

Extrahepatic Conditions Related to Hepatitis C

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Module 2: [Evaluation, Staging, and Monitoring of Chronic Hepatitis C](#)

Lesson 7: [Extrahepatic Conditions Related to Hepatitis C](#)

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Overview of Extrahepatic Manifestations

Background and Prevalence: Although hepatitis C virus (HCV) infection primarily affects the liver, other organ systems may become involved, which may result in a variety of clinical manifestations. The percentage of patients infected with chronic hepatitis C infection who develop some extrahepatic manifestation remains poorly defined. Nevertheless, some experts have estimated that approximately 40% of patients with HCV will develop at least one extrahepatic manifestation, but estimates of the specific extrahepatic conditions vary. Overall, there is a lack of strong evidence regarding the true prevalence of most of these extrahepatic conditions.

Need for Recognition: It is extremely important that clinicians consider the potential for HCV to cause extrahepatic manifestations in patients with chronic HCV infection ([Figure 1](#)). It is unclear how well clinicians recognize, diagnose, and treat such extrahepatic syndromes, especially since many patients with HCV infection may not have obvious manifestations of chronic liver disease. 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]). For extrahepatic conditions that require a clinical diagnosis, such as lichen planus, identifying the specific condition is much more difficult when utilizing larger datasets. 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.

Cryoglobulinemia

Definition of Cryoglobulinemia: Cryoglobulinemia refers to the presence of one (monoclonal) or more (mixed or polyclonal) immunoglobulins in the serum, which reversibly precipitate in vitro at temperatures below normal body temperature (less than 37°C). These immunoglobulins dissolve again when reheating the serum. Cryoglobulins typically are composed of a mixture of immunoglobulins and complement components.

Mechanism of Disease: In HCV-related cryoglobulinemia, immune complexes that contain HCV particles deposit in the walls of capillaries, venules, or arterioles, causing small vessel inflammation. In patients who develop cryoglobulinemia, HCV causes chronic stimulation of lymphocytes, which is thought to induce B-cell clonal expansion and production of antibodies, including rheumatoid factor.

Clinical Syndromes Associated with Cryoglobulinemia: A variety of clinical syndromes can be associated with cryoglobulinemia. The most common manifestations of HCV-associated cryoglobulinemia, along with the prevalence of the condition in patients with HCV and cryoglobulins, are shown in the following list:

- Mixed cryoglobulinemia vasculitis (4 to 40%)
- Fatigue, arthralgia, myalgia (35 to 54%)
- Renal disease (27 to 30%)
- Palpable purpura (18 to 33%)
- Neuropathy (11 to 30%)
- Sicca syndrome (10 to 25%)

Classification of Cryoglobulinemia: Cryoglobulinemia is classically grouped into three types according to the Brouet classification system. Type 1 cryoglobulinemia consists of isolated monoclonal immunoglobulin IgM and most commonly occurs in association with lymphoproliferative disorders; type 1 cryoglobulinemia represents only 10 to 15% of cases of cryoglobulinemia. Type 2 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 2 cryoglobulinemia is the most common type of cryoglobulinemia seen in HCV-infected patients. Type 3 cryoglobulinemia consists of mixed immune complexes, typically formed by polyclonal IgM, and it represents 25 to 30% of cases of cryoglobulinemia.

Association between HCV and Mixed Cryoglobulinemia: Multiple reports have shown a close association of HCV and mixed cryoglobulinemia, most often type 2 cryoglobulinemia. 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. Investigators have postulated that expansion of rheumatoid factor activity and cryoprecipitability is responsible for the vasculitis. Most patients with mixed cryoglobulinemia have evidence of chronic HCV infection: studies have shown from 50 to 100% of patients with mixed cryoglobulinemia cases have HCV infection. Conversely, most HCV-infected patients do not have mixed cryoglobulinemia, with estimates ranging from 10 to 50%

Clinical Manifestations of HCV-Associated Mixed Cryoglobulinemia: The majority of HCV-infected patients with cryoglobulinemia have either no symptoms or nonspecific clinical manifestations. A triad of purpura, myalgia, and arthralgia (Meltzer's triad) occurs in an estimated 30% of patients with HCV-related mixed cryoglobulinemia. Furthermore, approximately 30% of patients with mixed cryoglobulinemia develop renal disease. Additional clinical features that may develop with mixed cryoglobulinemia include peripheral neuropathy, skin ulcers, and lymphoproliferative disorders.

