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REVIEW ARTICLE

Hepatitis C virus and autoimmunity

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Abstract Hepatitis C virus infection is associated with several extrahepatic manifestations. About 60% of patients infected with HCV develop at least one extrahepatic manifestation. The majority of these diseases seem to be triggered through autoimmune mechanisms, such as autoantibody production, autoreactive T cells and complex autoimmune mechanisms leading to systemic autoimmune disorders. In this review we categorize these diseases into three groups according to the main pathogenetic process involved, in particular B-cell-mediated, T-cell-mediated and complex autoimmune systemic diseases.

Keywords Hepatitis C · Extrahepatic manifestations · Autoimmune mechanism · Mixed cryoglobulinaemia vasculitis · Lymphoma

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Introduction

Hepatitis C virus (HCV), a RNA virus, is a member of the Flaviviridae family. More than 170 million individuals worldwide are still chronically infected by HCV [1]. The acute infection is infrequently diagnosed because the clinical course is initially often clinically silent. Therefore, in most cases (80%) HCV leads to a chronic infection, followed by chronic hepatitis and some degree of fibrosis. The risk of aggravation and the development of cirrhosis are estimated at about 20% of affected patients. Severe complications and death are related to decompensation of cirrhosis, end-stage liver disease and hepatocellular carcinoma [2].

According to different studies, 40–80% of HCV-positive patients develop at least one extrahepatic manifestation (EHM) during the course of the disease, which is often the first and only clinical sign of chronic HCV infection [3]. Therefore, knowledge of EHM is also an important tool in the diagnosis of HCV infection.

Today, there has been growing interest in the pathogenetic role of chronic HCV infection leading to circulating autoantibodies, lymphoproliferative processes and autoimmune disease.

Pathogenesis of extrahepatic manifestations

The exact mechanism linking HCV infection with autoimmunity and lymphoproliferation is unknown. Moreover, sometimes it is not possible to define whether these EHMs represent true manifestations of HCV infection or if they are a consequence of the therapeutic regimen. Antiviral treatment with interferon-alpha (IFN-α) and subsequent clearing of HCV, for example, leads to

improvement in vasculitic symptoms. Otherwise, vasculitis may also be exacerbated and even cases of new onset of vasculitis and systemic lupus erythematosus (SLE) have been reported [4, 5].

Genetic susceptibility, toxicity and other environmental factors may play a role in the induction of autoimmunity by HCV (for example, concerning the prevalence of lymphomas, it is evident that a clear south–north gradient exists in part reflecting different HCV infection prevalence in the general population, therefore suggesting the contribution of environmental and/or genetic factors [6, 7]). These factors influence the ability of the host to clear the virus or sustain humoral or cell-mediated immune responses and trigger autoimmunity [8].

The development of autoimmune processes in patients with chronic HCV infection is intriguing as it may suggest an additional extrahepatic reservoir of HCV replication, as well as potential mechanisms by which viruses can trigger autoimmunity in general. Two main theories have been proposed for the induction of autoimmunity by viral agents [9]: (1) the molecular mimicry theory suggests that sequence similarities between viral proteins and self proteins can induce a crossover immune response to self antigens; and (2) the bystander activation theory proposes that viral infection of a certain tissue can induce local inflammation (e.g. by cytokine release), resulting in activation of autoreactive T-cells that were dormant or suppressed by peripheral regulatory mechanisms [10]. It has been speculated that HCV infection could initiate autoimmune processes through both mechanisms [11, 12].

The infected extrahepatic tissues, especially circulating blood cells, might act as a reservoir for HCV and play a role in both HCV persistence and reactivation of infection [13]. The specific tropism of HCV for circulating blood cells, in particular lymphotropism, provides a link between HCV and the development of autoimmune and neoplastic haematological processes [14].

Several components of the immune system have been investigated, leading to the suspicion of a global immune dysregulation during HCV infection [15]. The following components of the immune system are responsible for the expansion of autoimmunity in chronic HCV infection and include T cells and B cells.

T cells

$CD4^+/CD25^+$ regulatory T cells seem to be defective in untreated HCV-positive patients with mixed cryoglobulinaemia (MC) compared to asymptomatic MC carriers, MC-negative subjects or healthy controls [16]. Dominant T-cell suppression of B cells producing autoantibodies seems to be attenuated. An autoreactive T-cell response may be responsible for endocrine disorders in chronic HCV infection [17]. According to Akeno et al. [12], CD81 receptors are expressed on thyroid cells which are able to bind HCV envelope glycoprotein E2. This binding induces several signalling cascades and leads to IL-8 release. In summary, the authors suggested that the association between HCV infection and thyroid autoimmunity is due to HCV infection of the thyroid resulting in release of proinflammatory mediators such as IL-8, and induction of thyroid autoimmunity by bystander activation mechanisms.

