Extrahepatic Manifestations in Hepatitis C Virus Infection

Subjects: Gastroenterology & Hepatology

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Hepatitis C is a liver infection caused by the hepatitis C virus and is a major health problem that contributes to the global burden of chronic disease. Chronic infection can lead to liver cancer and death from end-organ damage. Despite the introduction of novel anti-viral therapy, the disease burden is still high.

extrahepatic manifestation hepatitis C virus hepatitis C infection

1. Introduction

Over 58 million people worldwide are infected with the hepatitis C virus (HCV), an estimated 2.4 million people in the United States live with hepatitis C, and about 400,000 people died from this disease in 2016 [1][2]. Chronic hepatitis C is associated with significant morbidity, and although the number of cases is decreasing, it is still a common reason for liver transplantation in the United States [3].

Approximately 25% of HCV-infected patients spontaneously clear the infection [4], but most patients become chronically infected with HCV and develop liver-related complications, including decompensated cirrhosis and hepatocellular carcinoma (HCC), which significantly contribute to mortality. However, non-liver-related hepatitis C manifestations can also develop in chronically hepatitis C-infected patients, and these extrahepatic manifestations also contribute to the disease burden, poor outcomes, and mortality in HCV-infected patients [5][6][7].

Extrahepatic manifestations of HCV can involve almost every organ system in the human body and include metabolic syndromes (diabetes mellitus, cardiovascular disease, cerebrovascular disease), autoimmune diseases (Sjogren syndrome, thyroiditis, arthritis), immune-mediated disorders (mixed cryoglobulinemia), malignancy (lymphoma), dermatologic conditions (lichen planus, porphyria cutanea tarda), and renal diseases [8][9][10] (**Figure 1**). These extrahepatic manifestations of HCV can increase mortality in chronic hepatitis C-infected patients and increase the risk of developing hepatic fibrosis and HCC; they also reduce the quality of life in patients and increase health care costs worldwide.

