Fulminating Onset Type 1 Diabetes with Positivity for Anti-GAD Antibody and Elevated Pancreatic Exocrine Enzyme Concentrations

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Abstract

A 52-year-old man was admitted to our hospital for diabetic ketoacidosis. On admission, Hb_{A1c} was 6.5%, anti-GAD antibody 10.3 U/ml, serum amylase 144 IU/*l*, lipase 169 U/*l* and elastase-I 1,000 ng/dl. There were no abdominal symptoms, and abdominal CT showed unremarkable findings. He was treated with intensive insulin therapy. After 1 month, urinary excretion of C-peptide was 3.8 μg/day. Serum pancreatic exocrine enzyme concentrations returned to normal after 3 months. After 10 months, anti-GAD antibody had become negative, but insulin therapy was still needed for glycemic control. This report concerns a case of autoimmune fulminating onset type 1 diabetes.
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Key words: diabetic ketoacidosis, fulminant type 1 diabetes, anti-GAD antibody, pancreatic exocrine enzyme

Introduction

According to the American Diabetes Association Expert Committee 1997 guidelines, type 1 diabetes mellitus can be classified into immune-mediated diabetes (type 1A) and idiopathic diabetes (type 1B) (1). While the former is characterized by the presence of islet-related autoantibodies such as anti glutamic acid decarboxylase (GAD) antibody and IA-2 antibody, the latter lacks immunological evidence of beta cell autoimmunity. The rate of beta cell destruction in type 1A diabetes is generally slow in adult patients (2, 3), and the levels of anti-GAD antibody in type 1A diabetic patients are persistently positive for a long time (4). Some forms of type 1B diabetes have no known etiology, and these patients are prone to have diabetes combined with ketoacidosis frequently. Recently, Imagawa et al reported that some patients with type 1B diabetes were characterized by a remarkable abrupt onset, the absence of islet-related autoantibodies and high levels of serum pancreatic enzyme concentrations (5). This subtype is called nonautoimmune "fulminant type 1 diabetes." However, the precise mechanism of beta cell destruction and the significance of the elevated serum pancreatic exocrine enzyme concentrations in this subtype of diabetes remain unclear. Here, we report a case of fulminant type 1-like diabetes with transient anti-GAD antibody positivity.

Case Report

A 52-year-old Japanese man, who had been in good health and drank little, had been suffering from thirst since November 30, 2001. General malaise and poor appetite developed gradually, and he was admitted to a local hospital on December 9. Laboratory data on admission were as follows: white blood cell count of 6,100/μl, hemoglobin of 15.4 g/dl, platelet count of 28.9×10^4/μl, total bilirubin of 0.8 mg/dl, aspartate aminotransferase of 49 IU/*l*, alanine aminotransferase of 64 IU/*l*, γ-glutamyltransferase of 19 IU/*l*, lactate dehydrogenase of 537 IU/*l*, total protein of 5.8 g/dl, amylase of 108 IU/*l* (normal range: 40–120 IU/*l*), creatinine of 0.8 mg/dl, urea nitrogen of 22.5 mg/dl, sodium of 138 mEq/*l*, potassium of 3.8 mEq/*l*, chloride of 102 mEq/*l*, C-reactive

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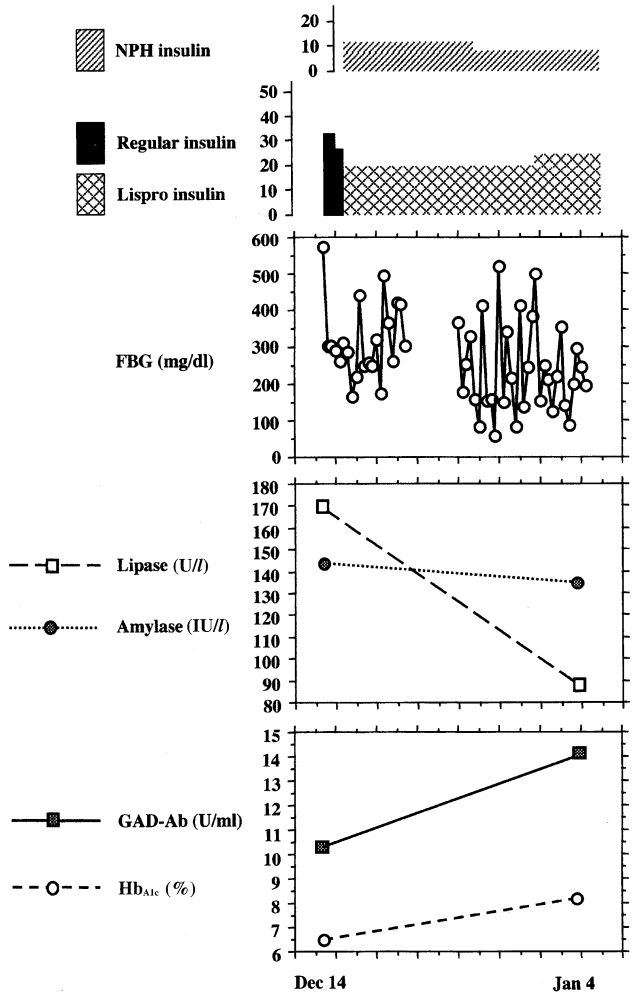

