Extrahepatic Conditions Related to HCV Infection

This is a PDF version of the following document:
Module 2:   Evaluation, Staging, and Monitoring of Chronic Hepatitis C
Lesson 7:   Extrahepatic Conditions Related to HCV Infection

You can always find the most up-to-date version of this document at
https://www.hepatitisC.uw.edu/go/evaluation-staging-monitoring/extrahepatic-conditions/core-concept/all.

Overview of Extrahepatic Manifestations

Background and Prevalence

Although hepatitis C virus (HCV) infection primarily affects the liver, other organ systems can become involved, which may result in a variety of clinical complications, including cryoglobulinemia, renal disease, dermatologic disorders, diabetes, and lymphomas (Figure 1).[1,2,3,4,5] The HCV-associated extrahepatic manifestations can have a major impact on morbidity, mortality, and medical costs.[6,7,8,9] The percentage of persons with chronic HCV infection who develop some extrahepatic manifestation remains poorly defined. Nevertheless, some experts have estimated that up to 38% of persons with HCV will develop at least one extrahepatic manifestation at some point.[10]

Need for Recognition

It is extremely important that clinicians consider the potential for HCV to cause extrahepatic manifestations in persons with chronic HCV infection (Figure 2). It is unclear how well clinicians recognize, diagnose, and treat such extrahepatic conditions, especially since many individuals with HCV infection may not have obvious manifestations of chronic liver disease and often have undiagnosed HCV infection. An awareness of the range of potential extrahepatic manifestations could facilitate earlier diagnosis and more appropriate and timely treatment of these disorders.

Quality of Evidence

Most of the literature on HCV-related extrahepatic manifestations consists of observational studies that have shown an association between a specific extrahepatic condition and the presence of HCV antibody and/or detection of HCV RNA. Most of these studies are prone to selection bias. A few studies have used large datasets, such as the Veterans Administration medical database, and these studies are most useful when the extrahepatic condition in question can be easily defined and the data is easily accessible (e.g., renal disease as determined by a creatinine level or glomerular filtration rate [GFR]).[11,12,13] For extrahepatic conditions that require a clinical diagnosis, such as lichen planus, identifying the specific condition is much more difficult when utilizing larger datasets.[14,15] Thus, it is important to keep in mind the original source and type of data when estimating prevalence of these extrahepatic conditions and considering the need for screening.

Relevance to Initiating DAA Therapy

The diagnosis of any extrahepatic HCV conditions necessitates urgent initiation of direct-acting antiviral (DAA) treatment of HCV, unless the person with HCV has already received successful treatment. Although both

public plans and commercial policies regarding approval for HCV treatment are constantly changing, these payers typically cover DAA therapies when any extrahepatic manifestation exists, despite level of hepatic fibrosis.

Cryoglobulinemia

Definition of Cryoglobulinemia

Cryoglobulinemia refers to the presence of one (monoclonal) or more (mixed or polyclonal) blood proteins in the serum, which reversibly precipitate in vitro at temperatures below normal body temperature (less than 37°C).[16] The blood proteins that precipitate are referred to as cryoglobulins, and they dissolve again when reheating the serum. Cryoglobulins are composed of either pure immunoglobulins or a mixture of immunoglobulins and complement.[16]

Mechanism of Disease

In HCV-related mixed cryoglobulinemia, end-organ disease is caused by an immune-mediated mechanism.[16] Specifically, immune complexes that contain HCV particles deposit in the walls of capillaries, venules, or arterioles, leading to endothelial activation, stimulation of chemotactic peptides, and an inflammatory response; the end result is leukocytoclastic vasculitis.[17,18] Among persons who develop cryoglobulinemia, HCV antigens drive chronic stimulation of B-lymphocytes, which is thought to induce B-cell clonal expansion and production of antibodies, with the potential for development of a B-cell non-Hodgkin's lymphoma.[17]

Clinical Manifestations Associated with Cryoglobulinemia

Most persons with chronic HCV infection and cryoglobulinemia have either no symptoms or nonspecific clinical manifestations. A triad of purpura, myalgia, and arthralgia (Meltzer's triad) is the most common presentation in persons with HCV-related mixed cryoglobulinemia.[16,19] Approximately 30% of persons with mixed cryoglobulinemia develop renal disease.[19] Additional clinical features that may develop with mixed cryoglobulinemia include peripheral neuropathy, skin ulcers, and lymphoproliferative disorders.[20] A variety of clinical syndromes can be associated with cryoglobulinemia. The most common manifestations of HCV-associated mixed cryoglobulinemia are shown in the following list:[16,18,19]

- Palpable purpura
- Chronic leg ulcers
- Arthralgias
- Weakness
- Myalgias
- Renal disease
- Peripheral neuropathy

Classification of Cryoglobulinemia

Cryoglobulinemia is classically grouped into three types according to the 1974 Brouet classification system; note that type I is considered monoclonal cryoglobulinemia, and types II and III are classified as mixed cryoglobulinemia.[21,22]

- **Type I Cryoglobulinemia**: This disorder consists of isolated monoclonal immunoglobulin (IgM or IgG) and most commonly occurs in association with lymphoproliferative disorders; type I cryoglobulinemia represents only 10 to 15% of cases of cryoglobulinemia.
- **Type II Cryoglobulinemia**: This type of cryoglobulinemia consists of mixed immune complexes, typically monoclonal IgM and polyclonal IgG. This type of cryoglobulinemia most often develops in persons who have chronic viral infections, such as HCV, hepatitis B virus, and cytomegalovirus (CMV), but also occurs in persons with chronic inflammatory states, such as systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome. Type II cryoglobulinemia is the most common type of cryoglobulinemia seen in persons with HCV infection. The type II cryoglobulins have rheumatoid factor

activity, which means these immunoglobulins bind to the Fc portion of IgG.
- **Type III Cryoglobulinemia**: This disorder consists of mixed immune complexes, typically formed by polyclonal IgM and IgG, and it represents 25 to 30% of cases of cryoglobulinemia.

Association between HCV and Mixed Cryoglobulinemia

Multiple reports have shown a close association between HCV and mixed cryoglobulinemia, most often type II cryoglobulinemia—70 to 90% of persons with mixed cryoglobulinemia have evidence of chronic HCV.[17,23] With HCV-related mixed cryoglobulinemia, immune complexes comprised of immunoglobulin and HCV particles precipitate in many organs, including the skin, kidneys, and peripheral nerve fibers.[16,18] Investigators have postulated that expansion of rheumatoid factor activity and cryoprecipitability is responsible for the vasculitis. All persons with mixed cryoglobulinemia have evidence of chronic HCV: studies have shown that 50 to 100% of persons with mixed cryoglobulinemia have chronic HCV. Accordingly, all persons with a diagnosis of mixed cryoglobulinemia should undergo screening for HCV infection. Conversely, given how rare mixed cryoglobulinemia occurs among persons with HCV, routine screening for mixed cryoglobulinemia in persons with chronic HCV is not recommended. Treatment of HCV and achievement of sustained virologic response (SVR) reduces the risk of developing manifestations of mixed cryoglobulinemia.[24]

Cryoglobulinemic Vasculitis

Clinical manifestations of cryoglobulinemia can vary with the most common presentation being vasculitis.[22] Chronic HCV is generally the most common underlying etiology, but lymphoproliferative disorders (with or without HCV) or autoimmune diseases such as Sjögren's or lupus can also be associated with cryoglobulinemic vasculitis. When no associated disease is identified, cryoglobulinemic vasculitis is referred to as essential cryoglobulinemic vasculitis.[25] The following describes key features of cryoglobulinemic vasculitis.

