



2016 Hepatitis C Virus: Global view

Rheumatic manifestations of hepatitis C virus chronic infection: Indications for a correct diagnosis

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Author contributions: All authors have contributed to conceive and design this review, to analyze the literature and revise the paper; and Palazzi C drafted the manuscript.

Conflict-of-interest statement: Authors have no financial interests which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

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Received: May 29, 2015

Peer-review started: June 4, 2015

First decision: September 11, 2015

Revised: November 17, 2015

Accepted: December 12, 2015

Article in press: December 14, 2015

Published online: January 28, 2016

Abstract

Hepatitis C virus (HCV) is a hepato- and lymphotropic

agent that is able to induce several autoimmune rheumatic disorders: vasculitis, sicca syndrome, arthralgias/arthritis and fibromyalgia. The severity of clinical manifestations is variable and sometimes life-threatening. HCV infection can mimic many primitive rheumatic diseases, therefore, it is mandatory to distinguish HCV-related manifestations from primitive ones because the prognosis and therapeutic strategies can be fairly dissimilar. The new direct-acting antiviral drugs can help to avoid the well-known risks of worsening or new onset of autoimmune diseases during the traditional interferon-based therapies.

Key words: Arthritis; Cryoglobulinemia; Diagnosis; Hepatitis C virus; Hepatitis C; Rheumatic; Sicca syndrome; Vasculitis

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Core tip: As a consequence of its lymphotropic nature, hepatitis C virus (HCV) can trigger and sustain a clonal B-cell expansion which causes a wide spectrum of autoimmune/lymphoproliferative disorders, through a multistep process. These extrahepatic manifestations become clinically manifest in 40%-70% of the patients and they can be frequently classified among the rheumatic ones. Furthermore, HCV can promote the production of several autoantibodies complicating the differential diagnosis between primitive and HCV-related rheumatic disorders.

Palazzi C, D'Amico E, D'Angelo S, Gilio M, Olivieri I. Rheumatic manifestations of hepatitis C virus chronic infection: Indications for a correct diagnosis. *World J Gastroenterol* 2016; 22(4): 1405-1410 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i4/1405.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i4.1405>

INTRODUCTION

Hepatitis C virus (HCV) is a linear, small size (55-65 nm) single stranded RNA virus belonging to the family of *Flaviviridae*. It is a bloodborne virus commonly transmitted because of inadequate sterilization of medical devices (syringes, needles) and unscreened blood products. Moreover, it can also be transmitted sexually and from mother to foetus but not through breast milk^[1]. HCV is a hepato- and lymphotropic agent and its infection usually occurs without symptoms and chronicizes in 70%-80% of cases leading to serious liver damage (cirrhosis and liver cancer) after years.

As a consequence of its lymphotropic nature, HCV can trigger and sustain a clonal B-cell expansion which causes a wide spectrum of autoimmune/lymphoproliferative disorders, through a multistep process^[2,3]. The extrahepatic manifestations become clinically manifest in 40%-70% of the patients and they can frequently be included among the rheumatic ones^[2,3]. Furthermore, HCV can promote the production of several autoantibodies complicating the differential diagnosis between primitive and HCV-related rheumatic disorders^[4,5].

HCV-RELATED VASCULITIS

The term cryoglobulinemia indicates the presence in the serum of one (monoclonal cryoglobulinemia) or more (mixed cryoglobulinemia, MC) immunoglobulins, which precipitate at temperatures below 37 °C and re-solubilize with heating. Cryoglobulinemic vasculitis (CV) mainly involves the small vessels^[3,6,7]. The pathogenetic mechanism consists in immune complexes deposition (containing cryoglobulins or not) and leucocytoclastic vasculitis is the commonest pattern detected by skin biopsy^[3,6,7]. Cryoprecipitates are made by several components including HCV core proteins, anti-core IgG antibodies, IgM rheumatoid factor (RF) and C1q proteins^[8].

Vessels are clinically involved in less than 5% of HCV infected subjects. The typical clinical manifestation of MC is represented by purpura, weakness and arthralgia^[3,6,9]. Purpura is mainly localized in the lower limbs (orthostatic purpura), is frequently palpable and often shows an intermittent course^[3,6,7,9]. In many cases it is mild, but very serious purpuric lesions, also with a confluent evolution, are not rare. Other skin lesions such as petechiae, ulcers (often preceded by Raynaud's phenomenon or acrocyanosis), necrosis and urticaria in both legs and toes can also occur^[9-11]. In two thirds of subjects the recurrence of purpura causes the appearance of an ochreous coloration in the lower part of legs^[9]. HCV is more frequent in elderly women and in patients with long-lasting HCV infection and in type II MC^[12,13].

Laboratory tests show HCV infection in about 80% of the totality of MC patients^[12]. RF is often present

because monoclonal RF is represented in type II MC, while type III MC contains polyclonal RF^[9]. C4 is frequently low while C3 is usually normal. However, both complement and cryocrit levels do not correlate with the severity of skin manifestations^[9].

