Masked type 1 diabetes mellitus (T1DM) unveiled by glucocorticoid replacement: a case of simultaneous development of T1DM and hypophysitis in an elderly woman

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Abstract. As a rare condition characterized by inflammation of the pituitary gland, hypophysitis usually results in hypopituitarism and pituitary enlargement. The most critical outcome of hypopituitarism is caused by secondary adrenal insufficiency. Glucocorticoid deficiency is a life-threatening condition, and patients who develop this deficiency require prompt diagnosis and treatment. However, a delayed diagnosis of hypopituitarism may occur due to its non-specific clinical manifestations. A common presenting sign of glucocorticoid deficiency is hypoglycemia. The amelioration of hyperglycemia has been observed in diabetic patients with adrenal insufficiency. We report the case of a 70-year-old Japanese woman who had suffered from fatigue and anorexia for several months; she was admitted based on refractory hyponatremia (sodium 125–128 mEq/L) and hypoglycemia (glucose 58–75 mg/dL). Laboratory findings and magnetic resonance imaging findings led to the diagnosis of panhypopituitarism caused by autoimmune hypophysitis. After receiving 10 mg/day of hydrocortisone, the patient developed severe hyperglycemia (glucose >500 mg/dL). Undetectable C-peptide levels and positive results of both insulinoma-associated antigen-2 antibodies and insulin autoantibodies indicated that she had experienced a recent onset of type 1 diabetes. The pathophysiological process indicated that overt hyperglycemia could be masked by the deficient action of glucocorticoids even in a diabetic patient with endogenous insulin deficiency. This uncommon case reinforces the importance of the prompt diagnosis and treatment of hypopituitarism. Clinicians should remain aware of the possibility of hidden diabetes when treating hypoglycemia in patients with adrenal insufficiency.

Key words: Adrenal insufficiency, Hypophysitis, Hypopituitarism, Type 1 diabetes, Hypoglycemia

ADRENOCORTICOTROPIC HORMONE (ACTH) deficiency occasionally develops in adults via autoimmune etiology (i.e., so-called autoimmune/lymphocytic hypophysitis), and this deficiency can be isolated or can occur in conditions that include a deficiency of other anterior pituitary hormones [1]. ACTH deficiency leads to secondary adrenal insufficiency, which causes a life-threatening condition. However, the diagnosis of adrenal insufficiency can be delayed because its clinical manifestations are non-specific; they include nausea, fatigue, weight loss, hypotension, and hyponatremia. Hypoglycemia is also a common presenting sign in patients with adrenal glucocorticoid deficiency. Glucocorticoids increase blood glucose levels by increasing hepatic gluconeogenesis and inhibiting the uptake and utilization of glucose in peripheral tissues. Glucocorticoid deficiency can lead to an amelioration of glycemic control and/or a reduction of the insulin dose in patients with diabetes [2-5], but it is unclear whether the hyperglycemia in type 1 diabetes could be ameliorated without insulin treatment when complicated with adrenal insufficiency. Here, we describe the case of a patient who latently developed type 1 diabetes with endogenous insulin deficiency concurrently with adrenal insufficiency due to autoimmune hypophysitis. Surprisingly, the patient’s hyperglycemia was completely masked, and it was unveiled by the physiologic dose of glucocorticoid replacement.
Case

The patient was a 70-year-old Japanese woman. There was no apparent family history of diabetes or autoimmune diseases. She had no remarkable medical history other than her medication regimen of a β-blocker (tablets), magnesium oxide, and benzodiazepine to treat her hypertension, constipation, and insomnia. She had suffered from general fatigue and anorexia for several weeks when she was admitted to the local hospital on the recommendation of her family physician (Fig. 1, Day –67). She presented severe hyponatremia (sodium 115 mEq/L) and hypothyroidism with free thyroxine 0.36 ng/dL and thyroid-stimulating hormone 9.85 μIU/mL. There was no evidence of glucose intolerance; the plasma levels of glucose and glycated hemoglobin were 70 mg/dL and 5.2%, respectively. An intravenous infusion of saline and levothyroxine 25 μg/day were administered, and as shown in Fig. 1, the patient’s serum levels of sodium then increased to 132 mEq/L and her physical condition improved sufficiently for discharge from the hospital 1 week later (Fig. 1, Day –59).

