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Case Report

Type 1 Diabetes, ACTH Deficiency, and Hypothyroidism Simultaneously Induced by Nivolumab Therapy in a Patient with Gastric Cancer: A Case Report

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Keywords
Nivolumab · Type 1 diabetes · ACTH deficiency · Hypothyroidism

Abstract
Nivolumab, a fully human IgG4 immune checkpoint inhibitor (ICI) antibody, has been approved for a variety of cancers. Several endocrine-associated immune-related adverse events have been reported, but the incidence rate is relatively low. This is a case of a patient with gastric cancer who underwent nivolumab therapy, leading to type 1 diabetes as well as adrenocorticotropic hormone (ACTH) deficiency and hypothyroidism almost simultaneously. A 70-year-old man with no previous history of diabetes was treated with nivolumab monotherapy for gastric cancer in November 2018. After 8 courses of nivolumab, he was diagnosed with type 1 diabetes associated with ICI; consequently, insulin therapy was initiated in March 2019. In April 2019, he was transported to hospital due to suffering from prolonged hypoglycemia, disturbed consciousness, and fever. He frequently experienced episodes of hypoglycemia, with poor controlled glycemia. His disturbed consciousness and fever also sustained. Further investigation of his hormones revealed low cortisol and ACTH levels, as well as hypothyroidism. His blood glucose control was improved after the introduction of hydrocortisone and thyroid hormone; he became alert and afebrile. In January 2020, he received a followed-up in an outpatient setting under insulin, hydrocortisone, and thyroid replacement therapy. Endocrine defect associated with ICIs, especially type 1 diabetes or ACTH deficiency, is a rare condition. To the best of our knowledge, this is the 1st case of multiple endocrinopathies simultaneously induced by nivolumab. Various endocrine concomitant defects should be taken into consideration when treating with nivolumab.

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Introduction

Immune checkpoint inhibitors (ICIs), targeting programmed cell death protein 1 (PD-1) or its ligand (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) have broadened options and improved efficacy in treating various cancers. Nivolumab, a human immunoglobulin G4 monoclonal antibody, binds to the PD-1 receptor interfering with the binding of PD-L1 and PD-L2, which results in decreasing the immune-suppressive signal from the T cells [1]. ICIs are reported to induce unique immune-related adverse events (irAEs) because of dysregulation of immune activation [2, 3]. Different irAE profiles based on type of ICIs are known, and pneumonitis, hypothyroidism, arthralgia, and vitiligo have been reported to be frequent irAEs with anti-PD-1 antibodies [4]. Endocrinopathies, such as thyroid dysfunction, adrenal insufficiency, hypophysitis, and type 1 diabetes mellitus, are also associated with ICIs, but the incidence of endocrinopathies other than thyroid dysfunction is very low [5]. This report highlights nivolumab-induced multi-endocrinopathies in which type 1 diabetes, adrenocorticotropic hormone (ACTH) deficiency, and hypothyroidism simultaneously occurred in a patient with gastric cancer.

Case Report/Case Presentation

A 70-year-old male with a medical history of hypertension was diagnosed with T3, N1, M0, stage IIB gastric cancer (Japanese Classification of Gastric Carcinoma, the 14th Edition) that was treated by distal gastrectomy in June 2012. In August 2016, the patient had a remnant gastrectomy due to T1b, N0, M0, stage IA esophagogastric junction cancer. He was also diagnosed with upper esophagus cancer. An endoscopic submucosal dissection was performed, and subsequent postoperative adjuvant chemotherapy (fluorouracil, cisplatin) was administered for the positive margin. In April 2018, 2nd-line chemotherapy (ramucirumab, paclitaxel) was conducted, due to an elevation in a tumor marker which led to a suspected relapse.

In November 2018, nivolumab was initiated because peritoneal dissemination was suggested by computed tomography. At that time, diabetes mellitus was not noted by investigations for which hemoglobin A1c (HbA1c) and casual blood glucose were 6.3% and 154 mg/dL, respectively. Eight months later, he was referred to our department due to blood sugar elevation (HbA1c 9.4%, casual blood glucose 219 mg/dL, C-peptide <0.03 ng/mL), for which insulin therapy was prescribed with a diagnosis of type 1 diabetes induced by nivolumab. At the time, free T4 and thyroid-stimulating hormone (TSH) levels were noted as normal. A month after the introduction of insulin, the patient was transferred to our hospital due to hypoglycemia and disturbance of consciousness. He required emergency hospitalization due to persistent impaired consciousness that was observed after the dextrose administration.

