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Hepatitis C-related arthropathy: Diagnostic and treatment considerations

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Abstract

Hepatitis C-related arthropathy is one of the most common extrahepatic manifestations of hepatitis C virus (HCV) infection. Although symptoms can be disabling, the prognosis typically is benign. Patients who have atypical chronic inflammatory arthritis with an unknown cause should be evaluated for HCV infection. Testing for antibodies against cyclic citrullinated peptide is useful for distinguishing HCV-related arthropathy from rheumatoid arthritis. Early recognition of HCV infection greatly influences the selection of drug therapy. Although no clinical guidelines are available, many liver disease specialists favor using a stepwise approach to treatment. Future research efforts that focus on the pathogenesis of HCV-related arthropathy and novel therapeutic approaches are needed. (J Musculoskel Med. 2010;27:351-354)

Hepatitis C virus (HCV) infection is the most common known blood-borne infection in the United States and a major cause of chronic liver disease.[1] About 4 million Americans have been exposed to HCV, according to data from the third National Health and Nutrition Examination Survey, and an updated analysis suggests that the true number of infected persons may exceed 5 million.[2] The prevalence is highest in persons aged 30 to 49 years; the disease is overrepresented in men and in African Americans.[3] The infection is chronic in about 80% of patients, and the rate of progression to end-stage liver disease (ESLD) averages 10% to 20% over 20 years.[4]

ESLD is a significant cause of morbidity, resulting in at least 8000 to 10,000 deaths in the United States annually. In addition, it is the leading indication for liver transplant in the United States. Markov modeling of a multicohort HCV-infected population in the United States projected an increase in liver-related morbidity and mortality, especially in persons older than 60 years.[5] Therefore, a better understanding of the natural history and available treatment options for chronic HCV infection and its extrahepatic manifestations is imperative.

Although the liver is the primary site of HCV infection, involvement of other sites—such as the musculoskeletal system—has attracted increasing interest. Extrahepatic manifestations typically are not life-threatening, but they contribute significantly to long-term morbidity in patients with HCV infection.

For this article, the authors have updated their discussion of hepatitis C-related arthropathy that first appeared in 2006 in The Journal of Musculoskeletal Medicine.

In a large prospective study of 1612 patients with chronic HCV infection, the MULTIVIRC group reported a 74% prevalence of extrahepatic manifestations.[6] Arthralgia and arthritis were the most common clinical manifestations in these patients; others included paresthesia, myalgia, pruritus, and sicca syndrome.

The exact mechanism by which HCV infection triggers arthritis has not been determined, but it is thought to be a local inflammatory response to synovial tissue damage caused directly by viral invasion or indirectly by deposition of cryoglobulin-induced immune complexes in synovial fluid. Early recognition of HCV infection and its associated extrahepatic manifestations greatly influences the timing and selection of drug therapy (Figure). In this article, we describe the diagnostic evaluation of patients who have HCV-related arthropathy and approaches to treatment.

Diagnosis

The presence of HCV in a patient with arthritis should generate strong suspicion of HCV-related arthropathy. Serological studies to detect HCV antibodies and molecular tests to quantify HCV RNA are the mainstays of diagnosis. The most frequently used tests are the third-generation enzyme immunoassays that detect antibodies to various HCV proteins. An abnormal antibody test result requires confirmation of viremia (HCV RNA) with molecular tests. Early detection and management of HCV infection may reduce disease transmission.

Identifying HCV genotype is not required for diagnosis, but it is useful for predicting response to interferon-based therapy and for determining the duration of therapy. To date, 6 genotypes have been identified, and more than 70% of HCV infections in the United States are caused by genotype 1.[7] Of note, neither the genotype nor the level of HCV viremia correlates with disease severity or prognosis.

Up to 30% of patients who have chronic HCV infection have normal liver enzyme levels; therefore, a normal test result does not rule out the diagnosis. In addition, elevated liver enzyme levels do not correlate with the severity of liver disease. The gold standard for assessing the severity of liver disease in patients with HCV infection is liver biopsy. However, liver biopsy is not required for the diagnosis. Although arthropathies are the most common extrahepatic manifestations of HCV infection, liver disease severity does not correlate with their presence or absence.

No radiological features distinguish HCV-related arthritis from arthritis caused by other disorders. However, an important clinical characteristic of HCV-related arthropathy is the lack of bone erosions on imaging; therefore, imaging is essential in the diagnostic workup to evaluate for other causes of arthritis. Neither synovial fluid analysis nor synovial tissue biopsy has been useful in the diagnosis of HCV-related arthropathy; ultimately, this is a diagnosis of exclusion.

