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A case of fulminant type 1 diabetes mellitus accompanied by myocarditis

Shinsuke Hiramatsu[1)], Keishi Komori[1)], Etsuo Mori[2)], Atsushi Ogo[1)], Shunichiro Maruyama[3)] and Seiya Kato[4)]

[1)]*Department of Metabolism and Endocrinology, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka 810-8563, Japan*
[2)]*Department of Cardiology, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka 810-8563, Japan*
[3)]*Department of Internal Medicine, Itoshima Medical Association Hospital, Fukuoka 819-1112, Japan*
[4)]*Department of Pathology and Cell Biology, Faculty of Medicine, University of the Ryukyus, Okinawa 903-0215, Japan*

Abstract. This report presents the case of a 47-year-old female patient with fulminant type 1 diabetes mellitus and myocarditis. Following a high fever, nausea, vomiting and diarrhea, diabetic ketoacidosis occurred and she was transferred to the hospital. The plasma glucose level was 63.6mmol/L and HbA1c was 7.0%. C-peptide was undetectable in her plasma. Blood gas analysis showed a pH of 6.99. Antibodies to glutamic acid decarboxylase nor insulinoma associated antigen-2 were not detected. She was diagnosed to have fulminant type 1 diabetes mellitus. Her electrocardiogram showed diffuse ST-segment elevations on the second day of admission, along with a positive troponin test. However coronary angiography revealed neither occlusion nor stenosis of the cardiac arteries. An endomyocardial biopsy revealed hypertrophic cardiomyocytes with a disarrangement of myofibers and the focal accumulation of mononuclear cells in the stroma, thus suggesting myocarditis or mild myocarditic change. Viruses are an important cause of myocarditis and the preceding flu-like symptoms indicate the association of viral infection with myocarditis in this case. The mechanisms by which fulminant type 1 diabetes mellitus occurs is still uncertain, but the presence of islet injury accompanied by myocardial inflammation in the current case suggested that a viral infection accounted for the onset of this type of diabetes.

Key words: Fulminant type 1 diabetes, Myocarditis, Diabetic ketoacidosis

FULMINANT type 1 diabetes is recognized as a novel subtype of type 1 diabetes, which is a non-autoimmune disorder characterized by a sudden onset, several days duration of diabetic symptoms, the absence of islet-related autoantibodies, exhausted beta-cell function, and elevated pancreatic enzymes in the serum [1, 2]. Although, the precise mechanisms by which beta-cell destruction occurs in fulminant type 1 diabetes are still unknown, an abrupt onset accompanied by flu-like symptoms, infiltration of lymphocytes and macrophages to pancreata and the presence of enterovirus-capsid protein in affected pancreata [3] suggest the involvement of viral infections with this disease. Furthermore, cases with this type of diabetes associated with myocarditis have been reported [4], which thus supports the involvement of a viral infection with the onset of fulminant type 1 diabetes. This report presents the case of a 47-year-old female in whom this type of diabetes occurred along with cardiac muscle injury and a biopsy specimen from the endocardium and myocardium revealed the presence of myocarditis.

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Correspondence to: Shinsuke Hiramatsu, Department of Metabolism and Endocrinology, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Jigyohama 1-8-1, Fukuoka 810-8563, Japan E-mail: hiramatsu@kyumed.jp

Case Report

A 47-year-old female was transferred to the hospital because of diabetic ketoacidosis. Her medical and family histories were unremarkable, except for appendicitis during childhood. She had been healthy until an episode of malaise occurred four days before admission. Three days later, she developed a high fever