A physical examination revealed that he had an impaired consciousness of E4V4M5 according to the Glasgow Coma Scale. His blood pressure was 153/80 mm Hg, his pulse was 100 per minute, he was respirating at a rate of 20 breaths per minute, and his temperature was 36.4°C. Other examinations, including the head and neck, chest, abdomen, and neurology, were otherwise normal.

A complete blood count and basic biochemical test produced an almost normal result, except for a slight anemia (Hb 10.8 g/dL) and hyponatremia (130 mmol/L) (Table 1). The patient experienced a prolonged fever and an impaired consciousness after admission and presented with frequent episodes of hypoglycemia. For these reasons, a further assessment of his hormones was conducted. The results of the hormone test were a low ACTH (3.4 pg/mL), cortisol (1.39 μg/dL), free T4 (0.66 ng/dL), and elevated TSH level (10.698 μIU/mL)

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Table 1. Laboratory data on admission

CBC	
WBC, /μL	4,500
Hb, g/dL	10.8
Plt, /μL	34.5×10^4
Chemistry	
AST, IU/L	82
ALT, IU/L	26
BUN, mg/dL	5.6
Cr, mg/dL	0.47
Na, mEq/L	130
Cl, mEq/L	96
K, mEq/L	4
CRP, mg/dL	1.06
Diabetes-specific data	
Glucose, mg/dL	329
HbA1c, %	8.6
C-peptide, ng/mL	<0.03
Anti-GAD antibody, U/mL	<0.5
Anti-IA-2 antibody, U/mL	<0.6

CBC, complete blood count; WBC, white blood cell count; Hb, hemoglobin; Plt, platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; Na, sodium; Cl, chloride; K, potassium; CRP, C-reactive protein; HbA1c, hemoglobin A1c; GAD, glutamic acid decarboxylase; IA-2, insulinoma-associated protein-2.

Table 2. Additional hormones assessment

GH, ng/mL	4.09
TSH, μIU/mL	10.698
ACTH, pg/mL	3.4
FSH, U/mL	<0.6
LH, mIU/mL	10.5
PRL, ng/mL	22.6
ADH, pg/mL	1.2
Somatomedin C, ng/mL	10
Free T3, ng/dL	1.64
Free T4, ng/dL	0.66
Cortisol, μg/dL	1.39
anti-Tg antibody, IU/mL	<10
anti-TPO antibody, IU/mL	24

GH, growth hormone; TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; ADH, antidiuretic hormone; Tg, thyroglobulin; TPO, thyroid peroxidase.

(Table 2). Imaging showed a slight enlargement of the thyroid gland by ultrasound and an otherwise normal pituitary gland with partial empty sella, as well as deviated pituitary stalk by magnetic resonance imaging.

We diagnosed him with nivolumab-induced type 1 diabetes, ACTH deficiency, and hypothyroidism. The ACTH deficiency was treated with steroid replacement after 12 days in hospital (hydrocortisone 10 mg/day). Hypothyroidism was treated with thyroid hormone

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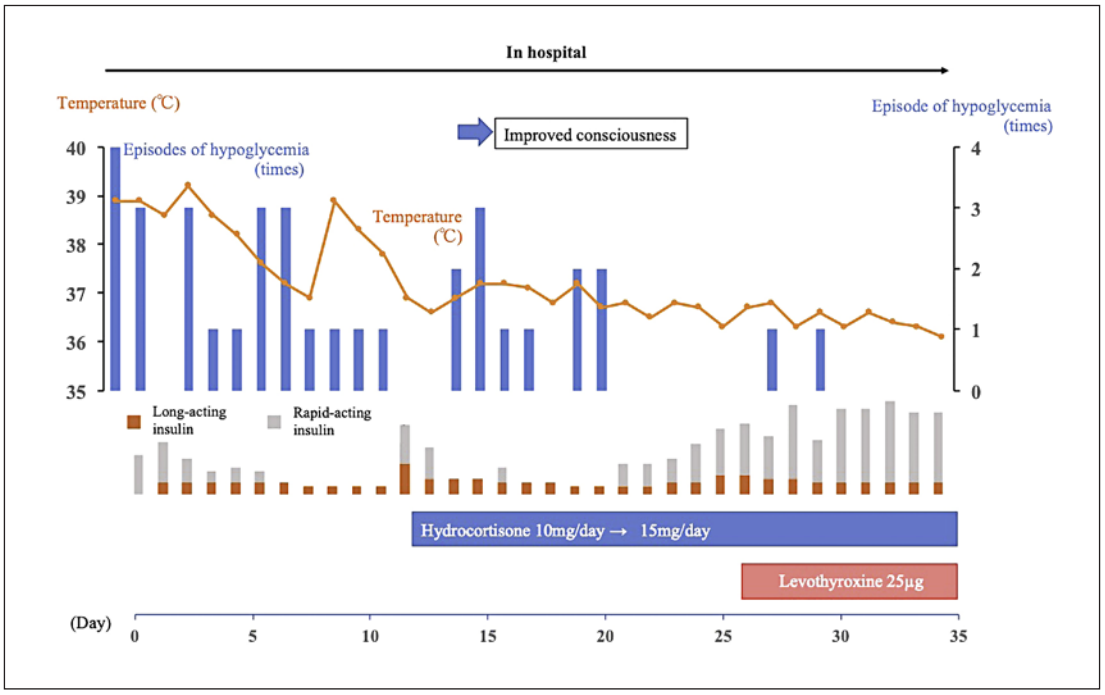

