Fulminant Type 1 Diabetes Mellitus and Fulminant Viral Myocarditis: A Case Report and Literature Review

Nobumasa Ohara, MD, Masanori Kaneko, MD, Hirohiko Kuwano, MD, Katsuya Ebe, MD, Toshio Fujita, MD, Tsuneo Nagai, MD, Tatsuo Furukawa, MD, Yoshifusa Aizawa, MD, and Kyuzi Kamoi, MD

Summary

A 35-year-old Japanese woman was admitted with coma following flu-like symptoms. She was diagnosed with diabetic ketoacidosis and fulminant type 1 diabetes (FT1D) and received intravenous infusion of insulin and saline. The next day, the ketoacidosis disappeared, and she recovered consciousness. However, extensive ST-segment elevations in the electrocardiogram appeared with a positive troponin test, and the patient developed pulmonary edema on day 3. An echocardiogram showed globally reduced wall motion of the left ventricle and mild pericardial effusion. Despite medical therapy with intravenous furosemide, carperitide, and catecholamines, her cardiac function deteriorated rapidly, with the left ventricular ejection fraction decreasing to 26% within 7 hours, and progressed to cardiogenic shock that afternoon. The patient received mechanical circulatory support for 4 days with intra-aortic balloon pumping and percutaneous cardiopulmonary support, and recovered fully from circulatory failure. A paired serum antibody test showed a significantly elevated titer against parainfluenza-3 virus, indicating a diagnosis of fulminant viral myocarditis. She was discharged on multiple daily insulin injection therapy, and her subsequent clinical course has been uneventful. In summary, we present a case of concurrent FT1D and fulminant viral myocarditis. Parainfluenza-3 viral infection was confirmed serologically and was considered to be a cause of both the FT1D and fulminant myocarditis. (Int Heart J 2015; 56: 239-244)

Key words: Fulminant type 1 diabetes, Parainfluenza-3 virus, Mechanical circulatory support, Cytokines

Myocarditis is an inflammation of the myocardium caused by a variety of factors, including bacterial and viral infections, toxins, and immunological disorders. Pathogens frequently causing viral myocarditis include Coxsackie viruses, adenovirus, and parvovirus B19, but other viruses also cause myocarditis, such as parainfluenza viruses. Myocarditis causes heart failure and can have a fulminant clinical presentation. Patients with fulminant myocarditis exhibit acute, severe hemodynamic compromise requiring hemodynamic support for survival, but can recover with minimal sequelae if they survive the initial phase.

Type 1 diabetes mellitus is a metabolic disease characterized by the destruction of pancreatic beta cells, which usually leads to an absolute deficiency of insulin secretion. Fulminant type 1 diabetes (FT1D) is a subtype of type 1 diabetes characterized by the abrupt onset of insulin-deficient hyperglycemia and ketoacidosis within a few days. Most patients have been identified from East Asia, particularly Japan, and infrequently from other regions or Caucasians. Viral infection is suggested to play a role in rapid beta-cell destruction, and a variety of common viral infections have been reported to be associated with the onset of FT1D.

Several cases of concurrent type 1 diabetes and myocarditis have been reported. Here, we report a patient with concomitant FT1D and fulminant viral myocarditis related to parainfluenza-3 infection and review reported cases of simultaneous type 1 diabetes and myocarditis.

Case Report

A 35-year-old Japanese woman with disturbed consciousness was admitted to our hospital in December 2012. She had a full-term normal delivery of her first child 6 weeks prior to admission. Urine glucose tests were negative during pregnancy and 4 weeks after delivery. Her medical and family histories were unremarkable. The patient had been healthy until an episode of fever, sore throat and cough, which occurred 5 days before admission. She developed abdominal pain and vomiting 3 days later, which were treated with levofloxacin at a local hospital.

