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HCV Infection – related autoimmunity

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ABSTRACT

The hepatitis C virus (HCV) infection is currently a worldwide health problem. Hepatitis C virus infection is given special attention because this virus has the propensity to induce various autoimmune phenomena. The observation that autoimmunity and HCV infection are associated is not new. Hepatitis C virus induces nonhepatic autoimmune manifestations only in susceptible individuals, particularly those carrying the HLA-A1, -B8, -DR3 haplotypes or the -DR4 allotype. It is generally difficult to differentiate true autoimmunity from mimicked autoimmunity on a clinical basis. HCV-infected subjects express a high prevalence of a variety of autoantibodies, usually in low titers. The mechanism of production of these antibodies in HCV infection remains obscure; it does not appear to be a nonspecific polyclonal B-cell stimulation. The non-organ-specific antibodies include the antinuclear, smooth muscle, antineutrophil, and liver-kidney microsomal antibodies at low titers. The clinical significance of most of these autoantibodies is not clear. The mechanism by which HCV infection induces anticardiolipin antibodies has not been elucidated. This review focuses on the current understanding and potential clinical implications of autoimmunity that may complicate HCV infection.

Keywords: HCV infection, autoimmunity, autoimmune diseases

Hepatitis C has emerged as a major worldwide public health problem. Susceptibility to infection has been related to immunological disturbances. The HCV is a single-stranded RNA virus of the Flaviviridae family that was identified in 1989 by Choo et al. HCV cannot be cultured. Tests for HCV infection have typically included both serologic assays for antibodies and molecular tests to monitor viral loads. The genome of HCV is very variable, having an extremely high

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spontaneous mutation rate. On the basis of the degree of variability, HCV isolates were classified into genotypes and subtypes. Six genotypes are currently recognized. Several studies have shown that the serological pattern of autoantibodies does not correlate with the particular genotype of HCV (1-3).

Hepatitis C virus is a hepatotropic and lymphotropic virus that has been found to be associated with various diseases and syndromes. Infection with HCV tends to become chronic in most infected individuals, reflecting an inability of the immune system to mount an effective antiviral response. Cytokines play a role in progression to cirrhosis. Elevated serum B-lymphocyte activating factor (BAFF) levels were associated with clinical and laboratory features of autoimmunity, suggesting that BAFF may play a role in HCV-related autoimmunity. Interleukin (IL)-6 is a multifunctional cytokine produced in response to inflammatory stimuli, including IL-1 and TNF-α, with pivotal roles in regulating the host immune response to infection. The rate of progression of parenterally-acquired chronic hepatitis C might be related to an up regulation of TNF-α/Fas pathways. The natural history of chronic HCV infection can vary dramatically between individuals. These individuals are considered chronically infected. The host immune response to HCV infection is composed of both a non-specific immune response, including interferon (IFN) production and natural killer (NK) cell activity, and a virus-specific immune response, including humoral and cellular components. Autoimmunity in HCV infection is not limited to autoantibody seropositivity but embraces the full spectrum of textbook autoimmune disorders. Distribution of the autoantibodies shows no differences between patients infected with different HCV genotypes (4-6).

Hepatitis C virus can induce nonhepatic autoimmune manifestations only in susceptible individuals, particularly those carrying the HLA-A1, -B8, -DR3 or the -DR4. HCV infection has been associated with an oligoarticular or polyarticular nonerosive arthritis that can clinically mimic rheumatoid arthritis. The association of haplotype HLA-B6 and -DR3 mixed cryoglobulinaemia and HCV infection has recently been demonstrated. HLA-DR4 histocompatibility antigen is elevated significantly in HCV infected patients with autoimmune diseases, including rheumatoid arthritis (RA). In theory, patients who are genetically predisposed to autoimmunity develop polyarthritis consistent with a RA diagnosis. The thyroid disease in the case of hepatitis C infection affects women with haplotype HLA-DR3 (7).

The following autoimmune diseases have been described in association with hepatitis C: thyroiditis, autoimmune hepatitis, lichen planus, membranoproliferative glomerulonephritis, Sjögren's syndrome, interstitial lung fibrosis, myasthenia gravis, peripheral neuropathy, celiac sprue, autoimmune thrombocytopenia, hemolytic anemia. The relationship between such autoimmune disorders as autoimmune gastritis and celiac disease and HCV infection has been indicated but remains speculative. However, HCV is not a major causative factor for most autoimmune diseases (8-11). The association between HCV infection, cryoglobulinemia and urticarial vasculitis is well documented. However, urticarial vasculitis is extremely rare in HCV infection when not complicated by cryoglobulinemia. Despite these associations, the etiology of these immune disorders and the possible relationship with HCV remain unclear (12).