HCV may also have extracutaneous manifestations, being renal involvement one of more severe ones. In patients with type II MC (IgMkRF positive), the renal involvement is characterized by membranoproliferative glomerulonephritis (MPGN) causing micro-haematuria and proteinuria^[14-17]. However, HCV can also induce non-cryoglobulin related MPGN in which IgG staining is the most typical finding. Furthermore, membranous glomerulonephritis in association with HCV-related MC was also described^[18,19]. MC-related MPGN has been also reported in patients with positive HCV-antibodies and undetectable HCV in serum, peripheral blood mononuclear cells and bone marrow; in these patients the HCV NS3 antigen was instead found in the glomeruli^[20].

A neurological involvement is often present in MC. The more frequent neurological complication of MC is a subacute distal sensory-motor polyneuropathy moreover, mono and multiple mononeuritis have also been reported. The severity of symptoms seems to be related to the level of cryocrit^[21,22]. The involvement of central nervous system (CNS) secondary to a vasculitic damage has been rarely reported. Some cases of cognitive function impairment associated with white matter brain lesions on MRI were attributed to HCV^[23-25]. Life-threatening MC-related manifestations are described in up to 10% of the cases; they mainly consist in progressive renal failure and in vasculitic acute damages localized in CNS, lung, and gastrointestinal tract^[26-28].

Cacoub *et al*^[29] found that the 19.3% of a group of 161 patients suffering from HCV-related vasculitis had a diagnosis of polyarteritis nodosa (PAN). This particular subset of PAN is characterized by severe and acute onset with more frequent fever, weight loss, gastrointestinal involvement, severe acute sensory-motor multifocal neuropathy, severe hypertension and microaneurysms in both liver and kidney^[29]. The rate of treatment-induced remission is high but more frequent relapses than in other forms of PAN can occur. Survival rates at 1, 3 and 5 years was similar to patients suffering from HCV-related CV^[29].

SICCA SYNDROME

Dryness of mucosae (in particular of mouth and eyes) is commonly reported by patient suffering from HCV chronic infection. In a large series of 1614 French HCV patients, sicca symptoms were reported in 11%^[30]. The clinical features may be indistinguishable from those observed in primary Sjögren's syndrome (SS).

HCV-associated sicca syndrome (SIS) is due to a functional impairment of exocrine glands related to a

mild sialoadenitis presenting some histological features distinguishable from those observed in primary SS^[31]. Focal lymphocytic infiltrates of SS are predominantly composed by CD4⁺ T-cells while the percentage of B-cells increases in late and more severe stages of the disease^[32,33]. Conversely, in the HCV-related focal sialoadenitis, CD8⁺ T-cells are more commonly found and the CD4⁺/CD8⁺ ratio is usually lower in comparison with SS^[31,34]. Furthermore, lymphocytic infiltrates are mainly localized in the pericapillary zones rather than in the peri-ductal areas, with no destruction of the ducts^[35,36]. Genetic differences were also found: in the HCV-SiS a frequent association with the HLA-DQB1*02 has been described while in the SS the HLA-DR3 allele is more common^[37,38]. Although the published data concerning HCV replication in the salivary glands are controversial^[36], the presence of the virus in both saliva and salivary epithelial cells has been clearly demonstrated^[39,40].

Differences concerning clinical aspects were also reported. Older age, liver disease, hypocomplementemia, cryoglobulinemia, lung disease are more common in HCV SiS; on the contrary, female sex, frequent and severe sicca symptoms and parotid gland enlargement are more common in SS^[41,42]. The frequency of anti-SSA/SSB antibodies is higher in SS although anti-SSA/SSB positivity was also described in HCV-SiS (up to 23%) as well as in subjects suffering from HCV chronic infection without SiS^[42,43]. Both disorders can be complicated by the emergence of a B-cell lymphoma^[3,31].

According to the America-European Consensus Criteria, patients with HCV-SiS cannot be classified as SS^[44].

MUSCULO-SKELETAL DISORDERS

Arthralgias are a common complaint of HCV-infected patients. Inflammatory joint involvement is quite rare. However, the Italian group of Iagnocco *et al.*^[45] described ultrasound features consistent with inflammatory signs of large joints (knees, hips or shoulders) in more than 95% of the enrolled HCV patients without any rheumatic symptoms. Articular symptoms are much less common as showed by French Authors which found joint pain in only 23% of their 1614 patients suffering from chronic hepatitis C^[30]. Arthritis is even more rare, in fact, the prevalence of HCV-related arthritis (HCVrA) was estimated in 4%-5% of the total of HCV patients^[4,46].