B cells

A nonspecific activation of the immune system triggered by HCV infection seems to be responsible for the production of autoantibodies directed towards non-strictly hepatic antigens, for example non-organ-specific autoantibodies (NOSA), rheumatoid factor (RF), etc. [15]. Additionally, the phenomenon of molecular mimicry also seems to be responsible for the induction of NOSAs [11].

Several studies have focused on the importance of sustained antigenic stimulation. The specific binding between the HCV E2 protein and the CD81 molecule of B cells led to the hypothesis of a possible role played by HCV in the promotion of a continuous polyclonal B cell response to viral antigens which favour the development of lymphoproliferative disorders (LPDs) [18]. It has also been hypothesized that immune complexes of HCV bound to IgG stimulate RF-expressing B cells through the B cell receptor and act in concert with undefined accessory molecules [19].

The highest levels of B-lymphocyte stimulator (BAFF) have been found in chronic HCV-infected subjects with clinical and laboratory features of autoimmunity [20]. HCV itself seems to be able to stimulate B cells through different pathways and mechanisms and therefore reduces 100-fold the level of antigen receptor ligation required for B-cell activation [21]. Moreover, the binding of HCV to B cells may also favour viral persistence by inhibiting NK-mediated cytotoxicity and drive the immune response towards a Th2 profile that is associated with enhanced humoral immune responses and autoantibody production [22]. This may be linked with an enhanced humoral immune response and autoantibody production. Besides B-cell activation (non-antigen-specific and antigen-specific), HCV seems to infect B lymphocytes directly.

Aberrant RF^+ B-cell lymphoproliferation represents the pathological trigger for MC [23]. The antigenic

dependence of these B cells is supported by evidence that HCV-associated MC and non-Hodgkin lymphoma (NHL) disappear after successful treatment of HCV infection.

As mentioned above, HCV infection may lead through a complex pathogenetic process to the development of LPDs. Usually after a long follow-up period patients with MC may develop lymphomas, and therefore MC is considered a borderline (benign/malignant) lymphoproliferative disease [24]. Additionally, an increased expression of bcl-2 protein, an inhibitor of apoptosis, has observed in patients with HCV-associated MC and may be a consequence of t(14;18) translocation that occurs during early B-cell development. Hence, it has been speculated that an initial polyclonal lymphoproliferation may result in the emergence of a clone protected from apoptosis. A combination of genetic factors, environmental factors and HCV itself [13] results in additional mutational events with activation of oncogenes (e.g. *myc* oncogenes) resulting in NHL [25–27].

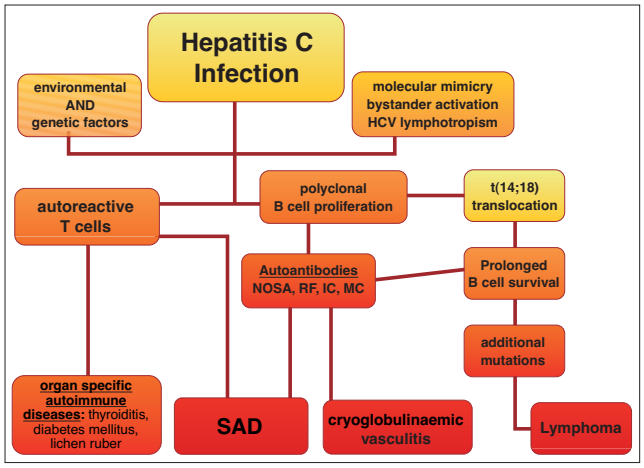

Fig. 1 Pathogenesis of extrahepatic manifestations in chronic hepatitis C infection (according to Ferri [8]) outlining the complex pathogenetic process of extrahepatic manifestations. Depending to the host (e.g. genetic factors) and unknown environmental factors, hepatitis C virus infection leads through several mechanisms (molecular mimicry, bystander activation and HCV lymphotropism) to the formation of autoreactive T cells and polyclonal B-cell proliferation. Autoreactive T cells and autoantibody formation cause cryoglobulinaemic vasculitis, organ-specific autoimmune diseases and systemic autoimmune diseases (SAD). In addition, continuous B-cell stimulation generates the development or rather selection of a B-cell clone (e.g. the t(14;18) translocation responsible for prolonged B-cell survival). Further genetic alterations (e.g. *myc* oncogenes) are responsible for the development of lymphomas

Finally, we suggest that an interaction between the humoral and cellular immune systems triggers an autoimmune process and is therefore responsible for the development of systemic autoimmune diseases (SAD) during HCV infection. In Fig. 1 these considerations are summarized (referring to Ferri et al. [8]). According to these considerations HCV-associated autoimmune-derived EHM can be divided into mainly B-cell-mediated, T-cell-mediated and complex (T- and B-cell-mediated) autoimmune diseases.

