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A Case of Fulminant Type 1 Diabetes Associated With Significant Elevation of Mumps Titers

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Abstract. Type 1 diabetes mellitus is classified as either autoimmune or idiopathic. Fulminant type 1 diabetes was originally reported as a subtype of idiopathic type 1 diabetes. Though involvement of viral infections has been suggested as a triggering mechanism, its pathogenesis remains unknown. Here, we present a case of fulminant type 1 diabetes associated with significant elevation of mumps titers. A 56-year-old Japanese man had suffered from nausea and generalized fatigue for two days before being transferred to our hospital in a confused state. Findings on admission revealed a high blood glucose level, near-normal HbA1c level, metabolic acidosis, and increased urinary ketone levels. Serum tests for islet-associated autoantibodies were negative. The serum, urinary C-peptide levels and the result of glucagon test indicated severe impairment of insulin secretion. These results were compatible with the diagnosis of fulminant type 1 diabetes. Also, he was suspected as having mumps infection on the basis of serological testing. These findings suggest that fulminant type 1 diabetes developed after mumps virus infection in our case. To the best of our knowledge, no other report has indicated an association between a recent mumps infection and the onset of fulminant type 1 diabetes. This case suggests an association between fulminant type 1 diabetes and mumps virus infection.

Key words: Fulminant type 1 diabetes, Type 1B diabetes, Virus mediated etiology, Mumps virus

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TYPE 1 diabetes mellitus is characterized by insulin deficiency due to severe destruction of pancreatic beta cells. It is now classified as autoimmune (immune-mediated) diabetes (type 1A) or idiopathic diabetes with beta-cell destruction (type 1B) [1]. However, the specific characteristics of the latter are largely unknown. Recently, Imagawa *et al.* reported that fulminant type 1 diabetes is classified into type 1B diabetes. Fulminant type 1 diabetes is characterized by rapid onset of diabetic ketoacidosis within a short period, normal to near-normal HbA1c level at onset and complete beta cell destruction [2]. A nationwide survey of fulminant type 1 diabetes in Japan revealed that fulminant type 1 diabetes accounts for approximately 20% of cases of type 1 diabetes [3]. Although involvement of viral infections as a trigger has been suggested because of the markedly acute onset, the pathogenesis of this type of diabetes remains unknown [2–3]. In this report, we describe a case of fulminant type 1 diabetes associated with significant elevation of mumps titers.

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Case Report

A 56-year-old Japanese man had suffered from nausea and generalized fatigue for two days before being transferred to our hospital in a confused state. Physical findings on admission were height 168 cm and body weight 78 kg, with a body mass index of 27.6 kg/m^2. His mother and brother have type 2 diabetes requiring oral hypoglycemic agent. Laboratory data on admission are shown in Table 1. His plasma

Table 1. Laboratory data on admission

Urinalysis	
glucose	4+
protein	2+
ketone	3+
Complete Blood Count	
WBC	28700/μl
RBC	382 × 10^4/μl
Hb	11.7 g/dl
Hct	35.6%
Plt	28.9 × 10^4/μl
Blood Chemistry	
Alb	3.4 g/dl
BUN	93.5 mg/dl
Cre	2.55 mg/dl
UA	13.5 mg/dl
GOT	72 IU/l
GPT	59 IU/l
LDH	395 IU/l
ALP	237 IU/l
γ-GTP	35 IU/l
T-Bil	0.6 mg/dl
Na	127 mEq/l
K	7.0 mEq/l
Cl	87 mEq/l
T-Chol	190 mg/dl
TG	242 mg/dl
HDL-C	40 mg/dl
Amylase	2461 IU/l
Lipase	8500 IU/l
Glu	766 mg/dl
HbA1c	7.1%
Arterial Blood Gas Analysis on 3 L/min oxygen by mask	
pH	7.129
pO_2	174.0 mmHg
pCO_2	8.0 mmHg
HCO_3^-	2.7 mmol/l
B.E.	–24.3 mmol/l

