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CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

Extrahepatic Manifestations of Hepatitis C Infection: Navigating CHASM

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Abstract This article describes the importance of extrahepatic systemic manifestations of chronic hepatitis C virus (HCV) infection. While most HCV literature focuses on liver injury and fibrosis progression, a spectrum of systemic disease processes, collectively called C hepatitis-associated systemic manifestations (CHASMs), are present in a high proportion of infected persons. These include thyroid disease (Hashimoto's thyroiditis, Graves disease, and thyroid cancer), cardiovascular disease (atherosclerosis, carotid artery disease, and coronary artery disease), renal disease (MPGN and glomerulosclerosis), eye disease (Mooren's ulcers and sicca syndrome), skin disease (PCT, vasculitis, and lichen planus), lymphomas (NHL and splenic T-cell), and diabetes. Mechanistic understanding of how HCV leads to CHASM processes could lead to development of new interventions. The role of early HCV treatment and cure may result in preventive strategies for a variety of complex disease states.

Key Points
- Systemic extrahepatic complications of HCV comprise a spectrum of disease states in many organs and systems.
- Effective treatment of HCV may reduce or eliminate some but not all of these systemic complications.
- Further research into early treatment intervention as a prevention strategy for systemic disease is warranted.

Keywords HCV · Extrahepatic · Thyroid · Vasculitis · Lymphoma · Diabetes · Neurologic

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Introduction

HCV infection results in a chronic disease state affecting over 170 million people worldwide. HCV is a hepatotropic virus with its primary site of replication in the liver. Viral kinetic models suggest that most infected individuals produce 10–13 trillion virions/day, primarily but not exclusively from hepatocytes. There is growing evidence that a variety of other tissues can support limited replication of HCV in sites outside the liver compartment. These infections may represent a tiny fraction of the viral population but may be quite significant in the development and modulation of systemic extrahepatic disease processes. Furthermore, immune response to HCV viral proteins links active infection and replication with a host of immune-mediated processes that can result in injury to distant organs. Finally, the direct effects of HCV on hepatic metabolism may have a significant impact on lipids, hormones, and counter-regulatory peptides that contribute to systemic disease states associated with the metabolic syndrome. In those with HIV infection, HCV infection in the liver may result in development of portal hypertension that exacerbates immune activation associated with shunting of blood flow. Taken collectively, understanding the disease processes directly and indirectly affected by HCV requires examination of disorders involving the thyroid gland, lymphocytes, skin, kidneys, pancreas, intestinal tract, the brain, eyes, blood vessels, and the heart. Overlapping organ and tissue involvement in those with

HIV infection can lead to difficult diagnostic dilemmas and accelerated pathogenesis in those with HIV/HCV coinfection.

Epidemiologic support for the importance of extrahepatic disease processes to patient outcomes comes from recent studies that demonstrate an association between achievement of HCV cure (as evidenced by sustained viral response (SVR)) and a decrease in both liver-related and all-cause mortality. Innes et al. reported mortality change in a Scottish cohort followed for a median time of 7.5 years. Non-liver mortality was reduced significantly with an adjusted hazard ratio of 0.68 compared to those who did not achieve viral clearance [1]. A large study of HCV-infected patients in the Veteran's Administration (VA) database demonstrated that non-liver-related mortality was significantly reduced among patients who achieved SVR who had comorbidities that included coronary artery disease, diabetes, and hypertension. It was suggested that decreased chronic inflammation associated with HCV was a key factor in mortality decline [2••]. This finding was supported by data from a five-center multinational study that included all consecutive patients enrolled between 1990 and 2003 with a median follow-up of 8.4 years. SVR was associated with an all-cause mortality hazard ratio of 0.26 and liver-related mortality hazard ratio of 0.06. Both reductions were highly statistically significant [3]. These studies point to the important role that HCV may play in non-hepatic causes of death. Therefore, an exploration of the specific effects that HCV may have, directly and indirectly, on extrahepatic organs and tissues is warranted (see Fig. 1). Since these processes may occur discretely or in combination within a single patient, we propose that they collectively be referred to as C hepatitis-associated systemic manifestations (CHASMs).