Figure 1. Hospital course. FBG: fasting blood glucose, Hb_{A1c}: glycosylated hemoglobin, GAD-Ab: anti glutamic acid decarboxylase antibody.

protein of 0.7 mg/dl, plasma glucose of 629 mg/dl and ketone body of more than 1,500 μmol/*l*. Laboratory data showed hyperglycemia and ketosis, and he was treated with subcutaneous insulin infusion therapy. However, his blood glucose level remained high, and he was referred to our hospital on December 14.

He was 164 cm tall and weighed 58 kg. Vital signs were body temperature of 36.9°C, blood pressure of 126/87 mmHg, and regular pulse of 119/min. Other physical examinations yielded no remarkable findings. Laboratory data on transfer to our hospital are summarized in Table 1, and showed 6.5% for Hb_{A1c}, 10.3 U/ml for anti-GAD antibody ("Cosmic", Tokyo, Japan; normal range: less than 1.4 U/ml), 144 IU/*l* for serum amylase, 169 U/*l* for lipase (normal range: 9–55 U/*l*) and 1,000 ng/dl for elastase-I (normal range: 72–432 ng/dl). The patient was diagnosed with diabetic ketoacidosis characterized by a relatively low Hb_{A1c} level, positive for anti-GAD antibody and elevated pancreatic exocrine enzyme concentrations. Abdominal enhanced computed tomography (CT) and magnetic resonance imaging (MRI) showed unremarkable findings.

Initial treatment consisted of intravenous infusion of regular insulin (5 U/h for the first 6 hours) and large volumes of saline (mainly 0.9% NaCl 4 *l*/first 12 hours). After these treatments, arterial blood gas analysis in room air showed pH 7.437, $PaCO_2$ 40.1 mmHg, PaO_2 88.5 mmHg, HCO_3^- 26.6 mmol/*l* and base excess 2.7 mmol/*l*, while the blood glucose level had decreased to 261 mg/dl. The patient was prescribed a 1,600 kcal/day diet followed by intensive insulin therapy. Nevertheless, his blood glucose levels remained unstable (Fig. 1). In January 2002, his urinary excretion of C-peptide was as low as 3.8 μg/day, anti-GAD antibody remained positive, and pancreatic exocrine enzyme concentrations remained elevated (anti-GAD antibody 14.0 U/ml, serum amylase 135 IU/*l*, lipase 88 U/*l* and elastase-I 423 ng/dl). No diabetic complications were detected. At discharge from our hospital, his plasma glucose level was between 77 mg/dl and 284 mg/dl with subcutaneous injection of 6 units of insulin lispro before breakfast, 8 units before lunch, 8 units before dinner, and 6 units of NPH insulin subcutaneously at 10 pm.

The levels of pancreatic exocrine enzymes returned to normal in February 2002 (serum amylase 84 IU/*l* and elastase-I 127 ng/dl). In September 2002, both anti-GAD and IA-2 antibodies had become negative (less than 1.3 U/ml and less than 1.0 U/ml, respectively), but the Hb_{A1c} level remained at 10.4% even with intensive insulin therapy (24 units of insulin lispro and 8 units of NPH insulin).

Discussion

Type 1 diabetes mellitus is caused by loss of insulin secreting capacity due to selective destruction of the pancreatic beta cells, and insulitis is the direct result of the autoimmune process. GAD is regarded to be the primary antigen for autoimmunity toward pancreatic beta cells (6), and anti-GAD antibody has definitively been proven to be a sensitive marker for diagnosis of type 1 diabetes (7). However, about 17% of the patients with type 1 diabetes do not have any islet-related antibodies (8).

The American Diabetes Association Expert Committee proposed that type 1 diabetes is subdivided into immune-mediated diabetes (type 1A) and idiopathic diabetes with beta cell destructions (type 1B) in 1997 (1). Imagawa et al described a subtype of type 1B diabetes characterized by the following criteria: 1) regardless of diabetic ketoacidosis, a low level of Hb_{A1c}, suggesting extremely acute onset; 2) no detectable islet-related autoantibody; and 3) high levels of serum pancreatic enzymes (5). Their patients had markedly elevated serum pancreatic enzyme concentrations without the clinical findings of acute or chronic pancreatitis, a finding with the T-lymphocyte infiltration of the exocrine pancreas, and a markedly reduced beta-cell mass without insulitis in the pancreas biopsy specimens. They termed this subtype as nonautoimmune "fulminant type 1 diabetes."

