Hypothesis

Rheumatoid Arthritis and Hepatitis B Virus: Evaluating the Pathogenic Link

Hepatitis B (HBV), a partially double-stranded circular DNA virus, represents one of the major causes of liver disease. Although about 90% of infected neonates eventually develop chronic infection, only about 5% of immunocompetent adults are unable to clear the virus. However, the resulting persistent infection carries the risk of developing potentially life-threatening chronic liver diseases and extrahepatic syndromes[1-5].

Rheumatoid arthritis (RA) usually presents as an unresolving polyarthritis of small joints with or without large joint involvement. RA is an autoimmune disease of multifactorial etiology. Although genetic predisposition (including the presence of particular HLA-DR4 and/or DR1 alleles) is significant in the development, clinical course, severity, and expression of extraarticular manifestations[6-8], the cause of RA remains elusive.

Three lines of evidence suggest a link between HBV and RA: (1) polyarthritis is a well established extrahepatic manifestation of acute hepatitis B, and is believed to be immune-complex mediated[4,5]; (2) the administration of recombinant hepatitis B surface vaccine (rHBsAg) may induce the onset of symptoms of rheumatic diseases and conditions including RA[9-12]; and (3) to date, 3 patients with HBV-linked chronic polyarthritis who fulfilled the diagnostic criteria of the American College of Rheumatology (ACR) for RA[13] have benefitted from antiviral treatment[14,15].

Despite these observations, the relationship of RA and HBV as well as the frequency and pathogenesis of polyarthritis in patients with chronic hepatitis B are highly controversial[3-5,14-22]. We reviewed pertinent articles, abstracts, and book chapters from a MEDLINE search encompassing a 34 year period (1966-1999) to determine the prevalence of HBV infection in patients with RA. Furthermore, based on available data, we aimed to evaluate the putative pathogenetic link of this DNA virus in RA: whether its persistence induces this debilitating disease or only perpetuates joint inflammation in patients with RA.

POLYARTHRITIS AND HBV

Extrahepatic syndromes associated with HBV can be classified in 2 main groups (Table 1). While those seen prior to the onset of acute viral hepatitis usually completely resolve, syndromes linked to chronic infection contribute to the morbidity and mortality of the persistent viral infection[3-5]. Robert Graves was the first to report on hepatitis virus-induced extrahepatic syndromes[23]. Although frank arthritis is most closely associated with acute hepatitis B infection, arthralgias were described in 10 to 35% of patients with clinically evident acute viral hepatitis[4,24,25] (Table 2). Acute HBV arthritis represents a polyarthritic syndrome, and tends to present in a symmetrical pattern quite reminiscent of RA. Polyarthritis with dermatological manifestations (Table 1) almost always occurs in the prodrome, preceding by as much as a month the icteric phase of viral hepatitis and usually resolving completely before the onset of hepatitis[3,4,16,19,26,27].

Three diseases including glomerulonephritis, mixed cryoglobulinemia syndrome, and polyarteritis nodosa (Table 1) are established sequelae to HBV persistence and may be mediated by immune complexes consisting of HBsAg and anti-HBs antibodies[3-5,21,29,30,33-35].

CHRONIC HBV-LINKED POLYARTHRITIS

Duffy and colleagues[21] described 3 patients with hepatitis and persistent synovitis lasting from 32 to 38 months. In 2 cases the polyarthritis eventually resolved following corticosteroid and cyclophosphamide treatment. Unfortunately, the course of liver disease was not reported. Scully[14] reported a young male in whom HBV persisted 10 months after the onset of acute hepatitis B and polyarthritis, and continued to present migratory polyarthralgia and tenosynovitis. His joint complaints resolved completely with the disappearance of HBsAg after a course of treatment with lymphoblastoid interferon (IFN alpha 2a). His case represents the first well-documented report on chronic hepatitis B-linked polyarthritis. Further, 2 patients meeting the diagnostic criteria for RA[13] were recently reported who developed chronic polyarthritis and liver disease and responded excellently to antiviral treatment[15]. These observations suggest that there are patients who are HBsAg-positive and may develop chronic HBV-induced liver disease and polyarthritis that is indistinguishable from RA at presentation.

