

Adjuvant immunotherapy plus chemotherapy and maintenance immunotherapy for pulmonary lymphoepithelioma-like carcinoma with hepatitis B virus infection, KRAS mutation and high expression of programmed death ligand 1: A case report

JING ZHU, QING-GUI XU, JIAO ZHU, RUI-XIANG ZHOU, YU-CHUAN ZHOU and ZHI-KE LI

Department of Oncology, The Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan 637000, P.R. China

Received September 6, 2025; Accepted February 9, 2026

DOI: 10.3892/ol.2026.15612

Abstract. Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare subtype of non-small cell lung cancer, often associated with Epstein-Barr virus (EBV) infection. It typically exhibits distinct epidemiological and molecular features compared to other lung malignancies. However, the clinical behavior and optimal therapeutic strategies for PLELC, particularly in the presence of concomitant viral infections or specific genetic mutations, remain poorly defined. This report comprehensively outlines the treatment process of a 58-year-old female patient diagnosed with PLELC in the right middle lobe of the lung. Following surgical resection, the diagnosis was confirmed as PLELC, which was found to be associated with hepatitis B virus (HBV) infection, KRAS mutation and high expression of programmed death ligand 1 (PD-L1). The patient subsequently received adjuvant treatment with immunotherapy (penpulimab) combined with chemotherapy, followed by penpulimab maintenance therapy, resulting in a progression-free survival of >44 months. At present, the patient is still alive and healthy, and can undergo regular follow-ups and re-examinations. Notably, preoperative testing showed a positive EBV status, which became negative post-surgery. This case highlights several key aspects. First, it examines the diagnostic and therapeutic characteristics of PLELC with a positive EBV test result before surgery that turned negative after surgical resection. Second, it assesses the influence of high PD-L1 expression and concurrent HBV infection on the efficacy and safety of immunotherapy. Third, it explores the clinical implications of the KRAS mutation in this unique tumor subtype. The overarching goal of this

exploration is to offer valuable clinical guidance for managing this rare and understudied subtype of lung cancer, particularly in the context of multimodal therapy involving immunotherapy.

Introduction

Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a type of lung cancer that accounts for <1% of all lung cancers. It belongs to non-small cell lung cancer (NSCLC). The stage at diagnosis is usually earlier than that of other NSCLC subtypes; thus, the prognosis is slightly better than that of others. PLELC is highly associated with Epstein-Barr virus (EBV) and is more common in middle-aged Asian women. Histological classification is similar to undifferentiated nasopharyngeal carcinoma (1), both of which are non-keratinized squamous cell carcinomas. Early surgical resection is the main treatment method (2) and chemotherapy also plays an important role. In recent years, the development of lifeomics has brought immunotherapy and targeted therapy into the vision of clinicians (3), making the precision treatment of rare tumors like PLELC possible.

PLELC is characterized by high programmed death ligand 1 (PD-L1) expression and lack of a driver gene: A 2020 study of 86 patients with PLELC showed that the PD-L1 expression rate was up to 78.9% (4). Among them, 47 cases were tested genetically, and only PD-L1 was positive. The proportion of PD-L1 expression in other studies with small sample sizes may not be statistically reliable. In 2022, a real-world study from five cancer centers in China was reported (5). A total of 770 patients with LELC were included, among which 598 were patients with PLELC. This was the largest sample size reported so far. Among 770 cases with LELC, 34 cases were tested for PD-L1, of which 25 cases were positive (73.5%) and 16 cases had high expression. At the same time, 305 cases were subjected to gene detection: 10 cases had an EGFR mutation, 3 cases had an anaplastic lymphoma kinase rearrangement, 7 cases had a tumor protein 53 gene mutation, 2 cases had a Notch receptor mutation and >90% of patients had no driver gene. Compared to a brief review in 2020 (6), the results of both studies are largely similar. Notably, the former included multi-site LELC, while the latter focused

Correspondence to: Dr Zhi-Ke Li, Department of Oncology, The Affiliated Hospital of North Sichuan Medical College, 1 Maoyuan South Road, Shunqing, Nanchong, Sichuan 637000, P.R. China
E-mail: lizhike1990@163.com

