Successful conversion surgery following tislelizumab with chemotherapy in a patient with stage IIIC lung adenocarcinoma harboring RET fusions: A case report and review of the literature

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Abstract. Immune checkpoint inhibitors (ICIs) have emerged as a beacon of hope for most patients with stage III non-small cell lung cancer (NSCLC) who are no longer surgical candidates. However, the literature on the use of immunotherapy in patients with NSCLC with rearranged during transfection (RET) gene fusions is scant. The present study reports the case of a 61-year-old female patient, diagnosed with stage IIIC lung adenocarcinoma, exhibiting two RET gene fusions and high programmed death-ligand 1 expression. Following four treatment cycles of tislelizumab in combination with pemetrexed and cisplatin, the patient was successfully downstaged, enabling radical surgery. The post-operative pathology analysis indicated a major pathologic response. This case study contributes to the growing body of evidence supporting the use of ICIs in treating locally advanced NSCLC with RET gene fusions.

Introduction

For most patients with stage III non-small cell lung cancer (NSCLC), adding surgical treatment after radiochemotherapy may not improve prognosis (1,2). However, recent years have seen encouraging results from studies incorporating immune checkpoint inhibitors (ICIs) into induction therapy for resectable lung cancer (3-6), leading to considerations of introducing this treatment modality to patients at later stages. Several driver gene mutations [such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase and proto-oncogene tyrosine-protein kinase] have been proven to be associated with poor outcomes of treatment with ICIs (7-9). This may be due to driver genes affecting the expression of programmed death-ligand 1 (PD-L1) in tumor and immune cells, tumor mutational burden (TMB) and the tumor infiltration of immune cells (7). However, studies on the efficacy of ICIs in patients with rearranged during transfection (RET) fusion are relatively few. RET fusions are generally thought to respond poorly to immunotherapy, for reasons similar to other driver genes (10-12). The present study reports the case of a patient with stage IIIC lung adenocarcinoma harboring RET fusions and high expression of PD-L1. The patient underwent single-port thoracoscopic lobectomy and systematic lymph node dissection after treatment with tislelizumab plus chemotherapy, and the results suggested that the patient achieved major pathological remission. This case highlights the potential therapeutic value of ICIs in patients with RET fusion.

Case presentation

A 61-year-old female patient was admitted to the Yueyang Central Hospital (Yueyang, China) due to blood in sputum for 1 month. In January, 2023, contrast-enhanced computed tomography (CT) revealed a 60x41x39 mm mass in the right lower lung, accompanied by localized atelectasis and multiple enlarged lymph nodes in the interlobar and mediastinal regions (Fig. 1A). A positron emission tomography (PET)/CT scan performed 12 days later showed abnormal ^{18}F-fluorodeoxyglucose accumulation in the right lower lung tumor, with a maximum standardized uptake value (SUVmax) of 19.0, multiple lymph nodes with increased glucose metabolism in the mediastinum (zones 2R, 4R, 3a

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Abbreviations: NSCLC, non-small cell lung cancer; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1; CT, computed tomography; PET, positron emission tomography; SUVmax, maximum standardized uptake value; MPR, major pathological response; pCR, pathological complete response; RET, rearranged during transfection

Key words: adenocarcinoma, immunotherapy, tislelizumab, RET, single-port thoracoscopic surgery

