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CASE REPORT

Simultaneous Anti-Tuberculosis and Anti-Tumor Treatment with Immune Checkpoint Inhibitors for Co-Existent Pulmonary Tuberculosis and Advanced Lung Cancer

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Background: Immune checkpoint inhibitors (ICIs) have emerged as the first-line treatment for driver-negative advanced non-small cell lung cancer (NSCLC). However, there is uncertainty regarding the availability and timing of ICI initiation in patients with NSCLC combined with pulmonary tuberculosis (TB). Additionally, the implementation of dual therapy for anti-TB and anti-tumor treatment poses significant challenges in terms of avoiding drug–drug interactions and reducing adverse reactions during clinical diagnosis and treatment.

Case Description: A 65-year-old male patient was admitted to our designated TB hospital following an out-of-hospital TB diagnosis. Relevant examinations were completed after admission, and chest computed tomography revealed that the patient had lung squamous cell carcinoma with multiple metastases in lymph nodes and liver. A multidisciplinary team (MDT) consisting of oncologists, pulmonologists, and clinical pharmacists followed evidence-based practices to determine treatment options. They evaluated the benefits and risks of ICIs and performed therapeutic drug monitoring for the dual treatment of anti-TB and anti-tumor drugs. After 18 days of anti-TB treatment, the patient successfully received ICIs combined with chemotherapy for NSCLC while continuing anti-TB therapy. The patient's anti-TB treatment plan was adjusted due to gastrointestinal reactions, bone marrow suppression, and liver function injury. Ultimately, both NSCLC and pulmonary TB were effectively controlled.

Conclusion: For patients with NSCLC complicated by pulmonary TB, after 2–4 weeks of effective anti-TB treatment, anti-tumor therapies, including ICIs, can be simultaneously implemented with the anti-TB treatment. Therapeutic drug monitoring is beneficial for avoiding serious adverse effects and ensuring the timely treatment of both diseases.

Keywords: anti-tumor therapy, immunotherapy, *Mycobacterium tuberculosis*, adverse effects

Introduction

The treatment of advanced non-small cell lung cancer (NSCLC) has entered the precision era of chemotherapy, molecular targeting, and immunotherapy. Among these treatments, immune checkpoint inhibitors (ICIs) can prevent tumors from inhibiting T cells and restart the tumor immune cycle by targeting immune checkpoints. This can significantly improve and prolong the objective response rate, progression-free survival, and overall survival of patients. ICI therapy has become the first-line treatment for advanced NSCLC.[1,2] However, the safety of ICIs in patients with cancer in the presence of an ongoing tuberculosis (TB) infection is altered. It has been reported that TB infection can occur during ICI treatment. Some patients have received anti-TB and ICI treatment at the same time and the dual treatment achieved good

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clinical results. However, there are no high-quality clinical studies that definitely answer whether lung cancer complicated by *Mycobacterium tuberculosis* (MTB) infection can be treated with ICIs.[3–5]

Moreover, there is a lack of reliable data on the management of latent TB infection (LTBI) after initiating ICI therapy, making it difficult to select appropriate treatment options for these patients. This report aims to discuss the timing of immunotherapy in patients with lung cancer and TB, as well as management strategies for serious adverse reactions, in order to provide a reference for clinical diagnosis and treatment.

Case Presentation

A 65-year-old male farmer was admitted to the hospital with a cough and blood-streaked sputum that persisted for more than 20 days. The patient had experienced similar symptoms 3 years ago but did not seek medical attention. Twenty days prior to their admission to our hospital, the patient was admitted to a local hospital due to recurring symptoms. Chest computed tomography (CT) and tracheoscopy indicated infection, and the patient underwent treatment for infection (levofloxacin 0.5 g qd) and hemostasis. The patient tested positive for interferon-gamma release assay with a result of 73.8 pg/mL and had 2644 MTB reads in their lavage fluid on next-generation sequencing.

Based on the patient's clinical symptoms and lung imaging findings, they were diagnosed with TB and then transferred to our designated TB hospital. After bronchoscopy at our hospital, it was found that the Xpert assay result for lavage fluid was positive, and the rpoB gene was detected as a rifampicin-sensitive type to diagnose pulmonary TB.

