A Case of Abrupt Onset Autoimmune Type 1 Diabetes Mimicking Fulminant Type 1 Diabetes

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Abstract. A 63-year-old male was admitted to our hospital with diabetic ketoacidosis. He had flu-like symptoms 10 days before admission and developed thirst, polyuria and anorexia with 9 kg of body weight loss in a week. Plasma glucose level on admission was 983 mg/dL and HbA1c was 7.5%. Despite high levels of serum pancreatic enzymes, lack of severe abdominal pain and no morphological change of pancreas in the abdominal CT scan eliminated the complication of classical acute pancreatitis. These findings suggested the diagnosis of fulminant type 1 diabetes. However, urinary and plasma C-peptide levels showed that insulin secretion was not completely depleted at onset. Furthermore, an examination of islet-related antibodies revealed the presence of high titer anti-GAD antibody. His HLA typing showed that DRB1*0901-DQB1*0303 and A24 were present. He has been doing well with continuation of insulin therapy. Over two years after onset, his plasma C-peptide level was gradually lowered, and anti-GAD antibody was still positive. Taken together, this is a rare case of abrupt onset autoimmune type 1 diabetes with transient but apparent exocrine pancreatic impairment at onset. Similar cases should be accumulated to clarify pathophysiological similarities and/or differences between fulminant type 1 diabetes and abrupt onset autoimmune type 1 diabetes.

Key words: Type 1 diabetes, Fulminant, Autoimmune, Pancreatic enzyme

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white blood cell count was 13300 /mm³ with 84% neutrophils, and his platelet count was 32.1 x 10⁴ /mm³. Serum electrolytes were the following: Na 120 mEq/L; K 5.9 mEq/L; Cl 88 mEq/L and Ca 8.6 mg/dL. Serum bun was 79.8 mg/dL; creatinine, 2.96 mg/dL; and uric acid, 11.3 mg/dL. Total serum protein was 7.6 g/dL with 60.4% albumin; GOT, 11 iu/L; GPT, 17 iu/L; LDh, 247 iu/L; γ-GTP, 83 iu/L; and total cholesterol, 221 mg/dL. Arterial blood gas analysis revealed pH, 7.059; PaO₂, 144.3 mmHg; PaCO₂, 8.5 mmHg; HCO₃, 2.3 mEq/L and base excess of -25.6 mEq/L. Plasma ketone body was remarkably elevated (14880 µmol/L; normal range, 28-120).

Fig. 1. Clinical course. Computed tomography scanning images of pancreas shows that there are no morphological signs of acute pancreatitis such as enlargement of the pancreas, pancreatic necrosis, or peripancreatic or pancreatic fluid collections [26]. PSTi: pancreatic secretory trypsin inhibitor

cose level was 79 mg/dL and 89 mg/dL on February 8 in 2006 and on November 18 in 2006, respectively (Figure 1). He had flu-like symptoms 10 days before admission and developed thirst, polyuria and anorexia with 9 kg of body weight loss in a week. Random plasma glucose level 5 days before or on admission was 473 or 983 mg/dL and HbAlc was 6.7% or 7.5%, respectively. He drank a large amount of Japanese tea, but not sweetened beverage during the abrupt onset of diabetes, eliminating the possibility of soft drink keto sis [8-10].

Physical examination on admission showed that his skin and tongue were dry due to the dehydration. His height was 161 cm and weight was 62.5 kg. Blood pressure was 104/56 mmHg. Laboratory findings revealed a red blood cell count of 408 x 10⁴ /mm³, hemoglobin at 13.5 g/dL, and hematocrit at 39.2%. The

Despite high levels of serum pancreatic enzymes (Figure 1), lack of severe abdominal pain and no morphological change of pancreas in the abdominal CT scan indicated that the diagnosis of coexisting acute
pancreatitis [11] was unlikely (Figure 1). These overall findings suggested the diagnosis of FT1DM. However, urinary and plasma C-peptide levels showed that insulin secretion was not depleted (urinary C-peptide on 5th hospital day, 14.6 μg/day; random plasma C-peptide on admission, 2.68 ng/mL). Furthermore, an examination of autoimmune antibody revealed the presence of high titer anti-glutamic acid decarboxylase (GAD) antibody (116.0 U/mL). Other autoimmune antibodies such as islet cell antibody (ICA), insulin autoantibody (IAA) or anti-insulinoma-associated antigen 2 (IA-2) antibody were not detected. Thyroid autoantibodies to thyroid peroxidase and thyroglobulin were negative. His HLA type was A02, A24, B35, B46 in class I antigen, and DRB1*0803, DRB1*0901, DQB1*0601, DQB1*0303 in class II antigen.

