Extrahepatic Manifestations of Chronic HCV Infection

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Abstract

Several extrahepatic manifestations have been reported in the natural history of hepatitis C virus infection (HCV). Up to 40-74% of patients infected with HCV might develop at least one extrahepatic manifestation during the course of their disease. Mixed Cryoglobulinemia (MC) is the most known and studied syndrome associated with HCV infection. It is a systemic vasculitis that may involve the skin, kidney and nervous system. A frequent reported association is that between HCV infection and non-Hodgkin lymphoma. The cryoglobulinemia may be the intermediary disorder, in fact some persistent forms of cyoglobulinemia can switch over to a more aggressive haematologic disorder. As compared to cutaneous vasculitis described in MC, HCV infection has been associated with dermatological disorders such as porphyria cutanea tarda and lichen planus. Thyroid disease (usually hypothyroidism) is commonly seen in people with HCV. Up to 25% have thyroid antibodies. Several studies described a correlation between HCV and lymphocytic sialoadenitis, similar to sialoadenitis associated with idiopathic Sjögren syndrome, but we can define as "pseudo-Sjögren syndrome" the one associated with HCV infection, because it shows several differences in the idiopathic form. In the course of chronic HCV infection, a common observation are rheumatological symptoms such as polyarthritis. The clinical pattern of joint involvement in the course of HCV infection varies from a rheumatoid arthritis-like form (very rare), to a non erosive oligoarthritis involving the large-sized and middle joints.

Key words

Extrahepatic manifestations - chronic HCV infection - mixed cryoglobulinemia - B-cell - non-Hodgkin lymphoma - pseudo-Sjögren syndrome

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Introduction

Several extrahepatic manifestations (EHM) have been reported in the natural history of Hepatitis C Virus (HCV) infection (1). According to different studies, 40-74% of patients infected with HCV might develop at least one EHM during the course of the disease (2,3). Further, EHM syndromes could represent the first signal of an HCV infection, as many patients show no hepatic symptoms. Pascual et al (4) first described an association between HCV and EHM in 1990, reporting two patients with mixed cryoglobulinemia. Subsequenttly, the involvement of all organs and systems was reported (kidney, skin, thyroid, eyes, joints, nervous system). In 1999 Zignego et al (5) classified EHM of HCV infection in four groups (Table I).

Table I Classification of extrahepatic manisfestations in HCV infection

Group A	association defined on the basis of strong prevalence and clear pathogenetic mechanism
Group B	prevalence higher than controls
Group C	syndromes to be confirmed or characterized
Group D	anecdotal observations

Pathogenesis

The infected extrahepatic tissues might act as a reservoir for HCV (6) and play a role in both HCV persistence and reactivation of infection. HCV as an etiological agent replicating and expressing viral proteins in extrahepatic tissues itself contributes to EHM associated with chronic HCV infection.

An important feature of HCV is that the virus avoids immune elimination. A consequence is chronic infection, an accumulation of circulating immunocomplexes and auto-immune phenomena (7). HCV shows a particular lympho-tropism other than hepatic tropism, that is responsible for many EHM.

Mixed cryoglobulinemia (MC)

Mixed cryoglobulinemia (MC) is the most known and studied syndrome associated with HCV Infection (8,9).

Cryoglobulins are immunoglobulins that reversibly precipitate at a temperature lower than 37°. Cryoglobulins have been classified by Brout et al (10) on the basis of the immunoglobulin clonality (Table II). HCV is strongly associated with MC type II and III (11). Cryoprecipitates usually contain large amounts of HCV antigen and/or antibodies against HCV (8).

