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Considering hepatitis C virus infection as a systemic disease

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ABSTRACT

Hepatitis C virus (HCV) infection is known to result in several adverse hepatic outcomes and has been associated with a number of important extrahepatic manifestations. The scope of extrahepatic clinical possibilities include systemic diseases such as vasculitis and lymphoproliferative disorders, cardiovascular disease, myalgia, arthritis, and sicca syndrome. These end-organ effects of HCV may dominate the clinical course beyond the hepatic complications and significantly worsen the long-term prognosis of infected patients. Until several years ago, the standard of care for the treatment of HCV infection had been interferon-alpha based regimens, which not only had limited effectiveness in achieving a cure but were often poorly tolerated, especially in patients with kidney disease. In those HCV- infected patients with significant systemic manifestations, the interferon-based regimens were problematic given their association with a wide variety of toxicities. The development of highly effective direct-acting antiviral (DAA) agents to treat HCV infection presented an opportunity to improve the HCV care cascade with the eradication of HCV in most infected patients and by reducing the burden of both hepatic and extrahepatic complications.

Key words: HCV, systemic disease, cryoglobulinemia, vasculitis, lymphoma, arthritis, myalgia, sicca syndrome

Introduction

Hepatitis C is a hepatotropic virus estimated to infect more than 170 million people worldwide. Infection with the virus is known to result in liver cirrhosis and hepatocellular carcinoma in a significant number of patients after several decades of infection. As such, HCV represents a global health challenge with an estimated liver-related mortality of 350,000 people/year [1]. It is also recognized as one of the hepatic viruses most often associated with extrahepatic manifestations (EHMs), which present in up to two-thirds of infected patients [2]. Extrahepatic syndromes may represent the first signal of HCV infection in some patients [3]. Several of these manifestations are common and well-described while others are less frequent [4–6]. Some of the extrahepatic manifestations, including mixed cryoglobulinemia and non-Hodgkin B-cell lymphoma, have a significant prevalence with unequivocal data supporting a causal relationship. Other manifestations have been noted to have a higher prevalence compared to controls, including adverse cardiovascular events (stroke, coronary artery disease), kidney disease, metabolic derangements, and neuropsychiatric (depression, impaired quality of life) disorders [7]. With the availability of safe and effective DAAs, the opportunity to achieve HCV eradication has important implications from both a therapeutic and preventative perspective to effectively manage both the liver and non-liver consequences of the disease. This review will outline the most important systemic extrahepatic manifestations of HCV infection for which good evidence is available to support a linkage between infection and the clinical syndrome.

Cardiovascular disease

The main cause of mortality in HCV-infected patients continues to be associated with liver disease (ie, cirrhosis, hepatocellular carcinoma) [8–14]. However, HCV-infected

patients have been demonstrated to incur an increased mortality due to extra-hepatic complications as well (i.e. cardiovascular, kidney disease, malignancy) [12,13,15–17]. Major adverse cardiovascular events (MACE) (stroke, coronary artery disease, heart failure, peripheral arterial disease) are currently recognized as important co-morbidities in patients with chronic HCV infection [18]. Evidence is available that other chronic infections can be triggers for MACE as well [19–21]. Their identification as cardiovascular risk factors may offer new perspectives in cardiovascular disease prevention and specifically how HCV and its treatment might impact on MACE [18]. HCV seropositivity associates with high rates of carotid-artery plaques, carotid intima-media thickening, and the risk of stroke independently of other well known atherosclerosis risk factors [19]. Hepatitis C virus is able to induce the production of pro-atherogenic cytokines [22] that may promote atherosclerotic plaque instability, supporting a role for the virus to increase cerebrovascular disease risk [23]. Importantly, cohort studies have suggested a positive impact of antiviral therapy on the incidence of stroke [24].

