

Hepatitis C Virus Infection and Its Rheumatologic Implications

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Abstract: Extrahepatic manifestations are frequently encountered among patients with chronic hepatitis C virus (HCV) infection. Many of these manifestations are autoimmune disorders, with added mortality and morbidity due to involvement of multiple organ systems. Symptoms of HCV infection and rheumatic diseases may be similar and include arthralgia, myalgia, arthritis, and vasculitis. Also, serologic abnormalities may be found in both cases. Some treatment modalities for HCV infection, including interferon therapy, may aggravate the symptoms of rheumatic diseases, thus confounding clinical presentation. It is imperative to distinguish whether symptoms such as arthralgia, myalgia, and arthritis occur in patients with HCV infection due to primary chronic HCV infection or to a newly developed rheumatologic disease process.

Hepatitis C virus (HCV) was first identified and cloned in 1989.¹ The overall course of HCV infection is typically chronic, systemic, and asymptomatic.² It is stated that approximately 3 to 4 million persons are newly infected with HCV each year. The World Health Organization estimates that 3% of the world's population has chronic HCV infection.³ According to the US Centers for Disease Control and Prevention, approximately 2.7 million persons have chronic HCV infection. It has been reported that, every year, an estimated 30,000 new cases of infection occur in the United States, and the number of deaths annually due to HCV infection and HCV infection-related complications is nearly 10,000.⁴

The diagnosis of HCV infection is difficult because the course of the disease is asymptomatic. It is usually diagnosed incidentally by serologic screening or in relation to diagnosis of end-stage liver disease.⁵ HCV infection primarily affects the liver; however, extrahepatic manifestations are not rare. Because there are so many extrahepatic manifestations, diagnosis can be challenging. Rheumatologic extrahepatic manifestations are observed in 2% to 38% of HCV-infected patients. This variability is attributed to the geographic region and design of the studies from which these statistics come.⁶⁻⁸ Rheuma-

Keywords

Hepatitis C virus, rheumatologic implication, autoimmune disease

tologic extrahepatic symptoms include arthralgia (23%), paresthesia (17%), myalgia (15%), pruritus (15%), and sicca syndrome (11%).⁹ Knowing the extrahepatic manifestations of HCV infection is important in diagnosis and treatment of the disease.¹⁰

HCV has been known as a hepatotropic and also lymphotropic virus. This lymphotropism plays an important role in the pathogenesis of virus-related autoimmune diseases. Lymphotropism and chronic stimulation of the immune system by several viral proteins may be responsible for non-organ-specific autoantibody production, such as rheumatoid factor (RF) and cryoglobulins.^{11,12} Anticyclic citrullinated peptide (CCP) positivity is considered specific for a differential diagnosis of arthritis in patients infected with HCV and is more significant for rheumatoid arthritis (RA) than the other causes.¹³ Increased interleukin (IL)-6 levels are observed in rheumatoid and HCV-related arthritis, but the cause of this increase is not related to HCV viremia or elevated transaminase levels. Thus, increased IL-6 levels are considered to play the main role in both rheumatoid- and HCV-related arthritis.¹⁴

Cryoglobulinemia is the main HCV-related autoimmune entity, and the relationship between cryoglobulinemia and HCV infection is well identified. It has been observed that approximately 80% of patients with cryoglobulinemia are infected with HCV. Other rheumatic diseases, such as RA, systemic lupus erythematosus (SLE), Sjogren syndrome (SS), polyarteritis nodosa (PAN), sarcoidosis, antiphospholipid syndrome, and osteosclerosis, are observed in patients with HCV infection. The true causal relationship between these diseases and HCV has not been well established.¹⁵ RA, SLE, SS, and PAN comprise approximately 95% of the HCV infection-related autoimmune diseases.¹⁶

This review emphasizes the importance of identifying rheumatologic manifestations that may be identified during diagnosis, treatment, and follow-up of HCV-infected patients. Also presented are some data on whether rheumatologic diseases that occur during the follow-up of HCV-infected patients are actually associated with HCV or primary rheumatic disorders (Figure).

Hepatitis C Virus and Rheumatoid Arthritis

Arthralgia is a frequent symptom in HCV infection.¹⁷ The clinical presentation of joint involvement varies and includes monoarticular, oligoarticular, or polyarticular involvement.¹⁸ It is important to distinguish between HCV-related arthropathy and RA. Most of the drugs given to patients with RA are hepatotoxic. If HCV-related arthropathy and RA are successfully distinguished from each other, liver toxicity caused by the RA drugs may be avoided.¹⁹ A prospective study has shown that 20% of



Figure. The relationship between HCV infection and rheumatologic diseases.

