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Autoimmune Diseases Co-Existing with Hepatitis C Virus Infection

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ABSTRACT

Autoimmunity and viral infections are closely associated fields, and viruses have been proposed as a likely aetiological, contributory or triggering factors of systemic autoimmune diseases. Hepatitis C virus seems to be the virus usually associated with the appearance of autoimmune diseases, and the relationship between chronic hepatitis C virus infection and some autoimmune disease has been studied. For some of these disorders their association with hepatitis C virus infection is well recognized while for others it remains probable or weak. Examples of autoimmune phenomena observed in chronic hepatitis C virus infection include rheumatoid arthritis, thyroid disease, cryoglobulinaemia, immune thrombocytopenic purpura, systemic lupus erythematosus and sjogren syndrome. To date, the etiological role and the pathogenetic involvement of the hepatitis C infection remains unknown.The aim of this study is to assess the presence of different autoimmune manifestations of hepatitis C virus infection reported in literature.

Key words: Autoimmunity; Hepatitis C Virus; Immune Mediated Disease

INTRODUCTION

Hepatitis C virus (HCV) is a member of the Flaviviridae family and associated with different autoimmune manifestations.[1] Based on different studies, 40-74% of HCV infected patients may experience other complications during the course of the disease that are principally immunological.[2,3]

The prevalence of HCV infection is much higher among some of these conditions and suggests a pathogenetic role of the virus. HCV is a trigger for the autoimmune reactions resulting in production of autoantibodies.[2,3] In recent years, Cacoub et al.[2] found positive ANA in 41% of patients, rheumatoid factor (RF) in 38%, anticardiolipin antibodies (aCL) in 27%, and antithyroglobulin antibodies in 13% of patients. Some of these antibodies such as anti-C-reactive protein correlated with the severity of liver disease.[4] Anti-HCV high seropositivity in chronic liver disease (CLD) patients may also point to an autoimmune processes in CLD.[5]

HCV may localize in several tissues besides the liver (including kidney, skin and salivary glands). These tissues might act as a reservoir for HCV and contribute in both persistence and reactivation of virus.[6]

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Therefore, replication and expression of viral proteins in these tissues may play a role in autoimmune manifestations associated with chronic HCV infection.

Identification of the type and extent of autoimmune disorders in patients with HCV infection is important for at least 3 reasons. First, this awareness can result in rapid diagnosis and treatment of these diseases. Second, some of these disorders such as membranoproliferative glomerulonephritis (MPGN) may ameliorate in response to antiviral therapy for hepatitis C and may provide an urgent indication for such treatment. Third, patients presenting with these disorders can be targeting for HCV testing.[7]

Existence of an autoimmune disorder in patients with hepatitis C infection limit the clinicians in decision for treatment of patients and it need more experience for this. The purpose of this study is to review the literature concering the association between HCV infection and different autoimmune diseases.

1. Blood Disorders

Various studies have shown that there is a specific tropism of HCV for many extrahepatic cell types, particularly for circulating blood cells.[8-11] HCV proteins and HCV RNA genomic sequences were identified both in peripheral blood mononuclear cells and bone marrow of chronically HCV infected patients.[12] These surveys providing a clear link between HCV and the development of autoimmune hematologic processes. This section is allocated to a specific study about the hematologic disorders which may be associated with chronic HCV infection.

1.1 .Immune Thrombocytopenic Purpura

Several studies have shown that thrombocytopenia is frequently observed in chronic hepatitis C. This condition may be an isolated symptom or may coexist with other extrahepatic manifestations (EM).[13]

Thrombocytopenia associated with chronic viral hepatitis is often thought to be due to hypersplenism resulting from hepatic cirrhosis and portal hypertension.[14]

In patients with cirrhosis, the thrombocytopenia may result from sequestration of platelets in the enlarged spleen secondary to portal hypertension.[15] However, thrombocytopenia can also be observed in patients with chronic hepatitis C without cirrhosis. Another mechanism is autoimmune reaction to platelets.

