


CASE REPORT

Spontaneous recovery of immune checkpoint inhibitor-induced thyroiditis with high free T4 level: A case report

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Abstract

We describe a case of severe hyperthyroidism with high free thyroxine and C-reactive protein levels, wherein thyroid function rapidly improved without treatment. In a similar case, conservative management with imaging follow-up can be considered.

KEYWORDS

high CRP level, high free T4 level, immune checkpoint inhibitors (ICI), thyroiditis, without steroids

1 | INTRODUCTION

A 69-year-old man was treated with nivolumab and ipilimumab combination therapy for renal cell carcinoma. Free thyroxine level was above 8.0 ng/dl. Imaging studies showed a new diffuse thyroid enlargement. A diagnosis of immune checkpoint inhibitor-related thyroid dysfunction was made. Thyroid function improved after 9 days without steroids.

Immune checkpoint inhibitors (ICIs) are widely used for many advanced cancers. ICIs have improved the prognosis of 10%–60% of patients with advanced cancer and metastases.¹ ICIs include programmed cell death protein 1 (PD-1) antibodies and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies. PD-1 on T cells binds to the

PD-L1 on target tumor cells and suppresses T-cell activation. Conversely, CTLA-4 on T cells binds to B7 on antigen-presenting cells and suppresses T-cell activation. PD-1 and CTLA-4 antibodies inhibit the binding of T cells to their target cells, resulting in T-cell activation.¹ T-cell activation induced by ICIs causes immune-related adverse events (irAEs) in various organs by enhancing T-cell activation against antigens of healthy tissues and increasing autoantibodies and inflammatory cytokines²; for instance, ICI injury occurs in the skin, gastrointestinal tract, and liver.³ ICIs can also affect the endocrine system, including the pituitary gland, thyroid gland, adrenal glands, and pancreas.⁴ In particular, we often encounter ICI-induced thyroid dysfunction in clinical practice.⁴ The reported overall incidence of hyperthyroidism and hypothyroidism is 2.9%

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and 6.6%, respectively.⁵ Anti-thyroid antibodies could be involved in ICI-related thyroid dysfunction⁶; however, the mechanism remains unclear. Thyroid dysfunction induced by ICIs is frequently temporary and/or mild; therefore, treatment is usually not required.⁶ However, steroids were used for a thyroid storm in a reported case.⁷ The previous report showed that severe hyperthyroidism cases of grade 3 or higher are rare (0.1%).⁵

Although steroid treatment tends to be routine practice for severe irAEs, regardless of the affected organs, one retrospective study reported that high dose glucocorticoid (HDG) treatment did not improve the outcome of ICI-related hyperthyroidism.⁸ Therefore, steroid treatment for hyperthyroidism is controversial. Severe cases with free thyroxin (T4) of >8.0 ng/dl are rare, and no standard treatment has yet been established. In addition, no cases of severe hyperthyroidism have been followed by imaging over a short time period. In this report, we present the case of a patient with severe hyperthyroidism induced by ICIs with thyrotropin (TSH) of <0.01 μ IU/ml, free T4 of >8.0 ng/dl, and C-reactive protein (CRP) of 24 mg/dl. The thyroid dysfunction improved in 9 days without treatment, and imaging confirmed improvement in thyroid enlargement.

2 | CASE PRESENTATION

A 69-year-old Japanese man underwent an endoscopic colon cancer resection 7 months before his visit. A right renal tumor and a right lung tumor were found on computed tomography (CT) at the time of surgery. The patient underwent a right lung tumor resection 5 months before presentation. The patient was diagnosed with metastases of renal cell carcinoma and a positive lymph node. After diagnosis, a laparoscopic radical nephrectomy was performed 2 months before presentation. The patient was treated with nivolumab and ipilimumab combination therapy, which was started 5 weeks before presentation. The second course was started on day-13, and his thyroid function and CRP level did not increase (Table 2). The patient had a sore throat, nasal discharge, fatigue, and loss of appetite 1 week before presentation. The patient was not aware of any neck pain or neck enlargement. The patient continued to have the above symptoms and was admitted to our hospital. Upon examination, the following results were obtained: temperature, 37.1°C; blood pressure, 123/73 mmHg; heart rate, 95 beats per minute; and peripheral oxygen saturation 97% on room air. His thyroid was mildly enlarged, but not hard, with no palpable mass and no tenderness. His laboratory data showed a white blood cell count of 6200/ μ l and a CRP level of 24 mg/dl. His thyroid function measurements included TSH below 0.01 μ IU/ml, free triiodothyronine (T3) of 13.7 pg/ml, and

