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TOPIC HIGHLIGHT

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Extrahepatic immune related manifestations in chronic hepatitis C virus infection

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Abstract

The association of chronic hepatitis C with immune related syndromes has been frequently reported. There is a great range of clinical manifestations affecting various systems and organs such as the skin, the kidneys, the central and peripheral nervous system, the musculoskeletal system and the endocrine glands. Despite the high prevalence of immune related syndromes in patients with chronic hepatitis C, the exact pathogenesis is not always clear. They have been often associated with mixed cryoglobulinemia, a common finding in chronic hepatitis C, cross reaction with viral antigens, or the direct effect of virus on the affected tissues. The aim of this review is to analyze the reported hepatitis C virus immune mediated syndromes, their prevalence and clinical manifestations and to discuss the most supported theories regarding their pathogenesis.

Key words: Hepatitis C virus; Autoimmune; Extrahepatic manifestations; Cryoglobulinemia

Core tip: Autoimmune manifestations appear with an elevated prevalence in hepatitis C virus (HCV) patients. Despite their frequency, the pathophysiology of most of these syndromes is not adequately elucidated. We searched thoroughly through the available data and provided a summary of variable clinical manifestations and immune mediated diseases presenting during chronic HCV infection. The differences between HCV-related autoimmune syndromes and other similar autoimmune diseases have been cited. Moreover, we listed and critically analyzed the most supported theories regarding their pathogenesis.

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INTRODUCTION

Chronic hepatitis C is a viral infection affecting 130-170000000 people worldwide. Its prevalence ranges from lower levels in the developed countries (0.1% in certain areas of the United Kingdom) to higher levels (15%-20%) in countries of the developing world[1]. Liver cirrhosis affects 15%-30% of hepatitis C virus (HCV) patients approximately 20-30 years after infection. However, apart from liver disease, chronic HCV infection is also responsible for many extrahepatic manifestations of variable etiology of which a large proportion consists of immune mediated syndromes triggered by HCV. In other words, chronic HCV infection through the activation of various not adequately elucidated immunological mechanisms may cause a broad range of hematological, neurological and rheumatological syndromes[2] (Figure 1). The aim of this review is to analyze the prevalence and the clinical characteristics of these autoimmune syndromes among HCV patients and provide the available scientific information

regarding their pathogenesis.

PROPOSED PATHOGENETIC MECHANISMS

HCV molecular mimicry

Autoimmune manifestations in chronic HCV infection have been associated with cross reactive immune reactions between epitopes detected on the viral polyprotein and human proteins[3-5]. For example the existence of common sequence homologies between cytochrome P4502E1 and HCV-NS5b protein is responsible for the production of auto-antibodies targeting self-proteins[4]. Another case of molecular mimicry is the homology between NS5 region and three human protein nitrogen oxide synthases, tyrosine kinase-Lck, proto-oncogene and hepatic growth factor activator[5]. As a result, the resemblance of HCV epitopes to human auto-antigens may be the triggering factor for the development of non-organ specific auto-antibodies causing tissue injury and promoting inflammatory reactions.

Cryoglobulinemia

Cryoglobulins are monoclonal or polyclonal immunoglobulins that precipitate when exposed to low temperatures and are classified as type 1 consisting of only one monoclonal immunoglobulin, type 2 consisting of mixed monoclonal and polyclonal immunoglobulins and type 3 consisting only of mixed polyclonal immunoglobulins. Type 2 and 3 cryoglobulinemia, also called mixed cryoglobulinemia (MC), are associated with chronic HCV infection[6]. The etiology of HCV-related MC is associated with chronic lymphocyte stimulation induced by HCV. This chronic stimulation leads to B-cell clonal expansion resulting in the production of IgM immunoglobulins with rheumatoid factor (RF) activity against anti-HCV specific IgG immunoglobulins. In fact, it has been described that HCV-related cryoglobulins and especially the IgG type, show specificity against the HCV core and the NS3 and NS4 epitopes[7]. The pathogenesis of MC-related manifestations is based on the deposition of cryoprecipitated immune complexes on the wall of small vessels. These complexes bind to C1q protein resulting in the activation of the complement cascade and the induction of inflammatory reactions affecting the endothelium and leading to the appearance of cryoglobulinemic vasculitis. This condition may affect several organs with potential serious complications. Cryoglobulins are detected in 40%-60% of HCV patients and are accompanied by clinical manifestations in 5%-10% of them[8]. Some of the most frequent manifestations are palpable purpura, arthritis, peripheral neuropathy and kidney disease. The laboratory findings accompanying this immune complex-mediated syndrome are RF positivity and low complement levels. The successful clearance of HCV with antiviral treatment usually leads to recession of cryoglobulinemic syndromes. However, in serious MC-related manifestations, corticosteroid therapy, cytotoxic agents, plasmapheresis and recently rituximab have been used in order to achieve rapid disease response[6].