Immune thrombocytopenic purpura (ITP) can be clustered as primary (also referred to as idiopathic thrombocytopenic purpura) or as secondary to an underlying disorders such as a malignant or nonmalignant disease.[16,17]

Chronic infection with HCV is one of the occurring conditions associated with nonmalignant secondary ITP.[16] To determine whether an association exists between HCV infection and secondary ITP, a fair number of cross-sectional and cohort studies were performed.[18-20] These trials are not enough to show a direct link between HCV infection and ITP. However, some studies indicate the high prevalence (13.4%) of HCV infection in chronic ITP patients.[18] In addition, some data such as detection of serum HCV antibodies in patients with autoimmune thrombocytopenic purpura[21] and production of a significant autoimmune reaction to platelets during chronic infection with HCV[10,20,22] demonstrated a higher occurrence of ITP in patients with chronic HCV infection than would be expected by chance. For example, Nagamine et al. have shown that Platelet-associated immunoglobulin G titers were significantly higher in patients with chronic hepatitis C (87.3±10.1 ng/10^7 cells) vs. those with chronic hepatitis B (30.3 +/- 6.4) or the control subjects.[10]

Additionally, in patients with untreated hepatitis C, both prevalence and severity of thrombocytopenia enhance in relation to the extent of disease.[23]

Different pathogenic mechanisms have been suggested to play a role in thrombocytopenia related to chronic HCV infection. Platelet sequestration in the enlarged spleen secondary to portal hypertension[24] and reduced synthesis of thrombopoietin[25] secondary to liver dysfunction may participate to progress of thrombocytopenia. Recent data suggest that HCV infection of platelets[26] and megakaryocytes[27] may participate in the induction or aggravation of thrombocytopenia. Molecular mimicry between antigens from HCV and platelet glycoprotein may be important in platelet clearance.[16]

Moreover HCV binding to membrane of platelets and subsequent binding of anti-HCV antibody could theoretically result in 'innocent bystander' phagocytosis of platelets.[26]

1.2. Autoimmune Hemolytic Anemia

There is emerging evidence that HCV infection plays a role in the etiology of autoimmune hemolytic

anemia (AIHA) which is severe autoimmune cytopenias.[28] Hyman and Southworth were the first to report an association between AIHA and chronic hepatitis.[29] In 1973, Panush and colleague described a patient suffered from chronic active hepatitis who presented with AIHA and positive-Coombs' test, and responded to treatment with steroids.[30] In 1982, Portell et al. described five patients with chronic hepathopathy and AIHA.[31] Nearly 20 years later, two cases of HCV infection associated with AIHA were described.[32] This disease may occur during the natural course of the infection and either during or after interferon(IFN) therapy.[32,33] Ribavirin(RBV) is the main drug responsible for anemia, and is commonly used in combination with IFN for the treatment of chronic hepatitis C. This drug can decrease in hemoglobin levels by an average of 1 to 3g/dl over the first eight weeks of treatment.[34]

A higher frequency of some immunologic markers including cryoglobulinemia and hypocomplementemia all potentiate the hypothesis that HCV-related AIHA has an autoimmune pathogenesis caused by chronic HCV infection.[11]

The hallmark of this disease is a warm-reacting, positive direct antiglobulin test. However, Fernández described an unusual case of Coombs'-negative AIHA with severe autoimmune leukopenia and neutropenia, that occurred simultaneously, in a patient with untreated hepatitis C infection.[35] Therefore a negative direct antiglobulin test does not entirely rule out the diagnosis of autoimmune hemolytic anaemia particularly in the rare case of IgA mediated immune hemolysis.[36]