Two months after the discharge, the patient was admitted to our hospital (Fig. 1, Day 1) because of severe fatigue and recurrent hyponatremia. She was lean (height 149.1 cm, weight 44.0 kg, body mass index 19.8 kg/m²), and her blood pressure and body temperature were within normal range (117/90 mmHg and 36.1°C). Neither pretibial edema nor skin/mucosal pigmentation were observed. As shown in Fig. 1, the patient’s hyponatremia (sodium 125–128 mEq/L) and recurrent hypoglycemia (glucose 58–75 mg/dL) did not resolve despite an intravenous infusion of saline and glucose for 3 days. Adrenal insufficiency was suspected as the cause of the refractory hyponatremia and hypoglycemia.

The patient’s laboratory findings (Table 1) revealed that she was suffering from central adrenal insufficiency complicated with deficiencies of multiple pituitary

| Laboratory Findings       | Value 1 | Value 2 | Value 3 |
|---------------------------|---------|---------|---------|
| HbA1c (%)                 | 5.2     | 5.1     | 6.8     |
| Glucose (mg/dL)           | 70      | 91      | 275     |
| Insulin (μU/mL)           | 0.4     | 0.4     | 0.5     |
| C-peptide (ng/mL)         | 0.39    | <0.01   |         |

Fig. 1 The clinical course of the patient, a 70-year-old Japanese woman. Red circles: fasting glucose levels. Blue triangles: serum sodium levels. Hospital Day 1: the day when the patient admitted to our hospital.
hormones. A magnetic resonance imaging (MRI) examination demonstrated the enlargement of the anterior pituitary gland and a thickened infundibular stalk with diffuse enhanced intensity by the contrast agent (Fig. 2A, B); it was consistent with the findings of hypophysitis. There was no evidence of infection, tumor, lymphoproliferative diseases, granulomatosis including sarcoidosis and tuberculosis, or vasculitis in the laboratory data (Table 1). A biopsy of the hypophyseal lesion to make a definitive diagnosis was considered to be too high risk of significant morbidity. We conducted a stimulation test to investigate the patient’s residual pituitary function (Table 2); the result revealed panhypopituitarism with a preserved response of growth hormone. The patterns of frequency of impaired adenohypophyseal hormones suggested that an autoimmune etiology was more likely over mechanical compression or invasion of tumor [6, 7]. Based on these examination results, we considered autoimmune (lymphocytic) hypophysitis was the most appropriate diagnosis.

Table 1  Laboratory findings on admission day.

| Blood test                  | Case | Reference       | Case | Reference |
|-----------------------------|------|-----------------|------|-----------|
| White blood cell (/μL)      | 4,100| 3,300–8,600     | 5.95 | 0.500–5.00|
| Neutrophil (%)              | 44   | 40.0–60.0       | 1.96 | 2.30–4.00 |
| Lymphocyte (%)              | 36   | 25.0–45.0       | 0.65 | 0.90–1.70 |
| Eosinophil (%)              | 11   | 0.0–7.0         | 1.23 | 0.13–9.88 |
| Red blood cell (×10^6/μL)   | 389  | 386–492         | 25   | 57–175    |
| Hemoglobin (g/dL)           | 11.3 | 11.6–14.8       | 11.4 | <157.8    |
| Hematocrit (%)              | 33.6 | 35.1–44.4       | 29.7 | 0.0–28.0  |
| Platelet (×10^9/μL)         | 21.2 | 15.8–34.8       | 12.3 | 0.0–16.0  |
| Sodium (mEq/L)              | 125  | 138–145         | <5.0 | 0.0–5.0   |
| Potassium (mEq/L)           | 4.4  | 3.6–4.8         | 3.1  | 0.0–0.4   |
| Chlorine (mEq/L)            | 83   | 101–108         | 1,645| 0.0–125.0 |
| Calcium (mg/dL)             | 8.6  | 8.8–10.1        | T-SPOT.TB |   |
| AST (IU/L)                  | 26   | 13–30           | 3.0  | <11       |
| ALT (IU/L)                  | 7    | 7–23            | <0.5 | 0.0–0.9   |
| γ-GTP (IU/L)                | 12   | 9–32            | 13.3 | 7.0–25.0  |
| Amylase (IU/L)              | 52   | 44–132          | <40  | 0–40.0    |
| C-reactive protein (mg/dL)  | 4.49 | 0.00–0.14       | 21   | 5–117     |
| Albumin (g/dL)              | 3.7  | 4.1–5.1         | 945  | 152–492   |
| Blood urea nitrogen (mg/dL) | 9.2  | 8.0–20.0        | PR3-ANCA | IU/mL | 0.5 | 0.0–2.0 |
| Creatinine (mg/dL)          | 0.61 | 0.46–0.79       | Urinalysis |   |
| Glucose (mg/dL)             | 91   | 73–109          | Insulin (μU/mL) | 0.4 | 2.2–12.4 |
| Insulin (μU/mL)             | 0.39 | 0.61–2.09       | C-peptide (ng/mL) | 0.39 | 5.1  | 4.9–6.0  |
| C-peptide (ng/mL)           | 0.39 | 0.61–2.09       | HbA1c (%)  | 5.1  | 7.2–63.3 |
| HbA1c (NGSP, %)             | <1.5 | 7.2–63.3        | ACTH (pg/mL) | <1.5 | 4.5–21.1 |
| Cortisol (μg/dL)            | <0.2 | 4.5–21.1        | Ketone (1+) | <1.5 | 4.5–21.1 |

