Arthritis and Hepatitis

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The evidence relating four clinically distinct rheumatologic syndromes to infection by the hepatitis B virus is reviewed. Acute hepatitis B is not infrequently heralded by a prodromal rash and rheumatoidlike polyarthritis. Chronic active hepatitis B more rarely is associated with transient arthritis or arthralgias. Polyarteritis nodosa may be a manifestation of hepatitis B infection in as many as 40 percent of cases, and recently the syndrome of “essential” mixed cryoglobulinemia has also been linked to infection with this virus. The finding of immune complexes of varying composition, sometimes with the viral antigen or its antibody (or both) contained in both the serum and synovial fluid suggests that these four syndromes are clinical manifestations of immune complex disease resulting from hepatitis B infection.

Since the discovery of Australia antigen as a marker for the serum hepatitis virus in the late 1960's, there has been a resurgence of interest in hepatitis in general and in hepatitis-associated syndromes in particular. With reference to the rheumatic diseases, four syndromes have been described which associate what we now call hepatitis B with rheumatic problems, either arthralgias or frank arthritis. The first is a transient, symmetrical polyarthritis of the rheumatic or rheumatoid type that occurs in the prodromal phase of icteric or anicteric acute hepatitis B. In recent years, it has also been observed that a similar type of arthritis can be seen at intervals in chronic active hepatitis. The third is polyarteritis occurring in patients with hepatitis B surface antigenemia. The fourth, and most recently described, is the apparent association with hepatitis B of “essential” mixed cryoglobulinemia,

or what had been termed earlier the “purpura, arthralgia, weakness syndrome.” In this review we describe the clinical and laboratory features of these syndromes and discuss the possible mechanisms for their pathogenesis.

Acute Hepatitis B and Arthritis

The first reported association of acute viral hepatitis with arthritis was ostensibly that of Sir Robert Graves in an 1843 textbook in which he made the following observation: “A person laboring under inflammation of the joints gets an attack of hepatitis accompanied by jaundice, and this is followed by urticaria.”

Since that time, a number of reports have described discomfort in joints of a transient nature preceding the icteric phase of hepatitis occurring in anywhere from 1 percent to 40 percent of cases. Clinically, the syndrome resembles one-shot serum sickness as induced experimentally by Dixon and co-workers. The symptoms are generally abrupt in onset and consist of low-grade fever, a symmetrical polyarthritis which may be additive or migratory in pattern, morning stiffness and other

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ARThRITIS AND HEPATITIS

ABBREVIATIONS USED IN TEXT
ADCC = antibody-dependent cell-mediated cytotoxicity
anti-HB,Ag = antibody to hepatitis B surface antigen
HB,Ag = hepatitis B surface antigen
PAN = polyarteritis nodosa

constitutional symptoms. The joints most commonly involved are the knees and small joints of the hands. For some reason, the feet are usually spared, but almost any peripheral joint may be involved, with either arthralgia or actual arthritis. In more than 50 percent of cases, a skin rash may accompany or follow shortly after the onset of manifestations in joints. Although usually described as urticarial, this rash may also be erythematous, maculopapular or petechial in nature.

This syndrome may last from several days to several months; in one large series the mean duration was 20 days. Only about 40 percent of the patients ever become jaundiced, in keeping with the accepted incidence of anicteric hepatitis B in general. If jaundice does occur, it may be present initially; more frequently, it develops two to four weeks after the onset of arthritis. The symptoms usually abate with the onset of jaundice or respond quite well to salicylate therapy alone.

It has been observed that when the episode of arthritis is longer in duration, the picture can much resemble rheumatoid arthritis. On occasion, a tentative diagnosis of rheumatoid arthritis has been made until either clinical jaundice or significantly abnormal liver test results have made the correct diagnosis apparent. In each of two reported cases, a nodule histologically resembling a rheumatoid nodule developed; however, the nodule did not recur during follow-up in either case. Typically, the arthritis and rash resolve at about the time that jaundice develops; however, there can be appreciable overlap of these developments, as previously mentioned and as exemplified by Graves's case description. In addition, the patients almost always manifest the more nonspecific symptoms of early viral hepatitis such as malaise, sore throat, anorexia and nausea; but in one large series, it was most often the joint discomfort and rash that motivated the patients to seek medical attention.

There is nothing distinctive about the routine laboratory studies except for the abnormal results of liver enzyme tests. Using a radioimmunoassay technique, Duffy and colleagues found hepatitis B surface antigen (HB,Ag) in the serum of 26 of 29 patients with this syndrome; antibody to HB,Ag (anti-HB,Ag) was found alone in the other three. In none were both antigen and antibody found.

