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HCV-related autoimmune and neoplastic disorders: the HCV syndrome

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Abstract

Hepatitis C virus (HCV) chronic infection may be associated with a great number of both hepatic and extrahepatic manifestations. HCV lymphotropism is responsible for poly-oligoclonal B-lymphocyte expansion, which is the common underlying alteration in a significant percentage of HCV-infected individuals. The consequent production of different autoantibodies and immune-complexes, including cryoglobulins, may lead to organ- and non-organ-specific immunological alterations. Mixed cryoglobulinemia, a small-vessel systemic vasculitis, is characterized by the coexistence of autoimmune and lymphoproliferative alterations; therefore, it represents the prototype of HCV-associated disorders. Moreover, HCV shows an oncogenic potential; several studies support its pathogenetic link with some malignancies, mainly hepatocellular carcinoma and B-cell lymphomas. On the whole, HCV-related disorders present a heterogeneous geographical distribution, suggesting a role of other important genetic and/or environmental cofactors. While the majority of HCV-infected individuals is asymptomatic or may develop only liver manifestations, a significant percentage of them may develop a variable combination of autoimmune–lymphoproliferative disorders. The resulting multiform clinico-pathological condition can be termed HCV syndrome. The natural history of HCV syndrome is the expression of multifactorial and multistep pathogenetic process, which usually proceeds from mild, often isolated manifestations to systemic immune-mediated disorders, and less frequently to overt malignancies.

Keywords: HCV; Hepatitis C; Cryoglobulinemia; Lymphoma; Autoimmunity; Cancer; Thyroid; Diabetes

1. Introduction

Patients with chronic hepatitis C virus (HCV) infection may develop a great number of extrahepatic manifestations [1–3], including mixed cryoglobulinemia (MC) that represents the prototype of HCV-associated disorders [1–6]. It is a complex immunological disorder characterized by multiple organ involvement [4–6]. Chronic hepatitis is detectable in over 2/3 of MC patients; this finding suggests a possible causative role of hepatotropic viruses in this disease [4–6]. Soon after the identification of HCV in 1989 its role in MC began to be investigated, and it was definitely established during the last decade on the basis of epidemiological, pathological, and laboratory studies [4–7]. Since MC syndrome mimics other immune-mediated disorders, a possible role of HCV in these conditions has also been investigated; the spectrum of possible HCV-associated diseases includes a wide number of organ-specific and systemic diseases [1–7]. Poly-oligoclonal B-lymphocyte expansion seems to be the common underlying alteration in a significant percentage of HCV-infected individuals [1–6,8]; some of them may develop a variable combination of both hepatic and extra-hepatic manifestations; the term 'HCV syndrome' can be used to refer to this complex clinical condition.

2. Pathogenesis of HCV syndrome

The main pathogenetic insights on HCV syndrome derive from studies regarding the biological peculiarities of this virus and its possible interaction with the host immune-system [1–8]. HCV has been recognized to be both hepato- and lymphotropic; HCV lymphotropism represents an important step in the pathogenesis of virus-related immunological disorders [9]. A number of epidemiological studies first suggested a pathogenetic role of HCV in MC, a disorder characterized by 'benign' B-lymphocyte expansion [4–8,10]. Interestingly, the same immunological alteration may also develop in a significant number of HCV-infected individuals, often in association with serum autoantibodies and/or mixed cryoglobulins [1–6,8,10,11].