B-cell-triggered autoimmune diseases during HCV infection

HCV-associated MC cryoglobulinaemia

Cryoglobulins are defined by the presence of circulating immunoglobulins that precipitate as serum is cooled below core body temperature and redissolved when rewarmed. Cryoglobulins have been classified by Brouet et al. [28] (see Table 1). HCV is strongly associated with MC type II and III. Cryoprecipitates usually contain large amounts of HCV antigen and/or antibodies against HCV [29].

Although more than 50% of patients with chronic HCV infection have circulating serum cryoglobulins (cryoglobulinaemia), the majority (90%) have no clinical symptoms and need no specific therapy for cryoglobulinaemia. MC develops in only 5–10% of these HCV-infected patients [30]. It is not known why HCV induces the production of MC in some patients but not in others. This may indicate that other factors besides HCV infection are needed for the development of MC.

The term “mixed cryoglobulinaemia” is used when patients with cryoglobulinaemia have clinical manifestations. It is a systemic vasculitic disease that is characterized by the deposition of circulating immunocomplexes in small and medium-sized blood vessels and subsequent complement activation that results in clinical manifestations.

According to Sene et al. [31] cryoglobulinaemic vasculitis is associated with advanced age, longer duration

Table 1 Classification of cryoglobulins

Type	Clonality of immunoglobulins	Associated diseases	Prevalence (%)
I	Monoclonal immunoglobulins (IgM > IgG > IgA)	Lymphoproliferative disease	10–15
II (mixed)	Polyclonal immunglobulins (mainly IgG) plus monoclonal immunoglobulins (IgG, IgM, IgA)	Mixed cryoglobulinemia; infections, autoimmune disorders, rarely essential	50–60
III (mixed)	Polyclonal immunglobulins (mainly IgG) plus polyclonal immunoglobulins (IgG, IgM, IgA)	Mixed cryoglobulinemia; infections, autoimmune disorders, rarely essential	30–40

of HCV infection, type II MHC and a higher MC serum level. Serum mixed cryoglobulins can be found in asymptomatic chronically HCV-infected individuals; this condition may be present for years before clinical onset of the disease [32].

MC syndrome is characterized by a typical clinical triad: purpura, weakness, arthralgia [33]; the most frequent target organs are skin, joints, nerves and kidneys.

Skin

More than 90% of patients with symptomatic HCV-associated MC develop palpable purpura, primarily of the lower legs. It is frequently intermittent, and is often the initial manifestation of HCV-associated MC. Histology typically reveals a leucocytoclastic vasculitis, with deposition of IgM RF, IgG, C3 and neutrophils in the vessel wall [34]. Laboratory investigation often reveals high RF titres, which is frequently the initial sign of HCV-induced MC. These purpuric lesions may occasionally progress to chronic and/or large ulcerations. Raynaud's syndrome and acrocyanosis, which evolve to digital ulcers, can also occur [35]. Besides vasculitis, various co-factors contribute to the development of cutaneous manifestations (orthostatic purpura and ulcers), in particular chronic venous insufficiency, physical stress, prolonged standing and haemorheological disturbances [36]. Patients with HIV coinfection who present to the HIV unit in our department have a considerably lower prevalence of vasculitis than those with HCV monoinfection. Interestingly, in accordance with our clinical observations, Ramos-Casals et al. have found that HCV and HIV coinfection significantly attenuates the clinical and immunological expression of cryoglobulinaemia, except in coinfected patients with high viral loads of the two viruses [37].

Renal involvement

HCV-associated MC renal involvement is reported in one-third of these patients and usually appears as a type I membranoproliferative glomerulonephritis [30]. It frequently predicts a poor clinical course. Manifestations range from isolated proteinuria to nephritic syndrome with variable progression towards chronic renal insufficiency.

Arthralgia

Patients with MC frequently complain about arthralgia, whereas clinical signs of arthritis are relatively rare. According to Fadda et al., MC-positive arthritis is consistently nonerosive, asymmetrical and pauciarticular [38].