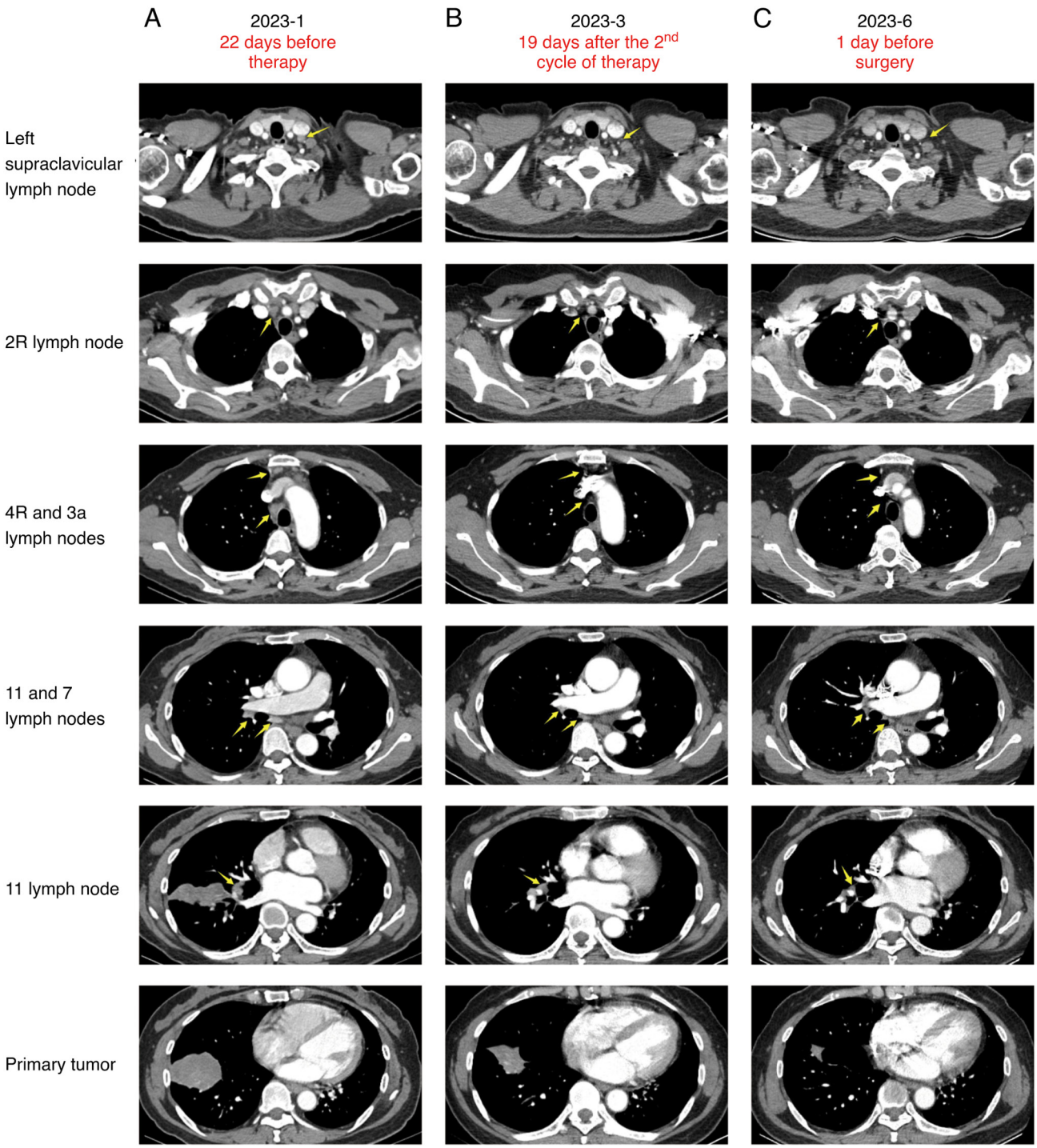

Figure 1. Timeline of computed tomography examinations prior to surgery. Compared with (A) before therapy, (B) after two cycles of therapy, the primary tumor lesion was significantly reduced (from 60x41x39 to 35x22x20 mm) and the lymph nodes with increased glucose metabolism in the left supraclavicular, 2R, 4R and 3a stations were significantly reduced in size. (C) After 4 cycles of therapy, the primary tumor had further shrunk (21x16x12 mm) and the previously present abnormal metabolic lymph nodes in the left supraclavicular and 3a region were no longer visible. The yellow arrows point at the corresponding lymph nodes.

and 7), left supraclavicular region and between the right lung lobes, suggesting metastasis (Fig. 2A). The metabolism of the thoracic vertebrae was mildly elevated, and no tumors or bone destruction were observed on the CT scan. It was then diagnosed as degenerative changes of the spine. The pathology report from the percutaneous lung biopsy indicated poorly differentiated adenocarcinoma (Fig. 3A). Gene mutation analysis showed a 10.57% abundance of RET-ABCC2 (R11:A7) gene fusion, 5.36% EPB41L3-RET (E5'UTR:R13) gene fusion and 4.93% PIK3CA gene mutation (exon 10 c.1633G>A p.Glu545Lys), while no other mutations were detected. The genetic testing was performed by Burning Rock Biotech using their clinically validated LungCore® 9-gene Panel (targeting EGFR, MET, ERBB2, KRAS, BRAF, PIK3CA, ALK, ROS1 and RET). Library preparation and hybridization capture were conducted with Burning Rock's proprietary LungCore®