Pathophysiology of Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis is considered a systemic small-to-medium vessel vasculitis.[22] In this disorder, damage to the vessels is thought to result from the deposition of immune complexes on the vessel wall, followed by subsequent activation of the complement cascade.[17] Only about 10 to 15% of persons with cryoglobulinemia develop cryoglobulinemic vasculitis.[22]

Manifestations of Cryoglobulinemic Vasculitis

Individuals with chronic HCV infection who develop cryoglobulinemic vasculitis most often have cutaneous manifestations, though any organ may be affected. Palpable purpura is evident in more than 90% of persons with cryoglobulinemic vasculitis, and is usually the first sign of cryoglobulinemia.[17,22] The finding of palpable purpura in a person with chronic HCV should raise an immediate suspicion of cryoglobulinemic vasculitis. On skin biopsy, findings typically show leukocytoclastic vasculitis, defined by neutrophilic infiltrates invading or damaging the dermal blood vessel wall.[26] Fatigue and arthralgias may also accompany skin findings. Kidney involvement can occur, presenting as glomerulonephritis with microhematuria, proteinuria, and variable renal insufficiency. Peripheral neuropathy can present as either distal sensory polyneuropathy or vasculitis-mediated mononeuritis multiplex.[22]

Diagnosis of Cryoglobulinemic Vasculitis

Specific diagnostic criteria or classification for cryoglobulinemic vasculitis have not yet been defined.[22] The diagnosis is typically made from the combination of history, skin findings, low complement levels, presence of cryoglobulins in serum, and histology that shows small vessel inflammation with immune deposits found in the vascular walls.[22]

Treatment of HCV-related Cryoglobulinemic Vasculitis

The approach to treating HCV-related cryoglobulinemic vasculitis is complex and depends on the severity of the cryoglobulinemia and end-organ involvement. Due to the complexity and potential severity of this disorder, treatment should be conducted by or performed in conjunction with a clinician who has expertise in this field. The four components of therapy that may be used in the treatment of HCV-related cryoglobulinemic vasculitis consist of (1) antiviral therapy for chronic HCV infection, (2) conventional immunosuppressive agents, (3) biologic therapies, specifically B-cell deleting monoclonal antibodies, such as rituximab, and (4) plasmapheresis.[16,17,27] In general, the approach to treatment depends on the severity of illness, which can range from mild-to-moderate (usually with only cutaneous involvement), to severe (with end-organ involvement), to life-threatening (typically rapidly progressing).[16] The goals of treatment are to provide prompt relief of active vasculitis and prevent further recurrences of cryoglobulinemic vasculitis. When immunosuppressing agents are being considered for treatment, it is important to screen for other possible viral infections, such as chronic hepatitis B virus (HBV) or HIV, which may require prompt treatment before the initiation of immunosuppressive therapy.

Role of DAA Therapy in HCV-Related Cryoglobulinemic Disease

Available data suggest that persons with chronic HCV infection and cryoglobulinemic vasculitis have SVR rates greater than 90% when using DAA therapy.[27,28,29] Clinical improvement of skin lesions, arthralgias, and cryoglobulinemia has been reported in most patients within 3 to 6 months of completing DAA therapy. Unfortunately, successful treatment of HCV with DAA therapy often does not uniformly result in remission of cryoglobulinemic vasculitis, particularly in moderate-to-severe disease.[27,28,29,30] Thus, DAA therapy for HCV infection in persons with cryoglobulinemic vasculitis should be considered as a component of an overall treatment strategy to successfully manage this multifaceted disorder.

Autoimmune Disorders

Asymptomatic Autoantibodies

Chronic HCV has been associated with a number of autoantibodies, the most common of which include antinuclear antibodies, rheumatoid factor, anticardiolipin antibodies, smooth muscle antibodies, and antithyroid antibodies.[31,32,33,34] In two studies, the prevalence of antinuclear antibodies and rheumatoid factor has ranged from 14 to 41% and 38 to 76%, respectively.[32,33] Many of these antibodies are not associated with extrahepatic disease, but their presence may lead to diagnostic dilemmas.

Autoimmune Hepatitis

In contrast to the multitude of largely asymptomatic autoantibodies found in persons with chronic HCV, anti-LKM-1 antibodies may be associated with autoimmune hepatitis in persons with chronic HCV, although the presence of these autoantibodies does not always predict autoimmune disease.[35,36,37] If a person with chronic HCV has positive anti-LKM-1 antibodies, it can be challenging to determine the primary cause of liver injury, but DAA treatment for HCV is recommended regardless. It is not routinely recommended that clinicians screen for antibodies associated with autoimmune hepatitis unless there is a specific reason to do so, such as persistently elevated aminotransferase levels of unclear etiology following successful HCV treatment.

Thyroid Disease

Thyroid disease occurs in an estimated 2 to 13% of persons with chronic HCV.[38,39] In a study of 630 participants with chronic HCV and no cirrhosis, investigators found that 17% had anti-thyroglobulin antibodies, and 21% had antithyroid peroxidase antibodies.[38] Among patients with HCV in this study, the prevalence of hypothyroidism was 13%, and serum thyroid stimulating hormone (TSH) levels were significantly higher in those with chronic HCV when compared to control arms from both iodine-deficient and iodine-sufficient areas.[38]

Sjögren's Syndrome

Several studies suggest an association between HCV infection and Sjögren's syndrome.[40,41] In a meta-analysis evaluating the frequency of extrahepatic manifestations of HCV, authors found that the pooled prevalence of Sjögren's syndrome across 11 studies was 11.9% among HCV-positive individuals, in comparison to 0.7% among HCV-negative controls.[6] Similarly, in a multicenter registry of patients with chronic HCV and systemic autoimmune diseases, Sjögren's syndrome was the most frequently reported (47.5%) systemic autoimmune disease (47.5%).[34]

Renal Disorders

Renal Manifestations Associated with HCV Infection

A subset of renal glomerular diseases are strongly associated with HCV infection.[42,43] In addition, individuals with chronic HCV can develop albuminuria without overt renal disease, particularly persons 60 years of age or older.[44,45] The evidence for HCV infection causing renal disease is mainly supported by epidemiologic data.[6,46,47,48,49] When HCV-related glomerulonephritis develops, it typically occurs many years, often decades, after initial infection with HCV. The Kidney Disease Improving Global Outcomes group (KDIGO), which published updated clinical guidelines on Hepatitis C and Chronic Kidney Disease in 2022, recommends screening for kidney disease in all persons with chronic HCV infection, as well as testing for HCV for those individuals with chronic kidney disease.[50] The KDIGO and other guidelines are uniform in recommending HCV screening in all persons receiving long-term hemodialysis.[50,51,52]

Mechanisms of HCV-Associated Renal Disease

Experts have postulated various potential mechanisms to explain how HCV potentially induces a wide range of renal diseases: (1) direct cytopathic effect of HCV RNA and proteins on renal cells, (2) systemic immune response to HCV mediated by cryoglobulins, HCV-antibody immune complexes, or amyloid deposition, (3) HCV-induced elevation in toll-like-receptor 3 messenger RNA expression and resultant proinflammatory cytokine production within glomeruli, and (4) insulin resistance and hyperinsulinemia have multiple pathways that may lead to a cascade of reactions that have deleterious effects on the kidney.[53]

Clinical Syndromes of HCV-Related Renal Disease

The most common HCV-related renal disease is membranoproliferative glomerulonephritis (MPGN), which is associated with type II mixed cryoglobulinemia.[54] Most HCV-related MPGN occurs as a result of mixed cryoglobulinemia (cryoglobulinemic MPGN or mononuclear cell-related MPGN).[55] Conversely, renal disease occurs in only 30% of persons with cryoglobulinemia. Most individuals with HCV-related MPGN develop hypertension, which is often severe and difficult to control. Approximately 5% of persons with HCV-related renal disease will develop glomerular renal disease that manifests as oliguric acute renal failure. Laboratory findings of cryoglobulinemia-associated renal disease include proteinuria, microscopic hematuria (with mild to moderate renal insufficiency), and low serum concentrations of complement components (C1q, C4, and C3). In addition to MPGN, other types of HCV-related renal disease (mainly glomerular diseases) also exist, including IgA nephropathy, postinfectious glomerulonephritis, membranous nephropathy, thrombotic microangiopathies, focal and segmental glomerulosclerosis, fibrillary or immunotactoid glomerulopathy, and glomerulonephritis associated with polyarteritis nodosa. These disorders, however, are all less common among persons with chronic HCV than HCV-related MPGN.

Clinical Outcomes of HCV-Related Renal Disease

A retrospective cohort study involving more than 470,000 adult veterans showed that persons with chronic HCV infection were more likely to develop end-stage renal disease (4.3 per 1,000 person-years) than HCV-seronegative patients (3.1 per 1,000 person-years).[13] A subsequent cross-sectional study showed that persons with HCV infection had a 40% higher likelihood of developing renal insufficiency—defined as serum creatinine levels greater than or equal to 1.5 mg/dL—compared with seronegative participants.[11]

Treatment of HCV in Renal Disease

One multicenter observational study of 139 patients with kidney disease from mixed cryoglobulinemia suggested that DAA treatment was associated with reduced mortality and improved kidney survival in that cohort.[56] Successful clearance of HCV with DAA therapy is associated with improved clinical outcomes, including reduced risk of chronic kidney disease and a survival benefit in patients on dialysis.[57,58] The

treatment of HCV in persons with renal disease is addressed in detail in this curriculum in the topic review Treatment of HCV in Persons with Renal Impairment. In general, modern DAA regimens are well tolerated, highly effective, and safe in persons with renal disease. The KDIGO 2022 guidelines emphasize that DAA therapy can be administered at all stages of kidney disease. In addition, the AASLD-IDSA HCV Guidance now recommends that no dose adjustment is required for HCV treatment in persons with renal impairment when the treatment regimen is a recommended DAA regimen; the one exception is that if ribavirin is added to a regimen, a dose adjustment of the ribavirin may be required.[59] The treatment of HCV in persons undergoing or who have undergone renal transplantation is highly complicated and should be performed only by a medical provider who has expertise in this area.

