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REVIEW

Extrahepatic Manifestations of Chronic Hepatitis C Virus: Review of the Literature

Andreea Florentina STOENESCU[a, b], Simin Aysel FLORESCU[a, b], Corneliu POPESCU[a, b], Stefan LAZAR[a, b], Geta VANCEA[a, b], Emanoil CEAUSU[a, c], Petre CALISTRU[a, b]

[a]"Dr. Victor Babes" Clinical Hospital of Infectious and Tropical Diseases, Bucharest, Romania

[b]"Carol Davilla" University of Medicine and Pharmacy, Bucharest, Romania

[c]Academy of Medical Sciences, Bucharest, Romania

ABSTRACT

Hepatitis C virus (HCV) affects other tissues besides the liver tissue, with the appearance of extrahepatic manifestations such as cryoglobulinemia, lymphoproliferative diseases, metabolic disorders, neuropsychiatric disorders and others. At the basis of their appearance are immune-mediated mechanisms stimulated by the HCV. The antiviral therapy with direct action initiated in all patients with chronic HCV infection acts on these manifestations, contributing to improving the quality of life, but also to eliminating a public health problem.

Keywords: hepatitis C, extrahepatic manifestations.

INTRODUCTION

Hepatitis C virus (HCV) infection is a condition with a significant global impact due to its high prevalence, important mortality rate and elevated risk of chronicity (85%), with severe and multiple complications, which entail remarkably high medical efforts and costs (1).

Hepatitis C virus is one of the most common causes of progressive degradation of the liver (after alcoholic liver disease and MASLD) which generates cirrhosis and hepatocarcinoma, currently constituting one important indication for liver transplantation (2). The main complications of chronic infection include severe liver fibrosis and cirrhosis, and 30-50% of patients with cirrhosis develop hepatocellular carcinoma (3).

Globally, approximately 71 million people are diagnosed with chronic HCV, with an incidence of 1.75 million new cases annually. Worldwide, over 350,000 deaths are registered each year (4). Although the incidence of new cases of HCV infection is decreasing due to the implementation of prevention strategies, the morbidity and mortality caused by this virus are increasing (5). Hepatitis C virus affects other tissues besides the liver, with the appearance of extrahepatic manifestations. Approximately 74% of patients causing chronic HCV develop at least one extrahepatic manifestation during the disease. Hepatitis C virus infection is currently considered a systemic

Address for correspondence:
Andreea Florentina Stoenescu, MD
Email: andreeastoenescu0193@gmail.com

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infection due to the ability of the virus to penetrate and multiply in the cells of other systems (6).

Extrahepatic manifestations can be classified according to either the affected organ or tissue or the pathogenic mechanism. ❑

MATERIALS AND METHODS

We conducted a series of systematic reviews to analyze the available literature on extrahepatic manifestations of HCV infection. The specific manifestations investigated by us included mixed cryoglobulinemia, chronic kidney disease (CKD) and end-stage renal disease (ESRD), type 2 diabetes mellitus (T2DM), B-cell lymphoma, lichen planus, Sjögren's syndrome, porphyria cutanea tarda, rheumatoid-like arthritis and depression.

We performed a comprehensive search of PubMed to identify relevant studies published between 2019 and 2024. The following search terms were employed: "hepatitis C," "HCV," "extrahepatic manifestations," "diabetes mellitus (DM)," "mixed cryoglobulinemia (MC)," "kidney," "renal disease," "lymphoma," "Sjögren's syndrome," "porphyria," "skin," "cardiovascular" and "neurological." Studies were excluded if they were published solely as abstracts, not written in English, or were letters to the editor. This article adopts a narrative review structure, providing a comprehensive overview and synthesis of the relevant literature on extrahepatic manifestations associated with HCV infection. ❑

RESULTS

Mixed cryoglobulinemia

Cryoglobulins are serum immunoglobulins that precipitate below 37 degrees Celsius and produce organ damage through an immune-mediated mechanism or hyperviscosity syndrome (2).

There are three types of cryoglobulinemia depending on the type of immunoglobulins involved. Types II and III, called mixed cryoglobulinemia, are encountered the most frequently in HCV infection and are characterized by a mixture of monoclonal IgM (type II), polyclonal IgM (type III) and IgG. Type II cryoglobulins use as an injury mechanism a vasculitis resulting from the deposition of immune complexes (3).