1.3. Cryoglobulinaemia

Essential mixed cryoglobulinaemia (EMC) is one of the best documented extrahepatic autoimmune manifestation in HCV infection which affects 36-54% of patients.[37,38] There are a high prevalence of HCV markers in EMC patients.[39] For example, HCV sequences were detected in mononuclear cells from bone marrow and peripheral blood in most patients with mixed cryoglobulinemia(MC). Sansonno et al. determined the relative virus load in peripheral blood lymphocytes of two cohorts of chronically HCV-infected patients with and without MC. They indicated that MC patients are characterized conspicuously by a higher quota of cell-associated viral load, a finding that might be associated with a higher production of cryoglobulins by the infected cells.[40] In addition, RNA sequences from the HCV within the cryoprecipitate, as well as in a number of lesions, most notably those of the skin have been identified.[41] EMC development appears to depend on the length of infection[39], the presence of anti-HCV antibodies and HCV antigens, and RNA in the damaged tissues.[41] The clonal B-cell proliferation in the blood and liver of patients with HCV hepatitis, being more common in those with MC[42], supports notion that there is a specific antigenic stimulation whit leads to B-cell proliferation in HCV MC.[43] The incidence of HCV infection in patients with EMC differs geographically and ranges from 40% to 100%.[44] Therefore, HCV appears to be a common etiological agent in MC; however, a different combination of unknown co-factors [infectious, genetic (such as HLA system), environmental] should be determinant for the appearance of various clinical patterns.[45,46] Moreover, certain HCV genotypes may predispose the infected patients to cryoglobulinemia. Gad et al. indicated cryoglobulinemia is prevalent in Japanese patients with chronic hepatitis C infected with genotype 1b.[47] Ramos-Casals and colleague also indicated that HCV patients with genotype 1 had a higher mean age at diagnosis of cryoglobulinaemia and a higher prevalence of cryoglobulinaemic symptoms, principally of vasculitic features.[48] It is mandatory for every patient with cryoglobulinemia to be evaluated for viral hepatitis tests.

1.4. Antiphospholipid Syndrome

A literature review indicates that anticardiolipin antibodies occur frequently in viral infections, such as HCV.[49] Nonethless, the association of HCV infection with antiphospholipid syndrome (APLS) remains a matter of debate.[50,51] To date, very little cases of APLS have been explained among patients having chronic HCV infection.[50,52] For example, Prieto et al.[50] indicated that HCV infection is associated with the occurrence of antiphospholipid antibodies(aPLs). Another studies of aCL in connection with chronic HCV infection have been conducted.[50,53] The results indicated that 3.3-37.3% of patients with HCV infection have positive aCL. It is suggested that HCV may facilitate the development of these antibodies and via this mechanism be involved in thrombotic disorders.[50] An alternative possibility is that aPLs are a mere epiphenomenon of HCV infection, without any causative role in the thrombotic events.[53]

Different studies have demonstrated that APLS-HCV patients showed a lower frequency of typical APS features such as peripheral or cerebral venous thrombosis[52] or neurologic features but a higher prevalence of some atypical or infrequent features such as myocardial infarction. Furthermore, these patients showed higher frequency of immunologic markers such as ANA, cryoglobulins, hypocomplementemia, and RF. It seems infective agents such as HCV may trigger a heterogeneous, atypical presentation of APLS.[52]

Several mechanisms may be involved in the induction of aPLs by viral infections. These includes first: cross-reactivity between viral antigens and phospholipids during the immune response to infection[54], second: the exposure of hidden phospholipids following cell membrane disruption by viruses[55] third: overexposes of phosphatidylserine on the membrane of the apoptotic cells.[56] It is not mandatory to check the APLS antibody in hepatitis C infected patients with any risk factor for acquiring the infection. And we need more researches regarding this subject.

2. Rheumatological Manifestations

Rheumatoid diseases were often associated with hepatotropic virus, mainly HCV[57], however their aetiological roles, in the pathogenesis of diseases is still a matter of debate[58]. HCV infection has been associated with a variety of rheumatologic manifestations, such as arthralgia, arthritis, vasculitis, and sicca syndrome.[59]

Among these conditions, arthropathy is one of the common EM of HCV infection; it is exhibited by up to 20% of infected patients. However, there is no single clinical picture of arthritis in patients with HCV infection.[60] A wide range of serological markers of rheumatic diseases such as RF were detected in HCV infected patients, which support the idea of an association between HCV infection and these disorders.[61] In addition liver disturbance is common in rheumatoid diseases.[57] This section focuses on HCV-associated rheumatic disorders which are nearly common in HCV positive patients.

