Thyroid dysfunction induced by immune checkpoint inhibitors and tumor progression during neoadjuvant therapy of non-small cell lung cancer: A case report and literature review

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Abstract. Immune checkpoint inhibitors (ICIs) have a demonstrable treatment response in patients with resectable non-small cell lung cancer (NSCLC). However, immune-related adverse events and tumor progression in patients administered ICIs are of great concern. The present case study is of a 59-year-old male with NSCLC (squamous, stage IIIA) who received neoadjuvant immunotherapy combined with chemotherapy before surgery. The patient first developed hyperthyroidism and then hypothyroidism, indicating that ICI-related thyroid dysfunction had occurred. Furthermore, the patient suffered from tumor progression and could not undergo resection. The present case called attention to the prevention and management of irAEs, and the precaution that should be taken with regard to tumor progression. The case also suggested that the development of ICI-related thyroid dysfunction may not predict an improved response to ICI therapies, which needs further evidence to illustrate.

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Abbreviations: CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FT3, free triiodothyronine; FT4, free thyroxine; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; NSCLC, non-small cell lung cancer; PD-1, programmed death protein 1; PD-L1, programmed death protein 1 ligand; TGAb, thyroglobulin antibodies; TSH, thyroid-stimulating hormone

Key words: thyroid dysfunction, irAEs, tumor progression, neoadjuvant therapy, NSCLC

Introduction

Lung cancer ranks second in the incidence rate of cancer and is the leading cause of cancer-related deaths worldwide, with 8.2 million deaths yearly (1). Non-small cell lung cancer (NSCLC) accounts for ~85% of lung cancer cases. Immune checkpoint inhibitors (ICIs) target programmed cell death protein 1 (PD-1) and its ligand (PD-L1) and have revolutionized the treatment of advanced NSCLC (2,3). PD-1 and PD-L1 trigger T lymphocyte function to kill tumor cells by blocking the PD-1/PD-L1/2 signaling pathways (4). Several trials have reported the value of ICIs in treating resectable NSCLC with a significant pathological response as the primary endpoint (5-7). However, due to the mechanism of action of ICIs, immune-related adverse events (irAEs) can occur during treatment. Significant irAEs can cause surgery delays and/or intraoperative complications. Tumor progression may occasionally occur due to toxicities or poor efficacy of ICIs (8,9).

Endocrine adverse events are among the most common toxicities of ICIs, and the most commonly affected endocrine organ is the thyroid (10). Most thyroid dysfunction is asymptomatic or mild. However, patients may present with symptoms of hypothyroidism, such as fatigue, anorexia, constipation, bradycardia or weight gain (11,12). Thyroid dysfunction during PD-1 inhibitor therapy is associated with a longer progression-free survival time and could be used as a potential marker to predict an improved response to treatment (13). However, another study has refuted this hypothesis (14). In the present study, a case of thyroid dysfunction and tumor progression in a patient with stage IIIA NSCLC treated with the PD-1 inhibitor pembrolizumab is reported.

Case report

A 59-year-old male with a 30 pack-year history of smoking was transferred to The Peking University People's Hospital

