Hepatitis: A Global Health Concern

Chapter 5

Extra-Hepatic Manifestations of Hepatitis C Virus Infection

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Abstract

Hepatitis C virus (HCV) chronic infection is characterized by both hepato- and lymphotropism responsible for either liver involvement and one or more extrahepatic manifestations (HCV-EHMs). In particular, HCV lymphotropism may represent a chronic stimulus for the immune-system leading to poly-oligoclonal B-lymphocyte expansion in a high percentage of HCV-infected individuals. The consequent production of auto antibodies and immune-complexes, among which mixed cryoglobulins, may produce different immune-mediated organ- and non-organ-specific disorders. The presence of serum cryoprecipitable immune-complexes, characterizes the mixed cryoglobulinemia syndrome (MCs); this is a small-vessel systemic vasculitis (also termed 'cryoglobulinemic vasculitis'), represents the prototypic disorder of HCV-EHMs. Noteworthy, HCV-infected patients with MCs may develop a frank malignant B-cell non-Hodgkin's lymphoma (B-NHL); this finding suggested a possible link between HCV itself and apparently 'idiopathic' B-NHL. Several clinico-epidemiological and laboratory studies underlined the HCV oncogenic potential; in addition to hepatocellular carcinoma, a causative role of HCV has been largely demonstrated in a significant percentage of isolated B-NHL, as well as in patients with papillary thyroid cancer. The latter malignancy may complicate the autoimmune thyroid involvement that is a frequent manifestation of HCV infection.

Besides typical hepatic manifestations, HCV-infected individuals may develop a variable combination of autoimmune disorders (arthritis, sicca syndrome, porphyria cutanea tarda, glomerulonephritis, peripheral neuropathy,

cardiovascular and pulmonary manifestations) and malignancies. Both hepatic and HCV-EHMs can be termed 'HCV syndrome', a complex, multiform condition; the natural history of HCV syndrome is the result of multifactorial and multistep pathogenetic process, varying from isolated, mild manifestations, to systemic life-threatening disorders, including malignancies. The heterogeneous geographical distribution of HCV-EHMs suggests an important role of different host genetic and environmental co-factors.

The epidemiological, etiopathogenetic, clinico-therapeutical aspects of HCV syndrome are examined in detail.

Keywords: Hepatitis C virus; Cyoglobulinemia; Mixed Cryoglobulinemia; Cryoglobulinemic Vasculitis; Autoimmunity; Thyroid; Diabetes; Lymphoma; B-cell NHL; Cancer

1. Introduction

Hepatitis C virus (HCV) has been identified in 1989 as the main agent of so-called nonA/nonB chronic hepatitis [1]; the virus infects about 200 million people world-wide, leading to both chronic liver disease and a number of extrahepatic manifestations (HCV-EHM). The striking association between HCV and mixed cryoglobulinemia syndrome (MCs) represents the first report regarding spectrum of HCV-EHM; it appeared in 1991 soon after the discovery of HCV [2]; since then, HCV-related MCs represented the prototype of systemic HCV-EHM. Moreover, the detection of HCV lymphotropism in patients with hepatitis C with/without MCs [3,4] decisively contributed to the knowledge of the complex etiopathogenetic mechanisms underlying HCV-EHM. The **Figure. 1** summarizes the main steps that characterized the clinical and laboratory investigations regarding the HCV-EHM, with the important identification of the etiopathogenetic link of HCV and MCs, extrahepatic malignancies, mainly B-cell non-Hodgkin's lymphoma (B-NHL), and other organ- and non-organ specific autoimmune disorders [5-8]. Taken together the complex of both hepatic and extra-hepatic HCV-driven diseases can be tagged as HCV syndrome **(Figure. 2,5,9)**. With the more recent availability of new direct acting antiviral (DAAs) with very high rate of HCV eradication a new era of this long history of HCV-EHM has begun **(Figure. 1,10)**.