Upon admission, the patient underwent a lung CT examination. The scan revealed a space-occupying mass in the hilum of the left lung measuring 46.3×33.7 mm, along with enlargement of the hilum and mediastinal lymph nodes, indicating possible lung cancer with metastasis. Additionally, the left lung showed signs of infection (Figure 1A). On the 3rd day of admission, an oral HRZE regimen (isoniazid 0.3 g qd, rifampicin 0.6 g qd, pyrazinamide 0.5 g tid, and ethambutol 0.75 g qd) for TB was initiated. However, after a week of treatment, the regimen was adjusted to the HELfx regimen (isoniazid 0.3g qd, ethambutol 0.75 g qd, and levofloxacin 0.5 g qd) due to adverse reactions such as nausea, vomiting, and elevated liver enzymes.

Further tests, including bronchoscopy and biopsy of the lump in the upper lobe of the left lung, revealed squamous cell carcinoma. A whole abdominal CT scan also showed multiple intrahepatic metastases. The revised diagnosis was

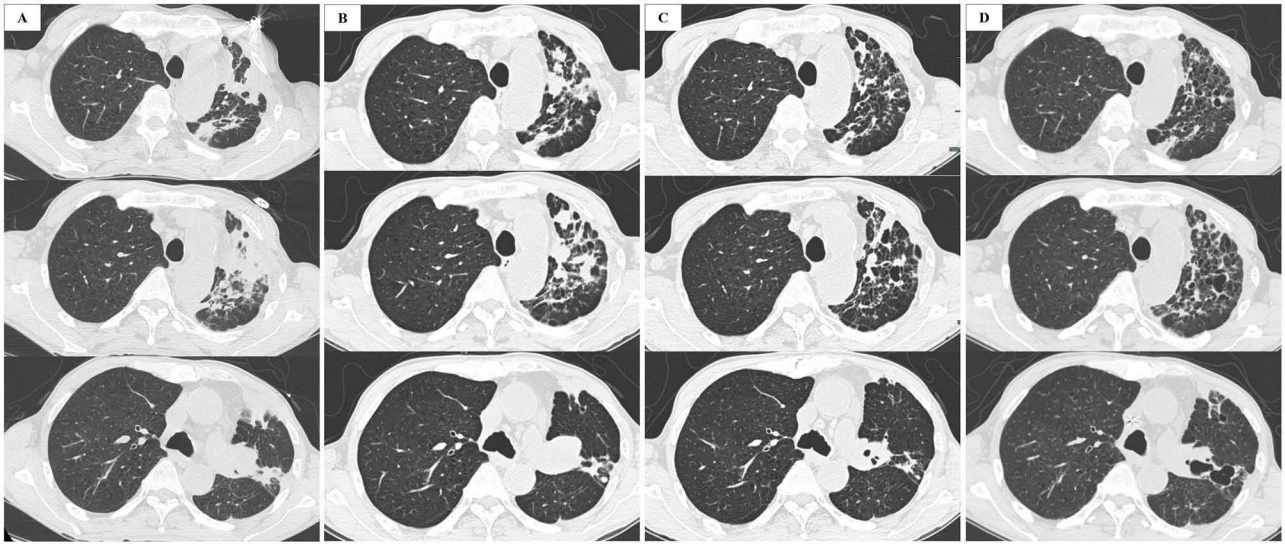

Figure 1 Changes in lung computed tomography scans before and after anti-TB and anti-tumor therapy: (**A**) Before treatment, imaging reveals a space-occupying mass (46.3x33.7 mm) in the left upper hilar area, along with enlargement of mediastinal and hilar lymph nodes. The presence of a tumor with metastasis was considered, along with simultaneous infection in the left upper lobe, two fibroproliferative calcification foci in the lungs, and two cases of emphysema. (**B**) After one month of anti-TB treatment, the infection in the upper lobe of the left lung exhibited decrease compared to the previous images. (**C**) After two cycles of anti-tumor therapy, the space-occupying mass in the upper hilar area of the left lung, along with lymph node enlargement in the mediastinum and lung hilar, had significantly reduced compared to the previous images. (**D**) After four cycles of anti-tumor therapy, the space-occupying mass in the left upper hilar area had further reduced in size.
Abbreviation: TB, tuberculosis.

lung squamous cell carcinoma with multiple lymph node and liver metastases, stage IV B (cT2bN2M1c), in addition to concurrent secondary TB. Gene detection did not identify any common lung cancer mutations, while the PD-L1 expression was 14%.