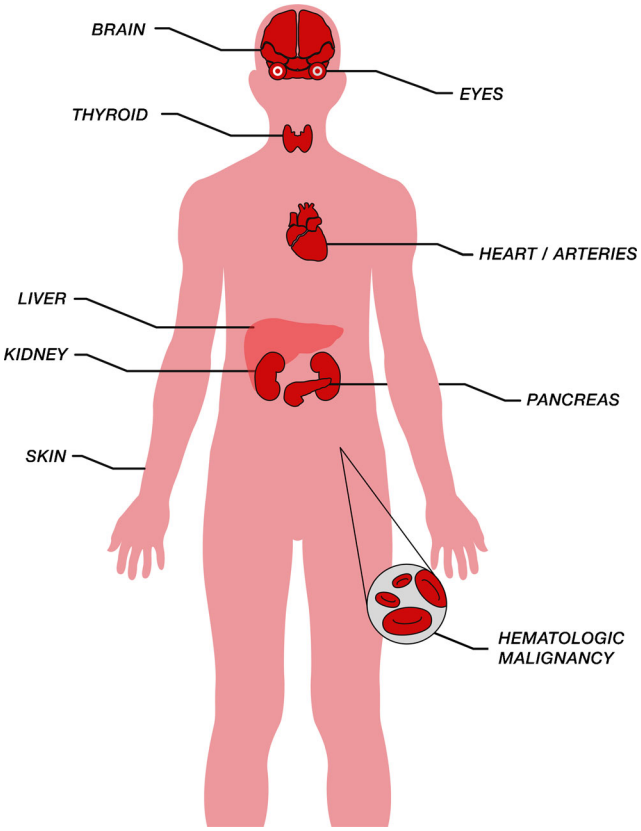

Fig. 1 Extrahepatic sites of disease associated with HCV infection

Thyroid Disease

Following approval of interferon alfa as treatment for HCV infection in 1991 came growing recognition that clinically significant thyroid disease was a common complication associated with therapy. Prospective studies demonstrated that up to 15 % of all treated patients developed clinically recognizable thyroid disease and up to 40 % developed thyroid antibodies. A typical pattern of disease was the development of severe thyrotoxicosis followed by development of hypothyroidism. Both Graves' disease and Hashimoto's thyroiditis were observed. These processes appear to have autoimmune etiology and are more common in women than men. The observation that discontinuation of interferon failed to resolve the condition led to the suggestion that interferon may trigger development of disease in those already predisposed to Graves' and Hashimoto's thyroid disease (see Table 1). Subsequent epidemiologic studies established the link between HCV infection and incidence of thyroid antibodies, prior to exposure to interferon alfa. In a French series, Tran and colleagues reported prevalence of 12.5 % of HCV-infected patients having thyroid antibodies, versus 1.7 % in non-HCV-infected controls (p=0.21) [4]. This observation has been confirmed in numerous countries. Mechanistically, this phenomenon would be best explained by direct infection of thyroid tissues by HCV. Bartolome et al. reported detection of HCV RNA in thyroid tissue derived from HCV-infected patients [5]. Recently, Blackard et al. described productive infection of a human thyroid cell line (ML1) with HCV. The thyrocytes demonstrated expression of CD81 which is a major receptor for the HCV complex. Both positive and negative-strand virus was identified in cell lysates. Interferon alfa inhibited HCV replication, and cell supernatants containing virus could infect native thyroid cells [6]. It has been postulated that active infection with HCV leads to upregulation of CXCL10 expression in thyrocytes, which promotes recruitment of Th1 lymphocytes. These cells secrete interferon gamma and TNF alpha which further upregulate the immune cascade within the thyrocytes leading to active clinical disease manifestations [7].

