

REVIEW ARTICLE

The Emerging Extrahepatic Manifestations of Hepatitis C Virus Infection in Chronic Hepatitis and Mixed Cryoglobulinemia

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Hepatitis C virus (HCV) is known to be responsible for both hepatic and extrahepatic diseases. Mixed cryoglobulinemia, Sjögren syndrome, and chronic polyarthritis are the most documented rheumatologic extrahepatic manifestations of HCV infection. The most frequent and clinically important extrahepatic endocrine manifestations of chronic HCV infection are thyroid disorders and type 2 diabetes mellitus. From a meta-analysis of the literature, a significant association between HCV infection and thyroid autoimmunity and/or hypothyroidism as well as a high prevalence of thyroid cancer have been reported. The pattern of thyroid disorders observed in HCV infected patients is characterized by the presence of elevated circulating anti-thyroid peroxidase antibodies with increased risk of hypothyroidism. Several clinical epidemiologic studies have reported that HCV infection is a risk factor for type 2 diabetes. The type of diabetes manifested by subjects with chronic HCV infection is not of the classical type 2 diabetes; in fact, HCV-related diabetic patients are leaner than the classical diabetic patients, and have a significantly lower LDL-cholesterol, and both systolic and diastolic blood pressure. Furthermore, patients with mixed cryoglobulinemia (mixed cryoglobulinemia) and chronic HCV infection with type 2 diabetes have more frequently non-organ-specific-autoantibodies than non-diabetic patients with mixed cryoglobulinemia and those with chronic HCV infection. Based on the above-mentioned findings, it has been hypothesized that diabetes in HCV infection may have an immune-mediated pathogenesis. In patients with chronic HCV infection, we found an increased risk of carotid artery plaque and carotid intima-media thickening. These findings suggested a possible role for chronic hepatitis C in the pathogenesis of carotid artery remodelling. Recently, high prevalence rates of anti-HCV antibodies were shown in patients with hypertrophic cardiomyopathy or dilated cardiomyopathy; association with myocarditis has also been suggested. Many studies have linked the Th1 immune response with HCV infection, autoimmune thyroid disorders and diabetes. These findings suggest that a possible common immunological Th1 pattern could be the pathophysiological basis of the association.

Keywords: Hepatitis C, Cryoglobulinemia, Thyroid Autoimmunity, Hypothyroidism, Thyroid Autoantibodies, Thyroid Cancer, Diabetes, Atherosclerosis, Cardiopathy, Th1 Immunity

Introduction

Hepatitis C virus (HCV) is known to be responsible for both hepatic and extrahepatic diseases.

HCV and mixed cryoglobulinemia

Mixed cryoglobulinemia is the most documented extrahepatic manifestation of HCV infection ^(1, 2). Mixed cryoglobulinemia is characterized by the

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presence of circulating immunocomplexes produced by a B cell lymphoproliferative disorder. The diagnosis of mixed cryoglobulinemia is made by the laboratory findings of presence of serum immunoglobulin (Ig) that precipitates at low temperature ($<37^{\circ}\text{C}$) and which can be solved by warming the serum. Type II mixed cryoglobulinemia is characterized by polyclonal IgG and monoclonal IgM with rheumatoid factor (RF) activity; type III mixed cryoglobulinemia is characterized by presence of polyclonal IgG and IgM (3). The association between HCV and mixed cryoglobulinemia has been confirmed by serological and molecular investigations (4, 5).

Studies performed in unselected populations of chronic HCV-positive subjects showed a very high prevalence of serum cryoglobulins ranging from 19% to $>50\%$ (3, 4). Cryoglobulins are generally present at low levels and symptoms are generally absent or very mild (3, 4). In the majority of cases, determination of serum cryoglobulin level has limited clinical significance. It has been shown that only 5%-10% of subjects with chronic HCV infection have clinically evident mixed cryoglobulinemia syndrome. Meta-analysis of the present data would be difficult for lack of a clear distinction between these two conditions. Mixed cryoglobulinemia is the cross-road between autoimmune and lymphoproliferative disorders; in fact, lymphomas are more frequent in patients with mixed cryoglobulinemia (5-9).

HCV and Sjögren syndrome

Epidemiological studies showed a close correlation between Sjögren syndrome and HCV; mixed cryoglobulinemia presents in patients with HCV-associated Sjögren syndrome. Actually, it is generally admitted that in patients with chronic HCV infection with or without mixed cryoglobulinemia, Sjögren syndrome may be frequently found. However, there is generally no typical auto-antibody patterns (4, 10).