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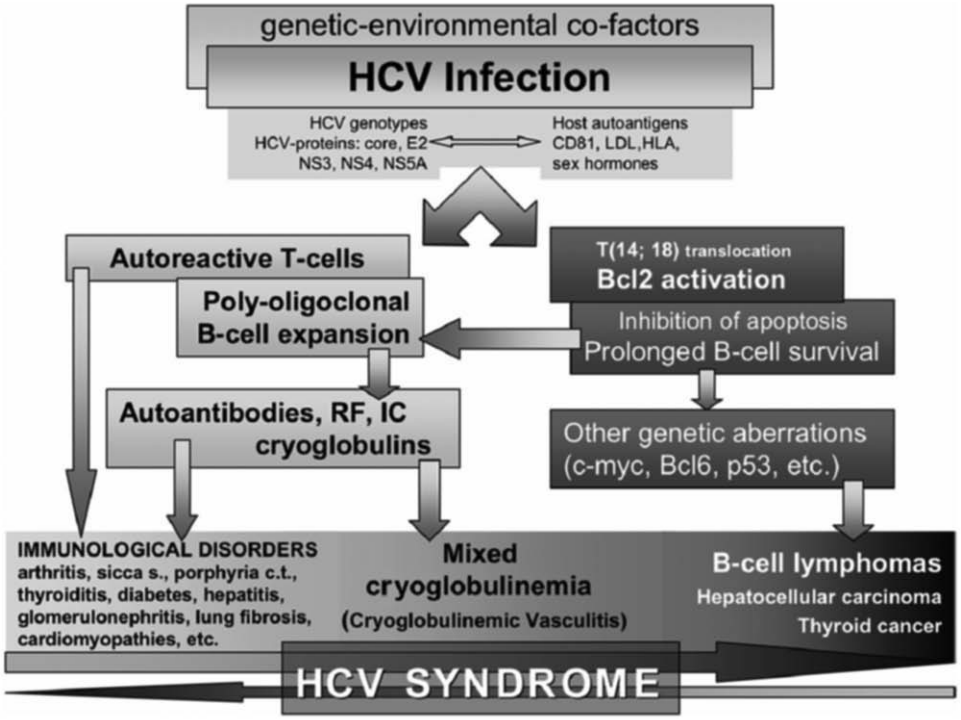

Fig. 1. Pathogenesis of HCV syndrome. HCV infection may exert a chronic stimulus on the immune-system; different pathogenetic factors may variably contribute to resulting clinical phenotype: (a) molecular mimicry mechanism involving HCV antigens and host autoantigens; (b) interaction between HCV envelope protein E2 and CD81 on both hepatocytes and lymphocytes; (c) genetic, hormonal, and metabolic background of the host; (d) unknown environmental factors. T(14;18) translocation with activation of Bcl2 proto-oncogene may lead to prolonged B-cell survival. 'Benign' B-lymphocyte expansion may be responsible for the production of various autoantibodies, including rheumatoid factor (RF) and cryo- and non-cryoprecipitable immune complexes (IC). Consequently, various autoimmune (organ and non-organ specific) disorders and cryoglobulinemic vasculitis may develop. The indolent B-cell proliferation of mixed cryoglobulinemia may be complicated by frank malignant lymphoma in about 10% of patients. Moreover, other proto-oncogene activations may ultimately lead to primary B-cell lymphomas or other malignancies. There is a clinico-serologic and pathologic overlap among different diseases; cryoglobulinemic vasculitis represents a cross-over between autoimmune and neoplastic disorders in the setting of HCV syndrome.

HCV is a positive, single-stranded RNA virus without a DNA intermediate in its replicative cycle, so that viral genomic sequences cannot be integrated into the host genome. It is supposable that HCV infection exerts a chronic stimulus to the immune system, which facilitates the clonal B-lymphocyte expansion [1,4–6,8,10,11].

