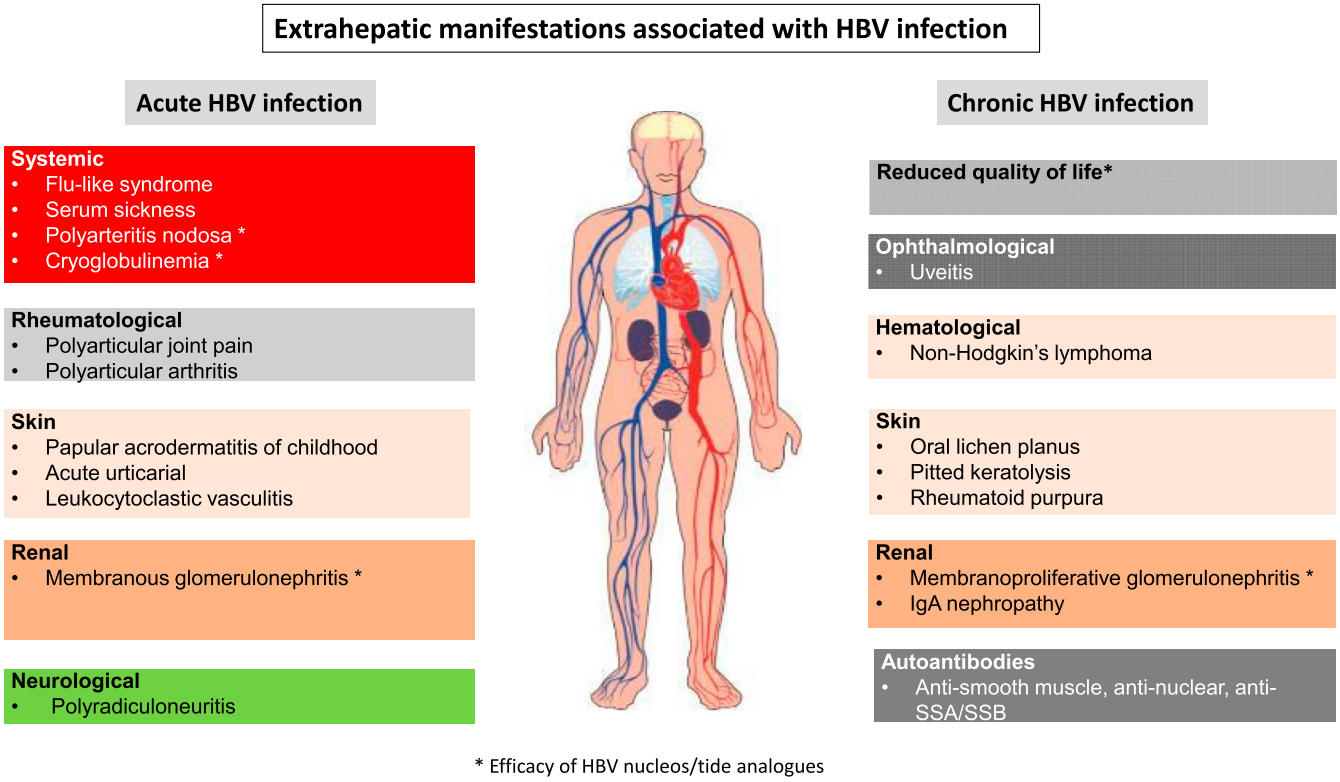

Figure 1. Main extrahepatic manifestations associated with hepatitis B virus (HBV) chronic infection.

subcellular inducers of inflammation (hepatocytes, macrophages, mitochondria etc.), and inflammatory molecules including cytokines, IFN stimulating genes, and microRNAs.

HBV is considered a noncytopathic virus, and the intrahepatic inflammatory leukocyte infiltrate is regarded as the histological hallmark of all chronic viral hepatitis. It is believed that the HBV-specific immune response is defective and dysfunctional but nonetheless induces chronic inflammatory responses in the liver in chronic hepatitis B (CHB) (19,20).

Furthermore, in response to viral infection, host cells produced type 1 IFN ,which are a family of major innate immune cytokines (21,22). In CHB, several IFN-stimulated genes (ISGs) are upregulated when compared with normal liver (23,24). ISGs can have additive effects to increase viral inhibition, and also few of them could increase viral replication (25). Moreover, HBV modulates liver macrophages function to favor its establishment. It impairs the production of the antiviral cytokine IL-1β while promoting that of IL-10 in the microenvironment (26).

In addition, HBV can also manipulate the microRNA regulatory networks in infected cells to create a permissive environment for viral replication. In liver samples from patients with CHB, miRNA-mRNA regulatory networks (mainly involved in inflammation and innate immune response) were found associated with disease progression (27). In another study, the expression of microRNAs, with roles in inflammation and immune response, was correlated with HBV-related advanced fibrosis (28).

HBV also targets mitochondrion and induces oxidative stress, which is a driver of inflammation (29). Mitochondria can trigger the inflammatory response through the Toll-like receptor 9, inflammasomes, and stimulator of IFN gene pathways and then further exacerbate hepatocellular damage (29,30).

