A Patient with Primary Biliary Cirrhosis Complicated with Slowly Progressive Insulin-dependent Diabetes Mellitus


Abstract

We report a case of primary biliary cirrhosis (PBC) complicated by slowly progressive insulin-dependent diabetes mellitus (SPIDDM). A 67-year-old woman was diagnosed as having PBC based on clinical manifestations and a positive result of anti-mitochondrial antibody. Furthermore, SPIDDM was diagnosed by her clinical course and a positive result of anti-glutamic acid decarboxylase antibody. Both PBC and SPIDDM are considered to be autoimmune diseases. However, the coexistence of PBC and SPIDDM is extremely rare. Liver cirrhosis sometimes accompanies hyperglycemia. When the etiology of liver cirrhosis is an autoimmune disorder such as PBC, SPIDDM should be considered as a cause of hyperglycemia.

Case Report

A 67-year-old woman patient had been followed at our outpatient department for diabetes mellitus (DM) and non-B-non-C liver cirrhosis for 7 years. She had no significant past history except for her blindness due to infectious disease at the age of 3 years old. She had no family history of DM or liver disease. The diagnosis of liver cirrhosis was made when hematoemesis due to esophageal variceal rupture was treated with endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL) therapy in 1996. At that time, she was also diagnosed as having DM from high fasting blood glucose (267 mg/dl) and high hemoglobin A1c level (6.8%). As her blood glucose was persistently high despite diet therapy, insulin therapy was started. However, her glucose level remained high and the dose of insulin was increased gradually. Although the dose of insulin was increased to 56 units per day in May 2001, DM was not controlled well (Fig. 1).

On February 21, 2002, she visited our outpatient Department of Orthopedics due to a walking disturbance. An X ray film showed fracture of the right femur. She was admitted to the orthopedics ward and underwent surgery for the fracture. After operation, control of DM worsened and her abdomen showed mild fluctuation suggestive of ascites. She was referred to our department for evaluation of liver function and control of DM.

She complained of slight abdominal fullness but she had no itching. Her physical examination revealed complete blindness and a clear conscious level. The palpebral conjunctiva showed no anemia, however, as her eye ball was atro-
PBC with Slowly Progressive IDDM

Figure 1. Clinical course of this patient. Hemoglobin A1c remained at a high level despite the increase of insulin. HbA1c: hemoglobin A1c.

Figure 2. Computed tomography revealed marked atrophic right lobe of the liver and splenomegaly. These findings were compatible with liver cirrhosis.

...phic, bulbar conjunctiva could not be evaluated. Her breathing sound was normal and her heart beat was regular without murmur. Abdominal examination revealed a mildly distended abdomen with fluctuation and splenomegaly with no hepatomegaly. Her right leg showed mild edema after operation, but the left leg showed no edema. Her palms were not erythematous and she had no vascular spider.

Her preoperative laboratory data were as follows: peripheral white blood cell count, 4.3×10^9/μl (normal range [NR], 3.5–9.5×10^9); hemoglobin, 10.5 g/dl (NR, 11.0–15.2); platelets, 5.6×10^9/mm³ (NR, 12–38); Fasting blood glucose (FBS), 366 mg/dl (NR, 65–105); hemoglobin A1c (HbA1c) 12.3% (NR, 4.3–5.8); prothrombin time, 89.2% (NR, 70–120); albumin 2.9 mg/dl (NR, 3.8–5.3); total bilirubin, 0.7 IU/l (NR, 0.2–1.2); aspartate transaminase, 80 IU/l (NR, 8–38); alanine transaminase, 61 IU/l (NR, 4–44); alkaline phosphatase, 1,199 IU/l (NR, 106–220); γ-glutamyltranspeptidase, 450 IU/l (NR, 3–45); blood urea nitrogen, 12 mg/dl (NR, 8–20); creatinine 0.4 mg/dl (NR, 0.6–1.3); Na 136 mEq/dl (NR, 135–147); K 4.1 mEq/dl (NR, 3.5–4.8) Cl 103 mEq/dl (NR, 98–108). Serum immunoglobulin levels were as follows: IgG 1,303 mg/dl (NR, 800–1,750); IgA 369 mg/dl (NR, 90–400); IgM 231 mg/dl (35–260). Both hepatitis B surface antigen and antibody to hepatitis C virus (HCV) were negative. However, the titer of antinuclear antibody (ANA) was positive (×1,280). The titer of anti-mitochondrial antibody (AMA) was ×40 (NR, <20). Furthermore, the M2 component of AMA was 129 (NR, <7).

Abdominal ultrasound (US) examination demonstrated a remarkably atrophic liver and an enlarged spleen. Minimal ascites was seen in the Douglas pouch. Computed tomography (CT) showed enlargement of the lateral lobe and atrophy of the right lobe of the liver and marked splenomegaly. US and CT showed no biliary tract stones. These findings were compatible with liver cirrhosis (Fig. 2).

As this patient had ascites, we could not examine a liver biopsy. However, based on the positivity for M2 component of AMA, the elevation of biliary enzymes, no viral markers and her clinical course, we diagnosed her as symptomatic PBC. Her liver function was equivalent to Child—Pugh: grade B.

The DM status of this patient showed insulin resistance. We thus re-evaluated the etiology of DM as follows. Insulin antibody was 5.3% (NR, <7). The titer of anti-glutamic acid decarboxylase (GAD) antibody was positive; 22.2 U/ml (NR, <1.5). Urine C-peptide was markedly reduced to 0.7 μg/day (NR, 20.5–198). Plasma C-peptide was 0.58 ng/ml (NR, 0.94–2.8). From these findings, a diagnosis of type 1 insulin-dependent DM was made. We specifically diagnosed slowly progressive IDDM complicated by PBC based on the clinical course and laboratory data. After the diagnosis was made, treatment with ursodeoxycholic acid at 300 mg/day was initiated. We increased the dose of insulin to control the blood glucose level. However, her blood glucose proved difficult to control.