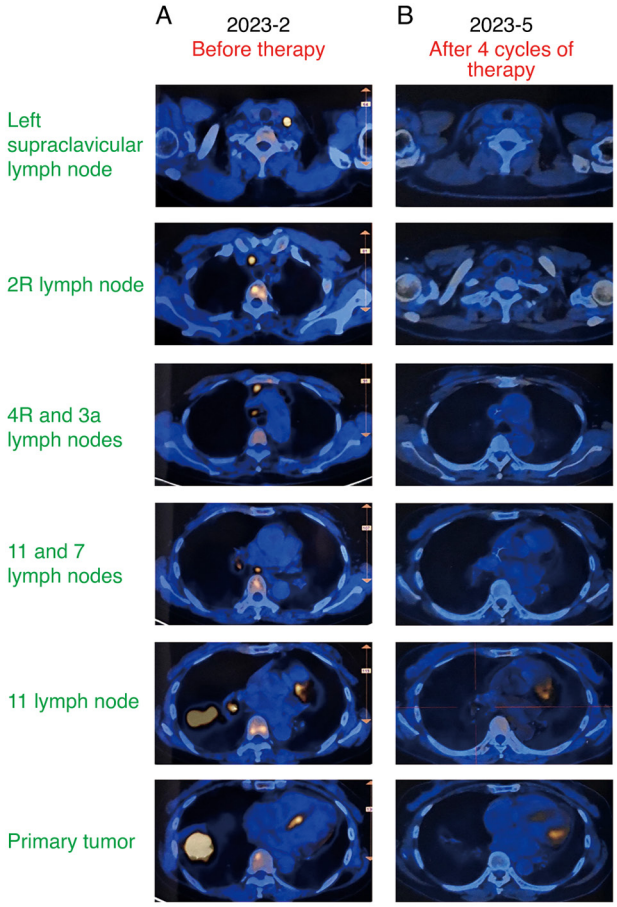

Figure 2. PET/CT examinations before and after induction therapy. (A) Before therapy, PET/CT showed that the tumor SUVmax was 19.0 and the left hyperplastic, 2R, 4R, 3a, 7 and interlobar regions had increased glucose metabolism. (B) After four cycles of treatment, the tumor SUVmax was 3.2 and all lymph nodes had a normal glucose metabolism. CT, computed tomography; PET, positron emission tomography.

NGS Kit, followed by sequencing on an Illumina Miseq DX platform. All experimental procedures strictly adhered to Burning Rock's ISO 15189-certified standard operating protocols, which encompass DNA extraction, hybridization capture, sequencing and bioinformatics analysis (13). Experimental details were described in Burning Rock's clinical test report (available upon request). Assessment of PD-L1 expression showed a tumor cell proportion score of 100% (Fig. 4).

Concurrent chemoradiotherapy followed by immunotherapy with durvalumab for 1 year is the current standard of care for patients with unresectable stage III NSCLC (14,15). However, the patient had a strong desire for surgery and refused pralsetinib or selpercatinib due to financial reasons. Therefore, from February 2023 to April 2023, four cycles of chemotherapy with 780 mg of pemetrexed and 110 mg of cisplatin, plus 200 mg of tislelizumab immunotherapy were administered.