2. Mixed Cryoglobulinemia Syndrome

The term cryoglobulinemia refers to the presence in the serum of one (monoclonal cryo-immunoglobulinemia) or more immunoglobulins (mixed cryoglobulinemia, MC), which precipitate at temperatures below 37°C and redissolve on rewarming. It is an *in vitro* phenomenon that in the majority of cases is not correlated to specific clinical symptom (s) **(Figure. 3)** [5, 7]. Cryoglobulinemia is usually classified into three subgroups according to immunoglobulin composition **Figure. 3**]. Type I cryoglobulinemia consists of only one isotype or subclass of immunoglobulin. Both type II and type III mixed cryoglobulins are immune complexes (IC) composed of polyclonal IgG, the auto-antigens, and mono- or polyclonal IgM, respectively; the IgM are the corresponding auto antibodies with rheumatoid factor (RF) activity. The mixed

cryoglobulinemia type II often shows a microheterogeneous composition, characterized by oligoclonal IgM or a mixture of polyclonal and monoclonal IgM [5,7]. This particular serological subset, termed type II–III MC, could represent an intermediate, evolutive state from type III to type II MC. Cryoglobulinemia type I is usually associated with well-known hematological disorders and it is often asymptomatic [5-7]. Similarly, circulating mixed cryoglobulins can be detected in a great number of infectious, including about 50% of HCV-infected individuals, or systemic disorders; generally they represent an isolated laboratory finding without any clinical consequences. In contrast, MCs constitutes a distinct disorder, firstly described in 1966 **(Figure. 1, 11)**, which is classified among systemic vasculitides. Organ damage of MCs, also termed cryoglobulinemic vasculitis **(Figure 3; 5-7)**, is secondary to vascular deposition of circulating IC, mainly mixed IgG-IgM cryoglobulins and complement, with the possible contribution of T- and B-lymphocyte infiltration, hemorheological alterations, and local factors. The histopathological hallmark of MCs is the typical leucocytoclastic vasculitic **(Figure. 4)**; according to its clinico-histological features, MCs is included in the subgroup of small-vessel systemic vasculitides, responsible for multiple organ involvement **(Figure. 4, 5-7)**. Generally MCs is included among rare diseases, but no adequate epidemiological studies of its actual prevalence have been carried out. Different cohort studies suggest that the prevalence of MC is geographically heterogeneous; the disease is more common in southern Europe than in northern Europe or North America [5-7]. Because of MCs clinical polymorphism a single manifestation, namely skin vasculitis, hepatitis, nephritis, peripheral neuropathy, etc. is often the only apparent or clinically predominant feature; therefore, patients with MCs are frequently referred to different specialties **(Figure. 2, 4)**; therefore, a correct diagnosis might be delayed or overlooked entirely, as well as the actual prevalence of MC can be underestimated [5-7]. In addition, the frequent dispersion of patients among different specialties, symptom composition of MCs may vary greatly among patient series from various tertiary care facilities. The MCs is more common in women than in men (F:M = 3:1) with disease onset frequently recorded in the fifth decade and in older people.

The epidemiology of MC is closely associated with hepatitis C virus (HCV) infection; in particular, HCV-infected individuals show low levels of circulating mixed cryoglobulins in over 50% of cases, without specific clinical relevance, while only 5% may develop overt MCs. Given the large diffusion of HCV infection a significant incidence of some late HCV-EHMc, such as MC, could be observed, especially in underdeveloped countries. In contrast, 'essential' MCs is generally seen in a significantly lower proportion of patients, more often reported in Northern Europe and Northern America. Clinically, MCs is characterized by a clinical triad of purpura, weakness and arthralgias, and by a variable combination of symptoms, including chronic hepatitis, membranoproliferative glomerulonephritis (MPGN), peripheral neuropathy, skin ulcers, diffuse vasculitis and, less frequently, lymphatic and hepatic malignancies **(Figure. 4, 5-7, 12, 13)**. The presenting symptoms of MCs vary greatly among patients; similarly, at the

