

Case Conference for CME
in JKMS

Endocrinology, Nutrition &
Metabolism



Received: Sep 14, 2022

Accepted: Nov 3, 2022

Published online: Nov 16, 2022

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Disclosure

The authors have no potential conflicts of
interest to disclose.

Case 5: A 41-Year-Old Woman With Palpitation

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PRESENTATION OF CASE 5

Dr. Jiwon Yang: A 41-year-old woman was admitted to this hospital because of palpitation and general weakness. The symptoms had lasted for about one week. She also complained of diaphoresis and dizziness. Her heart rate was increased to 110 beats per minute with normal blood pressure (127/61 mmHg), respiratory rate (20/min), and body temperature (36.9°C). Heart sounds were normal without murmurs. Complete blood count and blood chemistry showed no specific findings. Her thyroid function tests showed thyrotoxicosis: free thyroxine (free T4) of more than 12 ng/dL, total triiodothyronine (T3) of more than 8 ng/mL, and thyroid stimulating hormone (TSH) of less than 0.008 uIU/mL. An electrocardiogram showed increased heart rate (102/min) with sinus rhythm. Chest radiograph showed clear lungs with normal cardiac and mediastinal silhouette.

At about one week before the symptoms began, she had been treated with pembrolizumab for advanced cervical cancer. There were no clinical findings related to goiter or Graves' orbitopathy. Thyroid autoantibodies were within normal range except for thyroglobulin antibody (477.4 U/mL). Thyroid scan showed globally reduced uptake in the thyroid. Thyroid ultrasonography showed heterogeneous parenchymal echogenicity with increased vascularity (Fig. 1).

CLINICAL COURSE

Dr. Jiwon Yang: For her thyrotoxicosis, she was prescribed with propranolol (40 mg twice a day) and cholestyramine (9 g) with proper hydration. Despite the treatment, her symptoms and laboratory tests did not show any improvement. After usage of dexamethasone, her symptoms and laboratory tests showed improvement. After showing improvement of thyrotoxicosis, the patient was discharged and followed up at the outpatient department. About one year after the discharge, her thyroid function showed hypothyroidism (TSH: 9.948 uIU/mL; free T4: 0.87 ng/dL). The patient's thyroid function test results are summarized in Fig. 2.

The patient was examined by ultrasonography at the beginning of thyrotoxicosis symptom and follow-up. Especially, the degree of blood flow increase was measured by the vascularity index. The vascularity index indicates that the percentage of color pixels in the total grayscale pixels in a defined region of interest (ROI) from the microvascular flow image.¹ The patient's

Author Contributions

Conceptualization: Shin KS, Lee JM, Ha JH, Lim DJ, Baek HS. Data curation: Yang JW, Baek HS. Writing - original draft: Yang JW, Baek HS. Writing - review & editing: Shin KS, Lee JM, Ha JH, Lim DJ, Baek HS.

