CASE REPORT

Slowly Progressive Insulin-Dependent Diabetes in a Patient with Primary Biliary Cirrhosis with Portal Hypertension-Type Progression

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Abstract

A 73-year-old woman had previously been diagnosed with CREST syndrome, PBC and diabetes. Hepatic fibrosis was not evident, in spite of the transudative ascites and active esophageal varices. ACA were positive, whereas AMA and anti-gp210 antibodies were negative. She showed low urinary excretion of C-peptide and was weakly positive for anti-GAD antibody. She was diagnosed with a form of PBC that progresses via portal hypertension rather than liver failure and with SPIDDM. Her HLA type did not contain risk allele for IDDM or PBC. SPIDDM should be considered when patients with PBC with portal hypertension-type progression develop diabetes.

Key words: SPIDDM, primary biliary cirrhosis, portal hypertension, anti-centromere antibodies (ACA), CREST syndrome

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Case Report

A 73-year-old woman was admitted to our hospital in April 2009 for control of diabetes and ascites. She had no family history of diabetes or liver disease. She had developed Raynaud’s phenomenon at 40 years of age and sclerodactyly when she was 44. She had been diagnosed with calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome based on her clinical features and the presence of anti-centromere antibodies (ACA). At 65 years of age, a routine screening revealed abnormal serum alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (γ-GTP) levels, postprandial hyperglycemia, and elevated levels of hemoglobin A1c (HbA1c). She did not have a history of alcohol or drug abuse, and was negative for anti-mitochondrial antibodies (AMA), the M2 fraction of AMA, and viral markers for hepatitis B and C. A liver biopsy showed chronic non-suppurative destructive cholangitis (CNDS-D)-like bile duct injuries with granulomatous reactions, and intraepithelial lymphocytic infiltration (Fig. 1A). Based on these findings, the patient was diagnosed with primary biliary cirrhosis (PBC) and diabetes. After ursodeoxycholic acid (UDCA) and sulfonlurea (glimepiride 1 mg) were administered, her ALP level remained high, but her diabetes was well controlled.

In June 2009, at 73 years of age, the patient was referred to our hospital because of ascites and worsening diabetes. She presented with anemia, skin thickening, sclerodactyly, palmar erythema without vascular spider, hepatomegaly, an abdominal fluctuation suggestive of ascites, and edema of the leg. Her laboratory data (Table 1) showed elevations in ductal enzyme levels and a preserved hepatic reserve. Her diabetes was poorly controlled (FPG, 341 mg/dL; HbA1c, 79
She was positive for various autoantibodies, including anti-glutamic acid decarboxylase antibody (GAD Ab), Tg antibodies, and anti-centromere antibodies, but she was negative for AMA. Her human leukocyte antigen (HLA) type was DRB1*0101, DQA1*0501, and DQB1*020102/0501, DBP1*020102/0501, DQA1*0101.

Abdominal CT revealed hepatomegaly and collateral vascularization, in the paraesophageal region. Gastrointestinal endoscopic examinations showed esophageal varices (linear and white varices without red coloring). We performed hepatic venography to further investigate the collateral vascularization and esophageal varices. The patient’s wedged hepatic vein pressure (WHVP) was 11 mmHg and her hepatic venous pressure was 4 mmHg. The normal Hepatic Venous Pressure Gradient (the difference between the WHVP and the free hepatic venous pressures) value is between 1 and 5 mmHg (1). However, while transudative ascites were present, there was no evidence of portal hypertension. A needle liver biopsy was performed. The lobular architecture was relatively normal, and there was dense portal fibrosis without bridging. At the edges of the portal areas, abnormal blood vessels, frequently reported in idiopathic portal hypertension (2), were observed (Fig. 1B). Cholangitis, which had been detected in a previous biopsy (Fig. 1A), was not found.

Concerning the etiology of diabetes, the GAD Ab titer was 3.2 U/mL (normal range [NR], <1.5 U/mL). Plasma levels of basal circulating C-peptide immunoreactivity (CPR) and urinary excretion of CPR were as low as 0.3 ng/mL (NR, 0.94-2.8 ng/mL) and 12 μg/day (NR, 20.5-198 μg/day), respectively. We examined the responses of CPR and glucagon to arginine in the arginine challenge test. ΔCPR and Δglucagon were calculated from the difference between peak values and the base values of CPR and glucagon. Arginine challenge yielded a weak CPR response (ΔCPR, 0.1 ng/mL) and an exaggerated glucagon response (Δglucagon, 382 pg/mL), which are characteristic of type 1 diabetes (3). Based on these findings, a diagnosis of slowly progressive insulin-dependent diabetes mellitus (SPIDDM) was made. Basal-bolus insulin therapy (28 U/day of insulin lispro and 6 U/day of insulin glargine) reduced the patient’s HbA1c to 9.1%.