Intensive insulin therapy was initiated and plasma glucose level was normalized and ketoacidosis disappeared in a couple of days. Oral intake was initiated a day after admission, but increased serum pancreatic enzyme levels gradually lowered back to the normal range in 2-3 weeks only by the treatment for diabetes (Figure 1). Laboratory findings on January 10 in 2007 were the following: a red blood cell count 375 x 10^6 /mm^3; hemoglobin 12.2 g/dL; hematocrit 37.3%; BUN 16.7 mg/dL and creatinine, 0.74 mg/dL. The HbA1c level has been controlled at 6.1-6.5% over 25-30 units/day insulin. He has not developed major diabetic complications such as neuropathy, nephropathy or retinopathy in the course of the disease. One year after the abrupt onset of diabetes, GAD antibody was 7.3 U/mL and fasting plasma C-peptide was 0.82 ng/mL. Two years after the onset, GAD antibody was still positive (11.3 U/mL) and plasma C-peptide was 0.61 ng/mL and 0.90 ng/mL before and 6 min after intravenous glucagon (1mg) injection, respectively. As shown in Figure 1, the clinical course indicates the diagnosis of autoimmune type 1 diabetes which shows slow progression of pancreatic beta cell destruction despite abrupt onset with ketoacidosis.

Discussion

Imagawa et al. [4] described difference between FT1DM and nonfulminant autoimmune type 1 diabetes for their clinical characteristics. According to their report, FT1DM accounts for around 20% of the ketoacidosis-onset type 1 diabetes cases in Japan and has more severe metabolic derangement than in autoimmune type 1 diabetes [4]. The following findings in the present case meet the proposed criteria for FT1DM [5]: (1) the extremely abrupt onset (around a week) with the presence of ketoacidosis at diagnosis, (2) plasma glucose level ≥ 288 mg/dL (16.0 mmol/L) and HbA1c level <8.5% at first visit, (3) elevated serum pancreatic enzyme levels, and (4) preceding flu-like symptoms. However, the presence of high titer anti-GAD antibody at onset and the gradual functional destruction of pancreatic beta cells over two years after the onset of the disease definitively eliminate the diagnosis of FT1DM. Thus, the present case is diagnosed as abrupt onset autoimmune type 1 diabetes.

Although his urinary C-peptide level (14.6 μg/day) did not meet the criteria for FT1DM (<10 μg/day) at onset, it might be low enough to develop overt diabetes along with viral infection-associated insulin resistance. Despite having HLA-A24, known to be associated with rapid destruction of beta cell function [14], insulin secretion in this patient was gradually depleted over around 2 years after clinical onset. It is known that, in general, beta cell function is not completely destroyed at onset and the rate of beta cell destruction is relatively slow in autoimmune type 1 diabetes [15, 16], consistent with the autoimmune characteristics of this case.

Exocrine pancreatic involvement at clinical onset is more frequently observed in FT1DM than in acute (but not extremely abrupt) onset autoimmune type 1 diabetes [4]. Although diabetic ketoacidosis per se is known to induce non-specific elevation of serum pancreatic enzymes [17-20], there may be the damage of the exocrine pancreas through viral-associated inflammation.
in FT1DM [3, 5, 21]. More studies including the pancreas histology will be needed to clarify whether patients with abrupt onset autoimmune type 1 diabetes also exhibit nonspecific inflammation to the exocrine pancreas as well as the specific insulitis.

Susceptibility and resistance to the development of type 1 diabetes is known to depend largely on the genetic background [2]. According to previous HLA reports [5, 22-24], HLA DRb1*0901-DQb1*0303 haplotype, which was seen in this patient, appears to be associated with autoimmune type 1 diabetes rather than FT1DM in Japan. Interestingly, class II HLA haplotypes (DRb1*0803, DRb1*0901, DQb1*0601, DQB1*0303) in a FT1DM patient with positive anti-GAD antibody was identical to those seen in this patient [7], although frequency of DRb1*0803-DQB1*0601 or genotypic combination (DRb1*0901-DQB1*0303/ DRb1*0803-DQB1*0601) was not different between type 1 diabetes and control [22].

In conclusion, we report the rapidly progressing autoimmune type 1 diabetes with advanced flu-like symptoms and exocrine pancreatic involvement at onset, mimicking FT1DM. Viral infection may trigger the immune response leading either to non-specific alpha and beta cell destruction by T cells in typical FT1DM patients [5, 25] or to the specific insulitis through the production of islet-related antibodies in patients with abrupt onset autoimmune type 1 diabetes. Similar cases should be accumulated to clarify pathophysiological similarities and/or differences between FT1DM and abrupt onset autoimmune type 1 diabetes.

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References


