

# Hypothyroidism With ACTH Deficiency During Pembrolizumab Therapy for Lung Cancer: Case Report and Literature Review

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**Abstract.** *Background/Aim: Immune-checkpoint inhibitors have recently shown great promise in treating various cancers, but often cause immune-related adverse events (irAEs). Simultaneous drug-induced hypothyroidism and isolated adrenocorticotrophic hormone (ACTH) deficiency are rare irAEs. This combination of irAEs is associated with paradoxical endocrine dysfunction characterized by large amounts of thyroid-stimulating hormone (TSH) and small amounts of ACTH in the anterior lobe of the pituitary. We herein report a case of hypothyroidism with isolated ACTH deficiency during pembrolizumab therapy for recurrent lung cancer. Case Report: Our patient was a 66-year-old man with recurrence of squamous cell lung carcinoma. Four months after chemotherapy that included pembrolizumab, the patient presented with general fatigue and laboratory tests showed high concentrations of TSH with low concentrations of free-T4. He was diagnosed with hypothyroidism and levothyroxine was prescribed. His ACTH concentration was found to be low 1 week later when he developed an acute adrenal crisis with associated hyponatraemia. We then changed his diagnosis to*

*concurrent hypothyroidism with isolated ACTH deficiency. His condition improved after 3 weeks of administration of cortisol. Conclusion: It is difficult to diagnose a concurrent paradoxical endocrine disorder, such as hypothyroidism with isolated ACTH deficiency, as in the present case. Physicians should pay attention to symptoms and laboratory data to identify various types of endocrine disorders as irAEs.*

Immune-checkpoint inhibitors (ICIs), such as nivolumab, pembrolizumab and ipilimumab, have anti-tumour effects through T-cell activation and have recently shown great promise in the treatment of various cancers. Programmed death ligand-1 (PD-L1) is expressed in 35%-95% of non-small cell lung cancers and overall survival of patients with PD-L1 (tumour proportion score  $\geq 1\%$ ) is reportedly significantly longer in patients receiving pembrolizumab than in those receiving chemotherapy without ICIs (1, 2). However, ICIs can also cause various autoimmune-like responses in different organs; these are termed immune-related adverse events (irAE). Of these endocrine irAEs, thyroid dysfunction is the most common, affecting more than 10% of patients receiving ICIs (3). Care must be taken when treating such hypothyroidism because levothyroxine may lead to acute adrenal crisis when cortisol concentrations are low (4). It is standard practice to check carefully for adrenal insufficiency in patients with panhypopituitarism with low concentrations of thyroid-stimulating hormone (TSH) and adrenocorticotrophic hormone (ACTH), however, unexpected paradoxical endocrine disorders such as our patient's high concentrations of TSH and low concentrations of ACTH are more difficult to suspect and identify. Here, we describe experiencing this diagnostic pitfall through a patient with simultaneous hypothyroidism and hypopituitarism (isolated ACTH deficiency) during pembrolizumab therapy for recurrent lung cancer.

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**Key Words:** Hypopituitarism, hypothyroidism, immune-checkpoint inhibitors, immune-related adverse events, isolated ACTH deficiency, lung cancer.

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Table I. Laboratory data.

Peripheral blood		
RBC	327×10 <sup>4</sup> /μl	(435-555)
Hemoglobin	9.9 g/dl	(13.7-16.8)
Hematocrit	36.9%	(40.7-50.1)
WBC	8,040/μl	(3,300-8,600)
Neutrophils	62.7%	(40-60)
Eosinophils	2.5%	(2-5)
Basophils	0.5%	(0-2)
Monocytes	12.4%	(3-7)
Lymphocytes	21.9%	(25-40)
Platelet	37.4×10 <sup>4</sup> /μl	(15.8-34.8)
Blood biochemistry		
Total protein	6.1 g/dl	(6.6-8.1)
Albumin	3.8 g/dl	(4.1-5.1)
Creatinine	1.2 mg/dl	(0.65-1.07)
BUN	8.2 mg/dl	(8-20)
CRP	1.9 mg/dl	(0.65-1.07)
Endocrine markers		
TSH	41.22 μIU/ml	(0.35-4.94)
FT4	0.66 ng/dl	(0.7-1.48)
ACTH	<1.5 pg/ml	(7.2-63.3)
Cortisol	0.4 μg/dl	(4.5-21.1)
Renin	1.3 ng/ml/h	(0.2-2.3)

RBC: Red blood cell; WBC: white blood cell; BUN: blood urea nitrogen; CRP: C-reactive protein; TSH: thyroid-stimulating hormone; FT4: free thyroxine; ACTH: adrenocorticotropic hormone.

