Thyroid dysfunction induced by immune checkpoint inhibitors and tumor progression in neoadjuvant therapy for Non-Small Cell Lung Cancer: a case report and literature review

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Abstract

Background

The immune checkpoint inhibitors (ICIs) targeting anti-programmed death receptor 1 (PD-1) and its ligand (PD-L1) has shown promising value in resectable (stage IIIA) or potentially resectable (stage IIIB) non-small-cell lung cancer (NSCLC). However, the immune-related adverse events (irAEs) and tumor progression in neoadjuvant therapy are of great concern, which might result in surgical delay or failure to undergo resection. In addition, the association between the development of thyroid dysfunction and the cancer outcomes was controversial and highly concerned.

Case presentation

A 59-year-old male with NSCLC (squamous, IIIA) was received neoadjuvant immunotherapy in combination with chemotherapy before surgery. However, ICIs-related thyroid dysfunction occurred, and the patient experienced transient hyperthyroidism then transformed into hypothyroidism. Moreover, the patient suffered from tumor progression and was unable to undergo resection. He refused immunotherapy and was given chemotherapy for the subsequent treatment.

Conclusions

We presented the case of ICIs-related thyroid dysfunction and failure to undergo resection because of poor efficacy to elucidate clinical features of irAEs and tumor progression in the neoadjuvant immunotherapy, so as to timely and properly monitor the efficacy and safety of neoadjuvant immunotherapy in resectable NSCLC patients in clinical practice. Our case also demonstrated that the development of ICIs-related thyroid dysfunction might not predict the good efficacy of ICIs in NSCLC.

Introduction

Lung cancer (LC) remains the leading cause of cancer death worldwide with 8.2 million deaths per year[1]. Despite the advancement of surgery having improved the 5-year overall survival in early and locally advanced non-small-cell lung cancer (NSCLC)[2], there is still almost 50% of patients subsequently experienced recurrence after surgery alone[3]. The addition of neoadjuvant or adjuvant therapy provides the improvement of 5% in 5-year overall survival[4].

The immune checkpoint inhibitors (ICIs) targeting anti-programmed death receptor 1 (PD-1) and its ligand (PD-L1) have revolutionized the treatment for advanced NSCLC [5, 6]. Several trials have reported the value of ICIs in resectable (stage IIIA) or potentially resectable (stage IIIB) NSCLC with major pathological response as primary endpoint[7–9]. However, there are several considerations that ICIs might have some significant toxicities resulting in surgery delay and/or the intraoperative complications. Tumor progression might occur in some cases due to the toxicities or poor efficacy[10, 11].

Endocrine adverse events are among the most common toxicities experienced from ICIs and the most common endocrine organ affected by ICIs is the thyroid[12]. Previous data have illustrated that the thyroid dysfunction during anti-PD1 therapy is associated with improved outcomes and may serve as a parameter to predict a better therapy response[13]. However, there are some data opposed to this hypothesis[14]. Here, we reported a case of thyroid dysfunction and tumor progression after the treatment of the PD-1 inhibitor pembrolizumab and its clinical features and management in stage IIIA NSCLC. We also review the literature to comprehend the thyroid dysfunction, the tumor progression, and their association in immunotherapy for NSCLC.

Case Presentation

In September 2020, a 59-year-old male with a 30-pack-year history of smoking was transferred to Peking University People's Hospital. He had experienced shortness of breath after activity without any obvious causes for almost eight months, but had no chest pain, cough, expectoration and fever. Chest CT scanning found central-type occupation of left upper lobe with atelectasis in other hospital, and PET-CT was performed, showing that the central space was occupied in the upper lobe of the left lung, the lymph nodes in group 6 were slightly larger, and no abnormal uptake was found. The pathological puncture diagnosis was squamous carcinoma. Chest CT was performed again in our hospital, revealing that the volume of the upper lobe of the left lung decreased and consolidated, the upper lobe bronchus of the left lung was blocked and 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, which indicating the malignant lesion happened and multiple lymph nodes partially enlarged in mediastinal (Figure 1A). The clinical stage was T4N0M0(IIIA). The patient's general condition was assessed to be satisfactory, evaluated by Eastern Cooperative Oncology Group Performance Status (ECOG PS score=1). The thyroid hormone of this patient was all in the normal range. The free triiodothyronine (FT3) was 4.55 pmol/L, free thyroxine (FT4) was 17.16 pmol/L, triiodothyronine (T3) was 136.05 ng/dL, thyroxine (T4) was 10.6 µg/dL, thyroid stimulating hormone (TSH) was 1.016 mIU/L, and thyroglobulin antibodies (TgAb) was 21.8 IU/mL.

He underwent neoadjuvant therapy before surgery with pembrolizumab (200 mg, day1) plus carboplatin (450 mg, day1) and gemcitabine (2.2 g, day1,8) for two cycles from September 29 to October 20, 2020.