first examination, MC shows different clinico-serological patterns, varying from apparently isolated serum mixed cryoglobulins, in some cases associated with mild manifestations such as arthralgias and/or sporadic purpura, to severe cryoglobulinemic syndrome with multiple organ involvement **(Figure. 4, 5-7)**. The disease shows a combination of serological findings (mixed cryoglobulins with RF activity and frequently low C4) and clinico-pathological features (purpura and leucocytoclastic vasculitis with multiple organ involvement, including severe non-healing skin ulcers). In chronically HCV-infected subjects, asymptomatic serum mixed cryoglobulins can be found. This condition may precede the clinical onset of disease by years or decades. On the other hand, some patients show typical cryoglobulinemic syndrome without serum cryoglobulins, the hallmark of the disease. MC is characterized by a large amount of cryoprecipitable IC, with the cryoglobulins representing a variable percentage of them among different patients as well as in the same patient during follow-up. Therefore, repeated cryoglobulin determinations are necessary for a correct diagnosis in these patients [5-7]. In over two-thirds of patients **(Figure. 4)**, overt chronic hepatitis, generally with a mild to moderate clinical course, can be seen throughout the natural history of the disease. This manifestation, uncommon in other systemic vasculitides, has suggested the possible link with hepatotropic viruses leading to the discovery of the important association with HCV soon after its identification **(Figure. 1, 2)**. Chronic hepatitis may evolve to cirrhosis in about 25% of patients, while hepatocellular carcinoma is quite rarely recorded [5-7]. In a few cases, especially in patients with renal failure due to chronic glomerulonephritis, hepato-renal syndrome develops as a major life-threatening complication. Generally, there are no associations between the severity of clinical symptoms, such as glomerulonephritis, skin ulcers and/or diffuse vasculitis, and the serum levels of cryoglobulins and/or hemolytic complement [5-7,14]. Low complement activity is almost invariably detected in MC. It is characterized by a typical pattern independently of disease activity; namely, low or undetectable C4 with normal or slightly reduced C3 serum levels [5-7,14]. Some endocrinological disorders are significantly more common in patients with MC than in the general population, including thyroid disorders, diabetes and gonadal dysfunction [15,16]. B cell lymphoma is the most common malignancy found, often as a late manifestation of MCs as well as in patients with isolated HCV infection [5-7,14,17-19]. This complication may be related to peripheral B lymphocyte expansion and to lymphoid infiltrates found in the liver and bone marrow, which represent the pathological substrate of the disease [5-7,12]. The MCs classification is mainly based on the serological and clinical hallmarks of the disease, namely, circulating mixed cryoglobulins, low C4 and orthostatic skin purpura. Moreover, leucocytoclastic vasculitis, involving medium and, more often, small blood vessels (arterioles, capillaries and venules) is the typical pathological finding of affected tissues. It is easily detectable by a skin biopsy of recent vasculitic lesions (within the first 24–48 h) [5-7, 20]. In all cases, the detection and characterization of serum cryoglobulins by means of simple standardized methodology is necessary for a definite classification of MC syndrome **(Figure. 3, 4, 5-7, 9)**.

