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Case Report

Sudden, Sharp Turn in an AIDS Patient's Course Following the Onset of Fulminant Type 1 Diabetes

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A previously healthy 40-year-old Japanese male was urgently admitted with a 2-month history of dysphagia, 30-kg weight loss, and fever. Human immunodeficiency virus (HIV) antibodies and cytomegalovirus antigenemia were positive. Pneumocystis pneumonia and cytomegalovirus pneumonia were suspected. The patient was diagnosed with acquired immune deficiency syndrome (AIDS). Cytomegalovirus antigenemia became negative 20 days after the positive result. On hospital day 41, he experienced cardiopulmonary arrest. The clinical diagnosis was fulminant type 1 diabetes mellitus. He later developed hypoglycemia and was diagnosed with adrenal insufficiency accompanied by septic shock. He died of multiple organ failure 29 h post-admission to our ICU.

Key words: fulminant type 1 diabetes mellitus, human immunodeficiency virus, cytomegalovirus, hypoglycemia

Type 1 diabetes mellitus (T1D) is caused by severe insulin deficiency that typically results from an autoimmune destruction of pancreatic beta cells [1]. Fulminant type 1 diabetes mellitus (FT1D) is a subtype of T1D, characterized by the abrupt onset of insulin-deficient severe hyperglycemia, diabetic ketoacidosis (DKA), high serum pancreatic enzyme levels, and no diabetes-related autoantibodies [2].

Here we report the case of a patient infected with human immunodeficiency virus (HIV) who subsequently developed FT1D.

Case Report

A previously healthy 40-year-old Japanese male (173.5 cm, 56.8 kg) was admitted to our emergency department with a 2-month history of dysphagia, 30-kg weight loss, fever, dyspnea, and occasional cough with purulent sputum. He was febrile (100.2°F; 37.9°C), had an oxygen saturation of 86% while not receiving oxygen, a pulse rate of 128 beats per min, a respiratory rate of 30 breaths per min, and blood pressure values of 138/97 mmHg. He had an oropharyngeal cyst and inspiratory crackles in both hemithoraces. Laboratory findings were as follows: WBC count, 8,290 cells/mm^3; hematocrit, 34.2%; platelets, 268,000/mm^3; creatinine, 0.53 mg/dL; alanine aminotransferase, 26 U/mL; aspartate aminotransferase, 47 U/mL; total bilirubin, 0.5 mg/dL; β-D glucans, 207.0 pg/mL. The CD4 count was 28 cells/μL. Computed tomography (CT) revealed marked patchy to almost diffuse ground-glass opacity (Fig. 1). HIV antibodies (Western blot) and pp65 cytomegalovirus (CMV) antigenemia test (C7-HRP) were positive (15 infected cells/50,000 leucocytes).

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We suspected pneumocystis pneumonia (PCP) and CMV pneumonia, and we diagnosed the patient as having acquired immunodeficiency syndrome (AIDS). The mycobacterial culture examination and polymerase chain reaction for the detection of mycobacterium tuberculosis were negative. Pentamidine (240 mg×1/day i.v.), methylprednisolone (mPSL) (500 mg×2/day i.v.), and ganciclovir (250 mg×2/day i.v.) were initiated (Fig. 2). Antiretroviral therapy was not performed at that time. Thereafter, the patient's respiratory status improved (oxygen saturation was 100% while receiving 2 L of oxygen through a nasal cannula), with a good level of consciousness.

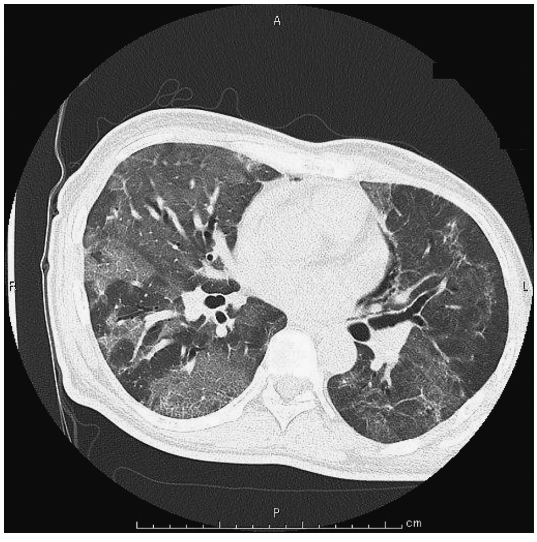

Fig. 1 CT revealed marked patchy-to-almost diffuse ground-glass opacity.