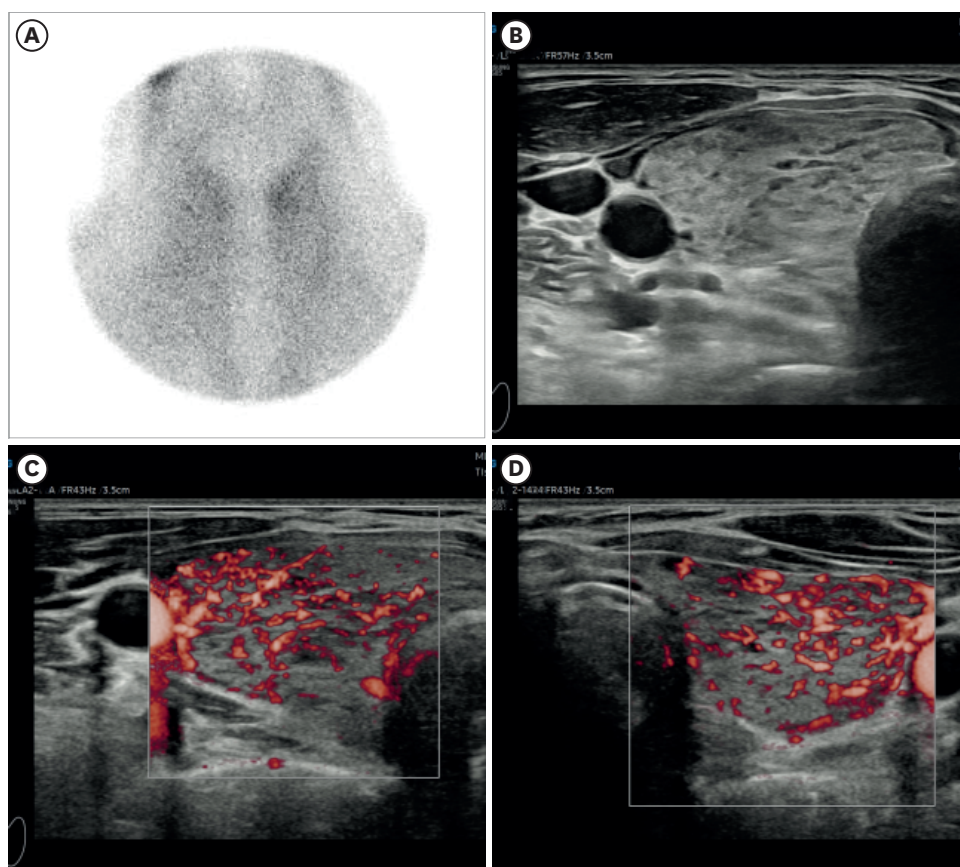


Fig. 1. Thyroid scan and ultrasonography image of the patient. (A) Thyroid scan image. Thyroid scan was correlated with destructive thyroiditis. (B) Gray scale ultrasonography of right thyroid lobe. (C) Microvascular flow image of right thyroid lobe. (D) Microvascular flow image of left thyroid lobe. Thyroid vascularity of both lobes showed an increase.

thyroid vascularity was increased until 19 days after the 3rd pembrolizumab injection. Captured image and the patient's thyroid function test results are summarized in Fig. 3.

CLINICAL IMPRESSION

Dr. Jiwon Yang: Thyroid immune-related adverse effect (irAE) associated with immune checkpoint inhibitor (ICI) treatment.

DIFFERENTIAL DIAGNOSIS

Dr. Dong-Jun Lim: Thyrotoxicosis refers to clinical symptoms and signs due to excess of thyroid hormone.¹ Although the term hyperthyroidism is used interchangeably these days, hyperthyroidism refers to overstimulation of the thyroid. On the other hand, passive release of thyroid hormones from inflammatory destruction of thyroid due to any reasons such as subacute thyroiditis, autoimmune thyroiditis, and drug-induced thyroiditis could also cause thyrotoxicosis.² The most common cause of hyperthyroidism is Graves' disease. Inflammatory destruction is referred to as destructive thyroiditis.

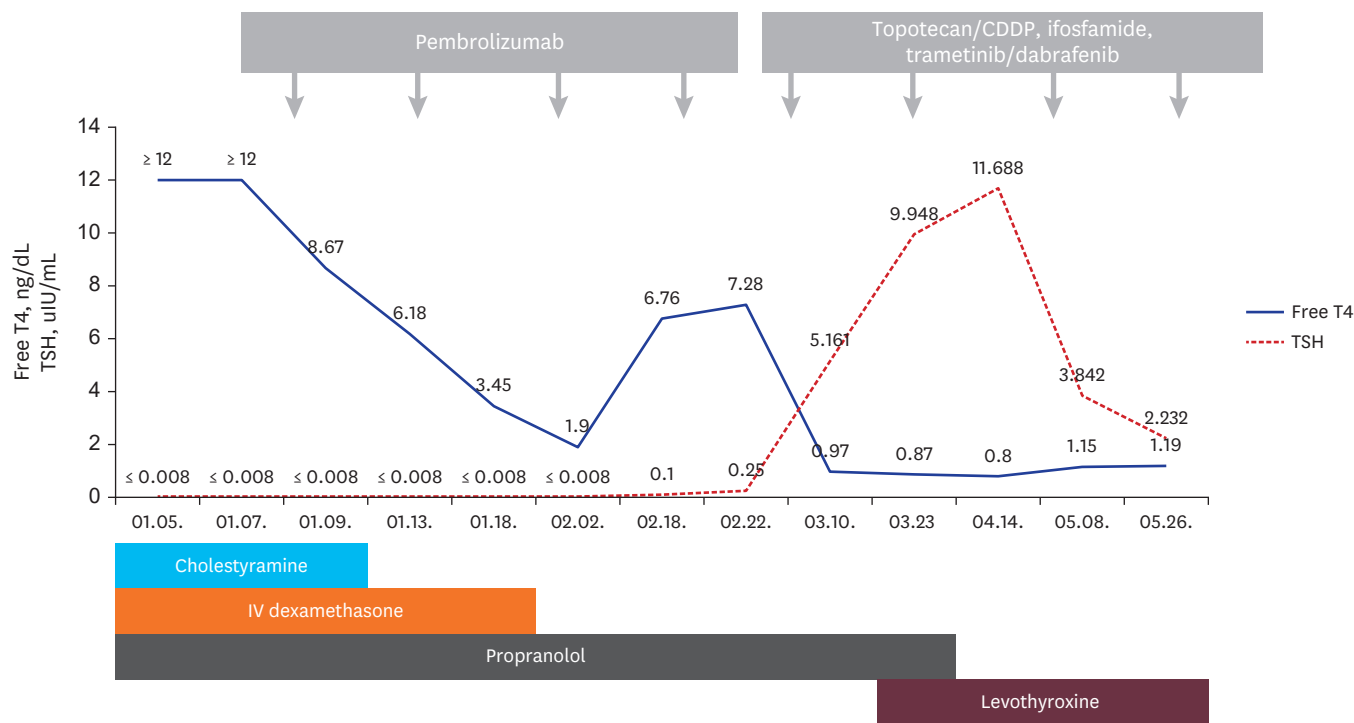


Fig. 2. About one year after recovery from thyrotoxicosis and discharge, she developed hypothyroidism. TSH = thyroid stimulating hormone, CDDP = cisplatin.

