

Difficulties in the differential diagnosis between primitive rheumatic diseases and hepatitis C virus-related disorders

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Introduction

Hepatitis C virus (HCV) is a single-stranded RNA virus that infects 170 million persons in the world (1-6). It causes a liver infection that becomes chronic in 70-80% of cases. This disease is frequently asymptomatic and can induce, usually after 20 years or more, severe complications such as cirrhosis and hepatocellular carcinoma. It can be transmitted by biologic fluids, principally blood, via transfusions, injections, and inappropriate decorative (tattoo), diagnostic or therapeutic procedures. Many have demonstrated that HCV is much more than a simple liver infection. Indeed this virus is involved in the pathogenesis of several autoimmune disorders that can affect almost any organ of the body (7,8). For this reason, it is frequently considered in the differential diagnosis in many fields of clinical medicine. In particular, rheumatic disorders (arthralgia/arthritis, vasculitis, sicca syndrome, fibromyalgia) are frequent and must be distinguished from primitive rheumatic diseases because the prognosis and therapeutic strategies can be fairly dissimilar. Furthermore, it should be remembered that patients suffering from primitive systemic rheumatic diseases are more prone to contract HCV infection because of hospitalisation and invasive medical procedures.

Arthralgia and arthritis

In a French study, generic arthralgias were described in 23% of 1,614 patients suffering from chronic hepatitis C (7). In Asia, a Korean group reported that 35% of HCV-positive subjects suffered from arthralgia or arthritis (9). Iagnocco and co-workers recently ex-

amined by ultrasound the knee, hip and shoulder of 29 HCV patients without any rheumatic symptoms (10). Results showed articular alterations in 96.5% of the enrolled persons (mainly in the shoulder and knee), with highly significant differences in comparison to the healthy controls.

A clinically evident arthritis seems to be much more rare. Buskila, who studied joint manifestations in 90 Israeli HCV-infected subjects, found arthralgia in 9% and arthritis in 4% (11). Our (unpublished) data on 481 patients with chronic hepatitis C indicate an arthritis prevalence of 4.8%.

Two Italian groups first reported an increased prevalence of HCV infection (8-14%) in patients classified as having rheumatoid arthritis (RA) (12, 13). D'Amico and co-workers hypothesized that HCV could have induced an RA-like arthritis (13). This supposition was confirmed later, as other studies have shown that hepatitis C virus-related arthritis generally falls into one of two clinical subsets (14-16): a more frequent, symmetrical RA-like form principally involving the small joints, and a less common mono-oligoarthritis involving the medium-sized and large joints, especially in the lower limbs. The latter often presents an intermittent course and appears to be somewhat associated with the presence of cryoglobulins in the serum.

The differential diagnosis between RA-like HCV-related arthritis and true RA can be problematic because their clinical picture may be very similar (Table I). The American Rheumatism Association classification criteria for RA are not useful for this purpose, because HCV-related arthritis can easily fulfil

Table I. Comparison of clinical and laboratory manifestation of HCV-related arthritis and rheumatoid arthritis (RA).

	HCV-related arthritis	RA
a. Peripheral symmetric polyarthritis	yes	yes
b. Erosions	possible (?)	yes (not at the onset)
c. Rheumatoid nodules	no	frequent
d. Prolonged morning stiffness	frequent	frequent
e. ESR elevation	~ 50%	yes
f. Rheumatoid factor	frequent	frequent
g. Anti-CCP antibodies	no	frequent

these criteria (17, 18). However, in RA-like HCV-related arthritis, the ESR can be normal and rheumatoid nodules are absent, while prolonged morning stiffness and positive rheumatoid factor are common in both disorders. Some authors have described RA-like HCV-related arthritis as non-erosive (15, 19), but others reported erosions in 20-30% of patients with HCV infection and polyarthritis (14, 16). In these cases, a fortuitous association between the presence of HCV and a true RA cannot be excluded. In this regard, it should be remembered that the studies which found an increased prevalence of HCV in RA patients (12, 13) and the study that showed the higher prevalence of erosive arthritis associated with HCV infection (16) were all conducted in Italy. In this country, the prevalence of HCV infection in adults is particularly high, varying from 3.2% to 24.6% in different geographical zones (20-24). Recent works from the USA and France did not report an association between RA and HCV (25,26). However, in our experience the course of HCV-related arthritis is usually much less aggressive than RA(17).