Three patients with hepatitis have been reported, in whom the typical syndrome of rash and polyarthritis was observed but hepatitis-associated antigen could not be found in either serum or synovial fluid. These findings suggested the possibility that the patients had hepatitis A with the typical rheumatic prodrome. However, the sera were sampled only in the icteric or post-icteric phase, when antigen titers are decreasing or may be negative by all but the most sensitive techniques. In other references to infectious hepatitis with arthritis, of pre-Australia-antigen vintage, the diagnosis was made on clinical grounds alone, or was made in cases not associated with injections or transfusions. Since we now know that there can be significant overlap in the incubation periods of hepatitis A and B and that the B virus is not infrequently transmitted by non-parenteral routes, claims for a similar rheumatic syndrome associated with hepatitis A remain unproven, although such a syndrome certainly is possible.

Routine synovial analysis is similarly nonspecific. In one series, leukocyte counts ranged from 465 to 90,000 per cu mm (mean, 24,000 per cu mm), with polymorphonuclear cells predominating in six and mononuclear cells in four. For another patient, there was good viscosity, and the leukocyte count was 7,150 per cu mm, with 75 percent polymorphonuclear cells. However, in another report of three patients, noninflammatory fluid was found (fewer than 2,000 leukocytes per cu mm), as it was in a patient of ours who was seen at the Los Angeles County/University of Southern California Medical Center. The synovial fluid complement levels, however, have almost uniformly been low when studied in the acute phase. Concomitant serum levels have also been low in most instances. An interesting inverse relationship between HB,Ag titers and complement component levels has been reported by Alpert and co-workers; in their group of 18 patients, none had detectable antibody to HB,Ag in the serum in the acute phase.

The low serum complement levels, the presence of HB,Ag and the lack of detectable antibody dur-
ing this syndrome are in keeping with the expected pattern of an acute illness that is very like serum sickness.\textsuperscript{10} Patients with viral hepatitis who do not have joint or skin symptoms do have normal or increased complement levels. This inverse correlation of antigen and complement suggests consumption of the latter by immune complexes containing HB,Ag; it also suggests that their deposition in synovium might be responsible for the articular symptoms. Earlier work had shown that HB,Ag does induce, in man, formation of an antibody that can form an immune complex and fix complement.\textsuperscript{15} Further evidence to support an immune complex pathogenesis for this syndrome includes the finding of HB,Ag by complement fixation techniques in serum and synovial fluid specimens simultaneously obtained in the acute phase,\textsuperscript{13} as well as cryoprecipitates containing immune complexes (that is, HB,Ag, IgG, IgM, IgA and complement components C3, C4 and C5). Interestingly, the cryoprecipitates from patients with hepatitis without arthritis contained only HB,Ag, IgG and IgM and were present in lesser concentration than in patients with hepatitis and arthritis.\textsuperscript{14} As antigen titers decreased and became undetectable during convalescence, free antibody became detectable in the serum.

Light microscopy examination of a synovial biopsy specimen from a patient with the acute hepatitis B arthritis syndrome showed areas of slight cellular proliferation, vascular congestion and occasional lymphocytes.\textsuperscript{2} Electron microscopy revealed 200- to 250-Angstrom round bodies with clear centers in the nuclei of some endothelial cells, and areas of endothelial cytoplasm were replaced by masses of similar particles. These particles are identical to those in liver nuclei of patients with acute hepatitis and have been shown to be the Australia antigen.\textsuperscript{19} This suggests that the antigen does reach the synovium, whether by direct invasion or through deposition as part of an immune complex. Duffy and co-workers,\textsuperscript{11} however, looked for HB,Ag in synovial fluid of three patients by electron microscopy and found none.

**Chronic Active Hepatitis**

Joint discomfort and occasional rash have long been mentioned in association with chronic active hepatitis, both with what had been termed lupoid hepatitis\textsuperscript{17,18} and in cases associated with chronic or recurrent hepatitis B antigenemia.\textsuperscript{20} In chronic active hepatitis, the joint complaints consist mainly of arthralgias of a fleeting nature and perhaps for this reason less investigation into the nature of this syndrome has been done. A recent report describes a case of asymmetrical polyarthritis with erythematous skin lesions in a patient with biopsy-proven, HB,Ag positive chronic active hepatitis.\textsuperscript{2} No anti-HB,Ag was found in the serum, as expected, and serum total hemolytic complement was very low. Examination of needle biopsy specimens of involved synovium revealed changes similar to those in the patients with acute hepatitis, including 200-Angstrom particles. Direct immunofluorescence for Australia antigen showed scattered fluorescence throughout the synovium.

