The Multifaceted Features of HCV Infection Beyond the Liver

Kazuhiko Koike

Abstract A major problem in patients with hepatitis C virus (HCV) infections is progression from acute to persistent infection, resulting in development of serious liver diseases including hepatocellular carcinoma. However, HCV infection is a multifaceted disease. Extrahepatic manifestations include cryoglobulinemia, glomerulonephritis, porphyria cutanea tarda, Sjögren's syndrome, and lymphoma, most of which are evoked by the virus or the interaction thereof with the host immune system. Recently, partly extrahepatic features of HCV infection, including disturbance of lipid metabolism and insulin resistance, have been described. Such metabolic disturbances provoked by HCV are now considered to be essential features of the pathogenesis of liver disease induced by HCV infection. Some of these diseases/syndromes are cured by antiviral treatment. In the present review, the systemic manifestations of HCV infection will be examined and their clinical relevance discussed.

Keywords Hepatitis C virus • Extrahepatic manifestation • Metabolic disease • Sjögren's syndrome • All-cause mortality • Hepatocellular carcinoma

1 Introduction

Worldwide, approximately 170 million people are persistently infected with hepatitis C virus (HCV), which induces a spectrum of chronic liver diseases, ranging from chronic hepatitis, through cirrhosis, and, eventually, to hepatocellular carcinoma (HCC) (Saito et al. 1990). HCV has received increasing attention because of widespread viral dissemination across broad communities, linked to very high incidences of HCC in those with persistent infections. Once liver cirrhosis is diagnosed in patients persistently infected with HCV, the annual risk of HCC is approximately 7 % (Ikeda et al. 1998), resulting in development of HCC in almost 90 % of HCV-associated cirrhotic patients by 15 years later. It was recognized

K. Koike, M.D., Ph.D. (✉)
Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
e-mail: kkoike-tky@umin.ac.jp

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Table 1 Extrahepatic manifestations of HCV infection

Extrahepatic manifestations	Clinical manifestations	Pathogenesis	Prevalence of HCV antibody	References
Cryoglobulinemia	Purpura, arthralgia, and renal impairments	Apoptosis suppression of B lymphocytes. Persistent stimulation of lymphocytes induces the B-cell clonal expansion leading to the antibodies production. Intrahepatic growth of CD5- and CD81-positive B lymphocytes has been observed, suggesting monoclonal IgM induction as a possible cause	80–90 %	Mayo (2002), Johnson et al. (1993), Agnello et al. (1992), Saadoun et al. (2006, 2007), Okuse et al. (2003), Misiani et al. (1994), Zuckerman et al. (2000), Cacoub et al. (2002, 2008), Ubara et al. (2000)
Renal impairment and glomerulonephritis	Membranoproliferative glomerulonephritis (MPGN), membranous nephropathy, mesangial proliferative glomerulonephritis, Henoch-Schönlein purpura nephritis, and tubulointerstitial nephritis	Accumulation of an immune complex formed by monoclonal or polyclonal IgM-κ with rheumatoid factor activity produced by HCV-infected B lymphocytes in the glomerular vascular endothelium and mesangium	10–60 %	Kasuno et al. (2003), Johnson et al. (1993, 1994), Arase et al. (1998), D'Amico and Fornasieri (1995), Sinico et al. (2000), Misiani et al. (1999), Dammacco et al. (1994), Saadoun et al. (2010)
Porphyria cutanea tarda	Solar photosensitivity and hepatic damage	A reduced activity of uroporphybrinogen decarboxylase associated with an excessive deposition of iron in the liver induced by HCV infection	60–100 %	Sarkany et al. (2001), Fargion et al. (1992), Okano et al. (1997)
Sjögren's syndrome	An aggregate of symptoms characterized by insufficient tear production by the lacrimal glands and insufficient saliva production by the salivary glands, causing dryness of the eyes and mouth	The involvement of host immunologic responses to HCV. HCV envelope proteins may induce cytokines	14–57 %	Fox (2005), Nagao et al. (2003), Haddad et al. (1992), Pawlotsky et al. (1995), Koike et al. (1997), Takamatsu et al. (1992), Arrieta et al. (2001)