The first step is t(14;18) translocation, demonstrated in a significant percentage of HCV-infected individuals, particularly in those with type II MC, with consequent Bcl-2 proto-oncogene activation [1–6,12] (Fig. 1). Besides, the identification of HCV envelope protein E2 able to bind the CD81 molecule expressed on both hepatocytes and B-lymphocytes seems to be crucial for HCV-driven autoimmunity [1–6,8]. CD81 is a cell-surface protein that, on the B-cell, is part of a complex with CD21, CD19, and Leu 13. This complex reduces the threshold for B-cell activation by bridging antigen-specific recognition and CD21-mediated complement recognition. The interaction between HCV-E2 and CD81 might increase the frequency of VDJ rearrangement in antigen-reactive B-cell [1,4–6,8,13,14]. One possible consequence could be the above-mentioned bcl-2 proto-oncogene activation observed in HCV-related autoimmune disorders [1–6,8]. Bcl-2 proto-oncogene is able to inhibit apoptosis, leading to extended cell survival [12]. The consequent B-lymphocyte expansion is responsible for the wide autoantibody production observed in HCV-infected individuals, including cryo- and non-cryoprecipitable immune complexes [1,4–6]. Specific autoantibodies may characterize some autoimmune disorders, while mixed cryoglobulins are the serological hallmarks of MC syndrome. Other mechanisms such as molecular mimicry involving particular HCV antigens and host autoantigens could be responsible for B lymphocyte activation and autoantibody production [6] (Fig. 1). Moreover, prolonged B-cell survival can expose these cells to other genetic aberrations [1,6,13–15], leading in some individuals to overt malignant lymphoma (Fig. 1). HCV exerts a well-known oncogenic potential as definitely demonstrated in patients with hepatocellular carcinoma and in a significant percentage of B-cell lymphomas [1,4–6,16]; interestingly, the same virus could also be involved in other malignancies such as thyroid cancer [17].

There is a great geographical heterogeneity in the prevalence of HCV-related MC as well as other immune-system disorders or neoplastic complications [1,4–6,18]. This epidemiological finding contrasts with the homogeneous diffusion of HCV infection worldwide; thus, HCV *per se* might be insufficient to drive the different

autoimmune–lymphoproliferative disorders observed in infected individuals.

The involvement of particular HCV genotypes, environmental and/or host genetic factors (Fig. 1) should contribute to the pathogenesis of HCV syndrome. However, the actual pathogenetic relevance of the above co-factors remains to be fully demonstrated [1–6,10].

The majority of HCV-infected individuals are asymptomatic, even for long periods of time; in these cases the infection does not affect the patient's quality of life and survival; in a small but significant percentage of patients the virus is responsible for both hepatic and extrahepatic disorders, usually as late manifestations (Fig. 1). The natural history of HCV syndrome is characterized by a multifactorial and multistep process that most frequently proceeds from mild, often isolated manifestations to systemic diseases, whose prototype is MC [4], and finally to overt malignancies [1–3,6].

3. HCV-associated disorders

The spectrum of HCV-associated disorders includes various immunological and neoplastic manifestations; in particular immune-mediated alterations may involve one or more tissues, from the skin to visceral organs [1,6]. According to the strength of association, HCV-related diseases can be grouped in three different levels (Fig. 2): level 1: the association with HCV is detectable in the majority of patients and confirmed by pathogenetic studies; level 2: the prevalence of HCV infection is significantly higher than in control subjects and often supported by preliminary pathogenetic studies; level 3: the possible association is suggested by limited clinico-epidemiological observations, but without definite pathogenetic link.