Abnormal monoclonal B cell expansion has been shown to be an effector in inducing mixed cryoglobulinemia (MC). In addition, there are specific links between these effectors/pathways and systemic diseases. Taken together, all these data are in favor of a systemic inflammation induced by HBV infection (Figure 2).

Current therapies for HBV chronic infection

Current treatments include PEG-IFN or NA (2–5). PEG-IFN has the advantage of achieving a sustained virological response after a limited course of treatment, in approximately 20% of patients. Limitations of PEG-IFN are the mild efficacy and its unfavorable safety profile. HBV DNA undetectability with long-term lamivudine (LAM) has been associated with a reduction in the incidence of HCC (31–33). Moreover, HBs loss has been associated with a favorable prognosis and is the ideal goal for therapy (34). Strategies focusing on reducing HBsAg will be crucial (35,36). Beyond the liver, patients with HBV extrahepatic-related manifestations are also candidates for therapy.

According to several guidelines, patients with EH manifestations associated with HBV chronic infection have an indication for treatment independent of liver disease severity (3–5). We have to recognize that there are not specific guidelines for HBV-related extrahepatic manifestations, and we have to rely on general HBV guidance from several societies (for instance AASLD, EASL, and APASL). It is generally accepted that the decrease of HBV replication to undetectable HBV DNA is the goal to obtain remission of extrahepatic manifestations to prevent complications. Vaccine campaign and the advent of highly effective NAs therapies in the past 15–20 years have resulted in a decrease in the prevalence of extrahepatic manifestations of HBV. However, strong epidemiological data (prospective studies) that would better quantify these changes are lacking.

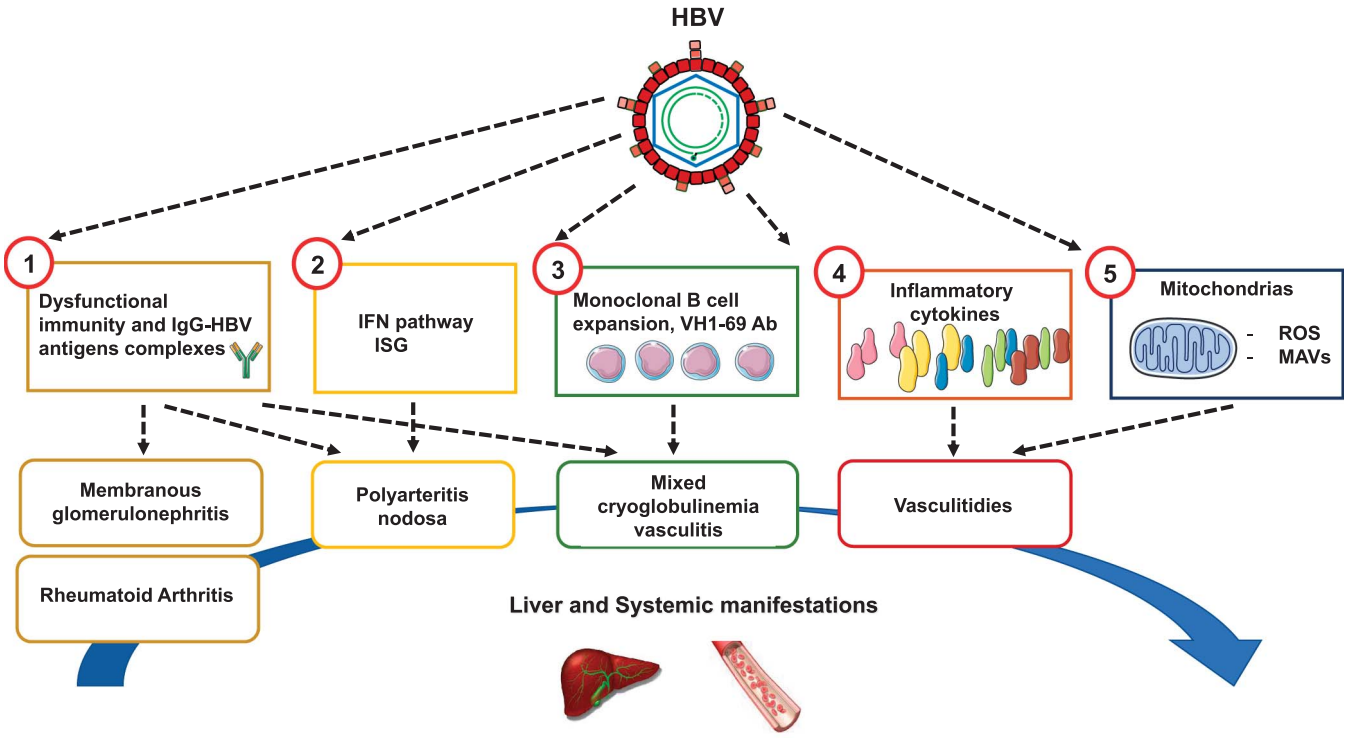

Figure 2. HBV infection and inflammation. Hepatitis B virus (HBV) infection induces inflammation through several pathways: (**a**) Dysfunctional immunity and IgG-HBV antigens complexes, (**b**) the type I interferon, with IFN-stimulated genes (ISGs), (**c**) monoclonal B cell expansion, VH1-69 Ab, (**d**) inflammatory cytokine production, (**e**) and targeting mitochondrion. HBV infection can induce oxidative stress, which is a driver of inflammation.

