Hepatitis Arthritis: HBV and HCV

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Introduction

Hepatitis B virus (HBV), a dsDNA virus of the *Hepadnaviridae* family, is estimated to affect around 400 million people worldwide. Transmitted vertically, sexually, or through blood-borne contact (transfusion or intravenous drug use), around 95% of adults exposed to the virus will mount an appropriate immune response leading to eventual viral clearance [1]. With the introduction of efficient preventive measures, such as universal vaccination of infants, prevention of perinatal transmission, and vaccination of high-risk adults, several studies have shown a decrease in the incidence of acute HBV infection [2]. The geographic distribution of HBV infection can be described as follows: 88% of the global population lives in areas of intermediate ($HBsAg^+$ prevalence 2–7%) or high endemicity (>7%) corresponding to African and East Asian territories, where most infections occur from vertical transmission, whereas the remaining 12% lives in low endemicity areas ($HBsAg^+$ prevalence <2%), roughly corresponding to North Europe and the United States, where HBV infection usually occurs in adulthood. In western countries the incidence of HBV infection has been furtherly diminished by widespread vaccination programs since the 1980s [3, 4].

Hepatitis C virus (HCV) is a hepatotropic virus estimated to infect about 130–170 million people worldwide. Infection with the virus is known to result in severe morbidity and mortality, especially by liver complications (cirrhosis and hepatocellular carcinoma) in a significant number of patients after several decades of infection. As such, HCV represents a global health challenge with an estimated liver-related mortality of 350,000 people/year. It has been shown as one of the hepatic viruses most often associated with extrahepatic manifestations (EHMs), which present in up to two-thirds of infected patients [5].

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Extrahepatic syndromes may represent the first signal of HCV infection in some patients [6]. Some of the EHMs, including mixed cryoglobulinemia and non-Hodgkin B-cell lymphoma, have a significant prevalence with unequivocal data supporting a causal relationship. Other manifestations have been noted to have a high prevalence, including adverse cardiovascular events (stroke, coronary artery disease), kidney disease, metabolic diseases, and neuropsychiatric (depression, impaired quality of life) disorders [7]. With the introduction of effective direct-acting antivirals (DAAs), the opportunity to achieve HCV eradication has important implications from both a therapeutic and preventative perspective.

This chapter will outline the most important rheumatic manifestations associated with HBV and HCV infection, with a focus on arthritis, for which good evidence is available to support a linkage between infections and the clinical syndrome.

Diagnosis and Classification of Hepatitis B Virus Infection

The diagnosis of HBV infection relies mainly on serology (hepatitis B surface antigen [HBsAg], hepatitis B envelope antigen [HBeAg], anti-HBs, anti-HBc [hepatitis B core antibody], and anti-HBe antibodies) and serum HBV DNA levels [3]. Serologic tests are used for the differentiation between acute, chronic, and past (resolved) infection, whereas HBV DNA levels are required for distinguishing active chronic hepatitis from the inactive carrier state in chronically infected patients as well as for the detection of occult infection in resolved HBV infection [8] (Table 10.1):

1. *Acute hepatitis B* is characterized by high aminotransferases (alanine aminotransferase [ALT] >10 the upper limit of normal [ULN]) and positive HBsAg and IgM anti-HBc antibodies. These patients are rarely encountered in rheumatology practice.

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Table 10.1 Laboratory in hepatitis B virus infection

		Chronic hep	Chronic hep		
	Acute hepatitis	HBeAg (+)	HBeAg (−)	Inactive carrier	Past infection
HBsAg	+	+	+	+	−
Anti-HBc	+	+	+	+	+
Anti-HBs	−	−	−	−	+/−
HBeAg	+	+	−	−	−
Anti-HBe	−	−	+	+/−	+
ALT	ULN (+++)	ULN	ULN	Normal	Normal
HBV-DNA	>20,000 IU/mL	>20,000 IU/mL	>2000 IU/mL	Undetectable	Undetectable

Abbreviation: ALT alanine aminotransferase, *ULN* upper limit normal
Adapted from Ref. [8]

