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## Extrahepatic manifestations of chronic hepatitis C virus infection

Patrice Cacoub<sup>1,2,3,4</sup>, Cloe Comarmond<sup>1,2,3,4</sup>, Fanny Domont<sup>1,4</sup>, Léa Savey<sup>1,4</sup>, Anne Claire Desbois<sup>1,2,3,4</sup>, David Saadoun<sup>1,2,3,4</sup>

<sup>1</sup> Sorbonne Universités, UPMC Univ Paris 06, UMR 7211, and Inflammation-Immunopathology-Biotherapy Department (DHU i2B), F-75005, Paris, France

<sup>2</sup> INSERM, UMR\_S 959, F-75013, Paris, France

<sup>3</sup> CNRS, FRE3632, F-75005, Paris, France

<sup>4</sup> AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, F-75013, Paris, France

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**Correspondance to** Pr Patrice Cacoub, MD. Department of Internal Medicine and Clinical Immunology, Hôpital La Pitié-Salpêtrière, 47-83, boulevard de l'Hôpital, 75651 Cedex 13. Paris. France

Tel: + 33 (0) 1 42 17 80 27; Fax: + 33 (0) 1 42 17 80 33; Email: patrice.cacoub@psl.aphp.fr

**ABSTRACT**

During hepatitis virus (HCV) chronic infection, extrahepatic manifestations are frequent and polymorphous. Initial description reported in large cohort of patients HCV-related autoimmune and/or lymphoproliferative disorders, from mixed cryoglobulinemia vasculitis to frank lymphomas. The relationship between HCV infection and such immune-related diseases has been formally demonstrated by epidemiological, clinical, immunological, pathological data and results of therapeutic trials. More recently, other non-liver related HCV-disorders have been reported including cardiovascular (i.e. stroke, ischemic heart disease), renal, metabolic, and central nervous system diseases. For these manifestations, most evidence come from large epidemiological studies; there is a need for mechanistic studies and therapeutic trials for confirmation. Beyond the risk of developing liver complications i.e. cirrhosis and liver cancer, HCV infected patients have an increased risk of morbidity and mortality related to non-liver diseases. HCV chronic infection should be analyzed as a systemic disease where extrahepatic consequences increase the weight of its pathological burden. The need of effective viral eradication measures is underlined.

Hepatitis C Virus (HCV) infection is a major health problem with 150-170 million people chronically infected. On one hand, these patients are at risk of developing liver complications i.e. cirrhosis and liver cancer, with an estimated liver-related mortality of 350,000 people/year. On the other hand, in large cohort studies, two third of HCV infected patients experienced extrahepatic manifestations (HCV-EHMs)<sup>1</sup>. Some of these conditions are well-documented and more common, while others are infrequent<sup>2-4</sup>. Soon after HCV discovery, HCV-related autoimmune and/or lymphoproliferative disorders, from benign mixed cryoglobulinemia to frank lymphomas, have been reported<sup>3,5</sup>. More recently, many other non-liver HCV-associated disorders have been reported including cardiovascular, renal, metabolic, and central nervous system diseases (**Table 1**). HCV infection showed a higher mortality rate for extra-hepatic complications<sup>6-9</sup>. All-cause mortality in HCV patients was increased more than twice with respect to HCV-negative<sup>10</sup>, probably related to serum HCV RNA positivity<sup>6</sup>. Viral eradication significantly reduced the rate of extra-hepatic deaths<sup>11-13</sup>. Recent therapeutic advances in the treatment of HCV, with the possibility to eradicate HCV following new direct antiviral therapies appears of major importance, for liver and non-liver manifestations of the disease.