Direct effect of the virus

The direct effect of the virus on the affected tissues and its correlation with extrahepatic immune syndromes will be discussed along with the clinical manifestations being analyzed in this review.

IMMUNE THROMBOCYTOPENIA

The elevated incidence of immune thrombocytopenic purpura (ITP) in chronic HCV infection has been reported in a number of studies. However, the exact pathophysiology of this immune mediated syndrome appearing in several viral infections is not clear yet. In a study comparing 120691 HCV-infected and 454905 matched HCV-uninfected United States veterans from 1997 to 2004, the incidence of ITP was found to be significantly higher in the HCV infected group ($P < 0.0001$). The overall incidence of ITP among the HCV-infected and HCV-uninfected veterans was 30.2 and 18.2 per 100,000 person-years respectively. Moreover HCV was associated with ITP with a hazard ratio equal to 1.8 (95%CI: 1.4-2.3)[9].

Consequently, ITP is considered to be a common immune complication of HCV infection. A very interesting fact is the existence of differences in the clinical and laboratory findings between HCV patients fulfilling the criteria for chronic ITP and uninfected patients with chronic ITP. For example, it has been shown that patients with HCV-related ITP have less frequent symptoms and higher platelet levels[10] (Table 1). These findings suggest that HCV-related ITP and chronic ITP share common immunological pathways but should be approached as two different clinical entities. With respect to pathogenesis, the most supported theory is based on the production of anti-platelet antibodies, resulting in platelet destruction through phagocytosis or through complement-dependent cytotoxicity. As chronic HCV infection is associated with the production of various autoantibodies such as anti-nuclear antibodies or cryoglobulins, the development of autoantibodies targeting the glycoproteins on the platelets' surface has been put under investigation in a number of studies. The most common target of these antibodies is glycoprotein (GP) Ⅱb/Ⅲa, followed by GP Ⅲa, GP Ⅱb, GP Ⅰb and GP Ⅰa, as reported in a study of 30 thrombocytopenic HCV patients[11]. In the same study, the levels of the GP-specific antibodies were inversely correlated to the patients' platelet levels ($P = 0.024$). A possible mechanism for the development of anti-platelet specific antibodies in HCV infection was proposed recently, based on findings concerning HIV-related thrombocytopenia. The presence of anti-GPIIIA49-66 antibodies inducing complement-independent platelet fragmentation in the serum of HCV-HIV co infected patients was investigated. The study finally showed that HCV core envelope 1 causes the production of anti-GPIIIA49-66 antibodies

