Original Article

Autoantibody Signature In Chronic Viral Hepatitis C And B

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Abstract

Background: Testing for liver-related autoantibodies should be included in the workup of patients with hepatitis or cholestasis of unknown origin. Although most of these autoantibodies are not disease specific, their determination is a prerequisite to diagnose autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC), and they are components of the diagnostic scoring system in these diseases. Chronic hepatitis C represents an important cause of morbidity and mortality because of it is widespread prevalence. liver involvement is only one side of the coin, as extra hepatic manifestations may complicate the course of the disease in over 70% of hepatitis C virus (HCV) infected individuals. Antibodies are a vital part of the immune response for recognition and elimination of invading organisms. However, when the immune system is dysfunctional, it can develop antibodies that react to self. The development of autoantibodies (auto-Abs) generally occurs during auto-immune disease, but their induction can also be a consequence of a chronic infection in susceptible individuals

Keywords: Chronic Viral Hepatitis C And B, Autoantibody

INTRODUCTION

Testing for liver-related autoantibodies should be included in the workup of patients with hepatitis or cholestasis of unknown origin. Although most of these autoantibodies are not disease specific, their determination is a prerequisite to diagnose autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC), and they are components of the diagnostic scoring system in these diseases (1)

Chronic hepatitis C infection:

Chronic hepatitis C represents an important cause of morbidity and mortality because of it is wide spread prevalence. liver involvement is only one side of the coin, as extra hepatic manifestations may complicate the course of the disease in over 70% of hepatitis C virus (HCV) infected individuals (2)

A wide variety of extra hepatic manifestations have been described in association with hepatitis C virus infections, including lympho proliferative disorders, cardiovascular disease, metabolic derangments, renal involvement, dermatologic manifestation and autoimmune diseases(3)

Antibodies are a vital part of the immune response for recognition and elimination of invading organisms. However, when the immune system is dysfunctional, it can develop antibodies that react to self. The development of autoantibodies (auto-Abs) generally occurs during auto-immune disease, but their induction can also be a consequence of a chronic infection in susceptible individuals (4)

A number of auto-Abs with different specificities have been identified. As some auto-Abs occurrence in plasma is disease specific, they can be used in the diagnosis and classification of autoimmune diseases (5)

The hepatitis C virus (HCV) infection causes liver damage by inducing cirrhosis and can also lead to hepatocellular carcinoma. Studies have demonstrated that the virus may be involved in loss of tolerance to self-antigens and thereby promotion

of auto-Ab production (4)

Various mechanisms for the production of autoantibodies in patients with HCV-related CLD have been proposed. Molecular mimicry between a component of a virus and a "self" protein may account for the production of autoantibodies in chronic HCV infection (6)

A sequence homology between the HCV poly protein and cytochrome p450 2D6 (CYP 2D6), which was identified as the antigenic target of antibodies to liver-kidney microsome type 1 (anti-LKM1), was previously reported .The reactivity against the viral protein induces the production of anti-LKM1 in HCV related CLD (7)

Polyclonal B-cell activation by persistent HCV infection has been proposed as another mechanism for the production of autoantibodies .B-cell proliferation seems to be essential for the development of autoimmune disorders. Genetic predisposition is also strongly related to the presence of autoantibodies in chronic HCV infection (3)

In particular, non-organ specific auto-Abs (NOSAs) including smooth muscle antibodies (SMA), anti-nuclear antibodies (ANA) and liver/ kidney microsomal-1 (LKM-1) antibodies are common and frequently found in sera of patients with chronic HCV (CHC) (8)

Some autoantibodies in chronic HCV infection have biochemical, histological, or genetic characteristics while other autoantibodies may predict the response to antiviral treatments, concomitant disorders, or prognosis in patients with HCV-related CLD (7)

Non organ specific autoantibodies (NOSA) in HCV-infected patients correlate with the severity of necro inflammation, fibrosis development, markers of liver damage: aspartate transaminase (AST) and alanine transaminase (ALT), alkaline phosphatase (AP) and levels of IgG (4)

Clinical and laboratory features of CHC can sometimes lead to a mistaken diagnosis of autoimmune hepatitis (AIH). AIH is characterized by a liver-specific autoimmune response, infiltrating immune cells, auto Abs in circulation, elevated immunoglobulin and serum transaminase level, and a favorable response to immunosuppression (9)

Chronic hepatitis C (CHC) patients with auto-Abs and long-standing disease had liver damage at the same level as the AIH cases. The appearance of auto-Ab positive CHC patients can show such high similarity to AIH that they can be misdiagnosed. This is especially the case for patients with extra hepatic symptoms (10)

The existence of detectable hepatitis C viral load with or without circulating antibodies specific to HCV can often be used to differentiate CHC from AIH. These two conditions, CHC and AIH involve different management strategies; chronic HCV infection has until recently often been treated with interferon-α (IFN-α) which can provoke liver auto-immunity (11)

The HCV infection can, in a few cases, develop into AIH, suggesting that the liver cells are damaged not only by the infection but also by an immune reaction to self. AIH on the other hand requires immunosuppression, a treatment that could induce viral replication in cases of co-infection (4)

Chronic hepatitis B infection:

