Fulminant Type 1 Diabetes Mellitus Presenting 11 Days after Delivery in a Patient of Mixed Genetic Background

Shoko Furukawa, Kazuya Fujihara, Ryo Kumagai, Momoko Isono and Hiroaki Yagyu

Abstract

The patient was a 25-year-old woman whose paternal family was Japanese, maternal grandfather was Filipino, and maternal grandmother was Chinese. Eleven days after delivery, she presented with excessive thirst and disturbed consciousness due to diabetic ketoacidosis. She was diagnosed as having fulminant type 1 diabetes associated with pregnancy (PF). The antibody concentration against glutamic acid decarboxylase was 1.2 (<1.5) U/mL, and human leukocyte antigen (HLA) class II haplotypes were DRB1*04:10-DQB1*03:02 and DRB1*15:02-DQB1*05:01. The present case had unique HLA class II haplotypes that have not been previously reported in association with PF.

Key words: type 1 diabetes mellitus, fulminant type 1 diabetes mellitus, pregnancy, diabetic ketoacidosis, human leukocyte antigen

(Intern Med 55: 1881-1885, 2016)  
(DOI: 10.2169/internalmedicine.55.6052)

Introduction

Fulminant type 1 diabetes mellitus (FT1DM) was first reported as a subtype of type 1 diabetes mellitus (T1DM) by Imagawa et al. in 2000 (1). FT1DM has several unique characteristics, such as an extremely acute onset accompanied by ketoacidosis, nearly normal HbA1c values despite a high plasma glucose concentration, generally negative for diabetes-related autoantibodies, virtually no C-peptide secretion at the onset of diabetes, and increased serum pancreatic enzyme levels (2, 3). In Japan, the prevalence of FT1DM among patients with ketosis-onset T1DM has been reported to be 20% (4), however, it has a very low prevalence in other ethnic groups, especially those of European descent.

FT1DM developing during pregnancy or immediately after delivery is referred to as FT1DM associated with pregnancy (PF) (5). Although the pathogenesis of PF is not fully understood, environmental factors such as viral infections have been suggested in both PF and FT1DM that is not associated with pregnancy (NPF) (4, 5). Genetic factors, such as human leukocyte antigen (HLA) class II, also contribute to the development of PF and NPF, though the relevant HLA class II haplotypes appear to differ in PF and NPF (6, 7). In this report, a patient with PF that developed 11 days after delivery is presented. She had a mixed genetic background (Japanese, Filipino, and Chinese) with unique HLA class II haplotypes that have not been previously reported in association with PF.

Case Report

The patient was a 25-year-old woman whose paternal family was Japanese, maternal grandfather was Filipino, and maternal grandmother was Chinese. She was referred to our hospital due to excessive thirst and disturbed consciousness that had developed one day prior. She had not had flu-like symptoms such as a sore throat, cough, or rhinorrhea. Eleven days before admission, she had delivered a girl at 40 weeks and 6 days by a Cesarean section due to cephalopelvic disproportion. While the newborn’s weight was high (3,948 g), the patient had never been noted to have impaired glucose tolerance or urinary glucose; the blood glucose level was 93 mg/dL, with negative levels of urinary glucose and ketone bodies 4 days before delivery.

On physical examination, the patient had impaired con-
Figure. Clinical course of this case. The HbA1c levels are controlled at around 7.0% with a total of 30-40 units per day (0.38-0.50 units/kg/day) of insulin. The GADab levels decreased to 0.3 U/mL eight months after onset.

