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TOPIC HIGHLIGHT

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Useful biomarkers for assessment of hepatitis C virus infection-associated autoimmune disorders

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Abstract

During the course of chronic hepatitis C virus (HCV) infection, various extrahepatic manifestations of autoimmune disorders may occur, including arthralgia/arthritis, sicca complex, purpura, cutaneous ulcer, and thyroid dysfunction. In addition, the prevalence of circulating autoantibodies is high among patients with HCV infection. Commonly detected autoantibodies in HCV-infected patients include rheumatoid factor, antinuclear antibody, anti-SSA/anti-SSB antibody, cryoglobulin, antineutrophil cytoplasmic antibody, anti-smooth muscle antibody, anti-liver and anti-thyroid autoantibodies. These autoantibodies may be associated with underlying autoimmune disorders or liver inflammation in HCV infection. A possible reason for antibody production is overactivation and proliferation of B lymphocytes, via the interaction with the surface protein of HCV. Because immunotherapy can cause HCV flare-up or liver damage, overdiagnosis of HCV-related autoimmune symptoms as primary autoimmune disorders should be avoided. This review describes biomarkers that are useful in clinically evaluating autoimmune manifestations and disorders associated with HCV infection.

Key words: Hepatitis C virus; Autoantibody; Autoimmune; Biomarker; Cytokine

Core tip: Patients with hepatitis C virus (HCV) infection may develop a variety of immunological manifestations simulating those observed in patients with autoimmune disorders. Concurrently, many laboratory abnormalities commonly present in autoimmune disorders may be detected. Overactivation and proliferation of B lymphocytes, *via* the interaction with the surface protein of HCV, contributes in part to these abnormalities. These clinical and laboratory findings can potentially mid-lead to the diagnosis of primary autoimmune disorders and result in inappropriate therapy. This review addresses the importance of several clinical and laboratory biomarkers and their usefulness in distinguishing HCV infection-related from primary autoimmune disorder-related etiologies.

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INTRODUCTION

Hepatitis C virus (HCV) infection is a chronic liver disease, and its worldwide prevalence is approximately 2%-3%[1]. The immune system cannot completely clear HCV infection in most affected patients. Thus, a great proportion of chronic HCV-infected patients may end up developing liver cirrhosis or hepatocellular carcinoma. In addition to liver damage, numerous extrahepatic manifestations have been observed among patients with HCV infection. The general symptoms are fever, fatigue, and weakness, and these nonspecific clinical symptoms may be present even when liver function is normal and the virus load is low. Furthermore, autoimmune-related manifestations may develop, including arthritis, arthralgia, dry eye, dry mouth, myalgia, and skin eruption[2,3] (Table 1). Autoimmune diseases such as rheumatoid arthritis (RA), mixed cryoglobulinemia, systemic lupus erythematosus (SLE), Sjögren syndrome (SS) and autoimmune thyroiditis may sometimes co-exist with HCV infection[4-6]. Circulating autoantibodies have been found in about 50% of patients with chronic HCV infection[7]. Antiviral treatment is likely to be beneficial for autoimmune-related manifestations[6]. Clinical manifestations and autoantibody profiles in chronic HCV infection can easily be misdiagnosed as classical autoimmune disorders. For example, polyarthritis or polyarthralgia of small joints, with positive rheumatoid factor (RF), may be present in individuals with HCV-related arthritis and can be confused with RA. In addition, dry eye and dry mouth with positive RF is easily misdiagnosed as primary SS. Moreover, cutaneous manifestations in patients with low titer of antinuclear antibody (ANA) or other autoantibodies, and hypocomplementemia may be over-diagnosed as SLE[8]. Because autoantibodies and autoimmune-like syndromes are frequent in patients with HCV infection, such patients must be carefully evaluated. This review will focus on the usefulness of these biomarkers in clinically evaluating patients with chronic HCV infection.