Systemic vasculitis

Polyarteritis nodosa. PAN is a systemic necrotizing vasculitis that affects medium-sized arteries and is primary in most patients (Figure 3). Patients with PAN usually present with a poor general condition, arthralgia, myalgia, peripheral neuropathy, amyotrophy, purpura, subcutaneous nodules, livedo, and hypertension. In more severe cases, PAN may also involve the heart, gut, lungs, and kidney.

The strong association between HBV infection and the occurrence of PAN has been demonstrated since the 1970s (37), with high annual incidence of PAN per million inhabitants in populations with high HBV prevalence (38). In a French series of 341 patients with PAN from all causes, HBV-associated PAN rate was 33.7% (6). In the 1970s, the frequency of PAN due to HBV reached 30% (39). It is a common manifestation in patients with HBV infection (39). Fortunately, the rate of HBV infection markers in patients with PAN has been declining (40,41). Immunization programs and current treatments explain the decrease of this extrahepatic manifestation in patients with HBV infection (less than 5%). The main manifestations of PAN appear in the first 6 months of HBV infection (6). Compared with patients with a primary form of PAN, those with HBV-associated PAN showed higher rates of weight loss; gastrointestinal, cardiac, and neurologic disorders; severe hypertension; and higher scores of vasculitis activity (Table 1) (40). Patients with HBV-associated PAN more frequently have elevated transaminases levels, gastrointestinal microaneurysms, and/or arterial stenosis (39). In HBeAg-positive CHB, recovery from the PAN generally occurs after HBeAg seroconversion. Relapses are more frequent, and mortality is higher in HBV-associated PAN compared with primary PAN (7,42). Gastrointestinal symptoms have been associated with early death.

Evidence for immune complex–induced disease is confined to HBV-related PAN; the role of IC in non-HBV-related PAN remains unclear. Impaired function of endothelial cells may be part of PAN or a consequence of it; in HBV-induced PAN, virus replication may directly injure the vessel wall. Endothelial dysfunction can perpetuate the inflammation through cytokine and adhesion molecule production. The etiopathogenesis in CHB involves the deposition of IC comprised of HBs and/or HBe antigens, followed by the local activation of complement cascades and the recruitment of inflammatory cells (43). Notably, higher viral load can promote the production of IC, leading to deposition at small or medium-sized arteries (44).

The treatment recommendation for severe HBV-associated PAN includes a short course of corticosteroids, repeated plasma exchanges, and antivirals (8,45). Corticosteroids, however, should be given only in cases of life-threatening organ involvement. Historical studies have tested vidarabine, IFN-alpha, and LAM (6,9,42,45). Among 115 HBV-associated PAN, 93 (81%) patients entered remission and 9 (10%) of them relapsed; 41 (36%) patients died. Compared with patients treated with corticosteroids alone or with cyclophosphamide/plasma exchange, those who have been given the antiviral strategy had lower relapse rate and death rate and higher rates of HBe/anti-HBe seroconversion (6). Antivirals are important to stop HBV replication, which is correlated with a higher frequency of PAN. Taking into account the high antiviral efficacy of recent NA, the current treatment of HBV-associated PAN should include NA and a short-term course of corticosteroids, whereas plasma