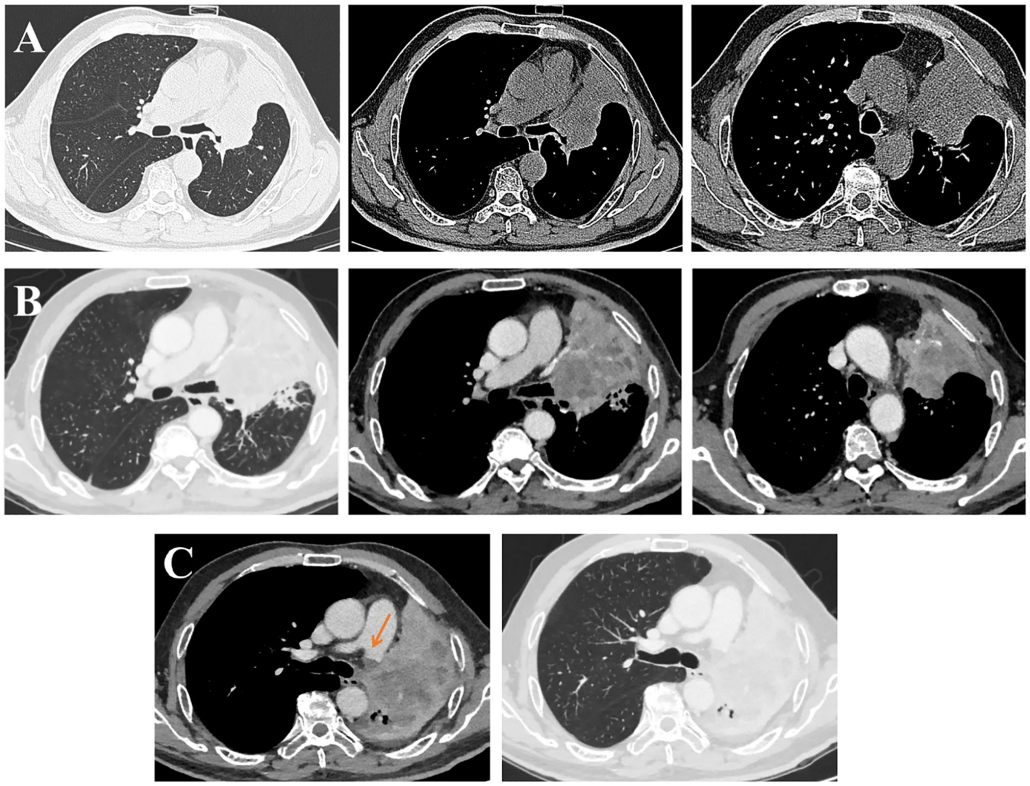

Figure 1. Chest computed tomography images of the patient during therapy. (A) Before therapy on September 27, 2020. (B) After the second cycle of neoadjuvant immunotherapy in combination with chemotherapy on December 8, 2020. (C) After the fifth cycle of chemotherapy on February 7, 2021. The orange arrow indicates the main trunk of the left pulmonary artery, which was completely invaded by the tumor. This demonstrated that the patient was unable to undergo surgery.

(Beijing, China) on September 2020. The patient had been experiencing shortness of breath after activity without apparent cause for almost 8 months. However, the patient did not complain of chest pain, cough, expectoration or fever. Chest computed tomography (CT) performed in another hospital revealed a central space-occupied lesion in the upper lobe of the left lung with atelectasis. Positron emission tomography-CT showed enlarged lymph nodes (zone VI) with no abnormal uptake of 18F-fluoro-2-deoxyglucose. The pathological section diagnosis was squamous carcinoma. The chest CT scan performed at The Peking University People's Hospital revealed that the volume of the upper lobe of the left lung was decreased and consolidated, and the upper lobe bronchus of the left lung was blocked. The soft tissue density shadow extended to the left main bronchus and the lower lobe bronchus of the left lung, resulting in a slight stenosis of the lower lobe bronchi. The results indicated that the malignant lesion occurred with multiple partially enlarged lymph nodes in the mediastinum (Fig. 1A). The clinical stage was T4N0M0 (IIIA) according to The Eighth Edition Lung Cancer Stage Classification (15).

The general condition of the patient was satisfactory. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) score (16) was 1. The thyroid hormone panel was in the normal range: Free triiodothyronine (FT3), 4.55 pmol/l (normal range, 3.5-6.5 pmol/l); free thyroxine (FT4), 17.16 pmol/l (normal range, 11.45-23.17 pmol/l); triiodothyronine, 136.05 ng/dl (normal range, 60-180 ng/dl); thyroxine (T4), 10.6 μg/dl (normal range, 3.2-12.6 μg/dl); thyroid-stimulating hormone (TSH), 1.016 mIU/l (normal range, 0.55-4.78 mIU/l); and thyroglobulin antibodies (TGAb), 21.8 IU/ml (normal range, <60 IU/ml).