Infection with HCV has been demonstrated to increase the risk of coronary artery disease after adjustment for traditional cardiovascular risk factors [25]. Patients with sustained virological response (SVR12; defined as negative viremia 12 weeks post-treatment) showed an improvement in myocardial perfusion defects whereas relapsing patients exhibited a worsening following a transient improvement [26]. The risk of MACE has been demonstrated to be higher in patients with HCV infection compared to controls, independent of the severity of the liver disease or the presence of more traditional cardiovascular risk factors [27]. In patients with compensated HCV cirrhosis, SVR12 was associated with a decreased risk of MACE (HR, 0.35; 95% CI 0.09-0.97) including stroke, myocardial infarction, ischemic heart disease, heart failure, peripheral arterial disease,

cardiac arrest, and cardiovascular death [28]. In a prospective study of patients with HCV infection and compensated cirrhosis, obtaining a SVR reduced overall mortality rate and risk of death from liver-related and non-liver-related causes and decreased the incidence of hepatocellular carcinoma (HR, 0.29; 95% CI 0.19–0.43) and hepatic decompensation (HR, 0.26; 95% CI 0.17–0.39). Patients with a SVR also had a lower risk of cardiovascular events (HR, 0.42; 95% CI 0.25–0.69) and bacterial infections (HR, 0.44; 95% CI 0.29–0.68) [29]. The beneficial impact that had been observed with IFN-based therapy has now been confirmed using IFN-free DAA regimens in prospective studies that have included extended follow-up [28–32].

Metabolic diseases

Metabolic disorders (diabetes and insulin resistance) occur with an increased incidence in patients with chronic HCV infection. Impaired glucose tolerance, commonly associated with obesity and metabolic syndrome, can progress into overt type 2 diabetes mellitus [33]. The presence of impaired glucose tolerance has been analyzed in HCV-infected patients who achieved SVR after successful treatment with pegylated interferon alfa (pegIFN) plus ribavirin. Of note, the therapeutic response to antiviral therapy was not altered by the presence of insulin-resistance. Additionally, failure of antiviral therapy and elevated body mass index were independent risk factors for the *de novo* appearance of impaired glucose tolerance after treatment. No new cases of insulin-resistance were registered in patients that achieved a SVR, suggesting a possible prevention of insulin-resistance onset and its progression to overt diabetes [34]. Impaired glucose tolerance has been found to alter the SVR rate to pegIFN plus ribavirin in HIV-HCV coinfecting patients [35]. An increased

risk of type 2 diabetes in HCV infected patients may be attributable to interactions between insulin resistance, steatosis of the liver and inflammatory mechanisms [36].

Many epidemiologic studies support the linkage between type 2 diabetes and HCV infection [37,38]. The mechanisms through which hepatitis C induces type 2 diabetes involve direct viral effects, insulin resistance, release of pro-inflammatory cytokines and other immune-mediated processes. HCV infection increases the risk of incident type 2 diabetes mellitus in predisposed individuals, independent of the stage of liver fibrosis [39]. Type 2 diabetes was more frequent in HCV than hepatitis B virus-related cirrhosis (OR 2.78; 95%CI, 1.6-4.79; P =0.0002) [40,41]. Clinical trials in HCV-positive patients have reported a reduction in complications from type 2 diabetes following successful antiviral treatment [11]. In addition, diabetic patients who received antiviral treatment showed an 84% reduction in the risk of ESRD, 47% decrease in ischaemic stroke and a 36% reduction in the risk of acute coronary syndrome compared with an untreated cohort [11]. The clinical impact of successful antiviral therapy on the long-term outcome of type 2 diabetes remains unknown.

Renal insufficiency

The most frequent and severe renal manifestations of HCV infection include glomerulonephritis (GN) associated with mixed cryoglobulinemic vasculitis and immune complex GN of the membranoproliferative glomerulonephritis (MPGN) type. Kidney involvement may begin with a nephritic syndrome presentation and acute renal failure, however in more than 50% of patients there may be only mild hematuria, microalbuminuria, sub-nephrotic range proteinuria and renal insufficiency. The pathogenesis of renal injury in HCV-infected patients involves the deposition of circulating immune complexes containing anti-HCV antibodies, HCV antigens and complement factors.

In addition, HCV-infected patients have a higher risk of chronic kidney disease (CKD), independent of other causes of renal impairment. Compared to HCV-negative controls, patients with chronic HCV infection appear to have more rapid progression of CKD and an almost two-fold increased risk of developing end-stage renal disease [42].

Renal biopsy in the HCV-infected patient often demonstrates a histologic pattern of type I MPGN in more than 70% of patients offering a nephritic presentation. Less frequent histopathologic patterns include focal segmental glomerulosclerosis and membranous glomerulopathy. Other associated histopathological lesions reported include crescentic GN, necrotizing vasculitis, interstitial inflammation and capillary luminal cryoglobulin thrombi (especially in patients with type III cryoglobulinemia). Immunofluorescence study demonstrates IgG, IgM, and C3 within most of the cryoglobulin deposits present in capillary loops; C1q was present in about one-third of the patients.

