Immunochemotherapy includes pembrolizumab for stage IIIB lung squamous cell carcinoma: a case report

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Background: Lung cancer is a malignant tumor with high morbidity and mortality, and its incidence continues to increase. With the emergence of new drugs and treatment modalities, the prognosis of lung cancer patients has improved to some extent. However, the prognosis of initially unresectable, locally advanced lung cancer with immunotherapy combined with chemotherapy remains uncertain.

Case Description: We report a case of a 57-year-old man diagnosed with stage IIIB la with negative targeted therapy-related gene mutation and a 2% programmed death 1/programmed cell death-ligand 1 (PD-1/PD-L1) expression level, who underwent transformation treatment with pembrolizumab after multidisciplinary consultation. Lung images indicated partial response after 4 cycles. However, preoperative examination found hypothyroidism considered the immune-related, and giving hormone replacement treatment after the endocrinology department consultation. Thyroid function improved after 1 month. The patient successfully underwent single-hole thoracoscopic radical lung cancer (left whole lung resection + mediastinal lymph node dissection). Postoperative pathology was consistent with major pathological remission (MPR). The patient was scheduled to receive 8 cycles of single-drug maintenance therapy with pembrolizumab after surgery. To date, no tumor recurrence and metastasis have been found at follow up, and maintenance treatment continues to improve.

Conclusions: This case reminds us that the induction treatment pattern of pembrolizumab combined with chemotherapy for subsequent conversion surgery can be a potentially curative treatment option for locally advanced stage IIIB patients. The monitoring of thyroid-related indicators is important during immunotherapy, especially in the first 1–2 months. The cause of thyroid dysfunction should be detected early so that it can be treated promptly to improve the prognosis of the patient. Pembrolizumab in combination with paclitaxel and platinum drugs provides a new option for patients with locally advanced stage IIIB lung squamous cell carcinoma who eager to undergo radical surgery.

Keywords: Lung cancer; immunotherapy; lung squamous cell carcinoma; transformation therapy; case report

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Introduction

Lung cancer is a malignant tumor with high morbidity and mortality (1,2). Conventional treatment methods include surgical treatment, chemotherapy, radiotherapy, and targeted therapy (3-5). With the emergence of new drugs and optimization of treatment modalities, the prognosis of lung cancer patients has improved to some extent (6,7). In recent years, attention has focused on the many approved antitumor new drugs, in addition to various small molecule tyrosine kinase inhibitors and macromolecular monoclonal

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antibodies, with most attention on tumor immunotherapy (8,9), represented by programmed cell death protein-1 (PD-1) inhibitors. Pembrolizumab, a PD-1 inhibitor that has shown promising results in tumor-related clinical trials, has been approved for new tumor indication and is recommended in antitumor guidelines in several countries (10-12). However, there are still few reports of patients with locally advanced lung squamous cell carcinoma having access to surgical resection after receiving pembrolizumab combined with chemotherapy. Here, we report a successful case of MPR confirmed by pathology after induction immunochemotherapy therapy.

Immune checkpoint inhibitors (ICIs) can restore the ability of the immune system to kill tumor cells, and has become a hot spot in the field of tumor treatment and research in recent years (13). ICIs are the key proteins to maintain immune balance (14), and disruption of their function can lead to dysregulated immune tolerance, causing immune damage to normal tissues and organs, producing immune-related adverse events (immune-related adverse events) including to mucosa, the endocrine system, intestine, liver, lungs, and heart (15,16). Pembrolizumab, an ICI, can disrupt the balance of the immune environment and can lead to toxic reactions similar to those of autoimmune diseases. Immune-associated thyroiditis is characterized by reversible or irreversible destructive thyroiditis and obvious hypothyroidism (17). In our case, the patient progressed from subclinical hyperthyroidism to hyperthyroidism, then to hypothyroidism, and finally underwent radical resection of lung cancer after endocrine replacement therapy. We present the following article in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3769/rc).

