Reumatol Clin. 2009;**5(2)**:71-75

Reumatología Clínica

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Review

Extrahepatic manifestations in patients with chronic infections due to the hepatitis C virus

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ARTICLE INFO

Article history:
Received March 28, 2008
Accepted May 15, 2008

Keywords:
Hepatitis C virus
Systemic autoimmune disease
Cryoglobulinemia

ABSTRACT

Autoimmunity and viral infections are closely related, and viruses have been proposed as possible etiologic or triggering agents of systemic autoimmune diseases (SAD). The hepatitis C virus (HCV), a linear, single-stranded RNA virus, identified in 1989, is recognized as one of the viruses most often associated with autoimmune features. The association between HCV and SAD has generated growing interest in recent years. The extrahepatic manifestations often observed in patients with chronic HCV infection (both clinical and immunological) may lead to the fulfillment of the current classification criteria for some SAD.

Manifestaciones extrahepáticas en pacientes con infección crónica por el virus de la hepatitis C

Palabras clave:
Virus de la hepatitis C
Enfermedad autoinmunitaria sistémica
Crioglobulinemia

RESUMEN

Existe una estrecha relación entre los procesos autoinmunitarios y las infecciones virales, un hecho que ha originado que se propusiera diversos virus como posibles agentes etiológicos o desencadenantes de las enfermedades autoinmunitarias sistémicas (EAS). El virus de la hepatitis C (VHC) es un virus ARN de cadena única identificado en 1989, y que en la actualidad se considera uno de los agentes virales más relacionados con el desarrollo de manifestaciones autoinmunitarias. La relación del VHC con las diversas EAS ha generado un interés creciente en los últimos años, ya que las manifestaciones extrahepáticas, que a menudo presentan los pacientes con infección crónica por el VHC (tanto clínicas como inmunológicas), pueden ocasionar el cumplimiento de los criterios clasificatorios vigentes de diversas EAS.

Introduction

The hepatitis C virus (HCV), which is the cause of 90% of what was previously known as "hepatitis non A non B" in our literature, was isolated in 1988 from an infected chimpanzee. It is a single stranded RNA virus with a lipid envelope which belongs to the *Flaviviridae* family, but to a genus which has remained isolated from *Flavivirus* (*Hepocivirus*). Its genome, formed by a little more than 9400 nucleotides, has several regions.

Patients with chronic HCV infection can have autoimmune manifestations with variable clinical relevance.[1] In some patients there is a subclinical alteration or the appearance of immunological alterations, while others can have clinical manifestations that can be very severe. Cacoub et al[2] have described in the largest series of

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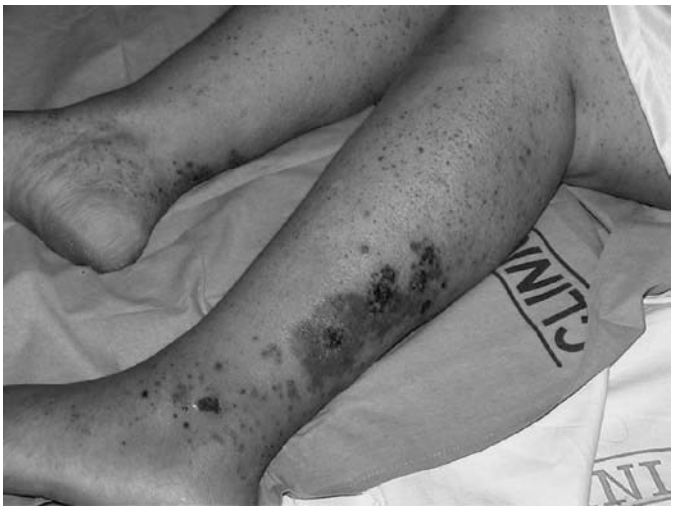

Figure 1. Palpable purpura in a patient with cryoglobulinemia and infection with hepatitis C virus.

patients with HCV published, some form of clinical or immunologic manifestation in 70% of patients. On the other hand, autoimmune conditions may finally lead to the diagnosis of HCV infection, due to the poor clinical or biological translation that is commonly observed in chronic HCV infection, with viremia in the absence of liver affection.