PATHOGENESIS OF AUTOANTIBODY PRODUCTION

HCV has a single positive-strand RNA genome and the envelope protein E2 on its surface. E2 can interact with CD81 receptors in hepatocytes, B and T lymphocytes, and thyroid cells and induce production of interleukin (IL)-8[9,10]. In addition, the interaction between E2 and CD81 activates B lymphocytes to induce production of numerous immunoglobulins and autoantibodies. These autoantibodies may play roles in the pathogenesis of autoimmune disorders in chronic HCV infection[11]. Cryoglobulin is another autoantibody that can cause immune complex deposition or directly activate neutrophils to attack endothelial cells, through activating the complement system. The consequence of cryoglobulinemia can result in vasculitis-related skin ulcer and immune complex-related glomerulonephropathy[9,12].

Table 1 Extrahepatic autoimmune-related signs and symptoms in patients with chronic hepatitis C virus infection

Clinical manifestations	Arthralgia/myalgia
	Arthritis
	Sicca syndrome
	Purpura
	Lymphadenopathy
	Pulmonary fibrosis
	Raynaud's phenomenon
	Fibromyalgia
	Thyroid dysfunction
Biological manifestations	Cryoglobulinemia
	Autoimmune hemolytic anemia
	Thrombocytopenia
	Hypocomplementemia
Autoantibodies	RF
	ANA
	Anti-SM and Anti-LKM1 antibody
	Anti-thyroglobulin and Anti-TPO antibody
	Anti-CL antibody

RF: Rheumatoid factor; ANA: Anti-nuclear antibody; Anti-SM: Anti-smooth muscle; Anti-LKM1: Anti-liver kidney microsomal type 1; Anti-TPO: Anti-thyroid peroxidase; Anti-CL: Anti-cardiolipin.

The presentation of E2 by antigen-presenting cells can activate helper T lymphocytes to produce pro-inflammatory cytokines and cause systemic inflammation in chronic HCV infection[13]. E2 may also directly interact with T cells to induce amplification of cytotoxic T cells[14,15]. The activation of immune system by virus or viral proteins finally leads to the production of many autoantibodies and clinical manifestations in patients with HCV infection.

RF

The autoantibody RF is directed against the Fc portion of immunoglobulin G (IgG). Patients with RA have a high rate of RF positivity; however, RF positivity is also a feature of other rheumatic diseases, including SLE, SS, mixed connective tissue disease, and polymyositis. Patients with chronic HCV infection may have RA-like polyarthralgia and polyarthritis with low RF titers. There is no difference in the prevalence of HCV infection between RA patients and the general population[16,17]. Nevertheless, RF positivity is more prevalent among patients with HCV infection compared to the general population[18]. RF production has been suggested due to activation of B lymphocytes resulting in antigen-dependent somatic hypermutation[19]. However, direct liver damage is not associated with RF induction in a murine model[20]. The titers of circulating RF have been shown to be associated with viral concentrations and antiviral therapy in patients with chronic HCV infection may reduce RF titers[21-23].

ANA

Antinuclear antibody is a serologic biomarker that is useful for diagnosing patients with autoimmune or connective tissue diseases. ANA titers are low in 15%-30%

Table 2 Organ involvement in mixed cryoglobulinemia related to hepatitis C virus infection

Organ	Manifestations
Skin	Purpura
	Leg ulcers
	Leukocytoclastic vasculitis
Nerve	Mononeuritis multiplex
	Sensory-motor polyneuropathy
	Central nervous system vasculitis
Kidney	Type 1 membranoproliferative glomerulonephritis
	Vasculitis of small renal artery
Gastrointestinal tract	Mesenteric vasculitis
Lung	Interstitial pulmonary fibrosis
Heart	Mitral valvular damage
	Coronary vasculitis
	Pericarditis

