Other Extrahepatic Manifestations of Hepatitis C Virus Infection (Pulmonary, Idiopathic Thrombocytopenic Purpura, Nondiabetes Endocrine Disorders)

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KEYWORDS

• Hepatitis C • Extrahepatic manifestations • Pulmonary • Endocrine
• Idiopathic thrombocytopenic purpura

KEY POINTS

- Hepatitis C Virus (HCV) infection may increase the risk for obstructive, interstitial, and vascular lung disease, lung cancer, and mortality in HCV-infected lung transplant recipients.
- HCV infection may increase the risk of idiopathic thrombocytopenic purpura, nonresponse to corticosteroids during the treatment, and higher rates of splenectomy.
- HCV infection may increase the risk of autoimmune thyroiditis, infertility, growth hormone and adrenal deficiency, osteoporosis, and low-trauma fractures.
- Targeted prospective cohorts may confirm these results mostly obtained from small case-control studies with different study populations and low level of evidence.

INTRODUCTION

Hepatitis C virus (HCV) is a widespread infection with an estimated prevalence of at least 1.8% in the American population and is a leading cause of liver-related morbidity and mortality worldwide.[1] In addition to hepatocytes, it also infects, and replicates in, extrahepatic tissues and peripheral mononuclear blood cells.[2,3] Therefore, it is not surprising that HCV infection is also associated with extrahepatic manifestations evolving

Disclosure Statement: The authors have nothing to disclose.

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Clin Liver Dis ■ (2017) ■–■
http://dx.doi.org/10.1016/j.cld.2017.03.014 liver.theclinics.com

simultaneously with, or independent from, viral hepatitis, cirrhosis, portal hypertension, or hepatocellular cancer. The prevalence of extrahepatic manifestations in HCV infection largely depends on the definition of this condition, but seems to concern up to 0.9% to 1.4% of 16,761 HCV-infected patients identified in various high-risk groups in Lazio, Italy.[4]

In this review, we summarize the current evidence for potential pulmonary and non-diabetic endocrine extrahepatic manifestations of HCV.

Pulmonary Manifestations of Hepatitis C Virus Infection

There is accumulating evidence on a potential interaction between HCV virus infection and pulmonary extrahepatic manifestations (**Table 1**). These range from potentially increased rates of obstructive and restrictive pneumopathies, as well as malignant and autoimmune manifestations. In addition to HCV-induced cirrhosis and/or portal hypertension, lung health seems to be influenced directly by HCV through changes to immune response by an alteration in T lymphocytes, eosinophilic granulocytes, and inflammatory cytokines, which may account for interstitial or alveolar inflammation and a higher rate of obstructive lung disease and lung fibrosis.[5–7]

Lung function and obstructive lung diseases

There are controversial data on the relationship between HCV infection and lung function. Cross-sectional analyses from the Third National Health and Nutrition Examination Survey among 9159 patients suggest an increase in forced expiratory volume in 1 second (FEV_1) and full vital capacity in anti-HCV antibody–positive versus –negative subjects; however, these associations were no longer significant after additional adjustment for cocaine and marijuana use as well as poverty income ratio.[8] Another cross-sectional study on the prevalence of HCV infection among patients with chronic obstructive pulmonary disease found a notably increased prevalence of HCV infection (7.5%; 95% confidence interval [CI], 6.52–8.48) in comparison with blood donors as a control group (0.41%; 95% CI, 0.40–0.42). In contrast with the aforementioned study, HCV-positive patients showed a significantly lower FEV_1 than HCV-negative patients ($34.7 \pm 8.6\%$ vs $42.7 \pm 16.5\%$).[9] However, these results may be due to a generally more advanced chronic obstructive pulmonary disease stage, leading to a significant selection bias. A small prospective cohort study among 59 patients assessed the decline in FEV_1 and diffusing capacity of the lung for carbon monoxide in current smokers and ex-smokers, which were significantly higher in HCV-positive patients than in HCV-negative patients.[10] The same study group interestingly detected an increased impaired reversibility with salbutamol among asthmatic HCV patients with no response to interferon therapy.[11]

Nevertheless, these results could not be confirmed in a cross-sectional analysis among 1068 human immunodeficiency virus (HIV)-infected individuals with no evidence of an independent association between markers of HCV exposure, chronicity, viremia, or HCV-associated end-organ damage with obstructive lung disease.[12] Whether HCV infection leads to a faster decline in lung function and to a potentially higher prevalence of obstructive lung disease still needs to be verified in large, prospective cohort studies in the general population.

Pulmonary hypertension

The role of HCV in the development, progression and improvement of pulmonary hypertension (PH), independent from or simultaneously with liver cirrhosis and portal hypertension, is not well-understood.