To initiate tumor treatment as soon as possible, the patient's anti-TB treatment was intensified, and linezolid 0.6 g q12h was added to the HELfx regimen. After 18 days of anti-TB treatment, the patient's cough and sputum symptoms improved. Following a discussion with the multidisciplinary team (MDT), the patient started the first cycle of the TC regimen (albumin-bound paclitaxel 0.2 g on day 1 and 8, plus carboplatin 0.5 g on day 1) combined with pembrolizumab 0.2 g on day 1. However, on the 7th day after chemotherapy initiation, the patient had a low platelet count (31×10^9 [(100–300) × 10^9/L]), a low white blood cell count (0.9×10^9 [(3.5–9.5) × 10^9/L]), elevated aspartate aminotransferase levels (86 U/L), and elevated alanine aminotransferase levels (60 U/L). On day 18 of treatment with linezolid (600 mg twice daily), we detected the trough concentration of linezolid to be 10.32 μg/mL (reference range 2–7 μg/mL), which was higher than the normal reference range according to therapeutic drug monitoring (TDM). Meanwhile, the peak concentrations of isoniazid (3.43 μg/mL; reference range 3–6 μg/mL), ethambutol (2.52 μg/mL; reference range 2–6 μg/mL), and levofloxacin (10.40 μg/mL (reference range 8–13 μg/mL) were also detected on the 25th day; all were in the normal range. Consequently, linezolid was stopped, the patient's condition improved after receiving symptomatic treatment, including liver protection and platelet and leukocyte enhancement.

Subsequently, under adequate therapeutic supervision, the patient successfully completed four cycles of anti-tumor therapy (TC regimen combined with pembrolizumab) and was then placed on long-term maintenance therapy with pembrolizumab. At the same time, the patient was treated with a triple anti-TB regimen (isoniazid, ethambutol, and levofloxacin) for consolidation therapy, and the drugs were stopped after the elimination of tubercle bacilli. The total anti-TB period was 9 months. The adverse reactions of pembrolizumab included fatigue, pruritus, rash, diarrhea, nausea, immune-related pneumonia, hepatitis, and myocarditis. The patient was followed-up for 1 and a half years, and no adverse reactions were found in the patient except for a slight increase in liver enzyme levels, which was mainly considered to be related to the use of anti-TB drugs. After the implementation of liver protection therapy, the liver enzyme levels improved, and no other discomfort was found.

The efficacy of the anti-TB treatment was evaluated after 1 month. CT examination showed that the infection in the left upper lung had decreased compared to before (Figure 1B). The sputum smear, TB culture, and blood T-SPOT tests all returned negative results. After the second cycle of anti-tumor therapy, significant reductions were noted in the size of the space-occupying mass in the left upper hilar area, as well as in the mediastinal and hilar lymph nodes. The clinical evaluation showed partial remission (Figure 1C), which was maintained after the fourth cycle of treatment (Figure 1D). The disease in other areas remained stable.

Discussion

The pathological diagnosis and clinical staging of this patient's lung squamous cell carcinoma were clear. Additionally, the molecular diagnosis, imaging, and clinical features of their secondary pulmonary TB were established, necessitating the patient to undergo both anti-TB and anti-tumor therapy. Notably, while it has been proven safe and effective for patients with tumor to receive cytotoxic chemotherapy and anti-TB therapy simultaneously,[4,5] this observation has been mainly in patients receiving PD-1/PD-L1 inhibitors, since the clinical application of ICIs to treat tumors began in 2014.[6,7]

Among solid tumors, lung cancer has the highest infection rate. Fujita et al[8] found that 1.7% of patients with lung cancer developed TB after ICI treatment, which was higher than the incidence among patients receiving chemotherapy alone (1.2%). However, evidence regarding ICI-induced TB is limited and varies. Bae et al[9] conducted an analysis of 141,550 patients with cancer to assess the risk of TB after exposure to ICI treatment. They found that while the incidence of TB in patients with cancer exposed to ICIs was eight times that of the general population, there was no significant correlation between the risk of TB in patients with cancer exposed to ICIs and non-exposed groups (HR: 0.73). Considering these findings, it is possible that the activation of MTB may be related to the cancer itself rather than ICI treatment, suggesting that LTBI is not an obstacle to the use of ICIs. Interestingly, retrospective studies have shown that some patients received both anti-TB and ICI treatment or restarted immunotherapy after improving with anti-TB treatment. In these cases, dual treatment had improved clinical benefits and the TB did not worsen or relapse.[3–5]