3. Etiopathogenesis of MCs and other HCV-EHMs

Several clinico-epidemiological studies reported that chronic hepatitis was one of the most common symptoms of MC; its prevalence progressively increases to over two-thirds of patients during the clinical course of the disease [8]. This observation has suggested since the 1970s a possible role for hepatotropic viruses in the pathogenesis of the disease, mainly hepatitis B virus (HBV), previously correlated with another systemic vasculitis, i.e. the polyarteritis nodosa. However, HBV may be a causative factor o in <5% of MCs patients **(Figure. 1, 5-7)**. In 1989, the discovery of HCV as the major etiological agent of non-A-non-B chronic hepatitis, was crucial for the etiopathogenetic studies of MCs. In 1990, two pioneering studies reported a significantly higher prevalence of serum anti-HCV antibodies in MCs patients compared to general population [5-7,21,20]. This association was deeply demonstrated in 1991, when the presence of HCV RNA was detected by polymerase chain reaction (PCR) in 86% of patients with MC [2]. Following this, an increasing number of studies including clinico-epidemiological observations, as well as both histopathological and virological investigations (HCV RNA detection by PCR and/or in situhybridisation) established the important role of HCV in the pathogenesis of MC **(Figure. 5)**. Overall, the prevalence of HCV infection in patients with MC ranged from 70% to almost 100% among different patient populations [5-7,12]. The clinical development of MCs and other HCV-EHMs is closely overlapping with the natural history of chronic HCV infection **(Figure. 1,5)**. MC phenotypes are also the result of genetic and/or environmental cofactors, which remain largely unknown **(Figure. 1, 5, 5-7)**. HCV has been recognized to be both a hepato- and lymphotropic virus, as suggested by the presence of viral replication in the peripheral lymphocytes of patients with type C hepatitis with/without MCs [3,4]. HCV is an RNA virus without reverse transcriptase activity; In this respect, the viral genome cannot integrate in the host genome. In this respect, chronic stimulation of the lymphatic system exerted through HCV epitopes, autoantigen production and/or a molecular mimicry mechanism has been suggested, similarly to Helicobacter pylori-associated MALT lymphoma of the stomach, for which a multi step process is necessary. Another important pathogenetic factor of MCs and other HCV-EHMs could be the interaction between the HCV E2 envelope protein and CD81 molecule, representing a strong stimulation of B-cell compartment **(Figure. 5)**. The following pathogenetic step may be the [14,18] translocation detected in B cells of HCV-infected subjects, regardless the presence/absence of MCs; it may lead to increased expression of Bcl-2 protein, responsible for abnormally prolonged B cell survival. The consequent B lymphocyte expansion **(Figure. 5; 23)** is responsible for the production of mixed cryoglobulins, RF, and other organ-specific autoantibodies. These latter may explain the possible complication with one or more organ- and non-organ-specific, immune-mediated diseases that characterize the HCV syndrome [5-7,9]. In addition, the prolonged B cell survival may represent a predisposing condition for further genetic aberrations, which may lead to frank B cell malignancy as a late complication of HCV-related MCs or in HCV-infected

patients developing apparently 'idiopathic' B cell lymphomas **(Figure. 5, 5-7, 18, 19)**. This association was first described in unselected Italian patients with idiopathic B cell lymphomas and later confirmed by different epidemiological and laboratory studies [17-19].

4. HCV-EHMs

The Figure. 6 shows the various HCV-EHMs classified according to the strength of association with the virus [5-7]. The MCs and B-cell lymphoproliferative disorders, mainly non-Hodgkin's lymphomas, are the most frequent and well-documented HCV-EHMs. The oncogenetic role of HCV is well demonstrated considering that the virus is the major etiological factor of hepatocellular carcinoma. Moreover, a possible role of this virus in the pathogenesis of malignant B cell neoplasias has also been suggested following the discovery of striking association between HCV and MC, a condition that may be complicated by B cell lymphomas, as well it was reinforced by the demonstration of HCV lymphotropism [3,4]. In 1994, a surprisingly high prevalence of HCV infection in unselected patients with B cell non-Hodgkin's lymphoma (B-NHL) was first reported [17]. Successively, an increasing number of epidemiological and laboratory investigations in patient series from different countries, as well as in animal models, confirmed the etiopathogenetic role of HCV in a significant percentage of patients with B-NHL [18,19]. As for HCV-related MC, this association is characterized by variable geographical distribution [5-7]. A significantly high prevalence of thyroid cancer complicating HCV-related hepatitis and HCV-related MC compared with controls was first noted in 1999 [15,24]. These data were subsequently confirmed in a case–control study, which reported a high prevalence of HCV in patients undergoing surgery for papillary thyroid cancer [25]. Overall, HCV infection was associated with a high risk for liver cancer, multiple myeloma, B-NHL and thyroid cancer **(Figure. 6)**. Besides MCs other cutaneous manifestations are often seen in HCV-infected subjects. Among these, porphyria cutaneatarda (PCT) is one of the most investigated [5-7,26]. PCT is the most frequent type of porphyria; it is characterized by reduced activity of uroporphyrinogen decarboxylase, an enzyme involved in the haem biosynthetic pathway, and by frequent chronic liver disease. Since uroporphyrinogen decarboxylase deficiency is an essential condition, but not sufficient, for definite classification/diagnosis of PCT, various triggering factors, including viral infection, should be taken into account [26]. A role of HCV infection has been investigated in several studies worldwide, which have reported a variable percentage of associations. It may be supposed that a genetically driven reactivity is decisive, while HCV may exert an indirect role, possibly as a triggering factor [5-7]. Peripheral neuropathy is a common complication of HCV infection, mainly in patients with cryoglobulinemic vasculitis, while central nervous system involvement is less common. Vascular manifestations, including central nervous system involvement, may represent a direct HCV-related manifestation, mainly observed in patient series from eastern Asian countries, and/or as late comorbidity of HCV syndrome, particularly in patients with more severe extrahepatic manifestations treated