Management of HCV-associated thyroid disease requires recognition of the process. All patients with HCV should have baseline TSH measurement to determine if hypothyroidism or hyperthyroidism is present. Some experts also recommend evaluation of thyroid antibodies in all patients, to include TPO-AB and Tg-Ab since positive antibodies represent a risk factor for development of clinically relevant disease. In the

Table 1 Effect of cure with interferon-based regimens versus DAA therapies

	peg-IFN + RBV	DAA-based therapies
Thyroid disease	No—may be exacerbated	Unknown
Eye disease	Unknown	Unknown
Neurologic disease	Unknown	Unknown
CAD	Decreased	Unknown
Type 2 DM	Unknown	Unknown
Sjögren syndrome	Possible improvement in sicca symptoms	Unknown
B-cell NHL	May lead to regression	May lead to regression
Renal disease	May improve	May improve
Skin disease	Lichen planus (+/−) PCT (+/−)	May reduce HCV-associated vasculitis

increasingly rare event that interferon alfa is part of an HCV regimen, TSH levels should be monitored every 3 months. The predictive value of thyroid antibodies for clinical disease is not known at this time [8]. Patients with incident thyroid disease should be managed medically. There are not sufficient data to determine long-term effects of clearance of virus with interferon-free regimens.

Eye Disease

Early epidemiologic studies of HCV-infected patients suggested a strong association between infection and certain relatively rare eye disorders. These include Mooren's corneal ulcers and sicca syndrome [9]. Decreased lacrimation leading to punctate keratitis and keratoconjunctivitis sicca are well described [10]. Recent evidence suggests that HCV may be present in corneal cells from ocular donors infected with HCV [11]. Other types of eye involvement include episcleritis, retinopathy, and retinal vasculitis. HCV is in the tears of approximately 10 % of those with HCV systemically [10].

A prospective, cross-sectional trial examining intraocular pressure measurements of HCV-infected patients and controls revealed that mean tonometry was significantly higher in HCV-infected patients versus blood donor controls [12]. However, increased incidence of glaucoma has not been described to date.

Brain and Nervous System

Involvement of the brain and nervous system in HCV infection represents a relatively active area of research. Involvement of the brain and nervous tissue is potentially related to several distinct mechanisms including (a) direct infection, (b) indirect stimulation of neurotoxic cytokine pathways, and (c) the development of central nervous system vasculitis.

The occurrence of neurocognitive changes associated with HCV is well described and occurs in up to 50 % of all HCV-infected persons. It manifests itself as fatigue and cognitive impairment [13, 14]. Neuroimaging supports the premise that HCV infection leads to changes associated with neurocognitive function aberrations [15]. Direct infection and replication of HCV have been described by several investigators. Brain tissue and cerebrospinal fluid have positive and negative-strand HCV RNA amplification indicative of active replication (as opposed to findings of only positive-strand RNA which could be attributed to blood contamination) [16–19]. Letendre et al. studied HIV/HCV-coinfected individuals and detected HCV by immune-based detection methods in astrocytes and macrophage-microglial cells [20•]. However, an in vitro study by Liu et al. attempted to infect human astrocytes with HCV. They found very restrictive replication despite the active binding and suggested that engagement of HCV with astrocytes led to strong IL-18 induction which led to direct neurotoxicity [21]. Another mechanism that has been suggested for neurotoxicity is associated with toll-like receptor (TLR) engagement. Activation of TLR2 following engagement of HCV core protein with dendritic cells appears to cause extracellular-signal kinase (ERK)-mediated retraction of neuronal processes [22].

In a post-mortem study of brain tissue of patients with HIV and HIV/HCV, investigators at Mt. Sinai hemisectioned brains and used a computer-aided virtual slide scanning system to examine arterioles and calculate an arteriolar sclerotic index. From this information, the authors determined the association of small-vessel cerebrovascular disease (SVD) with various potential etiologic factors. The strongest independent risk factor of cerebral SVD was the presence of HCV infection [23]. This supports other studies that suggest that there are greater white matter abnormalities in those with HIV/HCV coinfection versus HIV alone [24].

Peripheral neuropathy associated with HCV infection is well described and consists of sensory and sensorimotor symmetrical peripheral neuropathy. It is thought to be mediated through the development of cryoglobulinemia, which leads to vasculitis-associated nerve ischemia [25]. However, neuropathy has also been reported in those

without cryoglobulinemia indicating that alternate mechanisms may be in play [26].