On November 5, 2020, the patient suffered from thoracic cavity infection. The maximum temperature was 39.1 °C, with cough, greenish-yellow sputum and shortness of breath. The patient was treated with ertapenem, moxifloxacin, the imipenem and cilastatin sodium for injection, piperacillin sodium and tazobactam sodium from November 5 to December 17 successively until the patient's temperature was normal. During the process, the patient was found thyroid dysfunction and tumor progression. The thyroid function was found abnormal on November 11, with FT4 increasing to 43.54 pmol/L, FT3 increasing to 8.33 pmol/L, T4 increasing to 14 µg/dL, TSH less than 0.001 mIU/L and TgAb increasing to 223.8 IU/mL. For abnormal thyroid function, immune-related thyroid dysfunction might be the possible cause and there was no treatment given and monitoring was conducted regularly according to the clinical guidelines.

The chest enhanced CT was performed on December 8, 2020, showing that the maximum diameter of the tumor was 12 cm and the ipsilateral mediastinal lymph nodes were enlarged (Zone 6), which suggested metastasis might happen. (Figure 1B) The clinical stage was diagnosed as T4N2M0 (IIIB) according to the situation of the patient and the chest CT on December 14, 2020. Unfortunately, the patient cannot get surgery due to tumor progression of left main bronchus and left main pulmonary artery, the R0 resection was difficult to achieve. The Performance Status (PS) was 2 at this time. However, the patient refused immunotherapy due to the concerns about the irAEs of immunotherapy.

Since then, the patient received the third cycle chemotherapy with liposomal paclitaxel (240 mg, day1) plus carboplatin (500 mg, day1) for the second-line treatment on December 17, 2020. On January 14, 2021, the fourth cycle of chemotherapy was conducted. Meanwhile, the laboratory examination showed the patient had transformed into 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 12.5µg per day (fasting, more than half an hour apart from meals) was given. The dosage was increased to 25µg per day 3 days later, 50µg per day 1 week later, and 75µg per day 2 weeks later. On February 6, 2021, the fifth cycle was conducted. After the treatment of levothyroxine, FT3 returned to 3.19 pmol/L, FT4 returned to 14.69 pmol/L and TSH returned to 1.811 mIU/L through examination on February 7, 2021. The changes of thyroid function were shown in Figure 2. The patient continued to take levothyroxine 75µg per day. However, the chest enhanced CT (Figure 1C) showed that the left central lung cancer with invasion of the left pulmonary artery and some branches was more serious than before. Progressive disease (PD) was estimated after the response evaluation for the patient on February 7, 2021. The treatment in second-line showed poor efficacy in this patient. After then, the patient stopped the treatment and died in July 2021. The timeline of the patient's treatment course was shown in figure 3.

Discussion

Immunotherapy has changed the treatment pattern for NSCLC. Several trials exploring the efficacy and safety of monotherapy ICI or in combination with chemotherapy in neoadjuvant treatment of NSCLC have shown promising results. However, the immune-related adverse events (irAEs) and the poor response to immunotherapy aroused great concern[11, 15]. Our study has presented a case of irAEs and tumor progression after the treatment of the PD-1 inhibitor pembrolizumab in combination with chemotherapy. To the best of our knowledge, this is the first reported case of thyroid dysfunction and tumor progression in neoadjuvant immunotherapy for NSCLC.

In this case, ICIs in combination with chemotherapy were attempted to be used before surgery. However, the thyroid dysfunction occurred and the patient experienced transient hyperthyroidism then transformed into hypothyroidism. We suspected that this adverse event was induced by ICIs as there is no report that carboplatin and gemcitabine caused the thyroid dysfunction to our best knowledge. The causal relationship was assessed as "probable/likely" according to the adverse drug reactions causality assessment methods of WHO Drug monitoring center. Moreover, the patient suffered from tumor progression and was unable to undergo resection. The patient refused immunotherapy and was given chemotherapy for the following treatment.

In trials of resectable NSCLC, previous data showed that the hypothyroidism was the most commonly in ICIs-related thyroid dysfunction, varied from 0 to 26.7% in anti-PD-1 therapy, 4.8–11.1% in dual-ICI therapy and 0 to 10.0% in ICIs in combination with chemotherapy respectively (Table 1)[16, 7, 9, 17–22]. In addition, combination immunotherapy, baseline thyroid-stimulating hormone, female sex, and pre-existing thyroid disease would be the risk factors associated with immunotherapy related thyroid alterations according to relevant studies.[23–26]

Table 1
The incidence of thyroid dysfunction and failure to undergo resection of neoadjuvant immunotherapy