Table Laboratory findings

Urine		Total protein	6.3 g/dL
Specific gravity	1.015	Albumin	3.3 g/dL
Glucose	4 +	Aspartate aminotransferase	68 IU/L
Protein	±	Alanine aminotransferase	55 IU/L
Ketone body	++	Lactate dehydrogenase	344 IU/L
White blood cells	30,500 per mm^3	Creatinine kinase	479 IU/L
Hematocrit	37.4 %	Creatinine kinase-MB	74 IU/L
Hemoglobin	11.6 g/dL	Urea nitrogen	42 mg/dL
Platelets	199,000 per mm^3	Creatinine	1.9 mg/dL
Arterial blood gases		Sodium	126 mmol/L
pH	6.887	Potassium	5 mmol/L
Partial pressure of carbon dioxide	9.1 mmHg	Chloride	92 mmol/L
		Amylase	133 IU/L
Partial pressure of oxygen	180.5 mmHg	Elastase-1	1,600 mg/dL
		Glucose	63.6 mmol/L
Bicarbonate	1.7 mmol/L	HbA1c	7.0 %
		Fasting C-peptide	<0.03 ng/mL
		Urine C-peptide	<1.1 μg/day
		Acetoacetate	1,044 μmol/L
		3-hydroxybutyrate	3,122 μmol/L
		anti GAD antibody	<0.3 U/mL
		anti IA-2 antibody	<0.4 U/mL

(39.3^{o}C), nausea, vomiting and diarrhea and she went to the emergency department of her local hospital. On the day of admission, she felt difficulty in speaking and was admitted to the hospital. Glucosuria and ketonuria were detected and her blood glucose level was elevated to 63.6mmol/L. Arterial blood gas analysis showed a pH of 6.887, a partial pressure of carbon dioxide of 9.1 mmHg, oxygen 180.5 mmHg, and bicarbonate content of 1.7 mmol/L. She became lethargic and her blood pressure went down following admission, and she received an infusion of catecholamine. The findings of hyperglycemia, acidemia and ketonuria, indicated a diagnosis of diabetic ketoacidosis. Intravenous infusions with insulin and fluids were initiated and she was transferred to this hospital. She was stuporous, her blood pressure was 120/60 mmHg, pulse was 100 beats per minute, temperature 35.2 ^{o}C. Her breathing was deep, slow, labored and grasping; a pattern of Kussmaul breathing. The oral cavity was extremely dry as was her skin. The remainder of physical examination was normal. The HbA1c was 7.0% (The value for HbA1c (%) is estimated as an NGSP equivalent value (%) calculated by the formula HbA1c (%) =HbA1c (JDS)(%)+0.4%, considering the relational expression of HbA1c (JDS)(%) measured by the previous Japanese standard substance and measurement methods and HbA1c (NGSP) [5]) and C-peptide was undetectable in her plasma. Blood tests showed elevated aspartate aminotransferase, alanine aminotransferase and creatinine. The levels of pancreatic enzymes were also elevated. The sodium level was decreased to 126 mmol/L. Antibodies to glutamic acid decarboxylase or insulinoma associated antigen-2 were negative (Table). The human leukocyte antigen genotype was DRB1 *150101/*160201 and DQB1 *0602/*050201. No abnormality was found in her pancreas on computed tomography or ultrasound studies. The findings of a nearly normal glycated hemoglobin level and lack of insulin secretion with the absence of islet antibodies indicated a diagnosis of fulminant type 1 diabetes mellitus. Supplement with insulin and saline infusion was continued and on the second day of admission, blood glucose level decreased to 19.1mmol/L and a pH recovered to 7.249 and the bicarbonate content recovered to 14.8mmol/L. The sodium concentration increased to 143 mmol/L. She recovered her consciousness, but catecholamine infusion was required to maintain normal blood pressure. Her electrocardiogram showed diffuse ST-segment elevations in the absence of chest pain on the second evening in the hospital. She had a positive troponin test, and cardiac muscle enzymes were elevated (aspartate aminotransferase; 126 IU/L, creatinine kinase; 1,461 IU/L, lactate dehydrogenase; 458 IU/L). An echocardiogram revealed global hypokinesis of the left ventricle and the ejection fraction was slightly