2. *Chronic HBV infection* definition requires the presence of HBsAg in the serum for greater than 6 months. Most of the patients (70–80%) are inactive HBV carrier (normal ALT levels, low or undetectable serum HBV DNA) who rarely develop cirrhosis or its complications, whereas spontaneous clearance of HBsAg gradually occurs (1% per year). Approximately 20–30% of chronically infected patients though have active chronic hepatitis B (defined by elevated ALT and HBV-DNA levels) and, if left untreated, progress to cirrhosis and hepatocellular carcinoma. Two major subsets of *chronic hepatitis B* are recognized: *HBeAg positive and negative* [9].
3. *Past or resolved HBV infection* is defined by negative HBsAg and positive anti-HBc antibodies in the serum (with or without anti-HBs antibodies). Approximately 5–50% of rheumatic patients worldwide demonstrate this serologic profile. Among these patients, a small subset (<5%) can have occult HBV infection defined by the presence of HBV-DNA in the liver and occasionally in low levels in the serum (<200 IU/mL) [10]. This group of patients is challenging because they can rarely develop HBV reactivation with immunosuppression.

Pathogenesis of HBV Infection

HBV infection causes acute and chronic necroinflammatory hepatitis. The pathogenesis of HBV infection is still unknown. Massive hepatic injury occurring during chronic HBV infection seems to be immune mediated and depends on HBV-specific cytotoxic T-cells [11]; moreover, efficient control of HBV infection requires the synergic actions of both innate and adaptive immunity. Innate immunity induces in HBV-infected cells the production of type I interferons and several proinflammatory cytokines, including TNF-α, IL-1, IL-6, and IL-10, some of which are reported to suppress viral replication and/or to exert non-cytolytic viral clearance. The persistence of HBV infection may be associated with CD8+ T-cell loss of the ability to secrete enough TNF-α to kill infected hepatocytes (so-called "exhausted phenotype"). It has been shown that in TNF-α knockout mice and in etanercept-treated mice, HBV infection persists, with subsequent increase in HBV-specific CD8+ T-cells, serum and liver HBV-DNA, and antigen expression [12].

Cellular immunity is critical for the outcome of HBV infection: HBV-specific T-cells are involved in the control of viral infection, while non-specific NK cells infiltrate the liver leading to hepatocellular injury. In humans, IL-6 in combination with TGF-β and IL-1β drive naive CD4+ T-cell to differentiate into Th17 cells in a HBc-dependent fashion [13]. Th17 cells can produce multiple cytokines that trigger the recruitment and activation of neutrophils leading to massive tissue inflammation. Recent reports showed that in chronic hepatitis B infection (CHB), antigen non-specific Th17 response is increased and that the peripheral Th17 frequency is associated with the degree of liver damage [14].

Recent reports suggest that humoral immunity also plays an important role in the immune response to HBV. HBcAg is able to directly activate B-cells to produce specific antibodies in the absence of regulatory T-cells. However, immunosuppression and B-cell suppression are associated with viral reactivation. B-cells are thus involved in liver inflammation in HBV-infected patients, but whether they influence disease progression is still a matter of debate [15].

Clinical Manifestations

Arthritis in patients with HBV occurs in both the prodromal phase of acute infection and during chronic HBV infection. Arthritis can be the only presenting feature of acute HBV infection and in the prodromal phase of infection often resembles rheumatoid arthritis (RA), with a symmetrical polyarticular distribution involving proximal interphalangeal joints, ankles, and knees [16]. The presence of rash, fever, malaise, or myalgia may provide clues to the underlying diagnosis. Arthritis symptoms typically last days to months and often resolve with the onset of jaundice. Rheumatoid factor (RF) can be elevated in around 25% of cases, whereas

C3 and C4 are found to be low in around 40%, indicative of an immune-complex-mediated process [17].

Hepatitis C

Clinical Manifestations

Hepatitis C virus infection is one of the best mimes among all diseases. It can induce a number of signs and symptoms involving almost any organ of the body. Many rheumatic disorders must also be clearly distinguished from the HCV manifestations.

Arthralgia is reported in 6–20% of patients infected with HCV. It usually involves large joints, sometimes with effusion, bilateral, and with a symmetric pattern. Arthralgia most frequently involves fingers, knees, and back [18]. It is significantly more frequent in patients with cryoglobulinemia vasculitis (CryoVas) compared with those without vasculitis. As similar than HBV, the presentation may mimic RA, even the frequent positivity of RF in patients infected with HCV might lead to misdiagnosis.