The mechanisms involved in the pathogenesis of mixed cryoglobulinemia are the stimulation of lymphocytes by viral antigens or the direct viral invasion of B lymphocytes that will produce clonal expansion with the release of IgM and rheumatoid factor, and formation of immune complexes, with the appearance of vasculitis (7, 8).

There are significant differences in the survival rate recorded in patients diagnosed with chronic HCV and mixed cryoglobulinemia. Studies published in the pre-DAA (direct active antiviral) era showed an influence of mixed cryoglobulinemia on survival rates. In a group of 246 patients diagnosed with chronic HCV and mixed cryoglobulinemia, the 10-year survival rate was 74%: 84% in those with mixed cryoglobulinemia type III and 71% in subjects with mixed cryoglobulinemia type II (9).

A study conducted in Italy on a group of 231 patients with mixed cryoglobulinemia demonstrated the presence of HCV infection in 92% of subjects. The main causes of mortality were associated with vasculitis, cancer and liver diseases (10).

Regarding the clinical manifestations, purpura was most frequently present in 70-80% of cases, followed by arthralgias (bilateral, symmetrical, non-deforming) in 50-70% of cases; 40-50% of patients can associate peripheral neuropathy manifested by initially asymmetric, later symmetric painful paresthesia (11). At the same time or at a distance from the sensory impairment, there may be a motor deficit with damage especially to the lower limbs (12).

Glomerulonephritis can appear as a manifestation of vasculitis, with the membranoproliferative type I form being the most commonly encountered (13). A study conducted in the U.S. between 2008-2015, on a cohort of 56,448 patients diagnosed with chronic HCV, revealed a 2-3 times and a 14-17 times higher risk of developing membranoproliferative glomerulonephritis and cryoglobulinemia, respectively (14). Related results were found in another study conducted in the U.S. on a cohort of veterans from 1997 to 2004, where the risk of developing cryoglobulinemia was four times higher in those diagnosed with chronic C hepatitis (15).

The introduction of direct antiviral therapy, with the achievement of sustained virologic response, was associated with a significant reduction in mixed cryoglobulinemia and glomerulo-

nephritis (13). There are also cases where cryoglobulins persist even after achieving a sustained virologic response, with recurrence of vascular events, when the immune response becomes antigen-independent (16).

Lymphoproliferative diseases of B cells

Chronic HCV is associated with multiple lymphoproliferative diseases such as B-cell non-Hodgkin's lymphoma, monoclonal gammopathy and marginal zone lymphoma (11).

During our research, we identified a systematic review of 5,542 patients with non-Hodgkin B-cell lymphoma, in which the prevalence of HCV infection was 13% (17) (Table 1).

At the basis of the appearance of these lymphoproliferative diseases is the infection of lymphocytes directly involved in cell transformation with HCV. Several pathogenic mechanisms of their production have been described, including sustained stimulation of lymphocyte receptors by viral antigens, virus replication in B lymphocytes and their destruction (18). A significant role is attributed to glycoprotein E2, which by attaching to the CD81 receptor, present on B lymphocytes, creates a co-stimulatory unit on lymphocytes (7).

Direct-acting medication has also proven efficacy and safety in patients with chronic HCV and lymphoproliferative diseases. An observational study on a group of 20 patients with chronic HCV and diffuse B-cell lymphoma, who were treated with both DAA and chemotherapy medication, found an increased survival rate compared to a group of patients who no antiviral treatment over 52 weeks. Thus, antiviral therapy is a predictive factor for the survival rate and lymphoma regression (19).

Diabetes mellitus and insulin resistance

Multiple metabolic factors have been associated with chronic HCV infection. They may have an impact on the course of the disease, accelerating the progression to fibrosis and hepatocellular carcinoma (20).

Patients diagnosed with chronic HCV have an increased risk of developing type 2 diabetes and insulin resistance compared to healthy individuals.

Risk factors in the occurrence of diabetes are male sex, age over 40 years, family history of diabetes and genotypes 1, 2, 4 (13). Moreover, diabetes is a risk factor for the occurrence of decompensated cirrhosis and congestive heart failure (21).

We identified three studies, including one cross-sectional study and two meta-analyses. They totalized 84,454 patients and the total prevalence of diabetes mellitus was 16.06% (Table 2).

Insulin resistance, a component of the metabolic syndrome, may be present in up to 80% of patients infected with hepatitis C (25). The virus affects glucose homeostasis with the onset of insulin resistance. The HCV replicates in the beta-pancreatic cells, causing their destruction. Pancreatic beta-cells have a role in determining the level of insulin secreted to support glucose levels. Insulin signaling pathways (IRS-1, IRS-2) are also affected)26).