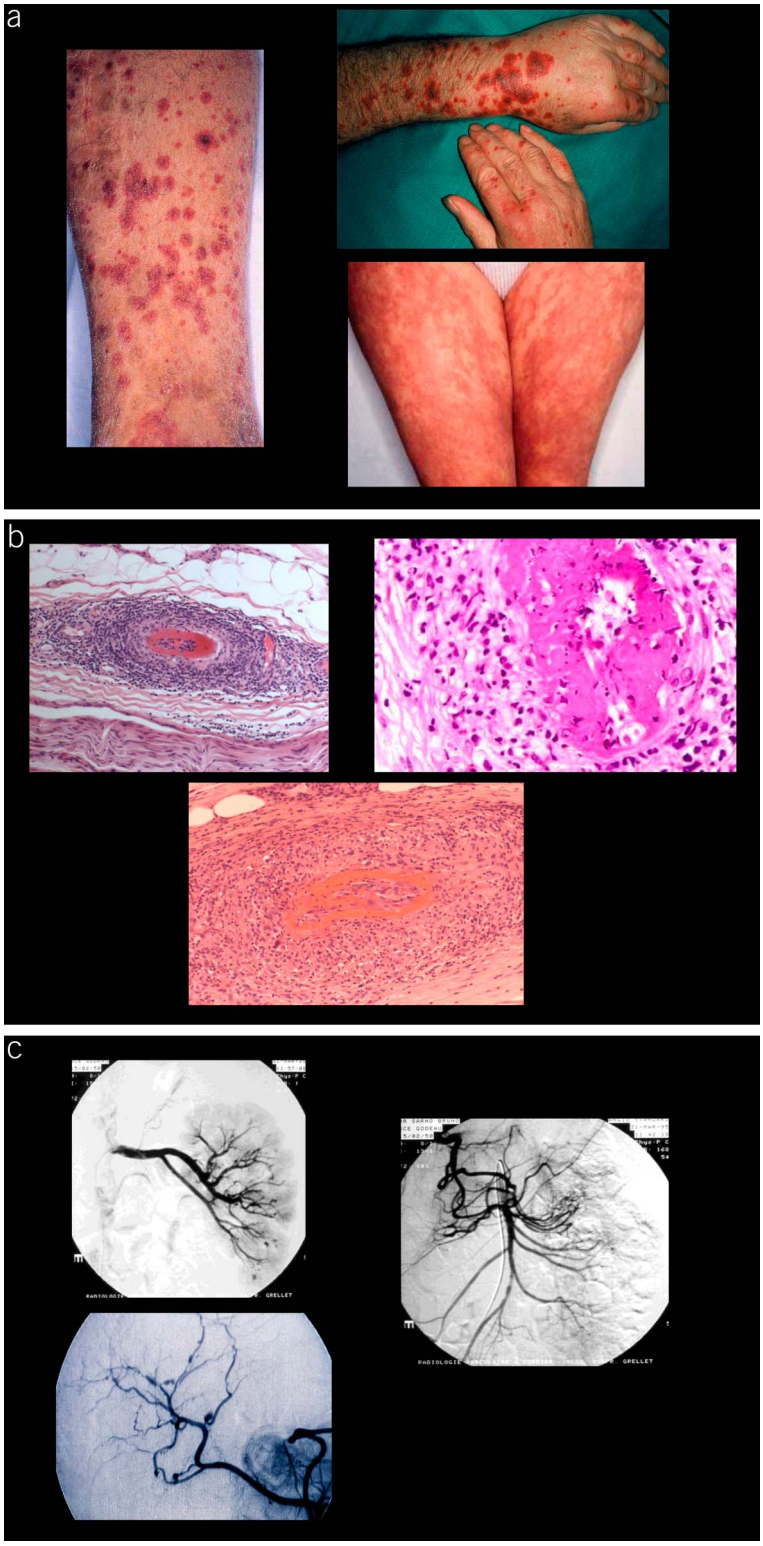

Figure 3. Features of HBV-related polyarteritis nodosa: (4**a**) Cutaneous vasculitis and livedo, (4**b**) peripheral nerve biopsy with typical necrotizing vasculitis in a medium size artery, and (4**c**) renal artery microaneurysms (a), stenoses and dilation of liver arteries (b), and stenosis of lower mesenteric artery (c).

exchanges should be used according to the presence of major organ involvement.

Of course, patients with HBV-associated PAN should always be treated with antivirals, started before any immunosuppressive medications. Most patients with HBV-associated PAN can be treated with antivirals monotherapy. Finally, glucocorticoids are recommended for patients with moderate to severe PAN. An induction treatment includes oral prednisone (1 mg/kg per day)

Table 1. Main characteristics of patients with primary vs HBV-related polyarteritis nodosa (*Pagnoux C et al, 2010* [ref. 40])

Features	Primary PAN	HBV-related PAN	*P* value
Number of patients	225	123	
Time to onset, mean ± SD, mo	8.9 ± 27.3	4.7 ± 12.4	0.05
Weight loss, mean ± SD, kg	5.4 ± 5.9	7.9 ± 7.2	0.001
Neuropathy, %	64.4	82.1	<0.0001
Recent onset hypertension, %	27.1	48.8	<0.0001
Severe hypertension, %	4.9	10.6	0.05
Orchitis, %	13.1	24.1	0.02
Skin involvement, %	57.8	35.0	<0.0001
Gut involvement, %	30.1	50.4	<0.0001
Cardiac involvement, %	4.4	13.0	0.004
FFS ≥ 1, %	33.3	52.9	0.002
BVAS mean ± SD	15.1 ± 7.6	19.1 ± 9.1	<0.0001
Microaneurysms/stenoses, %	49	71.2	0.006

BVAS, Birmingham Vasculitis Activity Score; FFS, Five-Factor Score; HBV, hepatitis B virus; PAN, polyarteritis nodosa.

given over a month and then slowly tapered over 6 months. Patients with more severe disease manifestations (i.e., gastrointestinal, cardiac, or neurological) can be treated with glucocorticoids and cyclophosphamide.

Mixed cryoglobulinemia vasculitis

MC vasculitis (CryoVas) is a systemic vasculitis that affects small and medium-sized vessels. The clinical manifestations range from purpura, arthralgia, and fatigue to more serious neurological and renal involvement. Cryoglobulinemia is defined as the presence of immunoglobulin that precipitates in the serum at 4°C and redissolves at 37°C. MC is characterized by the presence of type 2 or type 3 cryoglobulins, which consist of polyclonal IgG with monoclonal or polyclonal IgM with rheumatoid factor activity, respectively. Principal causes of CryoVas include infectious, autoimmune, and lymphoproliferative diseases (9).