Dermatologic Manifestations

Porphyria Cutanea Tarda

The dermatologic disorder porphyria cutanea tarda is the most common of the porphyrias, a group of disorders of heme synthesis. Both acquired factors and genetic factors typically play a role in the pathogenesis of porphyria cutanea tarda by reducing activity of the uroporphyrinogen decarboxylase enzyme.[60] Chronic HCV infection is one of the most commonly acquired factors associated with porphyria cutanea tarda—the reported prevalence of HCV infection in persons with porphyria cutanea tarda is approximately 50 to 60%.[61,62,63] The mechanism whereby chronic HCV infection increases the risk of porphyria cutanea tarda remains unknown.

- **Clinical Manifestations**: Porphyria cutanea tarda typically manifests as skin fragility, bruising, and blistering, which may become hemorrhagic in sun-exposed areas, particularly on the back of the hands.[60,62] Over time, hyperpigmentation, depigmentation, and a sclerodermoid appearance can develop, along with facial hirsutism.[64]
- **Diagnosis**: A preliminary diagnosis of porphyria cutanea tarda is usually made based on characteristic clinical manifestations in conjunction with an elevated plasma, serum, or urine porphyrin levels.[60] Persons with porphyria cutanea tarda should have studies performed that can detect the presence of iron overload, as well as testing for genetic mutations in the HFE (hemochromatosis) gene.
- **Treatment**: The mainstay of treatment consists of avoiding sunlight, avoiding alcohol, stopping any iron supplementation, stopping estrogen supplementation, and undergoing regular therapeutic phlebotomy (ranging from twice a week to every week), which reduces iron stores, improves heme synthesis, and effectively controls symptoms.[62] Individuals who cannot tolerate phlebotomy or who are anemic can take an oral iron chelator.[60] Low-dose oral chloroquine (125 mg twice weekly) or hydroxychloroquine (100 mg twice weekly) is an alternative to phlebotomy, but treatment with chloroquine or hydroxychloroquine requires monitoring for retinal damage, and it should be used with caution in persons with renal disease or cirrhosis.[65,66] There are case reports and small series describing improvement in porphyria cutanea tarda, but the mechanism for improvement is not clear; one possible explanation could be iron accumulation and oxidative stress.[67,68,69,70]

Lichen Planus

The cutaneous disorder lichen planus results from an immunologically mediated reaction involving CD8-T-lymphocytes to an unknown stimulus.[62,71] Several meta-analyses have shown that persons with lichen planus have about a 5 times higher risk of having chronic HCV infection compared with controls; other studies estimate that approximately 10 to 25% of persons with lichen planus have evidence of HCV infection.[14,15]

- **Clinical Manifestations**: Lichen planus lesions are flat-topped, polygonal, purple, pruritic papules, most often seen on the flexor surfaces of the extremities.[64] Lichen planus can also involve the face, oral cavity, gastrointestinal tract, scalp, genital area hair, and nails.[2,72]
- **Diagnosis**: The biopsy findings typically show dense lymphocytic infiltration in the upper dermis, often referred to as an irregular sawtooth appearance that suggests epidermal hyperplasia.[62]
- **Treatment**: In most persons with lichen planus, the lesions spontaneously resolve within a year. Individuals with symptomatic lichen planus may require treatment; most often, first-line therapy consists of a high-potency topical corticosteroid.[62,64,71] For persons with extensive or refractory disease, oral corticosteroids are often used.[71] Additional second- or third-line treatments include topical retinoids, systemic retinoids, and phototherapy.[71] In one report, four individuals from Japan with lichen planus had resolution of the skin lesions after successful treatment of HCV with DAA therapy.[73] Another report from Japan described a patient with oral lichen planus and HCV that improved with DAA treatment.[74] More data are needed to fully understand the impact of DAA treatment on lichen planus.

Insulin Resistance and Type 2 Diabetes

Prevalence

Several longitudinal and cross-sectional studies have shown that persons with chronic HCV infection have an increased risk of developing type 2 diabetes.[75,76,77] One meta-analysis quantified this risk as a 1.7-fold increased risk of developing diabetes in persons with chronic HCV infection compared with those not infected with HCV.[78] Persons with chronic HCV also have an increased risk of developing insulin resistance without diabetes.[79,80,81]

Pathogenesis

Several potential mechanisms have been considered to explain the association between HCV and insulin resistance, including HCV-induced fibrosis and cirrhosis, the direct viral effect on HCV on inflammatory cytokines, and the combined effects of obesity and HCV infection altering the insulin signaling cascade.[82,83]

Clinical Consequences

The development of insulin resistance and type 2 diabetes has significant negative consequences for persons with chronic HCV infection. Available data suggest that insulin resistance can accelerate hepatic fibrogenesis and this effect may be more pronounced with HCV genotypes 1 and 4.[77,80,84] Diabetes mellitus is also a major risk factor for metabolic-associated steatotic liver disease (MASLD) and metabolic-associated steatohepatitis (MASH). For persons with HCV and co-existing MASLD or MASH, it is thought that fibrosis progression is more rapid and more likely to become advanced. Therefore, the clinical consequence of diabetes in persons with HCV may include more advanced liver disease if the diabetes mellitus is not well controlled.

Management

The management of type 2 diabetes mellitus in persons with chronic HCV is multifactorial and includes treatment of HCV, weight loss (if needed), and pharmacologic therapy for diabetes.[85,86] Improved glucose metabolic and diabetes control have been reported with successful clearance of HCV with DAA therapy in a number of studies.[87,88,89] In an analysis of a large Veterans Administration database, DAA therapy was also associated with a reduced incidence of diabetes.[90] In addition to HCV treatment, most experts consider weight reduction and exercise as key elements in the management of persons with HCV and type 2 diabetes. In a study that examined a 3-month program of weight reduction and increased physical activity in 19 persons with chronic hepatitis C infection and steatosis, the authors reported progressive decreases in serum alanine aminotransferase and mean fasting insulin levels.[91] Chronic HCV infection is not considered a contraindication for the use of biguanides or thiazolidinediones for the treatment of type 2 diabetes.

Lymphomas

Relationship of HCV and Lymphomas

Chronic HCV infection has been associated with an increased risk of developing B-cell non-Hodgkin lymphoma (including diffuse large B-cell lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma, splenic lymphoma with villous lymphocytes, and extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue) as well as primary hepatic lymphoma.[92,93] There is a particularly strong association of HCV with B-cell non-Hodgkin lymphoma, with epidemiologic studies involving persons with chronic HCV showing a two-fold increased risk of developing non-Hodgkin lymphoma; this relative risk increases to approximately 35-fold in persons with symptomatic HCV-associated mixed cryoglobulinemia.[92,93,94,95] Roughly 5 to 10% of individuals with HCV-associated mixed cryoglobulinemia will develop non-Hodgkin lymphoma.[96] Among persons with B-cell non-Hodgkin lymphoma, the HCV prevalence is approximately 15%.[97] The increased risk of developing non-Hodgkin lymphoma is reduced but not eliminated after eradication of HCV. One study examined 3,209 persons with HCV, and the overall annual incidence of lymphoma was significantly lower in HCV-treated persons who achieved an SVR with interferon-based therapy when compared with those who had persistent HCV infection (hazard ratio 0.13).[98]

Pathogenesis

The exact mechanism that would explain the genesis of B-cell lymphomas in persons with chronic HCV infection remains unclear, but three major potential mechanisms have been proposed:[93,99]

- **Chronic Antigen Stimulation**: In this model, HCV antigens continuously stimulate external B-cell lymphocyte receptors (CD19, CD21, CD81), and this leads to upregulation of intracellular oncogenic signals and downregulation of tumor suppressive signals, with the end result being enhanced B-cell proliferation. Alternatively, chronic HCV antigen production may upregulate expression of immunoglobulin variable genes.
- **Direct Transfer by Viral Proteins**: The replication of HCV within B-lymphocytes produces a number of HCV proteins that can lead to induction of oncogenic signals and thereby cause transforming oncogenic effects. The HCV core and NS3 proteins have the strongest association with this transformation process.
- **"Hit and Run" Theory**: In this model, HCV transiently infects B-lymphocytes, and during this process, the virus can cause double-strand DNA breaks that induce cytidine deaminase and error-prone polymerases. These changes may involve mutations in tumor suppressor genes, including p53, BCL-6, and beta-catenin.