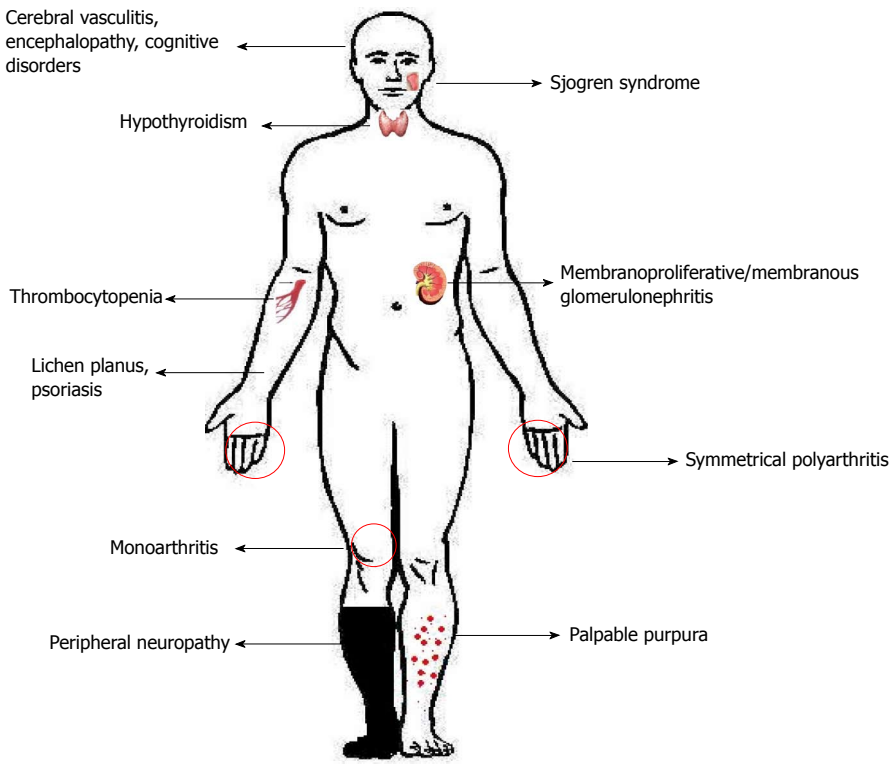

Figure 1 Immune manifestations of chronic hepatitis C.

Table 1 Differences in clinical and laboraratory findings between hepatitis C virus-related and non hepatitis C virus-related immune syndromes[10,46,47,52]

Immune syndrome	Features	HCV-related (% of patients)	Non HCV- related (% of patients)
Thrombocytopenia	Median age	54.9 ± 8 yr	40.3 ± 8 yr
	Platelets levels < 10×10^9/L	4	46
	Symptomatic thrombocytopenia	64	90
	Cryoglobulinemia	90	7
	Anti-cardiolipin antibodies	62	15
Polyarthritis	Clinical features	Milder non-erosive form of arthritis	Erosive arthritis
	Anti-CCP antibodies	4-11	75-83
	RF positivity	79-90	65-81
	Cryoglobulinemia	23	15
	Parotidomegaly	17	47
Sjogren syndrome	Liver involvement	94	3
	Cryoglobulinemia	60	10
	Anti-Ro/SS-A antibodies	17	38

HCV: Hepatitis C virus; Anti-CCP: Anti-cyclic citrullinated peptide antibodies.

by molecular mimicry, a mechanism that could possibly be responsible for a number of autoimmune syndromes induced by viral infections[12]. Finally another indication for the existence of an immune mediated mechanism leading to the appearance of thrombocytopenia in HCV patients is the response to steroids and intravenous Ig therapy[13].

NEUROLOGICAL MANIFESTATIONS

Chronic HCV infection has been associated with a variety of neurological manifestations, affecting the central nervous system (CNS) as well as the peripheral nerves and muscles. The most frequent neurological syndromes appearing in HCV patients are those correlated with MC and the presence of small vessel vasculitis[14]. However, it has been reported that in patients with MC-related vasculitic nerve lesions, the production of T helper 1 (Th1) cytokines such as interferon gamma and tumor necrosis factor alpha is enhanced while Th2 cytokines production is reduced[15]. This predominant Th1 response causes the activation of cytotoxic CD8+ T cells and monocytes that infiltrate the affected area and possibly contribute to the inflammation appearing in the nerve tissue. Moreover, the role of the direct effect of HCV on the nerve tissues has been recently investigated. This hypothesis is sup-

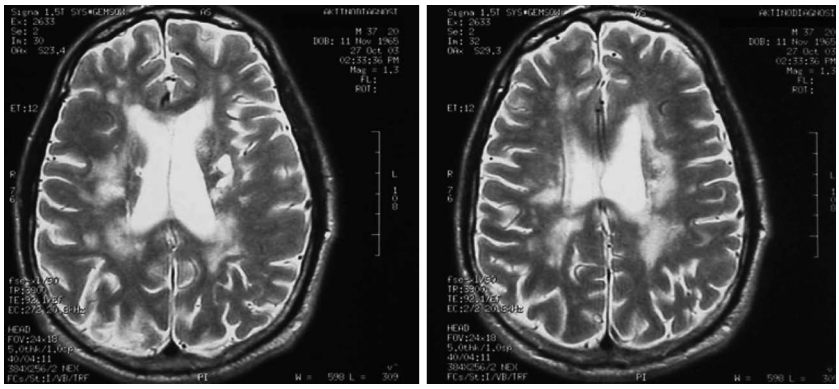

Figure 2 Brain magnetic resonance imaging showing foci of demyelination in a hepatitis C virus patient with mixed cryoglobulinemia and pyramidal signs[18].

ported by the fact that HCV RNA was detected in nerve and muscle histopathological specimens from patients with peripheral neuropathy and myositis without MC[16,17].