An important contribution in distinguishing RA from HCV polyarthritis could come from anti-keratin antibody detection. Kessel demonstrated that this test was positive in 60.6% of subjects with RA and in only 8% of persons with HCV-related arthritis (27). More recently, anti-cyclic citrullinated peptide (anti-CCP) antibodies have also been indicated as being very useful. They were detected in 76.6% of 30 patients with rheumatoid arthritis but in none of 31 patients with only HCV infection, as also in none of 8 subjects with HCV infection and joint involvement (28). In the experience of Toubi, the presence of IgA rheumatoid factor in HCVpatients suggests a diagnosis of HCV-related arthritis when the search for the IgM rheumatoid factor is negative (29). In some cases (especially in early arthritis), clearly distinguishing between the two can be impossible.

In any case, all patients with symmetrical arthritis should be differentiated from the more frequent subgroup of HCV-related arthritis. In some coun-

tries a similar joint involvement is the most frequent arthritic manifestation of HIV infection, another blood (and sexually) transmitted viral disease (30). Many other viral agents can cause non-erosive symmetrical polyarthritides, but these forms usually remit within several weeks.

The less common HCV-related arthritis subset, consisting in a non-erosive mono-oligoarthritis mainly localized in the lower limbs and that frequently has an intermittent course, should be differentiated from several primitive forms of arthritis, in particular crystal (urate and calcium pyrophosphate)-related arthritis and the spondyloarthropathies. HCV-related arthritis principally involves the ankles (16) and is obviously characterized by the presence of anti-HCV antibodies in the serum and (frequently) by type II or III cryoglobulinemia (with or without cutaneous vasculitis). In crystal-related arthritis, local signs of inflammation are commonly greater and crystals can be found in the synovial fluid. In gout, typical X-ray abnormalities have been described, such as deposits of urate in soft tissues, par-articular erosions and osteolytic areas (31, 32). However, these usually appear some years after the disease onset. In calcium pyrophosphate arthropathy, punctate and linear calcifications can be disclosed by X-rays in the fibrocartilage, articular cartilage, and in joint capsules (33). It should be remembered that these calcifications can be present in an absolutely asymptomatic manner, especially in aged patients, and that they can coexist with other rheumatic disorders.

Spine, chest, and sacroiliac joint involvement but also extra-articular manifestations such as peripheral enthesitis, tenosynovitis and bursitis are frequent in the spondyloarthropathies (ankylosing spondylitis, psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease and undifferentiated spondyloarthritis). Several imaging techniques (X-ray, MRI, CT, ultrasound) have been usefully employed to detect the different sites of involvement. In reactive arthritis, clinical and/or laboratory signs of triggering infections are present (34). Tagli-

one and co-workers from Italy reported an increased prevalence (12%) of HCV infection in 50 patients suffering from psoriatic arthritis (PSA) (35). Our data did not confirm this observation (36). The high frequency of PSA in Italy could have contributed to a fortuitous association (37).

The treatment of HCV-related arthritis is often based on the administration of NSAIDs, low doses of oral corticosteroids and hydroxychloroquine (17,38). Israeli authors suggested the employment of alpha-interferon and ribavirin (18).

Although little research has been performed in this field, the use of more aggressive therapies for HCV-related arthritis or for other arthritides in HCV-positive patients seems risky due to the possible negative effects on liver disease (39). For this reason, in our departments we test all patients observed with any arthritis for HCV infection. However, recent data reported the safe administration of tumor necrosis factor alpha antagonists (40-43) and methotrexate (44) in small groups of patients with rheumatic disorders and chronic hepatitis C.