Neuropathy

The incidence of neurological involvement is variable and can be as high as 55% [39]. Sensorimotor neuropathy may arise from the deposition of cryoprecipitable immune complexes in the vasa vasorum or rather from a vasculitis of the vasa vasorum. Additionally, a significant association between anti-GM1 and antisulphatide antibodies and the involvement of the peripheral nervous system has been observed in HCV-associated MC. Antineuronal reactivity may also be a direct trigger of neurological injury in this disorder [40]. The most frequently described form is a distal mild sensory neuritis [41, 42]. It is characterized by numbness, burning, pins and needles, skin crawling and itching that occurs most often on the hands and feet with nocturnal exacerbation. Bilateral, more often asymmetrical, polyneuropathies represent 45–70% of the MC polyneuropathies and mononeuritis multiplex 30–55% [43]. A few months to a few years after sensory symptoms, motor deficits may appear and affect the lower limbs. Painful paraesthesias and concomitant weakness, particularly in the lower limbs may abruptly occur [44], as may isolated mononeuritis, manifested by foot or wrist drop. Therapy with IFN-α can worsen MC-related polyneuropathy [45]. The involvement of the central nervous system is unusual and presents as transient dysarthria and hemiplegia [46, 47].

Xerostomia and xerophthalmia

Xerostomia and xerophthalmia is frequently observed in MC-positive patients, whereas only a few meet the classification criteria for a primary Sjögren syndrome (SS, see below).

Liver

The association between MC and severe liver damage has been discussed. According to Kayali et al., there is a highly significant association between cirrhosis and cryoglobulinaemia [48].

Endocrinological manifestations

Thyroid disorders, diabetes mellitus and erectile dysfunction [49, 50] are more frequent in HCV-positive

patients with and without MC syndrome than in the general population (see below).

Interstitial lung fibrosis

Interstitial lung fibrosis has been rarely reported in HCV-positive patients with or without MC [51].

Widespread vasculitis

This is a vasculitis with multiple organ involvement that affects only a small proportion of MC patients [52]. This severe complication involves the skin, kidneys, lungs, central nervous system and gastrointestinal tract. Sometimes intestinal vasculitis simulating an acute abdomen may suddenly complicate the disease. Immediate diagnosis of this life-threatening complication and subsequent immunosuppressive treatment are required.

The history and prognosis of MC syndrome are variable and highly dependent on renal involvement [8, 53].

Diagnosis

No standardized criteria are presently available for the diagnosis of MC syndrome. However, useful classifications according to Ferri et al. have been proposed [8, 54].

Laboratory investigations have revealed mixed cryoglobulins, low C4, normal C3, depressed total haemolytic complement levels, monoclonal proteinaemia or RF activity. In general, the level of cryoglobulins is not correlated with the severity of the disease [42]. Interestingly, a sudden decrease or sudden lack of cryoglobulins with or without abnormally high levels of C4 may be a signal of an ongoing lymphoma [55].

As mentioned above, MC syndrome is a borderline disease between autoimmune diseases and malignancies. Careful patient evaluation is necessary for a correct diagnosis of MC syndrome in order to differentiate it from other systemic autoimmune disorders. Moreover, an exact diagnosis of MC syndrome is required in order to prevent the development of malignancies through early clinical monitoring [8].

Therapy

According to the developmental stage of the disease (1. HCV infection, 2. LPD, and 3. MC) the treatment options vary. It can be treated with an aetiological, pathogenetic and/or symptomatic approach [8].

Pegylated IFN-α (Peg-IFN-α) and ribavirin therapy for HCV-associated MC is now established [56, 57]. The therapy has to eradicate the virus since treating the clinical manifestation leads only to a temporary control of the disease. Interestingly, studies have revealed that clinicoimmunological and virological response are generally strictly related [58]. It is suggested that IFN treatment, when successful, is able to help in preventing the evolution of HCV-associated MC LPDs [59]. In addition, a positive antiviral response is significantly related to the lack of detection of circulating B-cell clones with t(14;18) translocation, the basis for possible LPDs [53]. Nevertheless, antiviral therapy of MC syndrome is more complex for several reasons including the absence of standardized treatment protocols, the higher frequency of relapse and generic or MC syndrome-specific contraindications to antiviral treatment (e.g. acute nephritis, widespread vasculitis).

In patients in whom antiviral treatment is contraindicated or not tolerated or who are nonresponders, alternatives have to be used. These include corticosteroids, immunosuppressive drugs (azathioprine, cyclophosphamide), plasmapheresis and a hypoantigenic diet [53].

Several studies have shown that rituximab, a chimeric antibody against the CD20 B-cell-specific surface antigen, is effective in most patients with MC, leading to improvement or resolution of the syndrome and also to regression of the expanded B-cell clones [60]. However, this drug leads to an increase in HCV replication. Therefore, combination therapy with rituximab and Peg-IFN-α plus ribavirin appears logical and may target both the viral trigger and the downstream B-cell arm of autoimmunity [61]. Summarizing, the specific treatment should be individually tailored.