On admission, she was comatose, and her height and...
weight were 167 cm and 53 kg, respectively. Her body temperature was 34.3°C, and her blood pressure and pulse rate were 79/33 mmHg and 100 beats per minute, respectively. Her oral cavity and skin were extremely dry. No chest rales or heart murmurs were detected. Laboratory findings showed metabolic acidosis (pH 6.94), ketonemia, severe hyperglycemia (69.3 mmol/L), and myoglobinuria. In addition, serum levels of creatinine, potassium, liver transaminase, exocrine pancreatic enzymes, creatine kinase (CK), and C-reactive protein (CRP) were elevated (Table). A urinalysis showed no urinary leukocytes or bacteria. Abdominal computed tomography showed no abnormalities in the pancreas or kidneys, but marked fat deposition in the liver was found. A chest X-ray showed a mildly enlarged heart (Figure 1A), but an electrocardiogram (ECG) revealed no abnormalities (Figure 2), and her troponin test was negative. She was diagnosed with diabetic ketoacidosis, severe dehydration, acute renal failure, and rhabdomyolysis and received intravenous infusion of saline and insulin (Figure 3).

The next morning, the patient regained consciousness, and her temperature (36.2°C), blood pressure (107/59 mmHg), pulse rate (89 beats per minute), and arterial pH (7.36) had normalized. In addition, her plasma glucose levels had fallen to 19.9 mmol/L, and serum concentrations of sodium (143 mmol/L) and potassium (3.8 mmol/L) were normal. However, an ECG showed ST-segment elevation in leads II, III, aVF, and V3-6 without typical reciprocal changes that afternoon (Figure 2). She was free from chest pain or dyspnea, but a troponin test was positive. An echocardiogram showed normal cardiac function with a left ventricular ejection fraction (LVEF) of 60%.

The patient complained of chest pain and dyspnea on the morning of day 3 of admission and developed a moderately high fever (37.5°C). Her blood pressure and pulse rate were 118/85 mmHg and 96 beats per minute, respectively. Her third heart sound was audible, and a chest X-ray revealed acute pulmonary edema (Figure 1B). An echocardiogram revealed globally reduced wall motion of the left ventricle (LVEF 52%) and mild pericardial effusion. Her plasma brain natriuretic peptide (BNP) level (528 pg/mL) was high. Despite a responsive urine output of 1,300 mL within 4 hours following intravenous furosemide (20 mg), her respiratory state and cardiac function deteriorated with an LVEF of 46% on an echocardiogram; 3 hours later, she developed cardiogenic shock (systolic blood pressure below 90 mmHg; heart rate 136 beats per minute) with an LVEF of 26% that afternoon. In addition to medical therapy with intravenous carperitide and catecholamines, mechanical circulatory support was administered urgently using intra-aortic balloon pumping and percutaneous cardiopulmonary support.

The intensive cardiac support was effective, and cardiac function recovered without any fatal arrhythmias (Figure 3), with a peak plasma BNP level of 1,641 pg/mL on day 4. The medication was discontinued after 7 days. Her clinical course indicated a diagnosis of fulminant myocarditis. Laboratory findings 2 weeks after admission showed normalization of se-

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells</td>
<td>$4.46 \times 10^{12}$ /μL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12.9 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>39.4%</td>
</tr>
<tr>
<td>White blood cells</td>
<td>29,800 /mm$^3$</td>
</tr>
<tr>
<td>Platelets</td>
<td>29.0 $\times 10^{3}$ /mm$^3$</td>
</tr>
<tr>
<td>Plasma glucose</td>
<td>69.3 mmol/L</td>
</tr>
<tr>
<td>Serum immunoreactive insulin</td>
<td>&lt; 0.5 μU/mL</td>
</tr>
<tr>
<td>Serum C-peptide</td>
<td>&lt; 0.2 ng/mL</td>
</tr>
<tr>
<td>Acetoacetate</td>
<td>2,790 mmol/L</td>
</tr>
<tr>
<td>3-Hydroxybutyrate</td>
<td>12,850 μmol/L</td>
</tr>
<tr>
<td>Hemoglobin A1c (NGSP)</td>
<td>6.1%</td>
</tr>
<tr>
<td>Total protein</td>
<td>6.7 g/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.0 g/dL</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>374 IU/L</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>138 IU/L</td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>67.4 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.85 mg/dL</td>
</tr>
<tr>
<td>Uric acid</td>
<td>15.8 mg/dL</td>
</tr>
<tr>
<td>Sodium</td>
<td>124 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.9 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>85 mmol/L</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>16,486 IU/L</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>3.20 mg/dL</td>
</tr>
<tr>
<td>Serum amylase</td>
<td>813 IU/L</td>
</tr>
<tr>
<td>Serum lipase</td>
<td>174 IU/L</td>
</tr>
<tr>
<td>Anti-nucleoside antibody</td>
<td>&lt; 40 titer</td>
</tr>
<tr>
<td>Arterial blood gas analysis</td>
<td></td>
</tr>
<tr>
<td>under room air pH</td>
<td>6.94</td>
</tr>
<tr>
<td>Partial pressure of carbon</td>
<td>12.2 mmHg</td>
</tr>
<tr>
<td>dioxide</td>
<td></td>
</tr>
<tr>
<td>Partial pressure of oxygen</td>
<td>145 mmHg</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>2.5 mmol/L</td>
</tr>
<tr>
<td>Urinary myoglobin</td>
<td>218,000 ng/mL</td>
</tr>
</tbody>
</table>

