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Rheumatologic Manifestations of Viral Hepatitis B and C

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Abstract

The clinical course of viral hepatitis can get complicated by a myriad of rheumatic symptoms which can alter the management strategies and have a profound potential to impair the quality of life of the patient. Rheumatic complications are often seen with hepatitis B (HBV) and hepatitis C (HCV) virus infections. The mechanism of these rheumatic complications seems to be immune mediated. Chronic HBV infection is linked to several extrahepatic syndromes like polyarteritis nodosa, serum sickness like syndrome, essential mixed cryoglobulinemia and varied arthritic manifestations. The clinical picture in HBV can range from mild arthralgias to severe systemic vasculitis with renal involvement which can seriously jeopardize the life of the patient. Prompt recognition and therapy with antivirals and immunosuppressive medication have led to a remarkable improvement in the prognosis of HBV associated PAN. HCV infection has an unusual propensity to trigger autoimmune disorders, especially with cutaneous manifestations. Mixed cryoglobulinemia syndrome (MCs) constitutes the prototype of HCV-associated autoimmune-lymphoproliferative disorders and is characterized by palpable purpura, arthralgias and fatigue. Widespread vasculitis and B-cell Non hodgkins lymphoma (NHL) may complicate a minority of cases and they constitute the most dreaded spectrum of the disease which carries a dismal prognosis. The management of these vasculitic complications is further complicated as interferon therapy used as an antiviral agent could potentially worsen this autoimmune process. The availability of directly acting antiviral agents (DAAs) now seems to increase the therapeutic armamentarium against HCV although further studies are needed to confirm their benefit in patients of HCV with rheumatologic complications.

Keywords: Rheumatological; hepatitis; viral; PAN; arthritis; sicca

Mini Review

Occurrence of rheumatologic symptoms in patients with viral hepatitis is well known. Joint pains constitutes one of the prime symptom of a viral 'prodrome'. Upto a third of patients suffering from clinically apparent hepatitis B note significant rheumatologic symptoms before the onset of jaundice. Though the occurrence of viral prodrome causing arthralgias (joint pain without inflammation) is fairly common amongst all hepatitic viruses, hepatitis B (HBV) and hepatitis C (HCV) virus infections are notorious to cause various other rheumatologic complications including arthritis (joint pain with inflammation), fatigue, vasculitis, fibromyalgia and sicca syndrome. The precise

mechanism of these wide array of rheumatologic manifestations remains unclear although immune mechanisms seems to play a pivotal role [1] **(Table 1).**

Hepatitis B virus associated rheumatologic manifestations

Serum sickness-like syndrome (prodrome)

A prodromal phase mimicking a serum sickness like syndrome occurs in around 10% to 30% of acute HBV infection and usually presents 1 to 6 weeks before the onset of clinical hepatitis. This symptom complex has been termed as 'arthritis-dermatitis' prodrome. It is characterized by arthritis or polyarthralgias along with joint swelling and edema. The arthritis is usually symmetrical and generalized and tends to involve the small joints of hands and feet. It might also present with a monoarticular and asymmetric pattern mainly involving the large joints such as knees and ankle. The arthritis is usually extremely painful and does not correlate well with the amount of joint swelling. Its clinical presentation can mimic rheumatoid arthritis however the joint involvement is typically 'non destructive' [2]. The joint symptoms can be closely associated with dermatologic manifestations like maculopapular, purpuric, petechial rash, palpable purpura, erythema multiforme, lichenoid dermatitis and toxic erythema. Immunologically, the arthritis-dermatitis prodrome is similar to acute serum sickness and involves HBsAg-anti-HBs immune complexes (ICs). Clinical symptoms begin to occur in the phase when there is a relative antigen excess and soluble ICs, but as the titres of antibody begin to increase in amount, ICs become less soluble and are thus readily cleared with subsequent decrease in symptoms. This syndrome can last from days to months with a mean duration of around 20 days and it usually resolves with the onset of clinical hepatitis without a subsequent recurrence [3].