Peripheral neuropathy associated with MC in HCV infection presents as mononeuropathy, multiple mononeuropathy, or polyneuropathy, with sensory neuropathy being the most common of all[18,19]. Furthermore, the severity of the symptoms has been associated with the severity of cryoglobulinemia as expressed by the level of cryocrit[19].

As already mentioned, studies reporting MC negative HCV patients with peripheral neuropathy point to the direct role of HCV[20]. In a study comparing MC positive and MC negative HCV patients with peripheral neuropathy no significant differences in neuropathological characteristics were found, although patients with MC appeared to have more severe alterations of the nerve tissue structure[21].

Furthermore, patients with HCV-related MC may present with clinical syndromes affecting the CNS. Cerebral vasculitis may cause cerebrovascular events such as ischemic stroke and lacunar syndrome resulting in considerable morbidity[22,23]. In a study concerning 36 HCV patients with an ischemic stroke history, it has been demonstrated that anti-neutrophil cytoplasmic antibodies (ANCA) were positive in 58% of the patients with predominance of the c-ANCA pattern. Consequently, in chronic HCV infection, the production and circulation of a great range of autoantibodies apart from cryoglobulins may be the cause of larger vessel vasculitis. Additionally, MC-vasculitis affecting the CNS has been associated with encephalopathy and cognitive impairment both accompanied by white matter high intensity signals in magnetic resonance analysis[24,25]. Additionally, there has been a report of transverse myelitis attributed to chronic HCV infection with typical spinal MRI findings and clinical manifestations such as paraparesis and proprioceptive ataxia. The patient in this case report was MC negative and the demyelinative disorder was associated with the detection of HCV RNA in the cerebrospinal fluid[26]. However, demyelinative neuropathy affecting the CNS and causing pyramidal signs has also been described in a patient with HCV-related MC (Figure 2)[18]. It should be noted that the neurological symptoms receded after successful antiviral treatment in both cases. Therefore, HCV seems to have a definite role in the appearance of the above syndromes, though the exact mechanism is not yet known.

RENAL MANIFESTATIONS

A significant part of the autoimmune manifestations related to chronic HCV infection are the clinical syndromes involving the kidney. As indicated in other immune mediated clinical entities induced by HCV, MC is the main underlying factor responsible for the appearance of renal disorders.

The most common and best described renal syndrome related to HCV infection is the MC related membranoproliferative glomerulonephritis (MPGN). Histological findings indicate the presence of IgM immune complexes in the glomeruli accompanied by low complement levels in the patients' serum (Figure 3). The clinical manifestations of this disease range from asymptomatic hematuria and proteinuria to nephrotic syndrome and chronic renal dysfunction[27]. On the other hand, MPGN has also been observed in patients without cryoglobulinemia. In a recent study, it was shown that in HCV patients with MC-related MPGN, IgM staining was the most dominant, possibly due to the fact that cryoglobulins are mainly IgM type, while in MC-negative patients, IgG staining was the most typical finding[28]. Additionally, as described in a case report of an HCV patient with MPGN and leucocytoclastic vasculitis, despite the lack of MC, the complement levels in the serum were low[29]. This observation suggests the existence of immune complexes formed by HCV antigens and antibodies along with complement without the contribution of cryoglobulins.