Case presentation

In October 2020, a 57-year-old male smoker presented at our hospital with an ongoing cough for 9 months. There was no chest pain, hemoptysis, chest tightness, shortness of breath, hoarseness, dysphagia, or other symptoms. The patient had smoked 1–2 packs a day for >40 years. Physical examination showed stable vital signs, moderate nutrition (body mass index: 22.04) During the examination, enlarged lymph nodes were not touched on the bilateral collarbone, respiratory movement of both lungs was normal and symmetrical, double lung percussion was clear, and there was no obvious dry and wet rale and pleural friction. Tumor markers, such as carcinoembryonic antigen (CEA) and Alpha-fetoprotein (AFP), were at normal levels. There are three items of thyroid function as follows: TSH 1.108 mIU/L (normal range: 0.34–5.60 mIU/L), FT 34.46 pmol/L (normal range: 3.53–7.37 pmol/L) and FT4 10.23 pmol/L (normal range: 7.86–21.1 pmol/L). Chest computed tomography (CT) scan showed obstruction of the left lower lung bronchus with atelectasis, left hilar lymph node enlargement, mediastinal lymph node enlargement, and left pleural effusion (*Figure 1A*,*1B*). Bronchoscopy shows thickening of the mucous membrane of the left main bronchi, narrowing of the upper left bronchi cavity, and occlusion of the opening of the left lower bronchi. Biopsy indicated non-small cell carcinoma, consistent with squamous cell carcinoma. Epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) gene mutations tested negative. The expression level of PD-1/PD-L1 was 2% (*Figure 1C*). No obvious abnormality was seen in the head magnetic resonance imaging and bone examination. Based on PET-CT and other related examinations, the diagnosis of the patient was stage IIIB lung squamous cell carcinoma (cT3N2M0).

Lung squamous cell carcinoma was confirmed by biopsy, and was found to be local advanced stage with no opportunity for surgical resection. After admission, MDT was carried out. It is recommended that patients undergo transformation therapy based on immunotherapy combined with chemotherapy. The specific protocol is albumin-binding paclitaxel ivgtt + cisplatin ivgtt, q3w for 4 cycles, combined with pembrolizumab, q3w for 4 cycles.

The patient was given the first and second cycles of induction immunochemotherapy at November 9, 2020 and October 9, 2020, respectively. Repeat chest CT scan showed that the soft tissue shadow of the left hilum was significantly smaller than before treatment, and the atelectasis of the lower lobe of the left lung was dilated (*Figure 1D*). Laboratory results showed that the level of hypersensitive thyrotropin in serum decreased to 0.262 mIU/L, and the level of free T3 and T4 was normal, suggesting subclinical hyperthyroidism.

The third cycle of induction therapy was performed on December 1, 2020, during which thyroid function indicators were reviewed. Hypersensitive thyrotropin decreased <0.01 mIU/L, free T3 increased to 10.36 pmol/L, and free T4 increased to 70.29 pmol/L.

The fourth cycle of induction treatment was performed on December 24, 2020, during which thyroid indicators were reviewed, indicating hypothyroidism. After 4 cycles of induction therapy, the patient was returned to the hospital for preoperative evaluation, and chest CT scan was

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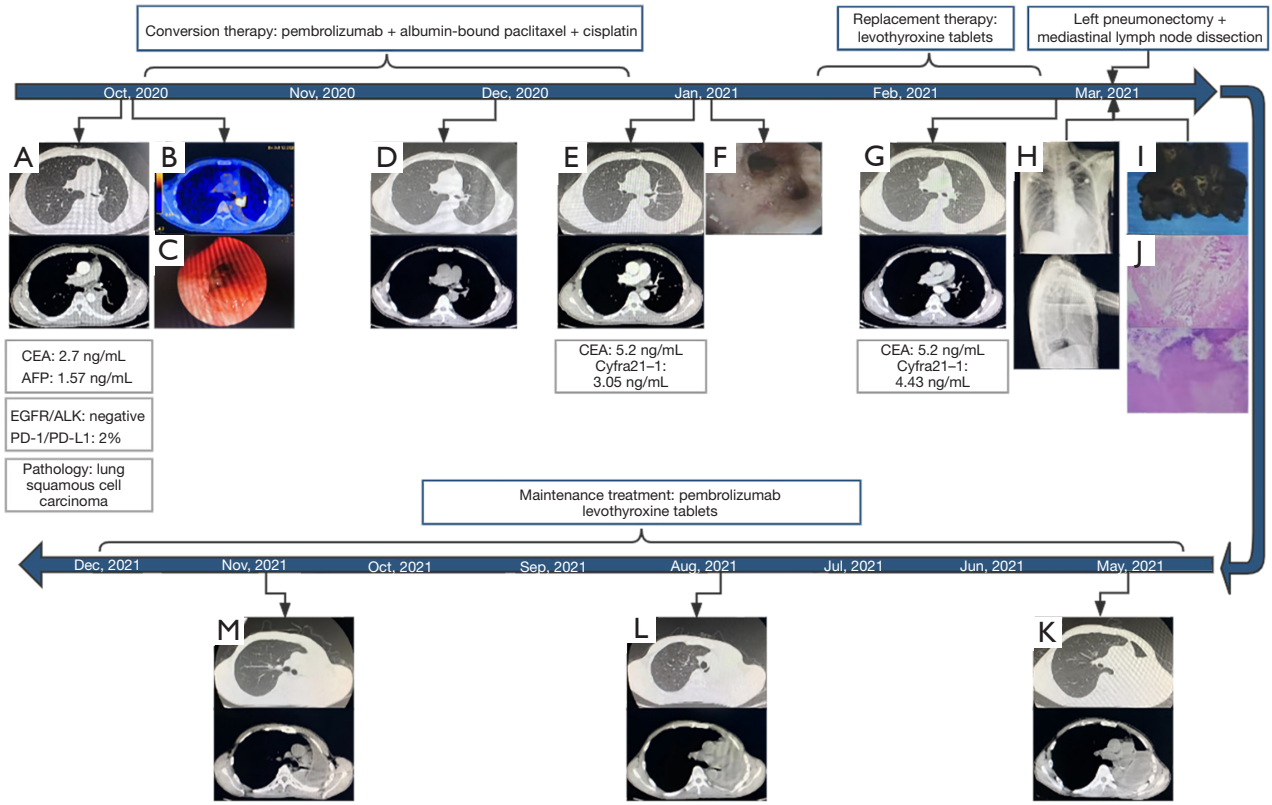

