Fulminant Type 1 Diabetes Mellitus Associated with Coxsackie Virus Type A2 Infection: A Case Report and Literature Review

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Abstract

A 65-year-old Japanese man presented to our hospital in June 2013 with a 6-day history of fever and fatigue, a 24-h history of thirst, and polyuria. His temperature was 37.8°C and he was alert. However, laboratory tests revealed severe hyperglycemia, undetectable C-peptide levels, and diabetic ketoacidosis. Serum antibody testing confirmed a Coxsackie virus A2 infection. A variety of viral infections are reported to be involved in the development of fulminant type 1 diabetes mellitus (FT1D). Our patient is the first reported case of FT1D associated with Coxsackie virus A2 infection and supports the etiological role of common viral infections in FT1D.

Key words: fulminant type 1 diabetes mellitus, Coxsackie virus A2, common cold, antiviral antibody, pancreatic enzyme, insulin therapy

(Intern Med 55: 643-646, 2016)

(DOI: 10.2169/internalmedicine.55.5292)

Introduction

Coxsackie viruses, single-stranded RNA viruses of the genus enterovirus, family picornavirus, are divided into two subgroups: A and B (1-3). At least 23 serotypes [serotypes 1 to 22 and 24] of group A and six serotypes [serotypes 1 to 6] of group B are recognized. The clinical manifestations of Coxsackie virus infections in humans are diverse, irrespective of subgroup or serotype and range from asymptomatic infections and common colds to fatal cases of flaccid paralysis or encephalitis.

Fulminant type 1 diabetes mellitus (FT1D) is a subtype of type 1 diabetes mellitus that is characterized by the abrupt onset of insulin-deficient severe hyperglycemia and diabetic ketoacidosis (DKA), which occurs within a few days (4). Most reported patients have been from East Asia, particularly Japan; cases from other regions or involving Cauca-

sians are rare (5, 6). It has been hypothesized that a viral infection may play a role in the pathogenesis of FT1D through the rapid and almost complete destruction of pancreatic beta cells. Studies have reported a variety of viral infections, including Coxsackie virus B1, B3, B4, A4, A5, and A6, to be involved in the development of FT1D (7, 8).

We herein report the case of a patient who developed FT1D accompanied by a Coxsackie virus A2 infection. In addition, all 22 previously reported cases in which a virus infection was considered to be involved in the development of FT1D are reviewed (7-21).

Case Report

A 65-year-old Japanese man who presented with acute thirst and polyuria in June 2013 was admitted to our hospital with a diagnosis of DKA. His medical history was unremarkable, with the exception of mild anemia and dyslipide-

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Received for publication March 7, 2015; Accepted for publication June 11, 2015

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Table 1. Laboratory Findings at the Time of Admission (June 2013).

Hematology		
Red blood cells	402 × 10 ⁴ /μL	(427–571)
Hemoglobin	11.9 g/dL	(12.4–17.2)
Hematocrit	35.5 %	(38.7–50.3)
White blood cells	11,190/μL	(4,000–9,000)
Neutrophils	87.6 %	(36.0–71.0)
Eosinophils	0.0 %	(< 11.0)
Basophils	0.3 %	(< 1.5)
Monocytes	4.0 %	(< 10.0)
Lymphocytes	8.1 %	(20.0–50.0)
Platelets	28.4 × 10 ⁴ /μL	(12.0–30.0)
Chemistry		
Casual plasma glucose	48.3 mmol/L	(3.9–7.8)
Serum C-peptide	< 0.2 ng/mL	
Serum immunoreactive insulin	< 0.5 μU/mL	
HbA1c (NGSP)	6.2 %	(4.6–6.2)
Glycoalbumin	20.9 %	(11.6–16.4)
Acetoacetate	1,275 μmol/L	(< 55)
3-Hydroxybutyrate	6,225 μmol/L	(< 85)
Total protein	6.7 g/dL	(6.7–8.3)
Albumin	3.7 g/dL	(3.8–5.3)
Total cholesterol	206 mg/dL	(130–220)
Triglycerides	94 mg/dL	(50–130)
Aspartate aminotransferase	19 IU/L	(13–33)
Alanine aminotransferase	19 IU/L	(8–42)
Amylase	276 IU/L	(41–112)
Lipase	80 U/L	(5–35)
Elastase-1	3,406 ng/mL	(< 300)
Phospholipase A2	890 ng/dL	(130–400)
Urea nitrogen	30.5 mg/dL	(8.0–22.0)
Creatinine	1.12 mg/dL	(0.60–1.10)
Sodium	130 mmol/L	(137–147)
Potassium	5.8 mmol/L	(3.5–4.7)
Chloride	94 mmol/L	(98–108)
C-reactive protein	5.81 mg/dL	(< 0.30)
Arterial blood gas analysis under room air		
pH	7.291	(7.35–7.45)
Partial carbon dioxide pressure	25.2 mmHg	(32–48)
Partial oxygen pressure	99.6 mmHg	(83–108)
Bicarbonate	11.8 mmol/L	(21–28)
Urinalysis		
Specific gravity	1.033	(1.006–1.030)
Glucose	4+	(–)
Protein	–	(–)
Ketone bodies	3+	(–)
Occult blood	±	(–)
White blood cells	–	(–)