### Case Report

The patient was a 66-year-old man who had undergone right upper lobectomy and lymph node dissection for squamous cell lung cancer (pathological T2N2M0 according to TNM classification 8th edition) approximately 1 year earlier. He had received adjuvant chemotherapy with four cycles of cisplatin and vinorelbine. However, 8 months after surgery, computed tomography (CT) of the chest showed multiple lung metastases in the lung fields bilaterally and mediastinal lymphadenopathy, resulting in a diagnosis of recurrence of squamous cell lung cancer. Immunohistochemical findings showed upregulated expression of programmed death ligand-1 (PD-L1) (tumour proportion 49%). He was therefore administered chemotherapy with four cycles of carboplatin, nab-paclitaxel and pembrolizumab, followed by additional cycles of pembrolizumab. Four months after commencing pembrolizumab, he presented with general fatigue. His tumours were found to be well-controlled; chest CT showing decreases in the sizes of his multiple pulmonary metastases and mediastinal lymphadenopathy. However, blood tests showed mild anaemia (haemoglobin 9.9 g/dl), hyponatraemia (potassium 129 mmol/l), hypochloraemia (chloride 95 mmol/l), and thyroid dysfunction [TSH 41.22 μIU/ml and free-T4 (FT4) 0.66 ng/dl] (Table I). We considered immune-related adverse events (irAEs) and diagnosed hypothyroidism

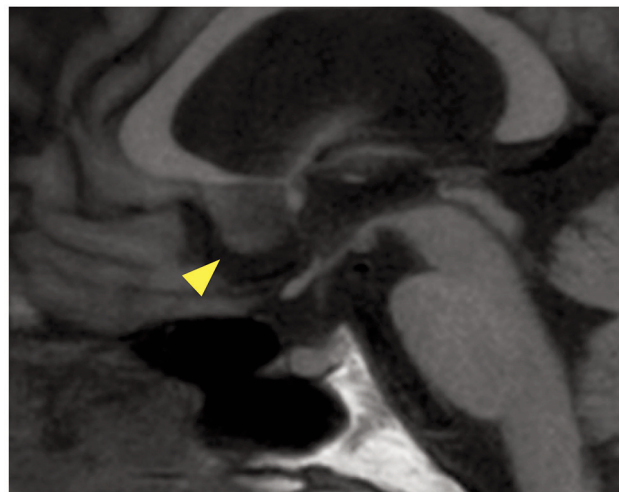


Figure 1. Brain magnetic resonance imaging scans showing normal size of the pituitary.

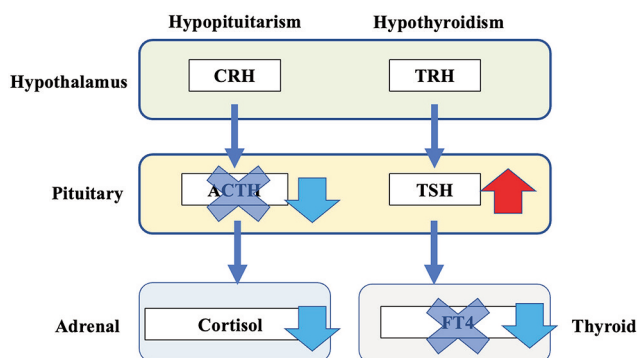


Figure 2. Schema of hypothalamus-pituitary-adrenal/thyroid axis in our case. The paradoxical endocrine dysfunction, which means the discrepancy between the levels of TSH and ACTH, occurred in the pituitary. Simultaneous drug-induced hypothyroidism and hypopituitarism characterized by isolated ACTH deficiency caused the high level of TSH and the low level of cortisol, respectively.