Figure 1 Graphical summary of our case. Soft tissue shadow of the left lung gate, considering central lung cancer with atelectasis (A), left lung hilar mass high-density shadow and mediastinal lymph node hypermetabolism (B) were examined by positron emission tomography-computed tomography (PET-CT) and bronchoscopy (C) bronchial biopsy pathology suggested squamous cell carcinoma. After 2 cycles of immunotherapy combined with chemotherapy transformation treatment, the soft tissue shadow of the left valve was significantly reduced compared with before, the left lower lobe was dilated compared with before (D), the soft tissue shadow of the left lobe was significantly reduced after 4 cycles of transformation treatment (E), and the bronchi bronchial blockage was significantly improved (F). After preoperative thoracic resection of lung cancer (G), postoperative chest X-ray indicated left chest pneumothorax (H), and tumor HE staining analysis showed a small number of squamous cell carcinoma residue accounting for 10% of the lesions under a 100× microscope (I-J). The patient then underwent pembrolizumab monotherapy for 8 cycles, interval review, change after left lung surgery, gradual absorption of left pleural effusion, and no tumor recurrence and metastasis (K-M). CEA, carcinoembryonic antigen; AFP, Alpha-fetoprotein; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PD-1/PD-L1, programmed death 1/programmed cell death-ligand 1.

conducted (*Figure 1E*). The results found that the shadow of soft tissue in the left hilum was significantly smaller and the lower left lung was inflated again, getting the opportunity of surgical resection (*Figure 1F*). However, it was noted that abnormal thyroid function was a contraindication to surgery due immune-related adverse events and symptomatic grade 2 hypothyroidism. After consultation in the endocrinology department, levothyroxine tablets were administered (January 21, 2021–February 25, 2021).

Thyroid function improved 1 month later, and chest CT scan showed that the soft tissue shadow of the left hilum was slightly smaller than before (*Figure 1G*). Excluding the contraindications to surgery, single-hole thoracoscopic radical resection of left lung cancer (left pneumonectomy mediastinal lymph node dissection) was performed at March 5, 2021. Postoperative chest X-ray is shown in *Figure 1H*. Postoperative pathology suggests that a small number of squamous cell residues account for less than 10% of the lesion, which is consistent with the IIb level of pathological response in neoadjuvant therapy. Pathology showed that there was no tumor at the incised end of the left main bronchus and no metastatic carcinoma in the lymph nodes

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(*Figure 1I,1J*).