Diabetes and insulin resistance	High plasma glucose and serum insulin levels. Improvement after achieving SVR	The involvement of insulin resistance and insulin secretory deficiency. Disruption of tyrosine phosphorylation of the insulin receptor substrate (IRS-1). The involvement of TNF-α which level is increased in HCV infection	50 %	Allison et al. (1994), Mehta et al. (2000), Petit et al. (2001), Zylberberg et al. (1999), Pradhan et al. (2002), Shintani et al. (2004), Aytug et al. (2003), Hui et al. (2003)
Lipid metabolism disturbances and steatosis	Hepatic steatosis and hypobetalipoproteinemia. Improvement after achieving SVR	Induction of SREBP-1c by HCV. Suppression of MTP activity leading to a reduction in VLDL secretion from the liver. Insulin resistance, which increses the release from the perioheral and uptake into the liver of fatty acids	50 %	Powell et al. (2005), Adinolfi et al. (2001), Castera et al. (2003), Moriya et al. (1997, 1998, 2001, 2003), Perlemuter et al. (2002), Moriishi et al. (2007), Tsutsumi et al. (2002)
Lichen planus	An inflammatory disease associated with abnormal chronic dermal and intraoral keratinization	The involvement of HCV-specific T cells	0–65 %	Scully et al. (1998), Bellamn et al. (1995), Nagao et al. (1995a, b, 1996, 1999, 2000), Arrieta et al. (2000), Doutre et al. (1992), Baccia et al. (1993), Protzer et al. (1993)
Oral cancer		Unknown	70–100 % (HCV-RNA)	Nagao et al. (1995a, b, 2000)
Malignant lymphoma	Non-Hodgkin lymphoma (NHL) and specific B-NHL subtypes (diffuse large B-cell lymphoma, marginal zone lymphoma, and lymphoplasmacytic lymphoma)	The involvement of myc gene mutation in some cryoglobulinemia patients. Enhanced mutations of immunoglobulin and protooncogenes	0–33 %	Machida et al. (2004), Mizuochi et al. (2011), Ito et al. (2009, 2010a, b), Gisbert et al. (2003), de Sanjose et al. (2008), Perl et al. (1989), Ferri et al. (1995), De Vita et al. (1995),

(continued)

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Extrahepatic manifestations	Clinical manifestations	Pathogenesis	Prevalence of HCV antibody	References
				de Sanjose et al. (2008), Hermine et al. (2002), Vallisa et al. (2005)
Autoimmune thyroid disease	Thyroid dysfunction (hypothyroidism)	The involvement of liver/kidney microsomal antibody type 1 (LKM1)	10 %	Montella et al. (2003), Testa et al. (2006), Antonelli et al. (2004), Muratori et al. (2005)
Idiopathic interstitial pneumonitis	Dry cough, short of breath, progressive course to respiratory failure	The involvement of activated T lymphocytes and eosinophils. Further studies are necessary but not have been achieved	28 %	Ueda et al. (1992), Kubo et al. (1996), Irving et al. (1993), Karim et al. (2001)
Myocardial impairment	Dilated cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia cardiomyopathy and chronic myocarditis	The involvement of host immunologic responses to HCV, particularly that of the human major histocompatibility (MHC) class II antigen. Further studies are necessary but not have been achieved	6–10 %	Matsumori (2000, 2006), Maisch et al. (2003)
Mooren's ulcer	Progressive ulcer associated with congestion and pain around the cornea	Further studies are necessary but not have been achieved	Unknown	Wilson et al. (1994), Moazami et al. (1995), Zegans et al. (1999), Jain et al. (2004)
Cognitive disorders and mental disorders	Depression, cognitive impairment and fatigue, and a reduction in the health-related quality of life	Unknown	28 % of chronic hepatitis C patients had depression. 33 % had cognitive impairment	Perry et al. (2008), Jacobson et al. (2010)
All-cause mortality in HCV-positives	Compared with anti-HCV seronegatives, anti-HCV seropositives had higher mortality from both hepatic and extrahepatic diseases			Lee et al. (2012), Mahajan et al. (2014)

relatively soon after the discovery of HCV that infection with the virus involves not only the liver but also other organs and tissues. Several extrahepatic manifestations, which are complicated disorders of organs other than the liver, occur in association with HCV infection (Gumber et al. 1995). In addition, disease manifestations that are extrahepatic in part, including disturbances in lipid and glucose metabolism, add to the multifaceted nature of HCV infection (Koike and Moriya 2005). Of the latter conditions, most are definitely associated with HCV infection in both clinical and basic terms, but the links between some others await verification via conduct of more case studies and/or pathogenetic analyses (Table 1).

2 Manifestations Associated with HCV Infection

2.1 Cryoglobulinemia

In many patients infected with HCV, cryoglobulinemia is subclinical, thus not symptomatic, but the incidence of the extrahepatic complication, essential mixed cryoglobulinemia (EMC), is highest in HCV-infected patients. The clinical symptoms of EMC include purpura, arthralgia, and renal impairments (Mayo 2002). The latter include membranoproliferative glomerulonephritis (MPGN), which occasionally progresses to renal insufficiency (Johnson et al. 1993). Approximately 80–90 % of EMC patients are infected with HCV (Agnello et al. 1992; Saadoun et al. 2006). Cryoglobulins were detected, using a highly sensitive gel diffusion method, in 70 % of patients chronically infected with HCV (Okuse et al. 2003).

Cryoglobulins are abnormal immunoglobulins that form white deposits at 4 °C but are liquids at 37 °C. Cryoglobulins are classified into three types, namely, monoclonal cryoglobulins (type I), polyclonal cryoglobulins (type III), and mixed cryoglobulins (type II). The cryoglobulinemia associated with HCV infection is mainly of the mixed type. Specifically, such patients produce monoclonal IgM and polyclonal IgG antibodies exhibiting rheumatoid factor activity (Brouet et al. 1974; Wong et al. 1996).