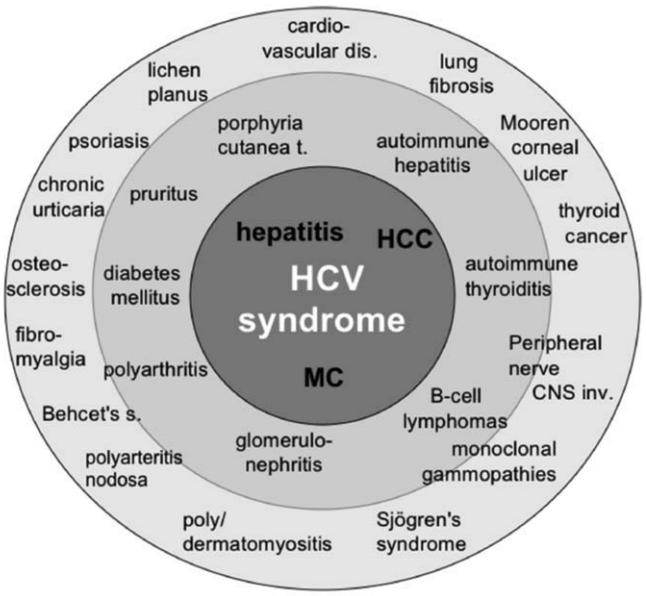

Fig. 2. Strength of association between HCV infection and different diseases that could be included in the HCV syndrome: level 1: the association with HCV is detectable in the majority of patients and confirmed by pathogenetic studies; level 2: significantly higher prevalence of HCV infection than in control subjects, often supported by pathogenetic studies; level 3: the possible association is suggested by limited clinico-epidemiological observations, without definite pathogenetic link.

3.1. Rheumatic diseases

Immune-mediated rheumatic disorders are the most frequent extrahepatic manifestations of HCV syndrome [1, 6]. Among these, MC represents the cross-over between classical rheumatic diseases, such as rheumatoid arthritis and Sjögren's syndrome, and other autoimmune–lymphoproliferative disorders [6] (Fig. 1). MC is usually classified among the systemic vasculitides, in the setting of small-vessel vasculitides; thus, MC syndrome and cryoglobulinemic vasculitis should be related to the same clinico-pathological condition [6]. Cryoglobulinemic vasculitis is characterized by a typical clinical triad – purpura, weakness, arthralgias – and multisystem organ involvement [4–6,10]; its pathological hallmark is the leucocytoclastic vasculitis, involving small and medium-sized vessels [4–6,10]. Vascular lesions secondary to the deposition of circulating immune complexes, mainly mixed cryoglobulins and complement, are responsible for cutaneous and visceral organ involvement [4–6,10]. Chronic hepatitis commonly shows a mild–moderate clinical course; it may evolve to cirrhosis in 1/4 patient, rarely complicated by hepatocellular carcinoma [4–6]. Membranoproliferative glomerulonephritis type I is one of the most important organ involvements of MC, while widespread vasculitis is a rare but harmful complication comparable to other systemic vasculitides [4]. Reduced hemolytic complement activity, with the typical pattern of low or undetectable C4, is typically found; however, both complement levels and cryocrit rarely correlate with the activity/severity of cryoglobulinemic vasculitis [4–6].

As mentioned above, the biological substrate of MC is B-cell expansion, which is responsible for the appearance of overt lymphoma in a number of patients, usually as a late manifestation [4–6,19–22]. Cryoglobulinemic vasculitis is frequently associated with HCV infection, especially in some geographical areas such as Southern Europe: in Italy the association is >95% [1,4–6]. Conversely, in the same geographical areas the prevalence of 'essential' MC is quite negligible; however, the etiopathogenesis of this rare condition represents an intriguing matter, which is discussed in another article of this supplement [23].

Because of its clinical polymorphism, cryoglobulinemic vasculitis may overlap with other rheumatic disorders such as Sjögren's syndrome and rheumatoid arthritis (Fig. 3); on the other hand, these rheumatic disorders may be occasionally associated with HCV infection [6, 24–34] (Fig. 2). Differential diagnosis between primary Sjögren's syndrome and cryoglobulinemic vasculitis may result very difficult in some patients; this is particularly true in patients with sicca syndrome, cryoglobulinemia and