HCV, hepatitis C virus; MC, mixed cryoglobulinemia; PAN, polyarteritis nodosa; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

patients infected with HCV suffer from arthralgia during a 1-year follow-up period.²⁰

How HCV infection triggers arthritis remains unclear. Three supported mechanisms may exist: direct invasion of the synovial tissue by the virus, autoimmune response to the virus in the synovium, and immune complex or cryoglobulin deposition.^{21,22} The virus may directly invade the synovium, or the cryoglobulin-induced immune complex in the synovial fluid may trigger local inflammation in the synovium.²³ Extrahepatic manifestations of HCV infection occur because HCV can replicate efficiently in extrahepatic tissues,^{24,25} although, in one study, samples from synovial fluid failed to distinguish HCV-related arthritis from RA.²⁶

HCV-related arthritis can present with signs and symptoms as well as joint involvement similar to RA. Thus, clinically, it may be almost impossible to distinguish HCV-related arthritis from RA.²⁷ RF positivity is approximately 70% to 80% in patients with RA, but in HCV-related arthritis, this positivity is between 54% and 82%.²⁸ RF is relatively nonspecific and may be present in several diseases.^{29,30} On the other hand, CCP antibodies are more specific for RA (96%-98%) and present in approximately 75% to 80% of patients with RA.^{31,32} However, recent studies have shown that anti-CCP antibodies are present in 4.5% to 7% of patients in whom HCV-related arthritis is diagnosed.^{28,33,34}

Many studies show that anti-CCP antibodies are a better diagnostic laboratory marker than RF for the diagnosis of RA in patients with HCV.³⁵ Anti-CCP antibodies are very specific for RA (96%-98%), and they are found in 60% to 75% of patients with RA.^{36,37} In addition, anti-CCP antibodies are more predictive of more aggressive and erosive RA.^{38,39} However, despite the high specificity of anti-CCP-positive antibodies for RA, few doctors argue for the use of these antibodies to differentiate HCV-related arthritis from RA.⁴⁰ In one study, anti-CCP

antibody was positive in 83% of patients with established RA and in 4.5% with HCV-related arthropathy.⁴¹

HCV-related arthritis can present with symmetric polyarthritis involving small joints similar to RA. However, it is less likely to lead to bone erosion or subcutaneous nodules.⁴² The assessment of synovial fluid or a synovial biopsy may not be useful for differentiation of the diseases.⁴³ History of blood transfusion, intravenous drug abuse, or hepatitis should lead to investigation of HCV infection in any patient presenting with polyarthritis, as it may be almost impossible to clinically distinguish HCV infection from RA.^{27,42}

The treatment of HCV-related arthritis is challenging. Interferon (IFN)- α treatment in patients with HCV-related arthritis may aggravate existing pain.⁴⁴⁻⁴⁶ General principles of management include treating the underlying HCV infection as well as using low-dose corticosteroids, nonsteroidal anti-inflammatory drugs, and hydroxychloroquine. Novel non-IFN-based antiviral therapies may eventually play a role in the future.

Hepatitis C Virus and Systemic Lupus Erythematosus

SLE is a common connective tissue disease, and its prevalence is estimated to be 15 to 200 per 100,000.^{47,48} Articular, mucocutaneous, renal, hematologic, central nervous system, liver, and lung involvement are well documented in this disease. The pathophysiology of SLE is multifactorial and includes environmental triggers, such as viral infections,⁴⁹ with HCV considered to be among the suspected viruses.⁵⁰ HCV infection and SLE may share common clinical and serologic features. The extrahepatic manifestations of HCV may mimic SLE, with associated symptoms such as arthralgia, myalgia, sicca syndrome, and antinuclear antibody (ANA) positivity.^{51,52} One study has shown that the prevalence of HCV infection in patients with SLE was greater than that of the general population.⁵³ In another study, the prevalence of HCV among patients evaluated for SLE was found to be 10%.⁵⁴ In a study from Egypt, the frequency of HCV infection among patients in a rheumatologic clinic was found to be 18.5%. Only 7% had clinical symptoms of HCV infection.⁵⁵

Known serologic abnormalities may occur in HCV infection. ANA positivity has been reported to be between 10% and 30%,^{56,57} and HCV infection is associated with cryoglobulinemia.⁵⁸ All except one study have shown that HCV antibody positivity is observed more frequently in patients with SLE than in patients with HCV infection.^{59,60} Hence, low-titer ANA, double-stranded DNA (dsDNA) positivity, fewer cutaneous features, liver damage, and cryoglobulinemia should alert physicians to carry out HCV screening in patients with SLE. It also has been

emphasized that HCV screening should be conducted before confirming the diagnosis of SLE.⁶¹⁻⁶³