A confounder in studies of HCV and neurocognitive dysfunction is the presence of liver disease. Hepatic fibrosis leads to development of porto-venous shunts that take portal blood derived from the gut to the systemic circulation. This blood contains neuroactive substances which cross the blood–brain barrier and lead to neurocognitive changes which are attributable to hepatic encephalopathy. These changes can be quite subtle and have been described as minimal hepatic encephalopathy or occult hepatic encephalopathy [27]. Despite that, there is a growing body of evidence that HCV directly affects the brain and nerves independently of hepatic mediated processes.

Coronary Artery Disease and Atherosclerosis

The association between atherosclerosis and chronic hepatitis C infection has been described in the literature. Adinolfi et al. demonstrated that viral load and steatosis were independently associated with carotid atherosclerosis [28]. Hsu et al. have demonstrated a clear link, showing that the 8-year cumulative incidences of acute coronary syndrome (ACS) and ischemic stroke were significantly lower in patients with HCV who were treated (with peg-interferon and ribavirin) as compared to those in the untreated cohort (2.21 % (95 % confidence interval (CI) 1.7 to 2.71 %) vs 2.96 % (95 % CI 2.46 to 3.45 %) for ACS (p=0.027) and 1.31 % (95 % CI 0.85 to 1.77 %) vs 1.76 % (95 % CI 1.44 to 2.08 %) for ischemic stroke (p=0.001) [29]. This is an overall estimated risk reduction of 23 % in ACS and 38 % in ischemic stroke. Petta et al. described a well-characterized cohort of 174 consecutive HCV-genotype-1-infected patients and 174 non-HCV-infected controls. Hepatic fibrosis associated with HCV infection was highly associated with the presence of carotid plaques. [30•]

Several mechanisms have been proposed, including direct damage from virions and immunologic mechanisms. Serum HCV RNA levels have been shown to be independently associated with carotid atherosclerosis. Other studies suggest that HCV may replicate within cells found in atherosclerotic plaque. [31]

Other authors advocate for an immune-mediated process that leads to atherosclerosis. HCV may cause damage to arteries that creates a pro-inflammatory milieu [32]. Specifically, Oliveira et al. measured elevated IL-6 and TNF-alpha in monoinfected patients with hepatitis C and demonstrated a direct correlation with these pro-inflammatory markers and Framingham scores. The Framingham score suggested that HCV-monoinfected, non-obese, non-diabetic patients have an intermediate cardiovascular risk, conferred by HCV alone. An analysis of the national VA database (ERCHIVES) among 237,069 persons including 111,436 HCV-monoinfected and 1616 HCV/HIV-coinfected patients also calculated Framingham scores and, contrary to the prior study, failed to find higher Framingham risk scores for HCV-infected patients [33]. However, the D.A.D. study and others have noted that the Framingham score may require adjustment in HIV-infected persons before use as a marker of actual cardiac risk [34]. No prospective trials have yet validated actual cardiovascular risk, however.

Diabetes

Numerous studies have reported the association between glucose intolerance and chronic hepatitis C infection. Bahtiyar et al. demonstrated that up to 1/3 of patients with chronic hepatitis C develop type 2 diabetes (T2DM), which is prevalence that is much higher as compared to the general population. It is also higher prevalence as compared to those patients with other chronic liver diseases such as HBV, alcoholic liver disease, and primary biliary cirrhosis [35]. Observational studies have noted that individuals with T2DM had higher prevalence of HCV infection as compared to non-T2DM control groups (odds ratio (OR)=1.26, 95 % CI 1.00–1.57) [36]. Interestingly, this association was not observed in an analysis of the NHASES 1999–2010 cohort. Diabetes and prediabetes was not associated with HCV antibody status [37]. This conflicted with another group analysis of the same cohort which did report that HCV was associated with an OR of 2.3 for the presence of diabetes [38]. Key differences in the two analyses were the nature of the controls, the definitions of diabetes utilized, and whether or not ALT level was controlled for. While the cohort studies are not conclusive, examination of the underlying pathophysiology provides some insights into why a true association may exist.