Table II Classification of cryoglobulins

Type	Clonality of immunoglobulins	Associated diseases
Type I	Monoclonal immunoglobulins (IgG or IgM)	Lymphoproliferative diseases
Type II (mixed)	Polyclonal immunoglobulins (mainly IgG) plus monoclonal immunoglobulins (IgM, IgG, IgA)	Mixed cryoglobulinemia
Type III (mixed)	Polyclonal IgG and polyclonal IgM	Mixed cryoglobulinemia

Mixed cryoglobulinemia is a systemic vasculitis characterized by the deposition of circulating immuno-complexes in small and medium-sized blood vessels resulting in clinical manifestations. Cryoglobulins can be found in patients with HCV infection in 19% up to 50% according to different studies (12-13). The prevalence of MC increases with the duration of the disease. Some studies of patients with chronic HCV and MC showed that the duration of the disease was almost twice as long than in patients without MC (12). Cryoglobulins are usually found at low concentrations and 90% of patients have few or no clinical manifestations (14). Only a small fraction of patients with MC associated with HCV (less than 15%) have symptomatic disease.

B-cell lymphoproliferation represents the pathological trigger (7). Indeed, it has now become clear that HCV shows a high tropism for peripheral lymphocytes, which may serve as its reservoir and a place for it to replicate (6). Flint et al described that the virus C binds to tetraspanin CD81 ligand on the surface of B- lymphocytes via E2 protein (the second portion of the HCV envelope) leading to activation of these lymphocytes (15). Initially, only polyclonal crioglobulins are produced, then a dominant B-cell clone emerges, producing monoclonal immunoglobulins.

Concentrations of HCV RNA and anti-HCV antibodies are much higher in the cryoprecipitate than in the serum (16). Some studies reported an association between MC and HCV genotype 2a, but this should be confirmed (17).

Clinical features of MC

Cryoglobulins may determine a variety of clinical manifestations. More common symptoms are general malaise, arthralgias and weakness.

Skin is commonly involved (95% of cases) with a cutaneous vasculitis ranging from palpable purpura (leukocytoklastic vasculitis) and petechiae in the lower extremities to large necrotic ulcerations. Biopsy of skin lesions shows immune-complexes vasculitis of small vessels with mononuclear infiltration. HCV antigens are detected in skin lesions in 40% of cases (18).

Kidney is frequently involved (35-60%) in the course of MC related to chronic HCV infection (19). The prevalent type of glomerulonephritis associated with MC is a membranous proliferative glomerulonephritis (MPGN) (20). Anti-HCV antibodies are universal in patients with both cryoglobulinemia and MPGN. HCV-RNA is present in nearly 81% of MC related MPGN versus only 25% of cases of noncryoglobulinemic MPGN (8). In 25% of cases patients develop proteinuria in nephrotic range (> 3 g/24 h), oedema, hypertension and hypocomplementemia. In 30% of cases renal involvement begins with a nephritis syndrome and acute renal failure (oliguric in 5% of cases). In 55% of cases patients present only mild hematuria, mild proteinuria and mild renal insufficiency. Renal involvement can be present at the onset of the disease in about 20% of patients (19). The presence of kidney impairment is a negative prognostic factor in the course of disease (21). Renal biopsy demonstrates immunocomplexes deposits of IgG, IgM with rheumatoid factor (RF) activity and C3 in capillary loops. The most characteristic histological findings are the capillary thrombi consisting of precipitated cryoglobulins at light microscopy. Less often HCV causes focal segmental glomerular sclerosis or membranous or proliferative glomerulonephritis (22).

The course of renal pathology is variable. A clinical regression is observed in 10-15% of patients with nephritic syndrome. In 30% of cases, the clinical trend is slow and renal function is maintained for many years. In 20% of patients the disease is characterized by recurrent episodes of nephritic syndrome. In less than 15% of MC patients dialysis is required for terminal uremia.

In 7 up to 90% of cases of MC there is a *peripheral neuropathy*, that represents one of the most serious complications of organ involvement in MC (23-24). MC related neuropathy is mostly sensory and is characterized by numbness, burning, needles and pins sensations, skin crawling and itching that occurs most often in the hands and feet, but can appear in other areas of the body. Sometimes a mononeuritis multiplex is present. Biopsy shows axonal damage with epineural vasculitic infiltration and endoneural microangiopathy. Therapy with interferon alpha can worsen a MC related polyneuropathy (25).