A recent study has shed additional light on the possible immune complex pathogenesis of the arthritis associated with chronic active hepatitis B. In a group of ten patients with chronic active hepatitis, three had arthritis and three others had arthralgias while the remaining four had no joint symptoms.\textsuperscript{16} Eight of ten had HB,Ag in the serum and in none was anti-HB,Ag found. As in arthritis with acute hepatitis,\textsuperscript{14} cryoproteins consisting of IgM, IgG, IgA, C3, C4 and C5 were found during the arthritis phase of chronic active hepatitis in two patients, and HB,Ag was concentrated several-fold in the cryoprotein when compared with serum levels. Since there is convincing evidence that mixed cryoglobulins in the serum represent circulating immune complexes,\textsuperscript{21} these findings constitute further evidence pointing to an immune complex pathogenesis for these syndromes. Cryoprotein immune complexes were also found in the serum of three patients with chronic active hepatitis and arthralgias but differed in that only IgG and C5 were found, but no IgM, IgA, C3 or C4. Cryoprecipitable immune complexes were not found in patients with uncomplicated chronic active hepatitis. Antibody to HB,Ag was detected in the cryoprecipitate of one patient.

**Polyarteritis Nodosa**

The finding of the newly discovered Australia antigen in the serum of patients with a clinical and pathologic syndrome indistinguishable from polyarteritis nodosa (PAN) was described in two articles published in 1970.\textsuperscript{6,12} It was then suggested, and has subsequently been shown, that immune complexes containing HB,Ag are present in such patients.\textsuperscript{25-26} The incidence of HB, antigenemia in polyarteritis nodosa has varied depending on the criteria used for diagnosis and the
sensitivity of the technique used for detecting the antigen, but it seems to approach 40 percent.

As reported by Duffy and associates\textsuperscript{11} and by Sargent and co-workers,\textsuperscript{27} such patients present clinically with the variable multisystem involvement of skin, muscles, nervous system, lungs and kidneys typical of polyarteritis, but in addition they show evidence of liver disease. These two groups of researchers reported on 19 patients with a multisystem disease presenting as polyarteritis and HB\textsubscript{a} antigenemia. History of drug abuse, exposure to patients with hepatitis or transfusions were notable in some. Most had fever, anemia and leukocytosis. Only three of 19 were jaundiced, but liver test abnormalities were present at some time in 17 of 19. Fourteen had polyarteritis, in some cases resembling rheumatoid arthritis, or arthralgia. Renal disease was present in 14 and was manifested by nephrotic syndrome, lesser proteinuria and microscopic hematuria, hypertension and renal insufficiency. Examination of renal biopsy specimens showed variable degrees of membranoproliferative glomerulonephritis. The typical microaneurysms and small infarcts characteristic of PAN were shown by angiography. Seven of the patients manifested congestive heart failure and three had clinical signs of pericarditis. Additional abnormalities included necrotizing vasculitis with bowel infarction, peripheral neuropathy including mononeuritis multiplex, central nervous system involvement, lower leg ulcerations and nonthrombocytopenic purpura in a few.

Seven of the 19 patients died of multisystem or liver disease.

In the sera of 18, HB\textsubscript{a}Ag was detectable; anti-HB\textsubscript{a}Ag was detected in sera of three of ten.\textsuperscript{11} In many, the antigen was found repeatedly and in others only intermittently over several years. Seven of ten had rheumatoid factor activity in the sera, but none had antinuclear antibodies. Complement levels were low in 13 of 19. Examination of liver biopsy specimens from 16 patients showed a spectrum of changes, ranging from mild periportal infiltration, acute viral hepatitis and chronic persistent or active hepatitis to post-necrotic cirrhosis. In five patients, repeat liver biopsy or autopsy studies showed progression of the histological changes.

Analysis of synovial fluid from six patients\textsuperscript{11} showed inflammatory joint fluid with an average leukocyte count of 10,000 per cu mm, usually with a predominance of polymorphonuclear cells.

Unlike the situation in acute hepatitis and chronic active hepatitis as outlined previously, complement levels in the synovial fluid were normal. In several cases, HB\textsubscript{a}Ag was detectable in the synovial fluid.

Ample evidence to substantiate an immune complex pathogenesis for hepatitis B associated polyarteritis nodosa has been presented by several authors.\textsuperscript{6,23-26} Immune complexes were detected by various methods: deposition of IgG, IgM, C3 and HB\textsubscript{a}Ag in arterial walls;\textsuperscript{6} passive hemagglutination and density gradient centrifugation;\textsuperscript{23} presence of HB\textsubscript{a}Ag and anti-HB\textsubscript{a}Ag and demonstration of viral particle aggregates by electron microscopy\textsuperscript{11,24,25} and by Raji cell assay and the blocking of antibody-dependent cell-mediated cytoxicity (ADCC).\textsuperscript{26} Some authors suggest that changes in the titer of HB\textsubscript{a}Ag and anti-HB\textsubscript{a}Ag and quantity of complexes, measured by these techniques, correlate well with clinical activity of the disease.