In epidemiological studies, a higher rate of MPGN was found in HCV-positive compared to HCV-negative hospitalized male Veterans (0.36% vs. 0.05%, $P < 0.0001$), but not for membranous glomerulopathy (0.33% vs. 0.19%, $P = 0.86$) [43]. A higher rate of renal insufficiency has been reported in HCV-infected patients compared with subjects without HCV infection after adjusting for age, gender, race, diabetes, and hypertension [44]. HCV infection may affect kidney function in the general population as it has been associated with reduced GFR, with an odds ratio up to 2.80 [45]. In addition, HCV infection appears to increase the risk of proteinuria in healthy individuals, with odds ratio 1.14-1.99, independent of diabetes mellitus, arterial hypertension, obesity, and dyslipidemia [46–50]. Among 22 HCV-infected patients with stage 3-5 CKD who were treated with DAAs, half of the patients were reclassified to an improved CKD stage, suggesting that HCV eradication might improve

the outcome [51]. Further studies are necessary however to confirm the positive impact of treatment on patients with more advanced CKD.

Cryoglobulinemia vasculitis

Mixed cryoglobulinemic vasculitis (CryoVas) is a systemic vasculitis which often presents with clinical manifestations including purpura, arthralgia and fatigue or more serious lesions with neurologic and renal involvement [52]. Circulating mixed cryoglobulins can be detected in 40%–60% of patients chronically infected with HCV, although overt cryoglobulinemic vasculitis develops in only approximately 15% of patients. Of all patients with CryoVas, infection with HCV is responsible for the clinical presentation in approximately 70-80% of cases [7,52,53]. The disease expression may range from mild clinical symptoms to fulminant life-threatening complications. The main skin presentation is a palpable purpura; chronic cutaneous ulcers, Raynaud's phenomenon, acrocyanosis, and digital ulcerations can also occur [52]. Patients present with arthralgia of large peripheral joints in 70% of cases, although rarely with overt arthritis. The most frequently described neurologic manifestation is a distal sensory or sensory-motor polyneuropathy, with painful and asymmetric paresthesia. Multiple mononeuropathy may occur less although far less frequently. An acute or chronic membranoproliferative glomerulonephritis with sub-endothelial deposits represents the large majority of cryoglobulinemia-renal diseases, strongly linked with the type II IgM kappa mixed cryoglobulinemia.

The diagnosis of cryoglobulinemia depends on the presence of a serum protein that precipitates at 4°C and dissolves at 37°C. Often accompanying chronic HCV infection, mixed cryoglobulinemia is characterized as either type II or type III which involves polyclonal IgG

with either monoclonal or polyclonal IgM with rheumatoid factor activity, respectively [54]. During the follow-up of patients with clinical manifestations of cryoglobulinemia, improvement in laboratory markers of disease, such as the serum level of cryoglobulinemia and additional surrogate markers (fourth component of complement level and rheumatoid factor activity) may be useful to monitor disease activity.

Factors predicting the clinical course of CryoVas in HCV-infected patients include advanced age, longer duration of infection, presence of a type II mixed cryoglobulin, and clonal B-cell expansions in both the blood and liver. The more significant negative prognostic factors are an age greater than 60 years at presentation and concurrent renal manifestations. Other important causes of mortality in these patients include liver injury, cardiovascular disease, infectious complications and lymphoma [55]. In one study of 231 patients, 79 of the 97 deaths were linked to vasculitis (46%), malignancy (23%), or liver disease (13%) [56]. Prior to the availability of the DAAs, HCV-CryoVas often resulted in progressive (renal involvement) or acute (gastrointestinal, cardiac, CNS, pulmonary hemorrhage) life-threatening organ damage, with mortality rates ranging from 20% to 80% [57,58].