Figure 1. Chest X-ray images. A: A chest X-ray performed in the supine position on admission showed a mildly enlarged heart. B: A chest X-ray performed in the supine position on day 3 of hospitalization revealed acute lung edema. C: A chest X-ray performed in the supine position 4 weeks after admission showed no abnormalities.
rum creatine kinase levels and improvements in inflammatory reactions, renal failure, and rhabdomyolysis. An echocardiogram 4 weeks after admission revealed normal cardiac function with an LVEF of 62% and mildly reduced apical wall motion without pericardial fluid, and a chest X-ray showed no abnormalities (Figure 1C). Her plasma BNP level was 240 pg/mL.

Fasting serum C-peptide was undetectable before and 5
minutes after intravenous glucagon loading. Tests for autoantibodies against glutamic acid decarboxylase (1.4 U/mL, reference range: < 1.5 U/mL), insulinoma-associated antigen-2 (< 0.4 U/mL), and insulin (< 125 nU/mL) were negative. Human leukocyte antigen (HLA) typing showed the presence of A02/24 and B40/54 class I genes and DRB1*04:05(−) and DQB1*04:01 class II genes, indicating a diagnosis of FT1D. The patient began insulin injection therapy on day 11 and was released from the intensive care unit. She was ambulatory on day 23 and was discharged on day 44, without any medications for the chronic phase of myocarditis, such as renin-angiotensin-aldosterone system inhibitors or beta blockers.15

One year later, an ECG showed a complete right bundle branch block (Figure 2). An echocardiogram showed normal function of the left ventricle with a LVEF of 63% and persisting mildly reduced apical wall motion. Her plasma BNP level was 18.9 pg/mL. Thallium-201 uptake was decreased at the apex, but computed tomography angiography of the coronary arteries was normal. Her clinical course has been uneventful without medications other than multiple daily insulin injection therapy.

**Paired serum antiviral antibody test:** Antibodies were measured in serum harvested at the time of admission and 4 weeks later 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, herpes simple virus, mumps and parvovirus B19. Of these, a significantly elevated antibody titer was detected only against parainfluenza-3 virus (4-fold; from × 40 to × 160) using a hemagglutination inhibition assay (Denka Seiken, Tokyo). The titer remained high 6 weeks (× 160), 3 months (× 320), and 12 months (× 320) after admission.

**Serum levels of cytokines throughout the myocarditis course:** Serum concentrations of cytokines such as tumor necrosis factor (TNF)-α, interferon-γ, interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-10, and IL-12 were measured at 9 time points (Figure 3). Samples were assayed at LSI Medience Corporation, Central Laboratory, Tokyo. Serum levels of IL-6 and IL-10 were high at the time of admission and then decreased within a few days. Levels of TNF-α and IL-1β rose from days 6 to 8 and then declined to nearly the minimum detection limits by day 14. Serum levels of the other cytokines were below the minimum detection limits (< 1.56 pg/mL for interferon-γ, < 15.6 pg/mL for IL-2, and < 0.25 pg/mL for IL-4) in all samples.