Fig. 1. The clinical course is shown. *x*-axis illustrates duration of hospital stay. *y*-axis on the left and orange line indicate his body temperature (°C), and *y*-axis on the right and bar graph show how many episodes of hypoglycemia the patient experienced per day. Orange and gray bar chart shows total daily long-acting and rapid-acting insulin dose. Hydrocortisone 10 mg per day was administered on day 12, which was increased to 15 mg per day on day 20, and levothyroxine was started on day 26.

treatment (levothyroxine 25 μg/day) 2 weeks after the steroid was initiated. Dose adjustment of insulin was done during steroid and thyroid hormone replacement therapy. Soon after the treatment, he became afebrile, alert, and a reduced number of hypoglycemic episodes was noted (Fig. 1). His activities of daily living (ADL) level was low, at bed rest, on the day of admission, but he regained a satisfactory level in ADL soon after the initiation of therapy. He was discharged on day 35 due to good progress, after adjusting the doses of hydrocortisone and insulin. In January 2020, he received a followed-up in an outpatient setting, with insulin, hydrocortisone, and thyroid replacement therapy and no relapses without nivolumab treatment.

Discussion/Conclusion

There are 2 important clinical issues evident from our case. Multiple endocrinopathies induced by nivolumab can possibly occur at the same time, despite low frequency of adverse events in each endocrine organ. Further hormone investigations are necessary when regular treatment intervention is not effective or unexplained symptoms are observed.

Firstly, multiple endocrinopathies induced by nivolumab can occur simultaneously. In a clinical trial of nivolumab administered to gastric cancer patients, a type of thyroid gland deficiency was reported in 4% of cases for which hyperthyroidism and hypothyroidism were seen in 0.6 and 3%, respectively. Type 1 diabetes and hypopituitarism/hypophysitis are rarer conditions, which were reported in 0.9 and 0.3%, respectively [6–8]. There are some previous

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reports of type 1 diabetes with isolated ACTH deficiency induced by nivolumab in a patient with breast cancer, diabetes with hypophysitis in a patient with lung cancer, or nivolumab-induced type 1 diabetes with thyroiditis [9–11]. There is also a case of nivolumab-induced hypothyroidism associated with isolated ACTH deficiency reported previously [12]. However, in our case, multiple endocrinopathies, i.e., type 1 diabetes, ACTH deficiency, and hypothyroidism, were seen simultaneously, which is very rare. In our patient's case, insulin therapy for type 1 diabetes occurred prior to ACTH deficiency and hypothyroidism, which made it difficult to diagnose these complications because episodes of hypoglycemia could often occur in type 1 diabetes treated with insulin other than ACTH deficiency or hypothyroidism.

Secondly, further hormone investigations should be taken into consideration when regular treatment intervention is not effective or unexplained symptoms are observed. In previous reports, there are 2 cases of endocrinopathies that developed within a month [9, 10] and 2 cases that developed a couple of months later [11, 12]. In the latter cases, new symptoms or abnormal data were found in sequence, which makes it easier to reach an early diagnosis and to provide treatment. In our case, there were persistent episodes of hypoglycemia, impaired consciousness, and fever, which could not be explained by proper treatment or examination. However, an examination provided us with a clue of complicated multiple endocrinopathies. Endocrine dysfunctions associated with cancer immunotherapies are uncommon and sometimes challenging to diagnose, but a delayed diagnosis could be fatal [13, 14].

In conclusion, it is important to keep in mind that rare endocrinopathies induced by nivolumab could possibly occur simultaneously, and further investigations of hormones are necessary and should be performed without delay.

Statement of Ethics

We followed the World Medical Association's Declaration of Helsinki. Informed consent was obtained from the patient for the publication.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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There were no funding sources.

Author Contributions

Shoko Marshall wrote the manuscript, and all authors treated the patient, collected data, read and approved the final manuscript.

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