Cryoglobulinemic Vasculitis (previously termed essential cryoglobulinemic vasculitis)

- **Pathophysiology of Cryoglobulinemic Vasculitis:** Cryoglobulinemic vasculitis is considered a systemic small vessel vasculitis. In this disorder, damage to the small vessels is thought to result from the deposition of immune complexes on the vessel wall followed by subsequent activation of the complement cascade. Fewer than 10% of patients with cryoglobulinemia develop cryoglobulinemic vasculitis.
- **Manifestations of Cryoglobulinemic Vasculitis:** Patients 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 patients with mixed cryoglobulinemia, and is usually the first sign of cryoglobulinemia. The finding of palpable purpura in a patient with chronic hepatitis C should raise an immediate suspicion for cryoglobulinemic vasculitis.
- **Diagnosis of Cryoglobulinemic Vasculitis:** Specific criteria of cryoglobulinemic vasculitis have not yet been defined. The diagnosis is typically made from the combination of history, skin purpura, low complement levels, circulating cryoglobulins, and histology that shows small vessel inflammation with immune deposits found in the vascular walls.

Treatment of HCV-related Cryoglobulinemic Vasculitis

- **Interferon alfa:** In patients with cryoglobulinemic vasculitis, experience with HCV treatment regimens that include interferon or peginterferon has shown that HCV RNA levels decrease to an undetectable range before cryoglobulin levels substantially decline. There is no evidence that patients with cryoglobulinemia have different SVR rates than patients without cryoglobulinemia. Low HCV RNA levels alone predict a favorable response of cryoglobulins to interferon monotherapy, but approximately 80% of these responders will relapse within 6 months after completion of interferon therapy. The combination of peginterferon alfa with ribavirin enhances and improves the response. Use of interferon or peginterferon in this setting remains controversial since treatment may precipitate and aggravate neuropathies, induce renal failure, and delay ulcer healing. Insufficient data exist regarding the treatment of hepatitis C-related cryoglobulinemia using regimens that include or consist entirely of new direct acting antiviral agents. Interferon-free regimens would theoretically provide an advantage by avoiding the interferon-related complications associated with treatment of cryoglobulinemia.
- **Corticosteroids, Cytotoxic Agents, and Plasmapheresis:** Some experts have used corticosteroids in combination with cytotoxic agents and plasmapheresis to treat rapidly progressive cryoglobulinemic vasculitis. Treatment with these agents should be administered by an expert (or in consultation with an expert) who has experience with treating this disorder.
- **Monoclonal Antibodies:** B-cell clonal expansion is a key finding in mixed cryoglobulinemia. Rituximab (*Rituxan*), an anti-CD20 monoclonal antibody, modifies the dynamics of B cells by deleting expanded clones in cryoglobulinemic patients. This treatment may provide protection against factors potentially involved in the pathogenesis of malignant B-cell transformation. Patients with HCV infection may have increased HCV RNA levels detected after treatment with rituximab. A few studies have investigated the use of rituximab in combination with peginterferon and ribavirin and have shown an improvement in results when compared with peginterferon and ribavirin alone. Treatment with rituximab should be administered by an expert (or in consultation with an expert) who has experience with use of rituximab.

Renal Disorders

Overview of Renal Manifestations Associated with HCV Infection: Some forms of renal disease are precipitated by chronic HCV infection. Conversely, patients with chronic kidney disease requiring hemodialysis have an increased risk of acquiring HCV infection. The evidence for HCV infection causing renal disease is mainly supported by epidemiologic data, with these data showing major geographic variation—the prevalence of HCV infection in nephropathies is 10 to 20% in the United States, whereas it is 60% in Japan. When HCV-related glomerulonephritis develops, it typically occurs many years, often decades, after initial infection with HCV.

