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Primary Pulmonary Lymphoepithelioma-Like Carcinoma Demonstrates a Favorable Response to Tislelizumab Combined with Chemotherapy: A Case Report

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Abstract

Background: Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare subtype of non-small cell lung cancer (NSCLC). Nevertheless, no universally acknowledged standards of care have been reported to be effective and productive for the treatment of this tumor. **Materials and Methods**: A patient with advanced primary pulmonary LELC was treated by employing a combination of tislelizumab and chemotherapy. **Results**: The patient displayed a favorable response to the combination therapy. The tumor size exhibited conspicuous abatement in contrast to the pre-treatment baseline, and the tumor markers normalized. **Conclusion**: The combination of immunotherapy with chemotherapy appears to be more effective than therapy alone for managing advanced primary pulmonary LELC. On that account, further clinical trials are imperative to establish this combination regimen as a potential first-line treatment option for advanced cases.

Keywords

Primary Pulmonary Lymphoepithelioma-Like Carcinoma, LELC, Tislelizumab, Immune Checkpoint Inhibitor

1. Introduction

Primary lymphoepithelioma-like carcinoma (LELC) is a rare and distinct subtype of non-small cell lung cancer (NSCLC). On the whole, LELC accounts for a negligible proportion of all lung cancer cases. Histologically, it not only bears a close

resemblance to undifferentiated carcinoma of the nasopharynx, but also is tightly correlated with to Epstein-Barr virus (EBV) infection. Epidemiologically, pulmonary LELC demonstrates a comparatively higher incidence among Asian populations, particularly in non-smokers, with a disproportionate prevalence in young females [1] [2]. For early-stage pulmonary LELC, surgical treatment is the mainstay of treatment; whereas advanced-stage patients are usually treated with a combination of chemotherapy and radiotherapy as the core of the treatment regimen. Although the prognosis of pulmonary LELC patients is more optimistic than that of patients with other NSCLC subtypes, some patients are still resistant to treatment and may experience local tumor recurrence or distant tumor metastasis at an early stage. Currently, there is no definitive and effective cure for advanced pulmonary LELC patients who have failed to respond to radiotherapy, so there is an urgent need to explore new therapeutic agents [3]. Nowadays, the speedy and substantial accomplishments in cancer immunotherapy have tremendously deepened the understanding and therapeutic strategies for this rare malignancy.

This study presents the case of a 30-year-old male diagnosed with advanced primary pulmonary LELC, who was admitted to the Department of Respiratory and Critical Care Medicine at the Second People's Hospital of Guangdong Province. Subsequent to multiple cycles of tislelizumab-based combination chemotherapy, the patient materialized effective disease stabilization.

2. Case Presentation

A 30-year-old male patient presented to a local hospital with complaints of "cough with blood-streaked sputum for over two months and worsening symptoms for one week". Initial chest CT revealed findings in alignment with a "right lower lung abscess with pneumonia". Following ineffective anti-infective therapy, the patient was transferred to our hospital for specific assessment and proper management. His medical history revealed a diagnosis of gout. The patient denied any history of smoking or alcohol consumption.

Upon admission, diagnostic evaluations were conducted in a comprehensive manner. Blood tests suggested a neutrophil ratio of 0.67, white blood cell count of 5.51×10^9/L, and lymphocyte ratio of 0.17. No fungi, bacteria, or acid-fast bacilli were detected in alveolar lavage fluid. Mycoplasma pneumoniae IgM and Chlamydia pneumoniae IgM were negative, while the rapid nucleic acid test for SARS-CoV-2 was positive. Tumor markers revealed elevated glycan antigen 125 (CA125, 76.12 U/mL), cytokeratin 19 fragments (CYFRA21-1, 20.40 ng/mL), and neuron-specific enolase (NSE, 27.49 ng/mL). Chest CT with contrast enhancement showed multiple space-occupying lesions in the right middle and lower lungs (**Figure 1**), accompanied by right pleural effusion and multiple solid nodules in both lungs. Whole-body PET-CT illustrated abnormally high metabolic activity in the posterior basal and dorsal segments of the lower lobe of the right lung, which was highly suggestive of lung cancer (**Figure 2**). Apart from that, metabolic activity was observed in multiple lymph node groups in the bilateral