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Due to the complexity and uncertainty surrounding the treatment of ICIs and TB development, the following recommendations are provided for screening MTB in patients with cancer: (1) TB and LTBI screening are recommended before ICI treatment; this is especially important for patients with one or more independent risk factors (such as age, immune status, disease history, drug history, etc). (2) Screening for TB should be conducted when there are changes in treatment as the disease progresses or when initiating glucocorticoids for immune-related adverse events. This is especially important for patients with prior exposure to TB. (3) If newly discovered or relapsed TB occurs during ICI treatment, it is recommended to suspend immunotherapy. The decision to restart ICIs should consider the control of TB, tumor status, drug tolerance, and overall patient well-being. (4) For TB diagnosed prior to ICI treatment, anti-TB therapy can be administered 2–4 weeks before initiating ICIs to reduce the MTB load.[10] The determination of when to start ICIs should be based on clinical benefits and risk control.

Based on the above evidence-based recommendations, a summary of the screening and treatment of LTBI in patients with advanced lung cancer is shown in Figure 2. In this case, the patient's clinical symptoms improved and the lung CT showed absorption of the focus of infection after 1 month of anti-TB treatment. Therefore, immunotherapy combined with chemotherapy for lung cancer was initiated. In the first cycle of drug combination therapy, the patient