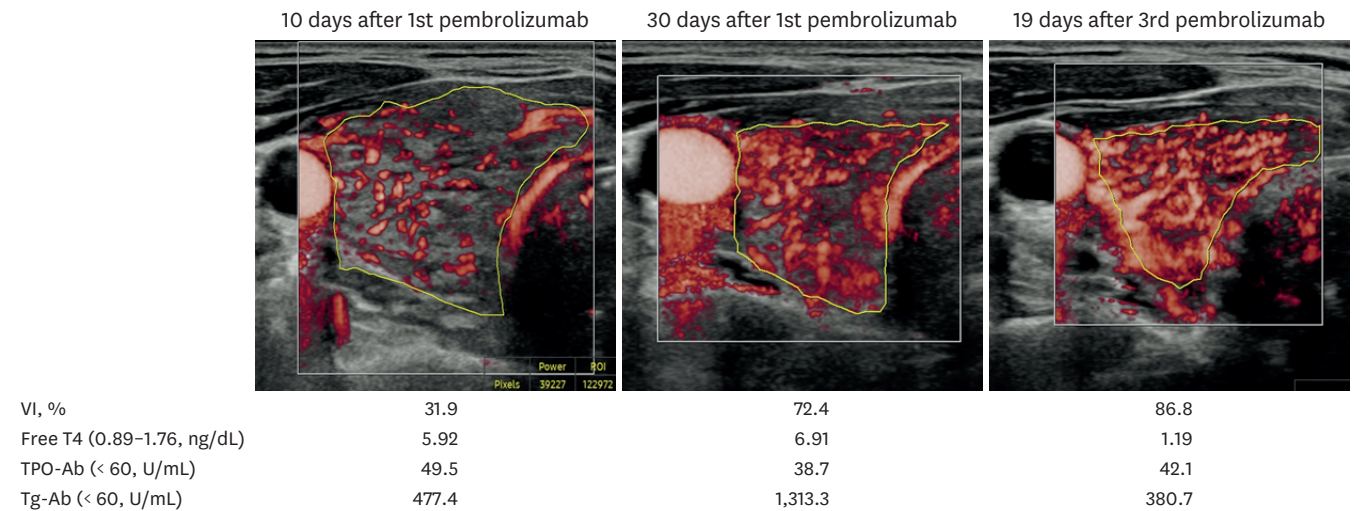


Fig. 3. Serial microvascular flow Doppler image and laboratory data of the patient. Vascularity of the thyroid showed persistently increased status during treatment with the immune checkpoint inhibitor. Free T4 = free thyroxine, TPO-Ab = thyroid peroxidase antibody, Tg-Ab = thyroglobulin antibody, VI = vascularity index, the percentage of color pixels in the total grayscale pixels in a defined region of interest from the microvascular flow image.

Careful and accurate differential diagnosis of thyrotoxicosis is important because it could affect the decision to use antithyroid drugs. Hypothyroidism can occur if antithyroid drugs are used in destructive thyroiditis.

ICI can also induce destructive thyroiditis.^{3,4} ICI-induced thyroiditis or irAE usually shows the course of overt or subclinical hypothyroidism followed by thyrotoxicosis. Therefore,

the clinical presentation of thyroid irAE could be thyrotoxicosis and hypothyroidism. While thyrotoxicosis presents with tachycardia, weight loss, fatigue, diaphoresis, and loose stool, hypothyroidism presents with bradycardia, edema, fatigue, and constipation.⁵ These symptoms are non-specific to ICI-induced thyroiditis. They could be confused with symptoms of tumor itself.⁶

Thyroid irAE should be assessed by thyroid function tests such as TSH, T3, and free T4. The interpretation of thyroid function tests from patients who were in treatment for tumors should be done carefully.⁷ When the etiology of thyroid dysfunctions is unclear, measurements of thyroid autoantibodies such as thyrotropin receptor antibody, anti-TPO antibody, and thyroglobulin antibody could aid differential diagnosis.⁸ Thyroid scintigraphy could be performed because of its ability to distinguish thyroid destruction from hyperthyroidism.⁹ Although Doppler ultrasound is not routinely used, it could aid the diagnosis by showing an increase of thyroid vascularity.^{1,9}

DISCUSSION

How much ICI treatment is used these days and how many of related thyroid irAEs are involved?