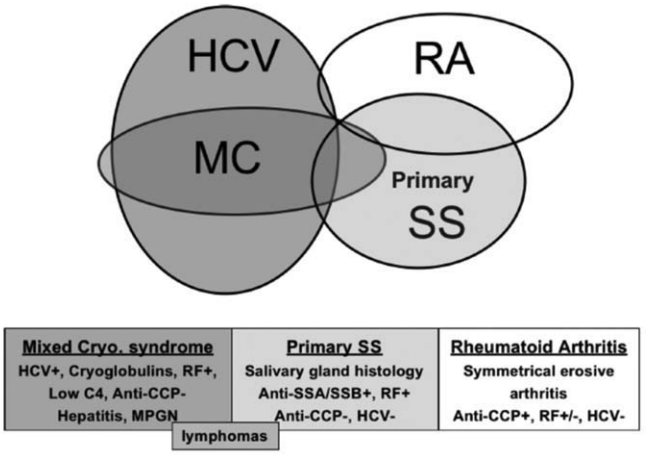

Fig. 3. Mixed cryoglobulinemia (MC) syndrome, primary Sjögren's syndrome (SS) and rheumatoid arthritis (RA) show a clinico-pathological overlap, including their possible association with HCV infection. Some important findings may be usefully employed for a correct differential diagnosis: the histopathological characteristics and severity of salivary gland involvement and specific autoantibodies (anti-RoSSA/LaSSB) are rarely found in MC patients; conversely, cutaneous leukocytoclastic vasculitis, visceral organ involvement (MPGM: membranoproliferative-glomerulonephritis, hepatitis), low C4, and HCV infection typically found in MC are seldom recorded in primary SS. Both MC syndrome and SS may develop a B-cell lymphoma. Finally, erosive symmetrical polyarthritis and serum anti-cyclic citrullinated peptide antibodies (anti-CCP) are specific findings of classical RA. RF: rheumatoid factor.

HCV-positivity [6]. In patients with Sjögren's syndrome, detection of mixed cryoglobulins is around 20% [35,36]; this finding seems to identify a particular clinical subset, characterized by a worse prognosis and frequent evolution to malignant lymphomas [35–38]. It is correct to classify these patients as MC/Sjögren's overlap syndrome [6,39]. The possible etiopathogenetic role of HCV in Sjögren's syndrome remains a controversial issue [6,40]. However, patients with HCV-associated Sjögren's syndrome show a significant low rate of anti-RoSSA/LaSSB (23%) along with a high prevalence of mixed cryoglobulinemia (50%), hypocomplementemia (51%), and systemic vasculitic manifestations (58%) (Fig. 3). This particular condition cannot be classified as primary Sjögren's syndrome [40]; at least 50% of patients could be better classified as cryoglobulinemic vasculitis with important clinico-prognostic and therapeutic implications [6]. The example of overlapping MC/Sjögren's condition suggests that in genetically predisposed individuals, HCV infection may trigger complex immune-system alterations, which may produce variable phenotypes mimicking different well-known diseases, namely Sjögren's syndrome, rheumatoid arthritis, dermatopolymyositis, etc. [6,20,24–40] (Fig. 3).

Chronic oligo-polyarthritis can be observed in HCV-infected individuals; it is often non-erosive and scarcely progressive. In patients with HCV-related cryoglobulinemic vasculitis the joint involvement is generally characterized by mild oligoarthritis, while symmetrical rheumatoid-like polyarthritis may complicate interferon treatment in HCV-positive patients [26,27]. Finally, given the relatively high prevalence of the two diseases, it is not rare to observe a simple association between classical rheumatoid arthritis and HCV infection. Figure 3 summarizes the main clinico-serological parameters for differential diagnosis between MC, Sjögren's syndrome and rheumatoid arthritis in the setting of HCV syndrome [6,41–43].

The actual relevance of other possibly HCV-related rheumatic disorders (Fig. 2), reported in anecdotal or limited patients' series, should be further investigated [25, 28–34].

3.2. Endocrine disorders

Thyroid involvement may be regarded as the most frequent and largely investigated endocrine alteration in HCV-positive patients.

The prevalence of abnormally high levels of anti-thyroid antibodies observed in these patients has varied markedly, ranging from 2% to 48% [44–47], with heterogeneous geographic distribution [18,48]. These discrepancies may be correlated to variable genetic predisposition [48] and environmental co-factors, such as iodine intake or diffusion of other infectious agents [49]. Moreover, subclinical hypothyroidism has been observed in 2–9% of patients with chronic hepatitis C [44–47,50], while miscellaneous thyroid alterations and elevated serum thyroid autoantibodies are generally higher in chronic hepatitis C than in hepatitis B or D [44–47,50].