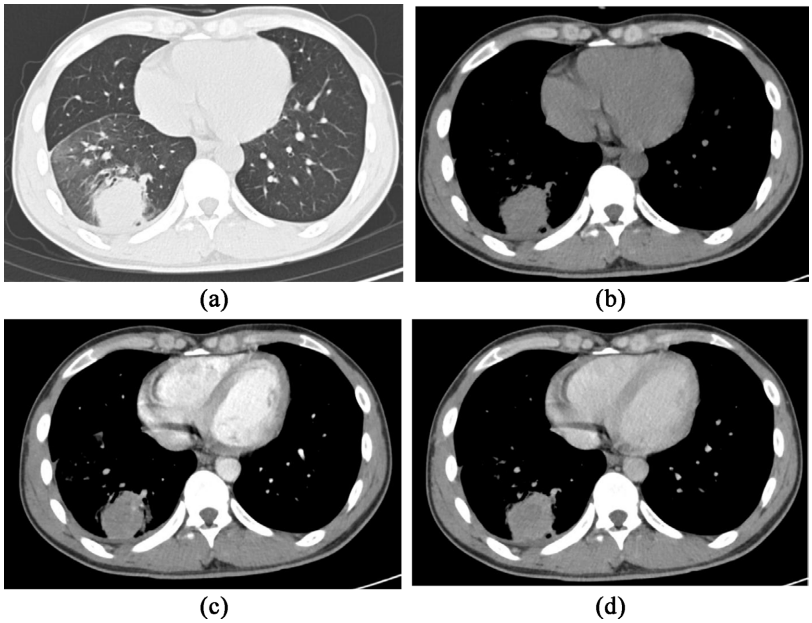


Figure 1. Correspond to the lung window, mediastinal window plain scan, arterial phase, and venous phase, respectively. The plain scan reveals an irregular mass in the right lower lung, characterized by an indistinct boundary, peripheral burrs, and surrounding patchy hazy opacities. Contrast-enhanced scans demonstrate heterogeneous moderate enhancement within the mass.

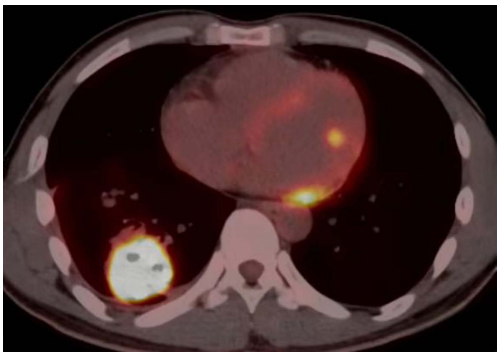


Figure 2. PET-CT showed right lower lung mass with abnormal FDG concentration and SUV_{max} of about 16.5.

hilar, mediastinal, and cervical regions, evidently demonstrating metastasis. Hepatic hilar lymph nodes exhibited slight metabolic activity, with metastatic lesions identified in the hepatic S4a and S7 segments. Notwithstanding the fact that multiple pulmonary nodules displayed no metabolic activity, metastatic involvement could not be excluded. Endoscopic biopsy confirmed the diagnosis of pulmonary LELC (**Figure 3**), staged as T2N3M1c (stage IVb). Immunohistochemical analysis showed CK/pan (+), P40 (+), TTF-1 (−), CD56 (−), Syn (−), S-100 (−), Vimentin (−), LCA (inflammatory cells +), P53 (approximately 60% moderate-strong +), and Ki-67 (~30% +). In situ hybridization detected EBERs (+). To exclude nasopharyngeal carcinoma metastasizing to the lungs, nasopharyngeal endoscopy with mucosal biopsy was performed, revealing no evidence of malignancy.

