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CASE REPORT

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A case of rheumatoid arthritis that developed autoimmune hepatitis associated with anti-Golgi complex antibody

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Abstract A 50-year-old woman, who had been diagnosed as having rheumatoid arthritis (RA) 7 months earlier, was admitted to our hospital because of liver dysfunction. Her laboratory data and histological findings satisfied the criteria for autoimmune hepatitis (AIH) as revised by the International AIH Group. Laboratory examinations (indirect immunofluorescence and immunoblotting analyses) revealed that anti-Golgi complex antibodies (AGA) were positive in her serum. AGA are thought to be closely associated with AIH and/or liver dysfunction according to several reports.

Key words Autoantibody · Autoimmune hepatitis (AIH) · Golgi complex · Liver dysfunction

Introduction

Autoimmune hepatitis (AIH) is a disease characterized by hypergammaglobulinemia, circulating autoantibodies, and an immunogenetic background. It is a disorder of unknown etiology which demonstrates a progressive destruction of hepatic cells, often progressing to cirrhosis.[1,2] Autoantibodies, such as antinuclear antibodies, antismooth muscle antibodies, antisoluble liver antigen antibodies (SLA), and antiliver–kidney microsome antibodies (LKM) are associated with AIH. Recently, a number of studies have reported that anti-Golgi complex antibodies (AGA) are associated with AIH and/or liver dysfunction.[3–6] We present a case of rheumatoid arthritis (RA) complicated by AIH associated with AGA.

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Case report

A 50-year-old woman was admitted to our hospital in December 1997 because of liver dysfunction. She had been diagnosed as having RA in May 1997, according to the criteria for RA of the American College of Rheumatology.[7] Since then, she had been treated with methylprednisolone (4 mg/day), methotrexate (MTX) (5 mg/week), and actarit (300 mg/day).[8,9] In November 1997, she began to lose her appetite and her laboratory data showed elevated levels of serum aspartate aminotransferase (AST) (323 IU/ml) and alanine aminotransferase (ALT) (868 IU/ml). Despite the cessation of MTX and actarit, her liver dysfunction continued. She was not alcoholic and had no history of blood transfusion. Her father had been affected by Sjögren's syndrome, but no other family members had experienced liver disease.

On admission, her height was 154.0 cm and her weight 46.0 kg. She was fully consciousness. Her blood pressure was 122/84 mmHg, and her heart rate was 96/min. Her body temperature was 35.9°C. Her conjunctivas were neither anemic nor jaundiced. Her cervical lymph nodes were not palpable, and her heart and respiratory sounds were normal. The liver and spleen were not palpable. The right proximal interphalangeal joints were swollen, and the bilateral wrists and the left knee were tender to the touch. She did not suffer from dry eyes dry mouth.

Laboratory test findings on admission showed the following data: white blood cell count, 6100/μl; hemoglobin, 13.5 g/dl; platelet count, 51.0×10^4/μl; AST, 262 IU/l; ALT, 654; lactate dehydrogenase, 282 (normal range 100–225); total bilirubin, 2.1 mg/dl; direct bilirubin, 0.5; alkaline phosphatase, 294 IU/l (normal 100–340); leucine aminopeptidase (LAP), 296 (normal 70–200); γ-glutamyl transpeptidase (γ-GTP), 182 (normal 7–40); total protein, 8.1 g/dl; albumin, 4.1; cholinesterase 876 U/l (normal 1000–2400); blood urea

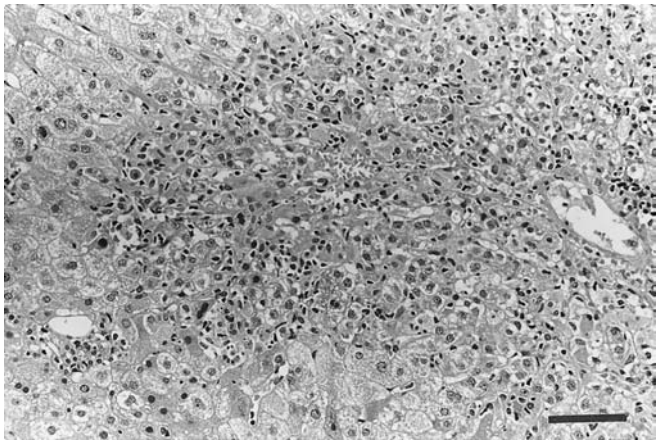

Fig. 1. Histological examination showed zonal necrosis around the central vein as well as spotty necrosis throughout the lobule. They were infiltrated by lymphocytes, plasma cells, neutrophils, and pigmented histiocytes. An apoptotic body is seen to the left. *Bar* 100 μm