Multiple factors predispose patients to develop a CryoVas. HCV has a tropism for lymphocytes, especially those of B cell lineage that can result in polyclonal activation and expansion leading to production of an IgM with rheumatoid factor activity [59]. Regulatory T cells (Tregs), known to modulate self-tolerance, are reduced in HCV-CryoVas patients. A reduction in Treg activity may contribute to autoreactive B-cell expansion (IgM⁺CD21^{-/low} memory B cells) thus driving the expression of autoimmune manifestations in HCV-CryoVas patients [60,61]. In patients with HCV-CryoVas, a negative correlation between the number of IgM⁺CD21^{-/low} memory B cells and Tregs (P = .03) and a positive correlation with the

number of T follicular helper (Tfh) cells ($P = .03$) and serum levels of cryoglobulin ($P = .01$) has been demonstrated [62]. Treatment with DAA-based regimens have been demonstrated to result in an increase in the number of Tregs ($1.5\% \pm 0.18\%$ before vs. $2.1\% \pm 0.18\%$ after therapy), a decrease in the percentage of $\text{IgM}^+\text{CD21}^{\text{low}}$ memory B cells ($35.7\% \pm 6.1\%$ before vs. $14.9\% \pm 3.8\%$ after therapy), and a decrease in the number of Tfh cells ($12\% \pm 1.3\%$ before vs. $8\% \pm 0.9\%$ after therapy) [62]. Patients with HLA-DR11 were shown to have an increased risk of CryoVas whereas those with HLA-DR7 were at decreased risk of type II mixed cryoglobulin production [63]. A single-nucleotide polymorphisms within an intronic region of NOTCH4 ($p=6.2 \times 10^{-9}$) and another between HLA-DRB1 and HLA-DQA1 ($p=1.2 \times 10^{-7}$) on chromosome 6 have also associated with HCV-CryoVas [64]. A high prevalence of homozygosity and a greater frequency of a particular allele of the BAFF promoter were found in HCV-CryoVas patients compared to HCV patients without vasculitis [65]. Different expression profiles of microRNAs in the peripheral blood mononuclear cells of these patients has been associated with the expression of lymphoproliferative and autoimmune disorders [66].

Most of the clinical manifestations of HCV-CryoVas have been shown to resolve after clearance of HCV with pegylated interferon (IFN) plus ribavirin [67,68], whereas virological relapsers usually experience a return of the CryoVas manifestations [69]. Due to the variety of HCV clinical manifestations in patients with CryoVas, a multidisciplinary approach along with appropriate therapeutic strategies are usually necessary. Current treatment recommendations for HCV-CryoVas are guided by major organ involvement and the severity of the disease [70]. In patients who have persistent CryoVas manifestations despite achieving a SVR, another clinical diagnosis should be considered, especially B-cell lymphoma [71]. In a study of 30 patients with a CryoVas syndrome, combination therapy with

pegIFN/ribavirin plus a NS3/4A protease inhibitor (boceprevir or telaprevir) resulted in a clinical remission and SVR in 67% of the cohort at 24 weeks post treatment [72]. Serious adverse events were reported in almost 50% of the patients. In another study, use of pegIFN/ribavirin in combination with boceprevir for 48 weeks (n=35) resulted in a drastic reduction of the cryocrit values and an accompanying improvement of CryoVas symptoms [73]. International clinical guidelines recommend treatment of the CryoVas syndrome with DAAs and also suggests that treatment be initiated early on and not delayed in patients with this type of clinically significant extrahepatic manifestation [70,74]. In a recent French study, combination of sofosbuvir (400 mg/day) plus ribavirin (200-1400 mg/day) for 24 weeks was associated with a high rate of complete clinical response of CryoVas (87.5%) and a low rate of serious adverse events (8.3%) [75]. Other recent studies confirm the safety and efficacy of the DAAs in difficult-to-treat patients [76,77]. Sise et al [78] reported a retrospective case series (n=12) of HCV-CryoVas patients treated with a sofosbuvir-based regimen [median age 61 years, 58% male, 50% cirrhotic]. All patients had undetectable HCV RNA by week 4 and a SVR12 was achieved in 10/12 (83%). Individual eGFR changes were impacted positively in 2/7 patients with active glomerulonephritis accompanied by a reduction in proteinuria in 3/3 cases. In an open-label, prospective, multicenter study, 41 consecutive patients with HCV-associated CryoVas (median age, 56 y; 54% women) received sofosbuvir (400 mg/day) plus daclatasvir (60 mg/day) for 12 (n = 32) or 24 weeks (n = 9) (79). All patients achieved a SVR12 following 12 weeks of therapy and 37 (90.2%) had a complete clinical response (defined by improvement of all the affected organs involved at baseline and no clinical relapse).

