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A Case of Type 2 Diabetes Mellitus in an Elderly Patient with Rapid Attenuation of Insulin Secretion that Resembled Fulminant Type 1 DM but with Incomplete Beta Cell Damage

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Abstract. We recently encountered a 66-year-old Japanese man who had suffered from acute hyperglycemia following flu-like symptoms during treatment of type 2 diabetes. Despite significantly increased plasma glucose levels, HbA1c was only slightly elevated. The possibility of autoimmune type 1 diabetes was excluded because of negative islet-related autoantibodies. Serum levels of pancreatic exocrine enzymes, amylase, lipase, and elastase-l were elevated. However, the insulin-secreting function of his islets was not severely damaged. This case is particularly notable for two reasons. First, it showed a fulminant type 1 diabetes-like clinical onset, but his beta cell function was fairly preserved. Second, it developed during the treatment of type 2 diabetes in an elderly patient.

Key words: Fulminant type 1 diabetes, Type 2 diabetes, Elderly

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TYPE 1 diabetes is an insulin-deficient status due to severe destruction of pancreatic beta cells, and is classified into two subtypes, type 1A and type 1B. Type 1A diabetes is caused by autoimmune mechanisms and is associated with islet autoantibodies, such as the GAD antibody, whereas type 1B is not. Recently, Imagawa *et al.* reported a cluster of cases among patients with type 1B diabetes that was characterized by its acute onset and progression, and named this type "fulminant type 1 diabetes" [1]. This subtype is known to be frequent among Japanese. Features of fulminant diabetes include 1) abruptly (within a week) and remarkably elevated plasma glucose levels associated with ketosis or ketoacidosis, frequently with flu-like or abdominal symptoms at onset, 2) a normal or slightly supranormal (below 8.3%) HbA1c level, 3) negativity for islet autoantibodies, and 4) elevated pancreatic exocrine enzymes [1]. In cases of fulminant type 1 diabetes, many previous reports have shown that the beta cell function to secrete insulin is rapidly and almost completely depleted, and patients often suffer severe clinical manifestations such as coma. Here we report a case of an elderly man who developed acute hyperglycemia during treatment for pre-existing type 2 diabetes. The clinical and pathophysiological conditions were similar to those of fulminant type 1 diabetes, but his symptoms were extremely mild, and the insulin-secreting capacity of the beta cells was not completely attenuated.

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Case Report

A 66-year-old man was admitted to our hospital because of hyperglycemia on August 30th, 2004. He had been diagnosed with type 2 diabetes 7 years previously

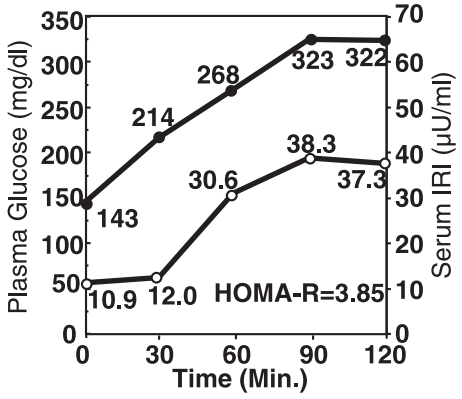

Fig. 1. Seventy-five grams oral glucose tolerance test (OGTT) performed one year before admission. Plasma glucose (solid circles) and serum IRI (open circles) concentrations were measured every 30 minutes for 120 minutes.

at a nearby clinic. A 75 gram oral glucose tolerance test (OGTT) performed one year before revealed a diabetic pattern, with both elevated fasting and postprandial plasma glucose levels (Fig. 1). The Homeostasis Model Assessment insulin resistance index (HOMA-R) was calculated as 3.85. At this time his height was 169 cm and weight 60.6 kg; his BMI was 21.2 kg/m^2, and his HbA1c level was 6.6%. He was advised to follow a 1,840 kcal per day diet and to exercise regularly. He also learned self-monitoring of blood glucose (SMBG) and started checking glucose levels himself. Other than these lifestyle corrections, he was treated with oral hypoglycemic agents, mitiglinide (30 mg/day), voglibose (0.6 mg/day) and pioglitazone (30 mg/day). With these treatments, his recent HbA1c level was well controlled between 5.5–6.5%. Twelve days before admission, he had flu-like symptoms and combination cold remedy and antibiotics were prescribed for 3 days. His symptoms (cough and rhinorrhea) soon disappeared, but his SMBG data gradually rose after that and reached a level higher than 400 mg/dl 5 days later. Although he had no signs of hyperglycemia, such as thirst or polyuria, he consulted the nearby clinic and the physician introduced him to our hospital for further examination and glycemic control.

