CASE REPORT

Type 1 Diabetes Mellitus and Pernicious Anemia in an Elderly Japanese Patient: A Case Report and Literature Review

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Abstract

We herein report the case of a 66-year-old Japanese man with acute-onset type 1 diabetes mellitus (T1D) accompanied by pernicious anemia. After 2 weeks of polyuria, the patient developed insulin-deficient hyperglycemia with diabetic ketoacidosis in the absence of verifiable islet-related autoantibodies and began insulin therapy in 2001. Eight years later, he developed gastric autoantibody-positive pernicious anemia and began methylcobalamin treatment. Previous studies have reported cases of slowly progressive autoimmune T1D concomitant with pernicious anemia. The present case suggests that potential associations with organ-specific autoimmune disorders should be considered during the long-term follow-up of T1D patients, even though verifiable islet-related autoantibodies are undetectable.

Key words: pernicious anemia, type 1 diabetes mellitus, insulin therapy, methylcobalamin, human leukocyte antigen, autoimmunity

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Introduction

Pernicious anemia is a macrocytic anemia caused by a vitamin B12 (cobalamin) deficiency that results from oxyntic gastric mucosa damage and intrinsic factor deficiency (1, 2). It is considered to be an autoimmune disorder due to the presence of gastric autoantibodies and is often associated with autoimmune thyroid diseases, and occasionally other organ-specific autoimmune disorders, such as type 1 diabetes mellitus (T1D) (3, 4).

T1D is a metabolic disease characterized by the destruction of pancreatic beta cells, which typically leads to an absolute deficiency in insulin secretion. It is a complex, heterogeneous disease, and depending on the manner of onset and progression, T1D is classified as acute-onset (“classical”), slowly progressive, or fulminant in Japan (5-9). Acute-onset T1D is characterized by the presence of diabetic ketoacidosis (DKA) at the time of diagnosis (clinical onset) and a lifelong insulin-dependent state thereafter.

Many cases of slowly progressive T1D concomitant with pernicious anemia have been reported, but only a few cases of fulminant or acute-onset T1D accompanied by pernicious anemia have been reported in Japan. We herein describe a patient with pernicious anemia that occurred 8 years after his diagnosis of acute-onset T1D. In addition, all 14 previously reported cases of Japanese patients with concomitant T1D and pernicious anemia are reviewed (10-23).

Case Report

A 66-year-old Japanese man with disturbed consciousness was admitted to our hospital in August 2001. His medical and family histories were unremarkable, and he had been healthy until an episode of a sore throat and a fever that occurred 2 weeks prior to admission. Several days later he de-
veloped thirst and polyuria. The patient was 155 cm in height and weighed 56 kg. His body temperature was 36.8 °C, his oral cavity was dry, and his blood pressure and pulse rate were 120/74 mmHg and 109 beats per minute, respectively. The laboratory findings revealed the presence of DKA (arterial pH 7.21, partial carbon dioxide pressure 19.1 mmHg, partial oxygen pressure 115.0 mmHg, bicarbonate 7.6 mmol/L, plasma glucose 51.4 mmol/L, urinary ketone bodies positive), a high HbA1c (National Glycohemoglobin Standardization Program, NGSP) value of 9.0% (24), and elevated serum amylase levels (331 IU/L). Tests for glutamic acid decarboxylase antibody (GADA) (<1.3 U/mL) and islet cell antibody (ICA) were both negative. Abdominal ultrasonography detected fatty deposition in the liver, but no abnormalities in the pancreas or kidneys were found. Following the correction of DKA using intravenous insulin and saline therapy, the patient regained normal consciousness and provided six consecutive urinary C-peptide excretions of 1.6, 0.1, 3.8, 14.1, 14.6, and 6.8 μg/day (mean value: 6.8 μg/day). He was diagnosed with acute-onset T1D, began insulin injection therapy, and was discharged in September 2001.

In October 2009, the patient was 74 years of age when he was admitted to our hospital with complaints of appetite loss and dysgeusia over the preceding 3 weeks. A physical examination revealed that he had pallor, anemic palpebral conjunctiva, a body temperature of 36.3°C, a blood pressure of 126/64 mmHg, and a regular pulse rate of 90 beats per minute. No struma, chest rales, heart murmurs, skin abnormalities, and palpable lymph node or spleen enlargements were detected, and the patient’s deep tendon reflexes were normal. A complete blood cell count showed no abnormalities in June 2008 (red blood cells 488×10^6/μL, hemoglobin 13.6 g/dL, hematocrit 39.3%, white blood cells 7,200/μL, and platelets 34.5×10^11/μL).