Although overt HCV-CryoVas develops in up to 15% of patients with HCV infection, it has been more rarely reported with HBV infection (46,47). The role of HBV as an etiologic agent of CryoVas was first suggested by the high incidence of liver involvement in patients with "essential" CryoVas who presented high rates of HBsAg and/or anti-HBc antibody. However, this study was performed before the availability of HCV tests (44). In studies from Europe (mainly France and Italy), cryoVas can develop in 1%–4% of patients with HBV infection (48–53). HBV infection might be more common in Chinese patients with cryoglobulinemia (54). The presentation of HBV-associated CryoVas had no peculiarity, and patients showed purpura (100%), arthralgia (71%), peripheral neuropathy (29%), GN (18%), and MC type 2/type 3 (88%/12%) (49). They were treated with steroids and antivirals. Under NA therapy, reversibility of most of CryoVas manifestations with a reduction of cryoglobulin level was observed (52,53). NAs therapy in HBV-related CryoVas yields high virological efficacy and satisfying clinical responses in most patients with mild-and-moderate but a low response in severe CryoVas (53,55). Early suppression of HBV viral load by NAs should be the main virological and clinical goal.

CryoVas is caused by IC-mediated inflammation (especially HBs antigen/anti-HBs) of small-sized blood vessels and is accompanied by the activation of complements (56). Notably, the presence of HBs antigen represents one of the main independent predictors of mortality in HBV-CryoVas (53). CD20-positive B cells are expanded and activated, playing a crucial pathogenic role in cryoglobulin production. Moreover, Visentini et al. (57) showed that chronic patients with HBV with MC had a massive monoclonal expansion of innate B cells producing a VH1-69-encoded antibody with a CD21(low) phenotype and low responsiveness to stimuli, which is typical of the VH1-69-expressing B cells commonly expanded in HCV-induced CryoVas. Satisfying results have been reported in clinical remission in patients with HBV-CryoVas with purpura and nephropathy treated with rituximab (a monoclonal antibody directed against CD20 B cells) in combination with NAs.

Renal manifestations

First described in 1971 (58), several types of GN have been associated with HBV infection, including membranous glomerulonephritis (MGN) (70%–85%), and more rarely membranoproliferative glomerulonephritis (MPGN), mesangial proliferative GN, and IgA nephropathy (59). Several differences have been observed between children and adults regarding the mode of presentation (Table 2). Renal disease may occur in 3%–5% of patients with chronic HBV infection (60). A large Chinese study showed that over time the prevalence of HBV-associated GN has decreased (61).

HBV-associated MGN seems in HBeAg-positive patients and is accompanied by proteinuria with normal renal function (62). The severity of the liver disease is not correlated with the development of MGN. The renal histologic appearance is indistinguishable from idiopathic MGN with subepithelial immune complex deposits on electron microscopy. HBV DNA has been identified by *in situ* hybridization assay in the nucleus and cytoplasm of the epithelial cells, and mesangial cells of the glomeruli (63). The cationic nature of IgG-HBeAg complexes enhances their deposition in the subepithelial space (59). HBV genotype A

Table 2. Main characteristics of HBV-related kidney diseases according to the time of onset (*Bhimma R et al, 2004* [ref. 59])

Features	Children	Adults
Mode of transmission	- Vertical transmission (Far East) - Horizontal transmission (United States, Africa, and Europe)	- Often unknown - Areas of high endemicity: horizontal transmission - Areas of low endemicity: frequent association with drug abuse or sexual transmission
Gender	Male dominance (>80%)	Less pronounced male dominance
Mean age of presentation	- Vertical transmission: infancy - Horizontal transmission: 5–7 yr	Any age group
Clinical presentation	- Asymptomatic - Nephrotic syndrome	- Nephrotic syndrome - Isolated proteinuria
Acute hepatitis	Low incidence	- Frequent in adults from nonendemic areas - Associated with intravenous drug abuse, homosexuality, and acquired immune deficiency syndrome
Histology	Membranous glomerulonephritis (>85%)	- Membranous glomerulonephritis, often associated with IgA nephropathy - Membranoproliferative glomerulonephritis
Evolution	- Spontaneous remission: 64% at 1-yr, 84% at 10-yr - Remission after HBe seroconversion - Preservation of renal function in > 95%	- Spontaneous remission: < 10% - Progression to renal failure: 25%–35% - Progression to end stage renal failure: 10%

HBV, Hepatitis B virus; HBe, Hepatitis B e ; IgA, immunoglobulin A.

seems to have the highest risk of MGN or MPGN. Acquired missense nucleotide mutations of the HBV-X gene were found in most patients with HBV-associated MGN (64). Antiphospholipase A2 receptor antibodies have been reported in 64% of HBV-associated MGN, a rate close to the rate found in idiopathic MGN, and HBV antigens colocalized with these antibodies (65). A genetic predisposition to HBV-associated MGN has been suggested as a result of impaired cell-mediated immunity and inadequate IFN-alpha production (66). Progression of HBV-related MGN toward end-stage renal disease occurs in 25%–35% of adults and less than 5% of children (62). Spontaneous biopsy-proven histologic resolution of MGN has been shown in children after HBeAg clearance. HBe seroconversion frequently accompanies remission.

