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Editorial

Extrahepatic autoimmune manifestations of chronic hepatitis C virus infection

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The hepatitis C virus infection (HCV) is currently a worldwide health problem. The chronic infection may progress to cirrhosis with the subsequent development of complications including ascities, encephalopathy, upper gastrointestinal tract bleeding and hepatocellular carcinoma.¹ The HCV is a linear, single-stranded RNA virus of the *Flaviviridae* family that was identified in 1989 by Choo et al.² 6 genotypes are currently recognized, being type 1 (75%), type 2 (approximately 10%), and type 3 (approximately 10%) the most frequently found in the United States.³ Based on previous reports, the HCV prevalence is around 3%, which corresponds roughly to 170 million infected people around the globe.⁴ In México the prevalence in blood donors is around 0.47% to 1.2%^{5,6} although a recent work from Benitez-Arvizu et al⁷ found a prevalence of 0.195% (10/5105), which is significantly lower than the estimated prevalence. Recent data indicate that in México HCV infection is now one of the two leading causes of liver cirrhosis.⁸ Vera de León et al⁹ reported to our knowledge the biggest epidemiological study conducted in Mexican population, they found that the highest incidence was on the fifth and sixth decade of life (28.5% and 26.7%, respectively), and that genotype 1 was the predominant type (72.2%). In the other hand type 2 and type 3 were the second and third most common (18% and 9.8% respectively).

The HCV is associated with multiple extrahepatic manifestations that occur in one third of patients with chronic infection and generally present in late stages of the disease;¹⁰ among these nonhepatic conditions that are now described to be associated with HCV infection include pulmonary fibrosis, cutaneous vasculitis, glomerulonephritis, porphyria cutanea tarda, hemocytopenias, lymphoproliferative syndromes and lichen planus.^{11,12}

The most important extrahepatic autoimmune manifestations include Sjögren's syndrome (SS), rheumatoid arthritis (RA), antiphospholipid syndrome (APS), and systemic lupus erythematosus (SLE).¹³ Thus, the purpose of this paper is to give an overview of the proposed extrahepatic autoimmune manifestations of chronic HCV infection.

Sjögren's syndrome

The first study linking the chronic HCV infection to SS was published by Haddad et al,¹⁴ they analyzed the association between lymphocytic sialadenitis of SS and HCV infection. In the chronic HCV infection the immunological characteristics have been associated with antibodies in 20%-40% of patients, of which are mostly antinuclear antibodies (ANA) and rheumatoid factor (RF).¹⁵ The main difference between primary SS and HCV-associated SS is the immunological pattern, with cryoglobulinemic predominance (mixed cryoglobulins, RF, hypocomplementemia) in the HCV-associated over specific primary SS serum markers such as anti-Ro/SS-A and anti-La/SS-B.¹⁶

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In patients with SS and HCV, viral RNA has been detected, and the findings have been discrepant in terms of prevalence; this can be due to the variability of serum titers among patients, and this may be related to the specific genotype involved.¹⁷

In the year 2002, the clinical differences between primary SS and HCV-related were described; among the most significant differences described include a decrease frequency of parotid gland inflammation, and an increase frequency of cryoglobulinemia, hypocomplementemia and hepatic involvement,¹⁵ although it has been described that HCV infection may mimic most of the clinical, histological, and immunological characteristics of SS.¹⁸

An important difference between primary SS and HCV-associated SS is the pathological appearance, in which HCV-associated SS is characterized by lymphocytic capillaritis of the glands, perhaps provoked by the virus itself that leads to atrophy of the glands. Nevertheless, there is nil inflammation of the gland's ducts which is one of the hallmarks of primary SS.¹⁹

Systemic lupus erythematosus

SLE is one of the most diverse autoimmune connective tissue diseases in terms of its serological and clinical characteristics. The chronic HCV infection may induce serologic and clinical characteristics that may mimic SLE, for instance, it has been described that the virus may induce arthritis, neuropathy, cytopenias, ANAs, and even anti-dsDNA. Actually the prevalence of chronic HCV infection is greater in SLE patients than in blood donors of the same geographical area.²⁰

The patients with HCV-associated SLE demonstrate a decreased frequency of cutaneous involvement and anti-dsDNA, and an increased prevalence of hepatic involvement, hypocomplementemia, and cryoglobulinemia. Thus, it is recommended that patients without typical cutaneous manifestations, low antibody titers and hepatic involvement should be tested for possible HCV infection.²⁰

Antiphospholipid syndrome

The association between APS and HCV infection is still controversial. In the year 2000 Stoeger et al²¹ analyzed 48 patients with chronic HCV infection, and they reported that patients with HCV infection had an increased prevalence of anticardiolipin IgG antibodies.

In a recent study of 45 cases with HCV infection, Ramos-Casals et al²² described that the most frequent clinical manifestations of HCV-associated APS were intraabdominal thrombosis and myocardial infarction. But the association of APS with HCV infection needs to be more described, and currently there are a couple of studies on that matter.

Rheumatoid arthritis

Rosner et al,²³ reviewed the prevalence and clinical characteristics of arthritis related to HCV infection. The most frequent clinical presentation was a chronic inflammatory polyarthritis, that may fulfill the American College of Rheumatology (ACR) classification criteria for RA in 50% of cases. Therefore Bombardieri et al²⁴ made an important discovery, they found that anti-CCP (anti-cyclic citrullinated peptide) was positive in 76% of patients with RA, 60% in patients with HCV and RA coexistence, and there were negative in all patients with HCV independently of their joint involvement. This suggests that the anti-CCP antibodies may be useful in differentiate patients with true RA and those with HCV-associated RA.

Conclusion

Since chronic HCV infection is one of the main causes of liver cirrhosis worldwide it is important to know the most common extrahepatic manifestations; of these manifestations, autoimmune are of special interest because it is generally difficult to differentiate true autoimmunity from mimicked autoimmunity on a clinical basis. For years now, HCV has been involved in the development of lymphoid tissue, cryoglobulinemia and autoimmunity-like diseases. Therefore, the more deep understanding of the HCV role in the development and mimicking of autoimmunity makes this an important field for basic and clinical research, thus it is crucial for us to differentiate true autoimmunity from HCV induced or mimicked disease because of the importance of early treatment of both conditions.

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