Study	ICI	Phase	N	Thyroid dysfunction		Failure to surgery				
				Hypothyroidism	Hyperthyroidism	Total	Disease progression	Inadequate lung function	Unresectable disease	Location of tumor
ICI monotherapy										
Tong et al.	Pembrolizumab	II	30	3/30 (10.0%)	0	5/30 (16.7%)	1/30 (3.3%)	0	4/30 (13.3%)	0
Eichhorn et al.	Pembrolizumab	II	15	4/15 (26.7%)	0	0	0	0	0	0
Gao et al.	Sintilimab	Ib	40	7/40 (17.5%)	3/40 (7.5%)	3/40 (7.5%) *	-	-	-	-
Forde et al.	Nivolumab	II	22	0	0	1/21 (4.8%)	0	0	0	1/21 (4.8%)
Dual-ICI										
Cascone et al.	Nivolumab Ipilimumab	II	21	1/21(4.8%)	2/21(9.5%)	4/21 (19.0%)	1/21 (4.8%)	1/21 (4.8%)	1/21 (4.8%)	0
Reuss et al.	Nivolumab Ipilimumab	II	9	1/9(11.1)	0	3/9 (33.3%)	3/9 (33.3%)	0	0	0
Chemotherapy with ICI										
Shen et al.	Pembrolizumab	-	37	1/37 (2.7%)	0	0	0	0	0	0
Shu et al.	Atezolizumab	II	30	3/30 (10.0%)	0	4/30 (13.3%)	1/30 (3.3%)	0	3/30 (10.0%)	0
Provencio et al.	Nivolumab	II	46	0	0	5/46 (10.9%)	0	0	3/46 (6.5%)	0
Tfayli et al.	Avelumab	II	15	0	0	4/15 (26.7%)	1/15 (6.7%)	3/15 (20.0%)	0	0
Yang et al.	Ipilimumab	II	24	0	0	11/24 (45.8%)	2/24(8.3%)	2/24(8.3%)	5/24(20.8%)	1/24(4.2%)
Note: *This study did not report on the specific reason for a patient not to proceed to the planned surgery.										

Given the incidence of the thyroid dysfunction, it is critical for us to master the clinical manifestations and management. The majority of thyroid dysfunction is asymptomatic or mild, and those with symptoms mostly presented with hypothyroidism, such as fatigue, anorexia, constipation, bradycardia or weight gain[27, 28]. Some patients initially present with hyperthyroidism, manifested as palpitations, sweating, fear of heat, diarrhea, tremor, and wasting, almost 50–90% of them undergo a brief hyperthyroidism period (usually a median of 1 month) and then turn to hypothyroidism[28].

The median onset time of hypothyroidism in advanced settings was 63 days (range from 24 to 141 days) and 70 days (range from 27 to 475 days) in the dual-ICI and monotherapy groups, respectively. Whereas the occurrence of thyrotoxicosis followed by hypothyroidism was 63 days (range from 35 to 141 days) and 84 days (range from 63 to 475 days) in the dual-ICI and monotherapy groups, respectively[29]. In our case, the patient was found hyperthyroidism after 44 days of ICI therapy and hypothyroidism was found after 106 days of ICI therapy.

The mechanism of ICIs-related thyroid dysfunction is still unclear. The hypothesis that the normal organs, tissues, and cells could be attacked when ICIs kill tumor cell might be the possible mechanism. ICIs might trigger T cell-mediated pathways that cause thyroid dysfunction subsequently[30, 31]. The clinical management of thyroid injury caused by ICIs should be determined by whether clinical symptoms occur, the type of thyroid dysfunction and the grade of thyroid dysfunction in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. [32]. The therapy regimens should be jointly formulated by endocrinologists and oncologists.

Unfortunately, tumor progression happened in this patient and he lost the surgery chance. In trials of neoadjuvant immunotherapy, the rates of failure to surgery ranged from 0 to 17% in anti-PD-1 therapy, 0 to 46% in ICIs in combination with chemotherapy and 19–33% in dual-ICI therapy respectively (Table 1) [16, 7, 9, 17–22]. Disease progression, inadequate lung function, unresectable disease, adverse events, location of tumor, or patient refusal might be the reasons that patient cannot undergo resection[11]. In our case, the disease progression contributed to the failure to undergo resection, which suggested that there was a great need for biomarker to predict the efficacy of the immunotherapy.

In addition, previous data showed that irAEs might be associated with better clinical outcomes[33], and the association between thyroid dysfunction and cancer outcomes has aroused great attention as thyroid dysfunction is among the most common irAE. Studies investigating the association between thyroid dysfunction and survival outcomes were shown in Table 2 [34–36, 13, 37–39, 14]. Previous data suggested that the development of thyroid dysfunction was

associated with improved outcomes and might serve as a predictive factor of therapy response. This association might be the result of the antigens shared between melanoma cells and normal melanocytes[13, 33, 37].

Table 2
Studies investigating the association of thyroid dysfunction with survival outcomes.