TABLE 1 Laboratory results at the time of hospital admission

Test	Value	Reference range
White blood cells ($\times 10^3/\mu$ l)	6.2	3.9–9.8
Neutrophils (%)	71	40–74
Red blood cells ($\times 10^4/\mu$ l)	423	427–570
Hemoglobin (g/dl)	12.9	12.0–17.6
Hematocrit (%)	36.7	39.8–51.8
Platelets ($\times 10^4/\mu$ l)	31.8	13.0–36.9
Albumin (g/dl)	3.4	4.1–5.1
Total bilirubin (mg/dl)	0.5	0.4–1.5
AST (U/L)	63	13–30
ALT (U/L)	51	10–42
Lactate dehydrogenase (U/L)	173	124–222
Creatine phosphokinase (U/L)	63	59–248
Alkaline phosphatase (U/L)	236	106–322
Gamma-glutamyl transpeptidase (U/L)	56	13–64
Sodium (mmol/L)	127	138–145
Potassium (mmol/L)	5.0	3.6–4.8
Chloride (mmol/L)	95	100–110
Blood urea nitrogen (mg/dl)	23	8.0–20
Creatinine (mg/dl)	1.14	0.65–1.07
Uric acid (mg/dl)	6.2	3.7–7.8
Glucose (mg/dl)	127	
estimated GFR	49.9	
C-reactive protein (mg/dl)	24.3	0–0.14
Procalcitonin	≥ 2.0	
TSH (μ IU/ml)	≤ 0.01	0.38–4.31
freeT3 (ng/dl)	13.7	2.17–3.34
freeT4 (pg/ml)	10.0	0.82–1.63
Thyroglobulin (ng/ml)	350	2.68–33.2
Anti-TPO antibody (IU/ml)	≤ 2.6	0–3.2
Anti-thyroglobulin antibody (IU/ml)	248	0–13.6
ACTH (pg/ml)	18.9	7.20–63.3
Cortisol (μ g/dl)	17.4	

Abbreviations: ACTH, adrenocorticotrophic hormone; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

free T4 was above 8.0 ng/dl (Table 1). The thyroid receptor antibody was below 1.0 IU/L, the anti-thyroglobulin antibody was 248 IU/ml, and the anti-thyroid peroxidase antibody was below 2.6 IU/ml. The neck ultrasonography (US) showed that both thyroid lobes were enlarged and the parenchyma was hypoechoic and heterogeneous. Blood flow in the thyroid parenchyma was mildly increased. The neck CT showed that both lobes were enlarged, with no tracheal compression (Figure 1). Although