In September 2014, the laboratory examination showed normal values for a complete blood count, an HbA1c (NGSP) level of 6.8%, undetectable serum gastritis. The patient began a regimen of the intramuscular administration of methylcobalamin, and his appetite loss and dysgeusia resolved within a few days. Two weeks later, the laboratory tests performed showed an improvement in anemia (red blood cells 271×10^6/μL, hemoglobin 9.0 g/dL, and hematocrit 30.8%) and normalization of serum levels of total bilirubin (0.4 mg/dL), aspartate aminotransferase (37 IU/L), alanine aminotransferase (39 IU/L), and lactate dehydrogenase (211 IU/L). The patient was discharged on day 22 of hospitalization, and one month later his blood cell count had normalized (red blood cells 474×10^6/μL, hemoglobin 13.0 g/dL, hematocrit 41.8%, white blood cells 5,800/μL, and platelets 33.9×10^11/μL).

The patient continued a therapeutic regimen of methylcobalamin replacement (500 μg/3 months) and injections of insulin lispro and insulin glargine (a total of 42 units/day) at the outpatient clinic. In September 2014, the laboratory examinations showed normal values for a complete blood count, an HbA1c (NGSP) level of 6.8%, undetectable serum C-peptide levels, and negative test results for autoantibodies against the pituitary, thyroid, and adrenal glands. The subsequent clinical course of the patient has been uneventful, and there have been no occurrences of additional autoimmune disorders or stomach malignancies related to autoimmune gastritis.

**Discussion**

An elderly Japanese man developed DKA approximately 10 days after the occurrence of hyperglycemic symptoms, and presented to our hospital in an insulin-dependent state. These findings were consistent with a definitive diagnosis of acute-onset T1D (9); the presence of the HLA-A*24, B*54, DRB1*04:05, DQA1*03:03, and DQB1*04:01 genes further supported this diagnosis (25-28). In addition, although the patient did not fulfill the diagnostic criteria for fulminant...
islet-related autoantibodies, which would be classified as destruction of islet beta cells in the absence of verifiable time, however, he was considered to exhibit an autoimmune considered to be an idiopathic case of T1D. At the same appear over time (30). The present patient tested negative antibody-negative (idiopathic cases) (9). In addition, if appear against islet antigens in the early phase of the dis- ease (5, 6, 9); these are typically referred to as autoimmune to those with slowly progressive T1D, have autoantibodies against islet antigens at any time during the course of diabetes and/or a positive insulin antibody test at onset. Type 1 diabetes mellitus was categorized as fulminant, acute-onset, or slowly progressive based on published criteria (7-9). The subtypes in cases 1, 3, and 14 were undetermined because of a lack of information regarding the duration of hyperglycemic symptoms prior to diabetic ketoacidosis (DKA) (10, 12) and the presence or absence of DKA at onset (23).

**Positive islet-related autoantibodies were defined by a positive test for one or more antibodies against glutamic acid decarboxylase, islet cells, or insulinoma-associated antigen 2 at any time during the course of diabetes and/or a positive insulin antibody test at onset.**