The mechanism(s) that link hyperinsulinemia and diabetes to HCV infections is an area of intensive investigation. Shlomai et al. examined the relationship between peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) and HCV infection in Huh 7.5 cells. PGC-1α was induced in HCV-infected cells which was accompanied by increased expression of glucose-6 phosphatase and increased glucose production. A mitigating response to N-acetylcysteine suggests that HCV-induced oxidative stress led to PGC-1α upregulation [39]. Host *IL28b* genotype has also been associated with the presence of insulin resistance. TT variants were significantly more likely to demonstrate insulin resistance as evidenced by increased HOMA scores [40]. TT patients are less likely to clear HCV spontaneously which would lead to an association between active persistent HCV infection and insulin resistance leading to type 2 DM.

Diabetes may also alter the natural history of HCV infection. T2DM is recognized as causing an altered cytokine milieu. Insulin resistance mediated by pro-inflammatory

cytokines may contribute to quicker development of steatosis and fibrosis [41, 42].

Sjögren Syndrome

The pathogenesis of Sjögren syndrome (SS) is thought to be secondary to both host factors (e.g., genetic predisposition) and exogenous factors. Viral agents in particular have been proposed as likely exogenous factors, and hepatitis C has been linked to causation of SS in a subset of patients. The association was first described in 1992 [43]. A recent systematic review confirms the strong association even when strict criteria are utilized [44]. The controversy lies in how to best define the association; does HCV truly act as a factor that leads to primary SS, or do the clinical symptoms seen represent a HCV-induced disease that mimics primary SS? [45] Ramos-Casals et al. proposed that primary SS and HCV-induced SS (SS-HCV) were two separate processes, as distinguished by epidemiologic, pathologic, and immunologic differences [46]. It was noted that SS-HCV typically presented at an older age as compared to primary SS, and a reduced female to male ratio was noted for SS-HCV as compared to the primary SS group. On histologic examination, the two groups essentially were the same. However, they differed by immunologic profile. The SS-HCV group demonstrated higher prevalence of cryoglobulinemia, rheumatoid factor, and hypocomplementemia and positive ANA with negative Ro/La.

Few studies have addressed the role of treatment of HCV. Sicca syndrome was improved with interferon or interferon/ribavirin therapy in patients that had SVR in a small series [47]. No data are available regarding direct-acting antiviral (DAA)-based cures.

B-Cell Non-Hodgkin's Lymphoma

The first report of non-Hodgkin's lymphoma (NHL) associated with HCV was in 1994 by Ferri et al. [48]. Numerous studies have since confirmed this association, although the degree of association varies greatly by country.

In the 1990s, investigators described very high prevalence of HCV in patients with mixed cryoglobulinemia [49]. While mixed cryoglobulinemia has since been shown to be implicated in a wide variety of clinical presentations, ranging from arthralgia to vasculitis to glomerulonephritis, it is highly associated with development of NHL. HCV-infected patients with symptoms of mixed cryoglobulinemia are approximately 35 times more likely to develop NHL as compared to the general population [50]. A meta-analysis by Dal Maso et al. evaluated 15 studies and summarized that about 10 % of NHL can be attributed to HCV infection in regions where HCV prevalence is high [51].

Treatment of hepatitis C with peg-interferon and ribavirin combinations led to complete and partial remissions of NHL among patients with HCV [52, 53]. Recently, case reports support the concept that interferon-free regimens (sofosbuvir + ribavirin) can be used to treat HCV, which subsequently led to lymphoma regression [54]. Prospective studies are lacking at this time, however.

Most studies have focused on the association between B-cell NHL and HCV; however, other studies suggest a possible link between more rare forms of lymphoma and HCV as well. The meta-analysis mentioned above by Dal Maso also demonstrated a connection between T-cell lymphomas and HCV infection. However, the studies were few and often with limited sample sizes and require further investigation.

Three mechanisms have been proposed that potentially explain the link between HCV and NHL induction: chronic antigenic stimulation, CD81 engagement on B and T cells (which may lead to activation of B cells), and direct infection of B cells by HCV [55]. The authors suggest that two or more oncogenic signals are required to initiate uncontrolled B-cell replication.