RHEUMATOID ARTHRITIS AND CHRONIC HBV

Vaccination with rHBsAg has been reported in association with a number of rheumatic conditions[9-12]. To date, at least 20 patients have developed RA after receiving rHBsAg vaccine[12]. In the majority of cases, HLA DR4 and/or DR1 antigens were present. Vaccination-linked RA was clinically

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Table 1. Extrahepatic manifestations linked to HBV infection.

Syndromes in the prodrome of acute hepatitis B	
Serum sickness syndrome	
Polyarthralgia, polyarthritis	
Dermatologic manifestations:	Macular or maculopapular eruptions, urticaria, purpura, Gianotti-Crosti syndrome (acrodermatitis papulosa infantum), Raynaud's phenomenon, erythema nodosum, digital infarction
Syndromes and diseases associated with chronic hepatitis B	
Established associations:	Glomerulonephritis, Mixed cryoglobulinemia syndrome, Polyarteritis nodosa
Putative associations:	RA, polymyalgia rheumatica, dermatomyositis, uveitis, myocarditis, neurological diseases, etc.

Table 2. Reports on (poly)arthritis in acute viral hepatitis.

	Patients (n)	Type of Hepatitis	RA-like Symptoms (%)
Graves (1843)[23]	9	unknown	100*
Klemperer (1926)[28]	2	infectious	100*
Klemola and Törmä (1949)[29]	150	infectious	11
Martini (1950)[30]	102	serum	17.6
Marner (1952)[31]	485	unknown	5
Gue and Bonner (1967)[32]	140	infectious	14
Fernandez and McCarty (1971)[16]	3	probably nonAnonB	100*
Alpert, *et al* (1971)[34]	18	HBsAg-positive	100*
Onion, *et al* (1971)[17]	3	HBsAg-positive	100*
Stevens, *et al* (1972)[40]	2	HBsAg-positive	100*
McCarty and Ormiste (1973)[19]	3	HBsAg-positive	100*
Schumacher and Gall (1974)[20]	2	HBsAg-positive	100*
Shumaker, *et al* (1974)[36]	14	10 HBsAg-positive 4 probably nonAnonB	100*
Duffy, *et al* (1976)[21]**	3	HBsAg-positive	100*
Morris and Stevens (1978)[22]**	1	HBsAg-positive	100*
Pease and Keath (1985)[26]	3	HBsAg-positive	100*
Scully, *et al* (1992)[14]**	1	HBsAg-positive	100*

*case report; **acute cases toward chronicity; infectious hepatitis: caused by hepatitis A or E virus; serum hepatitis: caused by hepatitis B or C virus.

indistinguishable from "genuine" RA[12]. Pope[11] described patients with vaccination-linked RA who shared the common HLA-DR haplotypes for RA (DR1*0101, *0301, *0401, *0404) that have the predicted binding anchor for peptides 96-104 aa and 161-169 aa within the HBsAg amino acid sequence, providing a possible link between HBV and RA. These recombinant peptides presented by different RA-specific HLA-DR alleles were able to stimulate Th0 or Th2 CD4+ lymphocytes resulting in proliferation and cytokine secretion[37,38]. It was hypothesized that rHBsAg vaccine-specific activation of CD4+ T cells might be an early event triggering other immunopathological mechanisms that eventually lead to RA in genetically predisposed patients[37,38].

Since the description of Australia (HBs) antigen[39], several authors have investigated the prevalence of HBV infection in RA (Table 3). In 1972, Desche-Labarthe described a young man with RA who had Australia antigen in his serum[49]. He concluded that this protein might have provoked and maintained chronic rheumatoid polyarthritis. Morris and Stevens reported a patient who developed RA as a sequel to acute hepatitis B infection[22]. Despite the resolution of hepatitis and disappearance of HBsAg, the polyarthritis persisted, progressed, and evolved into classic seropositive RA including radiographic erosions[21]. HBV might be a causative agent of autoimmunity leading to the development of RA, and this might occur after the clearance of HBV or the administration of rHBsAg vaccine.