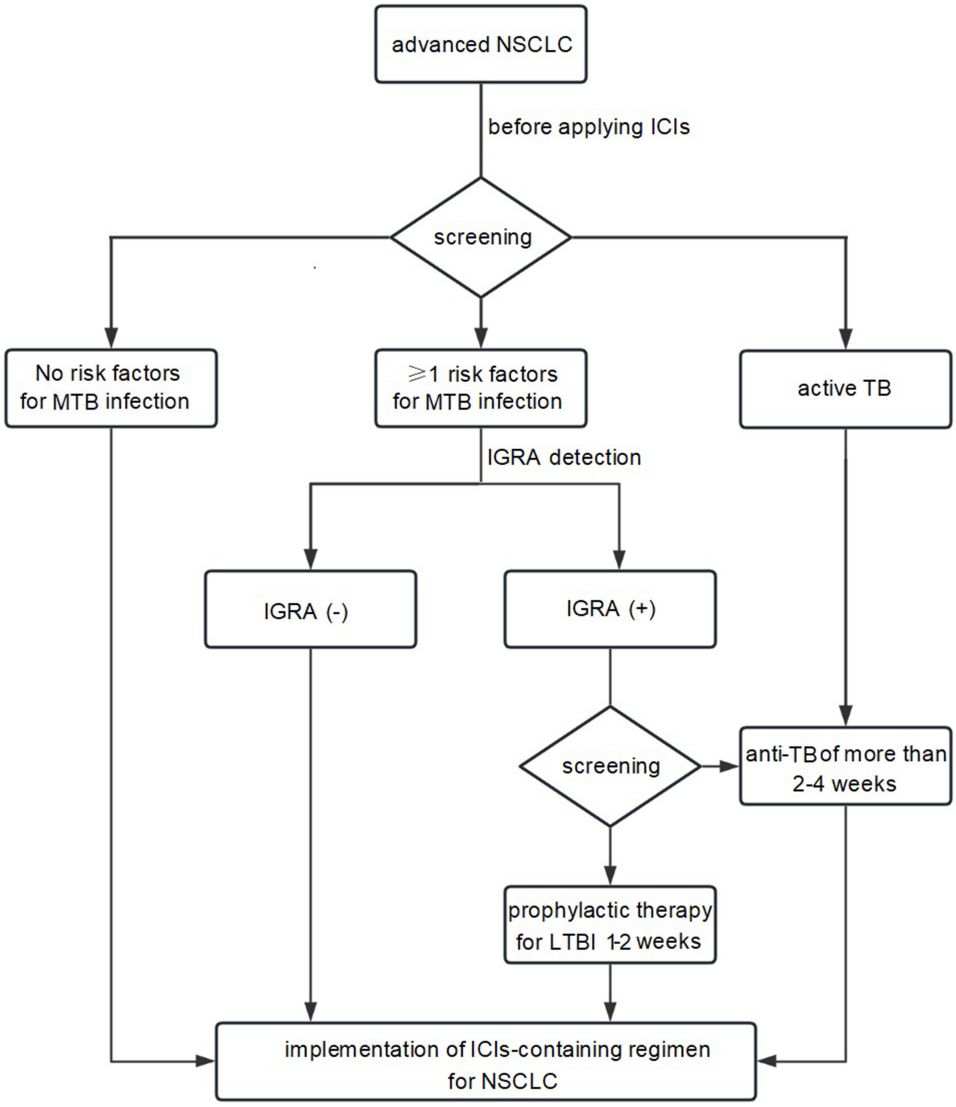

Figure 2 Screening and treatment flow for MTB during anti-tumor therapy involving immune checkpoint inhibitor.
Abbreviations: IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; ICIs, immune checkpoint inhibitors; TB, tuberculosis; MTB, Mycobacterium tuberculosis.

experienced mild liver function injury. According to the Roussel Uclaf Causality Assessment Method, anti-TB drugs (pyrazinamide and isoniazid) were considered as the probable cause, followed by chemotherapy drugs (carboplatin and paclitaxel). Typically, immune-mediated liver injury associated with ICIs typically occurs 8–12 weeks after the first medication.[11] Here, the patient's condition improved after receiving active symptomatic treatment with compound glycyrrhizin.

HRZE is often used in the clinical treatment of initial pulmonary TB, with rifampicin playing an important role. The patient discussed here did not choose rifampicin, mainly due to the following four reasons: (1) The patient experienced a large gastrointestinal reaction. (2) Rifampicin has the potential to increase liver enzymes. (3) Rifampicin may affect the efficacy of immunotherapy.[12] (4) Rifampicin can impact the metabolism of paclitaxel.[13] Second-line drugs (such as levofloxacin and linezolid) could be used without rifampicin in the anti-TB regimen. In 2023, the Chinese Society of Tuberculosis, Chinese Medical Association organized and wrote the expert consensus on the off-label use of anti-TB drugs (2023 Update). This expert consensus suggests that levofloxacin may be considered for treatment-sensitive TB when first-line anti-TB drugs do not constitute an effective treatment regimen.[14] In order to control TB in a shorter time, for the next lung cancer treatment we used an individualized treatment plan plus linezolid, mainly to control the early symptoms experienced by the patient.

When using multiple drugs concurrently, attention must be given to the risk of overlapping adverse reactions.[4] LEE et al analyzed 1155 cases of lung cancer with TB and found that over 60% of the patients received incomplete treatment due to concerns about drug risks and adverse reactions.[15] Notably, the simultaneous use of carboplatin, paclitaxel, and linezolid may increase the risk of myelosuppression, particularly thrombocytopenia. Therefore, it is recommended to avoid linezolid as much as possible during chemotherapy with platinum and taxoid drugs. Furthermore, TDM, based on pharmacokinetic theory, can be used to measure drug blood concentrations, assisting in the development of a reasonable and individualized drug administration plan. In this patient, the combination of anti-TB drugs, levofloxacin, and linezolid was tested. However, since their linezolid levels were outside the normal concentration range and aggravated their thrombocytopenia, it was advised to discontinue linezolid and monitor for any improvement. It is important to note that there is no standardized treatment model for lung cancer with TB, and individualized administration should be implemented based on specific clinical conditions.

Although the screening and treatment processes for LTBI in patients with advanced lung cancer, as summarized by us, have shown good results in individual cases, they still require verification through clinical trials with larger sample sizes and more rigorous designs.

Conclusions

For complex cases of NSCLC complicated with pulmonary TB, an MDT composed of oncologists, pulmonologists, and clinical pharmacists should collaborate closely. This team can fully utilize evidence-based medicine, TDM, and other skills to implement simultaneous treatment for both TB and cancer. This includes the use of ICIs once the TB is effectively controlled, with close monitoring of drug interactions and adverse reactions. Ultimately, this approach allows patients to receive the dual benefits of anti-TB and anti-tumor therapy.

Data Sharing Statement

Data will be provided by the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was supported by the Ethics Committee of Hangzhou Red Cross Hospital (No.: 2023YS028) and was carried out in accordance with the ethical standards of the Declaration of Helsinki.

Consent for Publication

Written informed consent was obtained from the patient and the Hangzhou Red Cross Hospital for publication of any potentially identifiable images or data included in this case report.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that the research is conducted in the absence of any commercial relations or financial relationships of interest that might be a constant source of interest.

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