Finally, with diet therapy and an increased dose of insulin, her DM improved with HbA1c declining to 8.6%. Considering her liver function and insulin resistance, we thought that this control level of DM was acceptable for this patient. She was discharged on May 7, 2002.

Discussion

Cirrhotic patients often become hyperglycemic following an oral glucose load. However, the glucose intolerance of cirrhotic patients can be distinguished from genuine diabetes mellitus as the fasting blood glucose is usually normal. Most patients compensate for the peripheral insulin resistance with increased pancreatic insulin secretion, resulting in high
circuiting insulin levels, a normal FBS and minimal glucose intolerance (5).

The present patient showed very high FBS and low plasma and urine C-peptide. These findings conflict with the theory of glucose intolerance in liver cirrhosis. Thus it was necessary to investigate the etiology of cirrhosis and DM more precisely. Non-alcoholic streatorhepatitis (NASH) may be one candidate for the etiology of liver cirrhosis. NASH is associated with obesity, female, diabetes mellitus, insulin resistance (6), and indeed, this case was a female patient with DM. Moreover, autoimmune hepatitis (AIH) must be ruled out in this case, because her ANA level was high. As this patient had ascites, we could not examine a liver biopsy. Therefore, it was difficult rule out these two diseases pathologically. However, this patient was positive for not only AMA, but also the M2 component of AMA. The M2 component of AMA is 88% sensitive and 96% specific for the diagnosis of PBC (1), and her biliary enzymes revealed a very high level. Considering the positivity for M2 component of AMA, elevation of biliary enzymes without biliary stones, and the lack of viral markers, we proposed her diagnosis as PBC clinically, rather than AIH or NASH and this diagnosis was based on the diagnostic criteria produced by the Study Group of Intractable Liver Diseases supported by Ministry of Health, Labour and Welfare of Japan.

As PBC frequently complicates autoimmune disease, we examined anti-GAD antibody to evaluate whether some autoimmune mechanism might have been implicated in the pathophysiology of DM in this patient.

Primary diabetes is classified into two categories. Type 1 is often used as a synonym for insulin-dependent diabetes (IDDM), and type 2 diabetes has been considered equivalent to non-insulin dependent disease (NIDDM). The etiologic mechanisms of type 1 and type 2 diabetes are immune-mediated and non immune-mediated, respectively (7). Type 1 diabetes results from autoimmunemediated destruction of β cells of the pancreas; in particular, markers of immune destruction, including islet cell autoantibodies, autoantibodies to insulin, and autoantibodies to GAD are present in 85–90% of individuals with Type 1 DM (8).

In Type 1 DM, the degree of destruction is quite variable from slowly to rapid progressive. The rapidly progressive form is not only commonly observed in children, but also may occur in adults. The slowly progressive form generally occurs in adults and it is sometimes referred to as latent autoimmune diabetes in adults (LADA) (7). Kobayashi recently advocated the concept of slowly progressive IDDM (SPIDDM) (9). The characteristics of SPIDDM include the following: 1) non-insulin requiring clinical phenotype at the onset of diabetes, 2) late age onset, 3) slow β-cell failure progression over several years with a persistently positive low titer of islet cell antibody (ICA) and high titer of anti-GAD antibodies, 4) autopsied pancreas pathologically demonstrates incomplete β cell loss, 5) higher family history of NIDDM, and 6) association with some genetic predisposition including HLA-DQA1*0301-DQB1*0401 and/or mitochondrial gene mutation at nucleotide pair 3,243, and a lack of association with HLA-A24. Therefore, SPIDDM is categorized as LADA (9). Patients with SPIDDM may have other autoimmune disorders such as Graves’ disease (10), Hashimoto’s thyroiditis (11), and Addison’s disease (12). Pietropaolo reported that the prevalence of anti-GAD autoantibody, which is common in subjects with type 1 diabetes, was 5.5% in patients with PBC (13).

PBC is also frequently associated with a variety of disorders presumed to be autoimmune in nature. Collagen diseases, systemic lupus erythematosus (2), autoimmune thyroiditis (3) and sicca syndrome (4) are frequently associated. Rare disorders associated with PBC have also been reported, including interstitial lung disease (14), ulcerative colitis (15), IgM-associated membranous glomerular nephritis (16), and autoimmune hemolytic anemia (17). To the best of our knowledge, this is the first reported case with SPIDDM complicated by PBC in Japan.

SPIDDM and PBC are both autoimmune diseases and they have common features. For example, infiltration of CD8+ T lymphocytes is observed in the exocrine pancreas in SPIDDM (18) and peripheral damage to be bile ducts is seen in PBC (19). Thus, CD8+ T lymphocytes might have played a pathological role in this case.

It is recommended that SPIDDM should be treated with a small dose of insulin. A small dose of insulin, resulting in a high rate of negative conversion of ICA and an improved insulin secretion, may be effective in preventing progressive β cell failure in patients with SPIDDM (20). However, progressive β cell failure was not prevented in the present patient despite the treatment with insulin. This result might be explained by the delay in diagnosis and treatment of PBC and SPIDDM. Moreover, insulin resistance of cirrhosis itself might have affected the poorly controlled blood glucose. Based on our experience with this case, we suggest that SPIDDM should be considered when patients with PBC develop DM.

References