On admission, physical examination revealed his weight to be 58.1 kg with a BMI of 20.3 kg/m^2. He had no family history of diabetes, and no history of excessive soft drink consumption. Laboratory data on admission are shown in Table 1. The plasma glucose level was significantly elevated, but the blood hemoglobin A1c level remained at 7.5%. Unfortunately, a blood gas analysis was not performed, but ketone bodies were detected in the urine. Pancreatic enzymes, amylase, lipase and elastase-1 levels were all elevated. The level of C-peptide excreted in the urine was decreased, but remained at 14 μg per day. The serum C-peptide levels before and 5 minutes after intravenal injection of 1 mg glucagon were also maintained at 0.6 and 1.3 ng/ml, respectively. Tests for the presence of islet autoantibodies, such as the anti-GAD antibody or insulinoma-associated protein-2 (IA-2) antibody, were

Table 1. Laboratory data on admission

Urinalysis	
Protein	(–)
Glucose	(4+)
Ketone	(+)
CBC	
WBC	6660/mm^3
RBC	443×10^4/mm^3
Hb	13.8 g/dl
Hct	38.9%
Plt	21.1×10^4/mm^3
Blood Chemistry	
TP	7.9 g/dl
GOT	27 IU/l
GPT	34 IU/l
LDH	184 IU/l
ALP	166 IU/l
BUN	18 mg/dl
Cre	1.0 mg/dl
T-Chol	177 mg/dl
TG	63 mg/dl
LDL-C	135 mg/dl
HDL-C	51 mg/dl
Glucose	519 mg/dl
HbA1c	7.5%
Pancreatic Exocrine Enzymes	
Amylase	129 IU/l
Lipase	280 IU/l
Elastase-1	1560 ng/dl
Insulin Secretory Functions	
Urinary C-Peptide	14 μg/day
Fasting serum C-Peptide	0.6 ng /ml
(After Glucagon Stimulus)	1.3 ng /ml
Islet Autoimmune Antiboby	
GAD autoantibody	1.3 U/ml
IA-2 autoantibody	<0.25 U/ml
HLA-DRB1-DQB1 genotypes	
DRB1*1501-DQB1*0602	
DRB1*1302-DQB1*0609	

negative. Abdominal ultrasound revealed no signs of pancreatitis or pancreatic tumors. HLA-DRB1-DQB1 genotypes revealed heterozygous haplotypes of DRB1*1501-DQB1*0602 and DRB1*1302-DQB1*0609.

Intensified treatment with insulin was started. The patient was administered insulin aspart three times a day subcutaneously before each meals and NPH insulin once a day at bedtime. The total insulin dose was 20 units per day at first, but the glucose level remained pertinaciously high, and we gradually increased the dosage of insulin, reaching a maximum 72 units per day on the 16th hospital day (Fig. 2). After that, however, the insulin requirement decreased; at discharge, the needed daily insulin dosage was 58 units. After discharge, the dosage was further decreased to 38–40 units per a day, a level at which his plasma glucose has been well controlled for a long period. His latest HbA1c level was 6.0% with 38 units of daily insulin 11 months after discharge. We performed a glucagon stimulation test at 3 months and 11 months after discharge, during which serum C-peptide levels remained unchanged (Table 2).

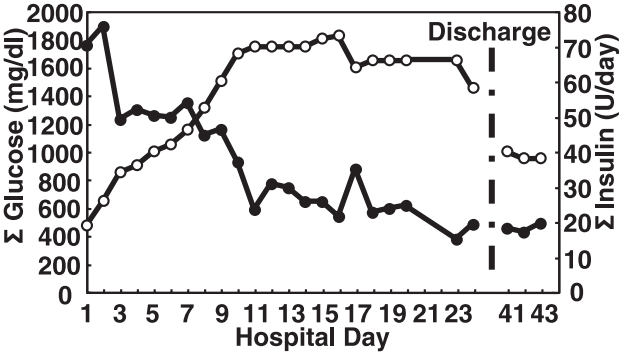

Fig. 2. Time course of glucose level and total insulin dosage. Σ Glucose (solid circles) represents the summation of self-monitored blood glucose (SMBG) data, which was measured 4 times daily, before every meal and at bedtime. Σ Insulin (open circles) represents the total injected dosage of daily insulin.

Table 2. Long-term follow up of insulin secreting function by glucagon stimulation tests. Serum C-peptide was measured before and 5 minutes after the intravenal injection of 1 mg glucagon.

Date	Pre (ng/ml)	Post (ng/ml)
2004/09/06	0.6	1.3
2004/12/22	0.5	1.1
2005/08/09	0.8	1.7