Host immune responses induced by hepatitis B virus (HBV) infection substantially drive disease progression and significantly influence the efficacy of antiviral treatments in HBV-infected individuals. Some studies have shown that non-virus specific inflammatory cells within the liver may also actively participate in HBV associated liver pathogenesis (12)

Hepatitis B virus (HBV) infection has been presented with circulating non-organ-specific autoantibodies associated to a variety of immunopathological manifestations. This included smooth muscle antibody, ANA and anti-LKM1. The serologic autoimmune phenomenon was also reported in patients who had received treatment with interferon (13)

Some reports demonstrate that the presence of these autoantibodies is possibly associated with more severe liver damage and cirrhosis, and might be negative prognostic factors for treatment response (14). Irrespective of whether the virus-induced production of autoantibodies is an epiphenomenon during the progression of viral hepatitis or a contributor to hepatocellular damage, the putative mechanisms for producing autoantibodies in viral hepatitis are considered to be mainly attributable to molecular mimicry or polyclonal B cell activation (15)

Several observations in many cases suggest that an extractable nuclear antigen antibody profile was prevalent in patients with chronic hepatitis B, and it was strongly correlated with both compensated and decompensated cirrhosis. Liver biopsy was carried out showing signs of severe fragmented necrosis and fibrogenesis, and lymphocyte and plasmocyte infiltrations were observed (16)

The appearance of autoantibodies in the pathogenesis of chronic HBV infection is also one of the manifestations of autoimmune disorders. In general, the human immune system starts to recognize antigens and gradually produces increasing affinity of the relevant antibody after antigen exposure (17). T follicular helper cells can be over the augmented capacity to help B cells for antibody secretion, which can induce liver inflammation and the production of antibodies in extra hepatic manifestations (18)

Patients with chronic HBV infections tend to develop an activated humoral response with type 2 T helper (Th2) cells producing IL-4, IL-5, and IL-10, which promote antibody production rather than viral clearance (14)

Interestingly, in terms of the correlation between autoantibodies and cirrhosis in CHB, the positivity of NOSA such as ANA was more prevalent in non-cirrhosis patients than in cirrhosis patients. When cirrhosis progressively develops, more and more parenchymal tissues are replaced by fibrotic tissue (17). In this setting, the specific auto antigens that are involved in the pathogenesis of AIH and PBC become deficient or less accessible to the immune system. Because autoantibody production is generally "auto antigen-driven", non-cirrhosis patients may produce more ANA than those with cirrhosis or later-stage chronic

hepatic diseases (14)

Non organ specific autoantibodies (NOSA):

Antinuclear Antibodies

Antinuclear antibodies were the first autoantibodies to be associated with AIH. However, they lack disease specificity. About 50–75% of AIH patients are ANA-positive (with or without anti-SMA). ANA can also be detected in healthy persons or patients with other liver diseases such as fatty liver disease, drug induced liver injury (DILI) disease, or viral hepatitis (19)

The pattern of ANA in AIH often is speckled or homogenous. ANA in AIH are directed against several antigens such as chromatin, histones, centromere, double and single stranded deoxyribonucleic acid (DNA), cyclin A, rib nucleoproteins or other nuclear antigens (20). A biochemical differentiation of these antigens is not recommended because they have not been associated with a certain clinical course or a higher diagnostic specificity for AIH. It is important to acknowledge that up to 20% of AIH patients may display anti-dsDNA antibodies; this may cause confusion with the diagnosis of systemic lupus erythematodes, which has to be ruled out in patients with respective clinical findings (21).

Ant smooth Muscle Antibodies

Similar to ANA, anti-SMA has been associated with AIH since the early days of the clinical definition of AIH. They are also not disease specific and can be detected in various liver diseases such as fatty liver disease (22). Anti-SMA is present in about 50% of patients with type I AIH and can be the only detectable autoantibody. In IFT, anti-SMA reacts with the smooth muscles of the lamina propria and muscularis mucosae of the stomach or arterial walls of the liver. On kidney tissue, anti-SMA show different staining patterns: the vascular/glomerular and the vascular/ glomerular/tubular (VGT) patterns are more specific for AIH than the vascular (V) pattern. The VGT pattern can be confirmed by IFT performed on fibroblasts or vascular smooth muscle cells (VSM47) (23)

Anti-Liver–Kidney Microsomal Antibodies (Anti-LKM)

Anti-LKM-1, but also anti-LKM-3 is defining type 2 AIH. In IFT, anti-LKM stain, the cytoplasm of hepatocytes and the proximal, larger renal tubuli, but not parietal cells of the stomach. The auto antigen that is recognized by anti-LKM-1 in AIH is cytochrome P450 (CYP) 2D6 (24)

Anti-LKM-1 is not AIH-specific and can also be found in patients with chronic viral hepatitis C (HCV). However, the epitopes that are targeted by anti-LKM-1 in HCV-infected patients differ from those in patients with AIH (19)

In contrast to anti-LKM-1, anti-LKM-2 targets a different isoform of the cytochrome P 450, namely CYP 2C9. Anti-LKM-3 can be found in few patients with AIH, but also in HCV and viral hepatitis D. They recognize members of the uridine glycuronosyl transferases family 1(25)

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