There is evidence that IFN use in the treatment of HCV infection can trigger autoimmune disorders, including SLE.⁶⁴ The frequency of autoimmune diseases in patients receiving IFN is between 4.3% and 18.5%.⁶⁴ Twenty-six IFN-induced SLE cases were reported between 1990 and 2010.^{65,66} The period between the beginning of IFN treatment and the occurrence of SLE symptoms varied from 2 months to 7 years.^{65,66} The symptoms in IFN-induced SLE regressed approximately 1 week after the discontinuation of IFN treatment.⁶⁷ Hence, patients receiving IFN treatment should be monitored for the development of autoimmune diseases, including SLE.⁶⁸

In summary, extrahepatic manifestations of HCV infection may mimic features that resemble SLE. Further testing of anti-Smith antibody, anti-dsDNA, and antinucleosome antibodies may help clinicians establish the diagnosis of SLE. Although the association between HCV and SLE is still uncertain, it has been suggested that HCV may play a role in triggering SLE.

Hepatitis C Virus and Mixed Cryoglobulinemia

Mixed cryoglobulinemic vasculitis (MCV) is known to be the most frequently encountered extrahepatic disease that HCV infection can trigger.^{69,70} MCV is immune complex-mediated vasculitis that affects small vessels due to the presence of cryoglobulins.^{71,72} Cryoglobulins are immunoglobulins (Igs) that are insoluble below 37°C and soluble after warming.⁷³ Cryoprecipitation was first described among patients with multiple myeloma in 1933 by 2 hematologists, Wintrobe and Buell from Johns Hopkins University. The term “cryoglobulin” was first used by Lerner and Watson in 1947.⁷⁴ The clinical triad of MCV, including purpura, arthralgia, and weakness, was initially described by Meltzer and colleagues in 1966.⁷⁵

According to the Brouet classification, cryoglobulins may be grouped into 3 types. Type 1 cryoglobulinemia includes isolated monoclonal Ig (IgM) and may account for 10% to 15% of cryoglobulinemia. It is usually associated with lymphoproliferative disorders. The IgG and IgA subtypes exist but are rare.⁷⁶ Type 2 cryoglobulinemia presents with IgM and polyclonal IgG and is mostly encountered in viral infections and inflammatory disorders.^{77,78} HCV can potentially induce type 2 cryoglobulinemia in 50% to 60% of cases. Type 3 cryoglobulinemia may present without monoclonal proliferation. Immune complexes are typically formed by polyclonal IgM. Some doctors believe that type 3 cryoglobulinemia may be a transition form between type 1 and type 2.⁷⁹

The underlying mechanism of HCV-induced MCV may be related to B-cell proliferation, which in turn

stimulates CD 5+ cells that are responsible for producing IgM RF. Studies have also shown that HCV may exert an inhibitory response to B-cell apoptosis via activity of B-lymphocyte activating factor.^{69,70}

In some studies, it was observed that anti-HCV and HCV RNA tests were positive in 40% to 90% of patients with mixed cryoglobulinemia (MC).^{58,80,81} However, studies also showed that the frequency of MC in patients with chronic HCV infection was 10% to 15%.⁷⁸ MCV clinically presents as cutaneous purpura, arthralgia, and weakness. Involvement of many other organ systems is also reported.⁸² Palpable purpura, supramalleolar ulcers, or Raynaud phenomenon in the lower limbs of patients with chronic HCV infection should make physicians think about the presence of MC. Besides symmetrical arthralgia in the hands and knees, involvement with the kidneys, liver, and nervous system can also contribute to the diagnosis. Approximately 70% of patients with HCV infection-related MCV have liver involvement and histopathologic finding of active hepatitis.^{83,84} Complement activation is possibly responsible for endothelial damage in HCV infection-related MCV.⁸⁵

The main aim of treatment is to eradicate the HCV infection. Serum HCV RNA induces complement activation and, therefore, increases the complement levels. Hence, treatment of HCV infection is important to decrease the circulating complements. The decrease in cryoglobulins and B-cell proliferation in the circulation is also important.

IFN- α and ribavirin remain the cornerstones of therapy for MC type 2.⁸⁶ Rituximab (Rituxan, Genentech/Biogen Idec) therapy with or without corticosteroids and plasma exchange may be beneficial therapeutic modalities in the treatment of MC, as it causes B-cell depletion.⁸⁷ The current standard treatment with triple therapy, including protease inhibitors plus pegylated IFN plus ribavirin, and potential non-IFN-based HCV treatment regimens have yet to be defined.