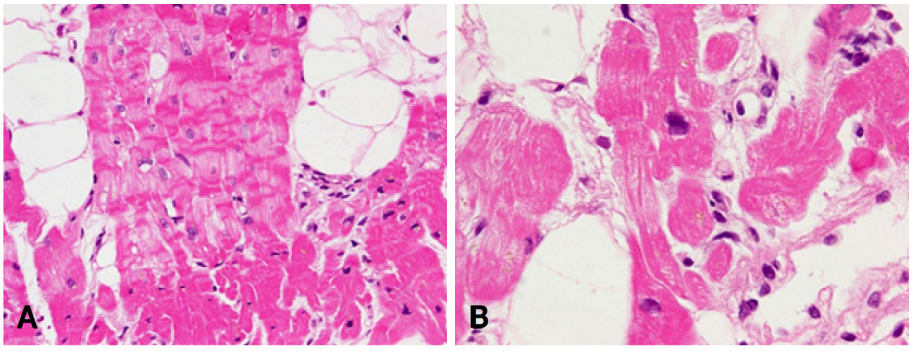

Fig. 1 Endomyocardial biopsy findings A: A mild accumulation of mononuclear cells was focally seen in the interstitium. Fat invasion was also associated in this case. (HE;100×) B: Hypertrophic cardiomyocytes demonstrated enlarged hyperchromatic nuclei and a disarrangement of myofibers. (HE;200×)

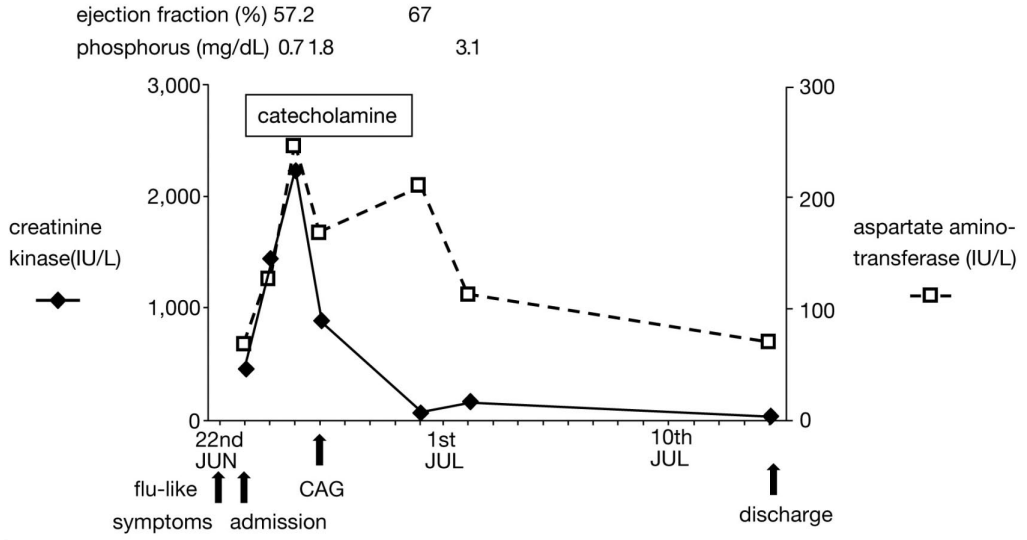

Fig. 2 Clinical course

depressed to 57.2%. Diagnostic considerations included acute coronary syndrome and myocarditis. Coronary angiography was performed on the fourth day. Left ventriculography showed mild diffuse not regional hypokinesis. The ejection fraction was 44%, left ventricular end-diastolic pressure 16 mmHg, pulmonary capillary wedge pressure 9 mmHg. Cardiac output was 4.1 L/min and the cardiac index was 2.6L/min. Angiography revealed normal arteries without any stenosis or obstructions, which indicated a diagnosis of myocarditis. A tissue sample of the endocardium and myocardium was taken during angiography. An endomyocardial biopsy revealed hypertrophic cardiomyocytes with the disarrangement of myofibers and focal accumulation of mononuclear cells in the stroma, thus suggesting myocarditis or mild myocarditic change. However, no fulminant inflammatory infiltration or severe myocytolysis were evident in our case (Fig. 1). Viral antibodies to parainfluenza1-3, rotavirus, cocsackie A-2-7, 9-10, B1-6, cytomegalovirus, EB virus, and HHV6-7 were examined, but none were elevated. The peak of creatinine kinase was on the third day of admission and then the level gradually decreased and returned to normal on the eighth day. ST-segment elevations also disappeared on the fourth day. An echocardiogram on the eighth day revealed a recovered ejection fraction of 67%. Infusion with catecholamine was tapered and ceased on the seventh day. Intravenous insulin infusion was ceased on the fourth day and insulin was given subcutaneously on a sliding scale followed by a fixed doses injection. Hypophosphatemia presented on the third day (0.7 mg/dL) and phosphorus was administered by infusion (Fig.