2.1. Rheumatoid Arthritis

Rheumatologic complications of HCV infection such as Sjogren's syndrome, arthritis and fibromyalgia are common.[60] Several studies indicated a high prevalence of HCV infection in patients with rheumatoid arthritis (RA) as a prototype for rheumatic diseases. For example in one study 23 (7.6%) of RA patients had HCV antibodies, and 7 (2.3%) had active infection by HCV.[62] However, opposite results were also reported.[63] Some of these investigations indicated that HCV may trigger the progression of RA particularly in genetically susceptible individuals.[64] In addition, elevations of RF have been described in patients infected with the HCV.[65] In particular, a positive IgM RF was detected frequently (>60%) in patients with HCV-related arthropathy.[65]

HCV-related arthritis usually manifests as rheumatoid-like, symmetrical inflammatory polyarthritis. The joints involved in HCV-related arthritis are similar to RA.[66] In patients with chronic HCV infection, there is a well defined picture of arthritis accompanied by the presence of mixed cryoglobulinemia that may produce an intermittent mono or oligoarticular, nondestructive arthritis involving large and medium size joints. 2% to 20% of HCV-infected patients experience arthritis and as 50% experience arthralgia.[62]

Differentiation between true RA and HCV-related arthritis may be complex. HCV-related arthritis usually shows a fairly benign course that, in contrast to true RA, is characteristically nondeforming and is not associated with articular bony erosions. Furthermore, unlike classic RA, erythrocyte sedimentation rate is augmented only in nearly half of the patients and subcutaneous nodules are lacking.[65] Patients with HCV-related arthritis are usually seropositive for RF, but anti keratin antibodies and anti-cyclic citrullinated peptide antibodies are a suitable markers to differentiate patients with RA from these with HCV-related arthritis.[61,67]

2.2. Systemic Lupus Erythematosus

The concept of association between systemic lupus erythematosus (SLE) and HCV infection formed on the basis of several observations. First, viruses might be one of the environmental agents that trigger SLE. Second, some of the most common HCV extrahepatic manifestations, eg. arthralgia, myalgia and sicca syndrome may mimic a rheumatic disease, especially SLE.[68] Third, SLE and HCV infection share many common immunological features such as hypocomplementemia, and autoantibodies such as antinuclear antibodies(ANAs) and anticardiolipin autoantibodies(anti-CLAbs).[69,70] To date, few researchers have investigated relationship between

HCV infection and SLE.[68,71] On the basis of information gained from some of these investigations, there are possible a causal link between HCV and SLE. This viewpoint is supported by observations, such as a higher prevalence of HCV infection in SLE patients (11%) than in blood donors (1%) and a higher prevalence of liver involvement or hepatic damage in SLE HCV-positive patients.[68,71]

One common complication for SLE patients is kidney involvement.[72] A number of studies provide hints that HCV may play a role in renal manifestations of SLE. For example, a few cases of lupus nephritis coinciding with HCV infection have been described.[73,74] Although this association is possibly not cause-effect related, it is probable that the altered immune response of SLE could facilitate HCV infection.[73] Furthermore, it is likely that different autoantibodies associated with HCV infection could further facilitate the development of lupus nephritis due to formation of immune complex(IC) deposits in the kidneys. Augmentation in serum B-Lymphocyte activating factor levels in patients with chronic HCV infection and SLE patients may participate to continuous B-cell activation and production of autoantibodies.[75]

2.3. Sjögren's Syndrome

To date, more than 250 cases of sjogren's syndrome(SS)–HCV have been described, making SS one of the systemic autoimmune disease (SAD) most-closely associated with HCV.[76,77] García-Carrasco et al. indicated that HCV infection was present in 14% of the patients with a previously considered primary' SS. This prevalence was significantly higher in patients with SS than that of the general population (1.2%).[77]

The occurrence of a typical autoimmune sialadenitis in HCV-positive patients, similar to that explained in primary SS and experimental evidence, propose that HCV might efficiently be involved in the SS pathogenesis.[78] Smyth et al. demonstrated that symptoms compatible with the sicca syndrome are considerably over-represented in those who have persistent chronic HCV infection, verified by their positive polymerase chain reaction (PCR) status. They also indicated that DQB1*02 was significantly associated with viral persistence.[79] Another possible reasons for the association between HCV infection and SS are a high prevalence of chronic HCV infection and anti-HCV antibodies in SS patients.[80] Arase et al. reported that 16.1% of hepatitis C infected patients had sialadenitis.[81]