The pathogenesis of cryoglobulinemia in HCV-infected patients remains poorly elucidated. However, persistent stimulation of lymphocytes induces B-cell clonal expansion, leading to the production of antibodies including rheumatoid factor, which become incorporated into cryoglobulins (Saadoun et al. 2007). Intrahepatic growth of CD5- and CD81-positive B lymphocytes has been observed, suggesting that induction of monoclonal IgM synthesis may be the cause of the disease (Curry et al. 2003). Tissue damage in patients with EMC-induced vasculitis would thus be T-cell mediated.

Antiviral agents including interferon (IFN) have been used to treat HCV-associated cryoglobulinemia (Lunel et al. 1994). Cryoglobulinemia symptoms improved in 15 of 25 patients with HCV-associated disease after IFN treatment commenced, but the symptoms recurred when treatment concluded (Misiani

et al. 1994). A combination of (PEG)-IFN and ribavirin has also been used to treat HCV-associated cryoglobulinemia. Administration of both drugs to nine EMC patients who had not responded to IFN monotherapy alleviated cryoglobulinemia in all nine, and improved clinical symptoms in seven of the nine (Zuckerman et al. 2000). Recently developed direct-acting antivirals (DAAs) for HCV are also effective, as these agents exhibit strong antiviral activities (Saadoun et al. 2014).

In addition, in patients with severe cryoglobulinemia, in whom antiviral agents may not adequately improve symptoms, combination therapy with IFN and steroids or immunosuppressants has been considered effective (Cacoub et al. 2002). Other treatment strategies, including plasma exchange therapy and splenectomy (Ubara et al. 2000), have also been attempted. Recently, rituximab was reported to improve vasculitis, including skin lesions, arthralgia, neuropathy, and glomerulonephritis (Cacoub et al. 2008).

2.2 Renal Impairments and Glomerulonephritis

Renal impairments associated with HCV infection include membranoproliferative glomerulonephritis (MPGN), membranous nephropathy, mesangial proliferative glomerulonephritis, Henoch-Schönlein purpura nephritis, and tubulointerstitial nephritis (Kasuno et al. 2003).

MPGN, in particular, is considered to be a typical example of the renal impairment associated with hepatic disease caused by HCV, and is also termed HCV-associated nephritis. In 1993, eight patients with HCV infections complicated by MPGN were reported, for the first time (Johnson et al. 1993). The incidence of HCV-associated nephritis has not yet been determined. In an autopsy study on 188 cases of chronic hepatitis C, 11.2 % exhibited MPGN, 2.7 % membranous nephropathy, and 17.6 % mesangial proliferative glomerulonephritis (Arase et al. 1998). The pathogenesis underlying HCV-associated nephritis is considered to be accumulation of an immune complex, formed by monoclonal or polyclonal IgM-κ, exhibiting rheumatoid factor activity. The antibody is produced by HCV-infected peripheral B lymphocytes, and is deposited in the glomerular vascular endothelium and mesangium (D'Amico and Fornasieri 1995).

The histopathological features of HCV-associated nephritis are similar to those of general MPGN of type I, but the former disease is occasionally associated with cryoglobulin deposition (Sinico et al. 2000). If EMC and nephrotic syndrome patients produce rheumatoid factor, HCV-associated nephritis should be suspected, and the presence/absence of HCV infection determined.

Antiviral therapies, including IFN, are effective when used to treat HCV-associated nephritis (Johnson et al. 1994). Administration of IFN to 14 patients with HCV-associated nephritis improved proteinuria, but relapse occurred after the end of therapy, in association with a relapse of HCV infection. IFN/ribavirin combination therapy, which is associated with a low relapse rate, has also been tested (Misiani et al. 1999). A combination of a steroid and

cyclophosphamide has been used as immunosuppressive therapy, but use of an immunosuppressant alone has not yet afforded good results (Dammacco et al. 1994). As patients with HCV-associated nephritis have been reported to have poor prognoses, the recent introduction of DAAs, as HCV treatments, may allow development of therapeutic procedures effective to treat the renal impairment associated with HCV infection. Also, addition of rituximab may be valuable in treatment of patients with HCV-related EMC exhibiting renal involvement (Saadoun et al. 2010).

2.3 Porphyria Cutanea Tarda

Porphyria cutanea tarda (PCT) is an acquired condition; patients exhibit photosensitivity to the sun, and hepatic damage caused by reduced activity of liver uroporphyrinogen decarboxylase (Sarkany 2001). The contributions of all of alcohol, excess iron, and medications to hepatic impairment were previously examined in the context of PCT development. However, as HCV infection is present in 60–100 % of patients with PCT, a linkage between such infection and the pathogenesis of PCT is suspected. The mechanism has not yet been clarified. It is assumed, however, that PCT is caused by a reduction in uroporphyrinogen decarboxylase activity associated with excessive deposition of iron in the liver, in turn triggered by HCV infection (Fargion et al. 1992).