Key words: pulmonary lymphoepithelioma-like carcinoma, KRAS mutation, programmed death ligand 1, hepatitis B virus, adjuvant treatment, penpulimab

solely on PLELC and all had negative KRAS mutations. The latter is a clearly more valuable reference, and in addition, selection bias in retrospective studies cannot be ignored. Based on these research findings, the relationship between high PD-L1 expression and prognosis in PLELC is yet to be fully understood. The correlation between high expression of PD-L1 and prognosis in PLELC remains elusive, as this is based solely on case reports, which often contradict each other. On the one hand, a meta-analysis in 2017 showed that PD-L1 expression is an unfavorable biomarker in PLELC and NSCLC, mainly manifested by reducing the overall survival. Additionally, increased PD-L1 expression is not associated with KRAS mutations (7). On the other hand, a 60-year-old Japanese woman with EBV-positive PLELC also had high PD-L1 expression. And after surgery, this patient was followed up for 30 months without recurrence (8). In clinical practice, the active use of immune checkpoint inhibitors is generally recommended and numerous patients appear to benefit from it (9). The impact of high PD-L1 expression on the prognosis of PLELC remains elusive and further research is still needed to elucidate its potential relationship. In pulmonary PLELC, the absence of mutations (or wild-type status) in relevant genes is a common finding. The co-occurrence of high PD-L1 expression and KRAS mutations is even rarer, with no documented cases in recent literature. KRAS mutations often mean that anti-EGFR treatment is ineffective, with fewer options and worse prognosis (10). Therefore, special efforts are needed when treating such patients, and identifying the patients and providing appropriate treatment plans are crucial.

Case report

In February 2021 (first visit), a 58-year-old woman was admitted to a local hospital due to cough and sputum. Chest CT revealed a 2-cm nodule in the middle lobe of the right lung. Due to personal reasons, no special treatment was given. In November 2021, the chest CT found that the nodule had increased to 3.8 cm, and thus, the patient came to Sichuan Northern Medical College Affiliated Hospital (Nanchong, China) for treatment. During the course of the disease, the patient occasionally coughed with white frothy sputum, without dyspnea or other discomforts. The Eastern Cooperative Oncology Group score was 1 (11). No significant medical, personal, marital, reproductive, menstrual or family history was found. On November, 2021, an enhanced chest CT scan, followed by a high-resolution CT and reconstruction, were performed. The CT scan showed a plain scan with enhanced imaging: Soft tissue nodules in the medial segment of the right middle lobe of the lung, mostly tumor-related lesions, possibly lung cancer. No metastasis was observed in the brain or bones. In November 2021, the preoperative screening for infectious diseases suggested that hepatitis B surface antigen (HBsAg) was >130 IU/ml (normal, <0.05 IU/ml) and hepatitis B E antigen was 1,322 S/CO (normal, 0.000-0.009 S/CO). Hepatitis B E antibodies, hepatitis B surface and hepatitis B core antibody were negative, and liver function tests indicated that aspartate aminotransferase (AST) was 37 U/l (normal range, 13-25 U/l) and alanine aminotransferase (ALT) was 27 U/l (normal range, 7-40 U/l). The diagnosis of HBV was consistent. However, HBV DNA testing was not performed

at this time, and further diagnosis and treatment were not performed.

Surgery was scheduled for November 2021: Under general anesthesia, the patient underwent thoracoscopic resection of the right middle lobe of the lung, thoracoscopic intrathoracic lymph node dissection, thoracoscopic adhesion lysis of the pleura and closed thoracic drainage (intraoperative frozen section pathology report from November 2021). Standard H&E staining procedure: After tissue was fixed with 4% formaldehyde, 4-5 μm paraffin sections were prepared. The staining steps included hematoxylin nuclear staining for 5-10 min, followed by differentiation and bluing, then eosin cytoplasmic staining for 1-3 min, and finally dehydration and mounting. Observation was performed using a brightfield microscope with typical magnifications of 40x (scale bar, $\sim 20 \mu\text{m}$) or 200x (scale bar, $\sim 5 \mu\text{m}$). The diagnosis for the 'right middle lobe' sample was cancer, suspected as squamous cell carcinoma. In December 2021 (this was from an analysis of the previous sample from November), the pathology report indicated the following: 'Right middle lobe' invasive cancer with pleural invasion, no residual cancer at the bronchial, vascular or lung ends. Immunohistochemistry (IHC): Thyroid transcription factor-1 (TTF-1) (-), novel aspartic proteinase A (Napsin A) (-), cytokeratin 5/6 (CK5/6) (+), P40 protein (P40) (+), Epstein-Barr virus (EBV)-encoded small RNA (EBER) (+), proliferation index (Ki-67) (+, $\sim 50\%$), supporting a diagnosis of PLELC of the right middle lobe (Fig. 1). IHC protocol summary: Samples were fixed in 10% neutral buffered formalin for 24-48 h at room temperature (RT). After paraffin-embedding, they were sectioned at 4-5 μm . Following heat-induced epitope retrieval (e.g., citrate buffer, 95-100°C, 20 min), samples were blocked with 5% normal serum (RT, 1 h). They were then incubated with primary antibody (4°C overnight) and then with HRP-conjugated secondary antibody (RT, 1 h). The following primary antibodies were used: TTF-1 (cat. no. 2509170599d; dilution, ready-to-use); Napsin A (cat. no. 250806074d; dilution, ready-to-use); CK5/6 (cat. no. 2509110744c6; dilution, 1:100); P40 (cat. no. 2510291006e; dilution, ready-to-use); Ki-67 (cat. no. 2511260731C7; dilution, 1:150; all from Fuzhou Maixin Biotechnology Development Co., Ltd) and PD-L1 (cat. no. P04565CN-03; dilution, 1:50; Dako; Agilent Technologies, Inc.). Secondary antibodies: General-purpose (cat. no. DD23; dilution, ready-to-use; Xiamen Talent Biomedical Technology Co., Ltd.). Staining was visualized with diaminobenzidine and counterstaining with hematoxylin was performed, followed by observation with a light microscope.