More recently, the prevalence of thyroid involvement was investigated in a large chronic hepatitis C patients' series and compared to control groups from the general population from regions with different iodine intake, as well as with patients with chronic hepatitis B [51]. Autoimmune thyroid involvement and hypothyroidism were significantly more frequent in patients with chronic hepatitis C than in the comparison groups, whereas the prevalence of hyperthyroidism was similar. Comparable findings were also observed in another study focusing on the thyroid abnormalities in patients with HCV-related MC [52]. On the whole, abnormalities in thyroid function should be included among the complications of HCV syndrome. These patients should be periodically screened for thyroid involvement in order to identify patients in need of treatment and to early diagnose the rare but harmful neoplastic complication [17,53].

Type 2 diabetes may be another important manifestation of HCV syndrome, regardless of the presence and severity of liver damage [54–56]. Initially, clinic-based studies found an excess of type 2 diabetes in non-cirrhotic HCV-positive patients compared with patients with chronic hepatitis of other origin [57,58], not confirmed by another large study [59]. A recent Italian case–control study evaluated 564 non-cirrhotic HCV-positive patients compared with 302 control subjects without history of alcohol abuse, drug addiction, or positivity for markers of viral hepatitis, and 82 non-cirrhotic HBV-positive patients [60]. A significantly higher prevalence

of type 2 diabetes was recorded in non-cirrhotic HCV-positive patients compared with control subjects (12.6% vs 4.9% and 7%, respectively; $p = 0.008$). Interestingly, the prevalence of type 2 diabetes in non-cirrhotic HBV-positive patients (7%) was fully in the range of the reported age-adjusted prevalence rates for the Italian population (4%). The comparison between clinical phenotype of hepatitic and diabetic patients showed that non-cirrhotic HCV-positive type 2 diabetes was characterized by slightly older age, higher BMI, serum triglycerides and blood pressure levels, and lower HDL cholesterol concentrations. Moreover, type 2 diabetic non-cirrhotic HCV-positive patients had a significantly lower BMI than type 2 diabetic control subjects and a slightly but significantly ($p < 0.05$) higher BMI than non-diabetic non-cirrhotic HCV-positive patients [61]. Type 2 diabetes *per se* is characterized by older age, overweight, dyslipidemia, and higher blood pressure levels, the so-called "metabolic syndrome" phenotype. In contrast, non-diabetic non-cirrhotic HCV-positive patients were lean and had low LDL cholesterol levels. Low LDL cholesterol levels have been correlated with HCV-induced hypobetalipoproteinemia due to a binding competition between the virus and hepatic LDL receptor [61]. Finally, sex hormone alterations have been observed in HCV-positive MC [62]. Erectile dysfunction has been anecdotally reported in patients with HCV-related chronic hepatitis undergoing alpha-interferon treatment [63]. In order to investigate the possible role of HCV infection in the gonadal dysfunction, 207 male patients with HCV infection (102 with cryoglobulinemic vasculitis) were compared with 207 age-matched males, randomly selected from a series of 2,010 Italian general population subjects previously investigated for erectile dysfunction [64]. Exclusion criteria were: patients aged over 55 years, alpha-interferon treatment during the last 12 months, presence of diabetes, renal failure, hypothyroidism, cardio-vascular and psychiatric disorders. Erectile dysfunction was significantly more frequent in HCV-infected individuals compared to control subjects ($p < 0.001$). Among sex hormone determinations, total and free testosterone plasma levels were abnormally reduced in HCV-positive patients with erectile dysfunction. Both erectile dysfunction and low levels of total and free testosterone were not related to the severity of liver damage. These sex-hormone alterations along with the possible contribution of peripheral neuropathy can be responsible for erectile dysfunction, which should be confirmed by further investigations [6,63]. The above findings further support the role of the host hormonal environment in the pathogenesis of HCV-driven autoimmune disorders: reduced endogenous immunosuppressive activity due to low levels of adrenal–gonadal androgens could amplify the autoreactive lymphocyte proliferation triggered by HCV infection [63,64].