### 1) ***Cryoglobulinemia vasculitis***

Mixed cryoglobulinemia (MC) vasculitis (Cryovas) is a small vessel vasculitis involving mainly the skin, the joints, the peripheral nerve system and the kidneys<sup>4</sup>. HCV infection is the cause of Cryovas in about 80% of cases. The disease expression is variable, ranging from mild symptoms (purpura, arthralgia) to fulminant life-threatening complications (glomerulonephritis, widespread vasculitis). Skin is the most frequently involved target organ: palpable purpura, chronic cutaneous ulcers, Raynaud's phenomenon, acrocyanosis, which may evolve to digital ulcerations. Neurologic manifestations range from pure sensory axonopathy to mononeuritis multiplex. The most frequent form is a distal sensory or sensory-motor polyneuropathy, presenting with painful, asymmetric paresthesia. Less frequently, multiple mononeuropathy may occur. Renal involvement is an acute or chronic type-I membranoproliferative glomerulonephritis with sub-endothelial deposits, strongly associated with the type II IgM kappa MC. The usual presentation is proteinuria with microscopic hematuria and a variable degree of renal insufficiency. Cryoglobulinemia is confirmed by the detection of protein precipitates in the patient's serum maintained at 4°C during at least 7 days, which dissolved at 37°C. HCV-MC are characterized as type II or type III cryoglobulins which consist of polyclonal IgG with monoclonal or polyclonal IgM with rheumatoid factor (RF) activity, respectively<sup>6</sup>. During follow-up, biological improvement can be assessed by the quantification of cryoglobulinemia and other surrogate markers (C4, CH50, RF).

During HCV infection, Cryovas is associated with advanced age, longer duration of infection, type II MC, a higher MC serum level and clonal B-cell expansions in both the blood and liver. The worse prognostic factors are an age > 60yrs at diagnosis and renal involvement<sup>14</sup>. The overall 5yrs survival rate after the diagnosis of Cryovas range from 90% to 50% in case of renal involvement. Increased mortality from liver involvement, cardiovascular disease, infection and lymphoma has been reported. In a retrospective Italian study of 231 patients, 79/97 deaths were linked to vasculitis (46%, of whom one-third due to renal involvement), cancer or haemopathy (23%), or liver disease (13%)<sup>15</sup>. Cryovas complications may result in progressive (renal involvement) or acute (pulmonary hemorrhage, gastrointestinal ischemia, cardiac, CNS involvement) life-threatening organ damage, with a mortality rate between 20% and 80%<sup>16,17</sup>. Intestinal ischaemia, pulmonary haemorrhage, high cryocrit levels and type II MC are associated with severe prognosis<sup>18</sup>.

There are multiple factors predisposing HCV-infected patients to develop Cryovas. Interaction between HCV and lymphocytes directly modulates B- and T-cell function and results in polyclonal activation and expansion of B-cell producing IgM with RF activity<sup>19</sup>. CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup>regulatory T cell are reduced in Cryovas patients<sup>20,21</sup> which may account for the expansion of peripheral auto-reactive B-cell that drive Cryovas. HLA-DR11 is associated with whereas HLA-DR7 appears to protect from Cryovas<sup>22</sup>. In a recent multi-center genome-wide association study significant associations were identified on chromosome 6, a single nucleotide peptide located within an intronic region of NOTCH4 ( $p=6.2 \times 10^{-9}$ ) and another found in between HLA-DRB1 and HLA-DQA1 ( $p=1.2 \times 10^{-7}$ )<sup>23</sup>. Specific virological factors have not yet been identified.

Most HCV-Cryovas manifestations respond to clearance of HCV during antiviral therapy with pegylated interferon (IFN) plus ribavirin<sup>24</sup>. Patients who relapse for HCV infection after responding to antiviral therapy usually relapse for the Cryovas with the return of viremia<sup>25</sup>. In case of persistent MC, relapse of vasculitis might also occur despite achieving a sustained virologic response (SVR); this situation should lead to look for a different underlying condition, especially B-cell lymphoma<sup>26</sup>. Recent use of triple anti-HCV therapy with pegylated-IFN/ribavirin and a direct antiviral agent (boceprevir or telaprevir) led to improved rates of SVR and Cryovas remission in HCV genotype 1<sup>27,28</sup>. Other direct-acting antivirals such as sofosbuvir and simeprevir have recently been licensed which facilitate the use of shortened courses of combination IFN-free therapy and are associated with high (>95%) SVR rates and few toxicities. International guidelines (i.e, EASL 2014)<sup>29</sup> state that treatment should be scheduled, not deferred, for patients with clinically significant extra-hepatic manifestations, like Cryovas. Rituximab is an interesting therapy in MC, as it targets B-cells, which are responsible for cryoglobulin production and finally Cryovas lesions. Two randomized controlled trial showed that rituximab has a better efficacy than conventional treatment (i.e., glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis)<sup>30,31</sup>. Two other controlled clinical trials showed

that addition of rituximab to pegylated-IFN/ribavirin led to a shorter time to clinical remission, better renal response rate, and higher rates of cryoglobulin clearance<sup>32,33</sup>.