Initial results indicated chronic HCV infection in a vast majority of autoimmune diseases, and although the refinement of HCV detection systems has modified these findings, the diversity of HCV-associated hepatic and extrahepatic autoimmunity remains striking (13, 14).

The immune response to HCV may include the development of cryoglobulins, rheumatoid factor, antinuclear antibodies (ANA), anti-cardiolipin (aCL), antithyroid (ATA), anti-liver/kidney/microsomal antibodies (anti-LKM), as well as HCV/anti-HCV immune complex formation and deposition. HCV infection is a significant cause of mixed essential cryoglobulinemia, which may then be complicated by cryoglobulinemic glomerulonephritis, vasculitis, diabetes mellitus, B cell lymphoma, myasthenia gravis, or celiac sprue. It has also been associated with membranous and membranoproliferative glomerulonephritis. Several findings confirm that HCV is the etiologic agent for mixed cryoglobulinemia and that the virus may be involved in the pathogenesis of vasculitis (3, 15-23).

The chronic HCV infection may induce serologic and clinical characteristics that may mimic SLE. For instance, it has been described

that the virus induce arthritis, neuropathy, cytopenias, ANAs, and even anti-dsDNA. Actually the prevalence of chronic HCV infection is greater in SLE patients than in blood donors of the same geographical area (24).

HCV infection tends to induce nonspecific autoimmune reactions, as demonstrated by the high prevalence of various non-organ-specific autoantibodies, usually in low titers. The clinical significance of most of these autoantibodies is not clear.

Several studies have attempted to assess whether HCV infection may be involved in the etiopathogenesis of rheumatic and autoimmune diseases. The results of most of these studies do not support the idea that HCV infection may play a pathogenic role in the development of systemic lupus erythematosus, antiphospholipid syndrome, or vasculitis.

The syndrome in which the link to HCV infection is the strongest is mixed cryoglobulinemia with or without associated vasculitis. A strong association exists between HCV and mixed cryoglobulinemia type II and III, and some studies also suggest an association between type I and HCV, in particular the HCV 2a/c genotype. More evidence that HCV infection causes mixed cryoglobulinemia is that the concentrations of HCV RNA and anti-HCV antibodies are much higher in the cryoprecipitate than in the serum. Many patients with mixed cryoglobulinemia have low serum complement levels.

The most common renal manifestation of HCV infection is membranoproliferative glomerulonephritis (MPGN) with or without mixed cryoglobulinemia. The prevalence is higher in patients with cryoglobulinemia. MPGN is strongly associated with chronic HCV infection and should be suspected when an infected patient develops significant proteinuria, especialy with cryoglobulinemia and hypocomplementemia. Nephrotic-range proteinuria (>3 g/24 hours) in a patient with chronic HCV infection should raise the suspicion of MPGN. Although approximately 80% of patients with HCV infection-related MPGN have no symptoms of liver disease, 50% have histological evidence of cirrhosis. The pathogenesis of HCV infection-related MPGN is probably immune-complex-mediated, as renal biopsies typically demonstrate deposition of IgG, IgM with rheumatoid factor activity, and C3.

There is a strong epidemiologic link between HCV and lymphocytic sialoadenitis, which closely resembles and is possibly related to sialoadenitis associated with idiopathic Sjögren's syndrome. HCV infection-related sialoadenitis may be differentiated from classic Sjögren syndrome by the absence of anti-SSA, anti-SSB antibodies, milder lymphocytic pericapillaritis, and absence of xerostomia and xerophthalmia in about 90% of patients (25).

The pathogenesis of HCV infection-related sialoadenitis is not completely understood. The proposed mechanisms include cross-reactivity between the HCV envelope and host salivary tissue or HCV envelope-mediated immune stimulation that is directed against salivary glands. Viral infection has long been suspected as a potential cause of Sjögren's syndrome and hepatitis C virus has long been suspected as a potential cause of Sjögren's syndrome because several viruses have been incriminated in the etiology of this disease, and a possible relationship between Sjögren's syndrome and hepatitis C virus (HCV) infection was postulated in 1992. This is probably not a true association but hepatitis C leads to a sialoadenitis resembling Sjögren's syndrome . HCV infects and replicates in epithelial cells from salivary glands of patients with SS or chronic sialoadenitis, suggesting that HCV shows a specific tropism for exocrine glands. Chronic HCV infection may mimic the main clinical, histological and immunologic features of primary Sjögren's syndrome and, finally, testing for HCV infection must be performed in patients with Sjögren's syndrome, especially in those patients with evidence of liver involvement or associated cryoglobulinaemia (26, 27).

The HCV-infected patients have various autoantibodies. These antibodies do not affect the outcome and they are not associated with any particular HCV genotype. The mechanism of production of these antibodies in HCV infection remains obscure, it does not appear to be a nonspecific polyclonal B-cell stimulation.