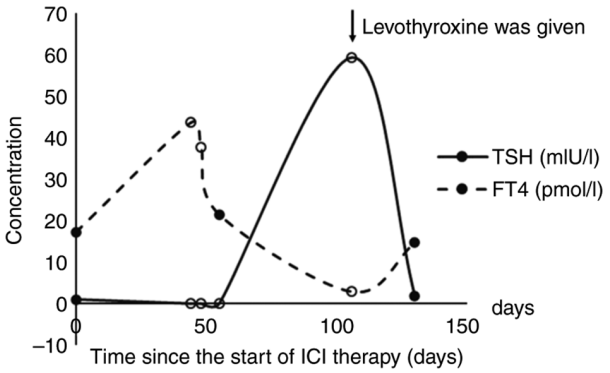

Figure 2. Changes in thyroid function of the patient during therapy. The normal value range of TSH is 0.55-4.78 mIU/l and FT4 is 11.45-23.17 pmol/l. The laboratorial index was in the normal range when the data point was a solid black circle. FT4, free thyroxine; ICIs, immune checkpoint inhibitors; TSH, thyroid-stimulating hormone.

The patient received neoadjuvant therapy before surgery. For this, two cycles of pembrolizumab (200 mg, day 1) plus carboplatin (450 mg, day 1) and gemcitabine (2.2 g, days 1 and 8) were administered from September 29, 2020 to October 20, 2020. On November 5, 2020, the patient developed an infection of the thoracic cavity. The maximum body temperature was 39.1˚C, with cough, greenish-yellow

Table I. Studies investigating the association of thyroid dysfunction with survival rate outcomes.

First author, year	Cohort size, n	ICI	Cancer type	Outcome	(Refs.)
Basak *et al*, 2020	168	Nivolumab or pembrolizumab	Metastatic melanoma; NSCLC; renal cell carcinoma	OS: HR, 0.18 (0.04-0.76), P=0.020; PFS: HR, 0.39 (0.15-0.998), P=0.050	(33)
Luo *et al*, 2021	744	Anti-PD-(L)1 monotherapy or anti-PD-(L)1 and CTLA-4 combination	NSCLC	PFS; HR, 0.68 (0.52-0.88), P=0.004	(34)
Kim *et al*, 2017	58	Nivolumab or pembrolizumab	NSCLC	OS: HR, 0.11 (0.01-0.92), P=0.041; PFS: HR, 0.38 (0.17-0.85), P=0.018	(35)
Osorio *et al*, 2017	51	Pembrolizumab	NSCLC	OS: HR, 0.29 (0.09-0.94), P=0.04	(13)
Thuillier *et al*, 2021	134	Nivolumab	NSCLC	OS: HR, 0.32 (0.16-0.62), P<0.001; PFS: HR, 0.36 (0.21-0.62), P<0.001	(36)
Zhou *et al*, 2021	191	Nivolumab or pembrolizumab	NSCLC	OS: HR, 0.356, P<0.001; PFS: HR, 0.393, P<0.001	(37)
D'Aiello *et al*, 2021	205	Pembrolizumab or nivolumab or durvalumab or atezolizumab	Lung cancer	PFS: P=0.353	(38)
Morimoto *et al*, 2021	70	Combination of immunotherapy and chemotherapy	NSCLC	OS: HR, 0.53 (0.13-2.26), P=0.39; PFS: HR, 0.46 (0.17-1.29), P=0.14	(41)
Koyama *et al*, 2019	139	Nivolumab or pembrolizumab	NSCLC	OS: P=0.011; PFS: P=0.012	(40)
Grangeon *et al*, 2019	270	Anti-PD-(L)1 therapy	NSCLC	OS: HR, 0.46 (0.25-0.86), P=0.01; PFS: HR, 0.58 (0.39-0.85), P=0.005	(39)
Percik *et al*, 2021	208	Anti-PD-(L)1 monotherapy or anti-PD-(L)1 and CTLA-4 combination	NSCLC	OS: HR, 0.87 (0.63-1.20), NA	(14)

HR, hazard ratio; ICIs, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed death protein 1; PD-L1, programmed death protein 1 ligand; PFS, progression-free survival; NA, not available.

sputum and shortness of breath. Ertapenem (1 g, once a day, from November 7 to November 17, 2020), moxifloxacin (0.4 g, once a day, from November 7 to November 17, 2020), imipenem/cilastatin (500 mg, every 6 h, from November 17 to December 3, 2020) and piperacillin/tazobactam (4.5 g, every 8 h, from December 2 to December 21, 2020) were administered until the patient's body temperature was normal.