Lymphoma

HCV-associated lymphatic malignancies may be observed during the course of MC [62, 63] or they may be independent forms in patients without MC [64]. The association between NHL and HCV infection has been examined in many retrospective case-control studies [7, 65, 66]. According to Monti et al. [67] patients with MC have a 35 times higher risk of NHL than the general population. Whether HCV is associated with an increased risk for all NHL subtypes or only certain subtypes is an important unresolved question. Generally, low-grade lymphomas are more frequently associated with HCV than high-grade lymphomas. The most common HCV-related lymphatic malignancy is B-cell-derived NHL [68]. More than half of those with HCV-related NHL show extranodal involvement (particularly the salivary

glands and liver) compared with only 19% of those with non-HCV-related lymphomas [69]. Among HCV-infected patients with splenic marginal zone NHL, treatment of infection with IFN-α-based regimens can lead to HCV clearance and, simultaneously, regression of NHL [70]. The diagnosis may be missed over a long period due to the occult presentation and/or the similarity to chronic HCV infection.

In light of the treatment options for MC syndrome (see above), the inclusion of antiviral therapy seems to be rational in therapeutic schemes for HCV-positive NHL. Although antiviral therapy (Peg-IFN-α and ribavirin) appears to be an attractive therapeutic tool for low-grade HCV-positive NHL [71], in intermediate and high-grade NHL, chemotherapy would be expected to be necessary and antiviral treatment may be suggested as maintenance therapy after completion of chemotherapy [72]. The use of rituximab in HCV-associated NHL, in monotherapy or in combination with antiviral treatment and/or chemotherapy appears very promising, especially in the setting of low-grade NHL, where rituximab monotherapy has been proposed as first-line treatment [73].

Autoantibodies associated with chronic HCV infection

Circulating autoantibodies, including antinuclear antibodies (ANA), RF, antiphospholipid (aPL) antibodies, cryoglobulins, anti-smooth muscle actin (SMA) antibodies, liver-kidney microsomal antibodies (LKM), and antithyroid peroxidase, are often detected in patients with chronic HCV infection [3, 74, 75]. ANA, RF and SMA are the most common. Other autoantibodies, for example anti-dsDNA, anti-extractable nuclear antigen antibody, anti-mitochondrial antibodies and anti-LKM, are infrequent. The autoantibody titres are low; there is no female predominance and no correlation with specific HLA-DR genes [23]. NOSA positivity seems to be associated with a more severe liver disease and a more advanced stage of liver fibrosis [76].

Gatselis et al. [74] found a negative correlation between the efficacy of antiviral treatment for HCV and the presence of ANA and SMA before treatment and their increase during therapy. A highly favourable treatment response was associated with an absence of ANA and a decrease in SMA titres during therapy. On the other hand, Stroffolini et al. [77] found no correlation between NOSAs and the main HCV features or the response to antiviral treatment. These autoantibodies are usually detected in the course of other autoimmune disease which is why the very same should be considered in the differential diagnosis. The presence of autoantibodies does not itself represent a contraindication to IFN-based treatment [15].

T-cell-triggered autoimmune diseases during HCV infection

Autoimmune thyroid disease

HCV infection is associated with a high prevalence of thyroid autoantibodies, but only a proportion of these patients also show thyroid dysfunction [78].

A striking association in autoimmune thyroid disease in the setting of HCV infection has emerged during IFN-α treatment. IFN-α is able to induce thyroid autoantibodies in HCV-infected individuals and precipitates thyroid dysfunction in patients with existing autoantibodies. Antiviral therapy is contraindicated in patients with thyroid disease not controlled by hormone therapy. The presence of autoantibodies without clinical manifestations is a relative contraindication to antiviral therapy. Antiviral therapy can be continued if there is good therapeutic control of preexisting thyroid disease [79].

Diabetes mellitus

The prevalence of type 2 diabetes is higher in patients with HCV-associated MC than in the general population [80]. Metabolic disorders in HCV-infected patients may be related to the development of steatosis or cirrhosis, whose clinical significance in HCV-infected patients has recently been emphasized [81]. However, cirrhosis alone seems not to explain the epidemiological link between HCV and diabetes mellitus. HCV may independently contribute to the development of diabetes. A high insulin resistance has been found in patients with chronic HCV infection [80, 82]. The role of HCV therapy and its effect on diabetes is a matter of debate. IFN-α therapy may induce insulin-dependent diabetes by stimulating an autoimmune process against pancreatic beta cells [83]. On the other hand, it has been suggested that IFN-α treatment might improve glucose intolerance in HCV-infected patients and therefore may be beneficial [84, 85].