Two different subsets of HCVrA were identified in some studies enrolling limited groups of patients: the more common symmetrical polyarthritis (SP) and the intermittent mono-oligoarthritis (IMO)^[47-50]. The SP subset shares several aspects with rheumatoid arthritis (RA): symmetrical involvement of wrists and hands; positive rheumatoid factor in more than 50% of patients, and increased markers of inflammation^[51-53]. However, the course of HCVrA is much less aggressive

when compared with RA and rheumatoid nodules were never reported^[51,53]. Two reports described joint erosions on 20%-30% of HCVrA patient radiographs^[47,50]. When these two studies were published serum tests for anti-CCP antibodies were still unavailable; as a consequence, a casual coexistence of both RA and HCV infection cannot be excluded. Anti-CCP antibodies can be helpful in the differential diagnosis between HCVrA and RA because they are rarely detected in HCVrA^[54,55]. However, in two recent studies anti-CCP antibodies were found in 20% and 33% of HCV patients with articular symptoms, respectively^[56,57].

The IMO subset of HCVrA typically involves the medium and large joints of the lower limbs, mainly the ankles^[51,53]. Its course is usually acute with frequent relapses. The IMO subset is closely related to the presence of MC in serum and to the cutaneous and laboratory manifestations of CV. Often IMO flares simultaneously occurs to skin flares of CV.

FIBROMYALGIA

A clinical picture characterized by widespread pain typical of fibromyalgia (FM) is reported by 1.9% to 57% of patients suffering from HCV chronic infection^[58-62].

Although in a Spanish study anti-HCV antibodies were found in 15.2% of the enrolled FM subjects, other studies did not confirm the increased prevalence of HCV infection in FM^[63,64]. However, HCV infection should be ever kept in mind as a possible cause of secondary FM^[4].

AUTOANTIBODIES

The occurrence of autoantibodies usually used in the diagnosis of rheumatic diseases during chronic HCV infection has been recently and extensively reviewed^[5].

Levels of RF, anti-CCP and anti SSA/SSB antibodies are increased as well as several other non-organ specific autoantibodies that have been reported in up to 79% of HCV-positive subjects^[65]. Higher frequencies were found for anti-nuclear antibodies (ANA) (\leq 63%), cANCA (\leq 64%), anti-Cardiolipin (\leq 62%), anti-DNA (\leq 25%).

ANA and anti-double stranded DNA antibodies, often present in low titres and with a speckled pattern, are clinically irrelevant. Inconsistent data were instead published as regards the clinical relevance of cANCA and anti-Cardiolipin antibodies^[5] in HCV patients. Some studies showed a correlation between anti-Cardiolipin antibodies, thrombocytopenia and thrombotic disorders^[66,67]. A single study reported an increased prevalence of purpura, skin nodules, livedo reticularis and Raynaud's phenomenon in cANCA-positive HCV patients in comparison with the negative ones. However, life-threatening manifestations commonly seen in the primitive ANCA-related vasculitis were absent^[68].

NOTES OF TREATMENT

The treatment of HCV-related rheumatic disorders includes: etiological therapies with antiviral drugs aiming to HCV eradication; and pathogenetic and symptomatic pharmacological approaches^[3]. They are not reciprocally exclusive and can be combined for best management of patients^[69]. Among their possible adverse effects, care must be taken to different formulations of INFα that can worsen or promote many autoimmune disorders such as arthritis, vasculitis, peripheral neuropathies and kidney disease. The combination of new anti-HCV agents will permit INF-free treatments^[70-72]. Combined/sequential therapies with antivirals and the anti-CD20 monoclonal antibody (Rituximab) represent a real progress in the treatment of most severe manifestations of HCV-related MC (renal involvement, skin ulcers, neuropathy, widespread vasculitis)^[69,73]. Some studies have also reported favourable results with rituximab alone. However, the persistence of MC despite HCV eradication with new antiviral drugs is possible^[74]. In severe cases, high oral doses of corticosteroids (prednisone 0.5-1.5 mg/kg per day) or intravenous pulses (methylprednisolone 0.5-1 g/d, for 3 d) followed by oral prednisone, are also often prescribed^[17]. Plasma exchange is useful to rapidly remove cryoglobulins and immune-complexes^[17]. Milder forms of CV can be easily managed with low doses of corticosteroids^[60] as well as HCVrA can be approached with low doses of steroids and/or hydroxychloroquine^[70].

CONCLUSION

Chronic hepatitis C virus infection can induce several rheumatic manifestations that should be differentiated from the primitive rheumatic ones. Treatments for these two kinds of disorders are usually different and the lack of detection of HCV infection could represent a real risk for patients. As a consequence, HCV testing should be routinely performed in patients showing rheumatic signs and/or symptoms. In some patients, it remains unrealistic, also for experienced rheumatologist, to discriminate if the presence of HCV is casual or plays an active role in causing autoimmune disorders.

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P- Reviewer: Cardoso CRL, Gong ZJ, Li ZF S- Editor: Ma YJ
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