Zuckerman et al. have suggested two different subsets of HCV-related arthritis [19]:

1. A *RA-like subset*, principally involving small joints, in which the RF is often present but the elevation of ESR is less frequent than in classic RA. Rheumatoid nodules have never been reported and classically are considered as a non-erosive disease. Prolonged morning stiffness is common.
2. A less common *mono-oligoarthritis* involving medium-sized and large joints, often showing an intermittent course. This form seems more strictly related to the presence of cryoglobulins in the serum.

Mono-oligoarthritis or symmetrical RA-like polyarthritis is induced by HCV; consequently, different forms of arthritis must be considered in the differential diagnosis. The first subset must be distinguished from spondyloarthritis. When the HCV-related arthritis course is intermittent, crystal-induced arthritis should also be considered in the differential diagnosis. True RA may be easily mistaken for HCV-related RA-like polyarthritis, particularly in the early stages of the disease when erosions and rheumatoid nodules are usually absent. Myalgia is less common, affecting about 2–5% of patients with HCV [20].

Cryoglobulinemia vasculitis (CryoVas) is a small vessel vasculitis involving the skin, joints, peripheral nerve system, and the kidneys. Cryoglobulinemia is defined by the presence of circulating immunoglobulins that precipitate at cold temperatures and dissolve with rewarming. During the last 15 years, progress has been made after the discovery of the HCV, which represents the cause of CryoVas in roughly 80%, mostly associated with a type II immunoglobulin (Ig) M kappa mixed cryoglobulin. Main symptoms include asthenia, purpura, arthralgia, myalgia, peripheral neuropathy, and glomerulonephritis [21]. Clinically or on imaging, there is no evidence of joint damage.

Skin is the most frequently involved target organ and is the direct consequence of the small-size vessel vasculitis. The main sign is *palpable purpura*, but chronic cutaneous ulcers may occur. Raynaud's phenomenon and acrocyanosis, which may evolve to digital ulcerations, can also occur. Neurologic manifestations range from pure sensory axonopathy to mononeuritis multiplex. The most frequently described form is a distal sensory or sensory-motor polyneuropathy. Polyneuropathy usually presents with painful, asymmetric paresthesia, which later becomes symmetric. Less frequently, multiple mononeuropathy may occur. Renal involvement is an acute or chronic type-I membranoproliferative glomerulonephritis with sub-endothelial deposits. It represents 70–80% of cryoglobulinemia renal diseases and it is strongly associated with the type II IgM k mixed cryoglobulinemia. The most frequent presentation is proteinuria with microscopic hematuria and a variable degree of renal insufficiency.

In a large cohort of patients with HCV-CryoVas, baseline factors associated with a poor prognosis were the presence of severe liver fibrosis (hazard ratio [HR], 5.31), central nervous system involvement (HR, 2.74), kidney involvement (HR, 1.91), and heart involvement (HR, 4.2) [22].

Apart from the detection of serum cryoglobulin, other laboratory abnormalities may provide surrogate evidence of the presence of cryoglobulinemia, such as low C4 serum complement fraction, decreased total hemolytic complement levels, presence of a serum monoclonal immunoglobulin or RF activity. Rheumatoid factor (RF) activity is found in 70–80% of patients with CryoVas, not correlated with the occurrence of joint disease. Anti-cyclic citrullinated peptide (anti-CCP) antibodies are usually absent in patients with HCV. Hypocomplementemia is a sensitive and important finding in CryoVas, being found in 70–90% of mixed cryoglobulinemia patients [23].

There are multiple immunologic factors predisposing patients infected with HCV to develop a CryoVas or other systemic rheumatologic manifestations. Chronic stimulation of B cells by HCV directly modulates B-cell and T-cell function and results in polyclonal activation and expansion of B cell–producing IgM with RF activity. There is an expansion of clonal CD21-/lowIgM1CD271 marginal zone-like B cells and a decrease of regulatory T cells [24]. Other factors are related to the infection by HCV of peripheral blood mononuclear cells, including peripheral dendritic cells, monocytes, and macrophages [25]. Under this trigger effect, oligoclonal or monoclonal IgM, which shares rheumatoid activity, is produced by a permanent clone of B cells that favors the appearance of immune complexes, formed by circulating HCV, anti-HCV polyclonal IgG, and the monoclonal IgM.