Treatment and Prognosis

Treatment of any patient with an HCV-related lymphoma should involve a hematologist-oncologist who has significant experience in managing lymphomas and a medical provider who has expertise in managing and treating HCV infection. The approach to treatment of HCV-associated B-cell lymphomas highly depends on whether the tumor is an indolent (low-grade) or more aggressive tumor, as well as the B-cell tumor subtype.[93,100,101]

Indolent B-Cell Lymphoma

Multiple reports and studies in persons with HCV-associated B-cell non-Hodgkin lymphoma have shown that successful HCV treatment can cause regression of low-grade lymphomas.[102,103,104,105,106,107] In these individuals, some experts now recommend initiating HCV treatment with direct-acting antiviral therapy if there is no immediate need for chemotherapy, with very close follow-up.[101,108]

Aggressive B-Cell Lymphomas

Treatment of aggressive B-cell lymphoma with chemotherapy in persons with chronic HCV infection (with ongoing viremia) is associated with increased rates of hepatotoxicity when compared with persons who do not have active HCV infection; results are mixed on whether HCV impacts the prognosis and survival of persons who undergo chemotherapy for B-cell lymphomas.[109,110,111] In persons with newly detected active HCV at the time of diagnosis of B-cell lymphoma, available data suggest that simultaneous treatment of HCV during chemotherapy improves rates of lymphoma response.[112,113,114,115] A meta-analysis of 58 studies using DAA therapy noted the association between sustained virologic response and progression-free survival, regardless of the type of antiviral used.[115] These studies have mainly involved interferon-based HCV treatment, but it is reasonable to expect the same benefit, with less toxicity, using interferon-free direct-acting antiviral therapy.[114] Most chemotherapy regimens used to treat HCV-associated B-cell lymphomas include rituximab in the overall multi-drug chemotherapy regimen.[102,108,110]

Cardiovascular Events

Association Between HCV and Cardiovascular Events

Multiple retrospective and observational studies have shown an association between HCV infection and cardiovascular disease (and cerebrovascular events), with the highest risk occurring among those who are HCV RNA-positive.[5,116,117,118] Specifically, individuals who are HCV antibody-positive have been shown to have a higher incidence of coronary artery disease, chronic stable angina, unstable angina, or acute myocardial infarction, when compared to HCV antibody-negative persons.[116,117,118] In one retrospective cohort, the risk of cardiovascular events was estimated to be 3.2% for HCV antibody-negative persons, 4.9% for all HCV antibody-positive persons, and 5.9% for HCV-viremic persons.[118] In addition, in a pooled analysis of 8 observational studies, HCV infection was associated with an elevated risk of cardiovascular and cerebrovascular events, with an odds ratio of 1.30 (comparing risk in persons with HCV infection versus those without HCV infection).[116] In a similar analysis using data from the U.S. Veterans Association, HCV infection was associated with a higher risk for cardiovascular disease, with an odds ratio of 1.25, despite individuals with HCV infection being younger, having lower lipid levels, and having a lower prevalence of hypertension when compared to those without HCV.[117]

Proposed Mechanism of HCV Increasing Cardiovascular Risk

The mechanism driving increased cardiovascular risk and HCV infection is likely multifactorial. It is well established that HCV can increase the risk for insulin resistance and diabetes, both of which can lead to endothelial dysfunction and low-grade systemic inflammation.[5,119] In addition, HCV has been associated with high proinflammatory cytokine levels and high inflammatory markers among stroke patients.[120,121]

Impact of HCV Treatment on Cardiovascular Risk

Several studies similarly show that HCV eradication can lead to a lower risk for cardiovascular disease, particularly among persons who have HCV treated with DAAs.[122,123,124,125]

Summary Points

- Chronic HCV infection is associated with a broad range of clinical conditions other than liver disease. The quality of the evidence for these extrahepatic associations is variable.
- Manifestations of HCV are thought to include (but are not limited to) cryoglobulinemic vasculitis; autoimmune conditions; renal disease with or without cryoglobulinemia; skin disorders including lichen planus and porphyria cutanea tarda; diabetes mellitus and metabolic syndrome; lymphomas; and cardiovascular disease.
- Successful treatment of HCV appears to (1) have benefit on some extrahepatic conditions, such as cryoglobulinemic vasculitis and renal disease, and (2) reduce the risk of some extrahepatic manifestations, such as lymphoma and diabetes.
- Clinicians should be aware of the potential for these conditions among persons with HCV infection, and clinicians should consider HCV as a potential etiology of these conditions in persons with unknown HCV infection status.
- For persons with chronic HCV infection, the development of an extrahepatic HCV-related manifestation is typically considered an urgent indication for HCV treatment.
- Payers (public and commercial) usually consider extrahepatic manifestations of HCV as reason to authorize coverage of DAAs.

Citations

1. Tang L, Marcell L, Kottilil S. Systemic manifestations of hepatitis C infection. Infect Agent Cancer. 2016;11:29.
   [PubMed Abstract] -

2. Sherman AC, Sherman KE. Extrahepatic manifestations of hepatitis C infection: navigating CHASM. Curr HIV/AIDS Rep. 2015;12:353-61.
   [PubMed Abstract] -

3. Gumber SC, Chopra S. Hepatitis C: a multifaceted disease. Review of extrahepatic manifestations. Ann Intern Med. 1995 Oct 15;123(8):615-20. Ann Intern Med. 1995;123:615-20.
   [PubMed Abstract] -

4. El-Serag HB, Hampel H, Yeh C, Rabeneck L. Extrahepatic manifestations of hepatitis C among United States male veterans. Hepatology. 2002;36:1439-45.
   [PubMed Abstract] -

5. Cacoub P, Saadoun D. Extrahepatic Manifestations of Chronic HCV Infection. N Engl J Med. 2021;384:1038-52.
   [PubMed Abstract] -

6. Younossi Z, Park H, Henry L, Adeyemi A, Stepanova M. Extrahepatic Manifestations of Hepatitis C: A Meta-analysis of Prevalence, Quality of Life, and Economic Burden. Gastroenterology. 2016;150:1599-1608.
   [PubMed Abstract] -

7. Negro F, Forton D, Craxì A, Sulkowski MS, Feld JJ, Manns MP. Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology. 2015;149:1345-60.
   [PubMed Abstract] -

8. Jacobson IM, Cacoub P, Dal Maso L, Harrison SA, Younossi ZM. Manifestations of chronic hepatitis C virus infection beyond the liver. Clin Gastroenterol Hepatol. 2010;8:1017-29.
   [PubMed Abstract] -

9. Cacoub P, Buggisch P, Carrión JA, et al. Direct medical costs associated with the extrahepatic manifestations of hepatitis C infection in Europe. J Viral Hepat. 2018;25:811-17.
   [PubMed Abstract] -

10. Songtanin B, Nugent K. Burden, Outcome, and Comorbidities of Extrahepatic Manifestations in Hepatitis C Virus Infection. Biology (Basel). 2022;12:23
    [PubMed Abstract] -

11. Dalrymple LS, Koepsell T, Sampson J, Louie T, Dominitz JA, Young B, Kestenbaum B. Hepatitis C virus infection and the prevalence of renal insufficiency. Clin J Am Soc Nephrol. 2007;2:715-21.
    [PubMed Abstract] -

12. Giordano TP, Henderson L, Landgren O, Chiao EY, Kramer JR, El-Serag H, Engels EA. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. JAMA 2007;297:2010-7.
    [PubMed Abstract] -

13. Tsui JI, Vittinghoff E, Shlipak MG, Bertenthal D, Inadomi J, Rodriguez RA, O'Hare AM. Association of

hepatitis C seropositivity with increased risk for developing end-stage renal disease. Arch Intern Med. 2007;167:1271-6.
[PubMed Abstract] -

14. Lodi G, Pellicano R, Carrozzo M. Hepatitis C virus infection and lichen planus: a systematic review with meta-analysis. Oral Dis. 2010;16:601-12.
[PubMed Abstract] -

15. Petti S, Rabiei M, De Luca M, Scully C. The magnitude of the association between hepatitis C virus infection and oral lichen planus: meta-analysis and case control study. Odontology. 2011;99:168-78.
[PubMed Abstract] -