of patients with chronic HCV infection, among whom a dense fine speckled pattern is usually noted[24,25]. ANA-positive compared to ANA-negative patients with HCV infection are older and have greater disease activity, higher serum immunoglobulin, and more advanced liver fibrosis[26-28]. HCV-infected patients with a centromeric ANA pattern and those with anticentromere antibodies typically have worse inflammation and hepatic fibrosis as compared with HCV-infected patients without ANA[29]. ANA positivity cannot be used to predict response to antiviral treatment[30,31]; however, individuals with non-1 genotype HCV infection and a high ANA titer (> 1:80) have a more sustained virological response[31]. Interferon and ribavirin therapy is considered appropriate in ANA-positive HCV-infected patients[32]. Inflammatory joint symptoms develop more frequently among ANA-positive patients[26,28].

Cryoglobulin

Cryoglobulins are circulating immunoglobulins that form crystals in serum at temperatures lower than 37 ℃ and re-melt when the temperature is re-warmed. On the basis of immunochemical structure, cryoglobulins are classified into three types[9]. Type I cryoglobulins are single monoclonal immunoglobulins usually related to B-cell proliferative diseases. Type Ⅱ cryoglobulins are mixed immunoglobulins (including monoclonal IgM and polyclonal IgG) and are typically associated with HCV infection. Type Ⅲ cryoglobulins are another type of mixed immunoglobulins containing polyclonal IgM and polyclonal IgG and can be found in numerous autoimmune diseases, including SS, SLE, and RA. Activation of memory B lymphocytes is noted in HCV-infected patients with mixed cryoglobulinemia[33]. Among individuals with HCV-related mixed cryoglobulinemia, nonspecific symptoms are reported, including arthralgia, fever, and weakness with positive RF activity[12,34]. Additional organs, including skin, nerve, kidney, gastrointestinal tract, heart, and lung may be involved during the course of HCV-related mixed cryoglobulinemia[9] (Table 2).

The most common cause of tissue injury in patients with HCV-related mixed cryoglobulinemia is immune-complex-mediated vasculitis. Circulating cryoglobulins can combine with other immunoglobulins and complements to form large immune complexes, and deposition of immune complexes may result in vascular inflammation and damage[35]. HCV-infected patients with mixed cryoglobulinemia have a higher risk of progression of liver cirrhosis[36]. Circulating cryoglobulins should be evaluated when patients with HCV infection have extrahepatic manifestations.

Anti-cyclic citrullinated peptide antibody

Citrulline is the post-translationally modified, deaminated derivative of arginine converted by the enzyme peptidylarginine deiminase (PAD)[37]. In humans, citrullination can occur during the processes of apoptosis, inflammation, and keratinization[38]. Many inflammatory cells express PAD, including RA synovial T and B lymphocytes, macrophages, neutrophils, and synovial fibroblasts[37,39,40]. These autoantigens (citrulline) induce production of anti-cyclic citrullinated peptide (anti-CCP) antibodies and may precede the onset of clinical symptoms of RA by several years. Reports indicate that the anti-CCP antibodies have greater specificity than RF for the diagnosis of RA[41,42]. Interestingly, a certain percentage of patients with HCV-related arthritis are also positive for anti-CCP antibodies[43]. In combination with detailed history taking, clinical manifestations and several other laboratory parameters, anti-CCP antibodies can serve as a useful and reliable laboratory marker for differentiating RA from HCV-related arthritis[44,45].

Anti-SSA/Ro and SSB/La antibody

The prevalence of sicca syndrome including dry eye and dry mouth is about 20% among patients with HCV infection[46]. Many similarities between HCV-related sicca syndrome and primary SS can be observed[47,48]. Patients with HCV-positive SS are usually older, more photosensitive, and more likely to have circulating cryoglobulins than patients with primary SS[49]. Although low titers of ANA and RF are common among patients with sicca syndrome related to HCV infection, SS-related autoantibodies (anti-SSA/SSB antibody) are uncommon. Thus, circulating anti-SSA/SSB antibodies are specific to primary SS and can be used to differentiate it from HCV-related sicca syndrome.