The HCV replication within salivary gland epithelial cells of patients with sicca syndrome and HCV infection was shown.[82] This further supports a possible association between HCV and SS. Arrieta et al.[83] indicated that HCV infects and propagates in epithelial cells from salivary glands of patients with SS or chronic sialadenitis. It is likely that in some people with a particular genetic background, infection of salivary epithelial cells could result in a lymphoid proliferation and, secondary, to the destruction of the glands.[84]

Liver involvement is frequently found in patients with primary SS.[77] In one study 21 out of 95 patients with primary SS had diagnosis of a specific liver disease such as HCV infection.[85] Ramos-Casals et al. indicated that the main cause of liver involvement in SS patients are chronic viral diseases.[86] They also showed that chronic HCV infection may mimic the main clinical, histologic, and immunologic features of SS.[87] Several studies[78,83] have assessed the morphologic and immunohistochemical characteristics of sialadenitis in HCV patients. The results indicated that HCV patients can promote patterns of salivary gland disease similar to those seen in primary SS patients. SS and HCV infections also have similar pathogenic characteristics. These derangements include overproduction of autoantibodies as a result of B-lymphocyte hyperactivity and expansion of $CD5^+$ B cells that are involved in the production of polyreactive autoantibodies and RF.[88] In addition the analysis of the three HCV infected patients demonstrated a predominance of B over T cells in the lymphocytic focus and an increased expression of T lymphocytes in the inflammatory infiltrate.[89]

Different mechanisms may participate to the pathogenesis of SS associated with HCV infection. These happen via a direct infection and proliferation of HCV in salivary glands, molecular mimicry between HCV and salivary glands, and formation of immune complex containing HCV.[90]

3. Glomerular Diseases

A relationship between HCV infection and glomerulopathies such as MPGN, membranous nephropathy, and IgA nephropathy were reported by several investigators[91,92] but it seems that the most common renal manifestation is MPGN with or without

cryoglobulinemia.[93] The prevalence of HCV infection in MPGN differs by country, from 60% in Japan to about 10% to 20% in the United States.[91] Patients may present with signs and symptoms of cryoglobulinemic systemic vasculitis, proteinuria, microscopic hematuria, acute renal failure, or nephrotic syndrome.[94] However, Patients with glomerulonephritis (Gn) may have no clinical evidence of systemic or liver involvement.

Different studies indicated that HCV infection is more common among patients with Gn than in those without.[95] A high seroprevalence of anti-HCV has been observed in patients with Gn in various countries and several factors such as the number of blood units transfused supposed to influence the anti-HCV seroprevalence.[96] The improvement of glumerolopathies with the disappearance of viral replication could be a strong argument for causal relationship between the virus and disease.[97] Furthermore, a causal association between HCV and Gn has been suggested based on the observation of virus-like particles as well as viral RNA within the kidney sections of patients with HCV-associated glomerulopathies.[98] Two main mechanisms may be involved in the glomerular immune deposit formation. They consist of trapping of circulating antigen-antibody complexes and the in situ formation of ICs within the glomerulus and the deposition of circulating antigen-antibody complexes, preformed outside of the kidney and secondarily deposited in the kidney.[99,100] It seems that ICs containing immunoglobulins, complement and toll like receptor agonist activity may develop local inflammation at the site of IC deposition.[101]

Direct effect of HCV infection may not be considered to be important for kidney damage. It may be an indirect effect involving the cytokine network with a reduced participation of T_H1 type cytokines, endothelial cell activation and an inequality among humoral and cellular response.[97]

Diagnosis of chronic HCV infection in patients with chronic kidney disease can be difficult.[102] The majority of these patients have normal serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values.[103] Some studies revealed that as few as 10% of paients with well-documented HCV infection had ALT or AST values above the upper normal limits.[103] Combination treatment of interferon and RBV is the standard treatment for HCV, but in renal insufficiency RBV has been contraindicated due to fear of side effects.[104]