Fibromyalgia

Fibromyalgia (FM) is a syndrome characterized by diffuse and chronic musculoskeletal pain and tenderness at specific anatomic sites (45,46). Other frequently associated symptoms are fatigue, headache, irritable bowel syndrome, and sleep disturbances (45, 46). This syndrome can occur in a primitive (idiopathic) manner or can be associated with several chronic diseases. In any case, patients suffering from this disorder represent one of the largest groups that are referred to rheumatology units. The prevalence of FM in HCV-positive subjects may range from 5% to 19% (47-49).

In the opinion of many authors, HCV patients do not represent a significant percentage of the large number of FM patients in the general population. On the contrary, Rivera and co-workers found anti-HCVantibodies in 15.2% of their FM group (50). In any case, HCV infection should be kept in mind as a possible cause of secondary FM, even

in subjects without raised transaminase levels in their serum (50).

Vasculitis

Hepatitis C virus-related vasculitis is essentially localized in the small vessels (venules, capillaries, arterioles) and is due to the deposition of circulating type II or type III cryoglobulins (mixed cryoglobulinemia) with a perivascular infiltrate of mononuclear cells (51-53). Vessels are involved in less than 5% of patients suffering from HCV infection (53). The typical triad of symptoms consisting in purpura, weakness and arthralgia is present in almost 4 of 5 patients at the moment of the diagnosis (54). Purpura is mainly localized in the lower limbs (orthostatic purpura) and can present an intermittent course. Other cutaneous manifestations such as petechias, ulcers or urticaria are not uncommon (54-56). The recurrence of purpura causes in two-thirds of subjects the appearance of an ochereous coloration in the lower part of the legs (54). C4 is frequently lowered (54). Associated clinical manifestations are frequent: arthralgias/arthritis, weakness, peripheral neuropathy, renal involvement, Raynaud's phenomenon, and sicca syndrome. Their prevalence is higher in MC patients being followed in rheumatology clinics (54) than in subjects from hepatology/internal medicine departments (57).

Recently the French group of Cacoub and co-workers described a medium-sized vessel vasculitis (polyarteritis nodosa type) affecting HCV-positive subjects, usually with a milder form of hepatitis (51, 58). An increased prevalence of HCV infection (5-12%) has been reported in patients with polyarteritis nodosa (PAN) (51). This severe subset is frequently characterized by visceral involvement (renal insufficiency, severe hypertension, ischemic abdominal pain), multifocal sensory-motor neuropathies, arthromyalgias, and cerebral vasculitis. Livedo reticularis and cutaneous necrotic lesions are comparable to those of isolated PAN. Often, a poor general physical condition and high levels of ESR and C-reactive protein are present as well. Histological findings consist in necrotizing

angiitis with a small amount of perivascular infiltrates of monocytes, lymphocytes and neutrophil granulocytes. In 2004, the same French group reported 3 cases of renal polyarteritis nodosa and 9 cases of systemic polyarteritis nodosa among 125 subjects suffering from HCV-related mixed cryoglobulinemia, indicating that such severe vasculitides are not rare in this type of patient (57). Other viruses such as HBV and HIV can equally induce cryoglobulinemic vasculitis and PAN (51).

Both small and medium sized vessel HCV-related vasculitides are usually clinically indistinguishable from other forms involving the same vessels. Abnormalities in liver tests or the presence of other HCV-associated disorders such as lichen planus, B-cells lymphomas, porphyria cutanea tarda, etc. may point to the correct diagnosis. In any case, HCV tests should be routinely performed in vasculitis.

P-ANCA and C-ANCA are occasionally found in HCV patients (59). Recently, ANCA directed against bactericidal/permeability increasing protein (BPI-ANCA) and cathepsin G (CG-ANCA) were found in about 10% of subjects with HCV-associated mixed cryoglobulinemia or chronic hepatitis C; these autoantibodies did not show any effects on the clinical status of the patients (59).