Detecting HCV-Related Renal Disease: The Kidney Disease Improving Global Outcomes group (KDIGO) in their most recent published clinical guidelines in 2008 recommends screening all HCV infected patients for kidney disease, and conversely testing all patients with chronic kidney disease for HCV.

Mechanisms of HCV-Associated Renal Disease: Experts have postulated three potential mechanisms to explain how HCV potentially induces renal disease: (1) direct viral tissue damage, (2) systemic immune response, and (3) insulin resistance. In the first proposed mechanism, damage to the renal parenchyma results directly from HCV RNA and HCV related proteins. In the second, the kidney injury results from a HCV-induced systemic immune response mediated by cryoglobulins, HCV-antibody immune complexes, or amyloid deposition. Most notably, when deposition of cryoglobulins occurs in the mesangium and glomerular capillaries, it has a major nephrotoxic effect. The third proposed mechanism links HCV and renal disease through elevated levels of fasting serum insulin and insulin resistance, as supported by data showing a higher prevalence of diabetes in HCV-infected patients. Insulin resistance and hyperinsulinemia have multiple pathways that may lead to deleterious effects on the kidney.

Clinical Syndromes of HCV-Related Renal Disease: The most common HCV-related nephropathy is membranoproliferative glomerulonephritis, also commonly referred to as mesangiocapillary glomerulonephritis. Most HCV-related membranoproliferative glomerulonephritis occurs in the context of cryoglobulinemia (cryoglobulinemic membranoproliferative glomerulonephritis, or mononuclear cell-related membranoproliferative glomerulonephritis). Conversely, renal disease occurs in only 30% of patients with cryoglobulinemia. Most patients with HCV-related membranoproliferative glomerulonephritis develop hypertension, which is often severe and difficult to control. Approximately 5% of patients 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). Less commonly, other types of HCV-related renal disease (mainly glomerular diseases) can develop, including IgA nephropathy, postinfectious glomerulonephritis, membranous nephropathy, thrombotic microangiopathies, focal and segmental glomerulosclerosis, and fibrillary or immunotactoid glomerulopathy.

Diagnosis: The diagnosis of HCV-related renal disease is confirmed by renal biopsy. Renal biopsy characteristically shows a pattern of membranoproliferative glomerulonephritis, with immune complex deposition in glomeruli inflammatory cells—both mononuclear cells and polymorphonuclear leukocytes—that infiltrate the glomerular capillaries. Other findings may include mesangial matrix expansion, splitting of capillary basement membranes, and intracapillary globular accumulation of eosinophilic material (representing precipitated immune complexes or cryoglobulins).

Clinical Outcomes of HCV-Related Renal Disease: In addition to the risk of renal disease progression, the overall prognosis for patients with HCV-related nephritis is poor because of the high incidence of co-infections and associated cardiovascular disease. A retrospective cohort study involving more than 470,000 adult veterans showed that patients with HCV infection were more likely to develop end stage renal disease (4.3 per 1000 person-year) than HCV-seronegative patients

(3.1 per 1000 person-year). A cross-sectional study showed that HCV-infected patients had a 40% higher likelihood for developing renal insufficiency—defined as serum creatinine levels greater than or equal to 1.5 mg/dL—compared with seronegative subjects.