Other Solid Organ Malignancies

Since many solid organ malignancies are relatively rare compared to the general population, it has been difficult to ascertain whether reported associations between HCV and solid organ tumors is real or artifactual. A recent abstract, utilizing data from the Kaiser Permanente Southern California tumor registry, examined this association using over 14 million patient years of data. Overall, head and neck cancer, esophageal cancer, stomach cancer, colorectal cancer, pancreatic cancer, lung cancer, prostate cancer, and renal cancer were increased. The dataset also supported increased risk of hematogenous malignancies including NHL and myeloma associated with HCV infection [56]. Similar data are reported in the Chronic Hepatitis Cohort Study (CHeCS) which examined health records from 12,126 HCV-infected persons and compared them to 122,795,010 records from the SEER cancer registry. Pancreatic cancer, rectal cancer, kidney cancer, and lung cancer risks were all increased as well as NHL [57].

Antonelli et al. first recognized the prevalence of thyroid carcinoma with hepatitis C infection in 1999 [58]. Subsequently, a large study examined the associations of HCV and a variety of cancers. The odds ratio for thyroid cancer association with HCV infection was 2.8 (95 % CI 1.2–6.3, $p=0.01$) [59]. There are no data regarding the effect of HCV cure on thyroid cancer incidence at this time. However, a retrospective analysis of the Veteran's Administration database failed to find an association between HCV and thyroid cancer, though a strong association with thyroiditis was noted [60]. Thyroid cancer was highly associated with HCV infection ($p<0.0001$) in the Kaiser Permanente analysis as noted above [56]. The

difference in these study results may be due to high rates of comorbidities in the VA population and lower proportions of women, which may obscure the ability to detect HCV-associated thyroid cancer.

Following observations of rising rates of renal cell carcinoma (RCC), investigators at Henry Ford Medical Center initiated a prospective evaluation of new RCCs and compared them to newly diagnosed colon cancer controls. HCV infection was highly associated with development of RRC (OR= 24.2) [61]. This finding is supported by the Kaiser Permanente retrospective registry as well [56].

Other than the large cohort studies described above, there are limited data regarding the association between pancreatic cancer and HCV infection and the findings are mixed. However, a meta-analysis examining eight case–control studies did find that anti-HCV seropositivity was associated with development of pancreatic adenocarcinoma (OR 1.21, 95 % CI 1.02–1.44).

Renal

A spectrum of HCV-related renal disease has been reported in the literature, including cryoglobulinemia leading to membranoproliferative glomerulonephritis (MPGN), non-cryoglobulinemia MPGN, IgA nephropathy, post-infectious glomerulonephritis, focal and segmental glomerulosclerosis, fibrillary glomerulonephritis, and immunotactoid glomerulopathy [62].

Mixed cryoglobulinemia is most commonly associated with hepatitis C, in which the cryoglobulins consist mainly of rheumatoid factor and IgG [63]. Cryoglobulins have been detected in about 50 % of patients with HCV infection; however, only about 1 % of these patients have high levels of cryoglobulins associated with known disease processes [64]. In terms of renal disease, cryoglobulinemia manifests with mild to moderate renal insufficiency with microscopic hematuria and proteinuria. Renal biopsy shows histology consistent with MPGN [65], with immune complex deposition frequently observed in the glomeruli [66].

In terms of therapy, most treatments have targeted either the immune response or viral replication or both. Two controlled trials have demonstrated improvements in cryoglobulins, rheumatoid factor, and creatinine levels with treatment with interferon alpha [67, 68]. Antiviral therapy (with interferon and ribavirin) has been shown to be successful for both HCV-related renal disease with cryoglobulinemia and HCV-related MPGN; however, relapse rates are often high [65, 69, 70]. However, with the advent of DAAs, some authors have published case reports with promising results. For example, De Nicola et al. reported a case of HCV-1-related cryoglobulinemic MPGN, with severe nephritic syndrome and rapidly progressive renal failure with treatment, who had complete resolution of her acute renal failure with combination therapy of telaprevir (DAA), peg-IFN, and RBV [71].

Dermatologic Manifestations

There are three main types of skin lesions that have been linked with hepatitis C infection: vasculitis associated with mixed essential cryoglobulinemia, porphyria cutanea tarda, and lichen planus.