Neurological involvement has been described also in patients with HCV infection without MC (26). Particularly there is neuropathy associated with polyarteritis nodosa in the course of HCV infection, that typically is an asymmetrical polyneuropathy with prominent motor symptoms.

Several authors have analyzed the association between MC and *liver damage*. In a recent meta-analysis of 19 studies on a total of 2,323 patients with chronic HCV infection an association between cryoglobulins and cirrhosis was found (27), so the presence of cryoglobulins according to the authors should be considered a prognostic negative risk factor for the development of cirrhosis in patients with chronic HCV infection. On the other hand, others studies

showed that symptomatic MC is associated with a low prevalence of cirrhosis (28).

Diagnosis of MC

There are no standardised criteria for MC diagnosis, but only classification criteria (29). These criteria include clinical (i.e. purpura, organ involvement) and serological data (i.e. C4 reduction, concentrations of cryoglobulins, RF positivity). Some patients with chronic HCV infection may show clear or even incomplete forms of MC. In the latter, a strict follow up of the patient with repeated determination of cryoglobulins is required.

Therapy of MC

Nowadays the strict, causal correlation between chronic HCV infection and MC is established so the MC therapeutical approach has changed. In MC with clinical symptoms the therapy should eradicate the virus since treating the clinical manifestations (i.e. vasculitis) without antiviral therapy leads only to a temporary control of disease.

Antiviral therapy is actually based on interferon alpha (IFNα) and ribavirin (30-31). Interferon can treat many of the clinical manifestations of MC, including skin vasculitis and renal disease.

Improvement of clinical MC is reported in 50 to 70% of cases, demonstrating that MC does improve with the reduction of HCV-RNA concentrations. The long term clinical answer is present only in 10% of cases and after the interruption of antiviral therapy, usually there is a relapse of clinical symptoms and an elevation of cryoglobulin titres. Combination therapy with IFNα plus ribavirin provides much better short-term and long-term results (30-31). In a recent pilot study, PEGylated IFN alfa 2b plus ribavirin achieved a higher rate of complete clinical response and sustained virologic response over a shorter treatment period than was previously reported with IFNα plus ribavirin treatment (32).

According to some authors, a positive antiviral response is significantly related to the lack of detection of circulating B cell clones with t (14; 18) traslocation, the basis for possible lymphoproliferative disorders (33).

In the case of renal involvement, when creatinine clearance is lower than 50%, ribavirin should be avoided.

In the presence of neuropathy, the use of IFN is discussed because some cases of neuropathy have been described as worsening or appearing de novo after the beginning of antiviral drug treatment (34).

When antiviral therapy is contraindicated or the clinical picture is mild other therapeutical strategy can be used. If the goal is to treat flogistic reaction, then commonly used steroids and colchicine are necessary. Steroids are sometimes used in combination with antiviral therapy (35). Steroids can increase viral replication, so they have to be used only for a short period and with mild dosage (except in the case of severe organ damage – neuropathy or nephropathy).

In order to improve immunocomplexes (cryoglobulins) clearance low antigen diets (Lac-diet) are prescribed. A LAC diet consists of a diet with a reduced content of alimentary macromolecules with high antigenic properties. This diet can improve minor manifestations of the MC and is generally prescribed at the initial stage of the disease (36).

Another therapeutical measure aimed to clear immunocomplexes is plasma exchange (selective apheresis) followed by immunosuppressive drugs. This measure is indicated in the presence of acute manifestations.

To inhibit immunoglobulin (cryoglobulin) synthesis, immunosuppressive drugs (cyclophosfamide, azathioprine) can be used in life-threatening organ involvement when there is no response to steroids. These drugs have severe side effects and can determine liver disease progression due to their immnuosuppresive effect (37).