During the hospital stay, the patient was found to have thyroid dysfunction and tumor progression. Thyroid function was found to be abnormal on November 11, 2020: FT4 increased to 43.54 pmol/l; FT3 increased to 8.33 pmol/l; T4 increased to 14 μg/dl; TSH decreased to 0.001 mIU/l; TGAb increased to 223.8 IU/ml. Immune-related thyroid dysfunction was hypothesized to be the possible cause of this abnormal thyroid function. No treatment was given for this dysfunction, and thyroid function was regularly monitored according to clinical guidelines.

An enhanced chest CT was performed on December 8, 2020. It showed tumor metastasis with enlarged ipsilateral mediastinal lymph nodes (zone VI). The maximum tumor size was 12 cm (Fig. 1B). The clinical stage was diagnosed as T4N2M0 (IIIB) on December 14, 2020, according to the patient's clinical condition and chest CT. Unfortunately, the patient could not receive surgery due to tumor progression in the left main bronchus and pulmonary artery, and the R0 resection was challenging. The ECOG PS score increased to 2. However, the patient refused immunotherapy due to concerns about irAEs.

The patient received a third cycle of chemotherapy with liposomal paclitaxel (240 mg, day 1) and carboplatin (500 mg, day 1) as a second-line treatment on December 17, 2020. On January 14, 2021, a fourth cycle of chemotherapy (240 mg liposomal paclitaxel on day 1; 500 mg carboplatin on day 1) was administered. Meanwhile, laboratory

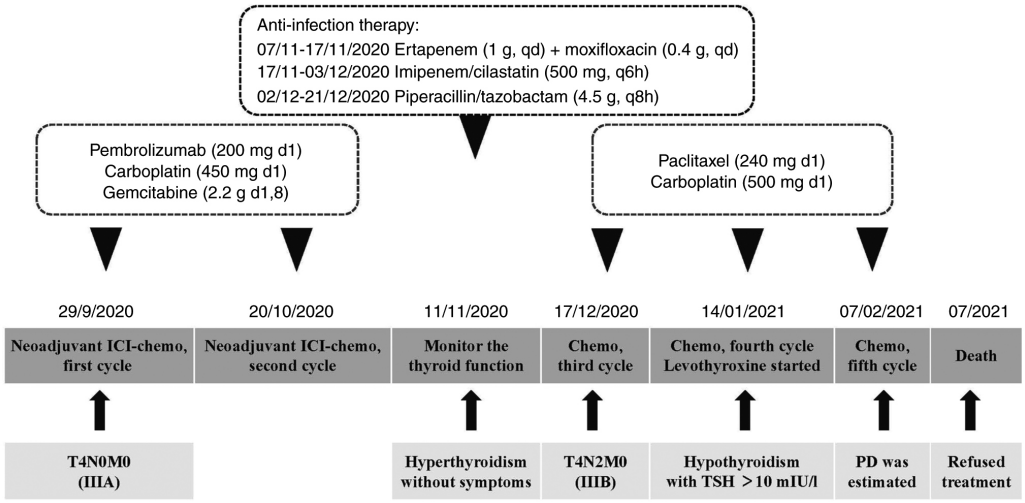

Figure 3. Timeline of the patient's treatment course. d, day; ICI, immune checkpoint inhibitor; PD, progressive disease; TSH, thyroid-stimulating hormone.

examination demonstrated that the patient had developed hypothyroidism, with FT3 decreasing to 1.04 pmol/l, FT4 decreasing to 2.84 pmol/l and TSH increasing to 59.244 mIU/l. Levothyroxine (12.5 mg daily, fasting, more than half an hour apart from meals) was administered. The dose increased to 25 mg 3 days later, 50 mg 1 week later and 75 mg 2 weeks later. On February 7, 2021, a fifth cycle of chemotherapy (240 mg liposomal paclitaxel on day 1; 500 mg carboplatin on day 1) was administered. After treatment with levothyroxine, FT3 returned to 3.19 pmol/l, FT4 returned to 14.69 pmol/l and TSH returned to 1.811 mIU/on February 7, 2021. The changes in thyroid function are shown in Fig. 2. The patient continued to take 75 mg levothyroxine daily.

Enhanced chest CT (Fig. 1C) was performed on February 7, 2021, which demonstrated that the cancer to the left lung had progressed with an invasion of the left pulmonary artery. Second-line therapy treatment (240 mg liposomal paclitaxel on day 1; 500 mg carboplatin on day 1) demonstrated poor efficacy in the patient. Subsequently, treatment was stopped and the patient died in July 2021. The timeline of the patient's treatment course is shown in Fig. 3.