After the second cycle of induction therapy, a CT with contrast scan showed that the primary tumor had shrunk to 35x22x20 mm. The lymph nodes with increased glucose metabolism in the left supraclavicular, 2R, 4R and 3a stations significantly reduced in size. The subcarinal and interlobar lymph nodes had also shrunk (Fig. 1B). After four cycles of induction therapy, a PET/CT scan was performed. The results showed complete metabolic response, with a primary tumor SUVmax of 3.2, indicating that tumor activity was suppressed (Fig. 2B). Therefore, after consulting with specialists (a thoracic surgeon, a respiratory physician, a medical oncologist, a radiation oncologist, a pathologist and a palliative care physician) in a multiple disciplinary team, surgery was scheduled. One day before the surgery, the patient had another CT with contrast scan. The results showed that the primary tumor focus had shrunk to 21x16x12mm. The lymph nodes with increased glucose metabolism in the left supraclavicular and 3a groups were no longer visible on the CT scan (Fig. 1C). On the 48th day after the end of induction therapy, the patient underwent right lower lobectomy and systematic lymph node dissection under general anesthesia with single-port thoracoscopy. The surgery successfully disconnected the right lower pulmonary artery, vein and bronchus, and performed *en bloc* resection of the mediastinal lymph nodes at stations 2, 4, 7 and 9 outside the membrane. The pathological examination revealed a tumor focus of 20x20x10 mm (the length and width of the maximum cross-sectional area and the corresponding vertical height on the gross specimen). The hematoxylin and eosin (H&E) staining was performed according to standard histopathological protocols. In brief, formalin-fixed, paraffin-embedded tissue sections (4-μm thickness) were deparaffinized in xylene, rehydrated through a graded ethanol series (100, 95, 70%) and rinsed in distilled water. Sections were stained with Harris' hematoxylin for 5 min, followed by differentiation in 1% acid ethanol (1% HCl in 70% ethanol) and bluing in 0.2% ammonia water. Counterstaining was performed with eosin Y for 1 min. Finally, sections were dehydrated through graded ethanols, cleared in xylene and mounted with a neutral resin-based mounting medium. After total excision of the tumor focus, a therapeutic response assessment was performed. Under the microscope, the examination primarily showed proliferative and hyalinized fibrous tissue with considerable infiltration of inflammatory cells, cholesterol crystals and multinucleated giant cells (Fig. 3B). Only one slide (out of four tumor bed slides, each ~15x15 mm) showed a 2-mm diameter cancer tissue with some tumor cell degeneration (Fig. 3C). The remaining tumor cells were ~0.5%, indicating that pathological remission of major pathological response (MPR) had been achieved. No tumor residue was found in any of the lymph nodes sent for inspection, suggesting the patient had achieved pathological staging ypT1aN0M0. The patient was discharged on the sixth day after surgery.

Starting from 21 days after the surgery, the patient received 200 mg of intravenous tislelizumab treatment every 21 days. Before and after the treatment, the oncologist conducted a medical history inquiry and physical examination of the patient. The patient underwent a CT scan of the chest and upper abdomen with contrast every 3 months after the surgery. Tumor markers in the blood were also reviewed every 3 months, including carcinoembryonic antigen, carbohydrate antigen (CA)-125, CA-50, CA-199, neuron-specific enolase, squamous cell carcinoma antigen and cytokeratin 19 fragment. As of the submission of the article, no tumor recurrence was found and the markers were normal.

Discussion

While most studies on neoadjuvant ICI therapy focus on patients with resectable NSCLC, the use of it as induction therapy

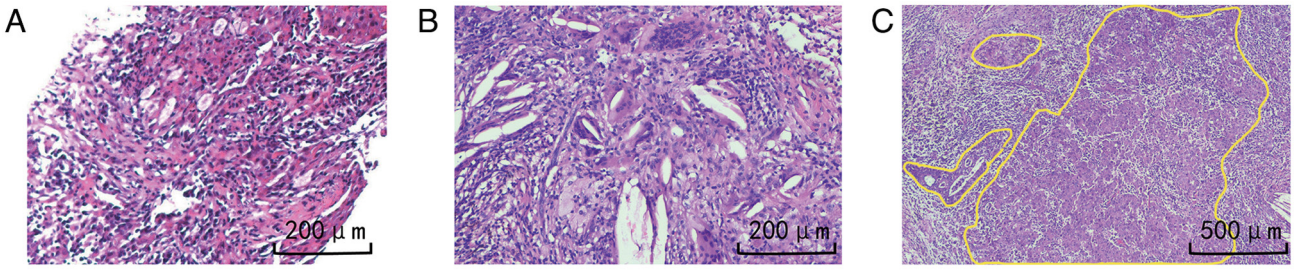

Figure 3. Pathological results. (A) Preoperative pathological image from percutaneous puncture suggested adenocarcinoma. (B) Postoperative pathological images primarily showed proliferative and hyalinized fibrous tissue with considerable infiltration of inflammatory cells, cholesterol crystals and multinucleated giant cells (scale bars, 200 μm; H&E stain). (C) The only one out of the four tumor bed slides, each ~15x15 mm, that showed cancer tissue with a diameter of ~2 mm, accompanied by slight tumor cell degeneration. The area circled by the yellow lasso indicates cancer tissue (scale bar, 500 μm; H&E stain).