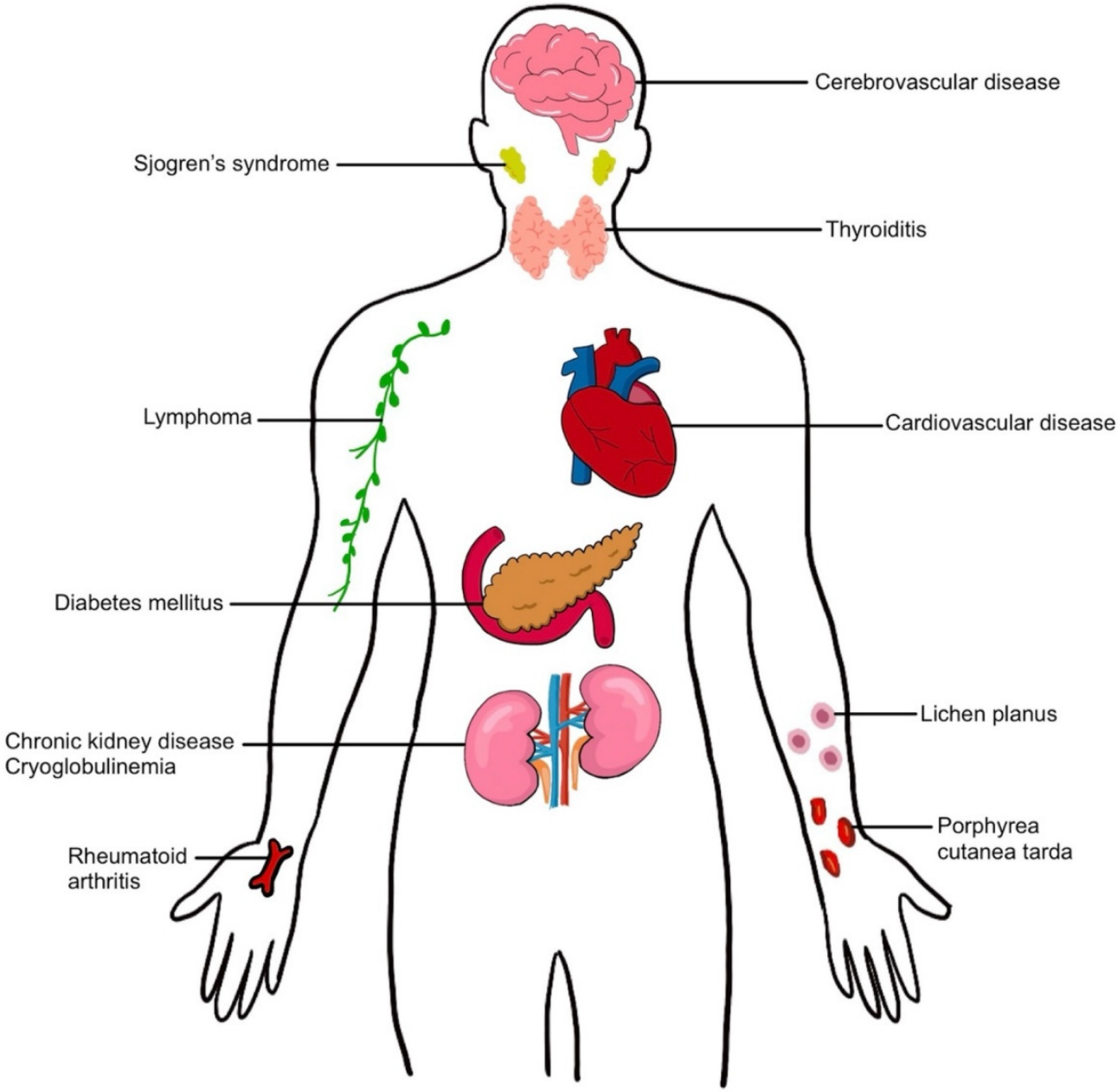

Figure 1. Extrahepatic manifestation in hepatitis C virus infection.

The primary event in hepatitis C infections involves viral replication in hepatocytes. Chang and co-investigators measured HCV replication in the human liver using in situ hybridization techniques to measure the HCV genome and replicative intermediate ribonucleic acids (RNAs) [11]. They determined that the number of HCV genomes ranged from 7-64 RNA molecules in individual hepatocytes. The maximum number of RNA genomes for a single cell was 74, and the number in the entire liver ranged from 1.8×10^{11} molecules to 1.8×10^{12} molecules. There was a gradient of dispersion around infected hepatocytes which suggested that infection spread to neighboring hepatocytes as the mechanism of viral spread in the liver. In addition, viral synthetic activities can compromise the normal metabolic activities in hepatocytes and increase the possibility of hepatocellular injury and death. The number of genomes per milliliter (mL) serum in the Chang study ranged from 3.4×10^6 molecules to 5.0×10^8 molecules. Schijman et al. determined the HCV load in 245 male and female patients with HCV infection. The

median HCV load was 344,000 international units/mL [12]. There were no major differences between male and female patients or between different viral genotypes (1a, 1b, 2, 3a, 4). These virions in the serum have the potential to reinfect hepatocytes and infect extrahepatic tissues.

The development of extrahepatic complications associated with hepatitis C infection involves complex interactions which include direct viral effects on tissue, the metabolic effects associated with hepatic infection and injury, and the host defense responses associated with ongoing infection [13]. Other factors which potentially influence the development of extrahepatic manifestations include obesity, alcohol use, and the viral genotype causing the infection. Metabolic consequences will also depend on the duration of the infection, the possibility of co-infection with other viral pathogens, and drug treatment effects. These various possibilities are discussed below in the sections on non-hepatic organ involvement in hepatitis C infections.

With new HCV treatments based on pangenotypic direct-acting antiviral (DAAs) therapy, over 90% of hepatitis C infected patients can have sustained virologic responses (SVR) within 2–3 months, and these regimens can be used in many patients with comorbidities who previously could not be treated [14]. Further, recent studies show that SVR was associated with a significant reduction in the risk of several extrahepatic manifestations of HCV [15]. HCV treatment can reduce medical costs by up to $25,000 per patient per year [16]. Therefore, the purpose of this research is to analyze the risk factors, disease burden, outcomes, and comorbidities of each extrahepatic manifestation of HCV to identify possible research priorities for future investigation. Despite the introduction of DAAs and the more than 90% rate of SVR, about 38% of patients with chronic HCV infection develop at least one extrahepatic manifestation [17] (**Table 1** and **Table 2**).

Table 1. Prevalence of extrahepatic manifestations in HCV infections.

EHMs	Authors	Study Method	Findings in HCV Patients (95%CI)
Diabetesmellitus	Younossi [9]	Systematic review (31 studies, n = 263,973)	Prevalence: 15% (13–18%)
	Younossi [18]	Systematic review (21 studies, n = 22,432)	Prevalence 19.0% (15.6–22.9%)
Cardiovascular and cerebrovascular disease	Lee [19]	Systematic review (36 studies, n = 341,739)	RR of cardiovascular events, MI, stroke 1.28 (1.15–1.42), 1.13 (1.00–1.28), 1.28 (1.18–1.39), respectively
	Petta [20]	Systematic review (22 studies, n = 390 602)	OR of CVD–related mortality, carotid plaques, and CVA 1.65 (1.07–2.56), 2.27(1.76–2.94), 1.30 (1.10–1.55), respectively
Mixed cryoglobulinemia	Younossi [9]	Systematic review (21 studies, n =	Prevalence: 30% (21.4–38.9%) OR 11.50 (4.56–29.00)