with long-term corticosteroids [5-7].

Glomerular and tubulo-interstitial renal involvement in both native and transplanted kidneys may be associated with HCV infection [27]. HCV-related glomerulonephritis may include various histopathological types: membranoproliferative glomerulonephritis (MPGN) type I with and without MCs and, less frequently, membranous nephropathy, fibrillary and immunotactoid glomerulonephritis, rapidly progressive glomerulonephritis and exudative-proliferative glomerulonephritis [27].

In some patients, MPGN is the presenting symptom of MC syndrome that may develop later in the course of the disease. Renal involvement is one of the most harmful complications of HCV-associated MC syndrome, and may severely affect the patient's clinical outcome [27, 8].

Thyroid involvement represents the most common and thoroughly investigated endocrine alteration in HCV-positive patients [15,25] in particular, subclinical hypothyroidism has been found in 2–9% of patients with chronic hepatitis C. Overall, autoimmune thyroid involvement and hypothyroidism were significantly more common in patients with chronic hepatitis C compared with general population [5-7,15].

Chronic immune-mediated inflammatory thyroid lesions may be responsible for the papillary thyroid cancer found in a significant percentage of HCV-infected subjects compared with controls [15]. On these bases, abnormalities in thyroid function should be included among the most frequent complications of HCV syndrome [6].

Type 2 diabetes may be another important manifestation of HCV syndrome, regardless of the presence and severity of liver damage [6,15].

5. HCV Syndrome

The strength of association as well as the pathogenetic role of HCV varies greatly among potentially HCV-related diseases and for each disease among patients' series from different countries [5-7,9]. Each disease itself may represent a clinical syndrome including different clinico-serological variants. These resulting phenotypes may be regarded as the expression of a variable combination of different – genetic, environmental, infectious – pathogenetic cofactors. In this scenario, HCV infection may be associated with distinct subsets of autoimmune and/or neoplastic diseases in the presence of specific host genetic predisposition and exogenous agents. The complex of HCV-related disorders is a continuum, as suggested by the clinical history of individual patients. It is not rare to see HCV-infected subjects with initial limited, mild manifestations, which may progressively evolve to more severe systemic manifestations, including malignancies **(Figure. 5,6)**.

Overall, HCV syndrome [6] is a multifaceted clinico-pathological condition **(Figure. 2)**. The HCV-EHMs are referred to different specialists according to prevalent clinical symptom (s); this aspect may clearly influence the evaluation of the relative prevalence of various manifestations **(Figure. 6,7; 6)**. The challenge for future investigations is to better elucidate the exact boundaries of this syndrome, the prevalence of each HCV-EHMs, and the actual pathogenetic role of HCV in different conditions.

6. Diagnostic Guidelines and Differential Diagnosis of HCV-EHMs

MCs represents a crossroads between some autoimmune diseases and malignancies (hepatocellular carcinoma, B cell NHL, papillary thyroid cancer) [6]. We can observe in the same patient a slow progression from mild HCV-associated hepatitis to various extrahepatic manifestations (arthralgia's, sicca syndrome, Raynaud's phenomenon, RF positivity, etc.) and, ultimately, to overt MC syndrome with typical clinico-serological manifestations. In a minority of HCV-infected patients, a malignancy may develop, generally after a long follow-up period. Therefore, a careful patient evaluation is necessary for a correct diagnosis of HCV-EHMs, following the diagnostic guidelines for patients with HCV-EHMs proposed by an international, multidisciplinary expert study group [6].