Apart from MPGN, there are several other nephrological syndromes reported in patients with HCV infection. Membranous glomerulonephritis is another relatively common immunological manifestation in HCV patients usually combined with the presence of immune complexes with or without cryoglobulinemia[30]. Moreover, focal segmental nephrosclerosis appearing with proteinuria

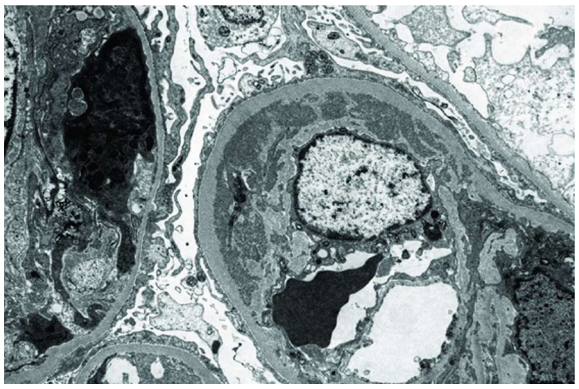

Figure 3 Membranoproliferative glomerulonephritis in a hepatitis C virus patient: endocapillary proliferation with extensive subendothelial deposits along the glomerular capillary walls. Mesangial deposits are present as well (electron microscopy), adapted from Ko *et al*[63].

and microhematuria responding to antiviral treatment has been also associated with HCV-induced autoimmunity[31]. In a recent case report, MPO-ANCA positive Wegener's granulomatosis with pulmonary and renal involvement in an HCV patient was documented[32]. Other reported histological types of kidney disease in HCV patients are benign nephrosclerosis, tubulointerstitial nephritis and minimal change nephritic syndrome[33].

Finally, the reported appearance of MC-related MPGN in 3 anti-HCV positive patients without detectable viral load is another interesting finding. PCR testing for the existence of HCV in peripheral blood mononuclear cells and bone marrow cells was negative while HCV-NS3 antigen was detected in the glomeruli[34]. This observation is further supported by the detection of HCV antigens in renal tissues of patients with glomerulonephritis without serologic proof of HCV infection[35]. Thus, HCV may reside in specific tissues even when it is not detected in the circulation. However, it should be noted that false negative results may occur due to HCV RNA and anti-HCV entrapment in the cryoglobulins.

CUTANEOUS MANIFESTATIONS

HCV infection has been associated with palpable purpura, lichen planus, psoriasis, and other syndromes with dermatological manifestations[36,37]. It has been already mentioned that a common manifestation of MC is palpable purpura caused by vasculitis of the small vessels of the skin (Figure 4). As shown by histological examination, leukocytoclastic vasculitis is the predominant pattern in the skin biopsies (Figure 3). Furthermore, in a study aiming to investigate the pathogenesis of skin manifestations due to MC vasculitis, the immunohistochemical and direct immunofluorescence analysis offered some interesting findings. HCV RNA was detected along with CD8+ T suppressor cells infiltrating the perivascular and subjunctional regions and inducing an inflammatory activity that involved keratinocytes and Langerhans cells[38]. Another study reported the detection of HCV in keratinocytes, ductal epithelial and vascular endothelial cells

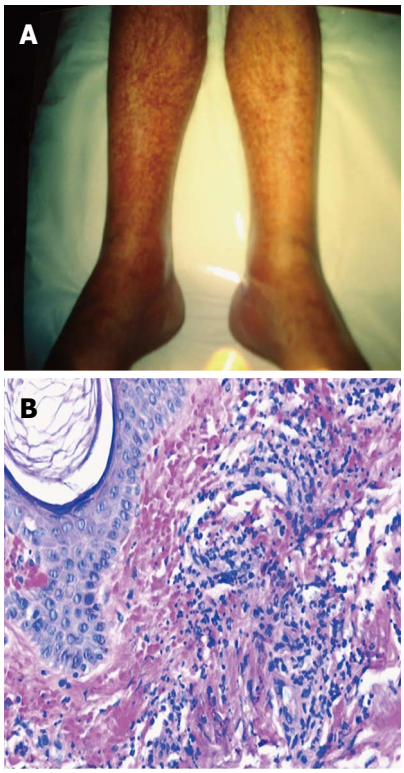

Figure 4 Cryoglobulinemic vasculitis affecting the skin. A: Palpable purpura (personal data); B: Leukocytoclastic vasculitis: predominantly lymphocytic mixed inflammatory infiltrate involving small vessels in the dermis (hematoxylin-eosin, original magnification 200) adapted from Ko *et al*[63].

only in the affected skin of HCV patients with MC and cutaneous vasculitis. HCV was not detected in normal skin specimens from the same patients. Moreover, the severity of the symptoms was associated with the levels of viremia[39]. In conclusion, autoimmune cutaneous manifestations in chronic HCV infection are the result of two distinct mechanisms. The presence of viral particles in keratinocytes, dendritic cells and the endothelium of the blood vessels in the affected skin, possibly induces the viral-dependent T-lymphocyte proliferation and infiltration of the tissues. Secondly the MC-related deposition of immune complexes in the endothelium is responsible for the appearance of cryoglobulinemic purpura.