Insulin resistance induces hepatic steatosis, thus influencing the evolution of chronic hepatitis (20).

Hepatic steatosis occurs in 40-80% of patients with chronic HCV infection (29). Hepatitis C virus stimulates lipid synthesis. These will be useful for increasing the assembly of viral lipoprotein particles, promoting the synthesis of lipotoxic phospholipids and ceramides, and inhibiting mitochondrial oxidation of fatty acids (13).

Insulin resistance precedes the onset of hyperglycemia in patients who will later develop type 2 diabetes. Along with the appearance of insulin resistance, viral genotypes 1 and 4 as well as the level of viremia are also involved in the pathogenesis of type 2 diabetes (26).

It should not be neglected that both insulin resistance and type 2 diabetes are risk factors for the occurrence of vascular disease.

Kidney damage

Hepatitis C virus infection is associated with an increased risk of developing chronic kidney disease in the general adult population (27).

TABLE 1. Study of B-cell lymphoproliferative diseases

Study (year)	Type of study	Numer of patients	Prevalence (%)
Gisbert *et al*[17]. 2003	Systematic review	5542	13%

TABLE 2. Studies of diabetes mellitus

Study (year)	Type of study	Number of patients	Average prevalence (%)
Zein *et al*, 2015 (22)	Cross-sectional	179	14.5%
Younosi *et al*, 2016 (23)	Meta-analysis	61.843	15%
Younossi *et al*, 2019 (24)	Meta-analysis	22.432	19%
Total		84.454	16.06%

Renal damage in patients with chronic HCV infection manifests itself most frequently in the form of membranoproliferative glomerulonephritis type I, with subendothelial deposits. This also occurs in an important percentage of patients with mixed cryoglobulinemia (28). It is manifested by the presence of proteinuria and microscopic hematuria, with or without alteration of renal function.

In a cohort study conducted in the USA, the 56,448 patients with hepatitis C had a 27% increased risk of developing chronic kidney disease compared to healthy controls. Also, the risk of membranoproliferative glomerulonephritis and cryoglobulinemia was higher in the first group (14).

Three pathogenic entities were identified following renal biopsies, with diffuse membranoproliferative glomerulonephritis being the most commonly encountered (80% of cases). Within it, the so-called pseudo-thrombi (cryoglobulins) that obstruct the lumen and the intracapillary accumulation of neutrophils and monoclonal cells, along with the mesangial extension can be seen. A form of glomerulonephritis with focal lesions is present in 10% of cases and mesangioproliferative glomerulonephritis in another 10% of cases.

Regarding the effect of antiviral medication with direct action, some studies reported a favorable effect on creatinine level and proteinuria, and showed its efficacy in reducing the risk of renal disease progression towards the end stage (16, 29). However, other studies have shown that eradicating the virus had no effect on the immune process either because B lymphocyte clones persist and the most severe manifestations of cryoglobulinemic vasculitis remain unchanged (30). More studies are still needed to establish the long-term link between antiviral medication and kidney damage.

Cardiovascular and cerebrovascular damage

Hepatitis C virus is a risk factor in the occurrence of cardiovascular diseases. The most commonly seen clinical manifestations are the onset of acute coronary syndrome (31), myocarditis and dilated or hypertrophic cardiomyopathy. Hepatitis C virus has also been associated with carotid atherosclerosis. Predictive factors for the occurrence of carotid atherosclerosis include hepatic steatosis, increased degree of hepatic fibrosis and age over 55 years. In a recent systematic review, the risk of cardiovascular disease was reported to be 1.5 times higher in patients with chronic hepatitis C (31). A meta-analysis showed that patients with chronic HCV infection, especially those with diabetes and hypertension, had a 1.65-fold and 2.27-fold increased risk of mortality from cardiovascular diseases and formation of carotid plaques compared to the healthy group (32).

Hepatitis C virus has a direct role in the production of atheromatous plaque. It replicates in the thrombotic structures and thus produces a chronic inflammatory reaction that will contribute to the growth and destabilization of the thrombus (21). The virus alters endothelial permeability and thus, smooth muscle cells will migrate from the tunica media to the surface of the tunica intima with the onset of endothelial dysfunction.

