



Pembrolizumab Induced Hypothyroidism: A Case Report

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ABSTRACT

Immune checkpoint inhibitors inhibit the inhibitory mechanism on the immune system, their side effects may be autoimmune diseases that occur due to excessive immune response. Pembrolizumab is an immune checkpoint inhibitor targeting PD-1. The most common clinical presentations of thyroid injury induced by pembrolizumab are destructive thyroiditis and overt hypothyroidism. Herein, we presented a case of pembrolizumab induced hypothyroidism.

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Introduction

There are two main forms of lung cancer: non-small cell lung cancer (NSCLC) (85% of patients) and small cell lung cancer (SCLC) (15%). WHO has classified NSCLC into 3 main types: adenocarcinoma, squamous cell carcinoma and large cell.^{1,2} The median overall survival and 5-year median survival rates for patients with non-small cell lung cancer were not promising until recently. The discovery of new agents and predictive biomarkers has played a role in improving prognosis in patients with advanced metastatic NSCLC.^{3,4} Immune checkpoint inhibitors are one of these agents.

The importance of monoclonal antibodies as immune checkpoint inhibitors, in the field of oncology is increasing day by day. Since these drugs inhibit the inhibitory mechanism on the immune system, their side effects may also be autoimmune diseases that occur due to excessive immune response. When these side effects occur, it is important to discontinue the drug and start steroids. In checkpoint inhibition, programmed cell death 1 (PD-1), PD-1 ligand (PD-L1) receptors and cytotoxic T lymphocyte associated protein 4 (CTLA-4) are among the targets. Pembrolizumab and nivolumab targeting PD-1, atezolizumab,



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avelumumab and durvalumab targeting PDL-1 are used in many malignancies in various indications.⁵ The most common clinical presentations of thyroid injury induced by pembrolizumab are destructive thyroiditis and overt hypothyroidism. In this case, we wanted to present a case of pembrolizumab induced hypothyroidism.

Case Report

A 64-year-old male patient with a known diagnosis of metastatic non-small cell lung cancer was admitted to the general internal medicine outpatient clinic with complaints of swelling in the legs, weakness, enlarged tongue, constipation, slowing of speech and dyspnea. He had no history of thyroid disease. Gemcitabine, cisplatin and pembrolizumab were started for the patient, who was diagnosed six months ago, for combined chemotherapy and immunotherapy. The patient received 7 cycles of pembrolizumab treatment. On physical examination, temperature was 36.3 °C and heart rate was 89 beats/min. He was conscious, oriented and cooperative. The patient had no hair and nail changes, and his skin looked pale yellow. Macroglossia was present. There were no rales or rhonchi on auscultation of the lungs. In the abdominal examination, the abdomen was slightly distended, there was no defense or rebound. Bilateral pretibial edema +++/+++ was present. The thyroid stimulating hormone (TSH) value measured before the patient's pembrolizumab use was 2.96 uIU/mL. In the laboratory tests of the patient at admission, TSH was 122 uIU/mL (reference values: 0.25-4.55 uIU/mL), free T3 <0.3 pmol/L, and free T4 1.86 pmol/L. Pembrolizumab was discontinued and chemotherapy was continued. The patient was started on 100 mcg of levothyron. Later, the dose of levothyron was gradually increased to 125 mcg. Simultaneously, 20 mg methylprednisolone was started and the patient was discharged with levothyron treatment. Seven weeks later, the patient's TSH value was found to be 20 uIU/mL.

Discussion

With the use of immune checkpoint inhibitors such as pembrolizumab, non-specific side effects such as weakness and fatigue often occur. In a meta-analysis of 38 studies and 2,551 patients, it was reported that the frequency of endocrinopathy induced by immune checkpoint inhibitors was 10% and hypothyroidism was the most common endocrinopathy.⁶ Pembrolizumab induced autoimmune thyroid disease may present as primary hypothyroidism due to thyroiditis or hyperthyroidism due to Graves' disease.⁷ In the phase 3 pembrolizumab study performed in advanced non-small cell cancer, hypothyroidism was observed in 8% of cases and hyperthyroidism was observed in 2-4% of cases.⁸ Pembrolizumab can be given for up to 2 years, as the optimal duration of treatment has not been defined. Therefore, immune-related side effects may occur late in therapy or even after discontinuation of therapy.⁹

In mild cases of symptomatic thyroiditis, symptomatic treatment can be used, but in more severe cases, hospitalization and immunosuppressant treatment may be required. In this context, it should be considered that immune side effects such as hypophysitis, adrenalitis, and thyroiditis may occur in malignancy patients using immune checkpoint inhibitors, and patients should be followed closely in terms of these side effects.

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: SEY, IBG; Study Design: SEY, IBG; Supervision: YO; Materials: IBG, YO; Data Collection and/or Processing: SEY; Statistical Analysis and/or Data Interpretation: SEY, YO; Literature Review: IBG, SEY; Manuscript Preparation: SEY; Critical Review: YO.

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