Followed by the confirmed diagnosis, the patient received anti-infective therapy, dexamethasone for inflammation, and tislelizumab (albumin-bound) immunotherapy combined with paclitaxel and cisplatin chemotherapy. He returned monthly for chemotherapy and immunotherapy. During the treatment period, the patient responded well to this combination therapy without any significant side effects and maintained good disease stability with a shrinking tumor. After six cycles of comprehensive treatment, no dramatic fluctuation was observed with regard to his general condition. Tumor marker levels, including CA125 (16.97 U/mL, normal: <35 U/mL), CYFRA21-1 (1.51 ng/mL, normal: <3.3 ng/mL), and NSE (14.73 ng/mL, normal: <16.3 ng/mL), decreased to within the normal range. Follow-up chest CT revealed a marked reduction in the solid component of the tumor compared to the initial imaging (Figure 4), and the patient achieved partial remission (PR) (according to RECIST 1.1). The follow-up plan is to continue to observe the follow-up and assess the long-term efficacy and durability of the response to this combination therapy.

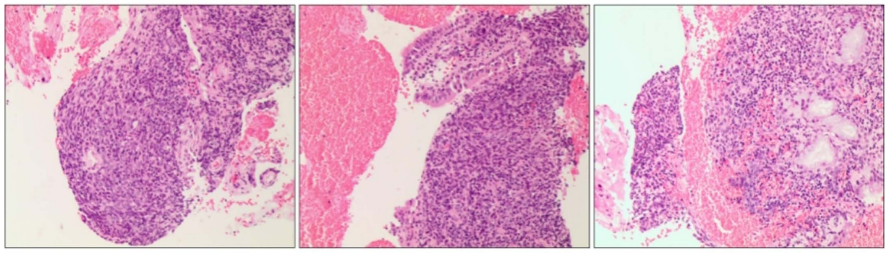
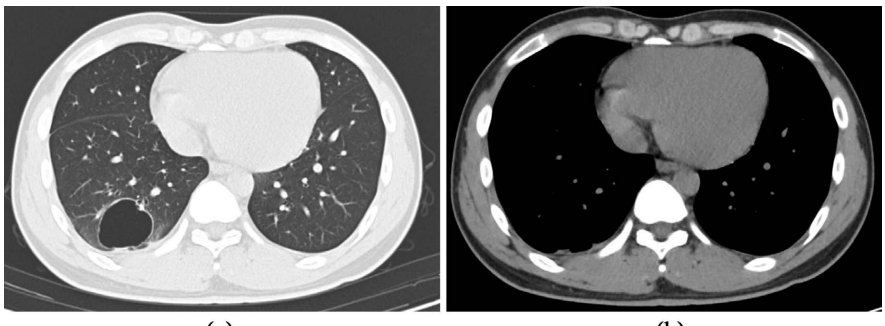


Figure 3. Histological examination revealed short spindle-shaped cells growing in sheets beneath the bronchial mucosal epithelium. The cells exhibited pale-staining vesicular nuclei, with some containing small nucleoli. The interstitium showed abundant infiltration by lymphocytes and plasma cells.



(a) (b)

Figure 4. After 6 cycles of combination therapy, the solid component of the right lower lung mass was significantly reduced and cavities formed compared to before, and the mediastinal window was not shown.

3. Discussion

Primary pulmonary LELC was first described in the 1980s [4]. It is predominantly observed in Asian populations, particularly in southern China (also including Hong Kong SAR) and Southeast Asia, where it is bound up with EBV infection

[5]. On the contrary, no remarkable correlation between EBV and pulmonary LELC has been observed in Caucasian populations [6]. It's particularly noteworthy that the clinical manifestations of pulmonary LELC are non-specific, with cough being the most common symptom. Other presentations consist of hemoptysis, chest pain, and weight loss, though some cases are incidentally detected during routine health checkups [7]. In 2015, the World Health Organization classified primary pulmonary LELC under the category of undifferentiated tumors in its histological classification of lung tumors [8].