7. Treatment of HCV-EHMs

The treatment strategies of patients with symptomatic HCV infection, the HCV syndrome, are necessarily influenced by the variable composition of hepatic and EHMs [10]. In individual patient, clinical and prognostic characteristics of HCV syndrome should be carefully evaluated taking into account either the degree of liver involvement and the presence of one or more HCV-EHMs [5-7,10]. We can draw comprehensive therapeutical guidelines based of different symptom composition largely variable among patients and in the single patient during the follow-up [10]. In clinical practice, it can be useful to look at the therapeutical strategy developed for patients with MCs, which may reproduce the different clinical variants of HCV syndrome [5-7,10]. This strategy is essentially based on three main levels of intervention **(Figure. 5)**: etiological treatment directed at HCV eradication by means of new direct acting antivirals (DAAs), pathogenetic therapies with immunomodulating-antineoplastic drugs, and symptomatic/pathogenetic therapies such as corticosteroids and plasmapheresis [10]. These three different therapeutic approaches are not mutually exclusive; combined treatments are usefully employed in patients with HCV-positive MCs, tailored on the single patient considering the composition and severity of clinical features **(Figure. 5, 5-7, 10, 28-31)**. The clinical usefulness of immunosuppressive treatments has been largely reported in cryoglobulinemic patients, particularly for patients treated with anti-CD20 monoclonal antibody therapy [5-7, 32]. Antiviral treatment, alone or in combination with immunosuppressors, may lead to HCV eradication and MCs remission [28-31] as above mentioned the beneficial effect of HCV erad-

ication is also observed in patients with B-cell NHL with/without MCs [10]. In theory, antivirals should be regarded as the gold standard treatment in patients with overt HCV-EHMs. The preemptive use of DAAs in HCV-infected individuals even in the absence of relevant clinical manifestations is a very critical issue, considering the necessary cost-benefit analysis.

On the other hand, the results of these treatments seems to be unpredictable, especially in patients with HCV-EHMs, this aspect is particularly problematic because of the absence of definite clinico-biological parameters predictive of possible recovery of immune-system alterations after HCV eradication. We can hypothesize the existence of a point of no return, possibly related to disease duration and/or host conditions, which may be critical for the restoring of HCV-driven autoimmune-lymphoproliferative alterations. Long-term clinical monitoring of HCV-infected patients according to current diagnostic guidelines is mandatory for a timely diagnosis and treatment of both hepatic and EHMs [10]. International Diagnostic and therapeutic guidelines for patients with HCV-CV have been recently proposed by an international, multidisciplinary expert study group [6].
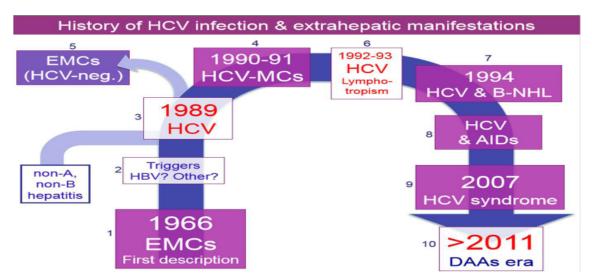
8. Figures