consciousness (Glasgow Coma Scale E2V4M5). As shown in Table 1, she developed diabetic ketoacidosis (DKA), with random sample glucose of 1,030 mg/dL, serum C-peptide reactivity (CPR) of 0.02 ng/mL, arterial pH of 7.042, bicarbonate of 4.1 mEq/L, and 3+ urinary ketone bodies. Despite the presence of DKA, the HbA1c value was within the normal range (6.0%), and urinary CPR was extremely low at 0.17 μg/day. In addition, the serum amylase, elastase-1, and lipase levels were increased to 136 (reference range: 30-120) IU/L, 2,690 (<300) ng/dL, and 171 (11-53) U/L, respectively. Antibody against glutamic acid decarboxylase (GADab) was 1.2 (<1.5) U/mL. Neither anti-insulin nor anti-insulinoma-associated antigen-2 antibodies were detected. HLA class II genotypes were DRB1*04:10-DQB1*03:02 and DRB1*15:02-DQB1*05:01. Paired serum examinations for viral infections such as influenza, Coxackie, HSV, HHV-6, CMV, and EBV, which are known to be associated with the development of FT1DM, showed no clear
<table>
<thead>
<tr>
<th>Age (years) after delivery</th>
<th>Onset day (days)</th>
<th>Duration after delivery (days)</th>
<th>Weight of newborn (g)</th>
<th>Serum glucose (mmol/L) (mg/dL)</th>
<th>HbA1c (mmol/mol)</th>
<th>(%)</th>
<th>Serum C-peptide (ng/mL)</th>
<th>Urinary C-peptide (mg/day)</th>
<th>Amylase (U/L)</th>
<th>Lipase (U/L)</th>
<th>Elastase-1 (ng/dL)</th>
<th>Arterial pH</th>
<th>Auto-antibody</th>
<th>HLA serotype</th>
<th>HLA genotype</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>3</td>
<td>3</td>
<td>3,072</td>
<td>74.9 (1,350)</td>
<td>0.2</td>
<td>2.0</td>
<td>2,054</td>
<td>104</td>
<td>490</td>
<td>7.01</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-</td>
<td>DR 9/12</td>
<td>ND&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(9)</td>
</tr>
<tr>
<td>33</td>
<td>14</td>
<td>4</td>
<td>3,212</td>
<td>78.5 (1,414)</td>
<td>62</td>
<td>7.9</td>
<td>&lt;0.1</td>
<td>8.8</td>
<td>372</td>
<td>90</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.03</td>
<td>-</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DR 4/8, DQ 1/4</td>
<td>ND&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>33</td>
<td>13</td>
<td>2</td>
<td>ND&lt;sup&gt;b&lt;/sup&gt;</td>
<td>66.4 (1,196)</td>
<td>49</td>
<td>6.7</td>
<td>0.2</td>
<td>1.6</td>
<td>44</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.12</td>
<td>-</td>
<td>-</td>
<td>DR 4/-, DQ 4/-</td>
<td>DRB&lt;sup&gt;1&lt;/sup&gt;*0405/0405</td>
</tr>
<tr>
<td>26</td>
<td>11</td>
<td>3</td>
<td>2,924</td>
<td>40.2 (725)</td>
<td>51</td>
<td>6.9</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.0</td>
<td>434</td>
<td>118</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.17</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>DR 4/10, DQ 4/5</td>
</tr>
<tr>
<td>29</td>
<td>7</td>
<td>1</td>
<td>2,888</td>
<td>46.4 (835)</td>
<td>54</td>
<td>7.1</td>
<td>0.15</td>
<td>1.6</td>
<td>142</td>
<td>130</td>
<td>470</td>
<td>7.10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>DR 6/11, DQ 1/3</td>
</tr>
<tr>
<td>36</td>
<td>2</td>
<td>1</td>
<td>1,100</td>
<td>36.1 (649)</td>
<td>46</td>
<td>6.4</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17.7</td>
<td>high&lt;sup&gt;c&lt;/sup&gt;</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>DR 4, DQ 3/4</td>
</tr>
<tr>
<td>25</td>
<td>11</td>
<td>2</td>
<td>3,948</td>
<td>57.2 (1,030)</td>
<td>42</td>
<td>6.0</td>
<td>0.02</td>
<td>0.1</td>
<td>136</td>
<td>171</td>
<td>2,690</td>
<td>7.04</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>DR 4/15, DQ 5/8</td>
</tr>
</tbody>
</table>

<sup>a</sup> duration shows the period of hyperglycemic symptoms before the diagnosis of diabetes.

<sup>b</sup> ND stands for ‘not described’.

<sup>c</sup> not mentioned particularly.
evidence of viral infection.