On hospital day 9, chest CT revealed that the patchy to almost diffuse ground-glass opacity had faded somewhat overall, and the infiltrative shadow had also decreased. β-D glucans decreased as well, to 127.8 pg/mL. CMV antigenemia became negative 20 days after the initial positive test. We decreased the ganciclovir to once per day (250 mg×1/day i.v.) 25 days after its initiation. The patient's blood glucose was 86 mg/dL, and the onset of diabetes mellitus (DM) was not confirmed at that time. However, on hospital day 13, the patchy to almost diffuse ground-glass opacity and the infiltrative shadow had become more prominent, and thus antiretroviral therapy was not administered. In addition, only 1 week had passed since the previous CD4+ cell count; as measurements were not taken at this point in time, an estimate of CD4+ cells is unavailable. On hospital day 28, CT revealed that the infiltrative shadow had worsened relative to the previous evaluation.

The patient became comatose and experienced cardiopulmonary arrest on hospital day 41. He was then transferred to our intensive care unit (ICU) after tracheal intubation and resuscitation and was found to be markedly dehydrated with systolic blood pressure 108 mmHg, diastolic blood pressure 49 mmHg, heart

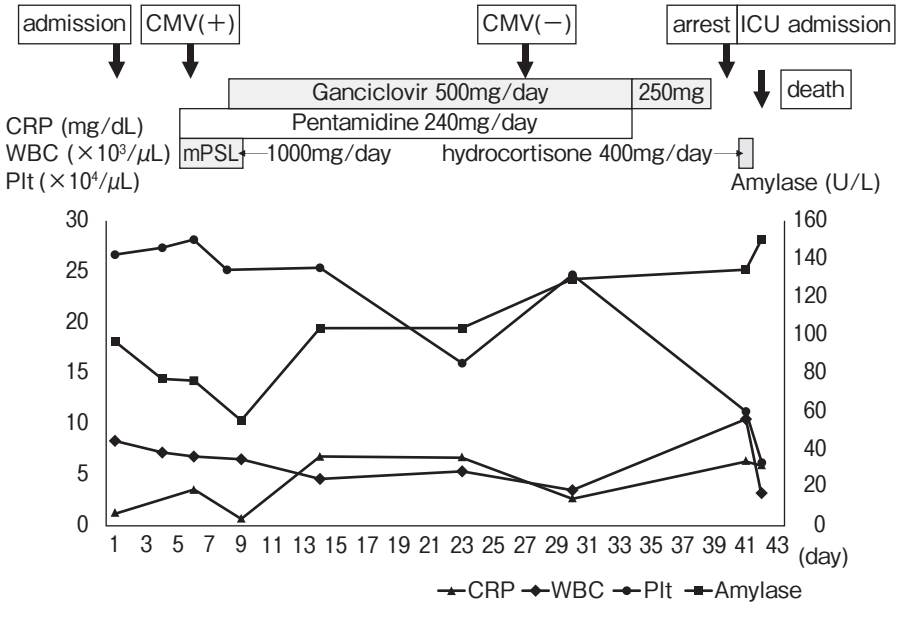

Fig. 2 Time course of the patient's laboratory data, antibiotic treatment, and steroid administration. mPSL: methylprednisolone.

rate 115 beats/min, and respiratory rate 28 breaths per min. His oxygen saturation was 100% while receiving 100% oxygen with an Ambu bag (10 L oxygen). After ICU admission, the patient was connected to a ventilator using the CPAP + PS mode (FiO2 1.0, PEEP3, PS 5). At that point, a blood gas analysis revealed a PaO_2 of 512 mmHg and pCO_2 of 31 mmHg, and his body temperature was 96.4°F (35.8°C). Laboratory findings were as follows (Table 1): WBC count, 3,000 cells/mm^3; hematocrit, 27.6%; platelets, 61,000/mm^3; creatinine, 3.60 mg/dL; alanine aminotransferase, 33 U/mL; aspartate aminotransferase, 29 U/mL; total bilirubin, 0.5 mg/dL. The laboratory data revealed severe hyperglycemic ketoacidosis (plasma glucose, 39.5 mmol/L [711.0 mg/dL]; 3-hydroxyburytic acid, 663 μmol/L [6.9 mg/dL]; arterial pH, 6.89; bicarbonate, 10.4 mmol/L), glycosylated hemoglobin (7.6% of total hemoglobin), and glycated albumin (30.0% of total albumin).

Our analysis of sera obtained at the patient's ICU admission revealed a rapid loss of C peptide to 0.03 ng/mL, from 5.88 ng/mL measured 19 days before the ICU admission. The pancreatic enzyme levels were elevated (serum amylase, 151 U/L). Glutamic acid decarboxylase antibodies were negative. A glucagon load test was not performed at that time. The patient was diagnosed with FT1D. His hyperglycemia and metabolic acidosis were treated with the standard treatment for DKA by measuring blood glucose levels at 30-min intervals, an infusion of 3,200 mL of normal saline and 5,200 mL of Ringer's acetate per day, and continuous insulin injections (3-5 units/h), which were gradually decreased.