Dr. Kabsoo Shin: Recently, the use of ICIs has been markedly increased because its efficacy for many solid tumors.⁹⁻¹¹ ICIs are humanized monoclonal antibodies made to regulate the tumor microenvironment, leading to enhanced antitumor effect.^{12,13} Although the mechanism of irAE to endocrine organ is not fully understood,^{8,13,14} the incidence of irAE associated with ICIs treatment is high.¹⁵ Thyroid dysfunction is one of the most frequently reported irAEs.¹⁵ According to one review article, the incidence of thyroid irAE is up to 31.3%.⁸ From one retrospective study with a large study population (n = 1,246), 42% of patients developed thyroid irAE.¹⁶ In the study with data from one referral hospital in Korea, 31.3% of patients of study population developed thyroid irAE.¹⁰

Is there any characteristic of thyroid dysfunction after ICI treatment?

Dr. Han-Sang Baek: Thyroid dysfunction associated with ICIs treatment follows the course of destructive thyroiditis.^{4,6} Thyrotoxic status proceed overt or subclinical hypothyroidism. Thus, patients who develop thyroid irAE should be monitored closely. The American Society of Clinical Oncology (ASCO) guideline recommends screening of TSH and free T4 before ICI treatment and monitoring every 4–6 weeks according to the symptom's severity.¹⁷ The patient in our case also experienced this course of thyroid dysfunction. The Doppler image of the patient suggests that ICIs could affect thyroid function for quiet a long time. In one study, 18-fluorodeoxyglucose (¹⁸FDG) uptake on positron emission tomography (PET) scan is increased in those with thyroid irAE.¹³ It suggests that ICIs can cause some inflammation, leading to destructive thyroiditis.

Is there any association between development of thyroid dysfunction and survival?

Dr. Han-Sang Baek: Lots of data from many studies suggest that thyroid irAE is associated with better overall survival.^{13,18} The 3-year survival year of patients with thyroid irAE was 55.7% while it was 24.6% without thyroid irAE in a study with data of 191 patients from one referral hospital in Korea.¹⁰ In another study with almost the same study design and number of study population, the mortality was about two times higher in those without thyroid

irAE than in those with thyroid irAE.¹⁸ It suggests that thyroiditis might be a biomarker for treatment response. In this regard, further study is needed to uncover the mechanism or factors associated with thyroid irAE.

Is there any predictive biomarker for thyroid irAE?

Dr. Han-Sang Baek: There is no reliable marker for predicting thyroid irAEs after treatment with ICIs.¹⁹ Especially, the role of antithyroid autoantibodies is controversial.^{16,20} In one study from a single center in Korea, the positivity for thyroid autoantibodies was able to predict the course of the disease.⁴ However, in another study with a small group of subjects, a low frequency of thyroid autoantibody was observed.²¹ In the study from a single center in Korea, there was no association between positivity of thyroid autoantibodies and thyroid irAEs.¹⁰

Body mass index (BMI) is another candidate with a predictive value because a lot of studies have suggested that higher BMI is associated with thyroid dysfunction.²²⁻²⁴ However, the result could be changed if subjects have different ethnicities. In a study from Korea, there was no difference in BMI distribution between those with thyroid irAE and those without thyroid irAE.

How to manage thyroid irAE?

Dr. Jeongmin Lee: The management strategy for thyroid irAE depends on TSH level and severity of symptoms. For thyrotoxicosis with asymptomatic or mild symptoms, it is reasonable to perform close observation because it is usually transient;^{9,17} β -blockers (e.g., atenolol or propranolol) could be used for symptom relief.¹⁷ On the other hand, for thyrotoxicosis with severe symptoms or life-threatening conditions, treatment with ICIs could be stopped and additional medical therapies such as steroid iodine and anti-thyroid drugs could be considered based on ASCO guideline.¹⁷

Hypothyroidism management depends on TSH level. TSH higher than 10 mU/L or any level of TSH elevation with symptom could be an indication for treatment.⁹ In addition, adrenal insufficiency should be ruled out before starting a hormonal treatment.¹⁷

CONCLUSION

Dr. Jeonghoon Ha: As the use of ICI increases, the number of patients who experience thyroid irAEs is also increasing. Physicians should understand the course of thyroid irAEs associated with the use of ICIs. They should perform proper management for patients with proper monitoring during ICI treatment.

Related questions

Available at <https://doi.org/10.3346/jkms.2022.37.e323>

ACKNOWLEDGMENTS

The Case Conference section is prepared from monthly case conference of Department of Internal Medicine, the Catholic University of Korea College of Medicine, Seoul, Korea.

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