Simultaneous Onset of Type 1 Diabetes Mellitus and Painless Thyroiditis Following Acute Pancreatitis

Gen Inoue, Takahiro Sakurai, Kiyoshi Tanaka, Takashi Akamizu, Hiroaki Masuzaki, Kiminori Hosoda, Tatsuya Hayashi, Yasunao Yoshimasa and Kazuwa Nakao

Abstract

A 24-year-old female suffered from acute pancreatitis, followed by simultaneous onset of painless goiter, elevation of thyroid hormones and diabetic ketoacidosis. Two months later, her insulin secreting function was severely decreased and positive for anti-GAD and anti-islet cell antibodies, whereas the serum glucagon level was normal, suggesting an autoimmune-related destruction specifically of β cells. In addition, the initial hyperthyroid state was followed by a hypothyroid phase which later recovered to an euthyroid state, suggesting an initial destruction of thyroid cells. Because anti-thyroidal antibodies were positive, it is likely that the thyroidal destruction was also autoimmune-related. This case implies common pathogenic mechanisms in the autoimmune-related destruction of β cells and thyroid cells.

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Key words: autoimmunity, β cell, thyroid follicular cell, painless destructive thyroiditis

Introduction

Type 1 diabetic patients often present with autoimmune thyroid disorders (1–4). Although several hypotheses regarding a common antigen and immune responses have been postulated (5–10), the exact mechanism of the association remains largely unknown. In this report, we describe a patient who presented an almost simultaneous manifestation of diabetic ketoacidosis and thyrotoxicosis due to the sudden onset of type 1 diabetes mellitus and painless destructive thyroiditis, respectively, both of which developed following acute pancreatitis. The possible pathological mechanisms are discussed.

Case Report

A 24-year-old woman had epigastric and back pain in the first week of January 1994. Her family pointed out an enlargement of her thyroid gland at that time. Although her mother had Graves’ disease, there was no family history of diabetes mellitus. She never had neck pain, but she consulted the previous hospital because of persistent epigastric pain, high fever and nausea on January 21, 1994. Since swelling of the pancreas on abdominal ultrasonography and elevation of pancreatic enzymes [serum amylase; 316 IU/l (normal range; 60–200), serum trypsin; 6,180 ng/ml (normal range; 1–10–460)] were pointed out, she was diagnosed as having acute pancreatitis. She was admitted for the treatment of acute pancreatitis on January 25. She was never icteric and had no history of alcohol drinking. Repeat ultrasonography indicated no abnormalities such as gall stones or choledochus anomalies, other than swelling of the pancreas. On January 27, although the serum amylase level was normalized, high fever with shivering, thirst and general malaise developed with markedly elevated blood sugar (805 mg/dl) and metabolic acidosis (pH; 7.367, pCO2; 18.5 mmHg, HCO3; 10.6 mmol/l, base excess; −11.5 mEq/l). At that time, the serum TSH level was undetectable, and triiodothyronine (T3) and thyroxine (T4) levels were 600 ng/dl and 17.4 μg/dl, respectively. Microsomal test and thyroid test were ×1,600 and ×400, respectively. Transfusion and insulin therapy up to 80 U/day were started in parallel with the therapy for acute pancreatitis (Fig. 1), and the metabolic abnormalities gradually recovered thereafter. However, insulin therapy (24–36 U/day) was continuously required, because her urinary excretion of CPR was never more than 3 μg/day.

She was admitted to our hospital for further evaluation of diabetes mellitus and thyroid disorders on March 9. She was treated with insulin (Penfill 30R 32 U, twice a day). On physical examination, her blood pressure was 116/74 mmHg, and pulse was 58/min, regular. The lungs, heart and abdomen were normal. The thyroid gland was 6.0 cm in transverse diameter and diffusely elastic hard. A urinalysis was significant for glycosuria, but no proteinuria was detected. Laboratory examinations were normal, including complete blood counts, blood chemistry, except that her fasting blood sugar was 116 mg/dl and total cholesterol level was 261 mg/dl. Glycosylated hemo-
globin A1c was 6.8%. Immunological examinations were positive for anti-nuclear antibodies (homogenous), but negative for anti-DNA antibody, anti-RNP antibody and LE cells. Serum complements were normal. Her HLA type was A 24/−, B 52/−, 4/−, C/− in class I antigen, and DR 2/−, −/1, DQ 1/− in class II antigen.

Endocrine data are shown in Table 1. Anterior pituitary, adrenal and ovarian functions were normal. Although her T3 and T4 were 39 ng/dl and 1.1 μg/dl, respectively, with elevated TSH (43.3 μU/ml) on March 11, indicating a hypothyroid state, she demonstrated an almost euthyroid state in the absence of

<table>
<thead>
<tr>
<th>Hormones</th>
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<tr>
<td>LH</td>
<td>0.91 mIU/ml</td>
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<tr>
<td>FSH</td>
<td>4.6 mIU/ml</td>
</tr>
<tr>
<td>PRL</td>
<td>6.7 ng/ml</td>
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Table 1. Endocrine Data

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<td>ACTH</td>
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<td>11.3</td>
<td>&lt;5.0</td>
</tr>
<tr>
<td>Cortisol</td>
<td>13.7</td>
<td>4.9</td>
<td>3.2</td>
</tr>
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Figure 1. Abdominal CT scan taken on January 28, showing swelling of pancreas.