IFN has been shown to be effective for treatment of PCT, in combination with avoidance of exposure to the sun, abstention from alcohol, and phlebotomy. IFN therapy normalized serum ALT levels, caused serum HCV-RNA to disappear, normalized porphyrin and ferritin levels, and improved clinical symptoms—including vesicle formation and hypertrichosis—in PCT patients infected with HCV (Okano et al. 1997).

2.4 Sjögren's Syndrome

Sjögren's syndrome is an aggregate of symptoms characterized by insufficient tear production by the lacrimal glands and insufficient saliva production by the salivary glands, caused by infiltration of exocrine lymphocytes, which in turn causes dryness of the eyes and mouth (Fox 2005).

An association of Sjögren's syndrome with certain viral infections has long been known, and reports indicating that 0–45 % of patients were positive for anti-HCV antibodies suggest that Sjögren's syndrome and HCV infection may be associated (Nagao et al. 2003). Differences in anti-HCV positivity rates may be attributable to regional differences in HCV infection rates. Also, lymphocytic sialadenitis, which resembles Sjögren's syndrome, was found in 16 of 28 patients (57 %) with HCV infection, but only 1 of 20 controls (5 %) (Haddad et al. 1992). Pawlotsky

et al. reported a 14 % prevalence of pathological abnormalities resembling Sjögren's syndrome in patients with HCV infections, compared to 0 % in controls without HCV infection. Of interest, the cited authors found that almost 50 % of patients with HCV infection had lymphocytic capillaritis of the salivary glands, which is found in all patients with sialadenitis. Lymphocytic capillaritis could therefore represent an early stage in the development of more severe lesions resembling the lymphocytic sialadenitis of Sjögren's syndrome (Pawlotsky et al. 1995).

Koike et al. found a direct association between HCV infection and sialadenitis in work with transgenic mice carrying genotype 1b HCV envelope genes, in which sialadenitis resembling Sjögren's syndrome develops spontaneously. In particular, it was noteworthy that lymphocytic capillaritis preceded sialadenitis in such animals (Koike et al. 1997), which may reflect the pathological sequence of development of Sjögren-like syndrome in humans chronically infected with HCV (Pawlotsky et al. 1995). In a clinical study, HCV-RNA was detected in salivary gland tissues from anti-HCV-positive patients with Sjögren's syndrome, via reverse transcriptase (RT)-PCR analysis (Takamatsu et al. 1992). Upon in situ hybridization of salivary gland tissue samples from 8 anti-HCV-positive and 11 anti-HCV-negative patients with chronic sialadenitis or Sjögren's syndrome, HCV-RNA was detected in all salivary gland samples from the anti-HCV-positive patients. Moreover, HCV-infected salivary gland epithelium supported viral multiplication (Arrieta et al. 2001). Such lines of evidence indicate that HCV plays some role in the development of the sialadenitis of Sjögren's syndrome, but it remains unclear whether HCV per se or an immunological response to HCV infection induces the condition.

No reports on the efficacy of IFN therapy for HCV-associated sialadenitis have yet appeared (Lunel and Cacoub 2000). Artificial lacrimal fluid and artificial saliva are used to alleviate dryness, and a non-steroidal anti-inflammatory drug or corticosteroid is administered to treat the fever and articular symptoms (Fox 2005).

2.5 Diabetes and Insulin Resistance

Allison et al. reported an epidemiological link between diabetes and HCV infection, but only in a cirrhotic cohort (Allison et al. 1994). This initial report made little impact, however, in view of the fact that glucose tolerance is well known to be impaired in patients with advanced chronic liver disease. Several other reports followed, both from the same group and others. The trend toward acceptance of a positive association between diabetes and HCV infection seems to have been triggered by a population-based study performed in the United States (Mehta et al. 2000), which found a solid association between the two conditions. In addition, it has been shown that comorbid diabetes is a risk factor for HCC (Hassan et al. 2002) in cirrhotic patients (Bianchi et al. 1994). These reports support the existence of an association between HCV infection and type 2 diabetes.

Petit et al. reported that insulin resistance was increased in chronic hepatitis C patients with even slight hepatic impairment, and that the index of impairment (HOMA-IR) correlated with the severity of liver fibrosis (Petit et al. 2001). Tumor necrosis factor (TNF)-alpha, the levels of which correlate closely with the extents of hepatic inflammation and fibrosis in chronic hepatitis C patients (Zylberberg et al. 1999), is considered to enhance glucose uptake in peripheral tissue and to promote gluconeogenesis in the liver, leading to induction of insulin resistance (Pradhan and Ridker 2002). However, any association between diabetes and HCV infection is difficult to establish, because cirrhosis, obesity, and old age are common in HCV patients. Hence, experimental systems have been employed. Shintani et al. used transgenic mice carrying the genotype 1b HCV core gene (Moriya et al. 1998), and found that (1) the HCV core protein induced insulin resistance in vivo; (2) tyrosine phosphorylation of the insulin receptor substrate (IRS)-1 in the insulin signal transduction pathway was disrupted; and, (3) the insulin resistance that developed was hepatic in nature, as shown by hyperinsulinemic euglycemic clamp analysis. The mice had high TNF-alpha liver levels, and administration of anti-TNF-alpha antibody improved insulin resistance. These results indicate that a direct link exists between HCV infection and type 2diabetes (Shintani et al. 2004).