In HBV-associated MPGN, the glomerular antigen deposited is the HBsAg because of its size restriction with IgG to the subendothelial space (67). Both type 1 and type 3 MPGN have been described in HBV infection. The clinical presentation includes a nephritic syndrome, with or without nephrotic proteinuria, and decreased levels of serum C3 and C4. Of note, in type 1 MPGN, kidney involvement appears after more than 10 years of CHB and it is associated with type 3 MC (68).

Independent of the type of nephropathy, in large longitudinal studies in the general population addressing end-stage renal disease, the pooled adjusted hazard ratio was 3.87 in HBV-infected patients (69).

Recently, several reports from China showed that renal involvement and HBV infection were common in Chinese patients with cryoglobulinemia (70,71). Although HBV-associated GN decreased over the past decade thanks to HBV vaccine campaign, it remains an important issue in endemic countries for HBV infection as China (72). A study including 101 HBV-GN showed that HBsAg status correlated with different clinicopathological characteristics and the deposition sites of IC (60).

The treatment of HBV-associated GN relies on antiviral therapy. Successful treatment with analogs (entecavir), with or without prednisolone or immune-suppressive therapies, have been reported in small series and/or case reports (73–75). Finally, diagnosis and treatment in early stage benefit patients' renal outcomes. Immunosuppressive therapy should be considered for severe renal disease, together with efficient antiviral therapy. For patients with HBV with MGN, PEG-IFN-alpha or NA are recommended (76). In a controlled randomized study of 40 children with HBV-associated MGN, regression of the proteinuria was noted in 80% vs 50% cases treated with IFN-alpha vs placebo; HBe seroconversion occurred in 80% vs 0% (77). The results with IFN-alpha in adults showed less efficacy (62). In another study, 8 of 15 adults had an HBe seroconversion and 7 of these had a reduction of proteinuria (78). Of note, the 8 responder patients had MGN, whereas 4 of the 7 nonresponder patients had MPGN. In a meta-analysis including the data from 6 therapeutic trials, of the 82 patients studied [IFN-alpha (N = 72), LAM (n = 10)], the remission rate of the proteinuria was 65% and the HBe seroconversion rate 62% (10). A recent meta-analysis of 13 studies including 325 patients confirmed the safety and renal efficacy of NAs (11). Corticosteroids may be given for a period of less than 6 months without a significant effect on HBV infection, as long as concomitant NA treatment is used (11). HBV-related MPGN with type 3 cryoglobulinemia should receive NA to control HBV viremia. HBV vaccination has been shown to successfully reduce the rate of childhood cases of HBV-related MGN because of horizontal transmission of the virus, but it will have no effect on HBV-related MGN because of acquired infection via vertical transmission (79). In a meta-analysis from Yang et al. (80) on the efficacy of NAs in patients with HBV-induced MGN, complete remission of proteinuria, total remission of proteinuria and HBeAg clearance increased significantly after antiviral therapy. In a recent study on 32 patients with HBV-MGN treated with ETV

and followed for 52 weeks, complete remission of MGN and HBV replication suppression were induced (74).

Hematological malignancies

There are strong epidemiological arguments for a link between CHB and non-Hodgkin B cell lymphoma (B-NHL). Initial studies carried out in Asia found CHB was 2–5 times more frequent in patients with B-NHL than in those without (81) or in the general population (82). More recent studies support such an association. The incidence of NHL in patients with and without HBV infection, in 2 large North American databases, showed a relative risk of HBV-infected patients of developing a NHL of 2.8 (83). A case-control Chinese study showed that HBV-infected individuals had a pooled odds ratio for NHL of 2.1 (84). Patients with HBV naturally acquired immunity (HBsAg-negative/anti-HBc-positive/anti-HBs-positive) had increased B-NHL risk with an adjusted odds ratio of 2.3 compared with 6.2 for those with current HBV infection (HBsAg-positive/HBeAg-positive). Wang et al. (85) found significantly lower rates of anti-HBs-positive and anti-HBc-negative patients among NHL cases than controls. A possible explanation is that an anti-HBs response, in the absence of anti-HBc, might have been especially effective in the control of HBV replication in lymphoid cells, thereby preventing any contribution of HBV to neoplastic transformation and development of NHL. However, this issue needs further studies to confirm the link between NHL occurrence and HBsAg/anti-HBs. A Taiwanese nationwide population-based cohort, including patients with (203,031) or without (203,031) HBV infection, reported a respective hazard ratio for the risk of NHL in the HBV-infected versus the non-HBV-infected cohort was 2.2, for diffuse large B-cell lymphoma (DLBCL) 2.7, and for other B-cell lymphoma 3.1 (86). In a meta-analysis, patients with DLBCL with CHB had significantly poorer 2- and 5-year overall survival and 2- and 5-year progression-free survival (87). Underlying mechanisms that may explain the increased risk of NHL in HBV infected patients remain unknown and the possible benefit of HBV antivirals on B cell lymphoproliferation (88).