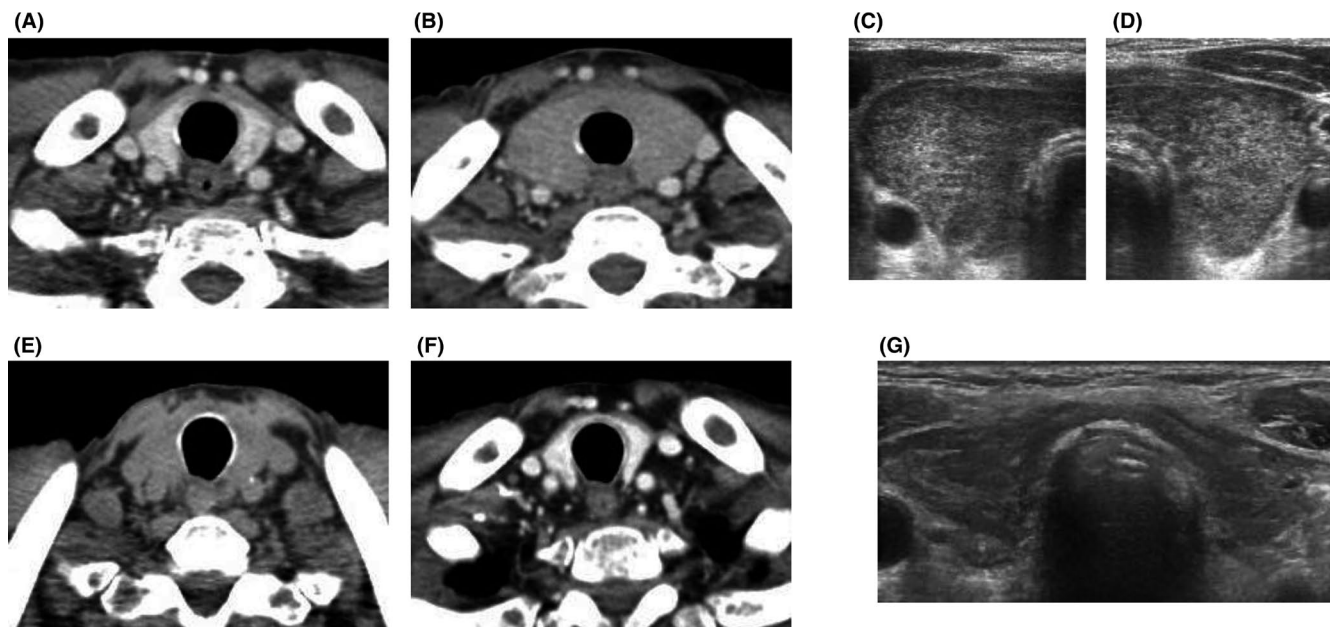


FIGURE 1 Changes in neck computed tomography (CT) and ultrasound (US) performed during the course of ICI-related thyroiditis are shown. (A) Neck CT taken on day 49 before the start of ICIs. (B) Neck CT taken on day 1 showing a diffusely enlarged thyroid gland. (C, D) Neck US taken on day 1 showing enlargement of both lobes (right/left lobe transverse diameter was 27/22 mm) and hypoechoic and heterogeneous parenchyma. (E) Neck CT taken on day 16 showing less thyroid enlargement. (F) Neck CT taken on day 84 showing atrophic thyroid gland. (G) Neck US taken on day 28 showing markedly less thyroid enlargement (right/left lobe transverse diameter was 18/13 mm). The parenchyma remained hypoechoic and heterogeneous

TABLE 2 Clinical course

Onset	Day −13	Day 1	Day 5	Day 9
TSH (μ IU/ml)	0.886	≤ 0.010	0.010	0.011
ft4 (pg/ml)	1.1	≥ 8.00	6.26	2.2
CRP (mg/dl)	0.29	24.28	5.42	2.62

Abbreviations: CRP, C-reactive protein; ft4, free thyroxine; TSH, thyroid-stimulating hormone.

his symptoms and vital signs were mild, he was thought to have grade 3 ICI-related thyroiditis based on his general condition and laboratory results, including high CRP and free T4 levels.⁹ Therefore, steroid treatment was considered. However, because his vital signs were not severe, we decided to monitor his general condition and laboratory tests closely without steroid treatment. Although he was easily fatigued, his thyrotoxicosis was not strong enough to require the use of beta blockers. His thyroid function recovered after 9 days, with CRP showing a tendency to improve (Table 2). Hyponatremia was observed on admission, and the sodium level tended to improve with improved appetite. As adrenocorticotropic hormone (ACTH) and cortisol levels were not low, we believed that hyponatremia was caused by insufficient intake. His subjective symptoms improved and he was discharged after 10 days.

The patient had no fever during his hospitalization. The blood culture, performed at the time of admission, was negative. His thyroid function declined 16 days after the onset of symptoms. The neck CT taken on day 16 showed that both thyroid lobes were less enlarged compared to the previous examination. The neck US taken 1 month after the onset of symptoms showed a normal-sized thyroid, but his parenchyma was hypoechoic and heterogeneous as in hyperthyroidism (Figure 1).

3 | DISCUSSION

We describe a case of seemingly severe hyperthyroidism with high free T4 and CRP levels. The thyroid function improved rapidly without steroid treatment. Two salient points can be made about this case. First, thyroid function improved in 9 days without steroids, although the free T4 level was higher than in the previous reports. Second, improvements of thyroid enlargement were monitored and verified by imaging.