In daily practice, HCV-Cryovas patients with mild to moderate disease should be given an optimal antiviral treatment. For patients with severe vasculitis (i.e. worsening of renal function, mononeuritis multiplex, extensive skin disease, intestinal ischemia...) control of disease with rituximab, with or without plasmapheresis, is required before initiation of optimal antiviral therapy<sup>4,34</sup>. Careful monitoring for adverse effects is mandatory, since some manifestations of HCV-Cryovas, such as peripheral neuropathy or skin ulcers, may worsen with IFN-based therapy. Low-dose corticosteroids may help to control minor intermittent inflammatory signs such arthralgia but do not succeed in case of major organ involvement. Other immunosuppressants should be given only in case of refractory forms of HCV-Cryovas, usually associated with underlying B-cell lymphoma<sup>35</sup>.

## **2) B-cell lymphoproliferative diseases**

A high prevalence of HCV infection in patients with B-cell non-Hodgkin's lymphoma (B-NHL) was reported in meta-analyses, with a gradient from north to south<sup>36-41</sup>. HCV was associated with marginal zone NHL (Odds ratio, OR 2.47) and diffuse large B-cell NHL (OR 2.24). A serum monoclonal gammopathy, more frequently IgMk, was frequently observed<sup>42</sup>. A lower cumulative incidence of lymphoma development in patients who eradicated the virus confirms this association and suggests that HCV treatment could be a preventive measure<sup>43</sup>. SVR induced NHL regression while a viral relapse was followed by the lymphoma recurrence<sup>44</sup>. HCV-positive splenic lymphoma with villous lymphocytes regressed after anti-viral therapy<sup>45</sup>. Regression of expanded B-cell clones following successful antiviral treatment have been reported with expansion of the same clones in virological relapsers<sup>46</sup>. The same picture was shown in patients with benign lymphoproliferative conditions (i.e. type II or III MC), whereas a persistent B cell clone despite a clinical remission was evidenced in SVRs with splenic lymphoma with villous lymphocytes<sup>45</sup>. This leads to the concept of no-return points in the HCV-driven lymphomagenesis, with a lymphoproliferation initially antigen-sensitive and then antigen-insensitive.

HCV-related lymphoproliferative disorders are the result of multiple and cooperating events, i.e. sustained activation of B-cells<sup>47,48</sup>, inhibition of B-cell apoptosis, genetic/epigenetic and environmental factors<sup>49</sup>. The lymphotropism agrees with a higher HCV infection prevalence in PBMCs and bone marrow<sup>50,51</sup> and was confirmed by *in vivo* and *in vitro* studies<sup>52,53</sup>. HCV-infected cells showed an increased rate of mutations of oncogenes and immunoglobulin genes. Transgenic models showed a correlation between the expression of HCV core and lymphoma<sup>54</sup>. The t(14;18) translocation causes increased Bcl-2 levels and abnormal B-cell survival<sup>55</sup> and disappear after antiviral

treatment<sup>46</sup>. The role of cytokines and chemokines has been studied<sup>19,56,57</sup>, with a special attention of the B-cell activating factor<sup>58,59</sup>.

Treatment of HCV-positive lymphoma with antiviral treatment should lead to the eradication of the etiologic factor. A clinical remission following antivirals was shown in low-grade B-cell NHL, mainly marginal zone lymphoma<sup>44,45,60-62</sup>. IFN-based treatment showed an improved overall survival in patients with indolent HCV-associated NHL<sup>62,63</sup>. Antivirals following NHL remission showed improved clinical outcome and prolonged disease free survival<sup>63,64</sup>. The use of rituximab in HCV-NHL, alone or in combination with antivirals and/or chemotherapy, appears interesting in low-grade NHL<sup>65</sup>.

### **3) Arthralgia/myalgia**

Arthralgia is reported in 40-80% of HCV-infected patients<sup>2,66</sup>. Patients present with symmetric joint pains, non-deforming, involving mainly knees and hands. HCV arthritis is less common. Rheumatoid factor (RF) activity is found in 70-80% of MC patients but it is not correlated with the presence of joint disease. Antibodies to cyclic citrullinated peptide are absent. Some treatment modalities for HCV infection, including IFN, may aggravate arthralgia and myalgia, thus confounding clinical presentation. It is imperative to distinguish whether symptoms such as arthralgia, myalgia, and arthritis occurring in patients with HCV infection are related to chronic HCV infection or to a newly developed rheumatologic disease.