Table 1. Laboratory Data on Transfer to Our Hospital

<Urinalysis>		γ-glutamyltransferase	72 IU/*l*
pH	5.0	Lactate dehydrogenase	503 IU/*l*
Protein	(+)	Cholinesterase	170 IU/*l*
Sugar	(4+)	Total protein	7.4 g/dl
Ketone body	(3+)	Albumin	4.7 g/dl
Occult blood	(+)	Amylase	144 IU/*l*
<Arterial Blood Gas analysis (room air)>		Creatinine	1.0 mg/dl
pH	7.10	Urea nitrogen	20.0 mg/dl
$PaCO_2$	10.8 mmHg	Sodium	131 mEq/*l*
PaO_2	131.1 mmHg	Potassium	5.8 mEq/*l*
HCO_3^-	3.2 mmol/*l*	Chloride	86 mEq/*l*
Base excess	–27.3 mmol/*l*	Total cholesterol	208 mg/dl
<Peripheral blood>		Triglyceride	356 mg/dl
Erythrocyte sedimentation rate	10 mm/h	C-reactive protein	0.4 mg/dl
White blood cell count	20,700/μl	Plasma glucose	576 mg/dl
Red blood cell count	539×10^4/μl	Hb_{A1c}	6.5%
Hemoglobin	16.9 g/dl	Ketone body	>1,500 μmol/*l*
Hematocrit	52.3%	GAD-Ab	10.3 U/ml
Platelet	32.4×10^4/μl	Lipase	169 U/*l*
<Biochemistry>		Elastase-I	1,000 ng/dl
Total bilirubin	0.63 mg/dl	CA19-9	24.84 U/ml
Aspartate aminotransferase	251 IU/*l*	Carcinoembryonic antigen	2.3 ng/ml
Alanine aminotransferase	379 IU/*l*	TPO-Ab	<0.3 U/ml
Alkaline phosphatase	268 IU/*l*	Tg-Ab	<0.3 U/ml
		Hepatitis B virus surface antigen	(–)
		Hepatitis C virus antibody	(–)

Hb_{A1c}: glycosylated hemoglobin, GAD-Ab: anti glutamic acid decarboxylase antibody, TPO-Ab: autoantibody to thyroid peroxidase, Tg-Ab: autoantibody to thyroglobulin.

Recently, Sakurai and Nishimura reported that a case of acute pancreatitis developed into type 1 diabetes (9). Their case was characterized by 1) a low Hb_{A1c} level; 2) low titers for viral antibodies and no detectable islet-related autoantibodies; and 3) elevated pancreatic exocrine enzyme concentrations with diffuse pancreatic swelling seen on abdominal CT. This type 1B diabetes case had sustained the high levels of serum pancreatic exocrine enzymes for 6 months, and the continuation of active pancreatic inflammation may have triggered simultaneous beta cell destruction. However, type 1 diabetes can not be induced only by elevated serum pancreatic exocrine enzyme concentrations, because acute pancreatitis does not usually develop into diabetes. The mechanisms of disease development in these cases with a remarkable abrupt onset, absence of islet-related autoantibodies and high levels of serum pancreatic enzyme concentrations remain unclear.

On the other hand, Shimada et al reported that a case of "fulminant type 1 diabetes" showed high levels of serum interferon-inducible protein 10 (IP-10) and GAD-reactive interferon-gamma-producing CD4+ cells, and suggested that T cell-mediated autoimmunity might be involved (10). Tanaka et al also reported that a case of "fulminant type 1 diabetes" showed CD8 T-cell-dominant insulitis on histopathological examination of the pancreas (11). Another study found an association of hyperlipasemia at clinical onset of insulin-dependent diabetes with a high titer of islet cell cytoplasmic autoantibodies (12). In addition, another case report stated that anti-GAD antibody level showed a gradual increase during the course of the disease diagnosed as "fulminant type 1 diabetes" (13). The mechanism resulting in "fulminant type 1 diabetes" with no detectable islet-related autoantibodies at clinical onset may thus be associated to some extent with autoimmunity.

In the present case, HLA type was A26, A11, B39, B61, CW7, CW8 in class I antigen, and DR8, DR9, DQ1, DQ3 (DRB1*0803, DRB1*0901, DQB1*0601, DQB1*0303) in class II antigen. Although DRB1*0901-DQB1*0303 are confirmed to be major susceptible HLA haplotypes in Japanese patients with type 1 diabetes, DRB1*0803-DQB1*0601 are found rarely and are considered a protective gene (14). We reported a case of fulminating onset type 1 diabetes with positivity for anti-GAD antibody and elevation of serum pancreatic enzyme concentrations transiently, which showed the characteristics of both type 1A and type 1B diabetes. Nakanishi et al have also reported cases of both fulminating onset type 1A and type 1B diabetes with transient elevation of serum pancreatic enzyme concentrations (15). Progressive forms of type 1 diabetes vary considerably from case to case. Similar cases need to be collected to clarify whether the

mechanism resulting in "fulminant type 1 diabetes" is indeed associated with autoimmunity.

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