Arthritis

After the acute prodromal phase the arthritis usually subsides but it may also persist intermittently or indefinitely. The resolution of arthritic symptoms paralleled HBsAg clearance. Joint involvement can also occur in the spectrum of chronic hepatitis B infection wherein it characteristically presents with erythematous skin lesions and an asymmetrical polyarthritis [2]. Synovial deposition of circulating ICs containing complement components, immunoglobulins and HBsAg-anti-HBs have been demonstrated in chronic HBV infection [4]. Wands et al. in their study found that in patients with arthritis and chronic HBV infection, presence of cryoprecipitates which contain IgG, IgM, IgA, C3, C4 and C5 were noted in the synovia of joints containing high concentrations of HbsAg whereas in patients with uncomplicated chronic HBV infection, these cryoprecipitates were not found [5]. The joint involvement is usually non destructive, thus there is rarely any radiographic evidence to assist with the diagnosis.

Essential mixed cryoglobulinemia (EMC)

EMC vasculitis was the nomenclature given for the idiopathic vasculitis caused by the deposition of cryoglobulins that contain polyclonal IgG and an IgM rheumatoid factor directed against the IgG, which are also labelled as mixed cryoglobulins. EMC is mainly linked to HCV infection although evidence of HBV in the cryoproteins of 74% of patients with EMC was demonstrated by investigators and 84% of these patients also had clinical and biochemical evidence of liver involvement [5]. This association was deemed controversial as the study by Popp et al. subsequently revealed that only 2 of their 12 patients with EMC had evidence of liver disease. Lunel et al. later reported a 15% incidence of EMC in 40 patients who are chronically infected with HBV [6]. The clinical syndrome of EMC is marked by a triad of purpura, recurrent arthritis and weakness which is eventually followed by pulmonary disease, glomerulonephritis and generalized vasculitis [2].

Polyarteritis nodosa (PAN)

PAN is a systemic vasculitis involving small or medium sized muscular arteries. It typically involves the visceral and renal vessels but spares the pulmonary circulation. HBV associated PAN is the typical form of classic PAN whose pathogenesis is ascribed to immune-complex deposition with antigen excess. It constitutes a rare complication of chronic HBV infection and is known to occur in only about 1- 5% of patients. On the other hand, HBsAg positivity is noted in 40% to 50% of patients with PAN [7]. The illness usually presents with abdominal pain, hypertension, eosinophilia, rash, polyarthralgias, polyarthritis and weight loss. It progresses to eventually involve the kidneys, skin, nervous system (central and peripheral) and gastrointestinal tract. The clinical spectrum of HBV-related PAN is identical to the typical PAN except for the following discrete exceptions: The gastrointestinal complications of beeding and perforation were seen in 46.3%, orchiepididymitis and renal infarction seen in 26% and malignant hypertension was noted in 29.6% patients. Serum antineutrophilic cytoplasmic antibodies (ANCA) are only occasionally detected in HBV-related PAN, unlike the typical PAN. (2) Fye et al reported that the disease activity is proportional

Table 1 Major Rheumatologic manifestations of Hepatitis B & C.

Hepatitis B	Hepatitis C
Arthritis	Arthritis
Serum sickness-like syndrome	Cryoglobulinemic vasculitis
Essential mixed cryoglobulinemia (EMC)	Sicca syndrome
Polyarteritis nodosa (PAN)	Miscellaneous : Osteosclerosis, Fibromyalgia, Behcets syndrome