Figure 1: History of HCV infection and extrahepatic manifestations (HCV-EHMs) and HCV syndrome. The figure summarizes the main steps leading to different HCV-EHMs and HCV syndrome: 1. The first description of mixed cryoglobulinemia syndrome (MCs) in 1966; 2. Given the high prevalence of chronic hepatitis in MCs patients, the possible triggering role of hepatotropic viruses was investigated; 3. The discovery of HCV; 4.the striking association of HCV with MCs deeply influenced the following studies; 5. Therefore, only a minority of patients may be classified as essential MCs (EMCs); 6. The demonstration of the HCV lymphotropism represents another decisive step; 7. Given the possible evolution of MCs to frank B-cell non-Hodgkin's lymphomas (B-NHL) suggested a possible role of HCV in 'idiopathic' B-NHL that was firstly demonstrated in 1994; 8. during the following years a number of autoimmune diseases (AIDs) were associated with HCV; 9. The term of 'HCV syndrome' encompassing both hepatic and EHMS was suggested; 10. the availability of direct acting antivirals (DAAs) opened a new era in the treatment of HCV syndrome with great opportunity to better understand the actual etiopathogenetic role of HCV in the diseases.
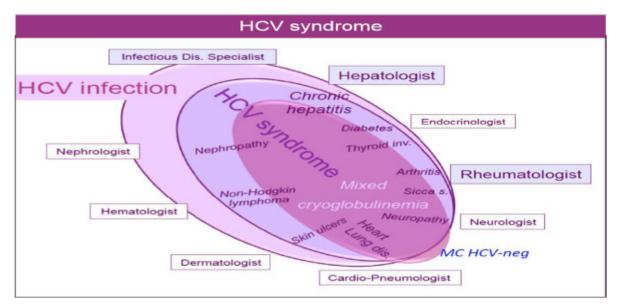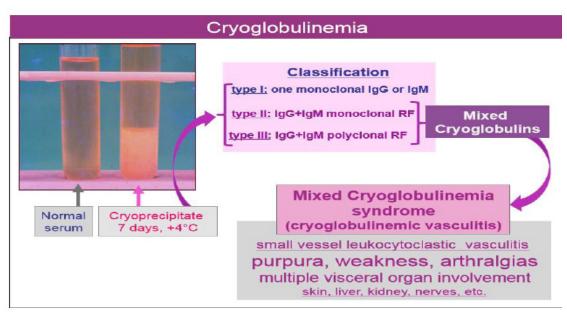
Figure 2: The HCV syndrome. HCV is anhepato- and lymphotropic virus responsible for a wide spectrum of both hepatic and extrahepatic diseases. The figure schematically reproduces the spectrum of hepatic and extrahepatic HCV-related manifestations (HCV-EHMs): the HCV syndrome. Besides HCV-infected patients without clinical manifestations or isolated liver involvement, HCV-EHMs may include a variety of non-organ and organ-specific autoimmune/lymphoproliferative and neoplastic disorders; therefore HCV-positive patients are commonly referred to different specialists according the prevalent clinical manifestation(s). Mixed cryoglobulinemia syndrome (MCs), also termed cryoglobulinemic vasculitis, represents the prototype of extra-hepatic systemic immune-mediated disorder characterized by multiple organ involvement. Only a minority of MC patients is HCV-negative.

Fiure 3: Mixed cryoglobulinemia syndrome (MCs). MCs is a small vessel, leukicytoclastic vasculitis. Serum cryoprecipitate (evaluated after 7 days' storage at 4°C) composed by polyclonal IgG (autoantigen) and monoclonal IgMk (autoantibody) immune-complexes, compared to normal serum sample; the presence of monoclonal, type I cryoglobulinemia is clinically asymptomatic and often detectable in patients with hematological disorders.
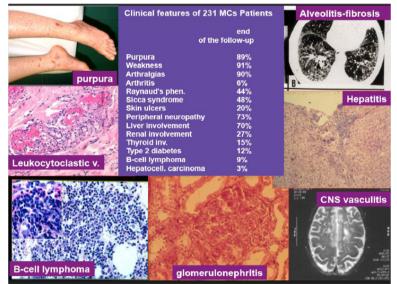
Figure 4: Prevalence of clinical symptoms in patients with mixed cryoglobulinemia syndrome (MCs)
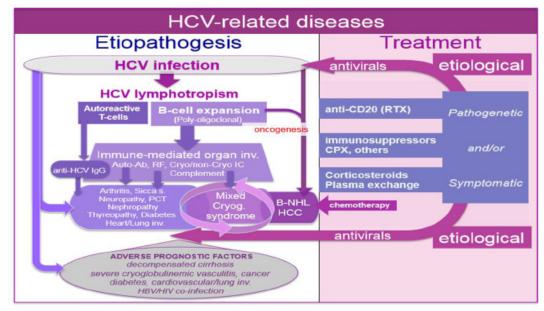