Table 1 Laboratory findings at the patient's hospital admission and at the onset of fulminant type 1 diabetes

Variable	On admission	After the onset of FT1D
Complete blood count		
White blood cell count (/μL)	8,290.00	3,000.00
Neutrophils (%)	76.50	97.00
Lymphocytes (%)	17.00	1.00
Monocytes (%)	4.80	2.00
Eosinophils (%)	0.40	0.00
Basophils (%)	0.40	0.00
Red blood cells ($\times 10^4$/μL)	370.00	296.00
Hemoglobin (g/dL)	11.60	8.90
Platelet count ($\times 10^4$/μL)	26.80	61.00
Biochemistry		
Blood urea nitrogen (mg/dL)	13.00	126.00
Creatinine (mg/dL)	0.53	3.60
Amylase (IU/L)	97.00	151.00
C-reactive protein (mg/dL)	1.15	0.03
Na (mEq/L)	139.00	153.00
K (mEq/L)	3.60	4.50
Cl (mEq/L)	98.00	101.00
Glucose (mg/dL)	120.00	711.00
HbA1c (%)	6.20	7.60
Urinalysis		
Glucose	−	−
Protein	1+	1+
Ketone body	−	+
Occult blood	−	−
Diabetes-related tests		
Serum CPR (ng/mL)	5.88 (23rd day)	0.03
Anti-GAD antibody	<5.0	<5.0

CPR: C-peptide Immunoreactivity, GAD: Glutamic Acid Decarboxylase

When the speed of the insulin infusion was reduced to 0.5 units/h or halted, the patient developed hypoglycemia (29 mg/dL or 39 mg/dL, respectively) and hypotension (systolic blood pressure 60-70 mmHg when dopamine was administered at 12 mg/h) at 17 or 21 h after ICU admission, respectively (Fig. 3). Procalcitonin (PCT) was 10.0 ng/mL and *Klebsiella pneumoniae* and methicillin-susceptible *Staphylococcus aureus* were isolated from 2 blood sample cultures (arterial blood) collected 22 h after the patient's ICU admission. We diagnosed adrenal insufficiency accompanied by septic shock, and hydrocortisone (100 mg×4 per day) was started. Although standard therapy was provided for septic shock, the patient died of multiple organ failure 29 h after his ICU admission. As discussed above, given his critical condition and sudden disease progression, we were unable to perform CT scans during the time period from before admission to the ICU to after his discharge from the ICU. Moreover, we did not measure the amount of CD4+ cells. An autopsy was not performed, as the family's consent could not be obtained.

Consent for publication: Written informed consent was not obtained from the patient for the publication of this case report and accompanying images, due to his sudden death from sepsis. As he wished not to inform his family or relatives that he was infected with HIV, we could not obtain written informed consent from his family or relatives either. The publication of this case report was approved by the Ethics Committee of Osaka Medical College (Osaka, Japan).

Discussion

Here we report the case of a patient with HIV infection who developed FT1D. We discuss the following 3 aspects: (1) the association between HIV/AIDS and FT1D, (2) FT1D onset despite negative CMV antigenemia, and (3) the cause of severe hypoglycemia during the course of FT1D. To the best of our knowledge, no previous studies have reported on HIV and/or FT1D as comorbidities.

What underlies the onset of FT1D despite negative CMV antigenemia? We propose 3 hypotheses. First, several types of viruses (including CMV) are known to be involved in the development of FT1D [3]. Potential mechanisms for the role of human CMV in T1D may involve "(1) molecular mimicry induced by T-cell cross-reactivity between human cytomegalovirus and GAD65 in pancreatic islet β-cells; (2) the persistence of HCMV specific CD4+ T-cells or a bystander activity; and (3) persistent infection in β-cells" [3,4]. FT1D may involve a similar type of pathogenesis. Kotani *et al.* [5] investigated the T-lymphocyte response against pancreatic beta cell antigens in F1TD, wherein a peripheral immune reaction was observed in 69.2% of F1TD