HCV is one of the viruses with a larger rate of genomic variations. The reason for this variation is "continuous infidelity" of the viral RNA polymerase, which leads to the inclusion of nucleotide substitutions in the genome of the virus with an elevated frequency. Through several mechanisms (molecular mimicry and/or autoantigen production), viral infections produce a chronic stimulus of the immune system.

Extrahepatic manifestations

Skin affection

Although the relationship of HCV infection with determined skin affections has been described, such as late skin porphiria or lichen planus, and skin purpura being the most frequently seen skin manifestation in patients with chronic HCV infection, which usually affects lower extremities (Figure 1). In most occasions it is a leukocytoclastic vasculitis related to cryoglobulinemia, although skin vasculitis has been described in the absence of cryoglobulins. Other types of skin vasculitis have been exceptionally been described, related to anti-neutrophil cytoplasm antibodies (ANCA), erythema nodosus or erytema multiformis. In the series by Cacoub et al,[2] observed skin affection in 55 (17%) of the 321 patients with HCV analyzed, including Raynaud's phenomenon in 21 (7%) cases, skin vasculitis in 19 (6%), pruritus in 20 (6%), late skin porphiriain 3 (1%) and lichen planus in 3 (1%).

Mucosal affection

Mucosal dryness, especially of the mouth and the eyes, has been described in close to 20% of patients with HCV. Most of these patients have diagnostic tests compatible with Sjögren's syndrome, such as positive ocular tests (Schirmer's test, Bengal rose staining) or lymphocytic infiltrates of the salivary glands.[3] Recently, HCV was isolated in the salivary gland biopsy of patients with Sjögren's syndrome and HCV infection, showing the capacity of HCV to infect salivary glands.[4]

Locomotor system affection

Joint affection is one of the main extrahepatic manifestations in patients with HCV and can appear in a patient with known HCV infection or can represent the initial clinical manifestation of such an infection. In order of frequency, the metacarpophalangeal joints, wrists, proximal interphalangeal joints, shoulders, knees, and ankles are affected. Studies that have analyzed the prevalence of joint affection in patients with HCV infection show diverse results. Cacoub et al[2] detected joint pain in 60 (19%) and arthritis in 6 (2%) of the 321 patients studied, while Buskila et al[5] described non erosing, non deforming polyarthritis in 4 of 90 patients with chronic HCV infection; the most frequently affected joints were metacarpophalangeal, proximal interphalangeal, wrists, shoulders and metatarsophalangeal joints. Because many of the patients with HCV and joint affection present positive rheumatoid factor, a difficult differential diagnosis with rheumatoid arthritis (RA) can occur, especially in patients with normal transaminases.

Diverse soft tissue affection has been described in patients with chronic HCV infection. Buskila et al[5] describe myalgia in 22/90 (24%) patients, although other studies have described carpal tunnel syndrome and palmar tenosynovitis. There is a growing interest in the relationship between fibromyalgia (FM) and HCV. Buskila et al diagnosed FM in 14 (16%) of their patients with HCV, a percentage similar to those found in other series. Most of the patients with HCV-FM were women (13/14). Other studies, in contrast, have found contradicting results and as a result the relationship between HCV and FM is still undefined.

Lung affection

Studies performed at the beginning of the nineties described a high frequency (close to 30%) of anti-HCV in patients with idiopathic lung fibrosis (ILF). These results have not been confirmed afterward. Recent studies, with more specific techniques, have not confirmed this relationship, detecting HCV infection in only 1 (2%) of 62 patients with ILF) a possible relationship between lung fibrosis and cryoglobulinemia, because lung alveolitis has been described in the context of a cryoglobulinemic syndrome (Figure 2). The fact that cryoglobulinemia can lead to lung alveolitis and then to lung fibrosis indicates that the relationship between ILF and HCV may be indirect and especially seen in patients with cryoglobulinemia.