Table 1. Laboratory Data on Admission

<table>
<thead>
<tr>
<th>WBC</th>
<th>6.320 × 10^9/μL</th>
<th>BUN</th>
<th>28 mg/dL</th>
<th>IgG</th>
<th>893 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>3.56 × 10^12/μL</td>
<td>Cr</td>
<td>0.39 mg/dL</td>
<td>IgA</td>
<td>389 mg/dL</td>
</tr>
<tr>
<td>Hb</td>
<td>9.9 g/dL</td>
<td>ALP</td>
<td>1725 IU/L</td>
<td>IgM</td>
<td>726 mg/dL</td>
</tr>
<tr>
<td>Ht</td>
<td>23.3%</td>
<td>GTP</td>
<td>142 IU/L</td>
<td>Anti-TPO Ab</td>
<td>2.7 IU/mL</td>
</tr>
<tr>
<td>Pts</td>
<td>261 × 10^3/μL</td>
<td>AST</td>
<td>19 IU/L</td>
<td>Anti-Tg Ab</td>
<td>2880 IU/mL</td>
</tr>
<tr>
<td>FPG</td>
<td>341 mg/dL</td>
<td>ALT</td>
<td>29 IU/L</td>
<td>HBSAg</td>
<td>Negative</td>
</tr>
<tr>
<td>HbA1c</td>
<td>9.1%</td>
<td>Amy</td>
<td>28 IU/L</td>
<td>ACA</td>
<td>Negative</td>
</tr>
<tr>
<td>(JDS value)</td>
<td></td>
<td>T-Bil</td>
<td>0.4 mg/dL</td>
<td>ANA</td>
<td>640</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TP</td>
<td>5.7 g/dL</td>
<td>Anti-GAD Ab</td>
<td>3.2 IU/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alb</td>
<td>3.9 g/dL</td>
<td>IA-2 Ab</td>
<td>&lt;0.4 IU/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PT</td>
<td>92%</td>
<td>ACA</td>
<td>120.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPR</td>
<td>0.3 ng/mL</td>
<td>Anti-gp210 Ab</td>
<td>0.7</td>
</tr>
</tbody>
</table>

JDS, Japanese Diabetes Society; PT, prothrombin time; Anti-TPO Ab, thyroperoxidase antibody; Anti-Tg Ab, thyroglobulin antibody; HBSAg, hepatitis B virus surface antigen; HCV, antibody to hepatitis C virus; ANA, anti-nuclear antibodies; AMA, anti-mitocondrial autoantibodies; Anti-GAD Ab, glutamic acid decarboxylase antibody; IA-2 Ab, insulinoma-associated antigen-2; ACA, anti-centromere antibodies.
Collectively, the present patient was diagnosed as having PBC, type 1 diabetes and autoimmune thyroid disease (AITD) based on positivity in Tg antibody and a heterogeneous internal echo finding of the thyroid. Therefore, it may be possible that our patient is included in the entity of autoimmune polyglandular syndrome type 3 that is composed of type 1 diabetes and AITD (4). In general, the prevalence of GAD Ab is significantly higher in patients with AITD than in healthy control subjects (5). However, the present patient’s HLA type was different from the frequent DRB1*0405-DQB1*0401 haplotype observed in type 1 diabetes and AITD (5). Chronic liver disease has also been implicated as a complication of Hashimoto’s thyroiditis, and the term “hepatothyroiditis syndrome” has been proposed to describe this condition (6). Thyroid disease is also found in about 10-15% of patients with PBC, and AITD is the most common (7). The prevalence of GAD Ab is 5.5% in patients with PBC, higher than that in the healthy population (8).

However, to the best of our knowledge, this is only the second reported case of SPIDDM complicated by PBC. SPIDDM (9), which is also referred to as latent autoimmune diabetes in adults (10), generally occurs in adults after a clinical course involving the control of type 2 diabetes with oral hypoglycemic agents. Because the level of GAD Ab was relatively low in the present patient, we should rule out insulinopenic type 2 diabetes in our patient. In this regard, we previously reported that arginine-induced CPR and glucagon responses were negatively and positively correlated with each other in patients with type 1 and type 2 diabetes, respectively (3). Autoimmune type 1 diabetes is caused by a targeted immune reaction that destroys β-cells while leaving the α-cell mass relatively unaffected (11). Therefore, intraislet insulin deficiency determines the exaggerated glucagon response to arginine in type 1 diabetes. Because the present patient showed a diminished insulin response and exaggerated glucagon response to arginine challenge, we came to the conclusion that our patient has type 1 diabetes rather than type 2 diabetes.

There are at least two different types of progression in PBC: hepatic failure-type progression, which is characterized by the presence of anti-gp210 antibodies, and portal hypertension-type progression, which is characterized by the presence of ACA (12). The present patient was positive for ACA and was therefore deemed to be at high risk of portal hypertension-type progression, rather than hepatic failure-type progression (12). Indeed, she presented with portal hypertension with transudate ascites and esophageal varices without advanced liver fibrosis. The reasons for the different types of progression are not known, but one could argue that specific immunological interactions in the presence of an additional autoimmune disorder may influence the clinical picture and favor a better liver disease outcome (13).

It might be possible that the pathology of SPIDDM and CREST-PBC overlap syndrome are associated in the present patient because exacerbation of diabetes and portal hypertension developed in parallel in the clinical course. SPIDDM and PBC are both autoimmune diseases and share common features. For example, infiltration of CD8+ T lymphocytes occurs in the exocrine pancreas in SPIDDM (14) and peripheral damage to the bile ducts is seen in PBC (15). Thus, CD8+ T lymphocytes may have played a pathological role in the present case. On the other hand, the HLA susceptibilities in type 1 diabetes and CREST-PBC overlap syndrome are different. HLA-DQA1*0301-DQB1*0401 haplotype is often present in SPIDDM (16), whereas HLA-Cw6 is often present and HLA-DR2 is often absent in CREST-PBC overlap syndrome (17). The HLA type of the present patient was different from other reported cases of IDDM and PBC. Thus, accumulation of the similar cases complicated with SPIDDM and CREST-PBC overlap syndrome will be necessary to shed light on the common pathology and genetic basis of this condition.

Generally, patients with PBC and collagen disease have lower rates of liver transplantation and liver-related death, and a slower rate of increase in bilirubin levels, compared to patients with PBC alone (18). More attention should be paid to the progression of portal hypertension (i.e., varices and ascites) and diabetic complications, which might be determinants of prognosis.

As a lesson from this case, we suggest that SPIDDM should be considered when patients with CREST-PBC overlap syndrome with portal hypertension-type progression develop diabetes.

The authors state that they have no Conflict of Interest (COI).

References