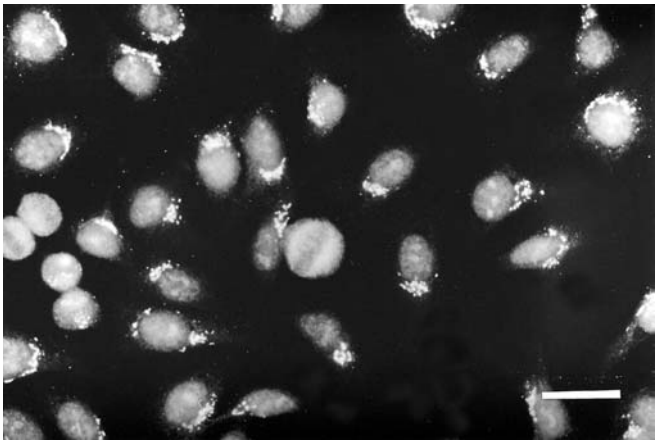

Fig. 2. Indirect immunofluorescence using HEp-2 cells showed positive granular staining mainly on one side of the nuclear membrane, thus indicating the presence of AGA. *Bar* 10 μm

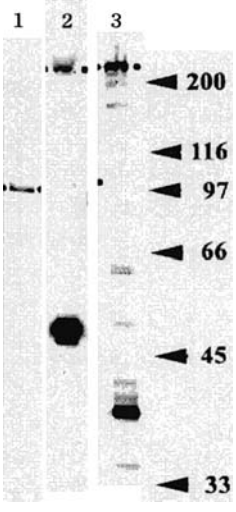

Fig. 3. An immunoblot analysis of the patient's serum revealed reactivities with several antigens of the Golgi complex, especially with a 245-kd protein (lane 3). The positive control sera showed reactivity with golgin-97 (lane 1) and golgin-245 (lane 2)

nitrogen, 12 mg/dl; creatinine, 0.6; sodium, 142 mEq/l; potassium, 3.8; chloride, 105; C-reactive protein, <0.3 mg/dl; rheumatoid factor, 218 U/ml; serum immunoglobulin (Ig) G, 2447 mg/dl; IgA, 379; IgM, 346. The coagulation tests were within normal limits. Antimitochondrial antibodies (AMA), as examined by the indirect immunofluorescence method, and anti-M_2 antibodies, as measured by ELISA, were both negative.

Serological markers for hepatitis viruses such as antihepatitis A IgM antibodies, hepatitis B surface antigen, hepatitis B core antigen, and anti-hepatitis C virus antibodies were all negative. Abdominal ultrasonography, computed tomographic scan, and magnetic resonance imaging detected no abnormality in the liver except for mild hepatomegaly. A histological examination of the liver revealed zonal necrosis around the central vein, and spotty necroses with lymphoplasmacytic infiltration and apoptotic bodies (Fig. 1). There was no fibrosis. These findings were consistent with those to be expected from a case of acute hepatitis.

Therefore, this patient was tentatively diagnosed as having acute hepatitis of unknown origin. As there was no evidence of viral hepatitis, the remaining possible causes of hepatitis were drugs or antoimmunity. Even after discontinuing both MTX and actarit, the state of liver dysfunction continued. In addition, a lymphocyte-stimulating test using these drugs revealed a negative finding. Therefore, additional laboratory examinations were performed. Antinuclear antibodies (ANA) were positive at a titer of 1:40, with a speckled pattern. Antismooth muscle antibodies were at a titer of 1:20 (normal < 1:20), and anti-LKM1 antibodies were negative. Antibodies to RNP, Sm, SS-A, SS-B, and Scl-70 were all negative. An indirect immunofluorescence analysis using HEp-2 cells as a substrate showed a staining pattern of the Golgi complex in the cytoplasm (Fig. 2). There were no staining patterns indicating the presence of anti-LKM1, anti-nuclear envelope, or antimultiple nuclear dot antibodies. Immunoblotting (Fig. 3) using the patient's serum confirmed the presence of anti-Golgi complex antibodies (AGA).

The patient was given a diagnosis of AIH based on the seropositivity for ANA, increased serum levels of aminotransferase and IgG, negative test results for virus infection, and histological findings of the liver biopsy specimen consistent with acute hepatitis. The γ-GTP and LAP levels were moderately elevated, but primary biliary cirrohosis was not involved because (1) AMA, anti-M2 antibodies, and anticentromere antibodies were all negative, and (2) no findings of chronic nonsuppurative destructive cholangitis were recognized in the liver specimen. According to the revised scoring system by the International AIH Group,[10] the score of this particular case was 17 points, which satisfied the criteria of definite AIH. Some articles have reported that AGA are associated with AIH and/or liver dysfunction.