Recently some studies described the use of Rituximab (monoclonal chimeric antibody against CD 20, a B-cell specific surface antigen) in MC with renal disease and vasculitis that was resistant or intolerant to IFN therapy (38-39). Rituximab has been reported to induce potential benefit in decreasing cryoglobulin values, reduce clinical manifestations and improve renal function. In these studies, the HCV level of the patients increased but there was no change in liver function.

Lymphoproliferative disorders

A frequent reported association is that between HCV infection and non-Hodgkin lymphoma (NHL) (40-41). The MC may be the intermediary disorder; in fact it has been previously observed that some persistent forms of cyoglobulinemia can switch over to a more aggressive haematologic disorder in up to 11% of cases (42). This evolution generally appears a long time after MC diagnosis and in long lasting infections. The association is higher with low grade NHL.

HCV viremia has been reported in up to 35% of patients with B cell lymphoma and almost 90% of NHL patients with cryoglobulinemia (43). There is contradictory evidence regarding the presence of HCV in malignant cells (44-45). Some studies did not detect HCV in the lymphoma cells; others have repeatedly demonstrated HCV-RNA in lymphoid organs and bone marrow cells.

Diagnosis may be missed over a long period, due to the occult presentation and /or similarity of symptoms to those of chronic HCV infection.

The mechanism may be due to long term HCV infection, resulting in clonal B cell expansion of immunoglobulin (cryoglobulin)-secreting lymphocytes, and ultimately a combination of genetic and environmental factors result in a mutational event with activation of oncogenes and resulting in NHL.

Another possibility is the inhibition of apoptosis of HCV-infected lymphocytes by t(18;14) traslocation, which results in a over-expression of the bcl2 oncogene, and a second mutation (myc oncogene) may lead to the development of lymphoma (46-47).

The most common types of NHL associated with MC

are follicular lymphoma (CFL), B-cell chronic lymphocytic leukaemia/small lymphocyte lymphoma (B-CLL), lymphoplasmocytoid/immunocytoma (LPL), and marginal zone lymphoma (MZL).

Approximately 65% of HCV-related NHL show extranodal involvement (particularly salivary glands and liver) compared with 19% of non-HCV related lymphomas (48). This characteristic is related to the hypothesis that B-cell NHL arises selectively from the marginal zone B-cell. The extranodal marginal zone cell lymphomas seem to derive from organized lymphoid tissue which develops in response to an infection or as a component of an autoimmune disease.

Several studies showed a strong link between HCV infection and mucosa-associated lymphoid tissue (MALT) lymphoma (49-50). HCV RNA has been isolated in the gastric mucosa of patients with MALT lymphoma, suggesting the possibility that HCV may be involved in its pathogenesis (50).

Other hematologic disorders in the course of HCV infection are gammopathies of uncertain significance (MGUS): usually they are gammopathies IgM/Kappa. MGUS are present in up to 11% patients with HCV infection without cryoglobulins. Some authors reported an association with HCV genotype 2a/c (51). These monoclonal gammopathies have to be monitorized in order to exclude the possibility of an evolution to multiple myeloma.

Limited data suggest that low-grade B-cell lymphomas might regress with HCV clearance induced by antiviral therapy with IFN (32-52); however high-grade B cell malignancies still require systemic chemotherapy.

Dermatological manifestations

Porphyria cutanea tarda

This is caused by the reduction of hepatic uroporphyrinogen decarboxylase activity, resulting in an over production and build up of the protein uroporphyrinogen in the blood and urine of patients. Clinical features include photosensitivity, skin fragility, bruising and vesicles and bullae that may become hemorrhagic; chronic findings include hypo or hyperpigmentation, alopecia, hirsutism and skin thickening.