Ab, antibodies; ACE, angiotensin-converting enzyme; ACTH, adrenocorticotropic hormone; ALT, alanine aminotransferase; ANA, antinuclear antibodies; AST, aspartate aminotransferase; GAD, glutamic acid decarboxylase; HbA1c, Glycated hemoglobin; IA-2, insulinnoma-associated antigen-2; IGF-1, insulin-like growth factor-1; IgG4, immunoglobulin G4; LH, luteinizing hormone, FSH, follicle-stimulating hormone; PR3-ANCA, serine protease-3-anti-neutrophil cytoplasmic antibodies; RPR, Rapid plasma regain; sIL-2R, soluble interleukin-2 receptor; T3, triiodothyronine; T4, thyroxine; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; γ-GTP, gamma-glutamyl transferase.
cortisone, and she needed insulin treatment. Four weeks after the initiation of insulin treatment, the patient’s glycosuria was improved and the patient took the physiological replacement of hydrocortisone and insulin that she had received during hospitalization. The clinical course supported the possibility that the etiology of the pituitary dysfunction was lymphocytic hypophysitis.

As shown in Fig. 1, we started the replacement of hydrocortisone 10 mg on Day 3. The levels of plasma glucose were extremely elevated (>500 mg/dL) just after the patient took the physiological replacement of hydrocortisone, and she needed insulin treatment. Four weeks after the initiation of insulin treatment, the patient’s hyperglycemia could be controlled by 25 units/day of insulin (21 units of lispro and 4 units of glargine). The fasting serum C-peptide levels was undetectable (<0.01 ng/mL) in spite of the elevated plasma glucose level (275 mg/dL), suggesting that the patient had developed type 1 diabetes. There was no evidence of pancreas cancer, pancreatitis, or other pancreas-destructive disease in computed tomography scanning. We retrospectively measured the levels of insulin, C-peptide, and anti-islet autoantibodies in the serum of the patient’s admission day, and those of serum insulin and C-peptide were already decreased at 0.4 μU/mL and 0.39 ng/mL, respectively. Insulinoma-associated antigen-2 autoantibodies and insulin autoantibodies were positive although glutamic acid decarboxylase autoantibodies were not detected (Table 1). We presumed that the patient had recently developed type 1 diabetes coincidental with the development of hypophysitis. The patient’s hyperglycemia was masked by the glucocorticoid deficiency and was uncovered by the physiological dose of hydrocortisone replacement. The patient showed mild polyuria during several days just after hydrocortisone replacement, but she soon recovered and could excrete oligohydria with a urine specific gravity of 1.027. She was not considered to have diabetes insipidus.

Eight months after the patient’s diagnosis of hypopituitarism, the enlarged pituitary was reduced and thinned (Fig. 2C, D). However, no clinical improvement on the endocrinological dysfunction was observed. She remained requiring replacements of the same dosage of hydrocortisone and insulin that she had received during hospitalization. The clinical course supported the possibility that the etiology of the pituitary dysfunction was lymphocytic hypophysitis.

### Discussion

We have presented a rare case of an elderly woman who recently developed type 1 diabetes and hypophysitis simultaneously. She presented recurrent hypoglycemia without the use of insulin although her endogenous insulin secretory capacity had been decreased to a level of dependence on insulin injections. Severe hyperglycemia was revealed by the subsequent physiologic replacement of glucocorticoid. This pathophysiological process indicated that overt hyperglycemia caused by insulin deficiency could be masked by deficient action of glucocorticoids even in a patient with type 1 diabetes.