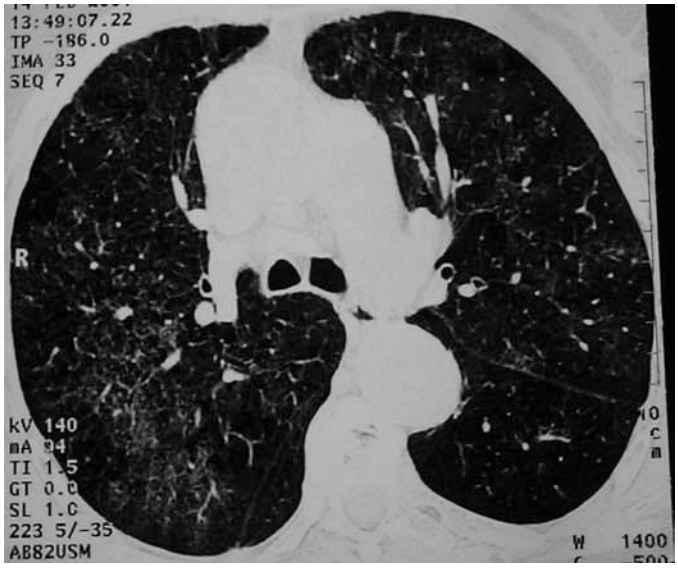

Figure 2. Lung alveolitis in a patient with cryoglobulinemia related to hepatitis C virus.

Nephropathy

The most common renal affection is glomerulonephritis (GN), related in many occasions to a cryoglobulinemic syndrome. The types of nephropathy most frequently related with HCV infection are membranoprolipherative GN, focal/segmental GN and membranous GN. Patients with HCV and membranoprolipherative GN usually represent 50% of cases, alterations of the urinary sediment and/or renal failure; nephritic syndrome in 25%, and, in the other 25%, nephritic syndrome. In contrast, most of the patients with membranous GN present nephritic syndrome. On the other hand, some patients with HCV infection can present renal affection in the absence of other cryoglobulinemic signs or symptoms. Finally, there is a possibility that in some of the patients with HCV, the renal affection is more directly related to a very evolved baseline liver disease (with hepatorenal syndrome) than to immunitary dysfunction.

Central nervous system affection

The most common neurological affection is polyneuropathy, usually sensorymotor, followed by multiple mononeuritis. In most cases, the affection of the peripheral nervous system (PNS) is part of the cryoglobulinemic syndrome and responds poorly to treatment with interferon. More rarely, other types of neurological affection have been described, such as stroke or cranial nerve affection. Cacoub et al described sensory peripheral neuropathy in 28 (9%) patients and motor peripheral neuropathy in 15 (5%), without any case of central nervous system (CNS) affection.

Thyroid affection

Several studies have found a prevalence of thyroid affection in patients with HCV that oscillates between 1.5% and 12%, and have described it in in both patients with hyper and hypothyroidism. This possible association has recently been subjected to a reanalysis because many cases could be related to the administration of interferon.

Diverse studies have detected antithyroid antibodies in patients with HCV, with prevalence between 3% and 20%, and that may reach 31% in patients previously treated with interferon. These large variations are surely owed to different epidemiological and ethnic profiles of the studied populations and the techniques employed. In large series of patients with HCV, antithyroglobulin antibodies were detected in 46 (11%) and antibodies to thyroid peroxidase in 27 (6%) of the 423 patients analyzed. Cacoub et al, for example, reported antythyroglobulin antibodies in 36/287 (13%) patients and antiperoxidase in 10/287 (3%).

Immunological alterations

According to a meta-analysis performed on 2.367 patients with HCV infection (Figure 3), we can divide the positivity of the different antibodies according to the percentage, and classify the antibodies in: frequent, with more than 30% (cryoglobulins and rheumatoid factor); relatively frequent, with 10%-20% (antinuclear antibodies, anti-smooth muscle antibodies, antiphospholipid and antithyroid antibodies), and, finally, infrequent, with less than 5% (anti-LKM antibodies, anti-DNA; antimitochondrial and anti-ENA antibodies).[6]