HBV AS A CAUSATIVE AGENT OF RA

Years ago, Fernandez and McCarty wrote that "no cases of (chronic) RA have been reported as a long-term sequel" of acute hepatitis[16]. Their view was further confirmed by others who observed that the arthritis associated with hepatitis did not appear to be destructive[36]. In the 1970s, several papers suggested that there was no evidence of HBV infection in sera of patients with RA (Table 3). In 1975, Roques screened 300 RA sera for HBsAg, and found 5% of patients were positive[45]. Despite this relatively high prevalence of HBsAg positivity, they concluded that the surface antigen did not seem to play a significant role in the evolution of RA. No rate of HBsAg positivity was given for a control population. Permin and colleagues investigated

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Table 3. Prevalence of serological markers of HBV infection in RA.

	Patients (n)	HBsAg (%)	Markers of HBV other than HBsAg (%)*
Gocke, *et al* (1970)[33]	49	0	ND
Ziegenfuss, *et al* (1971)[18]	NR	0	ND
Panush, *et al* (1971)[40]	40	0	ND
Stevens, *et al* (1972)[41]	29	0	ND
Burrell, *et al* (1972)[42]	29	0	ND
Burssens, *et al* (1972)[43]	152	0	ND
Lehmann, *et al* (1973)[44]	62	1.6	ND
Roques, *et al* (1975)[45]	300	5	ND
Noguera-Hernando, *et al* (1976)[45]	70	0	ND
Giordano, *et al* (1976)[46]	59	1.7	ND
Permin, *et al* (1982)[47]	74	4	16
Csepregi, *et al* (1999)[48]**	80	5***	11

ND: not done; NR: not reported; *the 'e' and core antigens of HBV, and antibodies to the surface, 'e' and core antigens of HBV; **Ref. 48 and unpublished data; ***3 patients' sera (75%) were viremic by polymerase chain reaction.

HBV-related serological markers (HBsAg, HBeAg, and anti-HBs and anti-HBe) in patients with RA. Sixteen percent of sera were found to have at least one marker of HBV infection. Of interest, the prevalence of HBsAg was 4%, which was approximately 20 times more than that of a healthy Danish population. They concluded that an altered immune response of patients with RA coupled with an increased tendency to become carriers of HBsAg might have been responsible for this unexpectedly high prevalence of chronic HBV infection[47]. An alternate explanation of cause and effect (HBsAg causing RA) was not considered. In another study 80 patients who fulfilled the diagnostic criteria for RA were referred prior to initiation of treatment with disease modifying and/or non-steroidal antirheumatic drugs and were screened for serological markers of HBV infection (HBsAg, HBeAg, anti-HBc, anti-HBe)[48]. The frequency of HBV markers was similar to that found by Permin[47]. Four patients (5%) were positive for HBsAg, compared to the background prevalence of HBsAg carriers in the Hungarian population of about 0.6%. Two patients had chronic HBV-linked polyarthritis and liver disease; one developed chronic hepatitis and RA; the fourth patient was the only HBsAg-carrier without evidence of liver disease[15,48]. Sera from patients with active liver disease were all HBV DNA positive.

CONCLUSION

Acute hepatitis B is associated with polyarthralgia/polyarthritis in up to 35% of cases. Case reports suggest that HBV may also result in chronic polyarthritis. These patients may benefit from antiviral treatment.

Vaccination with rHBsAg may be followed by the development of RA. This viral antigen might induce pathological T cell responses resulting in RA in genetically susceptible individuals. Therefore, a causal link seems to exist between HBV and RA in some patients.

Data indicate that up to 5% of patients with RA have evidence of ongoing HBV infection, and 11 to 16% of sera from patients with RA contain HBV-related serological marker(s). In the majority of patients with HBsAg-positive RA, HBV may be regarded as an epiphenomenon. However, there may be patients with RA for whom HBV or viral proteins might have been pathogenic.

Chronic HBV infection might result from the immunocompromised status of patients with RA. It is even possible that the frequently invasive diagnostic and therapeutic measures undergone by patients with RA may promote the acquisition of HBV during either hospitalization or outpatient followup.

Well-designed studies are clearly required to obtain more relevant data to elucidate the relationship between HBV and RA.

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