**Discussion**

The patient met the criteria for a definite diagnosis of FT1D.17 She had several findings in common with the onset of FT1D, including pre-existing flu-like symptoms, negative islet-related autoantibodies, elevated exocrine pancreatic enzymes, and elevated transaminases accompanied by fatty liver. In addition, the class II HLA was homozygous for DRB1*04:05-DQB1*04:01, which increases the susceptibility of Japanese individuals to FT1D.18

Soon after correcting the diabetic ketoacidosis, the patient exhibited circulatory collapse following extensive ST-segment elevation in the ECG. Acute myocardial infarction or takotsubo cardiomypathy was unlikely from her ECG records, echocardiogram findings, laboratory data, and clinical course.19-21 Based on the definition reported previously,12 a combination of FT1D and fulminant myocarditis was the most likely diagnosis.

Figure 4 presents a summary of previously reported cases of simultaneous type 1 diabetes onset and myocarditis.11-14 No similar trends in age, sex, HLA-DR, or HLA-DQ were observed. However, all patients exhibited a combination of FT1D and myocarditis within 2 weeks after flu-like symptoms with fever.

Parainfluenza-3 virus is a common respiratory pathogen that can cause myocarditis.3,4 In our patient, parainfluenza-3 viral infection was confirmed serologically and was considered to be a cause of both FT1D and fulminant myocarditis. This is the first reported case of FT1D associated with a
parainfluenza-3 viral infection.\(^\text{10}\) The patient developed myocarditis soon after ketoacidosis had been corrected with insulin and saline, as observed in previous cases (Figure 3). The pathogenesis of viral myocarditis involves direct viral-induced myocardial injury and post-viral immune-mediated myocyte damage, and the cytokine environment is crucial for immune-mediated myocyte damage.\(^\text{23-30}\)

Our patient exhibited high serum levels of IL-10 and IL-6, which decreased during the correction of ketoacidosis; TNF-α levels increased subsequently (Figure 3). Experimental studies on viral myocarditis have suggested that both IL-10 and IL-6 function as anti-inflammatory cytokines, and they attenuate myocyte damage and inhibit TNF-α elevation during the early inflammatory stage.\(^\text{27,28}\) A viral-induced immune reaction and cytokines are also suggested to play a role in the pathophysiology of the rapid destruction of pancreatic beta cells in FT1D, but there have been few reports on a specific role for IL-6 or IL-10 in the onset of FT1D.\(^\text{31}\) These findings suggest that serial changes in serum cytokines in our patient might be partly explained by viral myocarditis. Additionally, although the underlying reasons were unclear, the decreases in IL-10 and IL-6 suggest that viral myocarditis accompanied by the onset of FT1D might become clinically evident with corrected ketoacidosis, even when ECG abnormalities are not detected before treatment of ketoacidosis.

Despite severe hemodynamic compromise, the elevation in serum CK-MB levels was mild during the course of fulminant myocarditis in our patient (Figure 3). Since circulatory deterioration by myocarditis might depend not only on cardiomyocyte injury but also on interstitial edema or fibrosis,\(^\text{1,2}\) the mild elevation of the myocardial enzyme in our patient probably reflected relatively mild cardiomyocyte injury and was related to successful treatment with relatively short-term mechanical circulatory support.\(^\text{31}\)

In conclusion, we reported a case of concurrent FT1D and fulminant viral myocarditis. Viral myocarditis that is accompanied by the onset of FT1D might become clinically evident after correcting ketoacidosis, even when ECG abnormalities are not detected before ketoacidosis treatment. Therefore, monitoring cardiac function is required during the treatment of ketoacidosis in FT1D cases with suspected viral-induced myocardial dysfunction.

**ACKNOWLEDGMENTS**

We thank Dr Haruo Hanawa, Dr Taku Matsubara, and Dr Hirohito Sone for their excellent advice.

**DISCLOSURE**

Conflicts of interest: The authors declare no conflicts of interest.

**REFERENCES**


23. Matsumori A, Yamada T, Suzuki H, Matoba Y, Sasayama S. Increased circulating cytokines in patients with myocarditis and car-