4. Neurological Disorders

Comparison of the findings from different studies indicates that both peripheral and central nervous system (CNS) disorders have been contemplated as complications of HCV infection.[105,106] For instance in a prospective study of 321 patients with chronic HCV infection, 9% showed sensory peripheral neuropathy.[107] HCV RNA has been detected in peripheral nerve, muscle, brain tissue, and the CSF of patients with and without a broad assortment of nervous system disorders.[108] In the peripheral nervous system, which is the most frequent neurological disorder observed in HCV-infected patients, there is a strong association for vasculitic neuropathy with or without cryoglobulinemia.[109] The CNS can also be affected in patients with HCV infection.[110] It may act as an extrahepatic region for HCV replication[111] however, virus in the CSF may come from plasma.[112] Sacconi et al. described the occurrence of acute disseminated encephalomyelitis as an autoimmune demyelinating disease of the CNS in a patient with HCV infection.[113] Furthermore, HCV-associated CNS vasculitis has been explained in some patients.[105,109]

Encephalomyelitis and myelitis also may occur as a complication of HCV infection.[107,113] It seems that both direct viral invasion and immune-mediated mechanisms have been implicated in the pathogenesis of HCV-associated myelitis and HCV-associated neuropathy.[107,113] Demyelinating polyneuropathy may be related to the effects of HCV on lymphocyte proliferation.[114] Based on published data it was proposed that Guillain-Barré syndrome should be added to the list of autoimmune conditions associated with hepatitis C.[115] This disease culminates in the direct destruction of myelin sheath surrounding the peripheral nerves or of the axon of the nerve.

Different studies revealed that neurologic manifestations of HCV depends on different factors. The most important are a) injury of the vasa nervorum microcirculation by intravascular deposition of cryoglobulins leading to ischemia, and/or by necrotizing vasculitis from longstanding cryoglobulin precipitation, fixation of complement, and activity of rheumatoid factor b)direct vascular injury as a result of deposition of HCV RNA-containing cryoglobulin and direct infection of endothelial or perivascular mononuclear inflammatory cells, C) HCV may cause B-lymphocyte proliferation with formation of

autoantibody and IC culminating in a range of autoimmune diseases, such as neurologic disorders.[106]

5. Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is characterized by hypergammaglobulinemia, autoantibodies and a good response to immunosuppression.[116] According to a number of circulating autoantibodies two main subgroups of autoimmune chronic active hepatitis can be discriminated; AIH type 1 (AIH-1) and type 2 (AIH-2). Some of these antibodies are typical for AIH-1, like: ANA and anti-smooth muscle antibodies, or AIH-2: anti liver/kidney microsomes 1 autoantibodies (LKM1).[117] A number of these autoantibodies may be observed during the course of hepatitis C. Of particular interest are LKM antibodies.[70] The hypothesis of virus induction of AIH put forward by Storch in 1975.[118] Based on this theory, primary or secondary viral infection of lymphocytes as pathogenetical principle of AIH was confirmed.[118] HCV can trigger autoimmune reactions, which may then perpetuate on the basis of a permissive (immuno) genetic background.[119] Vento et al. described a case of AIH-2 that induced by HCV and persisting after viral clearance.[120]

Regarding false positive of anti HCV antibody by ELISA test in autoimmune hepatitis, some patients with AIH may be misdiagnosed as hepatitis C infection. Interferon alpha can exaggerated autoimmune hepatitis and can be dangerous in these cases.[121] It is very important to prevent this misdiagnosis by usage the molecular test for hepatitis C for accurate diagnosis.

6. Dermatological Manifestations

The skin could be a main targeted organ for EM in HCV infected patients.[122] In another word, dermatological manifestations are also part of other extrahepatic disorders associated with HCV infection.[123] This section will discuss about the common skin autoimmune disorders occur during HCV infection.