- Frequent antibodies. The presence of cryoglobulins in patients with HCV can be usually seen in 30%-50% of cases. In the series by Cacoub et al, cryoglobulins were detected in 110/196 (56%) of patients. The presence of cryoglobulins led to a higher frequency of vasculitis, purpura, glomerulonephritis, anticardiolipin antibodies, and rheumatoid factor, and a lesser frequency of sicca syndrome. In all of the studies performed in patients with HCV, cryoglobulins have been detected in 213 (37%) of 570 patients studied. On the other hand, detection of RF oscillates between 12% and 76% according to the studies. Of 794 patients analyzed, a total of 288 (36%) were positive for RF. In the series by Cacoub, RF was detected in 107/280 (38%). It is more than likely that the RF positivity is related to cryoglobulins. Although the percentage of antinuclear antibodies (AAN) in patients with HCV varies a lot between the different studies, due mainly to different techniques and the titer considered as positive, the analysis of the most important studies reveals that, on a total of 2367 patients with HCV under analysis, 450 (19%) presented titers of AAN ≥1:40. The study of antiphospholipid antibodies (APA) in patients with HCV is a controversial and very current topic. Of a total of 1073 patients analyzed in 8 studies, 183 (17%) presented anticardiolipin antibodies (aCL), although percentages varied a lot according to the study (between 8% and 37%).
- Infrequent antibodies. Antimitochondrial antibodies (AMA) are usually very infrequent in patients with HCV and their elevation in the larger series shows that only 4 of 1128 (<1%) patients were positive. Finally, the study of anti-DNA antibodies has been performed in a total of 464 patients with HCV, with positivity in 12 (3%), anti anti-ENA were sought in 444 patients with HCV, being positive in 11 (2%).

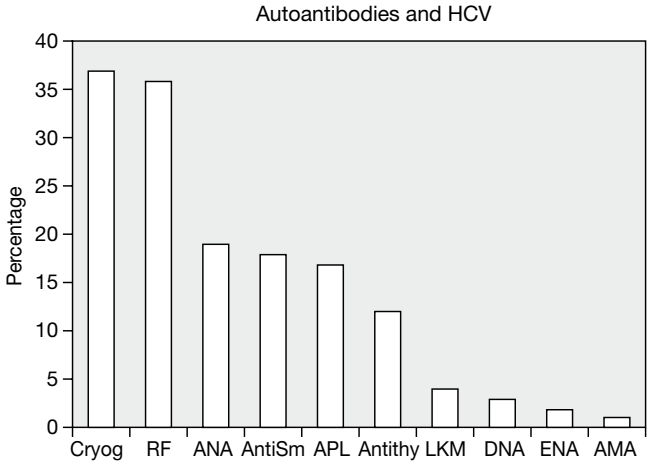

Figure 3. Prevalence of diverse autoantibodies in patients with hepatitis C virus: results of a metanalysis performed in 2367 patients. APA, antiphospholipid antibodies; ANA, antinuclear antibodies; AMA, antimitochondrial antibodies; antiSM, anti-smooth muscle; antithy, antithyroid; cryoglob, cryoglobulins; ENA, antibodies versus extractable nuclear antigens (Ro, La, Sm, RNP); RF, rheumatoid factor.

Relationship of HCV with systemic autoimmune disease

A novel aspect is the relation of HCV with defined systemic autoimmune diseases.[7] The appearance of extrahepatic manifestations and positive immunological results in a determined patient can lead to the diagnosis of a determined systemic autoimmune disease, after the corresponding criteria are applied.[8] In any way, HCV infection presents certain clinical and immune characteristics that lead to a differential diagnosis only with a determined set of systemic autoimmune illnesses (such as Sjögren's syndrome [SS], systemic lupus erythematosus [SLE] or RA)[9,10] and not with others (such as systemic sclerosis, Behçet's disease or systemic vasculitis[11]). We find intermediate situations in antiphospholipid syndrome[12] or sarcoidosis.[13] The clearer cases are SS (patients with HCV and dry mucosa as well as positive serology), SLE (joint affection, cytopenia, renal affection, hypocomplementemia and ANA) and