glucose level was 766 mg/dl and his HbA_{1c} level was 7.1% (normal range 4.3–5.8%). A diagnosis of diabetic ketoacidosis was made, based on the markedly increased urinary ketone levels, arterial blood pH of 7.129 (normal range 7.35–7.45) and a bicarbonate level of 2.7 mmol/l (normal range 22–26 mmol/l). The serum amylase and lipase levels were 2461 IU/l (normal range 30–120 IU/l) and 8500 U/l (normal range 9–55 U/l), respectively. Enhanced abdominal computed tomography (CT) showed no remarkable finding in pancreas on admission. The patient was treated by intravenous infusion of saline and insulin and eventually switched to intensive insulin therapy four times a day. Diabetes-related laboratory data are shown in Table 2. Serum tests for islet-associated autoantibodies (glutamic acid decarboxylase (GAD) antibody, insulin antibody, insulinoma-associated antigen-2 antibody (IA-2) and islet cell antibodies (ICAs)) were negative. The serum and urinary C-peptide levels were markedly decreased (0.1 ng/ml and 7.7 μg/day, respectively). An intravenous glucagon injection (1 mg) failed to produce any significant increase in the serum C-peptide level (which increased from 0.1 ng/ml to 0.3 ng/ml after six minutes), indicating severe impairment of insulin secretion. These results were compatible with the diagnosis of fulminant type 1 diabetes [2]. Genotypic analysis revealed that the patient was heterozygous for the HLA-DRB1 *0901-DQB1*0303, which usually encodes DR9-DQ3. The DR9-DQ3 haplotype is seen in 19.8% of the cases with fulminant type 1 diabetes [4].

We also conducted serological testing for the IgM and IgG antibody titers for mumps virus, rubella virus, varicella zoster virus, cytomegalovirus and Epstein-Barr virus (EBV) viral capsid antigen (VCA) by enzyme-linked immunoassays (EIAs); in addition, the

Table 2. Diabetes related laboratory data on admission

Urinary C-Peptide	7.7 μg/day
Fasting serum C-Peptide	0.1 ng/ml
(After Glucagon Stiumulus)	0.3 ng/ml
GAD antibody	<1.3 U/ml
IA-2 antibody	negative
HLA-DRB1-DQB1 genotypes	
	DRB1* 0901-DQB1*0303
	DRB1* 1302-DQB1*0604

Table 3. Viral antibody titers

		On admission	After 4 weeks
Mumps virus	IgM	—	
	IgG	3.3	16.1
Rubella virus	IgM	—	
	IgG	10.1	15
Varicella zoster virus	IgM	0.83	
	IgG	18	18
Cytomegalovirus	IgM	—	
	IgG	6.7	8.6
EBV-anti VCA	IgM	<10	
	IgG	10	20
Coxsackievirus (A7, B1-6)	CF	<4	<4
Herpes symplex virus	CF	<4	<4
EBV anti EBNA antibody	titers	<10	

serum complement fixing (CF) antibody titers for coxsackievirus (A7, B1-6) and herpes simplex virus, and the serum antibody titers for Epstein-Barr nuclear antigen (EBNA) were also determined. The results revealed significant elevation of the mumps IgG antibody titer (3.3 on admission and 16.1 after four weeks), but no abnormal results were shown in any of the other serological tests (Table 3). According to the current mumps definition and classification approved by the Council of State and Territorial Epidemiologists (CSTE) in 2007, this meets the laboratory criteria for mumps [5]. Therefore, we considered our patient as a suspected case of mumps.

Discussion

Although the definitive cause of fulminant type 1 diabetes is still unclear, susceptibility to fulminant type 1 diabetes is determined by a combination of genetic and environmental factors [2–4]. Two case reports have described fulminant type 1 diabetes developing after the reactivation of human herpes virus-6 or infection with the herpes simplex virus [6–7]. Elevation of IgA antibodies to enterovirus has also been observed in patients with fulminant type 1 diabetes, suggesting that recurrent enterovirus infection may be one of the triggers for the development of fulminant type 1 diabetes [8]. Mumps virus has an affinity for the pancreas, and several reports have discussed the relationship between mumps infection and the onset of autoimmune (type 1A) diabetes [9]. *In vitro* studies have suggested that cytokines released by mumps virus-infected cells and increased expression of HLA molecules by infected beta cells may lead to an immune response against the beta cells, eventually leading to complete loss of beta cell function [10]. The findings in our case suggest an association between fulminant type 1 diabetes and mumps virus infection.

Genetic factors may also contribute to the development of fulminant type 1 diabetes. Imagawa *et al.* reported that DR4-DQ4 haplotype is frequent in fulminant type 1 diabetes. Our patient was heterozygous for the HLA-DRB1*0901-DQB1*0303 haplotype, which usually encodes DR9-DQ3. In the Japanese population, DR9-DQ3 haplotype confers susceptibility to type 1 diabetes but 19.8% of patients with fulminant type 1 diabetes are heterozygous for this haplotype [4].

In conclusion, we experienced a case of fulminant type 1 diabetes associated with significant elevation of mumps titers. To the best of our knowledge, no other report has indicated an association between recent mumps infection and the onset of fulminant type 1 diabetes. Although our patient is classified as a suspected case of mumps, we consider that this report does add to the body of evidence of a viral etiology of fulminant type 1 diabetes. Further study is needed to elucidate the exact pathogenesis.

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