At the time of publication of the above findings, Aytug et al. reported on insulin signaling in biopsied liver specimens from patients with chronic hepatitis C (Aytug et al. 2003). Specifically, the cited authors measured changes in IRS-1, IRS-2, and phosphatidylinositol (PI)3-kinase levels. Upon insulin stimulation of the biopsy samples, the levels of insulin-receptor proteins and IRS-1 increased, whereas phosphorylation of the tyrosines in IRS-1 decreased the levels thereof to 50 % of baseline values, and also reduced the activity of the P13-kinase associated with IRS-1. These data were in agreement with those of Shintani et al., who explored the mechanism of insulin resistance in mice. Both studies found that impaired tyrosine phosphorylation of IRS-1 induced insulin resistance in animals infected by HCV. It is, however, surprising, in a sense, that the mechanism of insulin resistance induced by HCV infection is identical in both clinical samples and experimental animals, because, earlier, hepatic IRS-2 was thought to be more important than IRS-1 in terms of development of insulin resistance (Suzuki et al. 2004).

Insulin resistance in patients with HCV infections may have an additional significant clinical implication. In 260 patients with chronic HCV infections, Hui et al. sought to establish a relationship between liver histology, and indicators of glucose metabolism and insulin resistance, using the homeostasis model assessment of such resistance (HOMA-IR). It was found that insulin resistance was already evident in patients with stage 0 or 1 liver fibrosis, indicating that such resistance in HCV-infected patients was not attributable to advanced liver disease (Hui et al. 2003). HOMA-IR was a significant and independent predictor of hepatic fibrosis stage, and the speed of development thereof. Others have reported similar results (Hickman et al. 2003). These data are important because they implicate a role for hyperinsulinemia, and (by inference) insulin resistance in promoting progression of hepatic fibrosis. Insulin has been shown to aggravate not only

atherosclerosis, but also systemic inflammation and fibrosis. The liver would not be an exception in this context.

2.6 Lipid Metabolism Disturbances and Steatosis

Hepatic steatosis is frequently observed in chronically HCV-infected patients (Bach et al. 1992; Lefkowitch et al. 1993; Czaja et al. 1998). The liver fatty acid composition in core gene transgenic mice (Moriya et al. 1997, 1998) differs from that in fatty livers caused simply by obesity. The levels of carbon 18 monounsaturated fatty acids (C18:1), such as oleic or vaccenic acid, which encourage proliferation of cancer cells (Kudo et al. 2011), were significantly increased in transgenic mice. This was also true when liver tissues from hepatitis C patients, and obese patients with simple "fatty livers", were compared (Moriya et al. 2001). Patients with HCV infections also exhibit dyslipidemia as part of the phenotype of hypo-beta-lipoproteinemia (Moriya et al. 2003). Chronic hepatitis C patients, in whom the liver fibrosis stages were comparable to those of control patients with chronic hepatitis B, showed reduced serum levels of total cholesterol and apolipoproteins B1, C2, and C3, whereas the levels of apolipoproteins A1, A2, and E were similar to those of controls.

The mechanism of steatogenesis in hepatitis C patients has been investigated using (principally) the mouse model described above. At least three pathways are involved in development of steatosis. One is the insulin resistance pathway that frequently develops in hepatitis C patients, as well as in core gene transgenic mice, as described above (Shintani et al. 2004). Insulin resistance increases the peripheral release and hepatic uptake of fatty acids, resulting in lipid accumulation in the liver. The second pathway involves suppression of the activity of microsomal triglyceride transfer protein (MTP) by HCV core protein (Perlemuter et al. 2002). This, in turn, reduces the secretion of very-low-density-lipoprotein (VLDL) from the liver, increasing liver triglyceride levels. The last pathway involves the sterol regulatory element-binding protein (SREBP)-1c, which regulates the production levels of triglycerides and phospholipids. In HCV core gene transgenic mice, SREBP-1c is upregulated, but this is not true of either SREBP-2 or SREBP-1a (Moriishi et al. 2007). Such results have been obtained in both in vitro studies (Kim et al. 2007; Waris et al. 2007) and work with chimpanzees (Su et al. 2002). Thus, all three pathways result in development of hepatic steatosis in hepatitis C patients (Fig. 1). Steatosis exacerbates the production of reactive oxygen species and accelerates progression of liver disease.