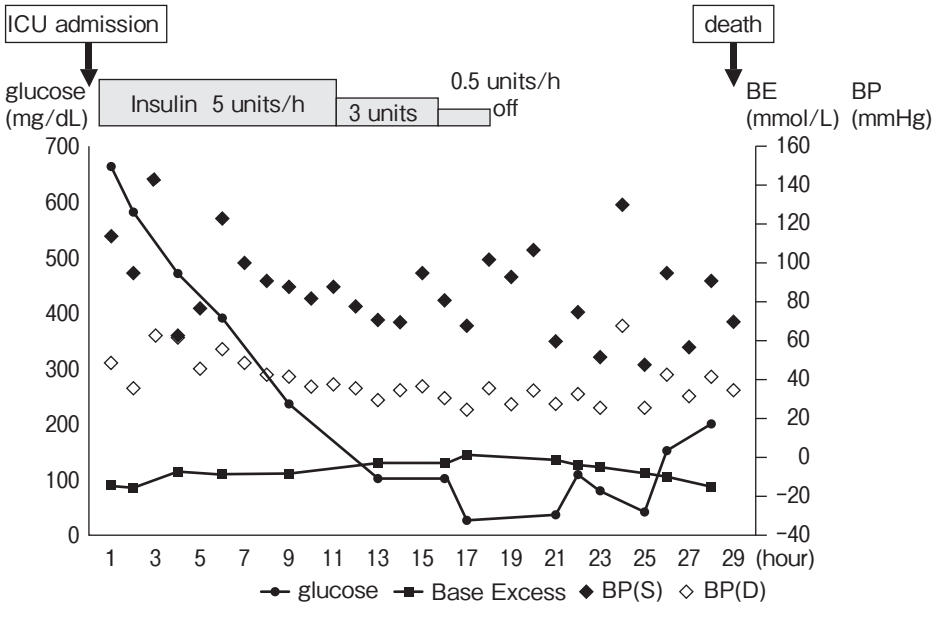

Fig. 3 Time course of the patient's blood pressure, laboratory data, and continuous insulin injections after ICU admission.

patients, indicating that autoreactive T cells might contribute to FT1D development. Although our patient's CMV antigenemia was lost and his FT1D was unaffected at that time, the downstream effects initiated by CMV infection may have proceeded gradually until FT1D onset.

Second, Kano *et al.* [6] reported that several types of herpesviruses can be reactivated in a severe drug-induced multiorgan reaction in the same sequential order as that observed in graft-versus-host disease. Although our patient's CMV antigenemia was negative before his FT1D onset, other viruses may have been reactivated in the patient, leading to the development of FT1D.

Third, the toxicity of pentamidine to beta cells in islets may be involved [7, 8]. Bouchard *et al.* [7] reported that patients treated with pentamidine for PCP exhibited severe fasting hypoglycemia during the treatment and had inappropriately high insulin levels in the post-absorptive state. In contrast, our patient did not exhibit severe fasting hypoglycemia from the time of the initiation of pentamidine administration to the onset of his FT1D (average glucose was 102.5 mg/dL during this period), making it unlikely that pentamidine was the cause of our patient's FT1D.

What caused the patient's severe hypoglycemia during the course of FT1D? This could be explained by adrenal insufficiency accompanied by septic shock. As reported by Annane *et al.*, "Severe sepsis may be associated with relative adrenal insufficiency or systemic inflammation-induced glucocorticoid receptor resistance" [9]. Our patient was in septic shock when he experienced severe hypoglycemia, since his procalcitonin was pretty high (10.0 ng/mL), a blood sample culture was positive, and he had severe hypotension. On the other hand, tuberculosis of the adrenals might have been negative, since the results of a mycobacterial culture examination and polymerase chain reaction for the detection of mycobacterium tuberculosis were negative.

CT scans on the patient's hospital day 28 showed no adrenal hemorrhage, and no evidence for Waterhouse-Friderichsen syndrome was observed. Moreover, CT scans were not taken before the patient's admission to or after his discharge from the ICU. Waterhouse-Friderichsen syndrome is typically caused by *Neisseria meningitidis*, but it has also been reported to be caused by *Streptococcus pneumoniae*, *Neisseria gonorrhoeae*, P*seudomonas aeruginosa*, *Escherichia coli*, *Haemophilus influenzae*, and *Staphylococcus aureus* [10]. In the present case, *Klebsiella pneumoniae* and methicillin-susceptible *Staphylococcus aureus* were isolated from 2 blood sample cultures (arterial blood) collected 22 h after his ICU admission. For cases that involve hypoglycemia and shock as in the present case, a differential diagnosis of Waterhouse-Friderichsen syndrome should be considered. Severe hypoglycemia during the course of FT1D is both very rare and a highly significant finding in this respect. However, we regret that the patient's cortisol and ACTH levels were not measured at the time of FT1D onset.

In conclusion, we report the case of a patient with FT1D and HIV infection who lost CMV antigenemia prior to FT1D onset and exhibited severe hypoglycemia during the course of FT1D.

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