After 8 cycles of pembrolizumab immunomaintenance therapy, the pleural effusion on the left side of the chest decreased gradually (*Figure 1K-1M*), and thyroid dysfunction was examined. It was still considered to be immune-related symptomatic grade 2 hypothyroidism. Levothyroxine sodium was used to regulate thyroid function in the maintenance treatment phase, which was well tolerated by the patient perioperatively and postoperatively. No serious or unexpected adverse events were reported. At present, 6 cycles of postoperative immune maintenance therapy have been carried out. No recurrence or metastasis has been found during follow up. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

We report a case of a patient with locally advanced stage IIIB lung squamous cell carcinoma. After receiving 4 cycles of chemotherapy combined with immunotherapy, imaging re-examination showed a significant reduction in the lung tumor and an opportunity for radical surgery. Single-hole thoracoscopic left pneumonectomy and mediastinal lymph node dissection were performed, and a low amount of residual squamous cells were seen under pathological microscope after operation, accounting for less than 10% of lesions, which was in accordance with MPR. The patients showed significant improvement in symptoms and imaging shows significant tumor regression after starting 4 cycles of conversion therapy with pembrolizumab combined with paclitaxel and carboplatin, suggesting the strong potential of combined immunochemotherapy in preoperative conversion therapy. In addition, the patient underwent left pneumonectomy, which is difficult and risky. It is important to maintain single lung function after operation. No postoperative radiotherapy is performed to avoid high-risk factors, such as radiation pneumonia. Therefore, we plan to carry out 8 cycles of immune monotherapy after operation, currently in the sixth cycle, and there is no recurrence or metastasis. It is further suggested that pembrolizumab combined with chemotherapy plays an important role in preoperative conversion therapy and postoperative monotherapy maintenance therapy in patients with initial unresectable lung squamous cell carcinoma.

Our patient successfully underwent radical resection of lung cancer. Postoperative pathology showed that there was no tumor at the cutting end of the left main bronchus, no metastatic cancer was found in the lymph nodes, and some of the lymph nodes were accompanied by reactions after treatment. Combined with clinical diagnosis, it suggests that the patient has lymph node metastases before treatment and disappeared after immunotherapy. At present, the evaluation of the efficacy after immunotransformation therapy is mainly focused on the exploration of primary tumors, and the pathological remission rate is defined by the residual tumor cells in the tumor bed after treatment (18). It has been reported that the pathological response of lymph nodes after neoadjuvant therapy is similar to that of the original tumor (19). Although the clinical significance of the percentage of remaining living tumor cells in the lymph nodes is not clear, the efficacy of immunotherapy can be assessed based on the changes of metastatic lymph nodes before and after treatment, combined with the comparison of the PET-CT results before and after transformation treatment. Pathology shows metastatic lymph nodes with a post-treatment response suggesting that immune transformation therapy is effective.

The specific adverse reactions of PD-1 receptor inhibitors are immune-related adverse reactions, although their overall incidence is relatively low. However, if sufficient clinical awareness is lacking, it can lead to serious or even fatal consequences (20). Thyroid dysfunction is the most common endocrine disease induced by ICIs (21). Severe thyroid toxicity can delay and result in the cessation of immunotherapy, putting patients at risk of tumor recurrence (22). In our case, early detection of thyroid dysfunction, timely diagnosis of its cause, and correct adjustment of treatment ensured that surgery was performed on time (*Figures 2,3*). It has been suggested that although immunotherapy can cause immune-related adverse events, it does not affect patients receiving immune transformation therapy and subsequent surgical excision (23). There is no evidence that immune-related endocrine adverse events affect the prognosis of patients with advanced lung cancer. Immune-related adverse events (IrAEs) can occur during the course of immunotherapy (24), so follow-up monitoring is also important. Thyroid autoantibody tests and radioactive iodine uptake rate should be performed prior to the use of PD-1 inhibitors, and thyroid-related indicators should be monitored after treatment, especially in the first 1

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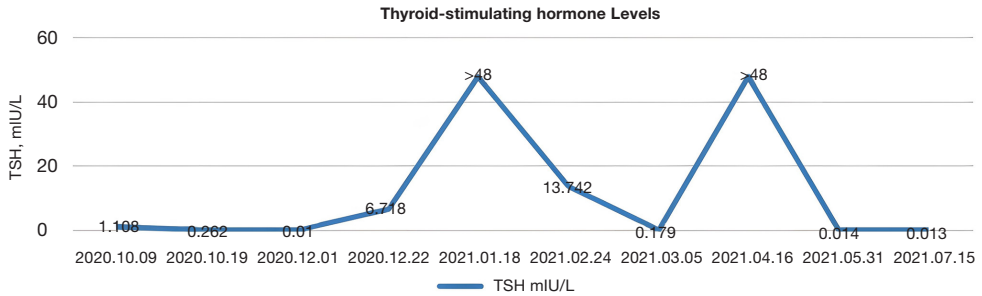

Figure 2 TSH changes in our patient during treatment with pembrolizumab and chemotherapy. TSH, thyroid-stimulating hormone.