Targeted therapy against B-lymphocytes using rituximab has been shown to have clinical benefit in patients with CryoVas syndrome [80–84]. In a randomized trial, treatment

with rituximab resulted in superior clinical outcomes compared to conventional immunosuppressants [85]. Similar results have also been reported in a placebo-controlled trial [86]. There was no risk of viral reactivation in HCV-infected patients, contrary to what has been reported in HBV infection [87]. In a study comparing rituximab plus pegIFN/ribavirin to pegIFN/ribavirin alone, the rituximab treated patients had a shorter time to clinical remission, better renal response rates, and higher rates of cryoglobulin clearance [88,89].

To summarize, in patients with a mild to moderate HCV-CryoVas syndrome, treatment with an appropriate DAA regimen is recommended. For patients manifesting a more severe systemic vasculitis (i.e. worsening kidney function, mononeuritis multiplex, extensive skin disease, intestinal ischemia) initial control of disease with rituximab, with or without plasmapheresis, is recommended along with DAA treatment. [90]. Low-dose corticosteroids may help to control associated inflammatory findings but are not adequate alone in cases of major organ involvement. Additional immunosuppressants should be given only in cases of refractory forms of CryoVas, which are frequently associated with underlying B-cell lymphoma [91].

B-cell lymphoproliferative diseases

An association of HCV infection with B-cell non-Hodgkin's lymphoma (B-NHL) was reported soon after identification of the virus [92,93] and this observation was subsequently confirmed in several meta-analyses [94–98]. Chronic HCV infection has been associated with marginal zone B-NHL (OR, 2.47; 95% CI, 1.44-4.23) and diffuse large B-NHL (OR, 2.24; 95% CI, 1.68-2.99). A serum IgMk gammopathy has been frequently noted in HCV-infected patients [99]. In addition, mixed cryoglobulinemia can be seen and is characterized by the clonal

expansion of CD27⁺IgM⁺ B cells producing a rheumatoid factor often encoded by the V_H1-69 and V_k3-20 genes [100,101]. It is widely believed that the clonal expansion of V_H1-69⁺ B cells in mixed cryoglobulinemia and in HCV-associated B-NHL is triggered by the protracted stimulation by a HCV antigen that, however, remains elusive [102].

The incidence of B-NHL is reported to be lower in HCV-infected patients who have obtained a SVR [103]. Furthermore, attaining a SVR was associated with NHL regression while recurrence of viremia was followed by relapse of the lymphoma [104,105]. HCV-positive splenic lymphoma with villous lymphocytes (SLVL) regressed after successful antiviral therapy [106]. Regression of clonal B-cell expansion following successful antiviral therapy has been described with novel expansion of the same clones in patients who relapsed [107,108]. This suggests no-return points in the HCV-driven lymphomagenesis, making the pathogenic mechanism progressively less dependent from the viral antigen [109].

HCV-related lymphoproliferative diseases appear to be the result of multiple events, including sustained B-cells activation, an aberrant B-cell survival, genetic/epigenetic and environmental factors [109,110]. The impact of prolonged antigenic stimulation has been demonstrated by the lymphotropism of HCV and the presence of HCV antigens in peripheral blood or liver infiltrating lymphocytes and lymph-nodes [111–113]. The linking of HCV surface E2 protein with the tetraspannin CD81 diminished the threshold for B-cell expansion [114]. B cell receptor (BCR) sequence analyses and affinity in HCV-related NHL showed conflicting results [102,115]. The higher prevalence of HCV infection in PBMCs and bone marrow [116,117] and additional *in vitro* studies support the lymphotropism of the virus [118,119]. The rate of mutations in oncogenes and immunoglobulin genes are increased in HCV-infected cells [120]. The expression of HCV core and lymphoma was correlated in

transgenic models [121,122]. The (14;18) translocation increased Bcl-2 levels and B-cell survival [108,123,124] that disappeared after antiviral therapy [107,125,126]. The role of cytokines and chemokines [59,127–130], including BAFF [110,131,132][65,133], and the role of microRNAs [66,134] have been studied extensively in HCV-related lymphoproliferative diseases.

Several studies showed a clinical remission following antiviral treatment in low-grade B-cell NHL, mainly in marginal zone lymphoma [105,106,135–138]. The use of IFN-based therapy in patients with indolent HCV-NHL has been associated with an improved overall survival [138]. IFN-based treatment is difficult because of the hematological toxicity of the drug. However, treatment with antivirals following remission of the lymphoma yielded a prolonged disease-free survival [139,140]. Rituximab alone or combined with antivirals and/or chemotherapy yielded good outcomes in low-grade B-NHL [89,141]. The availability of IFN-free protocols using DAAs providing high virological efficacy and no haematological toxicity should permit them to be used successfully with chemotherapy, taking into account possible drug-drug interactions between the agents [142–144].