Fatigue and Fibromyalgia

In a large prospective study, 19% of 1614 patients infected with HCV fulfilled the main diagnostic criteria of fibromyalgia (fatigue, arthralgia, and myalgia). Fatigue, with or without fibromyalgia, was the most frequent extrahepatic manifestation (35–67%) [26]. Many underlying factors were independently associated with fatigue, such as older age, female gender, presence of arthralgia/myalgia, as well as neuropsychological factors. Of note, after IFN-based treatment, only the group of patients with a sustained virologic response (SVR) showed a beneficial impact on fatigue. A benefit of treatment on arthralgia/myalgia was found in about 50% of patients, independently of the virologic response.

Sicca Syndrome

Sicca symptoms of either the mouth or eyes have been reported in 10–30% of patients infected with HCV. Less than 5% of patients with a defined Sjogren syndrome (SS) are HCV positive [27]. In a recent literature review, Younossi and colleagues reported a sicca syndrome prevalence of 11.9% in patients with HCV, with a risk ratio for sicca syndrome of 2.29 in patients infected with HCV compared with uninfected patients [28].

However, the criteria for SS diagnosis were based on the clinical questionnaire in some studies and were not well detailed. Although sicca symptoms are very common in patients infected with HCV, a characterized SS defined by the presence of anti-SSA or anti-SSB antibodies and typical salivary gland histology is uncommon. A large cohort study of patients with a definite SS (1993 international criteria) compared patients with HCV infection with those with a primary form. Patients with HCV-associated SS were older, more frequently male, and more frequently presented vasculitis, peripheral neuropathy, and neoplasia. They also had a different biological pattern: more frequently had a positive RF test, cryoglobulinemia, and less frequently anti-SSA or SSB antibodies [29]. The detection of HCV RNA and HCV core antigen in epithelial cells of patients with HCV-associated SS and the development of SS-like exocrinopathy in transgenic mice carrying the HCV envelope genes support the possibility of a direct impact of HCV on the development of sialadenitis [30].

Treatment

There is little experience in treating patients having HBV and HCV-associated arthritis, and the optimal treatment has not been established. The main objectives of treatment are to control the inflammatory process and, when required, to obtain a sustained clearance of the virus. Nonsteroidal anti-inflammatory drugs (NSAIDs), low doses of oral corticosteroids, and hydroxychloroquine (HCQ) are usually effective in controlling joint symptoms. Also, the risk for HBV and HCV reactivation during immunosuppressive therapy in patients with autoimmune diseases is a major concern.

Hepatitis B

Antiviral therapy is recommended for CHB patients who have HBV DNA levels >2000 IU/mL, serum aminotransferases above the upper limit of normal (ULN), and moderate to severe active liver necroinflammation and/or at least moderate fibrosis. The main objective of antiviral therapies are long-term suppression of viral replication, sustained HBeAg seroconversion for HBeAg+ individuals, and HBsAg clearance [31].

Long-term viral suppression is achieved in >95% cases with oral nucleic acid analogues (NAs), although HBsAg loss remains a hard to achieve target (<10%). Actually, therapies recommended for the treatment of CHB include *interferon-α (IFN)*, *pegylated-INF-α2a (PEG-IFN)*, and six *NAs* that can be classified into nucleoside (*lamivudine*, *telbivudine*, *emtricitabine*, *entecavir*) and nucleotide (*adefovir and tenofovir*) analogues, which have been shown a better safety profile [32]. Entecavir and tenofovir are potent HBV inhibitors currently recommended as first-line monotherapies. These agents have to be given either indefinitely (HBeAg-CHB) or for 12 months following HBeAg seroconversion in HBeAg+ CHB [33].

Treatment of Hepatitis C Infection

The cornerstone of HCV therapy is the capacity of treatments to achieve a SVR. Introduced in the early 1980s as a monotherapy, *interferon* (IFN) was found to be both poorly tolerated and poorly effective with a SVR in less than 10%. With *pegylated formulations of IFN* (Peg-IFN) optimizing its pharmacokinetics and combination with ribavirin for 48 weeks or longer, SVR rates increased to about 50%. During the decade 2000–2010, Mazzaro and colleagues first reported sustained clinical and virologic response in 44% of patients with HCV-CryoVas treated with *Peg-IFN* plus *ribavirin* for 12 months [34]. Saadoun and colleagues reported that the combination of *Peg-IFN plus ribavirin* compared with *IFN plus ribavirin* showed higher rates of complete clinical (67.5% vs 56.2%) and virologic (62.5% vs 53.1%) responses, regardless of HCV genotype and viral load [35].