Dermatological disorders

Dermatological diseases associated with chronic HCV infection include cryoglobulinaemic vasculitis (see above), porphyria cutanea tarda and lichen planus (LP). A strong association, about 50%, between sporadic porphyria cutanea tarda and HCV infection has been revealed [86, 87]. However, the pathogenetic mechanisms are unclear and an autoimmune pathogenetic pathway is unlikely. Other diseases, such as pyoderma gan-

grenosum, chronic urticaria, panarteritis nodosa, erythema nodosum, erythema multiforme, malacoplakia, pemphigus vulgaris, Behçet's disease and pruritus have been reported anecdotally and described only in a few case reports [86, 88, 89].

Lichen planus and oral lichen planus

Epidemiological data suggest a relationship between LP and chronic HCV infection [90, 91]. The aetiology of LP and oral LP (OLP) remains unclear. Skin biopsy typically shows a lymphocytic infiltrate in the upper dermis. The mechanism of epithelial cell destruction by cytotoxic T cells is speculated to be involved in the aetiology of LP and OLP.

HCV RNA has been found in LP lesional tissue using in situ hybridization and PCR techniques. HCV is unlikely to cause direct damage to epithelial cells since it is also found in normal mucosa. Moreover, HCV-specific T cells have been found in the oral mucosa of patients with HCV infection and LP. Therefore, it is speculated that HCV is implicated in the pathogenesis of LP. In OLP the oral cell damage is the result of direct immune aggression of epithelial cells expressing HCV antigens, or neoantigens expressed on epithelial cells infected with HCV could lead to this lichenoid inflammation [92].

Treatment with IFN-α with or without ribavirin has shown conflicting results: both improvement [86] and exacerbation of symptoms [93] have been reported.

Myocardial impairments

Hypertrophic dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia cardiomyopathy and chronic myocarditis have recently been associated with chronic HCV infection. According to Sanchez and Bergasa there is a multifactorial pathway responsible for HCV-induced cardiomyopathy, including direct damage to the myocardium by HCV, autoimmunity, and programmed cell death in genetically susceptible patients [94].

The perception of cardiomyopathy as an EHM of HCV infection is of great importance because the treatments available for chronic HCV at present are considered relative contraindications in patients with myocardial dysfunction. However, if causative and pathophysiological mechanisms underlying HCV-associated cardiomyopathy are further elucidated and if the myocardial damage is indeed caused by HCV, these patients would benefit from therapeutic interventions (IFN-α and ribavirin) that may result in eradication of the virus and reversal of myocardial dysfunction [95].

Idiopathic pulmonary fibrosis

Studies have demonstrated a higher frequency of HCV in patients with idiopathic pulmonary fibrosis rather than in controls [96]. Kubo et al. suggested that activated T lymphocytes and eosinophils are related to the pathogenesis of idiopathic pulmonary fibrosis associated with HCV infection [97]. Other studies disagree regarding this relationship. In these studies the prevalence of anti-HCV antibodies does not differ from that in other lung diseases [98, 99]. Moreover, idiopathic interstitial pneumonitis seems to be an adverse reaction to IFN-α therapy in patients with chronic HCV infection [100].

Systemic autoimmune diseases during HCV infection

Several EHMs in patients with chronic HCV infection may lead to the fulfilment of the current classification criteria for some SAD. A high degree of association between HCV infection and SS, SLE and rheumatoid arthritis (RA) has been described. The main differential aspect between primary and HCV-associated SAD is the dominance of cryoglobulinaemia-related markers (cryoglobulins, RF, hypocomplementaemia) over specific SAD-related markers (anti-extractable nuclear antigen antibody, anti-dsDNA, anticyclic citrullinated peptide) in patients with HCV [75].

Sjögren's syndrome

Recent data suggest a close association between HCV and SS [101]. In most cases HCV-associated SS is indistinguishable from the primary form in accordance with the classification criteria. Hence, MC syndrome and SS share some symptoms: xerostomia and/or xerophthalmia, arthralgia, purpura, RF, serum cryoglobulins and B-cell lymphoma as a possible complication [102]. However, chronic HCV infection should be considered an exclusion criterion for the classification of primary SS, because the virus may be implicated in the development of SS [103]. The main difference between HCV-associated MC SS and primary SS is the immunological profile, with a predominance of cryoglobulinaemia-related markers (MC, RF, hypocomplementaemia) over characteristic SS-associated markers (low anti-Ro/SS-A and low anti-La/SS-B autoantibodies) in HCV-associated SS. Clinically, the majority of these patients (90%) lack xerophthalmia and xerostomia, whereas arthritis, cutaneous vasculitis and neuropathy beyond alteration of liver function are more frequent. Although only a few of these patients have sicca symptoms, more than 75% have histological evidence or a test abnormality (Schirmer

test, sialometry) consistent with SS [102, 104]. SS related to HCV may evolve into a B-cell malignant lymphoma, especially in the presence of MC [105].