Treatment of HCV-related vasculitis is obviously influenced by the viral nature of the inducing agent. Interferon-(INF) treatment is quite effective in HCV-induced cryoglobulinemic vasculitis but a high frequency of relapses has been reported after discontinuation of the therapy (52). Worsening or new onset of joint, skin, nerve and kidney manifestations of HCV infection are possible using INF (16, 17, 58, 60). In severe cases corticosteroids, cyclophosphamide, plasmapheresis and rituximab have been used successfully (54,61). Combination therapy with INF and ribavirin seems to be more effective than IFN alone (62, 63), also in the long-term evaluation. The latter treatment plus corticosteroids and plasmapheresis was also effective in 3 cases of the PAN type of HCV-related vasculitis (64).

Sicca syndrome

Sicca syndrome (SiS) due to a functional impairment of the exocrine glands inducing mainly dryness of the eyes and mouth, is quite a common finding in patients with chronic HCV infection. In his large series of 1,614 French HCV patients, Cacoub observed sicca symptoms in 11% (7). The clinical and histological features may be indistinguishable from those observed in primary Sjögren's syndrome (SS) (65); however, the prevalence of several manifestations can be different in HCV-related SiS and SS. Ramos-Casals reported an higher frequency of liver disease (94% vs 3%), cryoglobulinemia (60% vs 10%) and hypocomplementemia (60% vs 8%) in HCV-related SiS in comparison with primary SS (65). On the contrary, parotid gland enlargement was prevalent in SS (47% vs 17%). Significant differences have also been described by De Vita in liver and lung involvement and hypocomplementemia that were prevalent in HCV-related SiS (66). Anti-SSA/SSB positivity is usually higher in SS; however, in some populations such as those of Italy a significant prevalence is also reported in subjects with HCV-related SiS (25%) (66) as well as in patients with HCV infection without SiS (36%) (67). In other countries, HCV seems to be less associated with anti-SSA/SSA antibodies production (68). Although the current classification criteria for SS proposed by the American-European Consensus Group consider HCV infection to be an exclusion criterium (69), De Vita indicates that HCV-related SiS should be considered a true SS, the triggering agent of which is known (66).

HCV-related SiS does not ameliorate after anti-viral treatment (70), suggesting the existence of an autoimmune process that can also continue when the causative agent is eliminated from the blood.

Systemic lupus erythematosus

Recent works have reported an increased prevalence of HCV infection in patients suffering from systemic lupus erythematosus (SLE) (71-73). HCV-positive patients diagnosed as having

SLE showed a lower frequency of cutaneous SLE features and positivity for anti-double-stranded DNA antibodies, but they had a higher incidence of liver involvement, cryoglobulinemia and decreased levels of C4 (72-73). These data induce one to consider the possibility that HCV infection with related autoimmune manifestations may be misdiagnosed as SLE in some subjects. In effect, many features that are observable in SLE such as arthritis/arthralgia, thrombocytopenia, anemia, glomerulonephritis, vasculitis, SiS, and Raynaud's phenomenon have also been well described in HCV infection (54, 74). Furthermore ANA (7, 75, 76) and anti-cardiolipin/anti-phospholipid (77) antibodies have been clearly identified in differing but significant percentages in several groups of HCV patients.

Conclusions

HCV infection can mimic many primitive rheumatic diseases through its autoimmune manifestations. As a consequence, HCV testing should be routinely performed in patients showing arthralgia, arthritis, or symptoms usually related to connective tissue diseases, especially in countries where this virus is widely diffuse in the population. The differential diagnosis is frequently arduous and sometimes impossible, because it is not easy to discriminate, in any given case, if the presence of HCV is casual or plays an active role in causing the autoimmune disorders. However, HCV detection is useful to administer appropriate treatments in subjects with rheumatic manifestations and also to avoid excessive risks for the liver or other organs involved by the viral disease.

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