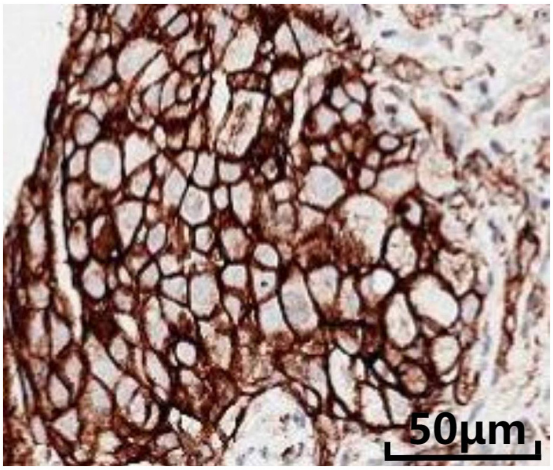

Figure 4. Immunohistochemistry indicated a high level of programmed death-ligand 1 expression (tumor proportion score, 100%; scale bar, 50 μm).

in advanced-stage NSCLC is controversial. Deng *et al* (16) reported 51 cases of unresectable stage III B NSCLC that underwent immunotherapy combined with chemotherapy, 31 of which then underwent minimally invasive surgical resection. During the follow-up period, the disease-free survival/progression-free survival (PFS) of these 31 surgical patients was significantly longer than that of the remaining 20 patients who did not undergo surgery. Zheng *et al* (17) also analyzed 59 patients with initial unresectable stage IIIB NSCLC who received induction pembrolizumab combined with chemotherapy and obtained similar results. The RATIONALE-315 study (18) showed that tislelizumab plus platinum-doublet chemotherapy could achieve a 56.2% MPR rate and a 40.7% pathological complete response (pCR) rate for patients with resectable stage II-IIIA NSCLC. It is esteemed that this treatment modality could also improve the survival of patients with advanced NSCLC.

Concurrent chemoradiotherapy has been the cornerstone of treatment of unresectable, locally advanced NSCLC and the PACIFIC study (NCT02125461) (19) established the foundation for consolidative immunotherapy after concurrent chemoradiotherapy to become the standard treatment for unresectable locally advanced NSCLC, as it reported a median overall survival (OS) of 47.5 months and a 5-year OS of 42.9% for the immunomaintenance therapy regimen after concurrent chemoradiotherapy. However, in the real world, ~55% of stage III lung cancer patients do not meet the inclusion criteria of the study (20). Of note, the 5-year OS rate for stage IIIC lung cancer is only ~13% (21). Historically, the mainstay of treatment for unresectable locally advanced lung cancer has evolved from radiotherapy alone, to induction chemotherapy followed by radiotherapy, to concurrent chemoradiotherapy, and finally to concurrent chemoradiotherapy followed by immunomaintenance therapy (22). However, the approach of local treatment after systemic induction therapy has not been widely studied. Theoretically, the treatment effect of chemotherapy plus immunotherapy followed by radiotherapy should not differ significantly from that of concurrent chemoradiotherapy followed by immunomaintenance therapy. However, if the tumor shrinks significantly enough, patients may have the opportunity for radical surgical resection. According to the Chinese Society of Clinical Oncology guidelines (15), for unresectable stage III lung cancer, systemic induction therapy may be chosen after multiple disciplinary team discussion. If radical resection is deemed feasible, surgery can then be performed. This approach is classified as a category 2 recommendation. Due to the patient's strong resistance to radiotherapy and the patient's strong desire for the opportunity to undergo radical surgical resection, the team decided to give the patient the chance.

However, the application of immunotherapy in patients exhibiting driver gene positivity remains another subject of debate. The AEGEAN trial (23) showed promising therapeutic effects of neoadjuvant durvalumab with chemotherapy. However, a subgroup analysis of 51 EGFR mutation-positive patients, who were included before the protocol revision, did not provide substantial evidence of clinical benefit with durvalumab as compared to placebo (24). The KEYNOTE-671 trial (25), which included 33 patients with EGFR mutations, indicated an improvement in event-free survival in the pembrolizumab group. However, the limited sample size of the study necessitates further investigation. A phase 2 clinical trial (CTONG2104) reported by Zhang *et al* (26) involved 18 patients with EGFR mutation who underwent neoadjuvant sintilimab with chemotherapy and subsequent surgery. The MPR rate was 44%, while the pCR rate was zero. Despite the less-than-optimal pCR rate, the MPR results appeared favorable when compared with previous results from preoperative targeted treatment [in the NEOS study (27), in which the patients were treated with osimertinib 80 mg orally once per

day for six weeks, followed by surgical resection, the MPR rate was 10.7% (3/28) and the pCR rate was 3.6% (1/28)].