16. Ramos-Casals M, Stone JH, Cid MC, Bosch X. The cryoglobulinaemias. Lancet. 2012;379:348-60.
[PubMed Abstract] -

17. Dammacco F, Sansonno D. Therapy for hepatitis C virus-related cryoglobulinemic vasculitis. N Engl J Med. 2013;369:1035-45.
[PubMed Abstract] -

18. Sansonno D, Dammacco F. Hepatitis C virus, cryoglobulinemia, and vasculitis: immune complex relations. Lancet Infect Dis. 2005;5:227-36.
[PubMed Abstract] -

19. Iannuzzella F, Vaglio A, Garini G. Management of hepatitis C virus-related mixed cryoglobulinemia. Am J Med. 2010;123:400-8.
[PubMed Abstract] -

20. David WS, Peine C, Schlesinger P, Smith SA. Nonsystemic vasculitic mononeuropathy multiplex, cryoglobulinemia, and hepatitis C. Muscle Nerve 1996;19:1596-602.
[PubMed Abstract] -

21. Brouet JC, Clauvel JP, Danon F, Klein M, Seligmann M. Biologic and clinical significance of cryoglobulins. A report of 86 cases. Am J Med. 1974;57:775-88.
[PubMed Abstract] -

22. Moretti M, Ferro F, Baldini C, Mosca M, Talarico R. Cryoglobulinemic vasculitis: a 2023 update. Curr Opin Rheumatol. 2024;36:27-34.
[PubMed Abstract] -

23. Cacoub P, Comarmond C, Vieira M, Régnier P, Saadoun D. HCV-related lymphoproliferative disorders in the direct-acting antiviral era: From mixed cryoglobulinaemia to B-cell lymphoma. J Hepatol. 2022;76:174-85.
[PubMed Abstract] -

24. Mahale P, Engels EA, Li R, et al. The effect of sustained virological response on the risk of extrahepatic manifestations of hepatitis C virus infection. Gut. 2018;67:553-561.
[PubMed Abstract] -

25. Dammacco F, Lauletta G, Vacca A. The wide spectrum of cryoglobulinemic vasculitis and an overview of therapeutic advancements. Clin Exp Med. 2023;23:255-72.
[PubMed Abstract] -

26. Ragab G, Hussein MA. Vasculitic syndromes in hepatitis C virus: A review. J Adv Res. 2017;8:99-111.
[PubMed Abstract] -

27. Roccatello D, Sciascia S, Rossi D, et al. The challenge of treating hepatitis C virus-associated cryoglobulinemic vasculitis in the era of anti-CD20 monoclonal antibodies and direct antiviral agents. Oncotarget. 2017 ;8:41764-41777.
[PubMed Abstract] -

28. Mazzaro C, Quartuccio L, Adinolfi LE, et al. A Review on Extrahepatic Manifestations of Chronic Hepatitis C Virus Infection and the Impact of Direct-Acting Antiviral Therapy. Viruses. 2021;13:2249.
[PubMed Abstract] -

29. Emery JS, Kuczynski M, La D, et al. Efficacy and Safety of Direct Acting Antivirals for the Treatment of Mixed Cryoglobulinemia. Am J Gastroenterol. 2017;112:1298-1308.
[PubMed Abstract] -

30. Danishwar M, Jamil Z, Khan S, et al. Persistence of Cryoglobulinemic Vasculitis after DAA Induced HCV Cure. J Clin Med. 2022;11::984.
[PubMed Abstract] -

31. Cacoub P, Musset L, Amoura Z, et al. Anticardiolipin, anti-beta2-glycoprotein I, and antinucleosome antibodies in hepatitis C virus infection and mixed cryoglobulinemia. Multivirc Group. J Rheumatol. 1997;24:2139-44.
[PubMed Abstract] -

32. Cacoub P, Renou C, Rosenthal E, et al. Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. The GERMIVIC. Groupe d'Etude et de Recherche en Medecine Interne et Maladies Infectieuses sur le Virus de l'Hepatite C. Medicine (Baltimore). 2000;79:47-56.
[PubMed Abstract] -

33. Clifford BD, Donahue D, Smith L, et al. High prevalence of serological markers of autoimmunity in patients with chronic hepatitis C. Hepatology. 1995;21:613-9.
[PubMed Abstract] -

34. Ramos-Casals M, Muñoz S, Medina F, et al. Systemic autoimmune diseases in patients with hepatitis C virus infection: characterization of 1020 cases (The HISPAMEC Registry). J Rheumatol. 2009;36:1442-8.
[PubMed Abstract] -

35. Reddy KR, Krawitt EL, Homberg JC, et al. Absence of anti-LKM-1 antibody in hepatitis C viral infection in the United States of America. J Viral Hepat. 1995;2:175-9.
[PubMed Abstract] -

36. Bianchi FB. Autoimmune hepatitis: the lesson of the discovery of hepatitis C virus. J Hepatol. 1993;18:273-5.
[PubMed Abstract] -

37. Monti V, Aghemo A, Rumi MG, Donato MF, Del Ninno E, Colombo M. The prevalence, clinical features and response to antiviral therapy of patients with chronic hepatitis C who are seropositive for liver-kidney microsome type 1 antibodies. Antivir Ther. 2005;10:715-20.
[PubMed Abstract] -

38. Antonelli A, Ferri C, Pampana A, et al. Thyroid disorders in chronic hepatitis C. Am J Med. 2004;117:10-3.
[PubMed Abstract] -

39. Tran A, Quaranta JF, Benzaken S, et al. High prevalence of thyroid autoantibodies in a prospective series of patients with chronic hepatitis C before interferon therapy. Hepatology. 1993;18:253-7.
[PubMed Abstract] -

40. Haddad J, Deny P, Munz-Gotheil C, et al. Lymphocytic sialadenitis of Sjögren's syndrome associated with chronic hepatitis C virus liver disease. Lancet. 1992;339:321-3.
[PubMed Abstract] -

41. Wang Y, Dou H, Liu G, et al. Hepatitis C virus infection and the risk of Sjögren or sicca syndrome: a meta-analysis. Microbiol Immunol. 2014;58:675-87.
[PubMed Abstract] -

42. Latt N, Alachkar N, Gurakar A. Hepatitis C virus and its renal manifestations: a review and update. Gastroenterol Hepatol (N Y). 2012;8:434-45.
[PubMed Abstract] -

43. Fabrizi F, Verdesca S, Messa P, Martin P. Hepatitis C Virus Infection Increases the Risk of Developing Chronic Kidney Disease: A Systematic Review and Meta-Analysis. Dig Dis Sci. 2015;60:3801-13.
[PubMed Abstract] -

44. Tsui JI, Vittinghoff E, Shlipak MG, O'Hare AM. Relationship between hepatitis C and chronic kidney disease: results from the Third National Health and Nutrition Examination Survey. J Am Soc Nephrol. 2006;17:1168-74.
[PubMed Abstract] -

45. Liangpunsakul S, Chalasani N. Relationship between hepatitis C and microalbuminuria: results from the NHANES III. Kidney Int. 2005;67:285-90.
[PubMed Abstract] -

46. Yamabe H, Johnson RJ, Gretch DR, et al. Hepatitis C virus infection and membranoproliferative glomerulonephritis in Japan. J Am Soc Nephrol. 1995;6:220-3.
[PubMed Abstract] -

47. Castillo I, Martinez-Ara J, Olea T, et al. High prevalence of occult hepatitis C virus infection in patients with primary and secondary glomerular nephropathies. Kidney Int. 2014;86:619-24.
[PubMed Abstract] -

48. Johnson RJ, Gretch DR, Yamabe H, et al. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. N Engl J Med. 1993;328:465-70.
[PubMed Abstract] -

49. Morales JM, Kamar N, Rostaing L. Hepatitis C and renal disease: epidemiology, diagnosis, pathogenesis and therapy. Contrib Nephrol. 2012;176:10-23.
[PubMed Abstract] -

50. Awan AAY, Berenguer MC, Bruchfeld A, et al. Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2022 Clinical Practice Guideline. Ann Intern Med. 2023;176:1648-55.
[PubMed Abstract] -

51. AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. HCV testing and linkage to care.
[AASLD-IDSA Hepatitis C Guidance] -

52. Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC Recommendations for Hepatitis C Screening Among Adults - United States, 2020. MMWR Recomm Rep. 2020;69:1-17.
[PubMed Abstract] -

53. Fabrizi F, Messa P, Martin P. Novel evidence on hepatitis C virus-associated glomerular disease. Kidney Int. 2014;86:466-9.
[PubMed Abstract] -

54. Roccatello D, Fornasieri A, Giachino O, et al. Multicenter study on hepatitis C virus-related cryoglobulinemic glomerulonephritis. Am J Kidney Dis. 2007;49:69-82.
[PubMed Abstract] -