In some sense, a chest CT scan is the preferable diagnostic modality for primary pulmonary LELC. Typical findings often include a well-defined, lobulated mass, sometimes accompanied by spiculations or vascular clusters. Internal features may involve cavitation, necrosis, or calcification, etc. Aside from that, contrast-enhanced scans typically reveal moderate to striking reinforcement [9]. On PET-CT, pulmonary LELC appears as hypermetabolic foci with markedly elevated standardized uptake values (SUVs), frequently accompanied by local infiltration and lymph node metastasis [10]. Definitive diagnosis is confirmed through pathological examination of tissue specimens, which, on a diagonostic level, is usually characterized by abundant lymphocytes adjacent to tumor cells and the formation of lymphoid follicles. Nonetheless, the histological features of metastatic undifferentiated nasopharyngeal carcinoma are indistinguishable from those of pulmonary LELC, which therefore necessitates nasopharyngeal endoscopy to exclude metastasis.

The treatment of primary pulmonary LELC hinges principally on the tumor stage. Early-stage patients typically actualize better outcomes through surgical resection of the tumor. For this reason, chemotherapy and radiotherapy are extensively adopted in advanced stages. Chemotherapy regimens are primarily platinum-based, with combinations such as cisplatin or carboplatin with paclitaxel, 5-fluorouracil or doxorubicin [6]. Immune checkpoint blockade targeting PD-1 has emerged as a novel treatment strategy for various cancers [11]. As revealed by an all-round and in-depth literature review, immune checkpoint inhibitors have demonstrated more favorable outcomes in virus-associated cancers. For instance, in Merkel cell carcinoma associated with Merkel cell polyomavirus, PD-1 inhibitors materialized an objective response rate of 56%, surpassing the rates realized by a multitude of conventional therapies [12]. Similar outcomes were reported in HPV-positive recurrent or metastatic squamous cell carcinoma [13]. As these findings suggest, virus-related tumors are more correlated with the response to PD-1 blockade. Moreover, tumors expressing PD-L1 are inclined to display an elevated response to immune checkpoint inhibitors [14] [15]. Such observations lay a robust theoretical foundation for the application of immune checkpoint inhibitors in treating primary pulmonary LELC.

In this case, the patient's disease achieved better control after six cycles of tislelizumab combined with paclitaxel and cisplatin. In comparison, Tang *et al.* documented a case in which a patient exhibited resistance to immunotherapy, resulting

in suboptimal treatment outcomes. Subsequently, the introduction of a regimen combining immunotherapy and chemotherapy led to remarkable clinical improvement [16]. This combination therapy, integrating immunotherapy and chemotherapy, has been utilized in the tailored management of advanced primary pulmonary LELC. By synergizing the mechanisms of these two modalities, combination therapy appears to outperform either treatment alone, potentially offering prolonged survival. As a consequence, this therapeutic strategy should be considered a preferred option for treating primary pulmonary LELC.

The generalizability and reliability of the findings are constrained by the inherent limitations of a single case report, which presents a minuscule sample size that lacks representativeness of an extensive patient cohort. Notably, the absence of a control group precludes a direct efficacy comparison between tislelizumab-augmented chemotherapy and alternative therapeutic protocols, thus complicating the attribution of observed benefits solely to the combination regimen. Moreover, despite the encouraging response noted during the follow-up period, the brevity of this duration casts uncertainty over the long-term outcomes. In light of these caveats, the imperative for additional research endeavors is underscored.

4. Conclusion

We report a case of an Asian patient diagnosed with EBV-positive advanced primary pulmonary LELC. The patient was treated with a combination of tislelizumab and chemotherapy, suggesting a desirable clinical response. The rarity of primary pulmonary LELC has posed significant challenges in evaluating the efficacy of such therapeutic approaches. As a result, there is an emergent necessity for well-designed clinical trials concentrating on combination therapies for rare lung cancers. These studies are not only advantageous for validating the efficacy of such treatments, but also can be enlightening and beneficial for the ongoing optimization of therapeutic strategies for these uncommon malignancies.

Ethics Statement

Written informed consent for the publication of all clinical details and images was obtained from the patient.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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