caused by pembrolizumab. We did not suspect concurrent hypopituitarism because the TSH concentration was high and magnetic resonance imaging (MRI) showed no evidence of inflammation in the pituitary gland (Figure 1). One week after commencing levothyroxine 25mg, blood tests showed more marked hyponatraemia (Na 118 mmol/l) and simultaneous adrenal insufficiency was diagnosed (ACTH: <1.5 pg/ml and cortisol: 0.4 μg/dl). Considering that our patient had secondary adrenal insufficiency caused by levothyroxine, we diagnosed isolated hypopituitarism complicated by hypothyroidism induced by pembrolizumab (Figure 2). We administered hydrocortisone (15 mg/day) for adrenal insufficiency and his condition improved greatly over the

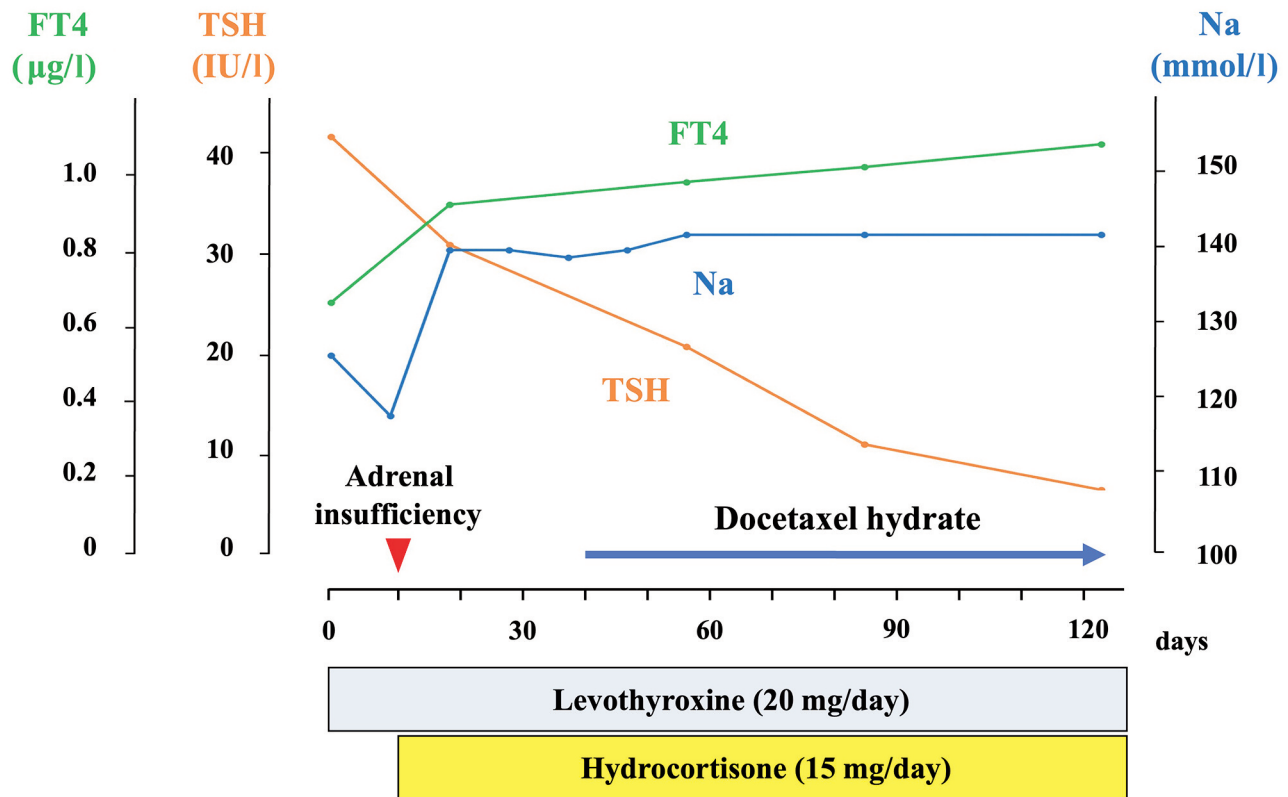


Figure 3. Time course of TSH, FT4, and serum potassium.

next 2 weeks (Figure 3). Three weeks after commencing cortisol, his hyponatraemia had resolved and docetaxel hydrate was substituted for the pembrolizumab. TSH and FT4 concentrations improved slowly, returning to normal 10 months after commencing levothyroxine. He continued to receive chemotherapy with both hydrocortisone and levothyroxine for 21 months after receiving pembrolizumab. However, he died of a cerebral haemorrhage soon after ceasing chemotherapy.