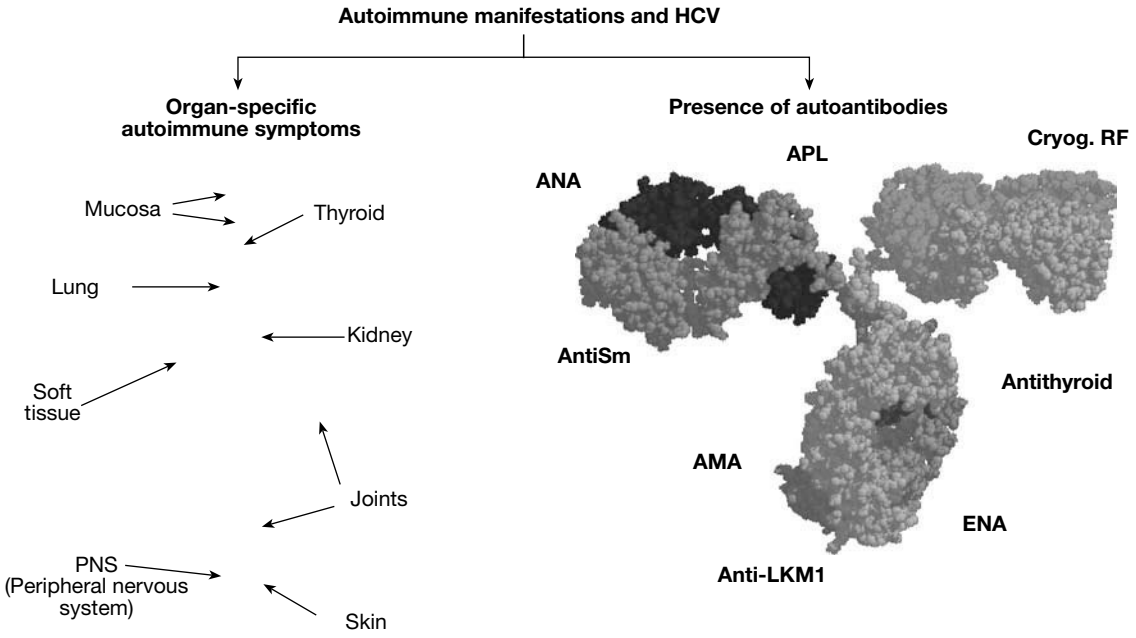

Figure 4. Autoimmune clinical and serological manifestations related to chronic infection by hepatitis C virus. APA, antiphospholipid antibodies; ANA, antinuclear antibodies; RF, rheumatoid factor; PNS, peripheral nervous system.

RA (joint affection with positive RF). Patients with HCV infection who have specific clinical or immunological characteristics of SpA and which are not normally seen in HCV infection, such as anti-ENA antibodies in the case of SS, lupus skin disease, anti-dsDNA or anti-SM in the case of SLE, or erosions or joint rigidity in the case of RA, have been described. In these patients one must consider if it is a casual or causal relationship, although the hypothesis of an ethiopathogenic relationship in some patients with a predisposing genetic background that puts them at risk for autoimmune disease is certainly attractive.

Conclusions

There is no doubt that HCV infection must be contemplated from a systemic context and not exclusively from the hepatic one. The appearance of extrahepatic manifestations and positive immunological results in a patient can lead to the diagnosis of a determined systemic autoimmune disease after the corresponding criteria have been applied. In any case, there is no doubt that the data accumulated during these 10 years of research of HCV point to two clear facts. The first is that cryoglobulinemia is related with a lot of the manifestations of an autoimmune nature (clinical or serological) which are present in patients with HCV and that the cryoglobulinemic syndrome seems to be the great "simulator" of systemic autoimmune disease in patients with HCV infection. The second is that there are determined autoimmune diseases such as SLE, SS, or RA that are more easily "simulated" by the HCV infection than others.

Extrahepatic clinical manifestations related to HCV can be observed in numerous localizations (Figure 4), most frequently joint affection (joint pain and/or arthritis), skin affection (purpura), neurological (polyneuropathy), renal (glomerulonephritis), lung (alveolitis), thyroid (thyroiditis), eye, mucosal (dryness) and soft-tissue (fibromyalgia). We could consider as "frequent" manifestations (with prevalences between 10% and 20% of patients with HCV) joint pain, dryness of mucosas and fibromyalgia, and as relatively frequent (between 5% and 10%) skin vasculitis, polyneuropathy, and glomerulonephritis (directly related to cryoglobulinemia) (Table).

Table
Prevalence of extrahepatic manifestations in patients with chronic Hepatitis C Virus infection

	Relation with cryoglobulinemia
Frequent manifestations (10%–20%)	
Joint pain	+
Dry mouth	–
Dry eyes	–
Chronic fatigue	–
Relatively frequent manifestations (5%–10%)	
Skin Vasculitis	+++
Polyneuropathy	+++
Glomerulonephritis	+++
Thyroiditis	–
Infrequent manifestations (<5%)	
Arthritis	+
Lung fibrosis	+/–
Lychen planus	–
Mooren's ulcers	–

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