### **4) Sicca syndrome**

Sicca symptoms of either the mouth or eyes have been reported in 20-30% of HCV infected patients, whereas less than 5% of patients with a Sjögren's syndrome are HCV-positive<sup>2</sup>. Many similarities exist between HCV-related sicca syndrome and "true" Sjögren's syndrome<sup>67</sup>. However a characterized Sjögren's syndrome defined by the presence of xerostomia, xerophthalmia, anti-SSA or anti-SSB antibodies and typical salivary gland histology is rarely found in HCV infected patients. HCV-positive Sjögren's syndrome patients are older and more likely to have a photosensitivity and cryoglobulinemia than patients with primary Sjögren's syndrome. Low titers of antinuclear antibodies and RF are common in patients with HCV-related sicca syndrome but the presence of Sjögren's syndrome-related autoantibodies (anti-SSA/SSB antibody) is uncommon. The expression of the HCV E1 and E2 glycoproteins in transgenic mice is associated with the development of sialadenitis<sup>68</sup>.

### **5) Auto-antibodies**

Biological immunologic abnormalities are frequent, including mixed cryoglobulins (60-90%), RF activity (70%), and antinuclear (20-40%), anticardiolipin (15%), anti-thyroid (12%) and anti-smooth

muscle antibodies (7%)<sup>1,2</sup>. These autoantibodies however are not associated with manifestations of a connective tissue disease except for mixed cryoglobulins. Reported underlying mechanisms include HCV-induced overactivation and proliferation of B lymphocytes.

## **6) Cardiovascular diseases**

Asian studies suggest the association between HCV infection and an increased risk of carotid-artery plaques and carotid intima-media thickening, independently of classical cardiovascular risk factors<sup>69</sup>. HCV infected patients showed a higher likelihood of having carotid atherosclerotic plaques compared to HCV negative controls<sup>70,71</sup>, particularly in those with active viral replication. Suggested mechanisms include the production of pro-atherogenic cytokines<sup>13</sup>. Other studies performed in HCV or HCV-HIV co-infected patients confirmed the link between HCV infection and carotid atherosclerosis<sup>70-73</sup>. Furthermore, retrospective cohort studies suggest a beneficial effect of antivirals on the incidence of stroke in HCV infected patients<sup>74</sup>. A prospective study conducted in three groups of diabetics followed during 8 years, showed a decreased cumulative incidence of ischemic stroke in treated vs. non-treated HCV infected patients<sup>12</sup>.

HCV chronic infection was shown to increase the risk of coronary artery disease, after adjustment for classical cardiovascular risk factors<sup>75</sup>. Anti-HCV positive patients had higher mortality rates of cardiovascular diseases compared to HCV negative controls (hazard ratio, HR 1.50; 95% CI 1.10-2.03)<sup>6</sup>. Patients with positive viremia showed higher rates of deaths, while HCV RNA negative patients had rates similar to controls. A large asian study analyzed 1,411 HCV subjects with diabetes mellitus treated with Peg-IFN plus RBV that were matched with 1,411 HCV-positive diabetic patients not treated with antivirals and with 5,644 HCV-negative diabetic patients<sup>97</sup>. After an 8-year median follow-up, the cumulative incidence of death significantly decreased from untreated to treated (23.6% versus 13.0%). The incidences of end-stage renal disease, ischemic stroke and acute coronary syndrome were lowest in the cohort of HCV-treated versus HCV-untreated patients. In addition, Maruyama et al. showed an improvement in the myocardial perfusion defect after antiviral treatment in patients who showed a SVR compared to those who relapsed<sup>76</sup>.

## **7) Renal insufficiency**

Type I membrano-proliferative glomerulonephritis associated with MC is the most common form of kidney disease associated with HCV infection. Patients present with clinical and histological picture in HCV-Cryovas that is an acute or chronic type-I membrano-proliferative glomerulonephritis with sub-endothelial deposits, with type II IgMκ cryoglobulinemia<sup>77</sup>. The most frequent presentation is proteinuria with microscopic hematuria and a variable degree of renal insufficiency. Acute nephrotic or nephritic syndrome can also reveal Cryovas renal involvement, with frequent new onset



arterial hypertension. Early serum complement component (C1q, C4) are very low. Chronic renal insufficiency may develop in 10-20% of HCV-Cryovas patients. Renal morphological features are characterized by important monocyte infiltrates with double contours of the basement membrane, large, eosinophilic and amorphous intra-luminal thrombi. Vasculitis of small renal arteries or extra-capillary crescents are rarely observed. Immunofluorescence studies show intra-glomerular sub-endothelial deposits of IgG, IgM and complement components. The electron microscopic features with sub-endothelial and intra-luminal deposits presenting a crystalloid aspect are pathognomonic.