Arthralgia and myalgia

Arthralgias are present in 30-70% of HCV-infected patients with mixed cryoglobulin syndrome [145,146]. Patients usually present with bilateral, symmetric, non-deforming joint pains involving mainly the knees and hands. HCV-associated arthritis, not linked to mixed cryoglobulin, is uncommon (<10%). Rheumatoid factor activity can be demonstrated in 70-80% of CryoVas patients due to the presence of a mixed cryoglobulin; it is not associated with the presence or the activity of joint manifestations. Radiographic joint destruction is uncommon. Exacerbation of the arthralgias and myalgias with IFN-based treatment

protocols can confound the clinical presentation. Clinicians should use these clinical patterns to help differentiate the rheumatologic manifestations that may occur in HCV-infected patients due to HCV infection itself such as arthralgia, myalgia, and arthritis versus those that may be attributable to a newly developed rheumatologic disease.

Sicca syndrome

An ocular and/or buccal sicca syndrome has been described in 20% to 30% of HCV-infected patients, whereas a definitive Sjögren's syndrome (xerostomia, xerophthalmia, anti-SSA/anti-SSB antibodies and typical salivary gland histology) is reported less than 5% of the time [145]. The presentation and diagnosis can be challenging when differentiating between a HCV-related sicca syndrome and "true" Sjögren's syndrome [147]. HCV-positive patients with a Sjögren's syndrome tend to be older and more likely to present with photosensitivity and a mixed cryoglobulinemia compared to those with a primary Sjögren's syndrome. The presence of low titers of antinuclear antibodies and rheumatoid factor activity are common in HCV-infected patients with sicca syndrome, whereas the presence of Sjögren's syndrome autoantibodies (i.e. anti-SSA/SSB antibody) are rare. The sialadenitis found in HCV-infected patients may be related to the sialotropism of the virus [148]. In transgenic mice, the development of sialadenitis has been associated with the expression of E1- and E2-HCV glycoproteins [149].

Autoantibodies

Autoantibodies such as mixed cryoglobulins (60-80%), rheumatoid factor activity (70%), antinuclear antibody (20-40%), anticardiolipin antibody (aCL) (20-15%), anti-thyroid

(12%) and anti-smooth muscle antibodies (7%) have frequently been reported in HCV-infected patients [2,145]. Connective tissue disease manifestations are generally not associated with the presence of these autoantibodies, except for mixed cryoglobulins and CryoVas as previously discussed. For example, while aCL occur frequently in viral infections, particularly in HIV (49.75%), HBV (24%) and HCV (20-15%), they are very rarely associated with anti-beta2 glycoprotein I antibodies and are not correlated with an increased thrombotic risk [150]. In patients with non-autoimmune liver diseases, the production of aCL is a non-specific phenomenon of the liver damage, and they have not been associated with thrombotic complications [151].

A wide array of systemic and autoimmune phenomena in HCV-infected patients have been reported [7,152]. Many of these extrahepatic manifestations are autoimmune disorders and are associated with incremental changes in mortality and morbidity due to the involvement of multiple organ systems [153]. Prior to the availability of the DAAs, the standard of care for HCV infection has been IFN-based regimens, which not only had limited efficacy but were also poorly tolerated, especially in patients with rheumatic diseases given their association with a wide variety of autoimmune toxicities [154]. CryoVasc can be successfully treated with antivirals aimed at HCV eradication and/or pathogenetic/symptomatic treatments directed to both immune-system alterations and the vasculitic process (rituximab, cyclophosphamide, steroids, plasmapheresis) [155]. In clinical practice, the therapeutic strategy should be modulated according to the severity/activity of the CryoVasc and specifically tailored to each individual patient's clinical presentation.

Conclusion

In summary, manifestations of a systemic disease are often present in patients with chronic HCV infection. These can include autoimmune, lymphoproliferative, cardiovascular, metabolic and renal disorders. In this context, nephrologists should be aware of these diverse and often clinically significant clinical manifestations of HCV infection and incorporate aggressive screening for undiagnosed HCV or re-infection in their CKD and ESRD patients.

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