The reference range for each parameter is shown in parentheses.
NGSP: National Glycohemoglobin Standardization Program (22)

mia, which had been treated with fluvastatin (20 mg/day) since he was 50 years of age. One of his brothers had rheumatoid arthritis. The patient developed a fever and fatigue 6 days before admission. Five days later, he developed thirst and polyuria and was treated with a general cold drug at a local hospital. However, his symptoms worsened, and he visited our hospital the next day.

On admission, the patient was alert, and his body temperature was 37.8°C. He had fatigue, thirst, and polyuria, but did not complain of headache, sore throat, myalgia, or respiratory or abdominal symptoms. He was 170 cm tall and weighed 61 kg. His blood pressure was 100/38 mmHg and his pulse rate was 94 beats per minute. His oral cavity was dry, but no redness or white patches were observed on the pharynx and no vesicular rash or ulcers were observed on

the oral mucous membrane. No chest rales or heart murmurs were detected. His abdomen was soft, flat, and non-tender, and his bowel sounds were normal. There was no exanthema on the skin, swelling of the superficial lymph nodes, muscle weakness, or peripheral edema. An arterial blood gas analysis revealed metabolic acidosis (Table 1). The laboratory findings showed a high white blood cell count, mild anemia, ketonemia, and severe hyperglycemia with normal HbA1c (NGSP) and a high serum glycoalbumin level. In addition, the patient's serum levels of creatinine, urea nitrogen, C-reactive protein, and exocrine pancreatic enzymes, including amylase, lipase, elastase-1, and phospholipase A2, were high. Chest and abdominal computed tomography detected fatty deposition in the liver, but no abnormalities were found in the lungs, pancreas, spleen, or kidneys. Blood and urine cultures were negative. He was diagnosed with DKA and acute renal failure and was treated with intravenous saline and regular insulin.

By the next morning, the patient's thirst and polyuria had resolved, and his temperature (36.7°C), blood pressure (105/51 mmHg), and pulse rate (59 beats per minute) had normalized. His plasma glucose had fallen to 9.2 mmol/L, and his electrolytes were normal. Subcutaneous insulin injection therapy with insulin aspart and insulin glargine was initiated that morning.