There is some evidence of the association between HCV and other glomerular diseases<sup>78,79</sup>. A large case-control study, carried out among U.S. male veterans hospitalized between 1992 and 1999<sup>80</sup>, identified 34,204 patients who were hospitalized with HCV infection (cases) and 136,816 randomly selected patients without HCV infection (controls). There was a greater proportion of membrano-proliferative glomerulonephritis among patients with HCV infection (0.36% versus 0.05%,  $P < 0.0001$ ). HCV infection was associated with a 40% higher prevalence of renal insufficiency compared with subjects without HCV infection, after adjusting for age, gender, race, diabetes, and hypertension<sup>81</sup>. Some large surveys have suggested an impact of HCV infection on prevalence and incidence of kidney disease in the general population<sup>80,82-84</sup>. Anti-HCV status was associated to low glomerular filtration rate (OR up to 2.80) and with proteinuria (OR 1.14 to 1.99)<sup>85-88</sup>, independently of common metabolic factors, such as diabetes mellitus, arterial hypertension, obesity, and dyslipidemia. In a recent population-based cohort, among 2,267,270 Taiwanese residents diagnosed with diabetes mellitus<sup>12</sup>, three groups were analyzed : 1,411 HCV infected patients who received pegIFN plus ribavirin (treated cohort), 1,411 HCV infected untreated controls and 5,644 HCV-negative diabetic patients (uninfected cohort). The 8-year cumulative incidence of endstage renal disease in the treated, untreated, and uninfected cohorts were 1.1% (95%CI, 0.3-2.0%), 9.3% (5.9-12.7%), and 3.3% (2.3-4.3%), respectively ( $P < 0.001$ ). Antiviral treatment was associated with HR of 0.16 (0.07-0.33%) for endstage renal disease.

The Kidney Disease Improving Global Outcomes (KDIGO) group recommends that all patients with chronic kidney disease should be tested for HCV<sup>89</sup>. KDIGO also recommends that patients with acute flares of HCV-Cryovas and membrano-proliferative glomerulonephritis be treated with IFN-based therapy. Ribavirin dosage should be closely monitored due to the risk of anemia and it should be avoided in patients with chronic kidney disease. HCV-Cryovas patients with kidney involvement showed greater renal response rates when treated with a combination of rituximab and pegIFN plus ribavirin compared with pegIFN and ribavirin alone. Of note, all these pictures should change rapidly with the use of new direct acting anti-HCV treatments.

## **8) Insulin-resistance and type 2 diabetes**

Insulin-resistance (IR) is a frequent condition, coexisting with obesity and metabolic syndrome, possibly evolving to type 2 diabetes. In a small cohort of patients treated with anti-HCV therapy, Taskoparan et al failed to establish a correlation between IR and chronic HCV infection<sup>90</sup>. The presence of IR was evaluated in HCV patients achieving a SVR after pegylated IFN plus ribavirin. On one hand, the treatment response was not impaired by IR. On the other hand, treatment failure and high body mass index were independent risk factors for *de novo* appearance of IR after treatment. No new IR cases were registered in SVR patients, suggesting that HCV eradication could prevent IR onset and its evolution to diabetes<sup>91</sup>. Insulin resistance has been shown to impair SVR rate to pegIFN plus ribavirin in HIV-HCV coinfecting patients<sup>92</sup>.

HCV-related type 2 diabetes mellitus may arise from a complex interaction between IR, steatosis and inflammatory processes<sup>93,94</sup>. Epidemiologic studies supporting the association between type 2 diabetes and HCV infection have been published in the early 1990s. In larger epidemiologic studies<sup>95,96</sup>, the prevalence of diabetes was higher in HCV- than in HBV-related cirrhosis [23.6% versus 9.4%; OR 2.78 (95%CI, 1.6-4.79); P =0.0002]. Diabetes was associated with the presence of a cirrhosis and male gender. An epidemiologic study conducted in Egypt in a pediatric population of 150 type 1 diabetic patients revealed a prevalence of HCV infection higher than in controls<sup>97</sup>.