Antiphospholipid antibodies: Anti-cardiolipin antibody IgG and IgM

The antiphospholipid antibodies include anti-cardiolipin (anti-CL) antibody IgG/IgM, lupus anticoagulant, and anti-β2-glycoprotein 1. The clinical symptoms of recurrent thrombus and fetal loss with circulating antiphospholipid antibodies can develop in individuals with antiphospholipid antibody syndrome (APS). The prevalence of anti-CL antibodies is higher in patients with chronic HCV infection compared to the general population; however, titers are lower than those in patients with SLE or APS[2,50,51]. In HCV infection, antiphospholipid antibody is not associated with APS progression or pathogen-

esis[50]. The prevalence of HCV infection is similar among APS patients and the general population[52]. In addition, interferon-α therapy in HCV-infected patients may induce the production of anti-CL antibody[53]. Nevertheless, antiphospholipid antibodies should be assessed when HCV-infected patients have recurrent thrombi, fetal loss or unexplained thrombocytopenia not-related to liver cirrhosis.

Anti-liver autoantibodies: Anti-smooth muscle antibody/ anti-liver kidney microsomal type 1 antibody

Several anti-liver autoantibodies such as anti-smooth muscle (anti-SM), anti-mitochondria, and anti-liver kidney microsomal type 1 (anti-LKM1) antibody can be detected in patients with HCV infection[25,54]. There is a positive correlation between anti-SM antibody levels and liver function[25]; however, this correlation is not seen in patients with hepatitis B virus infection. Anti-LKM1-positive patients with HCV infection have higher levels of circulating immunoglobulins and intrahepatic $CD8^+$ lymphocytes as well as greater activation of autoimmunity[55] and thyroid dysfunction[56]. The presence of anti-liver autoantibodies in HCV-infected patients do not lead to the overlap with autoimmune hepatitis, as determined by typical histological techniques[54]. Aggressive liver biopsy may be considered to confirm histological findings of autoimmune hepatitis when patients with HCV infection have persistent elevation of liver enzymes even after antiviral therapy.

Antineutrophil cytoplasmic antibody

The presentations of antineutrophil cytoplasmic antibody (ANCA) on indirect immunofluorescence include the cytoplasmic and perinuclear patterns (C-ANCA/P-ANCA), which are found in chronic HCV-infected patients with and without mixed cryoglobulinemia[57,58]. The clinical symptoms of ANCA-associated vasculitis include renal, dermatologic, pulmonary, and nervous system manifestations[59]. Extrahepatic manifestations of chronic HCV can be easily confused with ANCA-associated vasculitis, due to similar clinical presentations. Both pulmonary and nervous systems' manifestations are more frequent among individuals with ANCA-associated vasculitis[60]. In addition, ANCA-positive compared to ANCA-negative individuals with HCV infection have a higher prevalence of skin involvement, anemia, abnormal liver function, and elevated α-fetoprotein[61]. Circulating ANCA is not significantly affected by the treatment with interferon-α. Both corticosteroids and cyclophosphamide are considered appropriate for the treatment of HCV-related vasculitis with low levels of viremia[62]. In considering the complexity of vasculitis-associated clinical manifestations, ANCA should be evaluated in patients with chronic HCV infection presenting with refractory skin ulcer or symptoms of systemic vasculitis.

Anti-thyroid autoantibodies: Anti-thyroid peroxidase antibodies, anti-thyroglobulin antibodies