Figure 5: Etiopathogenesis and treatment of HCV syndrome. Left: the figure shows the etiopathogenetic cascade leading to HCV syndrome, which is a multifactorial and multistep process: the remote events include HCV infection and its lymphotropism, host predisposing genetic factors and, possibly, unknown environmental/toxic triggers. Chronic HCV infection induces profound immune-system alterations with prominent 'benign' lymphoproliferation, from one side, and oncogenetic alterations, from another side. Possibly a molecular mimicry mechanism and a direct infection of B-lymphocytes by HCV are responsible for multiple lymphocyte alterations. The main consequence is a 'benign' B-cell proliferation with production of various autoantibodies, among which rheumatoid factor (RF) and cryo- and non-cryoprecipitable immune complexes (IC). These serological alterations may be correlated with different organ- and non-organ-specific autoimmune disorders, including the systemic manifestations of MCs. The appearance of malignant neoplasias can be seen in a small but significant percentage of patients, usually as a late complication. Both autoimmune and neoplastic disorders show a clinico-serological and pathological overlap. Often, autoimmune organ-specific manifestations may evolve to systemic conditions, such as mixed cryoglobulinemia syndrome, and less frequently to overt malignancies. Conversely, it is not uncommon that patients with malignancies develop one or more autoimmune manifestations. In this scenario, MCs is at the crossing road between autoimmune and neoplastic disorders.

Right: The therapeutical strategies of HCV syndrome and in particular of MCs are essentially based on three main levels of intervention: the etiological treatment by means of antiviral drugs directed at HCV eradication, the pathogenetic therapies with immunomodulating/antineoplastic drugs, and the pathogenetic/symptomatic therapies such as corticosteroids and plasma exchange (see also text).

HCV: hepatitis C virus; IC, immune complexes; SS: sicca syndrome; PCT: porphyria cutaneatarda; RF, rheumatoid factor; MCs: mixed cryoglobulinemia syndrome.
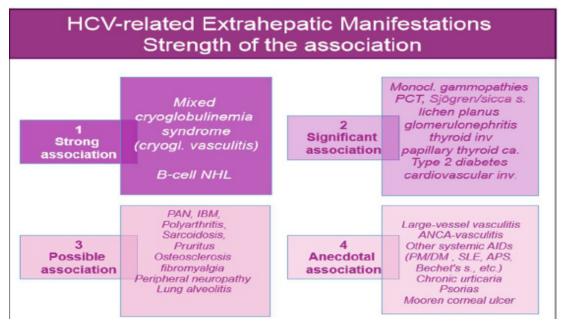
Figure 6: HCV-related extrahepatic manifestations classified according to the strength of association with HCV.
PCT: porphyria cutaneatarda; B-NHL: B-cell non-Hodgkin's lymphomas
PAN: periarteritisnodosa; IBM: inclusion body myositis; SLE: systemic lupus erythematous; PM/DM: polymyositis / dermatomyositis; APS: anti-phospholipid syndrome
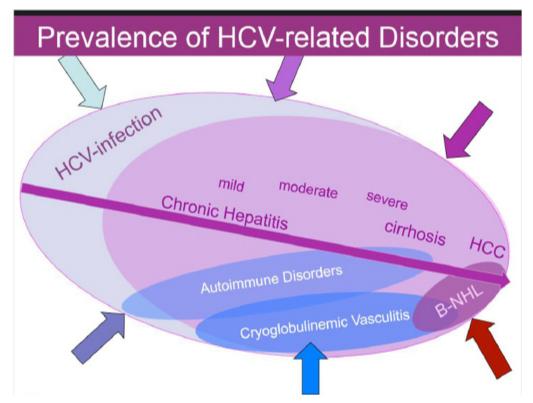

Figure 7: The complex of HCV-related hepatic and extrahepatic manifestations (HCV-EHMs). The figure schematically shows the complex of HCV-EHMs as analyzed by different observers. HCV-infection encompasses individuals with asymptomatic infection, patients with apparently isolated liver involvement, and patients with one or more HCV-EHMs. Clinico-epidemiological studies demonstrated a great geographical heterogeneity among different HCV-EHMs, as well as frequent discrepancies with regards to their prevalence reported in clinical studies from the same country. This latter may be related to both different specializations and/or variable methodological approaches of referral centers (arrows).

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