

# Metachronous Immune-Related Adverse Events Involving Type 1 Diabetes and Isolated ACTH Deficiency Associated with Pembrolizumab Monotherapy for Metastatic Head and Neck Cancer: A Case Report

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## 1. Abstract

**1.1. Background:** The application of Immune Checkpoint Inhibitors (ICIs) among patients with head and neck cancer nivolumab was approved in Japan in March 2017, while the application of pembrolizumab among patients with recurrent or metastatic head and neck cancer was approved in December 2019.

**1.2. Case Description:** The patient was an 80-year-old female with lip cancer (cT1N0M0). Ten years before ICI administration, she underwent skin tumor excision and reconstruction with local skin valves. At the time, the patient was pathologically diagnosed with squamous cell carcinoma and remained recurrence-free in the interim. However, 1 year ago, the patient developed right submandibular lymphadenopathy, and a right cervical dissection was performed. Two months postoperatively, right cervical recurrence and lung metastasis were detected. The patient was deemed eligible for ICI due to unresectable cervical recurrence and pulmonary metastasis. The Combined Positive Score of the submandibular lymph nodes was 100. Pembrolizumab monotherapy was initiated, and Complete Remission (CR) was achieved, based on the efficacy assessment five months after the initiation of the treatment. However, she developed diabetic ketoacidosis in the eighth month, and she was diagnosed with fulminant type 1 diabetes mellitus. Insulin induction was performed, but the patient developed adrenal insufficiency after 10 months. These were likely immune-related adverse events (irAEs), caused by pembrolizumab. The patient consulted at the oncology department, and pembrolizumab therapy was continued. The patient has remained in CR.

**1.3. Conclusions:** This is the first reported case of type 1 diabetes, treated with pembrolizumab monotherapy, in a patient with head and neck cancer in Japan. There have been no reports on the metachronous irAEs of type 1 diabetes and isolated adrenocorticotropic hormone deficiency, associated with pembrolizumab monotherapy for metastatic head and neck cancer. The study highlights the need for prompt screening of the irAEs. The interdisciplinary collaborative approach of the study promotes better management of the patients.

## 2. Introduction

### 2.1. Background

Immune checkpoint inhibitors (ICIs) such as nivolumab and pembrolizumab were approved in Japan in March 2017 and December 2019, respectively for the treatment of recurrent or metastatic head and neck cancer. ICIs might cause immune-related adverse events (irAEs), which are significantly different from those of conventional chemotherapy.

### 2.2. Rationale and knowledge gap

The irAEs associated with ICIs are still largely unknown. Although there have been several reports of type 1 diabetes and isolated Adrenocorticotropic Hormone (ACTH) deficiency in various cancers, the incidence of these irAEs in head and neck cancers is very rare.

### 2.3. Objective

In this report, we present a case of metachronous development of irAEs with type 1 diabetes and ACTH deficiency associated with

monotherapy for metastatic head and neck cancer.

This manuscript is written following the CARE checklist.

### 3. Case Description

An 80-year-old female with postoperative relapse of lip cancer (T1N0M0) presented with a cervical mass, following referral by the department of plastic surgery.

She had a medical history of small intestine carcinoid at 67 years of age.

Ten years before the first presentation, she underwent treatment for lip cancer (T1N0M0) and skin tumor excision with local skin flap reconstruction at the Department of Plastic Surgery. The pathological diagnosis was squamous cell carcinoma. After being recurrence-free for 9 years, she developed lymph node swelling in the right submandibular region and was referred to our department. She was diagnosed with cervical lymph node metastasis from lip cancer and underwent right cervical neck dissection. Two months after surgery, the patient developed right cervical lymph node relapse and lung metastasis. We prescribed ICI for unresectable cervical recurrence and lung metastases. The combined positive score (CPS) of the resected submandibular lymph nodes was 100, and pembrolizumab monotherapy was initiated. The administration dose was 200 mg/body weight at 3-week intervals.

With the initiation of pembrolizumab administration, the cervical lymph node swelling started subsiding, and five months after ICI treatment, the skin findings improved (Fig. 1E). The tumor was absent on computed tomography (CT) and showed a complete response (CR), which was maintained with the continuation of Pembrolizumab monotherapy.

On the 13th course of pembrolizumab administration (day 252), the patient complained of ill health with common cold symptoms and vomiting for 2–3 days. Blood tests revealed a blood glucose level of 407 mg/dl, which was previously unrecognized as a high blood glucose level. Although the HbA1c level was 6.6%, urine analysis revealed urinary glucose as 4+ and urinary ketones as 3+, which are suggestive of irAE development. We immediately consulted the Department of Nephrology, Metabolism, and Endocrinology for diabetic ketoacidosis (DKA) and fulminant type 1 diabetes mellitus. She was treated under emergency hospitalisation. Her general condition and level of consciousness were stable and was treated with continuous intravenous insulin and external fluid administration. After approximately one month of inpatient care, the patient was discharged from the hospital, pembrolizumab monotherapy was resumed with insulin treatment, and CR was maintained.

During the visit for receiving the 15th course of pembrolizumab (day 294), the patient complained of nausea and general fatigue for one week. The blood pressure was low (96/49 mmHg); however, the other vital signs were stable. Suspecting adrenal insufficiency, an urgent blood test was performed, which revealed hyponatrem-

ia (130 mmol/l), hypoglycemia (57 mg/dl), low cortisol (1.18 µg/dl), and normal ACTH 7.5 pg/ml (Table 2). Suspecting adrenal insufficiency, she was immediately referred to the Department of Nephrology, Metabolism, and Endocrinology and was admitted immediately. There was no pituitary enlargement noted in magnetic resonance imaging (MRI) of the head. A triad load test [thyrotropin-releasing hormone (TRH), Luteinizing hormone-releasing hormone (LHRH) and corticotropin-releasing hormone (CRH)] was performed, and ACTH levels were 1.05 pg/ml before loading, 5.42 pg/ml at 30 min, and 7.67 pg/ml at 60 min, which led to the diagnosis of isolated ACTH deficiency. She was administered 20 mg of hydrocortisone and was discharged when her general condition stabilized.