There is currently no treatment protocol or evidence-based therapy that shows the efficacy of IFN-α therapy in HCV-associated sialadenitis.

Rheumatoid arthritis

Arthritis and/or arthralgia frequently occur during the course of chronic HCV infection and can be seen either as part of the autoimmune process (e.g. associated with cryoglobulinaemia) or independently. HCV arthritis unrelated to cryoglobulinaemia is far less common but represents an independent entity.

Whether arthritis is specifically attributable to HCV infection or to the nonspecific result of a chronic inflammatory process is not clear. Various hypotheses regarding the pathogenic mechanisms have been proposed, e.g. the coexistence of arthritis and HCV. Some authors suggest that HCV is a trigger for the arthritis in genetically predisposed individuals or that HCV causes a distinct infectious arthritis.

Two subsets of articular involvement in the course of HCV infection have been identified: a polyarthritis involving small joints that resembles RA and a nonerosive oligoarthritis often involving the medium-sized and large joints [38]. According to Rosner et al. [106] chronic inflammatory polyarthritis is the most frequent clinical presentation of HCV-related arthritis, and fulfils the American College of Rheumatology (ACR) criteria in more than 50% of patients. The existence of morning stiffness, rheumatoid nodules, erosive arthritis and anticyclic citrullinated peptide antibodies may be useful to diagnose a true coexistence of RA and HCV. Recent data suggest that anticyclic citrullinated peptide antibodies are useful in discriminating HCV patients with true RA from those with HCV-associated arthropathy [107, 108]. HCV infection should be considered in the differential diagnosis in patients with atypical arthritis. The therapeutic regimen is poorly standardized and treatment decisions should be taken on an individual basis. Mild non-erosive oligoarthritis [28, 90] is often sensitive to nonsteroidal antiinflammatory drugs, low doses of corticosteroids or hydroxychloroquine. Arthritis associated with cryoglobulinaemia usually responds to antiviral (Peg-IFN-α and ribavirin) treatment.

Systemic lupus erythematosus

Viruses have been suspected as potential aetiological or triggering agents in the pathogenesis of SLE [109]. Chronic HCV infection can induce clinical and serological features (arthritis, cytopenias, nephropathy, ANA or anti-dsDNA) which in combination may meet the ACR 1982 criteria for SLE. Therefore, it is suggested that HCV infection may mimic or coexist with SLE. Hence, patients with chronic HCV infection should be tested for the presence of ANA and anti-dsDNA. On the contrary, HCV testing should be considered in the diagnosis of SLE, especially in patients with low titres of autoantibodies, liver involvement, cryoglobulinaemia and the absence of skin manifestations [110, 111]. Aggravatingly, there are several reports of the development of SLE in patients receiving treatment with IFN-α for HCV infection [4, 112].

Autoimmune Cytopenias

Thrombocytopenia

Thrombocytopenia, defined as a platelet count of <150,000/μl, is commonly observed in patients with HCV infection and has a chronic clinical course. It is often believed to be due to cirrhosis, portal hypertension and hypersplenism, and among patients with cirrhosis and splenomegaly, patients with HCV infection seem to develop lower platelet counts than those with other causes of cirrhosis. However, the pathophysiology of thrombocytopenia is complex and multifactorial. Another contributing factor in the development of thrombocytopenia seems to be the bone marrow suppression caused by HCV itself or IFN-α treatment. Thrombocytopenia in patients with HCV infection shares many clinical features of idiopathic thrombocytopenic purpura [113, 114]. Several pathogenetic hypotheses exist. It is speculated that immune complexes of RF IgM and HCV-IgG antibodies in cryoglobulinaemia type II could bind to Fc receptors on platelets prompting their clearance. It has also been proposed that HCV binds to platelets and induces the development of neoantigens on the surface of the platelets, thereby contributing to autoantibody formation against target platelet glycoproteins. Furthermore, thrombopoietin deficiency secondary to liver dysfunction leads to thrombocytopenia [115].