**Positive gastric autoantibodies were defined by a positive test for one or two antibodies against intrinsic factors or parietal cells.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th><em>HLA-DR</em></th>
<th><em>HLA-DQ</em></th>
<th>Age at diabetes onset (year)</th>
<th>DKA at diagnosis</th>
<th><strong>Islet-related autoantibodies</strong></th>
<th><em><strong>Subtype</strong></em></th>
<th><strong>Pernicious anemia</strong></th>
<th>Age at onset (year)</th>
<th>****Gastric autoantibodies</th>
<th>Other autoimmune disorders</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>N/A</td>
<td>N/A</td>
<td>28 (+)</td>
<td>N/A</td>
<td>Undetermined</td>
<td>Acute-onset</td>
<td>N/A</td>
<td>30</td>
<td>+</td>
<td>Hashimoto’s disease</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
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<td>N/A</td>
<td>N/A</td>
<td>5 (+)</td>
<td>N/A</td>
<td>Undetermined</td>
<td>N/A</td>
<td>Positive</td>
<td>8</td>
<td>N/A</td>
<td>Autoimmune neuropenia</td>
<td>11</td>
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<tr>
<td>3</td>
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<td>8</td>
<td>N/A</td>
<td>6 (+)</td>
<td>Negative</td>
<td>Undetermined</td>
<td>N/A</td>
<td>Positive</td>
<td>19</td>
<td>N/A</td>
<td>N/A</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
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<td>4</td>
<td>3, 4</td>
<td>60 (+)</td>
<td>Positive</td>
<td>Slowly progressive</td>
<td>Slowly progressive</td>
<td>N/A</td>
<td>72</td>
<td>N/A</td>
<td>N/A</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>4</td>
<td>8</td>
<td>65 (+)</td>
<td>Positive</td>
<td>Slowly progressive</td>
<td>N/A</td>
<td>Positive</td>
<td>69</td>
<td>N/A</td>
<td>Hashimoto’s disease</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>N/A</td>
<td>N/A</td>
<td>73 (-)</td>
<td>Positive</td>
<td>Slowly progressive</td>
<td>N/A</td>
<td>Positive</td>
<td>83</td>
<td>N/A</td>
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<td>15</td>
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<tr>
<td>7</td>
<td>Female</td>
<td>[DRB1* 08:02/15:02]</td>
<td>[DQB1* 04:02/06:01]</td>
<td>58 (-)</td>
<td>Positive</td>
<td>Slowly progressive</td>
<td>N/A</td>
<td>Positive</td>
<td>59</td>
<td>N/A</td>
<td>N/A</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
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<td>4, 13</td>
<td>NA</td>
<td>58 (-)</td>
<td>Positive</td>
<td>Slowly progressive</td>
<td>N/A</td>
<td>Positive</td>
<td>81</td>
<td>N/A</td>
<td>Vitiigo vulgaris Hashimoto’s disease</td>
<td>17</td>
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<tr>
<td>9</td>
<td>Female</td>
<td>[DRB1* 15:03/15:02]</td>
<td>[DQB1* 06:01/06:02]</td>
<td>53 (-)</td>
<td>Positive</td>
<td>Slowly progressive</td>
<td>N/A</td>
<td>Positive</td>
<td>61</td>
<td>N/A</td>
<td>Hashimoto’s disease</td>
<td>18</td>
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<tr>
<td>10</td>
<td>Female</td>
<td>4</td>
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<td>Fulminant</td>
<td>N/A</td>
<td>Positive</td>
<td>85</td>
<td>N/A</td>
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<tr>
<td>11</td>
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<td>13, 15</td>
<td>N/A</td>
<td>70 (-)</td>
<td>Positive</td>
<td>Slowly progressive</td>
<td>N/A</td>
<td>Positive</td>
<td>64</td>
<td>N/A</td>
<td>Hashimoto’s disease</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>4</td>
<td>N/A</td>
<td>59 (-)</td>
<td>Positive</td>
<td>Slowly progressive</td>
<td>N/A</td>
<td>Positive</td>
<td>59</td>
<td>N/A</td>
<td>N/A</td>
<td>21</td>
</tr>
<tr>
<td>13</td>
<td>Female</td>
<td>[DRB1* 04:05/04:06]</td>
<td>[DQB1* 03:02/04:01]</td>
<td>75 (-)</td>
<td>Positive</td>
<td>Slowly progressive</td>
<td>N/A</td>
<td>Positive</td>
<td>81</td>
<td>N/A</td>
<td>Hashimoto’s disease</td>
<td>22</td>
</tr>
<tr>
<td>14</td>
<td>Female</td>
<td>[DRB1* 11:01/15:02]</td>
<td>[DQB1* 03:01/06:01]</td>
<td>71 NA</td>
<td>Positive</td>
<td>Undetermined</td>
<td>N/A</td>
<td>Positive</td>
<td>73</td>
<td>N/A</td>
<td>Hashimoto’s disease</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>[DRB1* 04:05/13:02]</td>
<td>[DQB1* 04:06/06:09]</td>
<td>66 (+)</td>
<td>Negative</td>
<td>Acute-onset</td>
<td>N/A</td>
<td>Positive</td>
<td>74</td>
<td>N/A</td>
<td>N/A</td>
<td>Present case</td>
</tr>
</tbody>
</table>

*Human leukocyte antigen (HLA)-DRB1 and HLA-DQB1 genotypes are shown in square brackets.