Vasculitis, Mixed Essential Cryoglobulinemia

As explained previously, cryoglobulinemia has been described in about 50 % of patients with HCV and is thought to trigger development of the vasculitis. Cryoglobulinemic vasculitis is classified as a small-vessel vasculitis, with clinical symptoms that include palpable purpura on the lower extremities, as well as arthralgias and weakness.

Previously, mixed cryoglobulinemia was treated with peg-interferon and ribavirin. Rituximab was utilized as a second-line treatment option (or adjunct) if interferon and ribavirin failed [72]. However, with DAAs now becoming available, cohorts have begun to describe combination treatments with DAAs. A case report by Urraro et al. demonstrated complete remission of HCV-induced vasculitis with a combination treatment of rituximab, peg-interferon, ribavirin, and a DAA (boceprevir) [73]. Further studies are warranted to validate the effectiveness of the combined therapy, since this was a single case report.

PCT

Porphyria cutanea tarda (PCT) is the most common form of porphyria. PCT is secondary to the decreased activity of the enzyme uroporphyrinogen decarboxylase [74]. However, defects of the enzyme alone do not necessarily produce the phenotypic symptoms seen in PCT. Rather, exogenous factors such as iron overload, alcohol, and estrogen are required to produce manifestations of PCT, which includes blistering of the hands, forearms, and/or face, as well as cutaneous fragility [75]. Numerous studies have shown an association between hepatitis C infection and PCT, as well as development of PCT at an earlier age in HCV-infected patients as compared to those without HCV [76]. A systematic review found that 50 % of patients with the diagnosis of PCT have HCV infection. Conversely, PCT occurs in 1–5 % of those with chronic HCV [77]. HIV may be a significant cofactor in development of PCT [78]. The mechanistic underpinning of these observations remains unknown.

Studies have shown mixed results regarding remission of PCT with interferon-based treatments. Several case reports demonstrated resolution of the skin lesions and normalization of urine porphyrins and serum liver enzymes and ferritin with

interferon treatment [79, 80]. However, other studies refute these findings [81]. To the authors' knowledge, no cohorts have yet analyzed the effect of DAA therapy in regard to resolution of PCT.

Lichen Planus

Lichen planus is a chronic, inflammatory, mucocutaneous skin disease. The lesions are most commonly seen in the extremities, as well as nails, face, scalp, and genitalia. Lesions of the mucosa are most commonly seen in the oral cavity, nasal membranes, esophagus, stomach, bladder, vagina, and glans penis [82]. Studies have shown 9.8–23 % prevalence of hepatitis C seropositivity in individuals with lichen planus [83].

The mechanism behind HCV and lichen planus has not been clearly elucidated; however, it is suspected that it is an immune-mediated mechanism. Shared heptapeptides have been cited as a possible immunogen between several viruses including HCV and desmoglein-3 as well as other skin epitopes [84]. Despite this hypothesis, no clear pattern of resolution of lichen planus has been demonstrated with interferon treatment for HCV. Studies have shown conflicting results. Doutre et al. suggested that treatment with interferon alpha completely cleared lichen planus [85]. However, other studies have demonstrated that interferon may aggravate existing lichen planus [86, 87, 88]. There are no reported cases of DAA treatment and the outcome of lichen planus to date.

Conclusion

There are multiple systemic manifestations of HCV infection that can collectively be grouped and identified as part of CHASM syndrome. Many are unrecognized and poorly characterized in terms of pathophysiology and treatment effects. In patients with concomitant HIV infection, the clinical presentation may be complicated by overlapping risks related to immune activation, increased gut permeability, and direct/indirect HIV effects on end organs. Furthermore, there is significantly an overlap of HIV end organ and HCV extrahepatic pathogenesis which often significantly increases the risk of these diseases in the HIV/HCV coinfected host. There is an urgent need to address these disease processes because improved understanding may lead to earlier recognition, treatment and perhaps resolution, or even disease prevention. Furthermore, the current focus by payers on liver disease stage as a gateway to DAA access lacks recognition of the burden of HCV-mediated disease outside of the liver. Further study to show associations with SVR and decreased extrahepatic clinical outcomes is desperately needed to expand access to DAA.

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Compliance with Ethics Guidelines

Conflict of Interest Amy C. Sherman and Kenneth E. Sherman declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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