The prevalence of HCV infection in patients with porphyria is high, 40-50% depending on the country (53,54). HCV does not seem to induce alteration of porphyrin metabolism; perhaps C virus induces the disease in genetically predisposed individuals (55). Some authors suggest that porphyria cutanea tarda might be related to HCV-induced hepatic iron overload (56). Cacoub et al reported that the highest rates of porphyria cutanea were in patients with HCV-related liver cirrhosis, suggesting that cirrhosis may play a role in its development (2).

Antiviral therapy seems to ameliorate cutaneous lesions, but there still are no randomised clinical trial.

Lichen planus

Lichen planus is a recurrent pruritic eruption characterized by flat-topped violaceous papules that can develop on any skin site (arms, trunk, genital, nails and scalp), including mucosal membranes (oral).

The biopsy shows a lymphocytic infiltration (CD4+) in the upper dermis, with vacuolar degeneration of basal epithelium and the presence of acidophilic bodies, probably represented by apoptotic keratocytes (57). HCV seems to replicate in the epithelial (skin and mucosal) cells. Some studies suggest an association between HCV-induced cirrhosis and lichen planus, not infection alone.

The prevalence of positivity for HCV in patients with oral lichen planus (OLP) is estimated around 27% (58). HCV RNA has been found in oral mucous membrane biopsy supporting the association between OLP and HCV (59). Some authors describe an association between oral lichen and anticardiolipin antibodies in HCV patients, whereas others did not find any correlation (60-61). The answer to antiviral therapy is variable.

Endocrinological manifestations

Thyroid

The direct link between HCV infection and thyroid diseases is unclear, but thyroid disease (usually hypothyroidism) is more commonly seen in people with HCV than in the general population (62). About 13% of HCV infected patients have hypothyroidsm and up to 25% have thyroid antibodies (63).

Antiviral therapy can also induce thyroid disease or may unmask autoimmune disease (Graves disease, Hashimoto thyroiditis), with an estimate relative risk of 4.4% (64) and an incidence of 5-12% in HCV patients (65). Thyroid function will return to normal in about 50% of people who develop therapy related hypothyroidism, when treatment is stopped. The principal risk factor for developing thyroid disease in the course of antiviral therapy is the previous positivity for anti-thyroid antibodies (anti-peroxidase) especially in older women (66). Patients who develop an IFN induced thyroid disease perhaps are genetically susceptible (64).

Several studies reported a high prevalence of papillar thyroid cancer in patients with HCV infection (67).

Antiviral therapy is contraindicated in patients with thyroid disease not controlled by hormone therapy; the presence of autoantibodies against thyroid without clinical manifestations is a relative contraindication to antiviral therapy. In the case of a good therapeutical control of a pre-existent thyroid disease, antiviral therapy can be continued. During treatment, frequent controlled tests for thyroid functionality should be performed.

Diabetes mellitus

Diabetes mellitus (DM) is found more commonly in patients with chronic HCV infection than in the general population (68-69). Mason et al (69) suggested that HCV is only a risk factor for DM, independent from liver disease. A strong association has been described between cirrhosis and HCV genotype 2a. Some authors reported that DM in the course of HCV infection was strongly associated with

advanced liver fibrosis or cirrhosis (70). Zein et al (71) analysed the prevalence of DM in patients with cirrhosis due to HCV (25%), in alcoholic liver disease (19%) and in patients with cirrhosis due to cholestatic liver disease (13%). In patients with chronic HCV infection and DM, a high insulin resistance is found, not the presence of pancreatic anti-islet antibodies (72).

The role of antiviral therapy and its effects on diabetes is debated. Interferon is associated with the induction of anti-pancreas autoimmunity in some patients (73).

HCV and the rheumatologist

In the course of chronic HCV infection the finding of rheumatological manifestations is a common observation.

Arthralgias and/or arthritis are found in up to 74% of patients. Muscle involvement is common, frequently in the form of fatigue or in 10% of cases in a classic form of fibromyalgia (74). HCV-associated vasculitis is usually related to cryoglobulinemia, although a few cases of polyarteritis nodosa-like disease affecting the medium-sized vessels have been reported.