**Positive islet-related autoantibodies were defined by a positive test for one or more antibodies against glutamic acid decarboxylase, islet cells, or insulinoma-associated antigen 2 at any time during the course of diabetes and/or a positive insulin antibody test at onset.**

**Positive gastric autoantibodies were defined by a positive test for one or two antibodies against intrinsic factors or parietal cells.**

N/A: not available, ITP: idiopathic thrombocytopenic purpura

T1D (8) because his HbA1c (NGSP) value was higher than 8.7% at the first visit, the patient presented with several characteristic features of this disorder, including a prorome of flu-like symptoms, very low C-peptide levels, elevated se- rum pancreatic enzyme levels, a fatty liver at disease onset, and a negative test for islet-related autoantibodies (29).

T1D is considered to be an organ-specific autoimmune disorder, and many patients with acute-onset T1D, similarly to those with slowly progressive T1D, have autoantibodies against islet antigens in the early phase of the disease (5, 6, 9); these are typically referred to as autoimmune cases. The major autoantibodies of clinical and research interest include ICA, GADA, insulinoma-associated antigen-2 antibody, insulin autoantibody, and ZnT8 antibody; however, the sensitivity of each marker is still less than 80% (30), and a subset of patients with acute-onset T1D are autoantibody-negative (idiopathic cases) (9). In addition, if present, these autoantibody titers may decline and even disappear over time (30). The present patient tested negative for ICA and GADA at the onset of T1D and was therefore considered to be an idiopathic case of T1D. At the same time, however, he was considered to exhibit an autoimmune destruction of islet beta cells in the absence of verifiable islet-related autoantibodies, which would be classified as autoimmune T1D.

The patient developed pernicious anemia 8 years after the onset of T1D. Table presents a summary of previously reported Japanese cases that exhibited concurrent pernicious anemia and T1D. These cases included patients of all ages and both genders, however, most are older woman. The patients tended to exhibit T1D prior to pernicious anemia, with a time lag of up to approximately 10 years, and many were diagnosed with slowly progressive T1D. The present patient is the first reported adult case exhibiting established acute-onset T1D accompanied by pernicious anemia.

In countries with Caucasian populations, T1D is broadly divided into two forms: rapid onset or slow progression (31, 32). In general, the rapid onset subtype is referred to simply as T1D. The slow progression subtype is referred to as latent autoimmune diabetes in adults, and it has clinical features similar to those of the slowly progressive T1D subtype in Japan (6, 31, 32). In contrast to studies in Japanese patients, many studies of T1D Caucasian patients found a high prevalence of pernicious anemia as part of polyglan- dular autoimmune syndrome (PGAS) (1-4, 33-36). Additionally, genetic research has revealed that the genotypes HLA-DRB1*03 and DRB1*04 predispose patients to pernicious anemia associated with T1D and autoimmune thyroid dis-
eases (2, 3, 36, 37). In the present case, the patient had the HLA class II haplotype DRB1*04:05-DQA1*03:03-DQB1*04:01, which increases the susceptibility of Japanese individuals to PGAS (38). Therefore, associated autoimmunity may have played a role in the development of both T1D and pernicious anemia in the present case.

Among previously reported Japanese cases of concomitant T1D and pernicious anemia (Table), most patients had autoimmune T1D and gastric autoantibody-positive pernicious anemia either with or without autoimmune thyroid diseases, and thus, were considered to be affected by PGAS type 3 or 4 (38). There have been 2 reported cases of idiopathic T1D that exhibited a variety of organ-specific autoimmune disorders in addition to pernicious anemia, and had a time lag that was over 10-20 years from the onset of T1D (12, 19). In the present case, although the patient did not exhibit any autoimmune disorders other than pernicious anemia during the 13 years after the onset of T1D, careful long-term follow-up assessments may be needed to monitor the potential occurrence of additional organ-specific autoimmune disorders.

In conclusion, we herein reported an elderly Japanese man who developed pernicious anemia 8 years after the diagnosis of acute-onset T1D. This case suggests that potential comorbidities of organ-specific autoimmune disorders, including pernicious anemia, should be considered in T1D patients throughout an extended follow-up period, even though verifiable islet-related autoantibodies are not detected.

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

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References

24. Committee on the Standardization of Diabetes Mellitus-Related
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