55. Ferri C, Giuggioli D, Colaci M. Renal Manifestations of Hepatitis C Virus. Clin Liver Dis. 2017;21:487-497.
[PubMed Abstract] -

56. Pérez de José A, Carbayo J, Pocurull A, et al. Direct-acting antiviral therapy improves kidney survival in hepatitis C virus-associated cryoglobulinaemia: the RENALCRYOGLOBULINEMIC study. Clin Kidney J. 2021;14:586-92.
[PubMed Abstract] -

57. Park H, Wang W, Henry L, Nelson DR. Impact of All-Oral Direct-Acting Antivirals on Clinical and Economic Outcomes in Patients With Chronic Hepatitis C in the United States. Hepatology. 2019;69:1032-45.
[PubMed Abstract] -

58. Söderholm J, Millbourn C, Büsch K, et al. Higher risk of renal disease in chronic hepatitis C patients: Antiviral therapy survival benefit in patients on hemodialysis. J Hepatol. 2018;68:904-11.
[PubMed Abstract] -

59. AASLD-IDSA. HCV Guidance: Recommendations for testing, management, and treating hepatitis C. Unique populations: patients with renal impairment.
[AASLD-IDSA Hepatitis C Guidance] -

60. Bissell DM, Anderson KE, Bonkovsky HL. Porphyria. N Engl J Med. 2017;377:2101.
[PubMed Abstract] -

61. Fargion S, Piperno A, Capellini MD, et al. Hepatitis C virus and porphyria cutanea tarda: evidence of a strong association. Hepatology 1992;16:1322-6.
[PubMed Abstract] -

62. Dedania B, Wu GY. Dermatologic Extrahepatic Manifestations of Hepatitis C. J Clin Transl Hepatol. 2015;3:127-33.
[PubMed Abstract] -

63. Gisbert JP, García-Buey L, Pajares JM, Moreno-Otero R. Prevalence of hepatitis C virus infection in porphyria cutanea tarda: systematic review and meta-analysis. J Hepatol 2003;39:620-7.
[PubMed Abstract] -

64. Sayiner M, Golabi P, Farhat F, Younossi ZM. Dermatologic Manifestations of Chronic Hepatitis C Infection. Clin Liver Dis. 2017;21:555-564.
[PubMed Abstract] -

65. Ashton RE, Hawk JL, Magnus IA. Low-dose oral chloroquine in the treatment of porphyria cutanea tarda. Br J Dermatol. 1984;111:609-13.
[PubMed Abstract] -

66. Singal AK, Kormos-Hallberg C, Lee C, et al. Low-dose hydroxychloroquine is as effective as phlebotomy in treatment of patients with porphyria cutanea tarda. Clin Gastroenterol Hepatol. 2012;10:1402-9.
[PubMed Abstract] -

67. Tong Y, Song YK, Tyring S. Resolution of Porphyria Cutanea Tarda in Patients With Hepatitis C Following Ledipasvir-Sofosbuvir Combination Therapy. JAMA Dermatol. 2016;152:1393-1395.
[PubMed Abstract] -

68. Hatch MM, Nawas Z, Kollipara R, Tyring SK. Can curative antivirals benefit porphyria cutanea tarda in hepatitis C patients? J Eur Acad Dermatol Venereol. 2017;31:e194.
[PubMed Abstract] -

69. Wiznia LE, Laird ME, Franks AG Jr. Hepatitis C virus and its cutaneous manifestations: treatment in the direct-acting antiviral era. J Eur Acad Dermatol Venereol. 2017;31:1260-1270.
[PubMed Abstract] -

70. To-Figueras J. Association between hepatitis C virus and porphyria cutanea tarda. Mol Genet Metab. 2019 Nov;128:282-287.
[PubMed Abstract] -

71. Le Cleach L, Chosidow O. Clinical practice. Lichen planus. N Engl J Med. 2012;366:723-32.
[PubMed Abstract] -

72. Pilli M, Penna A, Zerbini A, et al. Oral lichen planus pathogenesis: A role for the HCV-specific cellular immune response. Hepatology 2002;36:1446-52.
[PubMed Abstract] -

73. Nagao Y, Kimura K, Kawahigashi Y, Sata M. Successful Treatment of Hepatitis C Virus-associated Oral Lichen Planus by Interferon-free Therapy with Direct-acting Antivirals. Clin Transl Gastroenterol. 2016;7:e179.
[PubMed Abstract] -

74. Misaka K, Kishimoto T, Kawahigashi Y, Sata M, Nagao Y. Use of Direct-Acting Antivirals for the Treatment of Hepatitis C Virus-Associated Oral Lichen Planus: A Case Report. Case Rep Gastroenterol. 2016;10:617-622.
[PubMed Abstract] -

75. Fabiani S, Fallahi P, Ferrari SM, Miccoli M, Antonelli A. Hepatitis C virus infection and development of type 2 diabetes mellitus: Systematic review and meta-analysis of the literature. Rev Endocr Metab Disord. 2018;19:405-20.
[PubMed Abstract] -

76. Wang CS, Wang ST, Yao WJ, Chang TT, Chou P. Hepatitis C virus infection and the development of type 2 diabetes in a community-based longitudinal study. Am J Epidemiol. 2007;166:196-203.
[PubMed Abstract] -

77. Negro F, Alaei M. Hepatitis C virus and type 2 diabetes. World J Gastroenterol. 2009;15:1537-47.
[PubMed Abstract] -

78. White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and

meta-analysis. J Hepatol. 2008;49:831-44.
[PubMed Abstract] -

79. Milner KL, van der Poorten D, Trenell M, et al. Chronic hepatitis C is associated with peripheral rather than hepatic insulin resistance. Gastroenterology. 2010;138:932-41.e1-3.
[PubMed Abstract] -

80. Moucari R, Asselah T, Cazals-Hatem D, et al. Insulin resistance in chronic hepatitis C: association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. Gastroenterology. 2008;134:416-23.
[PubMed Abstract] -

81. Kaddai V, Negro F. Current understanding of insulin resistance in hepatitis C. Expert Rev Gastroenterol Hepatol. 2011;5:503-16.
[PubMed Abstract] -

82. Negro F. Mechanisms of hepatitis C virus-related insulin resistance. Clin Res Hepatol Gastroenterol. 2011;35:358-63.
[PubMed Abstract] -

83. Bose SK, Ray R. Hepatitis C virus infection and insulin resistance. World J Diabetes. 2014;5:52-8.
[PubMed Abstract] -

84. Hui JM, Sud A, Farrell GC, et al. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression. Gastroenterology. 2003;125:1695-704.
[PubMed Abstract] -

85. Doyle MA, Singer J, Lee T, Muir M, Cooper C. Improving treatment and liver fibrosis outcomes with metformin in HCV-HIV co-infected and HCV mono-infected patients with insulin resistance: study protocol for a randomized controlled trial. Trials. 2016;17:331.
[PubMed Abstract] -

86. Harrison SA, Hamzeh FM, Han J, Pandya PK, Sheikh MY, Vierling JM. Chronic hepatitis C genotype 1 patients with insulin resistance treated with pioglitazone and peginterferon alpha-2a plus ribavirin. Hepatology. 2012;56:464-73.
[PubMed Abstract] -

87. Cacoub P, Desbois AC, Comarmond C, Saadoun D. Impact of sustained virological response on the extrahepatic manifestations of chronic hepatitis C: a meta-analysis. Gut. 2018;67:2025-34.
[PubMed Abstract] -

88. Ribaldone DG, Sacco M, Saracco GM. The Effect of Viral Clearance Achieved by Direct-Acting Antiviral Agents on Hepatitis C Virus Positive Patients with Type 2 Diabetes Mellitus: A Word of Caution after the Initial Enthusiasm. J Clin Med. 2020;9:563.
[PubMed Abstract] -

89. Sacco M, Saracco GM. The impact of direct-acting antiviral treatment on glycemic homeostasis in patients with chronic hepatitis C. Minerva Gastroenterol (Torino). 2021;67:264-72.
[PubMed Abstract] -

90. Butt AA, Yan P, Aslam S, Shaikh OS, Abou-Samra AB. Hepatitis C Virus (HCV) Treatment With Directly Acting Agents Reduces the Risk of Incident Diabetes: Results From Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES). Clin Infect Dis. 2020;70:1153-60.
[PubMed Abstract] -

91. Hickman IJ, Clouston AD, Macdonald GA, et al. Effect of weight reduction on liver histology and biochemistry in patients with chronic hepatitis C. Gut. 2002;51:89-94.
[PubMed Abstract] -