Autoimmune antibodies as far as antinuclear antibodies (ANA), RF, anticardiolipin antibodies (acL), cryoglobulins, anti-smooth muscle, anti-liver, kidney and microsomal antibodies, anti-thyroid peroxidase are detected in 40-65% of patients with HCV infection (1, 75-76). Characteristic lymphotropism of virus C is the basis of the increased production of autoantibodies (7).

These antibodies are usually detected in the course of other autoimmune disease (i.e. autoimmune hepatitis, rheumatoid arthritis - RA) which should be considered in the differential diagnosis, besides autoantibodies which can be detected even in other viral infections. The autoantibody titers are low, there is no women predominance, neither an association with specific HLA-DR genes (7). The prevalence and titer of these auto-antibodies are unaffected by IFNα therapy.

Sjögren syndrome

Several studies describe a chronic lymphocytic sialoadenitis similar to sialoadenitis associated with idiopathic Sjögren syndrome (SS) in approximately 50% of patients infected by HCV (77). Up to 6% of patients with SS are HCV positive as opposed to ~1 % in the general population .

Nevertheless, there are some substantial differences between the two forms so we can define as "Pseudo- Sjögren syndrome" that associated with HCV infection. Anti-SSA and anti-SSB antibodies are absent or present at a lower titre. Rheumatoid factor is positive in the majority of patients and is frequently associated with cryoglobulin positivity and hypocomplementemia. Clinically, xeroftalmia and xerostomia are mild or absent in 90% of patients, whereas arthritis, cutaneous vasculitis and neuropathy beyond alteration of liver function are more frequent (78). Histological samples show a milder lymphocytic pericapillaritis. The lymphocytic type of the infiltrate in the minor salivary gland biopsies shows a predominance of the CD8 lymphocytes in a proportion of 2/1, contrasting with what is observed in primary SS (79).

Abnormal liver parameters in patients with SS should require prompt HCV evaluation. A positive test for HCV should be considered as an exclusion criteria for the classification of primary SS.

Regarding the pathogenetic mechanism, some studies in mice, transgenic for HCV envelope protein, that develop an exocrinopathy similar to human SS, suggest a cross-reactivity between the HCV envelope and host salivary tissue, or an HCV envelope-mediated immune stimulation that is directed against exocrine glands (80). HCV antigens are not detected in affected glands, but HCV RNA is present in the saliva of patients with HCV-associated sicca syndrome.

Sjögren syndrome related to HCV may evolve into a B cell malignant lymphoma, especially if it co-exists with MC, showing the role of virus C in inducing B cell proliferation (48).

Few authors have described the evolution of SS associated with HCV when chronic hepatitis C is treated with antiviral therapy. Doffoel-Hantz et al (81) described a high incidence (more than 50%) of immunological IFN-mediated complications in patients with SS and HCV infection. When ribavirin was associated with IFNα, it gave a significant sustained virological response and lowered the IFN-mediated complications with a favourable outcome of SS.

HCV related arthritis

Arthritis in the course of chronic HCV infection can be seen either as part of the autoimmune processes (e.g., associated with cryoglobulinemia) or independently. HCV arthritis unrelated to cryoglobulinemia is far less common but represents an independent entity.

Epidemiological studies have shown important differences of arthritis prevalence in HCV patients. A French prospective study (82) of 309 patients with the diagnosis of RA were tested for HCV. In this group, an 0.65% prevalence of past or active HCV infection was found which did not differ from the prevalence of HCV in the general French population. This result did not support the participation of HCV infection in the pathogenesis of RA.

On the other hand, 303 patients in a Spanish study (83) with the diagnosis of RA were tested for HCV. HCV antibodies were found in 7.3% of RA patients vs. 0.95% of the general population. However, an HCV PCR-RNA was positive in only 2.3% of patients.