On day 7 of admission, the patient's blood chemistry showed improvements in inflammation (white blood cells, 3,970/μL; serum C-reactive protein, 0.29 mg/dL) and renal function (serum creatinine, 0.72 mg/dL; urea nitrogen, 11.1 mg/dL). His fasting serum C-peptide was undetectable (<0.2 ng/mL) before and 5 minutes after intravenous glucagon loading, indicating FT1D. He tested negative for islet-related autoantibodies, such as glutamic acid decarboxylase antibody (<1.3 U/mL), insulinoma-associated antigen-2 antibody (<0.4 U/mL), islet cell antibody (<1.25 JDF units), insulin antibody (<125.0 nU/mL), and zinc transporter-8 antibody (<10.0 U/mL). He was also negative for other organ-specific autoantibodies, such as pituitary cell antibody, thyroid peroxidase antibody, thyroglobulin antibody, thyroid-stimulating hormone receptor antibody, gastric parietal cell antibody, intrinsic factor antibody, and the adrenal cortex antibody. Human leukocyte antigen (HLA) typing showed A*11/24, B*51/67, and C*07:02/14:02 class I genes and DRB1*12:01/16:02, DQB1*03:03/05:02, DQA1*01:02/03:02, and DPB1*02:02/05:01 class II genes.

The patient was discharged in July 2013 after completing a diabetes mellitus self-management education program. His serum levels of amylase, lipase, elastase-1, and phospholipase A2 remained high in August 2013 and then normalized in September of the same year.

The patient continued to undergo treatment with multiple daily insulin injection therapy with insulin aspart and insulin glargine (a total of 30 U/day) as an outpatient. In January 2015, he weighed 56 kg, and laboratory examinations showed the following results: HbA1c (NGSP) 9.3%, casual plasma glucose 7.7 mmol/L, and undetectable serum C-

Table 2. Summary of Reported Patients with a Virus Infection Involved in the Development of Fulminant Type 1 Diabetes Mellitus.

Case	Sex	Age (years)	HLA-DRB1	HLA-DQB1	Viral infection		Appearance of symptoms before the onset of DKA	Impaired consciousness at the onset of DKA	Complicating disorders	Ref.
					Causal virus	Symptoms				
1	Female	60	[DR 4,12]	NA	Coxsackie B3	None	—	(+)	DIHS (diaminodiphenyl sulfone) on steroid therapy	9
2	Female	77	08:03/15:01	06:01/06:02	HHV-6 and cytomegalovirus	None	—	(+)	DIHS (carbamazepine) on steroid therapy	7, 10
3	Female	26	[DR 4,9]	[DQ 3,4]	Herpes simplex virus	Fatigue, headache, upper abdominal pain	1 month	(-)	Acute pancreatitis	11
4	Female	61	[DR 2,4]	NA	HHV-6	None	—	(+)	DIHS (mexiletine) on steroid therapy	12
5	Female	35	04:05/15:02	04:01/06:01	Coxsackie B3	Fever, fatigue	4 days	(-)	None	13
6	Male	64	04:05/(-)	04:01/(-)	Influenza virus B	High-grade fever	8 days	(+)	None	14
7	Male	23	04:05/(-)	NA	Rotavirus	Drowsiness, nausea, upper abdominal pain	NA	(+)	NA	7
8	Female	45	NA	NA	HHV-7	Fever, nausea, upper abdominal pain	NA	NA	NA	7
9	Male	57	04:05/(-)	NA	Rotavirus, HHV-6, and EBV	Fever, nausea, upper abdominal pain	NA	NA	NA	7
10	Male	38	NA	NA	Coxsackie B1 and A4	Headache, nausea	NA	NA	NA	7
11	Male	34	NA	NA	Coxsackie A6	NA	NA	NA	NA	7
12	Male	39	NA	NA	Coxsackie A5	Fever, headache, upper abdominal pain	NA	NA	NA	7
13	Male	61	NA	NA	Cytomegalovirus	Fever, nausea, upper abdominal pain, diarrhea	NA	NA	NA	7
14	Female	25	NA	NA	Cytomegalovirus	Fever, nausea, lower abdominal pain	NA	NA	NA	7
15	Male	56	09:01/13:02	03:03/06:04	Mumps virus	None	—	(+)	None	15
16	Female	39	12:01/(-)	03:03/04:02	Coxsackie B4	Nausea, fatigue	4 days	(-)	None	8
17	Female	49	04:05/15:02	04:01/05:02	Cytomegalovirus	Flu-like symptoms	2 months	(-)	Post kidney transplantation on immunosuppression therapy	16
18	Male	38	04:03/13:02	03:02/06:04	Hepatitis virus type A	Fever, myalgia, gastrointestinal symptoms	1 month	(-)	None	17
19	Female	70	15:01/16:02	05:02/06:02	EBV	Fever	18 days	(-)	Multiple myeloma treated with anti-cancer drugs and steroids	18
20	Male	60	04:05/09:01	03:03/04:01	Parvovirus B19	Erythema	7 days	(+)	None	19
21	Male	65	01:01/15:01	03:01/05:01	Cytomegalovirus	Nausea, diarrhea	4 days	(+)	Pre-existing treated diabetes	20
22	Female	35	04:05/(-)	04:01/(-)	Parainfluenza-3	Fever, cough	5 days	(+)	Myocarditis	21
○	Male	65	12:01/16:02	03:03/05:02	Coxsackie A2	Fever, fatigue	6 days	(-)	None	Present case