92. Dal Maso L, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. Cancer Epidemiol Biomarkers Prev. 2006;15:2078-85.
[PubMed Abstract] -

93. Peveling-Oberhag J, Arcaini L, Hansmann ML, Zeuzem S. Hepatitis C-associated B-cell non-Hodgkin lymphomas. Epidemiology, molecular signature and clinical management. J Hepatol. 2013;59:169-77.
[PubMed Abstract] -

94. Monti G, Pioltelli P, Saccardo F, et al. Incidence and characteristics of non-Hodgkin lymphomas in a multicenter case file of patients with hepatitis C virus-related symptomatic mixed cryoglobulinemias. Arch Intern Med. 2005;165:101-5.
[PubMed Abstract] -

95. Hartridge-Lambert SK, Stein EM, Markowitz AJ, Portlock CS. Hepatitis C and non-Hodgkin lymphoma: the clinical perspective. Hepatology. 2012;55:634-41.
[PubMed Abstract] -

96. Ferri C, Sebastiani M, Giuggioli D, et al. Mixed cryoglobulinemia: demographic, clinical, and serologic features and survival in 231 patients. Semin Arthritis Rheum. 2004;33:355-74.
[PubMed Abstract] -

97. Gisbert JP, García-Buey L, Pajares JM, Moreno-Otero R. Prevalence of hepatitis C virus infection in B-cell non-Hodgkin's lymphoma: systematic review and meta-analysis. Gastroenterology. 2003;125:1723-32.
[PubMed Abstract] -

98. Kawamura Y, Ikeda K, Arase Y, et al. Viral elimination reduces incidence of malignant lymphoma in patients with hepatitis C. Am J Med. 2007;120:1034-41.
[PubMed Abstract] -

99. Armand M, Besson C, Hermine O, Davi F. Hepatitis C virus - Associated marginal zone lymphoma. Best Pract Res Clin Haematol. 2017;30:41-49.
[PubMed Abstract] -

100. Tasleem S, Sood GK. Hepatitis C Associated B-cell Non-Hodgkin Lymphoma: Clinical Features and the Role of Antiviral Therapy. J Clin Transl Hepatol. 2015;3:134-9.
[PubMed Abstract] -

101. Zignego AL, Ramos-Casals M, Ferri C, et al. International therapeutic guidelines for patients with HCV-related extrahepatic disorders. A multidisciplinary expert statement. Autoimmun Rev. 2017;16:523-541.
[PubMed Abstract] -

102. Michot JM, Canioni D, Driss H, et al. Antiviral therapy is associated with a better survival in patients with hepatitis C virus and B-cell non-Hodgkin lymphomas, ANRS HC-13 lympho-C study. Am J Hematol. 2015;90:197-203.
[PubMed Abstract] -

103. Hermine O, Lefrère F, Bronowicki JP, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. N Engl J Med. 2002;347:89-94.
[PubMed Abstract] -

104. Arcaini L, Bruno R. Hepatitis C virus infection and antiviral treatment in marginal zone lymphomas. Curr Clin Pharmacol. 2010;5:74-81.
[PubMed Abstract] -

105. Rossotti R, Travi G, Pazzi A, Baiguera C, Morra E, Puoti M. Rapid clearance of HCV-related splenic marginal zone lymphoma under an interferon-free, NS3/NS4A inhibitor-based treatment. A case report. J Hepatol. 2015;62:234-7.
[PubMed Abstract] -

106. Sultanik P, Klotz C, Brault P, Pol S, Mallet V. Regression of an HCV-associated disseminated marginal zone lymphoma under IFN-free antiviral treatment. Blood. 2015;125:2446-7.
[PubMed Abstract] -

107. Merli M, Carli G, Arcaini L, Visco C. Antiviral therapy of hepatitis C as curative treatment of indolent B-cell lymphoma. World J Gastroenterol. 2016;22:8447-8458.
[PubMed Abstract] -

108. Pozzato G, Mazzaro C, Gattei V. Hepatitis C Virus-Associated Non-Hodgkin Lymphomas: Biology, Epidemiology, and Treatment. Clin Liver Dis. 2017;21:499-515.
[PubMed Abstract] -

109. Chen TT, Chiu CF, Yang TY, et al. Hepatitis C infection is associated with hepatic toxicity but does not compromise the survival of patients with diffuse large B cell lymphoma treated with rituximab-based chemotherapy. Leuk Res. 2015;39:151-6.
[PubMed Abstract] -

110. Ennishi D, Maeda Y, Niitsu N, et al. Hepatic toxicity and prognosis in hepatitis C virus-infected patients with diffuse large B-cell lymphoma treated with rituximab-containing chemotherapy regimens: a Japanese multicenter analysis. Blood. 2010;116:5119-25.
[PubMed Abstract] -

111. Zaky AH, Bakry R, El-sayed MI, Elwanis MA, Nabih O. Impact of treatment-related toxicity on outcome of HCV-positive diffuse large B-cell lymphoma in rituximab era. Hematology. 2014;19:412-6.
[PubMed Abstract] -

112. Hosry J, Mahale P, Turturro F, et al. Antiviral therapy improves overall survival in hepatitis C virus-infected patients who develop diffuse large B-cell lymphoma. Int J Cancer. 2016;139:2519-28.
[PubMed Abstract] -

113. Alric L, Besson C, Lapidus N, et al. Antiviral Treatment of HCV-Infected Patients with B-Cell Non-Hodgkin Lymphoma: ANRS HC-13 Lympho-C Study. PLoS One. 2016;11:e0162965.
[PubMed Abstract] -

114. Peveling-Oberhag J, Arcaini L, Bankov K, Zeuzem S, Herrmann E. The anti-lymphoma activity of antiviral therapy in HCV-associated B-cell non-Hodgkin lymphomas: a meta-analysis. J Viral Hepat. 2016;23:536-44.
[PubMed Abstract] -

115. Masarone M, Persico M. Hepatitis C virus infection and non-hepatocellular malignancies in the DAA era: A systematic review and meta-analysis. Liver Int. 2019;39:1292-1306.
[PubMed Abstract] -

116. Petta S, Maida M, Macaluso FS, et al. Hepatitis C Virus Infection Is Associated With

Increased Cardiovascular Mortality: A Meta-Analysis of Observational Studies. Gastroenterology. 2016;150:145-55.
[PubMed Abstract] -

117. Butt AA, Xiaoqiang W, Budoff M, Leaf D, Kuller LH, Justice AC. Hepatitis C virus infection and the risk of coronary disease. Clin Infect Dis. 2009;49:225-32.
[PubMed Abstract] -

118. Pothineni NV, Delongchamp R, Vallurupalli S, et al. Impact of hepatitis C seropositivity on the risk of coronary heart disease events. Am J Cardiol. 2014;114:1841-5.
[PubMed Abstract] -

119. Cacoub P. Hepatitis C Virus Infection, a New Modifiable Cardiovascular Risk Factor. Gastroenterology. 2019;156:862-4.
[PubMed Abstract] -

120. Adinolfi LE, Restivo L, Guerrera B, et al. Chronic HCV infection is a risk factor of ischemic stroke. Atherosclerosis. 2013;231:22-6.
[PubMed Abstract] -

121. Oliveira CP, Kappel CR, Siqueira ER, et al. Effects of hepatitis C virus on cardiovascular risk in infected patients: a comparative study. Int J Cardiol. 2013;164:221-6.
[PubMed Abstract] -

122. Adinolfi LE, Petta S, Fracanzani AL, et al. Impact of hepatitis C virus clearance by direct-acting antiviral treatment on the incidence of major cardiovascular events: A prospective multicentre study. Atherosclerosis. 2020;296:40-7.
[PubMed Abstract] -

123. Butt AA, Yan P, Shuaib A, Abou-Samra AB, Shaikh OS, Freiberg MS. Direct-Acting Antiviral Therapy for HCV Infection Is Associated With a Reduced Risk of Cardiovascular Disease Events. Gastroenterology. 2019;156:987-96.e8.
[PubMed Abstract] -

124. Nahon P, Bourcier V, Layese R, et al. Eradication of Hepatitis C Virus Infection in Patients With Cirrhosis Reduces Risk of Liver and Non-Liver Complications. Gastroenterology. 2017;152:142-56.e2.
[PubMed Abstract] -

125. Jaiswal V, Ang SP, Hanif M, et al. Cardioprotective effect of antiviral therapy among hepatitis C infected patients: A meta-analysis. Int J Cardiol Heart Vasc. 2023;49:101270.
[PubMed Abstract] -

References

- Cacoub P, Comarmond C, Desbois AC, Saadoun D. Rheumatologic Manifestations of Hepatitis C Virus Infection. Clin Liver Dis. 2017;21:455-64.
[PubMed Abstract] -