The risk of HBV reactivation during or after rituximab-based treatment in patients with NHL is higher in HBsAg-positive patients (89). This risk is mainly related to both the status of HBV infection (HBsAg-carriers or HBcAb-positive/HBsAg-negative patients) and the type of therapeutic regimen (B cell depleting agents). A prospective randomized trial demonstrated superiority of ETV over LMV-prophylaxis in reducing the risk of such HBV reactivation (6.6% vs 30%) and HBV-related hepatitis (0% vs 13.3%) (90). Prophylactic use of ETV would reduce the occurrence of HBV reactivation-related hepatitis and mortality in HBsAg-positive patients with DLBCL receiving rituximab-containing chemotherapy (91).

Rheumatological manifestations

The flu-like syndrome including joint pain and arthritis may occur during the preicteric phase of acute hepatitis. In approximately 20% of acute HBV infection, a serum sickness-like syndrome occurs 1–6 weeks before hepatitis, characterized by symmetrical nondestructive arthralgia or arthritis, involving small joints of the hands and feet, and sometimes a few large joints. During the acute phase, synovial fluid shows HBsAg and reduced complement levels. Skin manifestations occur in more than 50% of patients, and lesions can be maculopapular, purpuric, or petechial (92). Cutaneous vasculitis with immunoglobulins, complement, and HBsAg in vessel walls are revealed by skin biopsies. An urticarial lesion can be intermittent, and it is associated with hypocomplementemia.

Patients with RA are characterized by an increased risk of HBV infection compared with non-RA subjects (93). Whether RA has a pathogenic association with HBV infection remains unanswered. Chen et al. found HBcAg in the synovium of patients with RA with CHB (7 of 11, 64%) (92). In addition, more CD68-positive macrophages, CD20-positive B cells, and CD15-positive neutrophils infiltrated the synovium in those CHB patients with RA compared with the non-CHB group. Thus, the presence of HBV in RA synovium may be involved in the pathogenesis of local lesions and exacerbate disease progression in RA (94).

Patients with RA were compared with age- and sex-matched controls regarding the proportion of chronic HBV infection in a case-control study (95). Patients with RA have a greater proportion of chronic HBV infection than matched controls. Interestingly, in patients who have resolved HBV infection, treatment of RA can result in reappearance of HBsAg, called reverse seroconversion. In patients who resolved HBV infection and received immunosuppressant treatment of RA, risk of reversal of seroconversion is low but persists for up to 10 years (96). Patients with RA who previously resolved HBV infections should be monitored for levels of HBsAg and HBV DNA once immunosuppressive treatment of RA begins.

HBV status was independently associated with 1-year RA radiographic progression, although conflicting results have been published (97). Rheumatoid factor positivity occurs in a number of patients with HBV infection and may be challenging in differential diagnosis with RA (98). The absence of anticitrulline Ab in CHB may be helpful.

Autoantibodies

In a study including 190 patients with CHB, the most common serological manifestations were the presence of antismooth muscle and antinuclear Ab, cryoglobulinemia, and rheumatoid factor (99) (Table 3). The most common clinical manifestations were sensorimotor neuropathies, myalgia, arthralgia, Sjögren syndrome, GN, uveitis, Raynaud syndrome, psoriasis, and pruritus. In another study, the most common auto-Ab found in a series of 85 HBV-infected patients were antinuclear, anti-SSA, anti-SSB, anti-Scl70, antiribosome P, anti-Jo1, and anti-Sm (77). Blood CXCR5+CD4+ T cells of patients with CHB were able to induce B cells to secrete higher level of immunoglobulins than those of healthy controls.

Other miscellaneous extrahepatic manifestations

HBV infection and extrahepatic nonhematologic malignancies. Of note, chronic HBV infection is associated with several other malignant disorders including biliary, cervical, uterine, breast, thyroid, lung, and skin cancers (100). In a study from Taiwan, the authors showed that pancreatic (2.61%) and ovarian cancers (2.31%) are more common in HBV-infected patients than non-Hodgkin lymphoma (2.1%) (101). A recent prospective study involving 3 cohorts in China showed that HBV infection is highly associated with digestive system cancers including stomach, oral, colorectal and pancreatic cancer (102).