HCV and chronic polyarthritis

HCV-related chronic polyarthritis can be observed in HCV-positive subjects with various clinical presentations regardless of presence or absence of mixed cryoglobulinemia (10). In a recent study, (11) arthritis was present in 23 (15%) patients with chronic HCV infection and 12 (8%) patients with mixed cryoglobulinemia. A symmetrical polyarthritis was observed in 87% of 23 patients with chronic hepatitis while cryoglobulinemic arthritis was invariably asymmetrical and pauciarticular.

Endocrine disorders

The most frequent and clinically important extrahepatic endocrine manifestations of chronic HCV infection are thyroid disorders and type 2 diabetes mellitus.

HCV and thyroid disorders

Searching the literature (12, 13), we found 17 controlled studies; 12 of which reported a positive association between HCV infection and thyroid autoimmunity and or dysfunction, while five did not. Meta-analysis of data also revealed a significant association between HCV infection and thyroid autoimmunity (Table 1) and or dysfunction (Table 2) (12, 14). A high prevalence of thyroid cancer has been reported, too (12, 13, 15-17). The pattern of thyroid disorders observed in HCV infection is characterized by the presence of increased circulating anti-thyroid peroxidase antibodies (AbTPO), and increased risk of hypothyroidism in AbTPO-positive subjects (12, 13, 18, 19). These results were also confirmed in a recent historical cohort study on customers of US Veterans Affairs healthcare facilities from 1997-2004, which included 146,394 patients infected with HCV, that showed a significant increased risk for thyroiditis (20).

Table 1. Pooled data on thyroid autoimmunity (ATD) in patients with chronic HCV infection (with chronic hepatitis or HCV-Ab). Sum of healthy controls and HBV-infected patients for HCV-Ab were used as controls.

	HCV ⁺	ATD (HCV ⁺)	Controls and HBV ⁺	ATD (controls) and HBV ⁺	OR (95% CI)
Thyroid autoimmunity	2407	421 (17.5%)	3809	391 (10.3%)	1.65 (1.59-2.14)

Table 2. Pooled data on hypothyroidism in patients with chronic HCV infection (with chronic hepatitis or HCV-Ab). Sum of healthy controls and HBV-infected patients for HCV-Ab were used as controls.

	HCV ⁺	Hypo (HCV ⁺)	Controls and HBV ⁺	Hypo (controls) and HBV ⁺	OR (95% CI)
Hypothyroidism	1711	138 (8.1%)	1621	55 (3.4%)	2.60 (1.81-3.43)

HCV and diabetes

Epidemiology

Since 1994, several epidemiologic studies have reported that HCV infection is linked to

diabetes⁽²¹⁾, even if a general consensus has not yet been achieved^(22, 23). Almost all previous epidemiologic studies included a mixture of HCV patients without and with cirrhosis⁽²¹⁾. It is well known the cirrhosis, regardless of its etiology, is a risk factor for development of type 2 diabetes mellitus. The association between HCV infection in patients without cirrhosis and type 2 diabetes mellitus has been first studied in two of our studies, in patients with chronic HCV infection with mixed cryoglobulinemia⁽²⁴⁾ and in 563 patients with chronic HCV infection and chronic hepatitis⁽²⁵⁾. There are two population studies (National Health and Nutrition Examination Survey-NHANES III, 1988-1994) that showed an adjusted odds ratio of 3.8 for those who were aged 40 years or older and patients with chronic HCV infection⁽²⁶⁾ and increased incidence of type 2 diabetes mellitus⁽²⁷⁾. A few reports, too, suggested that treatment of HCV infection with interferon improves the glucose tolerance⁽²¹⁾ when HCV infection is eradicated. Combining all the above data indicates that chronic HCV infection is a risk factor for developing type 2 diabetes mellitus.

Mechanism

It is speculated that this is the insulin resistance⁽²¹⁾ which leads to the development of type 2 diabetes mellitus in patients with chronic HCV infection⁽²⁸⁾. Masini *et al.*⁽²⁹⁾ has recently demonstrated that HCV infection is present in human pancreatic beta cells and is associated with morphological cell changes and reduced *in vitro* glucose-stimulated insulin release. The type of diabetes manifested by patients with chronic HCV infection is not exactly of the classical type 2 diabetes mellitus. The labelling of patients with chronic HCV infection as type 2 diabetes mellitus is purely conventional and possibly inaccurate-the lines separating type 1 diabetes from latent autoimmune diabetes in adults (LADA) and from type 2 diabetes mellitus are fading away, as new pathogenetic information is obtained⁽³⁰⁾.