to the circulating IC levels, strongly attributing circulating ICs in the pathophysiology of HBV-related PAN [8]. Other investigators have reported a low complement level during the active vasculitic phase, thus implicating complement components in the pathobiology of HBV associated PAN [9]. The prognosis of PAN related to chronic HBV infection is poor with 30% to 50% dying from the vasculitic complications if left untreated. Corticosteroids, immunosuppressive medications, and plasma exchange therapy are used to treat typical PAN but their usage is restricted in HBV associated PAN due to its deleterious effects on HBV replication and liver disease. The combination of antiviral therapy along with steroids and plasma exchange is found to be useful in treating HBV associated PAN. The antiviral agents studied include vidarabine, which was replaced by interferon-α2b, and later by lamivudine. A three pronged strategy to treat HBV associated PAN was studied in 10 patients with newly diagnosed, previously untreated HBV-PAN. Patients initially received prednisone (1 mg/kg/day) for a period of 1 week to decrease the organ damage caused by inflammation associated with systemic vasculitis. This dose was tapered gradually and completely withdrawn by the end of week 2. Patients subsequently received 100 mg of oral lamivudine daily for 5 consecutive months. Plasma exchanges began at this point of time to remove the immune complexes. 9 of 10 patients in whom this regimen was tested had complete clinical recovery with no relapse during follow-up. 6 of the 9 patients (66%) became seropositive for anti-HBV antibodies within 6 months after treatment [10]. With the availability of newer potent antivirals like entecavir and tenofovir, the therapeutic armamentarium against HBV associated PAN is expected to increase although large studies are needed to confirm this. Excellent response to the combination therapy of corticosteroids and entecavir have been demonstrated in isolated case reports [11].

Hepatitis C virus associated rheumatologic manifestations

After the discovery of hepatitis C virus (HCV) in 1989, some epidemiological studies have pointed out the possible role of HCV in the pathogenesis of mixed cryoglobulinemia syndrome (MCs). It now constitutes the prototype of HCV-related autoimmune-lymphoproliferative disorders. HCV is linked to a wide array of rheumatic and extrahepatic manifestations together termed as HCV syndrome **(Table 2).**

The pathobiology of various HCV related disorders is complex and is poorly understood. HCV related lymphotropism is primarily responsible for B-lymphocyte expansion which subsequently results in the generation of excessive quantity of immune complexes, mainly mixed cryoglobulins with rheumatoid factor activity, as well as a myriad of other autoantibodies [12].

Mixed cryoglobulinemia (cryoglobulinemic vasculitis)

The classic pathologic feature of MCs is a leukocytoclastic vasculitis of capillaries,venules and small arteries. The disease is grouped among the systemic vasculitides, in the scenario of a small-vessel vasculitides, and the terms cryoglobulinemic vasculitis and MCs should be related to the same clinico-pathological entity [13]. The disease is typified by the classical triad of arthralgias, weakness and purpura. It has a multisystem involvement as a consequence of the deposition of circulating immune complexes on the vessel wall. Renal involvement is mainly in the form of membranoproliferative glomerulonephritis type I. Skin ulcers and peripheral neuropathy also typify the disease and markedly impair the quality of life. Finally widespread vasculitis and non hodgkins lymphoma may complicate the clinical picture leading to a dismal outcome [14]. The treatment of HCV-related MCs is very complex and challenging in view of its clinical polymorphism and intriguing. Treatment is primarily aimed at three different levels 1) The chronic HCV infection 2) The immuno-pathologic alterations 3) The immune complex-mediated cryoglobulinemic vasculitis.

As chronic HCV infection is known to stimulate the immune system, HCV eradication using the new directly acting antivirals (DAAs) or interferon therapy with ribavirin should be attempted in all patients. Immunosuppressive and immunomodulating drugs form the cornerstone of therapy. They include drugs like cyclophosphamide and an anti-CD20 monoclonal antibody (rituximab). De Vita et al. studied the usefulness of rituximab in patients with cryoglobulinemic vasculitis and showed a better survival and disease control in patients who received rituximab versus those who did not [15]. Among pathogenetic/symptomatic treatments, a low antigen-content diet is presumed to accelerate the clearance of circulating immune complexes by reviving the activity of the overloaded reticulo-endothelial system. The functioning of the mononuclear phagocytic system may improve with a reduction in the alimentary influx of macromolecules with a potential antigenic activity.