Beside HCC, gallbladder and extrahepatic bile duct, and hematological cancers that have been clearly associated with HBV infection, there has been some controversy concerning the increased risk for other types of cancer. However, recent studies from Korea (100), Taiwan (101), and the United States (103)

Table 3. Main biological extrahepatic manifestations associated with chronic hepatitis B virus infection (*Cacoub P et al, 2005, reference 44; and Lei Y et al 2016, reference 102*)

Biological manifestations	N = 190 *Cacoub*	N = 85 *Lei*
	n (%)	n (%)
Absence of auto-Ab	161 (85)	30 (35)
At least 1 auto-Ab	29 (15)	55 (65)
Antismooth muscle Ab	14 (7)	2 (2)
Antinuclear Ab	6 (3)	21 (25)
Antinucleosome Ab	4 (2)	ND
Anti-Sm Ab	ND	5 (6)
Cryoglobulinemia	3 (2)	ND
Rheumatoid factor	3 (2)	ND
Antiliver-kidney microsomal Ab	3 (2)	0 (0)
Antiribosomal P-protein Ab	ND	9 (10)
Anti-DNA Ab	0 (0)	ND
Antisoluble nuclear antigen Ab	0 (0)	ND
Anti-SSA Ab	ND	18
Anti-SSB Ab	ND	14
Anti-scl-70 Ab	ND	9 (11)
Anti-Jo-1 Ab	ND	6 (7)
Antimitochondrial Ab	0 (0)	2 (2)

Ab, antibodies.

suggest an increased risk of extrahepatic malignancies in patients with HBV chronic infection.

Patient-reported outcomes and quality of life

Baseline patient-reported outcome scores were significantly higher in HBV infected patients in many domains of SF-36, SF-6D utility, emotional and fatigue domains of chronic liver disease questionnaire, presenteeism, and total work productivity impairment in comparison to patients with HCV (104). Patients with HBV infection and effective viral suppression after antivirals have been showed to have PROs that were similar or better than the general population (105).

Neurological conditions

In addition of the neurological manifestations of HBV-induced extrahepatic diseases (altered mental state, depression, and psychosis), Guillain-Barré syndrome has been associated with both acute and chronic HBV infection. In patients with neuropsychiatric disorders and HBV infection, both HBsAg and HBV DNA have been detected in cerebrospinal fluid, and it is uncertain whether the virus itself or an immune-mediated reaction is responsible for these symptoms (106). Peripheral neuropathy was also described in a patient with chronic HBV (107).

Major adverse cardiovascular events and metabolic complications

In a systematic review examining 9 studies of 65,058 HBV-infected patients and 534,998 uninfected controls, HBV infection was not associated with the risk of coronary heart disease (108). The risk of stroke was analyzed from a Taiwan national database, in large series of 22,303 HBV-infected patients and 89,212 matched controls (109). The HBV group exhibited a lower stroke risk compared with the controls. In a meta-analysis including 83,475 HBV-infected patients and 593,949 uninfected controls, the risk of stroke was significantly lower in HBV-infected patients than in uninfected controls (110). Overall, CHB contrary to HCV infection does not seem to be associated with an increased risk of major adverse cardiovascular events, i.e., cardiac ischemic events, ischemic cerebrovascular events, or peripheral arterial disease.

Although CHB does not have a clear association with an increase in cardiovascular or metabolic diseases, recent data have shown that comorbid metabolic liver disease does accelerate disease progression in HBV. Liver biopsies from 420 hepatitis B surface antigen-positive adults who were not on HBV therapy were evaluated (111). Coexisting steatosis occurred in nearly a third of adults (13% had steatohepatitis) with chronic HBV in this North American cohort. Steatohepatitis was associated with advanced fibrosis and higher biochemical measures of hepatic inflammation over time. Therefore, in addition to viral suppression, screening for and managing metabolic abnormalities is important to prevent disease progression in HBV.

Table 4. Efficacy of antiviral therapy in hepatitis B virus-related extrahepatic manifestations

Extrahepatic manifestations	Treatment	No. of patients	Extrahepatic Improvements	Reference, author, yr
Polyarteritis nodosa	Corticosteroids + LAM + plasma exchanges	10	90% (9/10)	Guillevin et al. 2004 (ref 45)
Mixed cryoglobulinemia vasculitis	Steroids (8), NA (ETV:5, ADV:1, LAM:1, IFN:2)	17	No disease progression	Mazzaro et al. 2016 (ref 52)
MPGN	Steroids + NA (LAM, ETV, ADV)	317	Reduction of proteinuria by 4 fold	Zheng et al. 2012 (ref 11)
PRO	NA (LAM, ADV, TDF, ETV, TBV)	242	Reduction of viral load associated with increase PROs	Younossi et al. 2018 (ref 105)

ADV, adefovir; ETV, entecavir; HBsAg, hepatitis B surface antigen; LAM, lamivudine; MPGN, membranoproliferative glomerulonephritis; N/A, not applicable; PEG-IFN, pegylated interferon; PRO, patient-reported outcome; TAF, tenofovir alafenamide; TBV, telbivudine; TDF, tenofovir disoproxil fumarate.

CONCLUSION

Clinicians should be aware that HBV-infected patients may present many extrahepatic manifestations. Patients with HBV infection require checking for extrahepatic manifestations, and conversely, patients with a rare systemic disease should be tested for markers of HBV infection. Suppression of HBV replication usually improves extrahepatic manifestations. A table summarizing the efficacy of antiviral therapy in HBV-related extrahepatic manifestations is provided (Table 4). Most HBV-infected patients with symptomatic extrahepatic manifestations and/or organ damage should probably receive antivirals regardless of viral and/or liver indications. We need more information whether we should consider fatigue or decreased quality of life as an indication for treatment.

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CONFLICT OF INTEREST

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