Treatment of HCV-Related Renal Disease: The most recent (2008) guidelines from the Kidney Disease Improving Global Outcomes (KDIGO) group recommends treatment of HCV infection in patients with chronic kidney disease who have no contraindications to hepatitis C therapy. Unfortunately, there are no large-scale clinical trials of HCV therapy in persons with hepatitis C-related chronic kidney disease, especially those receiving renal replacement therapy. Treatment of HCV infection in patients undergoing renal replacement therapy 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

Leukocytoclastic Vasculitis: Leukocytoclastic vasculitis is a pathological term that describes the microscopic findings of a neutrophilic small vessel vasculitis. Cutaneous leukocytoclastic vasculitis is a clinical term that describes leukocytoclastic vasculitis limited to the skin. The cutaneous manifestations of leukocytoclastic vasculitis include petechiae, palpable purpura, nodules, ulcers, and other findings. These cutaneous manifestations usually involve the lower extremities. Clinical features of leukocytoclastic vasculitis can resemble multiple other disorders and biopsy is necessary to confirm the diagnosis. In this setting, some patients also develop peripheral neuropathy and it may be asymmetric. Leukocytoclastic vasculitis may occur with cryoglobulinemia. Histopathologic features of leukocytoclastic vasculitis include fibrinoid necrosis and a neutrophilic infiltrate invading or damaging the dermal blood vessel wall. Other tissues, such as lower extremity peripheral nerves, may show similar vasculitic changes involving the vasa nervorum. Similar to the treatment of mixed cryoglobulinemia, the treatment of leukocytoclastic vasculitis may include HCV therapy.

Porphyria Cutanea Tarda: The dermatologic disorder porphyria cutanea tarda is the most common form of porphyria. The reported prevalence of HCV infection in patients with porphyria cutanea tarda is approximately 45%. Among patients with chronic HCV infection, porphyria cutanea tarda disproportionately occurs in those with cirrhosis. Elevated urinary uroporphyrin levels are detected in only 0.5 to 22% of patients with chronic HCV infection. Porphyria cutanea tarda typically manifests as skin fragility, bruising, vesicles, and bullae, which may become hemorrhagic in sun exposed areas. Over time, pigmentation, depigmentation, hirsutism and a sclerodermoid appearance can develop. Patients 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 gene. The mainstay of treatment consists of avoiding sunlight and undergoing regular therapeutic phlebotomy (ranging from twice a week to every week), which reduces iron stores, improves heme synthesis, and effectively controls symptoms. In situations where phlebotomy is not an option, low-dose oral chloroquine sulfate or hydroxychloroquine sulfate has been tried with some success, but these oral therapies can cause direct hepatotoxicity. Insufficient data exist to determine whether treating hepatitis C infection and achieving SVR improves porphyria cutanea tarda.

Lichen Planus: The cutaneous disorder lichen planus results from an immunologically mediated reaction to an unknown stimulus. An estimated 10 to 40% of patients with lichen planus have evidence of HCV infection. Lichen planus are flat-topped, violaceous, pruritic papules with a generalized distribution, particularly on the extremities. Lichen planus can also involve mucous membranes, hair, and nails. The biopsy findings typically show dense lymphocytic infiltration in the upper dermis. In most patients with lichen planus, the lesions spontaneously resolve within a year. Patients with symptomatic lichen planus may require treatment; most often first-line therapy consists of a fluorinated topical corticosteroid. For patients with extensive or refractory disease, additional treatment modalities are available but an expert should manage this situation.

Insulin Resistance and Type 2 Diabetes

Prevalence: Several longitudinal and cross-sectional studies have shown an association of hepatitis C infection and the subsequent development of insulin resistance and type 2 diabetes. Among HCV patients, insulin resistance has been reported in 32 to 70%, metabolic syndrome has been reported in 26 to 51%, and type 2 DM has been reported in 14 to 50%. The NHANES cohort found HCV was associated with insulin resistance. A large 7-year prospective cohort study in Taiwan found HCV infection to be an independent risk factor for diabetes mellitus.

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

Clinical Consequences: The development of insulin resistance and type 2 diabetes has significant negative consequences for persons with chronic hepatitis C infection. Available data suggest that insulin resistance accelerates hepatic fibrogenesis. In addition, multiple studies have shown that insulin resistance significantly reduces sustained virologic response (SVR) rates with hepatitis C therapy. The insulin resistance impairment of hepatitis C treatment response rates appears related to the increased expression of suppressor of cytokine signaling 3 (SOCS3) and its inhibition of interferon-alfa signaling.