Autoimmune thyroid disease is an organ-specific immune disease with thyroid involvement and is characterized by the presence of circulating anti-thyroid autoantibodies such as anti-thyroid peroxidase (anti-TPO) antibodies, anti-thyroglobulin antibodies, and anti-thyrotrophin receptor antibodies. The prevalence of positive anti-thyroid antibodies, including anti-TPO and anti-thyroglobulin antibodies, is higher among patients with HCV infection compared to the general population[24,63-65]. However, the mechanism that triggers anti-thyroid autoantibody production is unclear. Thyroid dysfunction and anti-thyroid antibodies can be found before and after interferon treatment for chronic HCV infection[66-68]. It is possible that autoantibody production is induced by HCV infection or by an autoimmune phenomenon related to interferon therapy[64,69]. Noticeably, anti-TPO antibody production can be induced by thyroid autoimmunity after interferon-α therapy and may be associated with high concentrations of circulating B-cell-activating factor[70]. A recent study demonstrated that positive circulating anti-TPO antibodies (IgG2 subclass) may be a risk factor for progression of thyroid dysfunction in patients with chronic HCV infection[71]. Such patients should therefore undergo regular monitoring of thyroid function and anti-thyroid autoantibodies, especially during and after interferon-α therapy.

Anti-C-reactive protein antibodies

C-reactive protein (CRP) is produced during the acute phase of inflammation, mainly in response to IL-6[72]. Short-term mortality risk is higher among patients with liver cirrhosis and elevated CRP[73]. Anti-CRP antibodies have been detected in chronic HCV-infected patients with unknown mechanisms. A report suggests that the presence of anti-CRP antibodies is correlated with the presence of RF and cryoglobulinemia[74]. Advanced liver cirrhosis or liver damage and portal inflammation is found in HCV-infected patients with anti-CRP antibodies[74,75]. In general, HCV-infected patients with anti-CRP antibodies do not have noteworthy rheumatic manifestations. Anti-CRP antibody may serve as a useful biomarker of progression of liver cirrhosis and portal inflammation in patients with chronic HCV infection.

Non-autoantibody related biomarkers: Interleukin-6, chemokine ligand 10 and osteopontin

IL-6 is a proinflammatory cytokine and is usually elevated during acute infection and inflammation. The biological activities of IL-6 consist of immune regulation, hematopoiesis, inflammation, and oncogenesis[76,77]. HCV-infected patients with mixed cryoglobulinemia have significantly higher levels of circulating IL-6 as compared with those without mixed cryoglobulinemia and the levels are particularly high among patients accompanied with acute vasculitis[78] or autoimmune thyroiditis[79]. The levels of proinflammatory cytokines other than IL-6, including tumor necrosis factor-α and IL-1β, are also elevated in these patients[78,80].

Chemokine (CXC motif) ligand 10 (CXCL10) is a

Table 3 Immunological manifestations and useful autoantibodies in the patients with chronic hepatitis C virus infection

Clinical symptoms	Useful autoantibodies	Differential diagnosis
Polyarthritis/polyarthralgia	RF, anti-CCP	RA
Sicca (dry eye/dry mouth)	Anti-SSA/SSB	SS
Purpura	Cryoglobulin	Cryoglobulinemic vasculitis
Leg ulcer	ANCA, Cryoglobulin	Systemic vasculitis
Glomerulonephritis	ANCA, Anti-dsDNA	SLE, systemic vasculitis
Cytopenia	Anti-dsDNA	SLE
Hepatitis	Anti-SM, Anti-LKM1	Autoimmune hepatitis
Thrombosis	Anti-CL IgG/M	APS
Depression/fatigue	Anti-thyroglobulin, Anti-TPO	Autoimmune thyroiditis

RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide; ANCA: Anti-neutrophil cytoplasmic antibody; Anti-dsDNA: Anti-double strand DNA; Anti-SM: Anti-smooth muscle; Anti-LKM1: Anti-liver kidney microsomal type 1; Anti-CL: Anti-cardiolipin; Anti-TPO: Anti-thyroid peroxidase; RA: Rheumatoid arthritis; SS: Sjögren syndrome; SLE: Systemic lupus erythematosus; APS: Antiphospholipid antibody syndrome.

chemokine involved in recruiting activated T helper-1 lymphocytes to an inflammation site[81,82]. Increased levels of circulating CXCL10 are observed in patients with chronic HCV infection and are associated with mixed cryoglobulinemia and vasculitis presentations in these patients[83-85]. The increased circulating levels of CXCL10 are also associated with elevated interferon-γ[86]. Cryoglobulin in HCV-infected patients can trigger production of pro-inflammatory cytokines *via* the mechanism of immune-complex formation[9]. There is also evidence indicating that circulating CXCL10 and CXCL11 are elevated among HCV-infected patients with autoimmune thyroiditis[87]. Circulating CXCL10 can thus be used to evaluate the status of cryoglobulinemia and autoimmune thyroiditis during HCV infection.