Lichen planus, an inflammatory disease involving the skin and the mucous membranes, is one of the first dermatological disorders associated with chronic HCV infection. HCV RNA has been isolated from lichen planus skin lesions of HCV patients while it was not detectable in normal skin biopsies from the same patients. Consequently, HCV may be considered as a triggering factor for an immune mediated mechanism resulting in the appearance of lichen planus[40]. Psoriasis is another chronic inflammatory skin disease with a reported correlation to HCV and especially with antiviral interferon-based HCV treatment[41]. Furthermore HCV infection has been reported to correlate with erythema nodosum and erythema multiforme. Both dermatological disorders are a result of immunological reactions affecting the skin, while their exact connection with HCV remains unclear[42].

Table 2 Non organ specific autoreactivity in chronic hepatitis C virus infection[64-68]

Autoantibodies	Prevalence (%)	Clinical significance
Cryoglobulins	40-60	Associated with cryoglobulinemic vasculitis: Palpable purpura Kidney disease Peripheral neuropathy Arthritis
ANA	1.6-32	Controversial clinical significance
SMA	6-19.3	Often associated with: Patients' age
LKM-1	0.5-2.5	Fibrosis stage
AMA	0.5-1.4	Disease activity No influence on treatment response

ANA: Antinuclear antibodies; SMA: Anti-smooth muscle antibodies; LKM-1: Anti-Liver Kidney Microsomal Antibodies; AMA: Antimitochondrial antibodies.

RHEUMATOLOGICAL MANIFESTATIONS

Arthritis

The involvement of joints in HCV patients presenting with arthritis and arthralgias can be categorized in two different clinical types. The first type is the most common one and appears as symmetrical polyarthritis of small joints similar to rheumatoid arthritis (RA). The second one is MC-associated and appears as mono- or oligoarthriris affecting larger joints[43].

The rheumatoid-like arthritis reported in HCV patients is associated with a milder non-erosive form of arthritis in comparison with typical RA. The presence of HCV in the synovial tissue may be the cause of inflammatory arthritis, a hypothesis that needs to be confirmed by further studies[44]. In a recent study of 21 HCV patients with polyarthritis, it has been shown that the levels of interleukin 6 (IL-6) and the levels of its soluble receptors in their serum were higher than those measured in healthy controls. Elevated IL-6 appears also in patients with rheumatoid arthritis and plays an important role in the pathogenesis of the disease[45]. The differential diagnosis between the two clinical syndromes apart from the clinical differences is based on the testing for anti-cyclic citrullinated peptide antibodies (anti-CCP). As reported by a number of studies, rheumatoid factor is not a useful marker due to the fact that it is positive in both HCV-related arthritis and RA. On the other hand, anti-CCP antibodies are detected only in 4%-11% of HCV patients with polyarthritis while their frequency in patients with RA is 75%-83%[46,47]. These findings suggest that polyarthritis in HCV patients should not be associated with rheumatoid arthritis.

MC-related arthritis is estimated to affect 10%-30% of HCV patients. The chronic inflammation appearing in the affected joints is induced by the deposition of immune complexes in the synovial fluid. This type of arthritis is associated with older age and a longer history of chronic HCV infection and is often accompanied by palpable purpura. It affects medium and larger joints, predominantly the ankle. The detection of cryoglobulins in the serum of these patients confirms the diagnosis[44,45].