Management: In a study that examined a 3-month program of weight reduction and increased physical activity in 19 patients with chronic hepatitis C infection and steatosis, the authors reported progressive decreases in serum alanine aminotransferase and mean fasting insulin levels. Most experts consider weight reduction and exercise as key elements in the management of patients with hepatitis C infection and type 2 diabetes. In an effort to minimize the adverse impact of insulin resistance on hepatitis C treatment responses, investigators have studied the addition of an insulin-sensitizing agent, such as metformin or pioglitazone (*Actos*), during the course of treatment with peginterferon and ribavirin, but this approach has produced conflicting results with regard to sustained virologic response. Further, if an insulin-sensitizing agent is used in conjunction with hepatitis C therapy, it remains unclear which insulin-sensitizing agent to use and whether to start the agent simultaneously with or preceding the hepatitis therapy. In a recent study involving patients with genotype-1 infection, baseline insulin resistance did not have a significant impact on treatment responses in patients who received a triple-agent regimen that included telaprevir (*Incivek*). Hepatitis C infection is not considered a contraindication for the use of biguanides or thiazolidinediones for the treatment of type 2 diabetes.

Lymphomas

Relationship: Chronic hepatitis C infection has been associated with the development of 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. There is a high prevalence of HCV seropositivity (15%) in patients with B-cell lymphoproliferative disorders, especially B-cell non-Hodgkin lymphoma. Epidemiological studies have shown that patients who are positive for anti-HCV had a two-fold increased risk of developing non-Hodgkin lymphoma compared with non-HCV infected controls, and the relative risk increases to approximately 35-fold in patients with symptomatic HCV-associated mixed cryoglobulinemia. Roughly 8 to 10% of patients with hepatitis C-associated mixed cryoglobulinemia will develop non-Hodgkin's lymphoma. The increased risk of developing non-Hodgkin's lymphoma is not eliminated after eradication of hepatitis C.

Pathogenesis: The mechanism of the association between HCV and lymphomas is not certain but postulated that the benign B-cell lymphoproliferation seen in HCV-related MC might progress to low-grade NHL under continued antigen stimulation. For higher grade HCV related NHL without MC, it is thought that HCV may directly infect B cells and lead to their malignant transformation.

Treatment and Prognosis: Survival outcomes for patients with diffuse large B-cell lymphoma with HCV infection are worse than in patients without HCV infection. This may be due to hepatotoxicity of chemotherapy for the lymphoma. Achieving an SVR with treatment for HCV may reduce the risk of lymphoma. One study looked at 3209 patients with HCV—the overall annual incidence of lymphoma in these patients was estimated to be 0.2%. 84% of the patients had received treatment with interferon-based therapy and for those who had achieved an SVR, the risk of lymphoma was significantly reduced compared to those who had persistent HCV infection (hazard ratio 0.13).

Summary Points

- Hepatitis C virus is associated with a broad range of clinical conditions other than liver disease.
- Manifestations of HCV are thought to include (but are not limited to) cryoglobulinemic vasculitis, renal disease with or without cryoglobulinemia, skin disorders including cutaneous leukocytoclastic vasculitis and porphyria cutanea tarda, diabetes mellitus and metabolic syndrome, and lymphomas.
- The quality of the evidence for these associations is variable.
- Successful treatment of HCV appears to reduce the risk of some extrahepatic manifestations, such as lymphoma and diabetes.
- Successful treatment of HCV appears to have benefit on some extrahepatic conditions, such as cryoglobulinemic vasculitis and renal disease.
- Clinicians should have an awareness of the potential for these conditions in their patients with HCV, and clinicians should consider HCV as a potential etiology of these conditions in patients who do not carry an HCV diagnosis.

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Figures

Figure 1 Hepatitis C-Related Extrahepatic Manifestations

Patients with hepatitis C-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 Leukocytoclastic vasculitis Cryoglobulinemia vasculitis
Purpura	Cryoglobulinemic vasculitis Leukocytoclastic 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