However, the safety profile was not satisfactory, and such therapies often led to many severe adverse events, such as severe cytopenia, disabling fatigue, fever, and depression. In

addition, fatigue, arthralgia, and myalgia were frequently reported, which is a particular concern in rheumatic patients in whom distinguishing drug side effect from underlying disease was often difficult. Other autoimmune exacerbations, such as SS and systemic lupus erythematosus, have been reported after IFN treatments [36].

The Era of Direct-Acting Antiviral Therapy

In the last years, new oral, IFN-free regimens have been approved for the treatment of HCV infection. They have revolutionized the management of HCV infection, characterized by a dramatic efficacy leading to cure rates of 90–100% in all HCV genotypes, with minimal side effects and short duration (12–24 weeks) [37, 38]. Even in difficult-to-treat populations, including cirrhotic and previously treated patients, IFN-free DAA regimens have been reported to be very efficient. Numerous large prospective studies have been published with different DAA combinations, showing high antiviral potency [39].

For the treatment of *HCV-CryoVas*, the VASCUVALDIC study enrolled 24 patients (median age, 56.5 years; 50% cirrhotic) who received *sofosbuvir plus ribavirin* for 24 weeks. Seven patients also received immunosuppressive therapy: *rituximab*, *corticosteroids*, *and plasmapheresis*. Eighty-seven percent of patients were complete clinical responders, and SVR was obtained in 74% of patients at week 12 post-treatment [40].

Sise and colleagues reported a case series of 12 patients with HCV-CryoVas (median age, 61 years; 50% cirrhotic) treated with *sofosbuvir plus simeprevir* ($n = 8$) or *sofosbuvir plus ribavirin* ($n = 4$). Seven patients had evidence of renal involvement, including five patients with membranoproliferative glomerulonephritis. Four patients received rituximab concurrent with DAA therapy. An SVR at posttreatment week 12 was achieved in 83% of patients. Cryoglobulin levels decreased in most patients, with a median decrease from 1.5% to 0.5%, and disappeared in four out of nine cases [41].

Despite the unquestionable evidence of a viral cause and the obvious efficacy of antiviral treatments, immunosuppression remains a major treatment, especially in patients with HCV-CryoVas in cases of severe manifestations (renal, digestive, or cardiac involvements) or in patients with failure or contraindication to antiviral treatment. *Rituximab* (a monoclonal anti-CD20 antibody) targets activated B cells, which are responsible for cryoglobulin production and eventually CryoVas lesions. Randomized controlled trials showed that *rituxi*mab has better efficacy than conventional immunosuppressive treatments (i.e., *glucocorticoids*, *azathioprine*, *cyclophosphamide*, *or plasmapheresis*) or placebo [42, 43]. Two other controlled trials showed that the addition of rituximab to Peg-IFN/ribavirin led to a shorter time to clinical remission, better renal response rate, and higher rates of cryoglobulin clearance [44, 45].

Considering the very rapid and potent virologic efficacy of new DAA combination and the proven correlation between SVR and clinical response, the exact place of rituximab, plasmapheresis, or other immunosuppressive drugs remains to be defined.

Corticosteroids, used alone or in addition to IFN, did not favorably affect the response of HCV-CryoVas manifestations in controlled studies [46]. Plasmapheresis, which offers the advantage of removing the pathogenic cryoglobulins from the circulation, should be considered for rapidly progressive glomerulonephritis or life-threatening involvements. Immunosuppressive therapy is usually needed in association with plasma exchange in order to avoid the rebound increase in cryoglobulin serum level seen after discontinuation of apheresis [47].

Conclusion

Arthritis should be considered as a manifestation induced by HBV and HCV infection. There is not a specific clinical pattern, although frequently resembles RA, with a nonerosive phenotype. True RA may be easily mistaken for HBV- and HCV-related polyarthritis, particularly in the early stages of the disease when erosions and rheumatoid nodules are usually absent. Nonsteroidal anti-inflammatory drugs, hydroxychloroquine, and low doses of corticosteroids are the cornerstones of the treatment of HBV- and HCV-related arthritis. For HCV infection, the introduction of DAA has revolutionized the management, characterized by a dramatic efficacy leading to cure rates of 90–100% in all HCV genotypes. Immunosuppressive therapies, such as azathioprine, cyclophosphamide, rituximab, and plasmapheresis, are recommended in cases of severe manifestations or in patients with failure or contraindication to antiviral treatment.

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