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Increased serum aminotransferases associated with anti-mitochondrial antibodies in systemic lupus erythematosus patients with autoimmune liver disease

Cheng-Hai Li [a], Po-Shi Xu [b], Chun-Yan Wang [c], Guo-Lin Zou [a,d,*]

[a] *Department of Biochemistry and Molecular Biology, College of Life Sciences, Wuhan University, Wuhan 430072, PR China*
[b] *Central Clinical Laboratory for Rheumatology and Immunology, the People's Hospital of Henan Province, Zhengzhou 450003, PR China*
[c] *Department of Nephrology and Rheumatology, the First Affiliated Hospital, Zhengzhou University, Zhengzhou 450052, PR China*
[d] *The National Key Laboratory of Virology, College of Life Sciences, Wuhan University, Wuhan 430072, PR China*

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Abstract

Background: Serum aminotransferase activities are increased in many liver diseases, but the causes for the elevation might be difficult to determine. Whether the elevation of aminotransferases correlates with anti-mitochondrial antibodies (AMA) in systemic lupus erythematosus (SLE) patients with autoimmune liver disease deserves further consideration.
Methods: A meticulous review was done in a large SLE cohort searching for laboratory features of the presence of AMA. Forty-eight hospitalized SLE patients with AMA and 60 randomly selected SLE patients without AMA as a matched case control were enrolled into the retrospective study. Laboratory data were collected, analyzed and compared in SLE patients with and without AMA.
Results: Serum activities of aminotransferases were significantly increased in the 48 SLE patients with AMA compared with the 60 subjects without AMA. Meanwhile, we found a positive correlation between serum AMA titers and serum aminotransferase activities.
Conclusion: Although much remains to be learned about the pathogenesis of autoimmune liver disease associated with AMA, it is possible to suggest that AMA might contribute to the elevation of aminotransferases in SLE patients with the progressive disease.

Keywords: Systemic lupus erythematosus (SLE); Anti-mitochondrial antibodies (AMA); Alanine aminotransferase (ALT); Aspartate aminotransferase (AST)

1. Introduction

Systemic lupus erythematosus (SLE) is a common autoimmune disease characterized by the involvement of various organ systems and clinical manifestations are intricate and variable with the progression of disease. Liver involvement in the disease process of SLE is more often due to the known or unknown etiologies. It is important to note that abnormal liver tests manifested by an increase of liver aminotransferases in sera are frequently encountered in 25–50% of SLE patients [1,2]. Episodes of increased liver enzymes, especially for aminotransferases, are usually associated with episodes of the active lupus with liver involvement. However, the causes for these may be difficult to determine. Likewise, it is not completely clear whether it is drug-induced hepatitis or the result of other causes, such as viral hepatitis, autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), granulomatous hepatitis and alcohol abuse. Serum aminotransferases are sensitive indicators of

Abbreviations: ACR, American College of Rheumatology; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; AMA, anti-mitochondrial antibodies; PDC, pyruvate dehydrogenase complex; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; LD, lactate dehydrogenase; CK, creatinine kinase; T-BIL, total bilirubin; IIF, indirect immunofluorescence; ELISA, enzyme linked immunosorbent assay; IB, immunoblotting.

* Corresponding author. The National Key Laboratory of Virology, College of Life Sciences, Wuhan University, Wuhan 430072, PR China. Tel.: +86 27 87645674; fax: +86 27 68752560.
E-mail address: guolinzou@hotmail.com (G.-L. Zou).

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hepatocellular damage [3] and may be helpful in recognizing hepatocellular diseases [4], because the most common causes are given in such episodes in disease progression.

Anti-mitochondrial antibodies (AMA) form a heterogeneous group of antibodies, which target antigens are located mostly in the inner mitochondrial membrane of eukaryotic cells. The application of molecular biology in clinical medicine provides a clearer understanding of the AMA and has confirmed a cluster of mitochondrial autoantigens. As known, mitochondrial autoantigens are belong to a family of the 2-oxo acid dehydrogenase complexes (OADC) that include the E2 subunits of pyruvate dehydrogenase complex (PDC), branched-chain 2-oxo-acid dehydrogenase complex, and 2-oxo glutarate dehydrogenase complex [5,6]. To date, it is widely accepted that AMA is a sensitive serological hallmark of PBC, a chronic cholestatic liver disease of adults. Indeed, the pathogenetic significance and possible functional consequences of AMA are not fully clear and deserves further studies.