With a diagnosis of FT1DM, the patient was treated with insulin. Her condition improved, and urinary ketone bodies were negative on the third hospital day. Continuous subcutaneous insulin infusion was started after intravenous insulin infusion, with a total of 36.0 units per day (0.45 units/kg/day). Thereafter, her HbA1c levels were controlled at around 7.0% with insulin amounts nearly identical to those used initially. GADab levels became 1.2 and 0.3 U/mL four and eight months, respectively, after onset (Figure).

Discussion

We herein described a case of PF that developed 11 days after delivery. The patient had never shown a plasma glucose abnormality or urinary sugar during pregnancy, though her neonate was large for gestational age. Nearly all patients who develop T1DM during pregnancy or immediately after delivery (-2 weeks) are FT1DM, accounting for 22.7% of all FT1DM cases that develop in women of childbearing age (13-49 years) (7). Shimizu et al. reported that 4 of 22 PF patients developed FT1DM immediately after delivery, not during pregnancy, in a Japanese nationwide PF survey conducted from 2000-2004 (6). Similarly, 4 of 12 PF patients found in China from 2003-2010 developed FT1DM within 2 weeks after delivery (8). Thus, PF appears to develop during pregnancy rather than after delivery. In our review of the literature, seven cases of PF that developed after delivery were identified (Table 2) (9-14). The duration of hyperglycemic symptoms before the diagnosis of diabetes was short, only a few days, in all patients. Compared to the previous cases, the newborn’s weight was heavier and the levels of serum and urinary C-peptide were much lower in the present case (Table 2).

HLA class II genotypes have been estimated to account for 50% of all cases of acute-onset T1DM (15, 16). Similarly, HLA class II genotypes strongly confer susceptibility to the development of FT1DM (6, 7, 17). DRB1*04:05-DQB1*04:01 was significantly more frequent in NPF than in female control subjects of childbearing age in Japan (6). In contrast, there was no significant difference in the frequency of DRB1*04:05-DQB1*04:01 between PF and control subjects. The frequency of DRB1*04:05-DQB1*04:01 tended to be higher in NPF than in PF, however, the difference between the groups was not significant. The contribution of DRB1*09:01-DQB1*03:03 to Japanese PF is controversial. Although DRB1*09:01-DQB1*03:03 has been reported to confer strong susceptibility to PF (6), a significant association between DRB1*09:01-DQB1*03:03 and PF was not observed in another study (7).

In the present patient, the HLA class II haplotypes were DRB1*04:10-DQB1*03:02 and DRB1*15:02-DQB1*05:01. To the best of our knowledge, these haplotypes have not been reported as conferring susceptibility to FT1DM. Because the patient’s maternal grandfather was Filipino and her maternal grandmother was Chinese, the mixed genetic backgrounds might have led to a rare HLA haplotype for PF. In the Philippines, DRB1*15:02-DQB1*05:01 is a common DRB1-DQB1 haplotype in the general population (10%) (18, 19), and it is more frequent in Filipino than in Japanese or Chinese populations (20). Therefore, the HLA haplotypes in the present patient may have been affected by her Filipino background. The DRB1*15:02-DQB1*05:01 has been reported to be a protective haplotype for T1DM in Filipino people (21). In contrast to DRB1*15:02-DQB1*05:01, DRB1*04:10-DQB1*03:02, the other DRB1-DQB1 haplotype in the present patient, is a rare HLA haplotype in Filipino, Japanese, and Chinese populations (20). The analyses of DR4 haplotypes in Filipino persons showed that DRB1*04:05-DQB1*03:02, DRB1*04:05-DQB1*02:01, DRB1*04:05-DQB1*04:01, and DRB1*04:05-DQB1*04:02 were sensitive to T1DM, while DRB1*04:03-DQB1*03:02 was resistant (21). In the Chinese population, FT1DM patients had a higher frequency of DQA1*01:02-DQB1*06:01 than autoimmune T1DM cases and healthy controls (22). The present patient has none of the HLA class II haplotypes associated with susceptibility to T1DM or FT1DM in the Japanese, Filipino, or Chinese populations.

In summary, a patient with PF that developed immediately after delivery, whose HLA class II genotypes have not yet been reported to be associated with PF, was described. This report may provide some insights into the pathogenesis of PF.

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

Acknowledgement

The authors would like to thank Dr. Chiharu Tsutsumi for helpful discussions.

References