2). She learned how to monitor her blood glucose and inject insulin and after adjusting the insulin doses, she left the hospital at 23 days after admission.

Discussion

Fulminant type 1 diabetes is recognized as a novel subtype of type 1 diabetes, which is a non-autoimmune disorder characterized by a sudden onset, several days duration of diabetic symptoms, the absence of islet-related autoantibodies, exhausted beta-cell function, and elevated pancreatic enzymes in serum [1, 2]. HbA1c of the current patient was 7.0% and urinary C-peptide excretion was less than 1.1μg/day and ketoacidosis occurred without the preceding hyperglycemic symptoms, and these findings are consistent with the criteria for this type of diabetes [2].

Although, the mechanisms by which beta-cell destruction occurs in fulminant type 1 diabetes are not known, an abrupt onset accompanied by flu-like symptoms and infiltration of lymphocytes and macrophages to the pancreata suggests the involvement of viral infection with this disease. A Japanese survey on this type of diabetes revealed involvement of infection with coxsackie virus type A4,5,6 and B1, rotavirus, cytomegalovirus, EB virus and HHV6,7 [6]. Additionally, an immunohistochemical analysis of three autopsied patients who died from diabetic ketoacidosis after the onset of fulminant type 1 diabetes revealed the presence of enterovirus-capsid protein in all three affected pancreata [3]. The onset of fulminant type 1 diabetes in the current patient was followed by insufficient left ventricular performance. The clinical symptoms of heart failure and fever elevation, evidence of cardiac structural/functional perturbation such as wall motion abnormalities and troponin release, and the pathological findings of a disarrangement of myofibers and an accumulation of mononuclear cells are compatible with myocarditis. A large variety of infections, systemic disease, drugs, and toxins are associated with the development of myocarditis, and of those, viruses are an important cause of this disease. The patient's medical history ruled out drugs and toxins and the preceding flu-like symptoms indicates the association of viral infections with myocarditis. Based on our examination, no significant elevation of viral antibodies was detected, but the possibility that other viruses might also be associated was taken into consideration. Assays using either polymerase chain reaction or *in situ* hybridization would have been useful, but they were not performed in the current case. The simultaneous onset of myocarditis and fulminant type 1 diabetes in this case supports the involvement of viral infections with the onset of this type of diabetes.

Stress induced cardiomyopathy should be also considered because of the similarities in the clinical course and pathological features. This condition is reported in cases with pheochromocytoma or stress induced excessive catecholamine secretion and it is characterized by transient hypokinesis or dyskinesis in the left ventricle and the absence of obstructive coronary arteries. The pathological features are interstitial infiltrates of mononuclear lymphocytes, leukocytes, and macrophages, myocardial fibrosis, and contraction bands with or without myocytes necrosis. These inflammatory changes and myocyte damage are commonly seen in various types of myocarditis, so it is difficult to determine the exact etiology based on histological examinations alone. In spite of these similarities, stress induced cardiomyopathy was ruled out in this case because of the distribution of affected myocardium and the degree of cardiac enzyme elevations. Catecholamine cardiomyopathy usually affects the apical and the midventricular myocardium [7], but it does not cause diffuse hypokinesis, as was observed in our patient. The cardiac enzyme levels are also elevated in stress induced cardiomyopathy, but the elevations are typically mild in contrast to that observed in the current patient.

Another explanation for the myocardial damage is phosphorus deficiency. The association of hypophosphatemia with cardiac function is well documented [8, 9], and hypophosphatemia may have played a role in the insufficient cardiac output, but does not explain the ST segment elevation or histopathological changes in the present case.

Conclusion

This report presented a case of fulminant type 1 diabetes associated with myocarditis. The coincidence of these two diseases suggested that viral infection was involved in the onset of fulminant type 1 diabetes.

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