The main defense against hypoglycemia in healthy humans is an increased release of counter-regulatory hormones including glucagon, epinephrine, cortisol, and growth hormone, which raise plasma glucose levels by antagonizing the insulin action [8]. The glucagon response to hypoglycemia is impaired in patients with longstanding diabetes but not in those with recent-onset diabetes [9]. Since our patient had undergone regular

### Table 2  TRH, CRH, GnRH, GHRP-2 stimulation test

| Table 2  | TRH, CRH, GnRH, GHRP-2 stimulation test |
|----------|-----------------------------------------|
| Time (min) | 0 | 30 | 60 | 90 | 120 |
| TSH (μU/mL) | 14.63 | 18.38 | 21.87 | 6.36 | 21.08 |
| Free T4 (ng/dL) | 0.93 |
| Prolactin (ng/mL) | <0.6 | <0.6 | <0.6 | <0.6 | <0.6 |
| ACTH (pg/mL) | <1.5 | <1.5 | <1.5 | <1.5 | <1.5 |
| Cortisol (μg/dL) | 4.1 |
| LH (mIU/mL) | 3 | 7.8 | 10.9 | 13.5 | 13.2 |
| FSH (mIU/mL) | 10.1 | 12.2 | 13.4 | 15 | 15.2 |
| Estradiol (pg/mL) | <5.0 |
| Time (min) | 0 | 15 | 30 | 45 | 60 |
| GH (ng/mL) | 2.68 | 22.26 | 22.59 | 16.07 | 11.4 |

ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; GH, growth hormone; GHRP-2, growth hormone-releasing peptide-2; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone, FSH, follicle-stimulating hormone; T4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.
checkups by her family physician, it was confirmed that she had no previous history of overt diabetes. Her glucagon response might thus be considered still maintained, as in healthy subjects.

Considering her remarkable manifesting precedent hypopituitarism, we speculate that our patient developed adrenal crisis ≥ 2 months prior to the detection of hypophysitis and type 1 diabetes. Her substantial hypoglycemia might also have occurred due to decreased cortisol levels when she initially manifested hypopituitarism. It was reported that the epinephrine response was becoming attenuated in patients who experienced frequent antecedent hypoglycemia [9–11]. Our patient’s recent hypoglycemia may have led to the attenuation of her epinephrine response. The loss of counter-regulatory actions of cortisol and epinephrine could have caused her increased insulin sensitivity, which resulted in a masking of the hyperglycemia.

Complete diabetes remission derived from panhypopituitarism in pancreatectomized dogs was first documented in 1931 by Houssay et al., and it was also described in humans as the Houssay phenomenon in 1940 [12]. The phenomenon was rarely reported thereafter. Several studies showed that panhypopituitarism due to pituitary hemorrhage/infarction (including Sheehan’s syndrome) induced a remarkable reduction of insulin doses in patients with type 1 diabetes [3, 4, 13, 14]. A complete amelioration of diabetes induced by adrenal insufficiency was reported in patients with type 2 diabetes [5], but it has never been reported in a patient with type 1 diabetes with decreased insulin secretory capacity to an insulin-independent level as observed in our patient.

Lymphocytic hypophysitis is often associated with other autoimmune disorders, but its combination with type 1 diabetes was extremely rare until a few years ago [6]. Blocking antibodies against programmed cell death-1 (PD-1) and/or cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) have recently been applied as immunotherapeutic agents for various advanced cancers.

These immune checkpoint inhibitors can cause the development of endocrinopathies [15]. In recent studies, approx. 10% of the patients treated with a CTLA-4 inhibitor ipilimumab developed autoimmune hypophysitis [16, 17]. On the other hand, immunotherapy-related autoimmune diabetes is dominantly caused by anti-PD-1 therapies, and the clinical phenotype varies from typical fulminant type 1 diabetes to acute-onset type 1 diabetes [18]. Since our patient had no history of usage of these immunotherapeutic agents, it was assumed that hypophysitis and type 1 diabetes were developed coincidentally.

There are several reports of patients who developed both hypophysitis and type 1 diabetes after being treated with an immune checkpoint inhibitors [14, 19, 20]. A combination therapy of an anti-PD-1 antibody (nivolumab) and an anti-CTLA-4 inhibitor (ipilimumab) was recently approved for the treatment of malignant melanoma, renal cell carcinoma, and other cancers. The number of individuals who develop both type 1 diabetes and autoimmune hypophysitis may increase as the use of immunotherapy becomes widespread.

Conclusion

We described an intriguing case of an elderly female with hypophysitis and type 1 diabetes who developed recurrent hypoglycemia, without insulin use. Clinicians should understand that adrenal insufficiency can mask hyperglycemia even though the endogenous insulin secretory capacity was depleted.

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Disclosure

The authors have no conflicts of interest to declare.

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