Discussion

Fulminant type 1 diabetes is characterized by its remarkably acute onset and negative finding of islet-related autoantibodies [1]. Imagawa *et al.* gave its diagnostic criteria as follows: 1. ketosis or ketoacidosis within one week after the onset of hyperglycemic symptoms; 2. HbA1c <8.5% on the first visit; and 3. urinary C-peptide excretion <10 μg/day, or serum C-peptide <0.3 ng/ml at fast and <0.5 ng/ml after the injection of 1 mg of glucagon. Our case met the first 2 criteria but not the third, because the insulin secreting function of his islets was fairly well-preserved. However, this case showed other characteristics of fulminant diabetes; an absence of islet autoantibodies, an increase in pancreatic exocrine enzymes, and the existence of preceding infectious symptoms. These findings suggest that this case shows a pathophysiological state quite similar to fulminant diabetes, except that the secretory capacity of the beta cells was not completely destroyed. The preserved beta cell function could account for the lack of severe symptoms in this case, such as a disturbance of consciousness, that are associated with many cases of typical fulminant diabetes. Imagawa has reported that cases categorized as fulminant type 1 diabetes show more severely diminished C-peptide levels compared with autoimmune type 1 diabetes [1], and there have been only a few reports of fulminant type 1 diabetes in which the secretory capacity of the beta cells was shielded. Tanaka *et al.* reported a fulminant case in which urinary C-peptide levles improved from 9.5 μg/day on admission to 34.6 μg/day 6 months later [2]. Our case, however, already showed a higher C-peptide level on admission, and the beta cell function has remained consistent. In the report by Imagawa *et al.*, higher injected insulin dosages are reported to be needed in cases of fulminant type 1 diabetes (0.7–0.8 units/kg/day) than in cases of autoimmune type 1 diabetes (0.5–0.6 units/kg/day) [3]. In our case, good control of plasma glucose has been achieved using 0.67 units/kg/day of insulin, a dose that is intermediate between those used for the two types of type 1 diabetes.

There are several other features that distinguish our case from classical fulminant cases. First, it occurred in an elderly patient. Imagawa *et al.* reported that the occurrence of fulminant diabetes is distributed over quite a broad range of age, from 5 to 80 years old [3]. However, there have been only a few published case reports on patients over 65 years old [4, 5], which

seems to suggest that fulminant type 1 diabetes is relatively rare in the elderly population. Second, the onset in our case occurred during treatment of pre-existing type 2 diabetes. Cases that switch from type 2 diabetes to fulminant type 1 diabetes are extremely rare, reported only in a few conference records. Another explanation for why this case did not show any typical severe symptoms of fulminant diabetes may be that he had regularly been monitoring his glucose levels by himself during treatment for type 2 diabetes, and so was aware of any prominent increases in glucose levels, and sought help at our hospital before those symptoms appeared. The pre-existing insulin resistance could account for the need to administer large amounts of insulin, 72 units per day (1.24 units/kg) at the maximum dosage, to normalize his glucose levels during the early hospitalization period, despite the preserved capacitance of insulin secretion.

The reason for the partial deterioration of beta cell function in this case is uncertain. Conversion from type 2 diabetes to a fulminant-like condition could, in part, account for the mild exacerbation. In obesity-induced insulin resistance, hyperplasia of the beta cells is frequently observed as a result of compensatory increases in cell number, although insulin release from each cell is attenuated to some degree [6]. Such beta cell proliferation might have protected the islets from complete destruction in this case.

Another possibility is the effect of pioglitazone, an agonist of peroxisome proliferator-activated receptor-gamma (PPARγ), taken by this patient for treatment of type 2 diabetes. It is well understood that PPARγ ligands reduce inflammatory responses in various tissues. In fulminant type 1 diabetes, infiltration of T-cells in the exocrine pancreas is observed, and it is estimated that T-cell-mediated autoimmunity is involved in the onset [7]. Some reports have shown that pioglitazone ameliorates experimental autoimmune myocarditis [8] or multiple sclerosis [9] by modulating T-cell functions. Thus it could be supposed that pioglitazone effectively defused the destructive process in the onset of this case, which presumably resulted in the preserved beta cell function.

The genetic background of the host or pathogen may also be related to the severity of disease. It has been reported that most Japanese patients with fulminant diabetes have at least one of two HLA haplotypes, DQA1*0303-DQB1*0401 or DQA1*0302-DQB1*0303 [10]; Nakamura *et al.* reported that a homozygous HLA-DRB1*0405-DQB1*0401 haplotype is frequently observed in Japanese patients with fulminant type 1 diabetes [11]. The DRB1*1501-DQB1*0602 and DRB1*1302-DQB1*0609 HLA haplotypes, determined in our case, have not been reported elsewhere. It is of interest that the HLA-DQB1*0602 allele has been recognized to act as protection against susceptibility to autoimmune type 1 diabetes [12]. As for pathogens, some recent reports have shown that infections of several viruses contribute to the development of fulminant type-1 diabetes, including human herpes virus 6 (HHV-6) [4] and enterovirus [13], although we did not examine antibody titers for those viruses. Further study will be needed to clarify the relationship between the etiology of fulminant type-1 diabetes and the degree of damage.

In conclusion, we experienced a case of type 2 diabetes in an elderly patient whose insulin secretory property was drastically attenuated. His symptoms did not meet the diagnostic criteria for fulminant type 1 diabetes because of the relatively mild damage to his beta cells, but it resembled fulminant type 1 diabetes in its abrupt onset and elevated pancreatic enzyme levels. We consider it quite meaningful to accumulate cases such as this, that is, incomplete beta cell damage or transition from type 2 diabetes. Investigations of those cases may clarify the physiological and pathological differences between classical fulminant type 1 diabetes and other atypical conditions such as this case.

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