### **9) *Fatigue, depression, and cognitive impairment***

Neurocognitive morbidity in HCV infected patients do not completely correlate with the severity of liver disease<sup>98</sup>. Cognitive impairment may be expressed in a wide variety of medical and psychiatric conditions i.e. fatigue, depression, substance abuse... The detection of HCV genetic sequences in post-mortem brain tissue raises the possibility that the presence of HCV in the central nervous system may explain the reported neuropsychological symptoms and cognitive impairment<sup>99</sup>.

Health related quality of life (HRQoL) of HCV patients, before antiviral treatment, is diminished compared with controls<sup>100,101</sup>. HRQoL worsens with more advanced liver disease and therapy, leading to a reduction in adherence<sup>102</sup>. Based on the Short Form 36 (SF-36) Health Survey questionnaire, patients with HCV infection consistently show deficits in several domains, particularly those involving their physical role, general health and vitality, versus healthy controls<sup>101,103</sup>. HCV has been associated with a decreased ability to function both at work and at home, with obvious cost implications. Viral eradication correlates positively with improvements in HRQoL<sup>104</sup>. Compared to placebo, a combination of sofosbuvir plus ribavirin was not associated with HRQoL impairment<sup>105</sup>. Moreover, achieving SVR after 12 weeks of follow-up with SOF and ribavirin was associated with improvement in HRQoL.

Depression has been documented in 28% of HCV patients using the Structured Clinical Interview for DSM-IV Axis I Disorders<sup>106</sup>. HCV may directly affect the central nervous system through alterations in serotonergic and dopaminergic neurotransmission with resultant depressive symptoms<sup>107</sup>. This mechanism may explain other central nervous system symptoms seen in HCV infection, such as fatigue and cognitive impairment<sup>108-111</sup>. Prior to starting antivirals including pegIFN, mental health should be assessed, as patients with a history of major depressive disorder are at greater risk of developing depression during HCV treatment. Antidepressant or anxiolytic treatment may be considered before initiating IFN-based therapy.

Cognitive impairment is well described in chronic HCV infection. It is a common symptom in persons with end-stage liver disease<sup>112</sup>. In the HALT-C trial, 33% of 201 patients with advanced fibrosis who underwent neuropsychological testing had mild cognitive impairment on entering the trial<sup>113</sup>. Patients with chronic HCV infection who are free from co-morbid factors have higher levels of cognitive impairment than healthy controls<sup>114</sup>. HCV eradication leads to improved cognitive function<sup>115</sup> and cerebral metabolism<sup>108</sup>. Patients with SVR demonstrated significant improvements in verbal learning, memory, and visuo-spatial memory.

Fatigue is one of the most frequent and disabling complaints among HCV patients (50-67%), and it independently predicts poor HRQoL<sup>116</sup>. In a prospective study at the first visit of 1,614 HCV infected patients and in 412 healthy blood donors, fatigue was present in 53% of patients (51-56) versus 1% of controls (0-2)<sup>117</sup>. Fatigue was independently associated with female gender, age over 50 years, cirrhosis, and depression. Chronic fatigue is associated with bad sleep quality and increased nocturnal activity in HCV patients suggesting an alteration of sleep architecture in HCV-associated encephalopathy<sup>118</sup>.

***In conclusion***, beyond the liver, HCV chronic infection leads to a multifaceted systemic disease. Some extrahepatic manifestations are immune-mediated while others seem to be driven by chronic inflammation. Such extrahepatic manifestations should be well known by clinicians. They should have an impact in the care of HCV infected patients. The need of effective eradication measures is underlined.

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**A. Immune-related extra hepatic manifestations**

*mixed cryoglobulinemia*  
*cryoglobulinemic vasculitis*  
*B-cell NHL*  
*sicca syndrome*  
*arthralgia/myalgia*  
*auto-antibody production (i.e. cryoglobulins, rheumatoid factor, and antinuclear, anticardiolipin, anti-thyroid and anti-smooth muscle antibodies)*  
*polyarteritis nodosa*  
*monoclonal gammopathies*  
*immune thrombocytopenia*

**B. Inflammatory-related extra hepatic manifestations**

*type 2 diabetes mellitus type 2*  
*insulin resistance*  
*glomerulonephritis*  
*renal insufficiency*  
*fatigue*  
*cognitive impairment*  
*depression*  
*impaired quality of life*  
*polyarthritis/fibromyalgia*  
*cardiovascular disorders (i.e. stroke, ischemic heart disease)*

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**Table 1: Main extrahepatic manifestations in HCV infected patients**