The virus induces the activation of T-helper lymphocytes which in turn will stimulate macrophages to produce pro-inflammatory cytokines (IL-1, TNF alpha). They will present VCA M-1 on the endothelium, thus allowing T lymphocytes and monocytes to attach to the site of atheroma formation and promote its growth. TNF alpha stimulates the production of nitric oxide which causes a decrease in the contractile function of the heart (21).

Direct-acting antiviral therapy led to a decrease in the risk of cardiovascular and cerebrovascular events, as well as an improvement in carotid atherosclerosis. Prospective studies have shown a direct link between the elimination of the virus and the reduction or disappearance of carotid atherosclerosis and the reduction of the risk of cardiovascular diseases. An analysis of a cohort of veterans showed that the treatment with direct-acting antivirals led to a significant decrease in the risk of cardiovascular events and the achievement of a sustained virologic response (33, 34).

Neurological and psychiatric conditions

Neurological and psychiatric conditions are diverse and can vary from central nervous system conditions, peripheral polyneuropathy and neurocognitive conditions to psychiatric conditions (11).

The nervous system is also affected by the replication of HCV in neurons and the presence

of circulating chemokines and inflammatory cytokines (35).

The central nervous system involvement may result in cerebral vasculopathy, acute or subacute encephalopathy and inflammatory conditions. Pathogenic mechanisms related to the host's (excess) immune response, the production of immune complexes, cryoglobulins and autoantibodies participate in the occurrence of nervous system dysfunctions. The level of viremia is related to the risk of death from cerebrovascular disease.

Rapidly progressive leukoencephalitis, encephalomyelitis, myelitis represents inflammatory conditions which are produced by immune-mediated mechanisms (6).

Peripheral neuropathy caused by HCV can be both sensory and motor (35). It was identified both in known patients with mixed cryoglobulinemia and in its absence (6) and occurs through an inflammatory mechanism (42). The most frequent clinical manifestation is in the form of a symmetrical sensory or sensory-motor polyneuropathy. Asymmetric polyneuropathy and mononeuropathy can also be present, and in rare cases, motor polyneuropathy (6).

Depression and anxiety are psychiatric pathologies frequently encountered in patients diagnosed with HCV, having negative effects on their quality of life (36). The existence of depression can lead to decreased adherence to antiviral treatment, and thus the prognosis of the disease is affected. Depression can also be reactive to the physical and psychosocial sequelae of HCV infection and other extrahepatic manifestations (6). Depression and fatigue are more frequently reported even in patients who have early phase of infection, with a minimal level of liver inflammation (37).

Chronic hepatitis C affects the quality of life through the negative impact on patients' physical, mental and social status. In a study conducted on a group of 235 patients, following the application of the Short-Form 36 (SF-36) questionnaire and EQ-5D-3L questionnaire, the results revealed a reduced level of the quality of life, especially in patients known with cirrhosis and comorbidities (38). Another study showed a direct relationship between the degree of fibrosis and quality of life, which was affected with the advancement of liver dysfunction and the presence of cirrhosis and complications (39).

The therapy used in the past with Interferon or Pegylated interferon was associated with an increased prevalence of depression, along with other neuropsychiatric conditions, but which disappeared with the cessation of therapy (6). A reduction in metabolic activity at the level of the prefrontal cortex was detected following the imaging investigations performed in these patients, which correlates with a depressive status (40).

Skin disorders

Skin conditions are present in up to 17% of patients with HCV infection, with purpura and Raynaud's phenomenon being the most commonly seen ones. Lichen planus, porphyria cutanea tarda, acral necrolytic erythema can be found along with them (11).

Lichen planus is a skin and/or mucosal disease associated with chronic HCV and resulting from the host's immune response to viral antigens (41). The skin lesions have variable sizes and are distributed at the lumbar level, at the genital level, at the level of the wrists and forearms, at the dorsal surface of the hands and at the level of the knees without any differences in appearance compared to the lesions appearing in healthy individuals (42). After performing some meta-analyses, the results showed a five-fold higher prevalence of hepatitis C infection in patients with lichen planus, but also an increase in the prevalence of lichen planus of 2.5 to 4.5 in those with HCV (43, 44). Regarding the form localized to the oral mucosa, studies have shown the presence of a higher risk of malignant transformation in patients diagnosed with HCV compared to the group without HCV infection (45). Following the therapy with direct antiviral action, the condition is remitted or improved in a significant percentage of patients (46).