- Cacoub P, Vautier M, Desbois AC, Lafuma A, Saadoun D. Effectiveness and cost of hepatitis C virus cryoglobulinaemia vasculitis treatment: From interferon-based to direct-acting antivirals era. Liver Int. 2017;37:1805-13.
[PubMed Abstract] -

- Chaudhury CS, Sheehan J, Chairez C, et al. No Improvement in Hemoglobin A1c Following Hepatitis C Viral Clearance in Patients With and Without HIV. J Infect Dis. 2017;217:47-50.
[PubMed Abstract] -

- Ferri C, Ramos-Casals M, Zignego AL, et al. International diagnostic guidelines for patients with HCV-related extrahepatic manifestations. A multidisciplinary expert statement. Autoimmun Rev. 2016;15:1145-1160.
[PubMed Abstract] -

- Lens S, Rodriguez-Tajes S, Llovet LP, Maduell F, Londoño MC. Treating Hepatitis C in Patients with Renal Failure. Dig Dis. 2017;35:339-346.
[PubMed Abstract] -

- Li J, Gordon SC, Rupp LB, et al. Sustained virological response to hepatitis C treatment decreases the incidence of complications associated with type 2 diabetes. Aliment Pharmacol Ther. 2019;49:599-608.
[PubMed Abstract] -

- Obata F, Murakami T, Miyagi J, et al. A case of rapid amelioration of hepatitis C virus-associated cryoglobulinemic membranoproliferative glomerulonephritis treated by interferon-free directly acting antivirals for HCV in the absence of immunosuppressant. CEN Case Rep. 2017;6:55-60.
[PubMed Abstract] -

- Polo ML, Laufer N. Extrahepatic manifestations of HCV: the role of direct acting antivirals. Expert Rev Anti Infect Ther. 2017;15:737-746.
[PubMed Abstract] -

- Ramos-Casals M, Zignego AL, Ferri C, et al. Evidence-based recommendations on the management of extrahepatic manifestations of chronic hepatitis C virus infection. J Hepatol. 2017;66:1282-1299.
[PubMed Abstract] -

- Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet. 2015;386:1537-45.
[PubMed Abstract] -

- Rutledge SM, Chung RT, Sise ME. Treatment of hepatitis C virus infection in patients with mixed cryoglobulinemic syndrome and cryoglobulinemic glomerulonephritis. Hemodial Int. 2018;22 Suppl 1:S81-S96.
[PubMed Abstract] -

- Saadoun D, Resche Rigon M, Sene D, et al. Rituximab plus Peg-interferon-alpha/ribavirin compared with Peg-interferon-alpha/ribavirin in hepatitis C-related mixed cryoglobulinemia. Blood. 2010;116:326-34.
[PubMed Abstract] -

- Sise ME, Bloom AK, Wisocky J, et al. Treatment of hepatitis C virus-associated mixed cryoglobulinemia with direct-acting antiviral agents. Hepatology. 2016;63:408-17.
[PubMed Abstract] -

- Torres HA, Mahale P. Most patients with HCV-associated lymphoma present with mild liver disease: a call to revise antiviral treatment prioritization. Liver Int. 2015;35:1661-4.
[PubMed Abstract] -

Figures

Figure 1 Major Pathophysiological Mechanisms Implicated in Extrahepatic Manifestations of HCV Infection.

Source: Cacoub P, Saadoun D. Extrahepatic Manifestations of Chronic HCV Infection. N Engl J Med. 2021;384:1038-52.Reproduced with permission from the Massachusetts Medical Society. Copyright © 2021 Massachusetts Medical Society. All rights reserved.
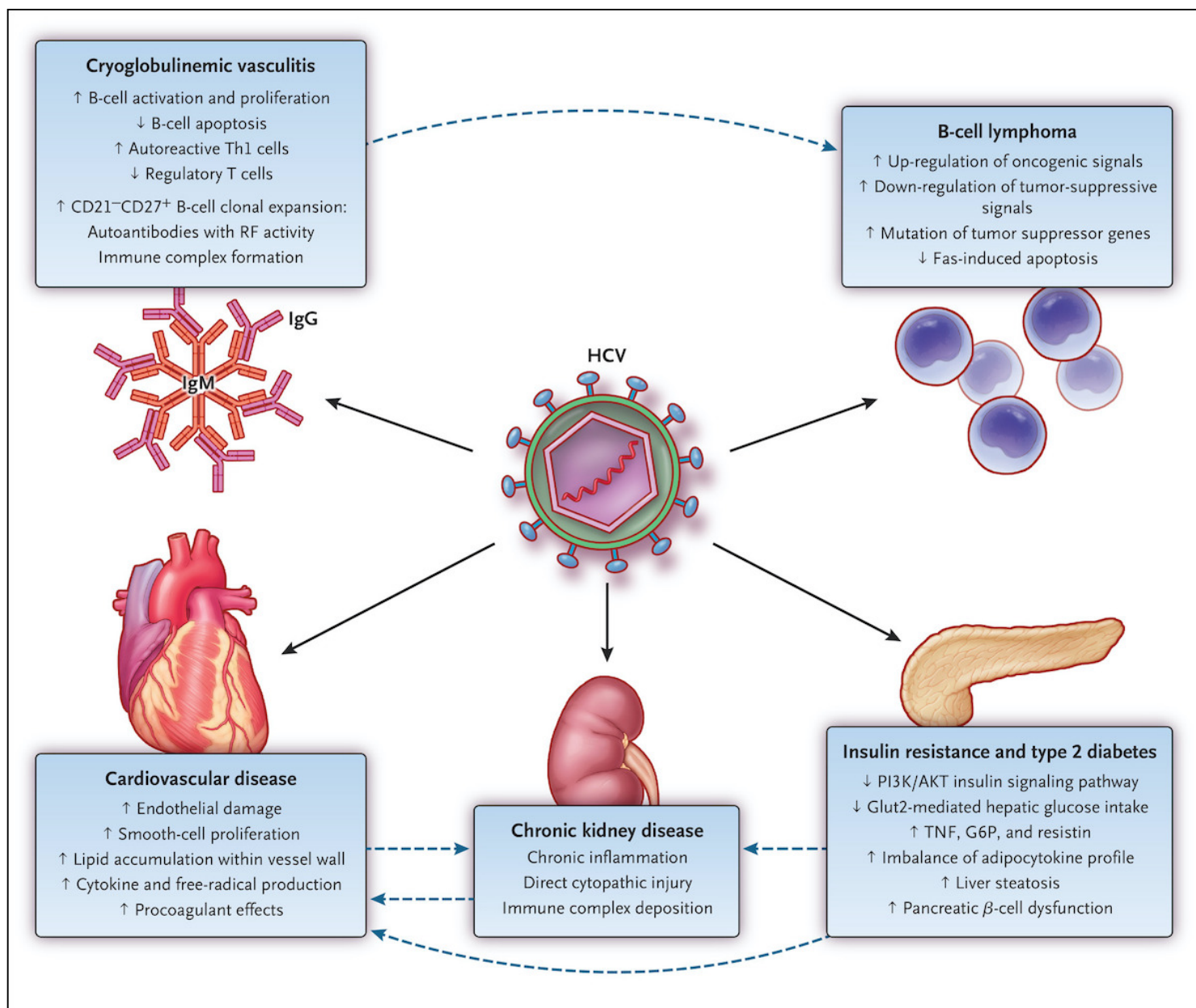
Figure 2 HCV-Related Extrahepatic Manifestations

Patients with HCV-related extrahepatic manifestations can develop an array of symptoms and clinical manifestations.

Hepatitis C-Related Extrahepatic Manifestations

Symptom/Manifestation	Potential HCV-Related Syndrome
Hypertension	Membranoproliferative glomerulonephritis Nephropathy Cryoglobulinemia
Skin disease	Lichen planus Porphyria cutanea tarda Cryoglobulinemia vasculitis
Purpura	Cryoglobulinemic vasculitis
Distal neuropathic pain	Membranoproliferative glomerulonephritis without cryoglobulin Cryoglobulinemia-Membranoproliferative glomerulonephritis
Renal insufficiency Hematuria	Membranoproliferative glomerulonephritis without cryoglobulin Cryoglobulinemia-Membranoproliferative glomerulonephritis
Lymphadenopathy	Lymphoproliferative disorder
Fever	Cryoglobulinemia Cryoglobulinemic vasculitis Lymphoproliferative disorder
Arthralgia, weakness	Cryoglobulinemia Lymphoma Cryoglobulinemic vasculitis