Initially, the patient had a higher free T4 level compared with the previously reported ICI-related thyroid disorder. The previously reported median free T4 level was 2.46 (range 1.20–6.32) ng/dl, and the median TSH was 0.02 (range 0.01–0.23) μ IU/ml in the hyperthyroidism phase associated with ICIs.¹⁰ In general, the median

free T4 in painless thyroiditis unrelated to ICIs was 2.5 (range 1.5–8.4) ng/dl.¹¹ Thus, the present case had higher free T4 level than that previously reported for ICI-related and unrelated thyroiditis. According to a report by Iyer et al.,¹⁰ the median time from the initial ICI treatment to hyperthyroidism is 5 weeks (after two ICI courses), and the median time from initiation of ICIs to hypothyroidism is 7 weeks. In the same report, approximately 30% of patients had mild symptoms, including fatigue and palpitations, which required treatment with beta blockers. In this case, the time to hyper- and hypothyroidism from the ICI initiation was 5 and 7 weeks, respectively. Although the free T4 level, in this case, was higher than that previously reported, the patient's symptoms were not severe. The course of onset was typical, and mild symptoms were consistent with ICI-related thyroiditis. Thus, we considered the possibility of ICI-related thyroiditis rather than painless thyroiditis.

In this case, the hyperthyroidism phase (from confirmation of hyperthyroidism to hypothyroidism) persisted for 2 weeks. Previous reports have shown that the hyperthyroidism phase persists for 6 weeks (median).^{10,12} We conducted thyroid function test more frequently than previous reports; thus, results cannot be easily compared. However, symptoms were not severe in this case, and the clinical course was mild based on the patient's thyroid function data. In contrast with the short period of symptoms in the present case, total thyroidectomy was eventually performed for ICI-related refractory thyroiditis.¹³ Inflammatory cytokine-rich conditions due to chronic inflammation, such as chronic lymphocytic thyroiditis and Hashimoto's thyroiditis, may result in increased PD-L1 expression.¹⁴ In another report, highly expressed PD-L1 levels were associated with irAE progression in patients with non-small cell lung cancer treated with pembrolizumab.¹⁵ Because PD-1 regulates T-cell activity in the periphery, the absence of PD-1 can cause tissue-specific autoimmunity.¹⁶ Thus, the PD-1/PD-L1 pathway may influence the development of autoimmune diseases. In this case, thyroid antibodies were not measured before administering ICIs, and the PD-L1 expression level was unknown. Although the degree of PD-L1 expression may influence the prognosis of ICI-related thyroiditis, the reason behind the rapid improvement in this case remains unknown.

Based on high free T4 and CRP levels, we considered steroid treatment. The use of steroids is recommended for severe irAEs.^{17,18} In the ICI-related thyroiditis, steroids are not routinely used; however, a report used steroids for severe ICI-related thyroiditis.⁷ Little evidence is available to support the use of HDG for the treatment of ICI-related thyroid dysfunction. One retrospective study showed that HDG did not improve the clinical outcome of ICI-related

thyroid dysfunction.⁸ Furthermore, short-term steroid use increases the risks of gastrointestinal bleeding, sepsis, and heart failure by 1.80-, 1.99-, and 2.37-fold, respectively.¹⁹ Thus, the risks and benefits should be considered before using steroids to treat ICI-related thyroid dysfunction. In the case described here, we decided not to use steroids because of stable vital signs, possibility of infection, and low benefit. The use of steroids for the treatment of ICI-related thyroid dysfunction should be carefully discussed, and further studies are required.

We were able to follow imaging changes in the ICI-related thyroiditis. To our knowledge, no reports have shown the imaging changes in the thyroid before and after severe hyperthyroidism over a short period. CT of ICI-related thyroiditis is described as a new diffuse enlargement that is heterogenous, and US is described as having low echogenicity.^{20,21} In patients with non-ICI-related thyroiditis, CT shows a hypoattenuating thyroid gland, which is believed to be due to the destruction of thyroid follicular cells and decreased thyroid iodine levels.²² In this case, the patient had a new diffuse enlarged thyroid gland that appeared hypoechoic and heterogeneous on CT and US, consistent with the previous reports. A rapid visual improvement was seen via imaging. In addition to the thyroid function tests, CT and US imaging studies may be useful in patients suspected of ICI-related thyroiditis with lack of specific symptoms.

4 | CONCLUSION

In conclusion, we described a case of ICI-related hyperthyroidism with rapid improvement, despite the high free T4 level, in the absence of steroid treatment.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

AUTHOR CONTRIBUTIONS

R. Hagiwara analyzed the clinical data and wrote the manuscript as first author. D. Suzuki wrote and edited the manuscript. H. Yamada edited and reviewed the manuscript. S. Tonezawa, R. Saikawa, S. Funazaki, M. Yoshida, S. Washino, T. Miyagawa, and K. Hara reviewed

the manuscript. All authors are aware of and approve the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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