Another skin manifestation is porphyria cutanea tarda. It occurs because of the direct action of the virus on oxidative mechanisms, with the production of a deficiency of uroporphyrinogen decarboxylase at the liver level, which will generate the accumulation of uroporphyrin and other decarboxylated porphyrins at the level of the skin (3). Two forms, familial and sporadic, have been described, with the latter being associated with HCV infection, manifested by painful vesicular lesions located most frequently in areas exposed to the sun (47). Following the analysis of 50 studies in a systematic review, a 47% preva-

lence of HCV in patients with porphyria cutanea tarda was reported (48).

Acral necrolytic erythema is pathognomonic for chronic HCV. It is manifested by painful erythematous lesions on the acral skin surfaces (49).

Sjögren syndrome

Sjögren's syndrome is a chronic autoimmune disease in which the exocrine glands are affected. It is more common in women. A study conducted in Taiwan showed a strong association between Sjögren's syndrome and HCV, especially in male patients under 55 years old (50). In another prospective study of 45 patients with known chronic HCV, Sjögren's syndrome was present in more than half of them. This subgroup was characterized by age over 55 years, absence of systemic manifestations, absence of anti-SSA and anti-SSB antibodies. Thus, we can talk about an entity different from primary Sjögren's syndrome (51). The pathogenic mechanism includes tissue injury produced by pro-inflammatory cytokines (52) and direct viral invasions (53).

Arthritis

Rheumatic manifestations such as arthralgia and myalgia are frequently associated with HCV (54). Chronic hepatitis C associated arthritis is more commonly characterized by the presence of a symmetrical, inflammatory polyarthritis at the level of the small joints or less often by an arthritis at the level of the large joints. The absence of subcutaneous nodules, bone erosions and antikeratin antibodies can be helpful in establishing the diagnosis (55).

Two meta-analyses were eligible to assess the risk of inflammatory arthritis, as summarized in Table 3. These studies included a total of 77,406 patients, with a prevalence of arthritis of 2.75%.

Several pathogenic mechanisms have been proposed, including direct viral invasion of synovial cells, followed by occurrence of a local inflammatory response, appearance of immune complexes, cytokines, especially in genetically susceptible individuals (55).

TABLE 1. Studies of arthritis

Study (year)	Type of study	Number of patients	Average prevalence
Younosi *et al*, 2016 (23)	Meta-analysis	10.970	1%
Younosi *et al*, 2019 (24)	Meta-analysis	66.436	4.5%
Total		77.406	2.75%

Thyroid involvement

Thyroid diseases are among the most frequently encountered endocrine dysfunctions in patients diagnosed with chronic HCV, with autoimmune thyroiditis and hypothyroidism being the most common ones (56).

In a recent study of 300 patients known with chronic HCV, primary hypothyroidism was identified in 10.6% of them and subclinical hypothyroidism in 6% of cases *versus* 4.6% and 1.3%, respectively, in the healthy control group (57).

The prevalence of thyroid disorders is increased in patients known to have mixed cryoglobulinemia associated with HCV. There are studies that support this claim. Antonelli *et al* performed a case-control study on a group of 93 patients known to have HCV and mixed cryoglobulinemia, in whom subclinical hypothyroidism was detected in 11% of cases, compared to 2% in the healthy controls. In that study, anti-thyroid peroxidase autoantibodies and/or anti-thyroglobulin autoantibodies were present in 31% of patients compared to 12% of controls. Moreover, anti-thyroid peroxidase autoantibodies were more frequently encountered in patients with hepatitis C and mixed cryoglobulinemia (28%) *versus* those with hepatitis C without mixed cryoglobulinemia (14%) (58).

There is insufficient data in the literature regarding the relationship between direct-acting antivirals and thyroid conditions. Monitoring of thyroid function is recommended in all patients with known HCV.

CONCLUSIONS

Chronic HCV infection can lead to a wide range of extrahepatic manifestations that affect different organs and systems in the body, in addition to the main impact on the liver. Extrahepatic manifestations have a significant impact on the health of patients with chronic HCV infection and their quality of life. Recognition of extrahepatic manifestations is important for providing care. A multidisciplinary approach involving hepatologists, infectious diseases physicians as well as various other specialties is often required to diagnose, monitor and treat clinical manifestations associated with chronic HCV in-

fection. Direct-acting antiviral therapy also has a favorable effect on the extrahepatic manifestations of chronic HCV infection. The hepatitis C elimination initiative, promoted by the World Health Organization, is of particular importance in reducing the number of these complications that bring an additional burden on morbidity and mortality. ❑

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