Recently, it has been reported that assembly and budding of HCV occur around lipid droplets accumulated within the endoplasmic reticulum (Miyanari et al. 2007). Furthermore, increases in saturated and monounsaturated fatty acid levels enhanced HCV-RNA replication. Such data suggest that regulation of lipid metabolism by the core protein plays a crucial role in the HCV life cycle. An inflammatory cytokine, TNF-alpha, is known to impair the insulin-signaling pathway via inhibition of

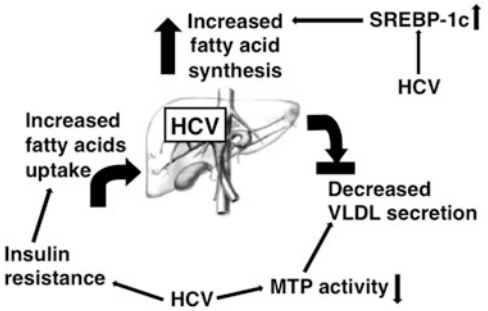

Fig. 1 HCV induces liver steatosis by affecting three lipid metabolism pathways. First, the HCV core protein induces insulin resistance, increasing the peripheral release and hepatic uptake of fatty acids. Second, the HCV core protein suppresses MTP activity, inhibiting VLDL secretion from the liver, thus increasing triglyceride levels in that organ. Lastly, a transcription factor, SREBP-1c, is upregulated by the HCV core protein, resulting in increased production of triglycerides. Thus, all three pathways are involved in the development of hepatic steatosis in hepatitis C patients. *MTP* microsomal triglyceride-transfer protein, *VLDL* very-low-density lipoprotein, *SREBP* sterol regulatory element-binding protein

tyrosine phosphorylation of IRS. Indeed, overproduction of TNF-alpha (Tsutsumi et al. 2002) has been reported to reduce phosphorylation of both IRS-1 and Akt in core gene-transgenic mice. Moreover, the hyperinsulinemia that developed was cured by depletion of TNF-alpha, suggesting that upregulation of TNF-alpha level contributes to core protein-induced insulin resistance (Shintani et al. 2004).

Hepatic steatosis is significantly associated with accelerated progression of liver fibrosis (Powell et al. 2005). A study on 180 hepatitis C patients for whom the dates of infection were known confirmed that steatosis of grades 3–4 was significantly associated with a higher annual rate of fibrosis progression, and that alcohol and steatosis acted together to increase fibrosis (Adinolfi et al. 2001). In another study on 96 untreated patients with CHC, who underwent serial liver biopsies, fibrosis progression was strongly associated with worsening of the steatosis, which was the only significant factor so associated upon multivariate analysis. (Castera et al. 2003).

2.7 Lichen Planus

Lichen planus is an inflammatory disease associated with chronic abnormal dermal and intraoral keratinization of unknown etiology. The assumed causes include viral or bacterial infection, immunological responses, circulatory disorders, allergy, mental stress, abnormal autonomic function, medication, and disorders of glucose metabolism (Scully et al. 1998).

A number of reports on relationships between lichen planus and HCV infection have appeared, but the anti-HCV antibody positivity rate in lichen planus patients

exhibited marked regional differences, ranging from 0 to 65 % (Bellamn et al. 1995; Nagao et al. 1995a). HCV reproduction in the skin and oral mucosal epithelium has been examined by in situ hybridization and RT-PCR (Nagao et al. 2000; Arrieta et al. 2000). HCV-specific T cells have been reported to be linked to the pathogenesis of the condition (Pilli et al. 2002), but none of HCV level, genotype, or pathological severity, was so associated (Nagao et al. 1996). Antiviral therapy (IFN) has been reported to be effective (Doutre et al. 1992). However, other investigators have reported that IFN rather induces or aggravates lichen planus (Baccia et al. 1993; Protzer et al. 1993). Thus, the effectiveness of IFN used to treat lichen planus remains debatable. Nagao et al. found no macroscopic changes in lesions 1 year after the end of IFN administration (to treat intraoral lichen planus lesions) in patients with chronic HCV infection, but macroscopic and histological improvements were evident 3 or more years after IFN administration ceased. It was assumed that not HCV infection, but rather the immunological response to such infection, was associated with development of oral lichen planus, as positive-strand HCVRNA was detected in the oral mucous membrane of some lichen planus patients although they had (histologically) recovered after IFN therapy (Nagao et al. 1999).

2.8 Oral Cancer

A relationship between HCV infection and oral cancer was first reported by Nagao et al., who found that the HCV infection rate was higher in oral cancer patients than in those with esophageal, gastric, or colorectal cancer (Nagao et al. 1995b). When HCV-RNA levels were examined in oral cancer tissues from 17 patients, via RT-PCR, positive-strand HCV RNA was detectable in all anti-HCV-positive patients, and negative-strand HCV-RNA in 71.4 % of such patients (Nagao et al. 2000). These findings indicate that HCV may possibly replicate in oral cancer tissues. No definite consensus has yet emerged on any relationship between oral lichen planus and oral cancer. However, as lichen planus is considered to be precancerous, oral examination may be necessary in patients with chronic HCV infections.