**Essential Mixed Cryoglobulinemia**

Finally, and most recently, an association between what has heretofore been called "essential" mixed cryoglobulinemia and the HB\textsubscript{a}Ag has been reported.\textsuperscript{28,29} This syndrome was first reported in 1966\textsuperscript{6} and clinically presents with nonthrombocytopenic-dependent purpura upon exposure to cold, diffuse arthralgias, generalized weakness, hepatosplenomegaly, and occasionally neuropathy and gangrene. In about 50 percent of patients, kidney involvement leads to renal failure in a rather short time. Histologically, an immune complex vasculitis and glomerulonephritis are present, with evidence of IgG, IgM and complement deposition at the sites of tissue damage. The mixed cryoglobulins isolated from the blood in these patients also consist of IgG and IgM, and occasionally IgA and complement components. The IgM may be polyclonal or monoclonal and has rheumatoid factor (antiglobulin) activity. The renal disease, when present, is the usual cause of death.

Presence of cryoproteins has been reported in patients who have positive HB\textsubscript{a}Ag test results\textsuperscript{30} and in others who have the previously mentioned syndromes. However, in "essential" cryoglobulinemia the amount of cryoprotein present is usually greater (from 1 mg per ml up to 5 mg per ml), and symptoms are precipitated upon exposure to cold. Within the past year, Levo and co-workers\textsuperscript{39} have reported that 60 percent of
patients who previously would have been classified as having the “purpura arthralgia weakness syndrome” have been shown to have evidence of $\text{HB}_\text{infection.}$ Of the serum specimens from their patients, only 12 percent contained free $\text{HB}_\text{Ag}$, but 48 percent had free antibody. Examination of the cryoproteins themselves showed that 74 percent contained either antigen or antibody. Examination by electron microscopy of the cryoprecipitates showed structures resembling the Dane particle of hepatitis B virus. Furthermore, liver involvement in “essential” mixed cryoglobulinemia was clinically or biochemically shown to be present in 84 percent of their patients. Though only a few had overt liver disease, studies of biopsy specimens from a number of patients showed a varying spectrum from minimal change to chronic active hepatitis and cirrhosis. Thus, we now have evidence that in many patients, “essential” mixed cryoglobulinemia is not essential at all but represents yet another syndrome in the spectrum of manifestations of hepatitis B virus infection in man.

Conclusions

Table 1 summarizes some features of the several rheumatic syndromes described in association with hepatitis B virus infection. Why should infection with the same virus produce so varied a clinical response? The answer probably lies in the nature of the immune response of the host to the infection. If we assume that immune complexes do, in fact, mediate at least the rheumatic manifestations of these syndromes, perhaps the size and composition of the complexes formed (class of antibody present, antigen or antibody excess) determine the phenotypic presentation of a single event, that is, infection with hepatitis B virus. This is suggested by the frequent discovery of high titers of free antibody in mixed cryoglobulinemia whereas the free antigen is more often found in polyarteritis and chronic active hepatitis. The cause of polyarteritis and cryoglobulinemia in which no definite evidence of hepatitis B infection can be found remains unknown, but failure to identify it may reflect the insensitivity of our assays for hepatitis B markers. Alternatively other causes, including infection with other viruses, must be considered.

<table>
<thead>
<tr>
<th>Type of joint problem</th>
<th>Type of disorder</th>
<th>Free antibody to hepatitis B surface antigen</th>
<th>Leukocyte sediment</th>
<th>Serum complement</th>
<th>Cryoglobulins (HB, Ag, anti-HB, Ag, C, C2, C3, C4)</th>
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<tbody>
<tr>
<td>Active arthritis</td>
<td>Active arthritis</td>
<td>Present in 75 percent</td>
<td>Present in 50 percent</td>
<td>Not present</td>
<td>Low</td>
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**REFERENCES**

Addiction to Ophthalmic Corticosteroids

**DR. LAIBSON:** We must remember, if you can get away without using steroids in any patient with herpes who has never had steroids before, you are far better off to give that a try, because we make our patients with herpes (in many cases) steroid addicts, and they are patients whom you will be seeing for many years to come. So the message is, try to do without steroids if you can, but if you absolutely have to, then in the early stages I would use concomitant antiviral drugs.

**DR. THYGESON:** We have a dentist, now retired, in Berkeley, California, who was started on a regimen of steroids in 1956 at a second recurrence and he is still receiving steroids, one drop a day. So, he has never had a remission from 1956 to the present. I have 26 such cases in the San Francisco area.

—PETER R. LAIBSON, MD, Philadelphia
—PHILLIPS THYGESON, MD, San Francisco

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