6.1. Lichen Planus

To date, many studies have been investigating the prevalence of HCV infection in lichen planus (LP) patients and vice versa, but there is no consensus among these *studies.*[124-127] Nontheless, since 1991, more than 80 case reports have supported the association between LP and HCV infection.[128] Based on several studies it could be deduced that HCV is the main correlate of liver disease in patients with LP.[124,125] For example in the cross-sectional study, 19.1% of the LP group was HCV positive, while a much lower prevalence of infection was detected in the control group (3.2%).[126] Interestingly, HCV infection was more common in patients with erosive OLP (58.8%) than in patients with non-erosive OLP (13.2%).[124] Furthermore, HCV-RNA was detected in skin and oral mucous membrane biopsy from LP patients and the association between oral lichen planus (OLP) and HCV were suggested by in situ hybridisation studies.[129] At the current time, the exact mechanism of action of virus in the initiation or progression of disease is not known. However, some studies support the proposition that host immune response rather than viral factors is of greater importance in the development of OLP lesions in HCV infected patients.[130,131] Detection of HCV viral sequences in oral tissue samples[132] and the presence of HCV-specific $CD4^+$ and/or $CD8^+$ T lymphocytes in the oral mucosa of patients with chronic hepatitis C and LP propose that HCV might be implicated in the progression of oral lesions through an immunological pathway.[133,134]

6.2. Vitiligo

Scientists have investigated the possible connection between vitiligo, characterised by the loss of melanocytes from the cutaneous epidermis and HCV infection. Nonetheless, to date, there has been no clear association between HCV infection and this autoimmune disease. It seems that the seroprevalence of HCV in patients with vitiligo is not different from that of a control group, despite case reports showing co-existence of these two diseases.[135-137]

6.3. Psoriasis

There are three important observations that propose a role for HCV in psoriasis. First, the existence of psoriasis in HCV infected patients.[138] Second, detection of anti-HCV antibodies in psoriatic patients.[139] Finally, detection of HCV-RNA by PCR in the skin lesions of psoriatic patients with HCV infection.[140] It is possible that the presence of HCV in the skin could trigger psoriasis through stimulating inflammatory cells to infiltrate skin lesions.[138]

6.4. Alopecia Areata

The potential role of HCV in the pathogenesis of alopecia areata (AA) is unknown.[141] However, It is

reported that this disease is encountered occasionally during the course of chronic hepatitis C[142] especially after alpha-interferon therapy for chronic hepatitis C infection. For example Okanoue et al.[143] followed 677 Japanese HCV infected patients receiving high-dose IFN and detected alopecia in 30%. This condition may complicate assessment of HCV association with AA.

7. Endocrine Disorders

Chronic HCV infection has also been associated with several endocrine disorders. In the following section a literature search was done to review different studies about the association of HCV infection with a number of more common endocrine diseases.

7.1. Autoimmune Thyroid Diseases

Among the most problematic and troublesome endocrine extrahepatic autoimmune manifestations of HCV infection are thyroid disorders. Several investigations propose a potential association between HCV infection and autoimmune thyroiditis (AT).[144-146] For example Ganne-carrie et al. suggested that AT is more frequent in patients with chronic HCV infection than in non-infected patients. In their study, the overall prevalence of thyroid abnormalities was higher in HCV infected patients than in controls (17% vs. 4%).[145] It is also interesting that the prevalence of anti-thyroid antibodies, anti-microsomal or anti-thyroperoxidase antibodies was high in patients with chronic hepatitis C before IFN therapy.[146] The prevalence of abnormal concentrations of anti-thyroid antibodies in patients with chronic HCV differed prominently, ranging from 2% to 48%.[147] Furthermore, a high prevalence of anti-HCV antibodies in patients with anti-thyroid antibodies and in patients with AT has been detected[148], although this finding was not confirmed in all studies.[149] Thyroid dysfunction may present in different forms such as Graves' disease(GD) and Hashimoto's thyroiditis (HT) which are also the most common causes of autoimmune thyroid diseases. There are limited reports of the prevalence and significance of HCV in HT[146,148,150] and GD.[151-153] These studies do not address the exact role of virus in the pathogenesis of GD and HT. Nontheless, two main hypothesis are proposed: primary cytopathic effect of virus and secondary-induced autoimmunity.[154] It has been suggested that virologic features of HCV, may influence progression of thyroid autoimmune disease[155] through mechanisms such as molecular mimicry.[156] It is also possible that HCV per se is not responsible for thyroid autoimmune dysfunction and it does seem to induce nonorgan-specific autoantibodies.[157]

It seems to be sufficient to suggest careful thyroid monitoring during the follow-up of patients with HCV infection. And follow up the patients before, during, and after starting therapy with interferon base.