It has been previously reported by three studies^(24, 25, 31) that patients with HCV-related type 2 diabetes mellitus are leaner than those with classical type 2 diabetes mellitus, and have a significantly lower LDL-cholesterol, and systolic and diastolic blood pressure. Furthermore, patients with mixed cryoglobulinemia and chronic HCV infection with type 2 diabetes mellitus have non-organ-specific-autoantibodies more frequently (34% vs. 18%) than non-diabetic patients with mixed cryoglobulinemia-HCV⁺⁽²⁴⁾. Based on all these data, it has been hypothesized that diabetes in HCV

infection may have an immune-mediated pathogenesis^(25, 31). This hypothesis is supported by the fact that autoimmune phenomena in patients with type 2 diabetes mellitus are more common than that previously thought⁽³²⁾. Since the prevalence of classic beta cell autoimmune markers in patients with chronic HCV infection has not been found to be increased⁽²¹⁾, other immune phenomena might be involved⁽³²⁾.

Association of thyroid disorders and diabetes

So far, only few serological studies have performed on the possible association of thyroid autoantibodies and anti-beta cell autoantibodies in HCV-infected patients^(12, 13). However, no clinical studies have investigated the possible association of thyroid disorders, rheumatologic disorders and type 2 diabetes mellitus in patients with chronic HCV infection.

Cardiovascular disorders

HCV and atherosclerosis

Among 4784 individuals studied, the HCV seropositivity was associated with an increased risk of carotid-artery plaque and carotid intima-media thickening⁽³³⁾. These findings suggested the possible role of chronic hepatitis C in the pathogenesis of carotid arterial remodelling⁽³³⁾. In another study, carotid artery plaque was positive in 24% and 64% of the core protein-negative and core HCV protein-positive subjects, respectively⁽³⁴⁾. Recently⁽³⁵⁾, 34 cardiac transplant recipients who were seronegative for HCV at the time of transplantation and who received hearts from HCV-seropositive donors were evaluated. The risk of mortality and vasculopathy was greatest in those who became seropositive for HCV. Furthermore, more recently HCV-RNA was localized in human carotid plaques⁽³⁶⁾. Other studies did however not confirm the association between the HCV infection and atherosclerosis^(37, 38).

HCV and cardiopathy

Matsumori, *et al.*,⁽³⁹⁾ recently showed the presence of anti-HCV antibodies in 10.6% of patients with hypertrophic cardiomyopathy and in 6.3% of subjects with dilatated cardiomyopathy; these prevalence rates were significantly different from control groups (2.4%). In another study,⁽⁴⁰⁾ genomic analysis for HCV was performed in three patients with chronic active myocarditis; it seemed that HCV replicated in myocardial tissue of these patients. HCV-RNA and HCV antigens were

detected in myocardial cells of patients with hepatitis C ⁽⁴¹⁾. Furthermore, mice transgenic for the HCV-core gene ⁽⁴²⁾ developed cardiomyopathy which appeared as left ventricular dilatation, and systolic and diastolic dysfunction as assessed by doppler echocardiography. However, studies carried out in Italy and Greece by other authors did not confirm the association between HCV infection and cardiomyopathy ^(43, 44).

Future perspectives

Even if solid data have been obtained on the association of chronic HCV infection and mixed cryoglobulinemia or lymphoproliferation, many points are left to be clarified:

- 1) The possible association of rheumatologic, endocrine (autoimmune thyroiditis, hypothyroidism, diabetes) and cardiovascular disorders in patients with chronic HCV infection.
- 2) The incidence of new cases of rheumatologic, endocrine (autoimmune thyroiditis, hypothyroidism, diabetes) and cardiovascular disorders in patients with HCV infection, both in clinical- and population-based studies (no data present in the literature, for most of these disorders).
- 3) Many studies have linked Th1 immune response to HCV infection ^(30, 31), mixed cryoglobulinemia ^(25, 32) and autoimmune thyroid disorders ^(33, 34). These findings suggest that a possible common immunologic Th1 pattern could be the pathophysiologic basis of the association. Further studies are needed to clarify this issue.

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