Figure 2. Clinical course and TSH and thyroid hormone levels of the patient. Just before the overt acute pancreatitis, MCHA was already positive, and the laboratory examination on February 1 revealed a hyperthyroid state with diabetic ketoacidosis (DKA). 123I-thyroid scan 20 days later showed increased uptake in the thyroid, which was revealed to accompany the hypothyroid state. The patient gradually recovered to euthyroid state without supplementation in May.
thyroid hormone supplementation 2 months later (Fig. 2). Anti-TSH receptor antibody was negative. ²⁹⁷¹Tc-labeled thyroid scan on March 11 revealed an increased uptake in the thyroid in the hypothyroid phase. The clinical course of thyroid function with the initial hyperthyroid state was thought to reflect a gradual recovery of thyroid gland subsequent to the thyroid destruction in January, compatible with a previous report describing the spontaneous histological improvement of the thyroid in the patients with painless thyroiditis (11).

Urine C peptide excretion was undetectable and serum C peptide level was less than 0.1 ng/ml. Exogenous glucagon or arginine administration did not elicit an elevation of serum C peptide, whereas serum immunoreactive glucagon was over 135 pg/ml, indicating a β cell specific defect in pancreatic islets (Fig. 3). Anti-glutamic acid decarboxylase (GAD) antibody was positive (4.3 Index value) with capture-ELISA method, and anti-islet cell antibody (ICA) was also positive (×20). Insulin (over 20 U/day) was constantly required for blood sugar control throughout the course. Thus, she was diagnosed as simultaneously having type 1 diabetes mellitus and painless destructive thyroiditis following the episode of acute pancreatitis.

**Discussion**

The patient had a family history of Graves’ disease, suggesting some genetic predisposition for autoimmune thyroid disorders. In addition, the microsomal test was already positive just before overt pancreatitis. Therefore, it is highly likely that she had some autoimmune abnormality for thyroid even before the onset of the episode. However, the swelling of thyroid gland was pointed out for the first time after the development of epigastric pain, and the absence of anti-TSH receptor antibody and the time course of thyroid function reinforce the diagnosis of painless destructive thyroiditis, which might be induced by etiologies other than those for the previous abnormality in thyroid autoimmunity. In this case, the inducers for acute pancreatitis or the modulatory changes of immune response by the pancreatitis were suspected to have induced painless thyroiditis. However, to our knowledge, there are no other reports suggesting the association between acute pancreatitis and painless thyroiditis. In the literature, a transient decrease in adrenal cortical hormones or postpartum state is reported as an inducer for painless thyroiditis (12, 13). However, a greater part of painless thyroiditis, including postpartum thyroiditis, is considered to be autoimmune-related, because it is very often accompanied with the presence of anti-thyroid antibodies (13).

On the other hand, an association between acute pancreatitis and the onset of type 1 diabetes mellitus is sometimes reported (14). Recently, the characterization of a minor part of type 1 diabetic patients with acute pancreatitis is reported to be discriminated from classical type 1 diabetes patients with autoantibody to β cell-derived antigens such as anti-GAD antibody (15). In this case, ICA and anti-GAD antibodies were positive. Therefore, it is likely that type 1 diabetes mellitus in
this case was autoimmune-related, although her HLA type in the DR region is DR2. Acute pancreatitis in this case could be also suspected to be autoimmune-related, because there were no specific causes to induce acute pancreatitis such as alcohol drinking or gall stones and because several viral antibody titers examined were negative or low, including those for cytomegalovirus, adenovirus 3, rubella, mumps, coxsackie A and B, influenza A and B, and Epstein-Barr virus.

The prevalence of the autoimmune thyroid disorders in type 1 diabetic patients is reported to be 7–38%, which is female predominant (4, 7). Although the cause of the frequent association remains to be fully elucidated, several common pathophysiological mechanisms have been postulated. It is reported that the CD8 positive T cell proliferation in response to TSH receptor peptide or GAD is impaired in Graves' disease and type 1 diabetes mellitus, respectively (16). In addition, anti-GAD antibody, a typical marker for autoimmune-related type 1 diabetes mellitus, is often positive in autoimmune thyroid disorders (5, 6, 17). Thus, the autoantigenicity or the immune response for autoimmunity for thyroid and β cells might share common pathological components. Although the etiology of acute pancreatitis in this case was unclear, it is possible that the exposure of β cell-derived auto-antigen induced by pancreatitis caused autoimmunity for both β cell and thyroid, and lead to the destruction of β cells and thyroid follicles, followed by the onset of type 1 diabetes mellitus and destructive thyroiditis, respectively. This case is pathophysiologically intriguing to consider the common association of autoimmune thyroid disorders and type 1 diabetes mellitus. The abrupt exposure of auto-antigen derived from β cells or thyroidal cells might induce the destruction of both cells on the basis of a certain genetic predisposition.

References

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