Discussion

Immunotherapy has changed the pattern of treatment for NSCLC. Several trials exploring the efficacy and safety of monotherapy ICI or in combination with chemotherapy in neoadjuvant therapy of NSCLC have demonstrated promising results (5-7). However, irAEs and poor response to immunotherapy have raised great concerns (9,17). In the present study, a case of irAEs and tumor progression after treatment with the PD-1 inhibitor, pembrolizumab, in combination with chemotherapy was presented. To the best of our knowledge, this is the first reported case of thyroid dysfunction and tumor progression during neoadjuvant immunotherapy for the treatment of NSCLC.

In trials reporting resectable NSCLC, hypothyroidism was the most common ICI-related thyroid dysfunction (5,7,18-25). The incidences ranged from 0.0-26.7% in anti-PD-1 therapy, 4.8-11.1% in dual-ICI treatment and 0.0-10.0% in ICI in combination with chemotherapy (Table SI) (5,7,18-25). Furthermore, combination immunotherapy, baseline TSH, female sex and preexisting thyroid disease were risk factors associated with immunotherapy-related thyroid alterations (26-29). The patient of the present study received immunotherapy in combination with chemotherapy, which could be a personal risk factor for thyroid dysfunction. The mechanism of ICI-related thyroid dysfunction is not yet clear. The hypothesis that normal organs, tissues and cells are damaged by ICIs may be a possible mechanism (30,31).

Unfortunately, tumor progression occurred in the patient of the present study without the opportunity for surgery. In neoadjuvant immunotherapy trials, surgical failure rates ranged from 0.0 to 16.7% in ICI monotherapy, from 0.0 to 45.8% in ICI in combination with chemotherapy and from 19.0 to 33.3% in dual-ICI treatment (Table SI) (5,7,18-24). Disease progression, impaired lung function, unresectable disease, adverse events, tumor location or refusal from the patient may be reasons why patients cannot undergo resection (9). In the present study, the progression of the disease contributed to the failure to undergo resection, suggesting that a biomarker is of great need to predict the efficacy of immunotherapy.

IrAEs may be associated with improved clinical outcomes (32). Studies investigating the association between thyroid dysfunction and survival outcomes are shown in Table I (13,14,33-41). The development of thyroid dysfunction is associated with improved outcomes and may serve as a predictive factor for the response to therapy. This association may be due to the antigens shared between melanoma cells and normal melanocytes (13,32,36).

However, certain studies did not demonstrate a significant trend towards improved survival rate in patients with NSCLC and thyroid dysfunction (14,41). In the present case report, the patient developed hypothyroidism but had a poor prognosis. Furthermore, another study also did not find significant differences in the mortality of patients with thyrotoxicosis and those without thyroid dysfunction (42). By contrast, significant differences have been observed in patients with overt or subclinical hypothyroidism compared with those without thyroid irAE (42). The patient of the present study developed thyrotoxicosis that developed

to hypothyroidism, similar to thyroiditis. The association between types of thyroid dysfunction and prognosis in patients with cancer must therefore be investigated in randomized and experimental studies.

The efficacy and safety of neoadjuvant immunotherapy in resectable NSCLC should be monitored and assessed. Although neoadjuvant immunotherapy has demonstrated potential pathological benefits in patients with resectable NSCLC, irAEs should not be ignored and tumor progression can still occur. The development of thyroid dysfunction may not always predict a better response to ICI therapy.

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Availability of data and materials

All data generated or analyzed during the current study are included in this published article.

Authors' contributions

XL, YiL, RW, LH, YF, XX and LS made substantial contributions to conception and design. XL and XW participated in the anti-tumor treatment, obtained medical images, advised on patient treatment and analyzed patient data. XL, XW, SW and YaL contributed to the acquisition and interpretation of data. XL and XW were involved in drafting the manuscript. XL, XW, YiL and XX revised the manuscript critically for important intellectual content and confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by The Ethics Committee of The Peking University People's Hospital (approval no., 2021PHB018-001) and was conducted in accordance with the Declaration of Helsinki.

Patient consent for publication

Informed consent for publication was obtained from the patient and the patient's relative.

Competing interests

The authors declare that they have no competing interests.

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