In clinical practice, AMA might have no diagnostic value for SLE but are present with low prevalence in such patients with variant form of autoimmune liver disease. Clinical expressions of SLE are highly variable in different geographic areas probably ascribable to both genetic and environmental factors. For these reasons, we retrospectively reviewed our experience and selected SLE patients as the object of this research in order to assess clinical and laboratory features in 2 patient groups, one with autoimmune liver disease associated with AMA and another with SLE alone, and to definitively establish whether this disease feature correlates with AMA. Based on the large number of this SLE series, the objective of our work is also to provide information about clinical outcomes of SLE patients in the AMA positive group.

2. Materials and methods

2.1. Patients and samples

A retrospective review of medical records was performed on 365 hospitalized patients with SLE searching for clinical and laboratory data of serological positive AMA by indirect immunofluorescence (IIF) from February 2003 to February 2005 in the Department of Nephrology and Rheumatology, the First Affiliated Hospital, Zhengzhou University and the Department of Rheumatology and Immunology, the People's Hospital of Henan Province. All patients with SLE were diagnosed, treated and gave informed consent for different investigations during the hospitalization. Each met the criteria for SLE of the American College of Rheumatology (ACR) [7] and the disease activity of each subject was previously assessed and quantified by the SLE disease activity index (SLEDAI) [8]. Information on each individual is stored in computer data base files and is available on detailed clinical records. At presentation, 56 of 365 patients (15.3%) were positive for AMA, of which 8 out of 56 individuals with known or suspected hepatopathy as the probable causes of hepatic dysfunction, such as viral hepatitis, AIH, drug- or toxin-induced hepatitis, fatty liver or hyperlipemia, Chinese herbs treatments and alcohol abuse, had been carefully excluded and the remaining 48 were enrolled into the retrospective study. Of these, 41 were women and 7 were men, mean age 28.3 ± 7.8 y, mean disease course 5.8 ± 2.7 y and mean SLEDAI score 14.9 ± 4.4, all of whom were admitted to hospital with the onset of clinical manifestations of active lupus. At the same time, 60 SLE patients with the active disease without AMA were randomly selected as a matched case control. For this cohort of SLE patients, clinical and laboratory features could only be attributed to SLE for the purpose of comparing with the AMA-positive patient cohort. There was no significant difference in SLE patients with and without AMA in gender, age and disease course.

To be considered, among the 48 SLE patients with AMA, each individual had to have at least 3 biochemistry profiles or liver function panels during the hospitalization. Meanwhile, at least 3 serum samples were sequentially collected at that time: at the onset of hospitalization or at relapse of disease (before treatment), during the hospitalization and at the end of hospitalization (after treatment), and stored at -70 °C until the assays were conducted. All the 48 patients were negative for smooth muscle antibodies, type 1 liver–kidney microsomal antibodies, and autoantibodies to soluble liver proteins. Immunoblotting (IB) analysis for M_2 (PDC), M_4 (sulfite oxidase) and M_9 (glycogen phosphorylase) and enzyme-linked immunosorbent assay (ELISA) for anti-M_2 were previously performed. Were there no laboratory data integrity of AMA, the testing of stored serum for AMA was made a judgment anew.

The majority of patients with SLE in the 2 groups progressed to their disease on a background of nonspecific symptoms such as fever, malaise, weight loss, and new rash, which just reflect constitutional upset. Four patients in the AMA-positive group present with abdominal pain, 5 with arthralgia and 11 with muscle pains. For liver involvement in the same AMA-positive group, 8 patients manifested by hepatomegaly, 6 by splenomegaly, 5 by jaundice and 3 by ascites. Therapeutically, in brief, all these SLE patients in the 2 groups were treated with conventional corticosteroids with or without immunosuppressive drugs. In addition to conventional treatment for the improvement of liver biochemistries, all these patients in the AMA-positive group received ursodeoxycholic acid at the daily dosage of 10–15 mg/kg body weight for the inhibition of mitochondrial dysfunction caused by exposure to hydrophobic bile acids. Long- or short-term application and effectiveness of treatment with ursodeoxycholic acid was on the condition of clinical and biochemical evaluation of the disease activity.