Pembrolizumab monotherapy was continued, and CR was maintained for 540 days after ICI treatment was started.

## 4. Discussion

### 4.1 Key Findings

In the present case, type 1 diabetes mellitus and isolated ACTH deficiency (adrenal insufficiency) developed metachronously. The patient was administered ICI due to unresectable cervical recurrence and pulmonary metastasis. The CPS of the submandibular lymph nodes was 100. Pembrolizumab monotherapy was initiated, and CR was achieved. However, she developed diabetic ketoacidosis in the eighth month, and she was diagnosed with fulminant type 1 diabetes mellitus. Insulin induction was performed, but the patient developed adrenal insufficiency after 10 months.

### 4.2. Strengths and Limitations

To the best of our knowledge, there have been no reports of these two irAEs occurring metachronously in a single patient, which is considered extremely rare. The study contributes to this novel aspect. However, further investigation is required for understanding the occurrence of irAEs.

### 4.3. Comparison with Similar Researches

IrAEs occur in 70–80% of patients treated with ICIs and occur within 3–6 months after the initiation of treatment [1]. In addition to interstitial lung disease, pituitary dysfunction, and skin disorders, conditions like thyroid dysfunction, type 1 diabetes mellitus, and myasthenia gravis are involved.

The frequency of endocrine-related irAEs induced by ICI for various types of carcinomas is summarized in Table 3 [2,3]. Hypothyroidism is the most frequent endocrine-related irAE, adrenal insufficiency observed in the present case ranges from 0–4.5%, and type 1 diabetes is very rare. Moreover, multiorgan irAEs have been reported [4], including lung disorders, acute hepatitis, skin disorders, and colitis.

Adrenal insufficiency (isolated ACTH deficiency) with pembrolizumab was observed in one case (on day 163) when pembrolizumab monotherapy was administered in the KEYNOTE048 study

[5] for head and neck cancer; however, there was no such case reported in the chemotherapy combination group. In pituitary disorders caused by anti-PD-L1 antibodies, there was no swelling of the pituitary gland associated with inflammation and only reduced ACTH secretion was reported [6]. In contrast, anti-CTLA-4 antibodies such as ipilimumab often lead to panhypopituitarism, with MRI showing pituitary enlargement and an onset at approximately ten weeks [7]. The occurrence of pituitary inflammation (hypophysitis) is relatively rare during treatment with anti-PD-1 antibodies (0–0.9%) and anti-CTLA-4 antibodies such as ipilimumab (0–10%). The reasons for this difference in frequency and clinical features remain unclear [8].

There were no cases of type 1 diabetes mellitus associated with pembrolizumab reported in the KEYNOTE048 study [5], either as monotherapy or in combination with chemotherapy. Furthermore, there are no such reports in PubMed or other databases. In the KEYNOTE 181 study of esophageal cancers, the onset time was similar to that in the present case (252 days) [6]. Type 1 diabetes mellitus is reported to be less frequent but a more severe form of irAE [9]. The incidence of type 1 diabetes in Japan with nivolumab, a similar PD-L1 inhibitor as pembrolizumab, was reported to be 0.33%, with a mean median age of 63 years and a mean time from nivolumab treatment to the onset of type 1 diabetes of 155 days [10]. Deaths from fulminant type 1 diabetes and diabetic ketoacidosis associated with pembrolizumab have also been reported [11]

#### 4.4. Explanations of Findings

Metachronous occurrence of type 1 diabetes and isolated ACTH deficiency was observed in the patient. These were likely irAEs caused by pembrolizumab monotherapy for metastatic head and neck cancer. The Keynote048 study demonstrated that the higher the CPS, as in the present case, the better the anti-tumor effect of pembrolizumab [5,12]. The association between the irAEs of pembrolizumab and CPS in our department is presented in Table 4. IrAEs occurred more frequently in patients with CPS >20, with a frequency of 12% (5 events, 4/33 cases; adrenal insufficiency, 2 cases; hypothyroidism, 1 case; drug-induced hepatitis, 1 case; and type 1 diabetes, 1 case). The CPS, in this case, was as high as 100, which may have facilitated the antitumor effect and led to irAEs. IrAEs with pembrolizumab occur in various patients but are not rare. Some reports have revealed that irAEs are associated with the antitumor effects of drugs [13].

#### 4.5. Implications and actions needed

It is essential to monitor blood glucose, perform urinalysis frequently and detect atypical but suggestive findings of type 1 diabetes and ketoacidosis, such as common cold symptoms, gastrointestinal symptoms, and general fatigue, as in the present case. Moreover, educating patients about the symptoms of hyperglycemia and diabetic ketoacidosis, such as dry mouth, polyuria, general fatigue, nausea, vomiting, and abdominal pain is necessary. HbA1c levels

may not be high in patients with fulminant type 1 diabetes. An immediate consultation system for various irAE target organs and early intervention with an interdisciplinary approach must be considered.

#### 5. Conclusions

This is the first report of metachronous IrAEs involving type 1 diabetes and isolated ACTH deficiency, associated with pembrolizumab monotherapy for metastatic head and neck cancer. IrAEs with pembrolizumab occur in various patients but are not rare. It is necessary to be familiar with each irAE and be aware of its characteristics. Keen observation of the symptoms and parameters associated with irAEs is necessary. Immediate and appropriate collaboration with other specialists is considered significant for the management of severe irAEs to improve the quality of life of patients.

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