Cryoglobulinemic skin ulcers are usually predominant in the lower limbs and are non healing and painful. They are often complicated by local infection and may potentially affect the quality of patients life. The therapeutic aim for treating cryoglobulinemic skin ulcers include both local and systemic treatments.

Sicca syndrome

Both experimental and epidemiological studies have depicted frequent relation between sicca syndrome and HCV infection. Chronic lymphocytic sialadenitis has been noted in patients with HCV infection and HCV is known to replicate in the epithelial cells of the salivary glands of patients with sicca syndrome [13]. Patients with MCs often develop a mild sicca syndrome in the paucity of typical serologic or histopathological changes. Detection of mixed cryoglobulins in few of the patients with primary sjogren syndrome seems to detect a particular subset of patients who are characterized by frequent evolution to malignant B-NHL and thus carry a worse prognosis. Topical therapy and antiviral treatment have been advocated for the treatment of this clinical complication associated with HCV.

Arthritis

Chronic arthritis is a less common feature associated with HCV. It is often a less aggressive oligo-polyarthritis. Patients presenting with both arthritis and HCV infection can either harbour a simple comorbidity of RA and HCV or have HCV-associated arthritis, with or without MCs. The first scenario can be treated with a standard treatment protocol for RA. Hepatitis C related involvement of liver

Table 2 HCV related rheumatic diseases in the setting of HCV syndrome.

		HIGH	MEDIUM	LOW
	RHEUMATIC DISEASE	Mixed cryoglobulinemia	Sicca syndrome Arthritis Osteosclerosis	Sjogrens syndrome Polyarteritis nodosa Poly/dermatomyositis
HCV Syndrome				
	OTHERS	Hepatitis HCC	B cell NHL Porphyria cutanea tarda Glomerulonephritis	Thyroid cancer

should be considered in choosing the therapy for RA. DMARDs, in particular Leflunomide and methotrexate, may be considered only after carefully evaluating and monitoring the liver functions. Usage of biologic therapy such as rituximab and anti-TNFα has been employed without potential side effects in patients with RA who have concomitant HCV infection. A rheumatoid-like symmetrical polyarthritis may often complicate IFN treatment in HCV-positive patients [16].

Osteosclerosis

It is an acquired, painful disorder of the skeletal system characterized by a marked increase of bone mass and is a very rare disease entity described in adults infected with HCV [17]. It is characterized by periosteal stretching which leads to diffuse bony pains. Radiographic survey shows thickening of the cortices of long bones and bony sclerosis. It has been postulated that HCV alone or in association with other unknown agents may infect and alter bone cells or their precursors. These alterations seem to occur by the generation of bone growth factors, such as osteoprotegerin andinsulin-like growth factor. Javier et al. reported a case of skeletal recovery following treatment of HCV with interferon and ribavirin based therapy further strengthening the relationship between viral infection and osteosclerosis [18].

Other HCV-related rheumatic diseases

Several case reports in literature also link HCV with poly-dermatomyositis, fibromyalgia, polyarteritis nodosa, behcets syndrome and antiphospholipid antibody syndrome though the data reported in the literature is scarce [19,20]. These patients need to be carefully evaluated as immunosuppressive medications used to treat these rheumatic conditions might alter the viral replication and worsen the clinical course of HCV.

Conclusion

Rheumatic manifestations occurring as a part of the clinical spectrum of viral hepatitis is more commonly seen with HBV and HCV. They add to the diagnostic dilemma with their myriad presentations complicating the course of the disease. Multisystem organ involvement and aggressive vasculitis can confer a dismal prognosis to these subset of patients. Timely diagnosis and prompt treatment of the viral infection and underlying vasculitis forms the best management strategy for this group of patients.

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