HCV infection-related neuropathies are usually associated with mixed cryoglobulinemia, although a few may be related to polyarteritis nodosa. The neuropathy caused by HCV infection-related polyarteritis nodosa is typically an asymmetrical polyneuritis with prominent motor symptoms (28).

These include vasculitis and cryoglobulinemia, which may cause symptoms similar

to those of Wegener granulomatosis. Thus, one may encounter patients with a suggestive clinical picture and cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) possibly linked to HCV infection rather than to Wegener granulomatosis.

Hepatitis C viral infection is involved in cases of mixed cryoglobulinemia (MC) and porphyria cutanea tarda (PCT). Recent evidence has incriminated HCV in many cases that, in the past, would have been diagnosed as essential MC. This syndrome is characterized by palpable purpura, arthralgias, and general weakness associated with cryoglobulins composed of different immunoglobulins with a monoclonal component (rheumatoid factor) in type II and polyclonal immunoglobulins in type III (20).

Affected patients often present with signs and symptoms of vasculitis involving one or more organ systems. An increasing number of recent reports suggest that cutaneous lesions are a major is a correlation between the presence of palpable purpura, the most frequent cutaneous lesion, and cryoglobulin levels.

An epidemiological association of hepatitis C with lichen planus, neuropathies, and other diseases has been observed, the etiological role and the pathogenic involvement of the hepatitis C infection remains unclear. Furthermore, the question of whether these extrahepatic diseases are autoimmune has not been clarified.

Several findings confirm that HCV is the etiologic agent for MC and that the virus may be involved in the pathogenesis of the vasculitis. By immunohistochemical or *in situ* hybridization methods, HCV infection has been found in association with IgM and IgG in the cutaneous vasculitic lesions of some patients (suggesting a direct role for HCV infection in the development of MC). On the other hand, in systemic vasculitis, as in polyarteritis nodosa, HCV infection does not seem to play an important role.

The prevalence of HCV infection is higher in patients with SLE than in healthy control subjects. Also, the usual clinical manifestations of SLE are different in patients infected with HCV. These infected patients however, had a higher frequency of hepatic involvement, cryoglobulinemia, and low C4 and CH50 levels. The findings also suggest a possible link between HCV infection and SLE. The investigators divided SLE patients with anti-HCV antibodies into three groups: 1) patients with a false-positive result on the antibody assay; 2) patients with HCV infection and true SLE; 3) patients with a lupus-like syndrome that may have been caused by HCV infection. HCV testing should be considered in the diagnosis of systemic lupus erythematosus (SLE), especially in patients without typical SLE manifestations (29).

The association between antiphospholipid syndrome (APS) and HCV infection is still controversial. Most studies reported no clinical manifestations of APS in anticardiolipin antibodies (aCL) and HCV-positive patients before or during the follow-up visit. This finding, along with the absence of lupus anticoagulant (LA) activity, justifies the lack of clinical manifestations of APS in HCV-infected patients. The mechanisms by which HCV infection induces aCL antibodies has not been elucidated. HCV infection has been implicated in the induction of antiphospholipid antibodies (aPL). Most studies agree that the mean levels of IgG and IgM isotypes of these antibodies are low to moderate in patients with HCV infection and significantly lower than those found in patients with APS. A recent report described the development of an APS during the course of HCV infection (30,31). It does not recommend routinely testing for HCV infection in patients with APS. Anticardiolipin antibodies are mostly the natural or nonpathogenic type. Occult HCV infection was present in a significant proportion of patients with aCL positive thrombotic disorders (32).

Existing studies have not answered the question of whether HCV plays a pathogenic role in the development of thyroid dysfunction and autoimmune thyroiditis (33).

The anti-CCP antibodies may be useful in differentiating patients with true rheumatoid arthritis (RA) and those with HCV-associated RA (34). ❑

CONCLUSION

We present a review of the recent literature concerning HCV infection-related autoimmunity.

Prevalence of autoimmune disorders in patients with HCV infection is differentely appreciated. Autoimmune disorders may be due to dysfunction of both cell and humoral immunity.

It is estimated that at least one antibody is present in HCV chronic infected patients

[antinuclear (ANA), rheumatoid factor (RF), anti-liver/kidney/microsomal (anti LKM), antineutrophil cytoplasmic (ANCA), antimitochondrial (AMA), antiphospholipid (aCL), antithyroid (ATA)].

The best demonstrated autoimmunity in HCV infection is related to the deposition of immune complexes in mixed cryoglobulinemia with leukocytoclastic vasculitis: urticaria, arthritis, glomerulonephritis, neuropathy.

Other autoimmune manifestations are not related to immune complexes deposition and vasculitis: Sjögren's syndrome, thyroiditis, porphyria cutanea tarda, lichen planus.

It is crucial to differentiate true autoimmunity from HCV induced or mimicked disease because of the importance of early treatment or both.

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