HCV-associated autoimmune haemolytic anaemia

Coombs-positive autoimmune haemolytic anaemia can occur as an extrahepatic immunological abnormality in treatment-naive patients with chronic HCV infection [116–118]. HCV-related autoimmune haemolytic anaemia seems frequently to be associated with autoim-

mune diseases, cryoglobulins and cirrhosis. However, treatment with IFN-α or ribavirin may also cause haemolytic anaemia and therefore has to be excluded as causal factor [119, 120].

Antiphospholipid syndrome

Investigators have frequently reported the occurrence of aPL antibodies in patients with chronic HCV infection [3, 75, 121, 122]. The clinical significance of aPL antibodies in patients with HCV infection is controversial. Harada et al. [123] have found that these antibodies are frequently present in HCV-infected patients but that they are not pathogenic. According to Ramos-Casals et al. [124], HCV-infected patients with aPL sydrome (APS) have a lower frequency of typical APS features (peripheral thrombosis, neurological features). The main APS-related features in HCV-infected patients are intraabdominal thrombotic events and myocardial infarction. Cojocaru et al. [125] investigated the prevalence of anticardiolipin antibodies in patients with asymptomatic chronic HCV infection-related acute ischaemic stroke. They found that patients with chronic HCV infection and related ischaemic stroke have a higher incidence of anticardiolipin antibodies. They suggest that it is clinically relevant if anticardiolipin antibodies are associated with HCV.

In summary, aPL antibodies are frequently found in patients with chronic HCV infection. Although most investigators claim that these antibodies are not pathogenic and therefore an epiphenomenon of the infection, a higher prevalence of thrombotic events has also been reported.

Autoimmune hepatitis

Autoimmune hepatitis (AIH) may also be associated with HCV infection [126]. Both, MC and AIH have mixed cryoglobulins. The differential diagnosis is difficult and causes a diagnostic challenge. MC syndrome is often presented with leucocytoclastic vasculitis, hypocomplementaemia and glomerulonephritis, whereas anti-SMA are more frequently seen in autoimmune hepatitis [8]. In turn, in many patients with AIH and hypergammaglobulinaemia, anti-HCV tests have turned out to be false-positive [127]. Accurate diagnosis is necessary (AIH or HCV with EHM) since treatments differ. Standard treatment of AIH is prednisolone alone or in combination with azathioprine [128]. Others have suggested that patients with combined features of HCV and AIH should undergo a course of corticosteroids to assess biochemical and histological response [129].

Dermatomyositis

There are few reports of the relationship between dermatomyositis and HCV infection. Several reports indicate that the immune response to HCV infection or HCV itself may be important in the pathogenesis of dermatomyositis in some patients [110, 130].

Other HCV-associated disorders

Mooren corneal ulcerations

Mooren corneal ulcerations are associated with HCV infection and cause pain, inflammation, tearing and loss of sight. IFN-α therapy leads to an improvement in these ulcers, which recur when the treatment is stopped [131]. The association is conflicting. According to Wang et al. [132], Mooren corneal ulcerations are not associated with HCV infection.

Osteosclerosis

Osteosclerosis, characterized by increased bone mass, has also been attributed to chronic HCV infection. Patients usually complain of painful extremities during the active phase of the disease [133].

Sarcoidosis

Sarcoidosis seems to be triggered by antiviral therapy (mainly IFN-α). Even treatment-naive HCV-infected patients develop sarcoidosis with mainly pulmonary involvement and also with cutaneous involvement. Sarcoidosis may initially manifest or be reactivated during or shortly after treatment with antiviral therapy in patients with chronic HCV infection [134, 135].

Conclusion

Evidence for HCV infection should always be sought in patients with nonspecific chronic fatigue, or rheumatic, haematological, endocrine and dermatological disorders.

Conflict of interest statement The authors declare that they have no conflict of interest related to the publication of this article.

Abbreviations

AIH autoimmune hepatitis
ANA antinuclear antibodies

APS antiphospholipid syndrome
aPL antiphospholipid antibodies
dsDNA double-stranded deoxyribonucleic acid
EHM extrahepatic manifestations
HCV hepatitis C virus
HLA-DR human leukocyte antigen
IFN-α interferon-alpha
Peg-IFN-α pegylated interferon alpha
LKM anti-liver kidney antibodies
LP lichen planus
LPD lymphoproliferative diseases
MC mixed cryoglobulinaemia
MHC major histocompatibility complex
NHL non-Hodgkin lymphoma
NOSA non-organ-specific autoantibodies
OLP oral lichen planus
RA rheumatoid arthritis
SAD systemic autoimmune diseases
SMA smooth muscle actin
SS Sjögren's syndrome

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