Clinical presentation

The most frequently reported symptoms in chronic HCV infection are generalized fatigue, weakness, right upper quadrant abdominal pain, and arthralgia. Patients who have HCV-related arthropathy present with symptoms that range from mild arthralgia to debilitating arthritis.

The vast majority of patients who have HCV-related arthropathy are accounted for by 2 clinical subsets: rheumatoid-like arthritis and cryoglobulin-related arthritis.[8] The former sometimes is confused with true rheumatoid arthritis (RA) because some of the signs and symptoms are identical. Both subsets are characterized by a chronic inflammatory

polyarthritis, but in HCV-infected patients, the polyarthritis is symmetrical, may be nondeforming, and primarily involves the small joints. A significant proportion of patients with this form of polyarthritis fulfill the American College of Rheumatology (ACR) criteria for RA, and the majority test positive for rheumatoid factor (RF). Therefore, because of the high prevalence of positive RF in patients with HCV-related arthropathy, this test cannot be used reliably to distinguish this condition from classic RA.

Differentiating HCV-related arthropathies from classic RA is essential. In contrast to patients who have RA, those with HCV-related arthropathies experience minimal morning stiffness and do not exhibit rheumatoid nodules or radiological features of erosive arthritis. Serological tests used to detect antibodies against cyclic citrullinated peptide (anti-CCP) may be useful in determining a true coexistence of RA and HCV infection, because these antibodies are positive only in patients with RA. [9,10] Because the initial presentations of RA and HCV-related arthropathy can be identical, it is recommended that all patients with a clinical presentation of symmetrical arthritis be tested for HCV antibody and anti-CCP. The diagnostic role of other serological tests, such as antikeratin antibody, is yet to be determined.

Cryoglobulin-related arthritis occurs in 10% to 30% of patients with HCV-related arthritis.[8] It is a monarticular or oligoarticular, nondeforming condition that usually involves medium or large joints; its course is intermittent and benign. Typically, cryoglobulin-related arthritis occurs in older patients who have a long history of chronic HCV infection.

Treatment

Symptomatic treatment

In patients with very mild arthritis, conservative management using analgesics with anti-inflammatory activity (eg, NSAIDs) is recommended to reduce joint pain and swelling. Although there have been a few reports of hepatotoxicity with long-term use of NSAIDs, these drugs can be used safely in patients with mild to moderate chronic HCV infection (ie, noncirrhotic).[11] To date, no randomized controlled studies have shown increased liver-related adverse effects with use of NSAIDs in this population.

In clinical practice, these drugs are used routinely in patients with HCV infection during interferon-based therapy. However, in patients with advanced liver disease, such as cirrhosis, the use of NSAIDs is somewhat contraindicated because of their nephrotoxic effect as well as the risk of GI bleeding from esophageal and gastric varices.

In patients who are unresponsive to NSAIDs and in those who have contraindications to their use, short-term, low-dose prednisone (5 to 10 mg/d) is an option. Although high doses of corticosteroids have been shown to increase viral replication, leading to a transient rise in HCV viral load, the use of short-term, low-dose prednisone has a minimal impact on HCV viral replication and is not an absolute contraindication in patients who have HCV infection.[12]

HCV infection with concomitant RA

Use of disease-modifying antirheumatic drugs (DMARDs) is indicated in patients who have HCV infection and concomitant RA. Most experts recommend a stepwise approach, starting with nonbiologic DMARDs, with an option to use biologic DMARDs in those who are nonresponsive to nonbiologics.

Methotrexate (MTX) is the nonbiologic DMARD that rheumatologists most often use, but concerns about its potential hepatotoxicity have limited its use in patients with underlying

HCV infection. Because of the hepatotoxic effects of MTX, other nonbiologic DMARDs, such as hydroxychloroquine (HCQ) and sulfasalazine (SSZ), have been used as alternatives.

ACR guidelines published in 2008 provided recommendations pertaining to the use of DMARDs that are based on the severity of liver disease using the Child-Pugh-Turcotte (CPT) classification.[13] The CPT score (A to C) is used to assess severity and prognosis of cirrhosis; Child A patients have the best prognosis. According to the ACR guidelines, in the setting of chronic HCV infection, (1) MTX is contraindicated in all patients in CPT class A, B, or C; (2) SSZ is contraindicated in patients in CPT class B or C; and (3) HCQ is contraindicated in those in CPT class C.