RET fusion accounts for only 1-2% of lung adenocarcinoma cases (28-30). Although selective RET inhibitors, such as selpercatinib and pralsetinib, significantly improved the prognosis for patients with advanced lung cancer with RET fusions (31-33), the potential benefit of ICIs in individuals with RET fusions remains elusive, largely because these patients are usually excluded from clinical trials or specifically analyzed. Small-sample retrospective studies suggested that patients with RET fusions may not benefit from ICIs (10-12). One possible cause is that RET fusions are closely related to low PD-L1 expression and low TMB (10). Previous studies have indicated that ICIs may be more effective for patients with high PD-L1 levels and high TMB (34,35). In the study by Lu *et al* (36), out of 20 patients who underwent PD-L1 testing, only 5 (25%) had PD-L1 expression with a tumor cell proportion score >50%. In the study by Offin *et al* (37), only 5 out of 26 patients (19%) had PD-L1 expression >50%. In the study by Yan *et al* (10), only 22 out of 129 patients (17.8%) had PD-L1 expression >50%. Among the 28 patients who underwent ICI treatment, only 7 (25%) had PD-L1 expression >50%, and 15 (53%) had PD-L1 expression ≥1%. Despite the small number of patients, those with PD-L1 expression ≥1% showed a trend towards prolonged PFS compared to those with PD-L1 expression <1%. In this present case, the expression of PD-L1 was very high. This may be a significant reason for the effectiveness of ICI. The patient was not tested for the TMB for financial reasons. Since a high TMB is more likely to occur in smoking patients (38,39), it may be suspected that this factor has little effect in this case. In addition, mutations in driver genes may alter the tumor immune microenvironment, thereby affecting the efficacy of immunotherapy (8). However, contrasting findings have emerged from a recent study suggesting that RET mutations may actually offer a positive predictive response to ICI therapy (40), proposing that RET fusion and RET point mutations may trigger distinct molecular pathways in cancer. RET fusion lung cancers may also be heterogeneous in terms of concomitant genetic alterations. Lu *et al* (36) reported 2 cases of KIF5B-RET fusion with high levels of PD-L1 expression, which showed good clinical benefits from ICIs. The two patients received pembrolizumab and durvalumab, respectively. In the present case with very high PD-L1 expression, tislelizumab combined with chemotherapy achieved remarkable results. To the best of our knowledge, the present study is the first report of the successful treatment of a patient with advanced lung adenocarcinoma and RET fusion using tislelizumab with chemotherapy, who was initially not eligible for surgery, then became eligible and was subjected to surgery.

Currently, there is a lack of research focusing on the impact of PIK3CA mutation on the effectiveness of immunotherapy for lung cancer. PIK3CA mutation is significantly associated with poor survival (41) and may result in resistance to EGFR-tyrosine kinase inhibitors in patients with NSCLC (42). PIK3CA mutations may also promote tumor lymph node metastasis (43).

The present study presented a case of metastatic RET fusion NSCLC treated with induction tislelizumab with chemotherapy, leading to an MPR. However, the potential benefits of this treatment modality in broader patient groups remain unclear due to the relatively brief mid-term follow-up in the present case. To evaluate the safety and effectiveness of this novel treatment strategy, further exploration through extensive clinical trials is necessary. Considering the low incidence rate of RET fusions in patients with lung cancer, more retrospective data are needed to demonstrate the value of immunotherapy in these patients. For patients with initially unresectable locally advanced lung cancer, it is esteemed that prospective randomized controlled trials will determine whether surgery is more effective than radiotherapy when systemic therapy can downstage the disease.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

DHT and TC conceived the study. RQ extracted and organized the original data. DHT wrote the main part of the original manuscript, and FW and QZ wrote a literature review of the progress in the discussion section. QL analyzed and interpreted the patient's imaging results, and LH interpreted the patient's pathology results. DHT and TC 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 research protocol was approved by the Ethics Committee of Yueyang Central Hospital (Yueyang, China; approval no. 2024-054), and the patient provided written consent for the plan. This study was also conducted in accordance with the Declaration of Helsinki.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the present case report and the accompanying associated images.

Competing interests

The authors declare that they have no competing interests.

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