## Discussion

We herein report a rare case of simultaneous hypothyroidism and isolated ACTH deficiency during pembrolizumab therapy for recurrent lung cancer. Endocrine dysfunctions are reportedly the commonest irAEs, and the reported rates of thyroid and pituitary irAEs being 13.5%-20.8% and 0.4%-3.25%, respectively (5). Hypopituitarism is classified into three categories depending on the part of the pituitary gland affected: the anterior pituitary gland (adenohypopituitarism), posterior pituitary (infundibuloneurohypopituitarism), or the whole pituitary (panhypopituitarism). Patients with adenohypopituitarism generally have decreased secretion of ACTH, TSH, growth hormone, prolactin, luteinizing hormone,

and follicle stimulating hormone. However, a variant of adenohypopituitarism, namely isolated ACTH deficiency, has recently been identified. It is characterized by decreased secretion of ACTH and normal secretion of other pituitary hormones (6). The frequency of isolated ACTH deficiency as an irAE is reportedly only 0.87% (7); thus, simultaneous hypothyroidism and isolated ACTH deficiency must be extremely rare.

Twelve cases, including the present one, of hypothyroidism with isolated ACTH deficiency as irAEs have been reported (Table II) (8-18). Eight of these patients had isolated ACTH deficiency after having hypothyroidism, whereas the remaining four had both irAEs simultaneously. Notably, to the best of our knowledge there are no reported cases of hypothyroidism developing after isolated ACTH deficiency. Six of these patients had received nivolumab, five pembrolizumab, and one nivolumab and ipilimumab. The most commonly associated tumour was lung cancer (five patients) followed by melanoma (three), gastric cancer (one), kidney cancer (one), urothelial cancer (one), and breast cancer (one).

The symptoms of thyroid and pituitary irAEs are non-specific and similar, including general fatigue, appetite loss, nausea, and anorexia (5, 19). In the present case, our patient presented with only general fatigue. As shown in Table II,

Table II. Reported cases of patients with primary hypothyroidism and isolated adrenocorticotrophic hormone (ACTH) deficiency after treatment with immune checkpoint inhibitors (ICIs).

Author year (Reference)	Age/ Sex	Tumor	ICI therapy	History of hyperthyroidism after ICI therapy	Order of disease	Time from first ICI to hypothyroidism (months)	Time from hypothyroidism to hypopituitarism (months)	Symptoms		Laboratory findings		MRI findings
								Hypothyroidism	Hypopituitarism	Hypothyroidism	Hypopituitarism	
Kastrisiou <i>et al.</i> , 2017 (8)	66/M	Lung	Nivolumab	+	Allochronic (thyroid→ACTH)	5.5	1.5	Dizziness, fatigue, anorexia, withdrawal	Fatigue, anorexia, nausea	-	-	Normal
Ariyasu <i>et al.</i> , 2018 (9)	63/F	Melanoma	Nivolumab →Ipilimumab	+	Allochronic (thyroid→ACTH)	8	0.3	General fatigue	NA	Hyponatremia, liver dysfunction, CRP elevation	Hyponatremia	Normal
Machado <i>et al.</i> , 2019 (10)	55/M	Lung	Nivolumab	+	Allochronic (thyroid→ACTH)	6.5	12	-	Fatigue, asthenia, weight loss	-	-	Normal
Takeno <i>et al.</i> , 2019 (11)	72/F	Melanoma	Nivolumab	+	Allochronic (thyroid→ACTH)	13	9	General malaise	General malaise, anorexia	-	Hyponatremia, hypoglycemia	Normal
Ohara <i>et al.</i> , 2019 (12)	69/F	Lung	Nivolumab	+	Allochronic (thyroid→ACTH)	2	4	-	Anorexia, fatigue, general weakness	-	Hyponatremia, hypoglycemia	Mild atrophy of anterior pituitary
Yamagata <i>et al.</i> , 2019 (13)	59/M	Lung	Pembrolizumab	-	Allochronic (thyroid→ACTH)	2	4	-	-	-	-	Normal
Zeng <i>et al.</i> , 2019 (14)	54/M	Kidney	Nivolumab	-	Allochronic (thyroid→ACTH)	2	6	-	slight fever	-	Hypoglycemia	Normal
Doodnauth <i>et al.</i> , 2021 (15)	85/M	Urothelial	Pembrolizumab	-	Allochronic (thyroid→ACTH)	13	3	-	-	-	-	Normal
Takebayashi <i>et al.</i> , 2018 (16)	58/F	Melanoma	Nivolumab	+	Simultaneous	6	-	Fatigue, sense of weakness	Hyponatremia hypercalcemia	Normal	Normal	Normal
Oristrell <i>et al.</i> , 2018 (17)	55/F	Breast	Pembrolizumab	-	Simultaneous	12.5	-	Severe hypotension	Hyponatremia	Normal	Normal	Normal
Sasaki <i>et al.</i> , 2021 (18)	73/M	Gastric	Pembrolizumab	+	Simultaneous	5	-	General fatigue, fever	Hypoglycemia	Normal	Normal	Normal
Present case	66/M	Lung	Pembrolizumab	-	Simultaneous	4	-	General fatigue	Hyponatremia	Normal	Normal	Normal