2.9 Malignant Lymphoma

HCV replicates in lymphocytes, although not robustly (Ito et al. 2010a), and short-term HCV culture systems using lymphocytes have been developed (Ito et al. 2001; Shimizu et al. 1992). Infected lymphocytes may undergo malignant transformation, leading to development of malignant lymphoma, after acquisition of certain genetic mutations (Machida et al. 2004; Mizuochi et al. 2011; Ito et al. 2009, 2010b). HCV infection is considered to be associated with development of malignant lymphoma,

particularly the pathogenesis of non-Hodgkin's B-cell lymphoma (Gisbert et al. 2003; de Sanjose et al. 2008). Some cryoglobulinemia patients have been assumed to develop non-Hodgkin's B-cell lymphoma in association with *myc* gene mutation (Perl et al. 1989). The anti-HCV positivity rate in patients with non-Hodgkin's B-cell lymphoma ranges from 0 to 33 % (Gisbert et al. 2003). Such variation may be associated with regional differences in HCV infection rates. Fourteen of 500 patients with chronic HCV infections had disease complicated with non-Hodgkin's B-cell lymphoma, and HCV-RNA was found in peripheral blood lymphocytes of all patients (Ferri et al. 1995). Positive- and negative-strand HCV-RNAs were detected in parotid glands of patients with parotid non-Hodgkin's B-cell lymphoma associated with HCV infection, and the presence of HCV in the parotid gland was confirmed by in situ hybridization (De Vita et al. 1995). Data from the International Lymphoma Epidemiology Consortium confirmed an association between HCV infection, and NHL and specific B-NHL subtypes (diffuse large B-cell lymphoma, marginal zone lymphoma, and lymphoplasmacytic lymphoma) (de Sanjose et al. 2008).

The treatment of HCV-associated malignant lymphoma is similar to that for non-HCV-associated non-Hodgkin B-cell lymphoma. However, recently, IFN monotherapy, or IFN and ribavirin combination therapy, has been reported to be effective. IFN was effective when used to treat certain specific lymphomas, including splenic lymphoma associated with production of villous lymphocytes (Hermine et al. 2002). Administration of pegylated IFN and ribavirin to 13 patients with HCV-associated non-Hodgkin's B-cell lymphoma afforded complete responses in 7 (Vallisa et al. 2005).

2.10 Autoimmune Thyroid Disease

The relationship between thyroid disease and HCV infection has been analyzed in a number of studies (Montella et al. 2003; Testa et al. 2006), and a causal linkage has been suggested. The incidence of thyroid dysfunction was assessed in 630 chronic HCV patients, without cirrhosis or HCC, who had not been treated with IFN. These patients had higher levels of thyroid-stimulating hormone, and lower levels of free thyroxine and triiodothyronine, than controls. In addition, the patients exhibited hypothyroidism and tended to have anti-thyroglobulin and anti-thyroid peroxidase antibodies. These findings suggest that a relationship exists between HCV infection and thyroid disorder (Antonelli et al. 2004). A possible relationship between such infection and thyroid cancer has attracted recent attention. The mechanism underlying the pathogenesis of thyroid disease associated with HCV infection has not yet been elucidated, but involvement of liver/kidney microsomal antibody type 1 has been suggested (Muratori et al. 2005). In general, patients with thyroid disorders caused by HCV infection are asymptomatic, and require no special treatment. Thyroid disorders are also known to develop as adverse reactions to IFN-alpha therapy for chronic HCV infection (Prummel and Laurburg 2003). Thyroid

dysfunction caused by administration of IFN-alpha is generally transient, resolving spontaneously after completion of treatment. Thus, discontinuation of IFN-alpha is not required in most cases.

2.11 Idiopathic Interstitial Pneumonitis

Viral infection has been suggested to be a cause of idiopathic interstitial pneumonitis. In terms of HCV infection, the anti-HCV positivity rate was 28.8 % in 66 patients with idiopathic interstitial pneumonitis (IIP), thus significantly higher than that in 9464 normal controls (Ueda et al. 1992). Any role for HCV infection, however, in the pathogenesis of idiopathic interstitial pneumonitis, remains unclear. Activation of T lymphocytes and eosinophils was suggested to be a feature of IIP pathogenesis associated with HCV infection, because increases in the counts of activated T-lymphocytes and eosinophils were noted in bronchoalveolar fluids from 13 chronic hepatitis C patients, although the total cell counts were identical to those of normal subjects (Kubo et al. 1996). Some studies, however, suggest that no relationship exists between HCV infection and IIP (Irving et al. 1993); further work is necessary. IIP has also been reported as an adverse reaction to IFN therapy in chronic HCV patients, who often exhibit high pretreatment KL-6 levels, suggesting that IIP might potentially develop. Recovery from IFN therapy-induced IIP is achieved by discontinuation of therapy, but steroid administration is required in some cases (Karim et al. 2001).