All patients had diabetic ketoacidosis (DKA) or ketosis at the onset of fulminant type 1 diabetes mellitus.

All cases were Japanese, except for case 18, who was Korean.

The human leukocyte antigen (HLA)-DR and HLA-RQ serotypes are shown in square brackets.

EBV: Epstein-Barr virus, DIHS: drug-induced hypersensitivity syndrome, HHV: human herpesvirus, NA: not available

peptide. His subsequent clinical course has been uneventful.

Paired serum antiviral antibody test

Antibodies titers were measured in serum samples that were taken at the time of admission (June 2013) and 4 weeks after admission to test for rotavirus, adenovirus, echovirus 6 and 9, Coxsackie virus type A2-A7, A9, A10, A16 and B1-B6, parainfluenza virus 1-3, influenza virus A and B, Epstein-Barr virus, human herpes virus 6 and 7, cytomegalovirus, simple herpes virus, hepatitis A, B, and C viruses, mumps, and parvovirus B19. Of these, a significantly elevated antibody titer was only detected against Coxsackie virus type A2 (more than three steps: from a titer <1:4 to a titer 1:32) by a neutralization test (Nissui Pharmaceutical, Tokyo, Japan). The titer remained high 3 months (1:32), 6 months (1:32), and 1 year (1:32) after admission.

Discussion

The patient developed severe hyperglycemia and DKA

with normal HbA1c (NGSP) and undetectable C-peptide levels after 1 day of hyperglycemic symptoms. These findings are consistent with a diagnosis of FT1D (23). The presence of elevated serum pancreatic enzymes, negativity for verifiable islet-related autoantibodies, and pre-existing flu-like symptoms support this diagnosis.

Coxsackie A2 virus infection, although asymptomatic in many cases, produces common colds, gastroenteritis, respiratory illness, and exanthema (1-3). It can also cause herpangina; less frequent manifestations include aseptic meningitis, paralysis, myocarditis, or hemolytic uremic syndrome. Our patient presented with fever and fatigue without any other symptoms before developing FT1D, and the Coxsackie A2 virus infection was confirmed serologically.

Table 2 summarizes the reported cases in which virus infection was proven to be involved in the development of FT1D (7-21). These cases include adults of both sexes. All of the patients were Japanese, except for case 18, who was Korean (17). Some of the patients had the class II HLA DRB1*04:05-DQB1*04:01 or DRB1*09:01-DQB1*03:03

haplotype, which increase the susceptibility of Japanese individuals to FT1D (24). Many of the patients presented with flu-like or gastrointestinal symptoms, regardless of the causative virus and quickly developed FT1D with or without diabetic coma. Our patient is the first reported case of FT1D to be associated with Coxsackie virus A2 infection. This case supports the etiological role of common viral infections in the development of FT1D.

In conclusion, our patient developed a Coxsackie virus A2 infection that manifested as fever and fatigue and which was involved in the development of FT1D. This case highlights the need to assess individuals with both common colds and acute hyperglycemic symptoms for the presence of DKA, even if they are alert when presenting to the hospital.

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

Acknowledgement

We thank the clinical laboratory technicians of Nagaoka Red Cross Hospital for their helpful technical support.

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