3.3. Neoplastic disorders

The oncogenic role of HCV infection in hepatocellular carcinoma (HCC) has been definitely established [65]. Since 1993, a possible role of this virus in the pathogenesis of malignant B-cell neoplasias has been also suggested [66]. This hypothesis was clinically suggested by the striking association of HCV and MC, a condition predisposing to B-cell lymphomas, and strongly supported by the HCV lymphotropism [4–9,19–22]. A surprisingly high prevalence of HCV infection in unselected Italian patients with B-cell non-Hodgkin's lymphoma (B-NHL) was first reported in 1994 [67]. Following this first observation an increasing number of epidemiological and laboratory investigations in patients' series from different countries, as well as in animal models, definitely demonstrated the etiopathogenetic role of HCV in a significant percentage of B-NHL patients [16, 68–73]; again, the association shows a variable geographical distribution as observed for HCV-related MC [16,73]. This particular virus-induced lymphoproliferation presents two main variants: lymphomas complicating HCV-positive MC and isolated HCV-positive B-NHL [5,6,73]. B-NHL may develop in patients with type II MC, usually after a long-term follow-up [4–6,19–22,73]. It can vary from diffuse large B-cell lymphoma (observed in 40–50% of cases) to marginal-zone lymphoma (extranodal, nodal or splenic) or, more rarely, B-cell chronic lymphocytic leukemia (B-CLL) and lymphoplasmacytic lymphoma/immunocytoma (LPL/Ic) [4–6,73]. The malignancy may be related to peripheral B-cell expansion and to lymphoid infiltrates observed in the liver and bone marrow of MC patients [4–6,15,73,74]. These infiltrates have been regarded as "early lymphomas", since they are sustained by lymphoid components indistinguishable from those of B-CLL and LPL/Ic [4–6,73]. However, unlike frank malignant lymphomas, they tend to remain unmodified for years or even decades and are followed by overt lymphoid tumours in about 10% of cases [1,4–6,20,73,74]. These characteristics justify the proposed term of "monotypic lymphoproliferative disorder of undetermined significance (MLDUS)" [1,4–6,73]. Of interest, type II MC-related MLDUS has its highest incidence in the same geographic areas where about 30% of 'idiopathic' B-NHL patients also display HCV-positivity, and where an increased prevalence of HCV genotype 2a/c has been observed in both MC and B-NHL [1,4–6,73,75].

3.4. Renal involvement

Chronic HCV infection has been correlated with glomerular and tubulointerstitial renal involvement in both native and transplanted kidney [1,4–6,76–80]. HCV-associated glomerulonephritis may include various histopathological types: membranoproliferative glomerulonephritis (MPGN) with and without mixed cryoglobulinemia, and less frequently membranous nephropathy, fibrillary and immunotactoid GN, rapidly progressive GN [71], exudative-pro-

liferative GN [1,4–6,76–80]. Cryoglobulinemic glomerulonephritis, namely type I MPGN, is more commonly found, while 'primary' MPGN represents less than 1/3 of HCV-associated MPGN [76]. This latter has been described mainly in the USA and Japan [76–81]. However, the real prevalence of MPGN without detectable cryoglobulinemia is difficult to assess; it may represent a subclinical form of MC, possibly due to difficulties and/or inadequate methods in detecting serum cryoglobulins [5,76]. In some patients MPGN is the presenting symptoms of MC syndrome that may develop later in the course of the disease [4–6,76]. Renal involvement is one of the most harmful complications in HCV-associated MC syndrome, and may severely affect the patient's clinical outcome [4]. It is the consequence of cryo- and non-cryoprecipitable immune-complex deposition in the glomeruli. The exact role of HCV in the aetiology of glomerulonephritis is not universally accepted; however, the presence of HCV particles in immune complexes seems to support an indirect involvement of this virus in the pathogenesis of glomerulonephritis [1,4–6,76,82].