Whether arthritis is specifically attributable to HCV infection or rather to the non specific result of a chronic inflammatory process, is not clear.

There are various hypotheses regarding the pathogenic mechanisms. Some authors suggest that arthritis and HCV infection co-exist by chance; others that HCV might act as a trigger of disease in genetically predisposed individuals, with mechanisms that include direct invasion of synovial cells by the virus eliciting local inflammatory response,

cytokine-induced disease or immune complex disease. Some even suppose that HCV causes a distinct infectious arthritis. In addition, it has to be considered that HCV is associated with behaviors that are linked to, yet unknown, infectious agents.

Two subsets of articular involvement in the course of HCV infection have been identified: a polyarthritis involving small joints that resembles RA, very rare and usually milder, and a non erosive oligoarthritis involving the medium-sized and large joints often showing an intermittent course (84) that is frequently associated with cryoglobulinemia. Rheumatoid factor is positive in 50-80% of cases. Antibodies anti-cyclic citrullinate peptide (anti –CCP) are positive in less than 6% of patients with HCV-associated arthritis which may help to differentiate the two conditions (85). Cryoglobulins may or may not be present (21). Other incidental antibodies can be detected (ANA-10-38%, antiDNA-5%, acL-25%, anti-SSA-1%) (86).

The course of HCV-infection is often occult, without elevation of liver enzymes. The identification of HCV-infection in rheumatic patients is important to minimize the risk of aggravating hepatitis by prescription of hepatotoxic drugs and because of the availability of IFNα as a potential virus eradicating agent. HCV infection should be considered in the differential diagnosis in patients with atypical arthritis.

Few data about HCV-associated arthritis treatment are reported in the literature. As a consequence, the therapeutic approach for this disorder is still largely empirical and poorly standardized. Nonsteroidal anti-inflammatory drugs (NSAIDs), hydroxychloroquine, and low doses of corticosteroids are the cornerstones of the treatment of HCV-related arthritis, but some authors describe an incomplete relief of symptoms, especially in the rheumatoid-like subset. Intake of low doses of corticosteroids and NSAIDs is more effective in subjects belonging to the mono-oligoarthritis group. In severe forms, immunosuppressive drugs could be used, typically methotrexate, but with caution, because these medications may determine hepatotoxicity. Treatment decisions should be taken on a case-by-case basis. An etiologic therapy with INFα and ribavirin is indicated when required by hepatic or systemic involvement, because occasionally it can induce or worsen autoimmune disorders. Treatment with INFα and ribavirin may lead to a substantial clinical improvement of HCV-related arthritis even without a complete biochemical or virological response. Arthritis associated with cryoglobulinemia usually responds to antiviral treatment.

Because of the few data available at the moment, the usually non-aggressive course of HCV-associated arthritis does not justify the use of antiviral drugs as a current therapy.

Other syndromes

Hypertrophic and dilative cardiomyopathy has been recently associated with HCV chronic infection (87).

Idiopatic pulmonary fibrosis (IPF). Several studies have demonstrated a higher frequency of HCV in patients with IPF rather than in controls (88). Yamaguchi et al found an increase in lymhocyte and neutrophil number in broncho-alveolar lavage fluid in patients with HCV chronic infection, suggesting that HCV can induce alveolitis (89).

Mooren corneal ulcerations are associated with HCV and can cause pain, inflammation, tearing and loss of sight (90).

Osteosclerosis. Clinically patients complain of painful extremities during the activity phase of the disease. Recently it has been associated with HCV infection (91).

Conclusions

Hepatitis C virus infection can present with numerous EHM**.** Frequently, EHM are more serious than the hepatic disease itself and are present even in patients with persistently normal ALT levels. Hepatitis C virus can be the cause of commonly seen problems in the rheumatology practice such as arthritis, fibromyalgia, vasculitis and “pseudo-Sjögren syndrome”. HCV therapeutic decisions might depend on the type of EHM.

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