Hepatitis C Virus and Sjogren Syndrome

Several studies suggest a close correlation between SS and HCV infection. However, the role of HCV infection in the pathogenesis of SS is still unclear.^{88,89} It is unknown whether HCV infection mimics SS or if HCV has a direct role in the etiopathogenesis of SS. Various outcomes were observed in studies related to the prevalence of HCV infection in patients with SS. These outcomes varied according to study and regional differences. The coprevalence of HCV and SS was reported to be 49% in one study⁹⁰ and 80% in another.⁹¹ In a European study, anti-HCV antibody in patients with primary SS varied between 2% and 26%.⁹²

According to the American and European Consensus Study Group, HCV must be ruled out to diagnose pri-

mary SS. It is important to differentiate primary SS from HCV infection-related SS (HCV-SS).⁹³ Male dominance, older age, and anti-Ro/La negativity more commonly suggest HCV-SS.⁹⁴ The variability of liver function tests and the risk of malignancy development are higher in patients with primary SS than in patients with HCV-SS. Immunologically, ANA positivity in patients with HCV-SS is about 70%.⁹⁵ Anti-Ro/La negativity may support the diagnosis of HCV-SS. However, in one study, some subgroups of patients with HCV-SS and Ro/La positivity were observed.⁹⁴ Almost half of patients with HCV-SS test positive for cryoglobulins. Cryoglobulinemia may predict future extraglandular manifestations. After the diagnosis of cryoglobulinemia, an increase in the risk of development of hypocomplementemia, liver involvement, and neoplasia is observed.^{95,96} In addition to cryoglobulinemia, hypocomplementemia and RF are important markers for the diagnosis of HCV-SS.

Hepatitis C Virus and Polyarteritis Nodosa

PAN is a systemic and necrotizing vasculitis of medium and small-sized arteries. This condition, which was previously shown to be associated with hepatitis B virus infection, may also be associated with HCV infection.^{97,98} The risk of development of HCV-related PAN may be 5% to 12% in chronic HCV infection.⁹⁹ In a study of 161 patients with chronic HCV infection and HCV-related vasculitis, 31 (19.3%) patients were given a diagnosis of PAN. Compared with HCV-associated MCV, HCV-related PAN was associated with more severe symptoms. However, it was also observed that HCV-related PAN was associated with a higher rate of clinical remission.¹⁰⁰

Hypocomplementemia is an important marker for the diagnosis of HCV-related PAN. Moreover, cutaneous manifestations (especially purpura) are observed more frequently, and C-reactive protein and the erythrocyte sedimentation rate are higher in HCV-related PAN.¹⁰¹ The finding of motor mononeuropathy on clinical examination, which is present in almost 90% of patients, may be more useful.¹⁰² Symptoms such as cerebral vasculitis, severe hypertension, and ischemic abdominal pain also may be observed in patients with HCV-related PAN.

Antiviral therapies and corticosteroids are the cornerstone treatments for HCV-related PAN. Some specialists also suggest plasma exchange, cyclophosphamide, and rituximab in resistant cases.¹⁰³

Hepatitis C Virus and Sarcoidosis

Sarcoidosis is a systemic inflammatory disease characterized by the formation of noncaseating epithelioid cell granulomas in the organs. The etiology of the disease is still not well understood.¹⁰⁴

The relationship between chronic HCV infection and sarcoidosis was first described in 1993.¹⁰⁴ This relationship can be IFN-related or completely unrelated to IFN treatment. IFN-related sarcoidosis is rare but well defined in the literature. Studies have shown that the incidence of sarcoidosis may vary between 0.09% and 0.2% in HCV-infected patients undergoing IFN treatment. The incidence rate seems low, but it is higher than the rate seen in the general population.^{105,106}

Symptoms of sarcoidosis develop in almost two-thirds of patients during the first 6 months of IFN treatment.¹⁰⁵ However, data also demonstrate that the disease may occur toward the end of treatment. IFN-related sarcoidosis presents mostly with lung and cutaneous findings. Thus, HCV-infected patients treated with IFN therapy should be carefully evaluated for development of sarcoidosis.¹⁰⁶ Although rare, non-IFN-related sarcoidosis has been reported in chronic HCV infection. IFN-related sarcoidosis clinically progresses in a benign fashion. Patients with mild symptoms may continue with IFN treatment. However, IFN treatment should be stopped in patients whose symptoms do not regress. In such cases, corticosteroids and hydroxychloroquine can be considered as possible treatment options.¹⁰⁵⁻¹⁰⁷

Conclusion

Extrahepatic manifestations are frequently encountered among patients with chronic HCV infection. Several of these manifestations can mimic autoimmune disorders. Moreover, primary autoimmune disorders can coexist with HCV infection. They cause mortality and morbidity by affecting multiple organ systems. Arthralgia, myalgia, sicca symptoms, and vasculitis are some clinically common syndromes. Serologic abnormalities such as ANA and RF positivity are common in both HCV infection and primary autoimmune disorders. Some treatment modalities for HCV infection, such as IFN, can induce or aggravate the symptoms of rheumatologic diseases. In patients with HCV infection, it is critical to distinguish whether these syndromes occur secondary to chronic HCV infection or a primary rheumatologic disease, as this differentiation is critical in tailoring appropriate therapeutic management.

The authors have no relevant conflicts of interest to disclose.

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