These recommendations emphasize the importance of assessing the severity of liver disease before using nonbiologic DMARDs in patients with HCV infection. The anti–tumor necrosis factor inhibitors are the biologic DMARDs most frequently used in patients with RA. Although several studies have reported safe and effective use of biologic agents in this population, their exact role in patients with RA and concomitant chronic HCV infection is unclear. Further studies are required before these drugs can be recommended in this population.

HCV infection with cryoglobulinemia

Unlike for patients with concomitant RA, DMARDs are not an essential part of the therapeutic options, because of the lack of the classic findings of bony erosions that characteristically are found in RA. For patients with mild to moderate cryoglobulinemia, treatment with antiviral therapy alone is recommended, provided there are no contraindications. For patients with severe cryoglobulinemia, such as severe debilitating disease or systemic involvement (glomerulonephritis and neuropathy), a combination of immunosuppressive and antiviral therapy is preferred.

The current standard antiviral treatment for patients with chronic HCV infection is the combination of pegylated interferon and ribavirin. Interferon has both antiviral and immunomodulatory effects, and it has been beneficial in the management of chronic HCV infection. Interferon therapy is contraindicated in patients who are actively involved in substance or alcohol abuse; have severe depression or neuropsychiatric syndromes, autoimmune disorders, or decompensated cirrhosis; or are pregnant.

The goal of antiviral therapy is to control joint inflammation, eradicate the virus, and achieve a sustained virological response (defined as the absence of HCV RNA 6 months after completion of treatment). A sustained virological response is achieved in 40% to 50% of patients with genotype 1 and about 70% to 80% of patients with genotypes 2 and 3.[14]

Several studies have found a strong correlation between clinical improvement in arthropathy and the disappearance of HCV RNA and cryoglobulins in the serum. In these patients, reduction in HCV RNA levels typically precedes cryoglobulin decline.

Of note, symptoms often reappear in these patients after therapy is withdrawn. Clinical relapse usually is associated with recurrence of HCV viremia and may require long-term therapy for complete remission.

For patients with severe disease, the combination of antiviral therapy (pegylated interferon and ribavirin) and rituximab (an anti-CD20 monoclonal antibody that depletes B cells) is preferred. The rationale for using rituximab is based on the findings that HCV directly activates polyclonal B cells, resulting in clonal expansion. Therefore, depletion or suppression of B cells results in a reduction of cryoglobulin formation.

In the largest study that used this combination, rituximab, 375 mg/m^2, was given weekly for 4 weeks, followed by antiviral therapy.[15] The addition of rituximab to conventional antiviral therapy led to a shorter time to clinical remission and a higher rate of complete response and cryoglobulin clearance. Furthermore, the addition of rituximab was well tolerated.

The available therapeutic options for patients with HCV-related arthropathy have evolved over the years. In spite of advances, there are no consensus treatment guidelines to address the clinical spectrum of this condition. Therefore, management of HCV-related arthropathy should be individualized. Future research efforts that focus on the pathogenesis of HCV-related arthropathy are needed, along with novel therapeutic approaches that are safe in patients with liver disease.

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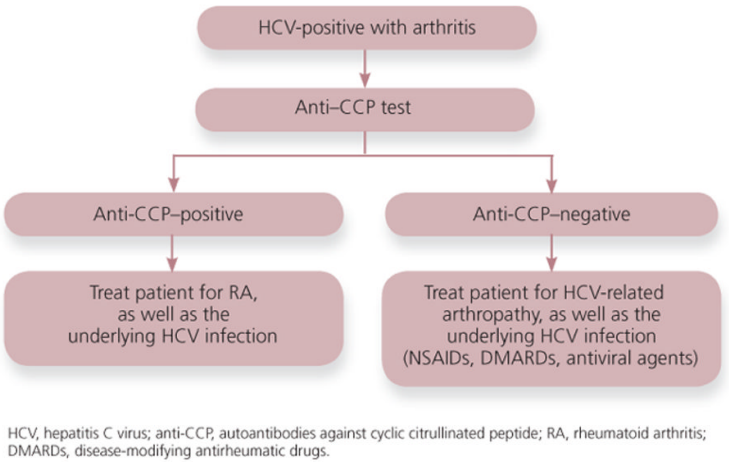

HCV, hepatitis C virus; anti-CCP, autoantibodies against cyclic citrullinated peptide; RA, rheumatoid arthritis; DMARDs, disease-modifying antirheumatic drugs.

Figure.
An algorithm for treatment of patients with hepatitis C-related arthropathy