MRI: Magnetic resonance imaging; N.A.: not available.

these patients had mostly non-specific manifestations except for loss of consciousness caused by hypoglycaemia and hypotension caused by adrenal deficiency (8-18). Patients with hypothyroidism alone tend to be asymptomatic (62.5%) in Table II (8-15). In our hospital, laboratory data of TSH and FT4 is available immediately, whereas measurement of ACTH takes several days. Relying on physical examination alone may lead to overlooking co-existing irAEs. As shown in Table II, 10/12 (83.3%) patients with hypothyroidism and isolated ACTH deficiency had hyponatraemia and hypoglycaemia (8-18). Thus, laboratory tests may be useful for diagnosing concurrent irAEs in asymptomatic patients receiving ICIs.

MRI findings were normal in almost all reported patients (92%) with hypothyroidism and isolated ACTH deficiency (Table II). A systematic review investigating isolated ACTH deficiency as an irAE revealed that MRI findings were normal in 93% (n=60) of the patients (7). However, the pituitary was enlarged in almost all patients with autoimmune panhypopituitarism (20). Importantly, physicians should remember that endocrine dysfunction may be present in patients whose pituitary glands appear normal on MRI.

Recent reports have indicated that age (<60 years), high body mass index, sarcopenia and history of autoimmune disease are clinical risk factors for irAEs (21). In addition, high neutrophil-lymphocyte ratio, absolute monocyte count, absolute platelet count and higher baseline albumin have also been reported as the predictive biomarkers (21, 22). Kurimoto *et al*. reported that early change of serum thyroglobulin, thyroid auto-antibodies and cytokine level were associated with development of thyroid-related irAEs (23). These studies suggested that these biomarkers may detect the irAEs. Further studies for predicting irAEs are necessary.

In the present case, we experienced a paradoxical endocrine dysfunction with high TSH and low ACTH level, although these hormones are secreted in the anterior lobe of the pituitary (Figure 2). This pattern of endocrine dysfunction may increase because the use of ICIs has increased in various cancers, and patients with multiple irAEs were reported to comprise 9.0% of patients receiving anti-PD-L1 therapy (24). Therefore, it is important to suspect the possibility of paradoxical endocrine dysfunction and evaluate comprehensively various types of hormones to follow up the treatment by ICIs.

## Conclusion

This report has presented a rare case of simultaneous drug-induced hypothyroidism and hypopituitarism characterized by isolated ACTH deficiency during pembrolizumab therapy for recurrent lung cancer. Hypothyroidism with isolated ACTH deficiency as an irAE is very rare; however, it is important to be careful about the possibility of concurrent isolated ACTH deficiency even if the level of TSH is high

because the administration of levothyroxine prior to cortisol can cause acute adrenal crisis in the presence of irAEs. In addition, the comprehensive follow-up of hormone levels is useful for the diagnosis of irAEs; careful attention to the symptoms and laboratory data might prevent diagnostic pitfalls relating to various types of irAEs during treatment with ICIs.

## Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

## Authors' Contributions

Asato Hashinokuchi searched the literature and wrote the manuscript. Akira Haro provided direct patient care, searched the literature, and edited the manuscript. All Authors read and approved the final manuscript.

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