3.5. Other HCV-related disorders

Miscellanea of organ- and non-organ specific, immune-mediated diseases can be correlated with HCV infection. One of the most largely investigated is porphyria cutanea tarda (PCT) [1,83–87]. This is the most common type of porphyria, characterized by reduced activity of uroporphyrinogen decarboxylase (URO-D), an enzyme involved in the heme biosynthetic pathway, and by frequent chronic liver involvement. Since URO-D deficiency is a 'sine qua non' but not sufficient condition for overt PCT, various triggering factors, including viral infection, have been proposed. A role of HCV infection has been investigated in several studies worldwhile reporting a wide range of association [86]. The pathogenesis of HCV-related PCT is particularly intriguing; both metabolic factors, in particular altered genes involved in iron metabolism [87], and a cross-reactivity of host versus HCV antigens have been proposed [85]. On the whole, HCV-positive patients without PCT do not show significant alteration in porphyrine metabolism [1,83]; therefore, it is supposable that a genetically driven reactivity is decisive, while HCV may exert an indirect role, possibly as triggering factor. HCV-related lichen planus is another important association, in particular the orally located lichen, with a variable geographic prevalence [1,88]. Moreover, several mucocutaneous manifestations are variably reported in HCV-infected individuals, generally referring to limited or anecdotal observations [1]. HCV-positive patients may develop acute episodes or chronic manifestations of well-known skin diseases; these symptoms are expressions of immune-mediated cutaneous injury, triggered by HCV antigens and often amplified by interferon treatment [1,88]. In many cases cutaneous manifestations, often with the contribution of peripheral nerve alterations, severely affect the patients' quality of life [4]. While peripheral neuropathy is a common complication of HCV infection, mainly in cryoglobulinemic vasculitis [4–6,89], central nervous system involvement is less common; it is more often observed in patients with overt MC syndrome [1,90]. Vascular manifestations, including central nervous system involvement, may represent late comorbidities of HCV syndrome, particularly in patients with more severe extra-hepatic manifestations and long-term steroid treatment. Some cardiovascular manifestations have been reported during HCV infection, but not confirmed by other studies [1,91,92]. Finally, an intriguing, still controversial aspect is the possible etiopathogenetic role of HCV in autoimmune hepatitis (AIH) [1,4–6,18,93–95]. Patients with autoimmune hepatitis may present mixed cryoglobulins, HCV infection, and extrahepatic manifestations such as thyroiditis, sicca syndrome, arthritis [65]; vice versa, patients with HCV infection show one or more non-organ-specific auto-antibodies. In this respect, the antigenic target specificity of HCV-related autoantibodies shows only quantitative differences compared to those associated with "primary" autoimmune hepatitis [1]. Again, the heterogeneous geographical distribution of HCV-associated autoimmune hepatitis [18] suggests a possible involvement of various pathogenetic co-factors; among these HCV might trigger a peculiar AIH clinico-serological subset, prevalently in specific geographical areas.

4. Conclusions

The strength of association as well as the pathogenetic role of HCV varies largely among different diseases and for each disease among patient series from different countries. Generally each disease *per se* represents a clinical syndrome, including different clinico-serological subsets; these latter are the resulting phenotypes of multiple – genetic, environmental, infectious – pathogenetic cofactors. In this scenario, HCV infection, with the contribution of other pathogenetic agents, may reproduce distinct autoimmune or neoplastic disease subsets. The complex of HCV-related disorders is a continuum, as suggested by some patients' clinical history that may display the entire spectrum. It is not rare to observe HCV-infected individuals with mild, often limited manifestations, which may progress, generally during a long-lasting follow-up period, to more severe systemic manifestations, including malignancies (Fig. 1).

On the whole, HCV syndrome is a multifaceted clinico-pathological condition; the challenge of future investigations is to better elucidate the exact boundaries of this syndrome and the actual pathogenetic role of the virus in different conditions.

Conflict of interest statement

None declared.

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