Study	N	ICI	Cancer	Outcome
Basak et al [34]	168	Nivolumab or Pembrolizumab	Metastatic melanoma; NSCLC; and 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
Luo et al [35]	744	Anti-PD-(L)1 monotherapy or Anti-PD-(L)1 and CTLA-4 combination	NSCLC	PFS-HR: 0.68 (0.52-0.88)
Kim et al [36]	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
Osorio et al [13]	51	Pembrolizumab	NSCLC	OS-HR: 0.29 (0.09-0.94); P = 0.04
Thuillier et al [37]	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
Zhou et al [38]	191	Nivolumab or Pembrolizumab	NSCLC	OS-HR: 0.356; P < 0.001; PFS-HR: 0.393, P < 0.001
D'Aiello et al [39]	205	Pembrolizumab or Nivolumab or Durvalumab or Atezolizumab	Lung cancer	PFS: P = 0.353
Percik et al [14]	208	Anti-PD-(L)1 monotherapy or Anti-PD-(L)1 and CTLA-4 combination	NSCLC	OS-HR: 0.87 (0.63-1.20)

However, another study showed that there was no significant trend toward improved survival in patients who developed thyroid dysfunction in NSCLC patients[14]. In our case, the patient has developed the hypothyroidism while the prognosis is poor. Whether there is a specific association between the anti-thyroid immunity and the anti-tumor immunity is unclear and larger randomized studies and basal experimental studies are needed to illustrate this question.

There are also some limitations in our case report. At first, the failure to undergo resection was associated with the tumor progression of the patient rather than the irAEs, which indicated that the patient showed poor response to the immunotherapy plus chemotherapy and the biomarker of the neoadjuvant therapy needed further study. Another limitation in our study is the fact that numerous phase II/III clinical trials are still undergoing for investigation of the safety and efficacy of neoadjuvant immunotherapy in resectable NSCLC patients. Long-term follow-up of these studies are needed to define the role of neoadjuvant immunotherapy in resectable NSCLC.

Conclusion

In conclusion, although results of clinical trials of neoadjuvant immunotherapy have shown potential pathological benefits in resectable NSCLC for patients, irAEs cannot be ignored and tumor progression might happen. Our case has presented the clinical features of thyroid dysfunction and tumor progression, calling for timely and proper monitoring the efficacy and safety of neoadjuvant immunotherapy in resectable NSCLC. We also presented the case that the development of thyroid dysfunction cannot predict the better therapy response of ICIs.

Abbreviations

- Common Terminology Criteria for Adverse Events (CTCAE)
- Eastern Cooperative Oncology Group Performance Status (ECOG PS)
- free triiodothyronine (FT3)
- free thyroxine (FT4)
- immune checkpoint inhibitors (ICIs)
- immune-related adverse events (irAEs)

non-small cell lung cancer (NSCLC)

progressive disease (PD)

programmed death receptor 1 (PD-1) and its ligand (PD-L1)

thyroglobulin antibodies (TGAbs)

thyroid stimulating hormone (TSH)

Declarations

O Ethics approval and consent to participate

The study was approved by the Ethics Committee of Peking University People's Hospital (Approved number: 2021PHB018-001) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the patient's relative for participating in this study.

O Consent for publication

Informed consent was obtained from the patient's relative.

O Availability of data and materials

All data relevant to this study are included in this published article.

O Competing interests

The authors have no disclosures and no competing interests.

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O Authors' contributions

The contributions were made by all authors. Xinyi Li and Xun Wang contributed to the identification and selection of case and the first draft of the manuscript. Yi Liu, Ruilin Wang, Lin Huang, Yufei Feng, Xiaohui Xie, and Luwen Shi drafted the initial manuscript. Xun Wang, Shaodong Wang, and Yanguo Liu contributed to the management of the patient and edited the manuscript. All authors read the article and approved the final version.

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• Compliance with Ethical Standards

O Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

O Research involving Human Participants and/or Animals

The study was approved by the Ethics Committee of Peking University People's Hospital (Approved number: 2021PHB018-001) and was conducted in accordance with the Declaration of Helsinki.

O Informed consent

Informed consent was obtained from the patient's relative.

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Figures

Figure 1

The chest CT of the patient during the therapy

Note: (A). Before the therapy in September 27, 2020, (B). After the second cycle of neoadjuvant immunotherapy in combination with chemotherapy in December 8, 2021, and (C). After the fifth cycle of chemotherapy in February 7, 2021

Figure 2

The changes of thyroid function for the patient during the therapy

Note: The normal value interval of TSH is from 0.55 to 4.78 mIU/L and the normal value interval of FT4 is from 11.45 to 23.17 pmol/L. The Solid label indicated that the laboratorial index was in the normal range.

Figure 3

The timeline of the patient's treatment course