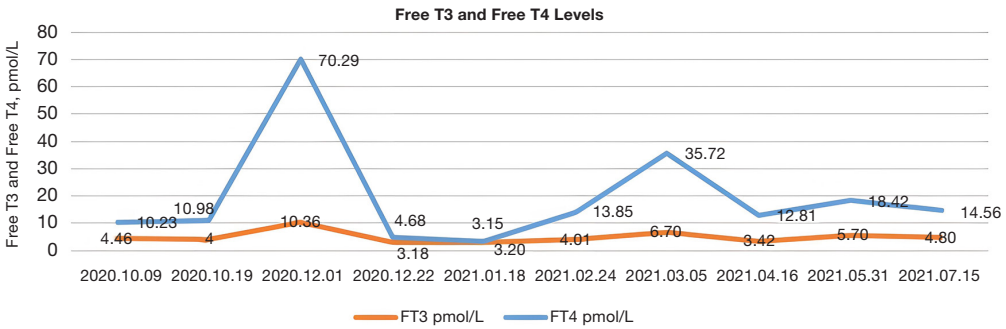

Figure 3 Thyroid hormone changes in our patient during treatment with pembrolizumab and chemotherapy.

to 2 months of treatment, to determine the cause of thyroid dysfunction, so that appropriate treatment can be given to improve the prognosis of patients.

Here, we reported a case of a patient with lesions located in the hilum involving the main bronchus, with the mediastinal lymph nodes (LN) metastasis (group 4,5 LN). After detailed staging, it was found to be locally advanced stage and there was no indication of operation. The MDT was carried out, and the treatment plan was discussed in detail by the thoracic surgery department, respiratory department, and oncology department. Each department complements each other, and the preoperative transformation treatment plan of pembrolizumab combined with chemotherapy was agreed upon. The patient developed immune-associated hypothyroidism after 4 cycles of conversion therapy. After consultation in the endocrine department, an alternative treatment plan was established and the transition to the perioperative period was smooth. Our treatment process indicated the advantages of MDT in the treatment of advanced lung tumors.

Pembrolizumab is a humanized IgG4 monoclonal antibody against PD-1. Based on the results of KEYNOTE-010, the study included patients with advanced/metastatic non-small cell lung cancer who had previously received treatment, whose tumors expressed PD-L1 on at least 1% of the cells. The results showed that, compared with docetaxel, pembrolizumab had a good survival benefit, and a more significant survival benefit was observed in patients with tumor PD-L1 expression levels ≥50% (25). KEYNOTE-024 compared the efficacy of pembrolizumab and platinum chemotherapy in patients with previously untreated non-small cell lung cancer. For metastatic non-small cell lung cancer with a PD-L1 tumor ratio score of at least 50%, pembrolizumab provides long-term, clinically significant long-term overall survival benefits compared with chemotherapy (26). According to the above results, in patients with a PD-L1 tumor ratio score of ≥50%, pembrolizumab has replaced cytotoxic chemotherapy as the first-line treatment (27). According to the results of KENYEN-042, the median overall survival in patients with non-small cell lung cancer with a PD-L1 tumor ratio score ≥1% was significantly longer than that in the chemotherapy group (28,29). FDA has approved a single dose of pembrolizumab for first-line treatment of unresectable III or IV stage non-small cell lung cancer with PD-L1TPS ≥1% and without sensitive mutations (30).

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The KEYNOTE-407 study compared the efficacy of pembrolizumab combined with carboplatin plus paclitaxel/albumin combined with paclitaxel and first-line chemotherapy in patients with advanced lung squamous cell carcinoma. The results showed that pembrolizumab combined with chemotherapy could significantly prolong the median progression free survival (PFS), and subgroup analysis showed that patients with different PD-L1 expressions could benefit from combined chemotherapy (31,32). Based on the above results, the FDA and National Medical Products Administration (NMPA) approved the first-line treatment of advanced squamous Non-Small Cell Lung Cancer (NSCLC) with pembrolizumab combined with carboplatin + paclitaxel/albumin paclitaxel (33).

Conclusions

In conclusion, we have witnessed patients with locally advanced squamous lung cancer who were initially not indicated for surgical resection having the opportunity for radical surgery after receiving four cycles of immunotherapy combined with chemotherapy. Postoperative pathology also confirmed the efficacy of this regimen. After postoperative single-drug immune maintenance therapy, no recurrent lesions were found on review at present. Pembrolizumab combined with paclitaxel and platinum chemotherapy provides a new choice for locally advanced stage IIIB lung squamous cell carcinoma patients undergoing radical surgery.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3769/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3769/coif). The authors have no conflicts of interest to declare

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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