2.12 Myocardial Impairments

Causal relationships between HCV infection and certain myocardial impairments have been suspected; the impairments include dilated cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia cardiomyopathy, and chronic myocarditis (Matsumori et al. 2000; Matsumori 2006). The rate of serum anti-HCV positivity was 6.3 % (42/663) in patients with hypertrophic cardiomyopathy and 10.6 % (74/697) in those with dilated cardiomyopathy, thus higher than the rate (2.4 %) observed among age-matched Japanese blood donors (Matsumori et al. 2000). Positive- and negative-strand HCV-RNAs were detected in cardiac muscle samples of these patients, indicating potential intramyocardial HCV multiplication (Matsumori 2006). HCV-RNA has also been detected in cardiac muscle samples from patients with arrhythmogenic right ventricular dysplasia cardiomyopathy and chronic myocarditis, suggesting that HCV plays a pivotal role in the genesis of myocardial impairments (Maisch et al. 2003).

In terms of the cause of myocardial impairments associated with HCV, the involvement of host immunological responses to HCV, particularly that of the human major histocompatibility (MHC) class II antigen, has been suggested

(Matsumori 2006). The suggested relationships between myocardial disorders and HCV infection require further investigation.

2.13 Mooren's Ulcer

Mooren's ulcer is a progressive ulcer associated with congestion and pain around the cornea. HCV infection has been suggested to contribute to development of this disease (Wilson et al. 1994; Moazami et al. 1995). IFN has been reported to be effective for treating HCV-associated Mooren's ulcers, but ocular pain became exacerbated following IFN discontinuation; hence, caution is required when treating such patients (Wilson et al. 1994). Systemic corticosteroid administration has also been reported to be effective. However, some investigators are of the view that no association exists between HCV infection and Mooren's ulcer (Zegans et al. 1999; Jain et al. 2004). Further detailed studies would clarify this issue.

2.14 Cognitive and Mental Disorders

Certain mental, psychiatric, and cognitive disorders have been associated with HCV infection in a number of studies. Those include depression, cognitive impairment, and fatigue; all reduce health-related quality of life. For further information, please refer to the comprehensive reviews that have appeared on this issue (Perry et al. 2008; Jacobson et al. 2010).

2.15 All-Cause Mortality in HCV-Seropositives

Recently, several studies on all-cause death levels in HCV patients have been performed. One was a community-based long-term prospective study in Taiwan. In this work, 23,820 adults aged 30–65 years were enrolled during 1991–1992, and vital status was ascertained via computerized linkage to national death certificate profiles in the years 1991–2008. Of all subjects, 1095 were anti-HCV positive and 69.4 % had detectable serum HCV-RNA levels. Compared to anti-HCV seronegative subjects, the seropositive subjects exhibited higher mortalities from both hepatic and extrahepatic diseases. The multivariate-adjusted hazard ratios (with 95 % confidence intervals) were 1.89 (1.66–2.15) for all causes of death; 12.48 for hepatic diseases, 1.35 for extrahepatic diseases; 1.50 for circulatory diseases; 2.77 for nephritis, nephrotic syndrome, and nephrosis; 4.08 for esophageal cancer; 4.19 for prostate cancer; and 8.22 for thyroid cancer. Thus, anti-HCV seropositives with detectable HCV-RNA exhibited significantly higher mortality from not only

hepatic, but also extrahepatic diseases, than did anti-HCV seronegatives (Lee et al. 2012).

Similarly, Mahajan et al. evaluated mortality among patients with HCV infection, who were in care, in the Chronic Hepatitis Cohort Study (CHeCS) conducted from 2006 to 2010 in the United States. Mortality was compared with national Multiple Cause of Death (MCOD) data from 12 million US death certificates issued in 2006–2010. It was found that the CHeCS cohort exhibited higher mortalities from both hepatic and extrahepatic diseases: non-alcoholic liver-related death levels were 24.4-fold higher in the CHeCS cohort; deaths from liver cancer 8.7-fold higher; deaths from cancers other than liver cancer 1.28-fold higher; deaths from circulatory disease 1.42-fold higher; deaths from diabetes 1.77-fold higher; and deaths from genitourinary conditions 3.75-fold higher (Mahajan et al. 2014). Thus, HCV-positive patients exhibit higher mortality not only from liver diseases but also from extrahepatic diseases, confirming that extrahepatic manifestations of HCV infection, such as EMC, diabetes, or disorders in lipid metabolism (as described above) increase the mortality rates of such patients.

3 Conclusion

HCV infection is a multifaceted disease exhibiting both hepatic and extrahepatic manifestations caused by viral replication. Although the risk of death from extrahepatic conditions is lower than that associated with hepatic disease, it is important to be aware of the extrahepatic manifestations and diseases associated with HCV infection so that appropriate antiviral or immunomodulating treatments are administered, in a timely manner, to cure patients thus affected.

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