Treatment was with 100 ml/day intravenously of a glycyrrhizin preparation (containing 120 mg glycyrrhizin, 60 mg cystein, and 1200 mg aminoacetic acid). As the high tran-

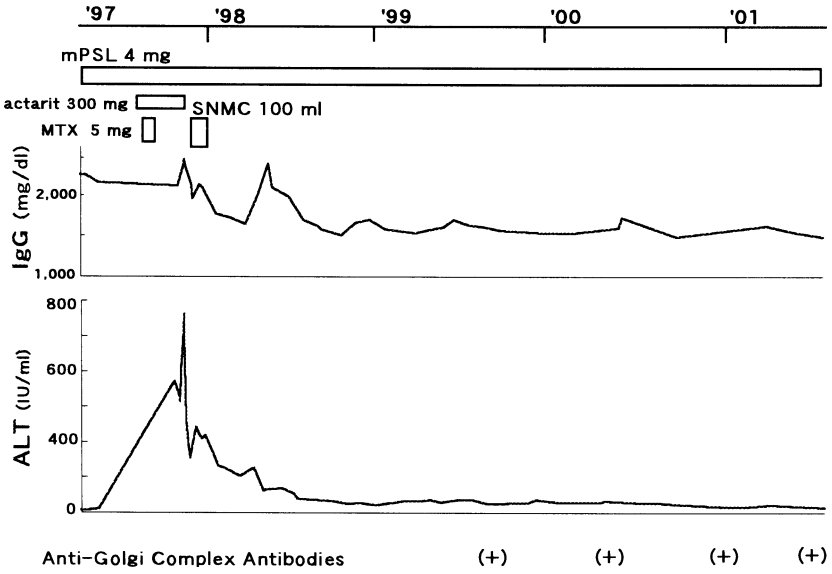

Fig. 4. Clinical course of this patient. *SNMC*, glycyrrhizin preparation; *mPSL*, methylprednisolone; *MTX*, methotrexate. SNMC (100 ml/day) was administered on admission

saminase levels responded well to this treatment (Fig. 4), the dosage of methylprednisolone (4 mg/day) which had previously been administered for the treatment of RA was not increased. The patient's ALT level showed an initial decrease from 1125 to 306 IU/ml after the administration of the glycyrrhizin preparation, and it eventually dropped to less than 50 IU/ml 11 months later (Fig. 4). She was discharged on the 24th day after admission.

Discussion

The Golgi complex plays an important role in a variety of cellular activities such as the assembly of secretory proteins, the formation of lysosomes, the differentiation of membranous organelles, phospholipid synthesis, glycosylation, and sulphation.[11]

There are various autoantigens in the Golgi complex, and their molecular weights range from 35 kd to 376 kd.[12–16] In this case, an immunoblotting analysis revealed serum reactivity to several Golgi complex antigens, and especially to a 245-kd protein (see Fig. 3). This molecule had been cloned and designated as golgin-245 by Fritzler et al.[17] This Golgi complex autoantigen is known to bear structural similarities to the granin family of proteins. Subsequently, another study group has identified a 230-kd Golgi complex autoantigen that is related to golgin-245.[18] Antibodies to 97-kd Golgi complex antigen (golgin-97) have been reported to be associated with secondary Sjögren's syndrome (SjS).[14] In this case, no such autoantibodies were detected (see Fig. 3).

AGA was first identified in the serum of a SjS patient with lymphoma in 1982.[19] AGA are thought to be relatively rare autoantibodies, as previously reported by Taniai et al.,[6] where AGA was detected in only 10 cases (RA, 3 cases; AIH + RA, 1 case; RA + systemic sclerosis, 1 case; systemic lupus erythematosus (SLE), 1 case; fever of unknown origin, 1 case; acute glomerulonephritis, 1 case; transient granulocytopenia, 1 case; monoarthritis, 1 case) out of 8070 serum samples submitted to a commercial reference laboratory for autoantibody testing. Fritzler et al.[3] have identified eight patients (SLE, 1 case; SjS, 1 case; noninfectious hepatitis, 1 case) as being AGA-positive in 3600 subjects. Among these eight, five had liver dysfunction. Taniai et al.[6] have reported an AGA-positive case of AIH which was subsequently complicated by RA. Hong et al.[4] reported two AGA-positive RA cases presenting with mild liver dysfunction. Yang et al.[5] reviewed the characteristics of 13 AGA-positive patients with connective tissue diseases. Among these, eight (62%) had a liver dysfunction as indicated by raised liver enzyme levels. Summarizing these previous reports, AGA can be thought to be closely associated with AIH and/or liver dysfunction.

However, to date, only two AGA-positive cases (the present case and the case of Taniai et al.) have been associated with AIH. The common characteristics of these two cases were as follows: (a) they were complicated by RA; (b) a histological examination revealed findings of acute hepatitis; (c) glycyrrhizin was effective for the treatment of AIH, and corticosteroid was virtually unnecessary (cf. prednisolone at an initial dose of 30–40 mg/day is usually administered for the treatment of AIH). Differences between the two cases were as follows: (a) onset of RA preceded that of AIH in the present case; (b) the antismooth muscles antibodies were negative in the present case.

The further accumulation of similar cases will allow us to elucidate the characteristics of AIH associated with AGA more precisely.

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