Osteopontin (OPN) is a phosphorylated acidic arginine-glycine-aspartate-containing (delete a space ahead of containing) glycoprotein and is expressed by various cells, including macrophages, neutrophils, dendritic cells, natural killer cells, T and B lymphocytes[88]. OPN has important roles in promoting inflammation, tissue remodeling, fibrosis, and angiogenesis[89]. Serum OPN levels are positively correlated with the severity of liver damage and cirrhosis in patients with chronic hepatitis[90,91]. OPN levels are significantly elevated in HCV-infected patients with rheumatic manifestations, including sicca syndrome, arthritis, vasculitis, pulmonary fibrosis, and neurologic and renal involvement and those positive for autoantibodies like RF or ANA[91]. Elevated serum OPN has also been observed in patients with HCV infection-associated B-cell non-Hodgkin lymphoma[92]. Thus, circulating OPN is an important biomarker for HCV infection associated autoimmune disorders and lymphomagenesis.

CONCLUSION

Autoimmune-related clinical symptoms and signs can develop during the course of chronic HCV infection. Concurrently, many laboratory abnormalities commonly present in autoimmune disorders may be detected. Abnormal autoimmune-related immune dysregulation of B and T lymphocytes, directly or indirectly mediated through the interaction with virus or viral surface proteins, plays important roles in the progression of autoimmune manifestations associated with HCV infection. These clinical and laboratory findings can potentially mislead to the diagnosis of primary autoimmune disorders and result in inappropriate therapy.

A number of useful biomarkers can be used in the differential diagnosis of autoimmune disorders during the course of HCV, as shown in Table 3. Anti-CCP antibodies are useful for differentiating between RA and HCV-related arthritis. Anti-SSA/SSB antibodies are useful for differentiating between primary SS and HCV-related sicca syndrome. When HCV-infected patients have refractory cutaneous purpura or ulcer, cryoglobulin and ANCA should be determined to evaluate the possibility of cryoglobulinemic vasculitis and systemic vasculitis. Circulating ANCA and anti-dsDNA should be measured in HCV-infected patients with glomerulonephritis, to monitor the development of SLE and systemic vasculitis. Anti-dsDNA should also be checked in HCV-infected patients with unexplained cytopenia and positive ANA. When patients have persistent abnormal liver function but low HCV titers, anti-SM and anti-LKM1 antibodies and when necessary liver biopsy should be evaluated to exclude the possibility of autoimmune hepatitis. Anti-CL antibodies are useful markers when HCV-infected patients have recurrent thrombi or fetal loss with unexplained thrombocytopenia not-related to liver cirrhosis. Regular monitoring of thyroid function and anti-thyroglobulin and anti-TPO antibodies is suggested for chronic HCV-infected patients, especially during interferon-α therapy and those with symptoms of fatigue, depression or symptoms/signs suggesting thyroid dysfunction.

Furthermore, during the course of HCV infection, increased production of cytokines and chemokines related to systemic inflammation can be detected. Because immunotherapy can cause changes of these inflammatory mediators as well as induce HCV flares or liver damage, this factor has to be considered when evaluating the autoimmune status of HCV-infected patients. Collectively, adequate evaluation of circulating autoantibodies, cytokines and chemokines is sometimes necessary when HCV-infected patients have extrahepatic manifestations or in considering the possibility of co-existing autoim-

mune disorders or even malignancy.

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