Sjogren syndrome

Sjogren syndrome is an autoimmune disease affecting the salivary and lacrimal glands, causing xerophthalmia and xerostomia. It is sometimes accompanied by arthritis and other systematic symptoms. A higher incidence of this immunological disorder in HCV patients has been previously noticed. The prevalence of Sjogren syndrome in HCV patients is estimated to be 26% to 53% depending on the diagnostic criteria[48,49]. The existence of HCV RNA in the salivary glands of HCV patients with Sjogren syndrome is a controversial subject, while the most supported theory is the cross-reactivity between HCV antigens and the salivary gland tissue[50,51]. The immunological parameters found in HCV patients fulfilling the criteria for Sjogren syndrome appear to have some differences from those reported in patients with primary Sjogren syndrome. The prevalence of anti-SS-A and anti-SS-B antibodies is lower in HCV patients, while the prevalence of cryoglobulinemia, hypocomplementemia and antinuclear antibodies is higher. There are also clinical differences as HCV patients with Sjogren syndrome appear to be older with less frequent parotidomegaly and higher prevalence of liver involvement[52]. With respect to the histopathological features, HCV patients showed a lesser degree of inflammation with a predominance of CD8+ T lymphocytes in the salivary gland tissue[53]. Moreover, HCV patients are reported to present with a different serological cytokine pattern associated with T helper type 2 response[54]. In conclusion, HCV related Sjogren syndrome, though similar in many aspects with primary Sjogren, is induced by immune mechanisms strongly associated with chronic HCV infection.

Other rheumatologic syndromes

Chronic HCV infection is often characterized by the presence of a number of auto-antibodies with or without clinical manifestations (Table 2). Anti-cardiolipin antibodies have been reported though their clinical significance is controversial[55]. In a multicenter study of HCV patients with autoimmune diseases, anti-phospholipid syndrome was one of the most frequently reported diseases, as well as systemic lupus erythematosus (SLE)[56]. A possible correlation between SLE and HCV infection may be attributed to the fact that both syndromes are accompanied by the presence of immune complexes, hypocomplementemia and vasculitis. Patients affected by both HCV and SLE appear less frequently with butterfly erythema and have lower rates of positive anti-dsDNA antibodies, but present more often with cutaneous vasculitis[57]. Finally, CREST syndrome is considered a relatively rare autoimmune manifestation affecting HCV patients, while anti-centromere antibodies are reported to be positive in 1% of them[58].

THYROID DISORDERS

Thyroid disorders and mainly Hashimoto disease have been greatly associated with interferon therapy in HCV patients. However, the presence of anti-thyroid antibodies and hormonal disorders, such as subclinical hypothyroidism, have been reported to appear more frequently even in untreated HCV patients, though the correlation is not strongly established yet[59,60].

Thyroid cells express CD81 receptor on their surface and thus are possible targets for HCV binding. In an experimental study it was shown that the HCV E2 protein binds to the surface of thyroid cells expressing CD81 receptor leading to the production of IL-8, a strong mediator of inflammatory reactions. Therefore, it was hypothesized that HCV triggers autoimmune thyroiditis through a bystander activation mechanism[61]. Additionally, another study has shown that HCV has the ability to infect thyroid cells in vitro through CD81 receptor. This ability primarily suggests that thyroid glands may consist of an extrahepatic location for HCV replication and provides a possible explanation for the appearance of autoimmune thyroiditis in chronic HCV infection[62]. Nevertheless, the exact mechanisms from the entrance of HCV in the thyroid cells to the appearance of this autoimmune disorder remain to be clarified.

CONCLUSION

The hypothesis that HCV is involved in the appearance of several autoimmune syndromes is strongly supported by a significant number of studies. Some of the immunological pathways that participate in the pathogenesis of these manifestations have been elucidated. The circulating immune complexes, the cross-reactivity between HCV and auto-antigens, the direct effect of HCV on the affected tissues, the interactions between interleukins and other inflammatory agents are some of the mechanisms proposed to explain the reported immune diseases. However, there are still many aspects of the diseases' pathophysiology that need to be clarified. For example the role of genetic predisposition as an important factor for the appearance of the autoimmune syndromes only in a proportion of HCV patients should be investigated. Moreover, the effect of interferon therapy on the immune diseases is another intriguing field. As it is known, while interferon therapy may provide the cure for some conditions such as cryoglobulinemia, it may also cause the exacerbation of other syndromes. Consequently, when facing an HCV patient presenting with an autoimmune manifestation, it should be always clarified whether this manifestation is associated with HCV infection and then proceed to the appropriate therapy. The upcoming interferon-free therapies may provide an additional option for these patients in order to avoid undesired effects. Therefore, it is clear that the association of HCV with autoimmunity provides a field of great range that should be further investigated.

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