EHMs	Authors	Study Method	Findings in HCV Patients (95%CI)
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	Park [21]	Retrospective cohort (n = 55,646)	HR 16.91 (12.00–23.81)
Chronic kidney disease [44]	Park [21]	Retrospective cohort (n = 56,448)	HR of 1.27 (1.18–1.37)
Lymphoma	de Sanjose [22]	Case control (n = 11,053)	OR of Marginal zone lymphoma, DLBCL, and lymphoplasmacytic lymphoma 2.47 (1.44–4.23), 2.24 (1.68–2.99), 2.57 (1.14–5.79), respectively
	Pozzato [23]	Systematic review (50 studies, n = 21,262) [45][46]	RR of NHL 2.3 (1.8–2.9)
Porphyria cutanea tarda	Gisbert [24]	Systematic review (50 studies, n = 2167)	Prevalence: 47–50% OR 275 (104–725)
	Younossi [9]	Systematic review [24](7 studies, n = 970,315)	Prevalence: 0.5% (0.1–0.8) OR 8.53 (4.15–17.52) [9]
Lichen planus	Alaizari [47] [25]	Systematic review (19 studies, n = 4326)	OR 6.07 (2.73–13.48)
Sjogren syndrome	Younossi [9]	Systematic review (11 studies, n = 38,789)	Prevalence: 11.9% (7.6–16.2%) RR 2.29 (0.19–27.09)
[49]	Yeh [26]	[48] A population-based analysis (n = 48,145) [49]	OR 2.49 (2.16–2.86)
Rheumatoid arthritis	Younossi [9]	Systematic review (4 studies, n = 210,538) [48][50][51]	Prevalence: 1% (0.0–2.0%) OR 2.39 (1.52–3.77)
	Younossi [18]	Systematic review [52] (5 studies, n = 18,234)	Prevalence: 4.5% (0.6–25.7%) OR 2.49 (1.79–3.45)
Thyroiditis	Shen [27]	Systematic review (12 studies, n = 3603)	Prevalence of hypothyroidism: 6.36% [53] OR 3.10 (2.19–4.40)

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iron overload by phlebotomy before initiating IFN-based therapies, which produced a better response and improved SVR rates in chronic HCV infection [54]. With DAAs therapy, porphyrin levels are decreased significantly or completely reduced to normal levels, but data are limited [53]. A recent study by García-Fraile recruited 13 patients with HCV infection, and PCT demonstrated that SVR after DAAs treatment leads to PCT resolution [55].

2.2. Lichen Planus

Lichen planus is a chronic inflammatory disorder affecting the skin and mucosal surfaces, it is a T-cell mediated disease affecting stratified squamous epithelium of the skin and/or mucus membranes. The classic manifestations include pruritic, polygonal, and purple papules or plaques, and the condition commonly affects middle-aged adults. Lichen planus may appear in the skin, mucous membranes, scalp, nails, and genitalia. Oral lichen planus presents

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response to HCV causes skin disease [62]. Genetic factors have been considered a possible factor in the development of oral lichen planus in HCV-infected patients involving HLA-DR6 compared to those without HCV infection. However, this research was conducted in Italy, and geographic differences have been postulated as a factor in developing oral lichen planus [63][64]. Another study showed that patients with oral lichen planus and HCV infection have higher levels of CD8+ lymphocytes in lamina propria compared with patients with oral lichenoid reaction [65]. Figueiredo hypothesized that the host immune system is responsible for oral lichen planus more than direct viral effects [66].

Table 2. Independent factors and disease burdens of EHMs.

EHM	Independent Factor	Disease Burden
Diabetes mellitus [28][29][30][31]	Cirrhosis, aging, obesity, family history of DM, HCV genotype (1,2,4) [59]	Increased risk of hepatic fibrosis, Increased risk of HCC
Cardiovascular disease [19][20][32][33][34]	DM, HTN, HIV coinfection	Increased risk of MI, cardiac dysfunction, heart failure [57]
Mixed cryoglobulinemia and renal disease [21][35] [25]	Cardiovascular disease, liver failure, infections, chronic renal failure	Increased risk of CKD
Lymphoma [36][37]	Geographic variations	Increased risk of developing chronic hepatitis, cirrhosis, and HCC [60]
Sjogren syndrome [38][39][40]	Older age, liver disease activity	May increase risk of developing MALT lymphoma, malignant B cell non-Hodgkin lymphoma
Rheumatoid arthritis [41]	Smoking, previous history of arthritis	Data limited [62]
Thyroiditis [27][42][43]	Female, geographic variability	Data limited

DM, Diabetes mellitus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HTN, hypertension; HIV, human immunodeficiency virus; MI, myocardial ischemia; CKD, chronic kidney disease.

2.2.3. Burden and Outcomes after Treatment

Interferon (IFN) therapy is controversial in the management of HCV in patients with comorbid lichen planus, as there have been reports of both improvement and aggravation of lichen planus symptoms [67][68][69]. Studies on treatment with IFN-free DAAs are limited, and a case series with a small sample reported successful outcomes in HCV-associated oral lichen planus in all seven patients [70].

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