7.2. Insulin dependent Diabetes Mellitus

There is a hypothesis that diabetic patients may be at increased HCV infection risk.[158] Different epidemiological studies have indicated a relationship between HCV infection and diabetes mellitus, showing that diabetes could represent another EM of HCV infection. Although, in these studies, HCV infection seems to be primarily associated with type 2 diabetes (formerly called non-insulin-dependent diabetes mellitus (NIDDM), and not type 1 diabetes or insulin-dependent *diabetes* mellitus (*IDDM*).[159]

Zein et al. indicated a higher prevalence of diabetes in patients with cirrhosis due to HCV (25%) or alcoholic liver disease (19%) than in patients with cirrhosis due to cholestatic liver disease (1.3% the same as in the general population).[160]

The higher risk of HCV infection may influence the progression of insulin resistance (IR) which is the best predictor for the development of diabetes.[161] It is also suggested that IR may participate in fibrotic progression in chronic HCV infection.[161]

The prevalence of the main markers of pancreatic autoimmunity such as glutamic acid decarboxylase antibodies (GADAbs), tyrosine phosphatase antibodies in patients with chronic hepatitis C, with and without diabetes mellitus were evaluated in different studies. The results indicated that patients with chronic hepatitis C do not have a significantly higher prevalence of pancreatic autoantibodies in comparison with normal population.[162] Nontheless, a number of studies have supported the relationship between HCV infection and the progression of autoimmune diabetes.[163,164]

The exact mechanisms underlying HCV -mediated IDDM still is not well understood and several investigators proposed crossreactive mechanisms to operate in the generation of autoimmunity in HCV infection. This hypothesis is supported by the discovery of remarkable amino acid similarities between HCV and GAD65, protein tyrosine phosphatase islet cell antigen-2 and phogrin.[165]

8. Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a possible autoimmune manifestation of HCV infection.[166] A number of studies have suggested an association between IPF and viruses such as hepatitis C.[167] However, there is still some ambiguity with respect to the association between HCV infection and IPF.[168] The following lines of evidence would provide varying degrees of support for a pathogenetic link between HCV infection and IPF. First, there is a higher frequency of HCV markers in IPF patients such as anti-HCV antibodies, increased prevalence of HCV infection and viral replication[169], second, there is an increased count of lymphocytes and neutrophils in bronchoalveolar lavage fluid in patients with HCV chronic infection.[170] Third, the frequency of pulmonary fibrosis was higher in patients with cryoglobulinemia related to HCV than in croglobulin-negative patients.[171] It is suggested that pulmonary fibrosis in HCV-related cryoglobulinemia is triggered by vascular deposition of circulating HCV-containing ICs.[172] Furthermore, sometimes IPF is aggravated or manifest after treatment with alpha interferon.[173]

9. Other Systemic Autoimmune Diseases

A number of other, mostly immune-mediated conditions may possibly have been related to HCV infection. These include sarcoidosis[174], polychondritis[175], spondylitis ankylosing[176], mooren ulcer[177], autoimmune gastritis[178] and myasthenia gravis.[179] It must be mentioned that the possible relationship between HCV and these diseases have not yet been completely elucidated and new studies must be done to gain a more through understanding of the role of HCV in these disorders.

CONCLUSION

The exact cause(s) of autoimmune diseases are not known. It appears unlikely that a single explanation is sufficient to explain the different phenomena that are observed in autoimmunity. A clear explanation of the agents that may participate to provoke or pave the way for development of autoimmunity is difficult, but there are a number of evidences to suggest viruses as probable etiologic or triggering agents in the pathogenesis of autoimmune disease. Among different viruses HCV infection can present with various autoimmune disorders. Occasionally, these diseases are more important than the hepatic disase itself and are present even in patients with persistantly normal ALT levels. In other words autoimmune diseases could signify the first signal of HCV infection, as many patients exhibit no hepatic symptoms.

Unfortunately, the present data are related only to case reports and it demands for more research in this subject in future.The association between HCV infection and multiple autoimmune conditions which are confirmed during different studies may have important diagnostic and therapeutic implications in the clinical daily practice.

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