Hybridization *in situ*: EBER monoclonal antibody (cat. no. 25080502; dilution, ready-to-use; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.). The patient only underwent *in situ* hybridization (ISH) testing on the lung tumor tissue resected by surgery, and no fluorescence ISH (FISH) testing was performed. ISH was performed using the EBER Detection Kit (In Situ Hybridization; product code, ISH-7001; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.) according to the manufacturer's instructions. Previous experience suggests that FISH is not a routine testing method for lung cancer (12).

Histological examination revealed infiltration by numerous lymphocytes and plasma cells. IHC analysis confirmed squamous cell carcinoma (positive for cytoplasmic CK5/6 and nuclear P40) and ruled out an adenocarcinoma component

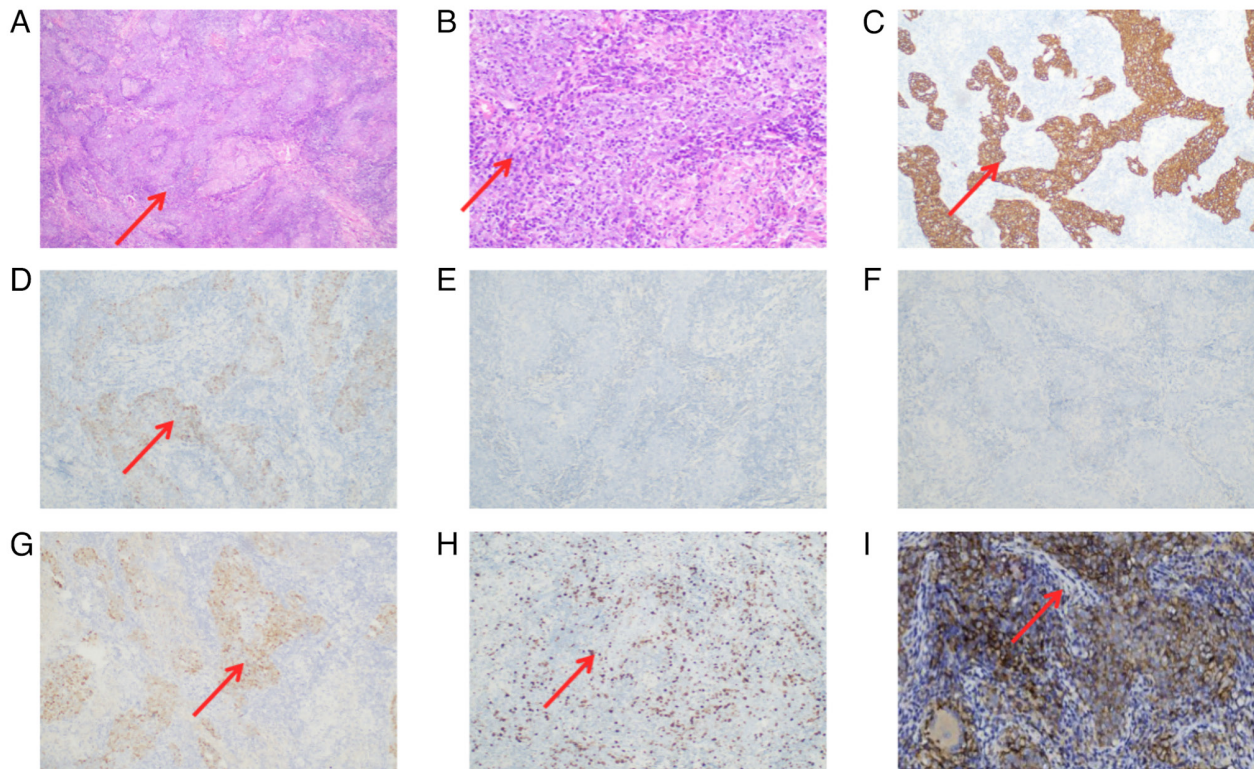


Figure 1. Pathology and IHC of the pulmonary lymphoepithelioma-like carcinoma. (A and B) Histological analysis. (A) heterologous cells were arranged in clusters (magnification, x40); (B) the nuclei of heterologous cells were vacuolated and the nucleoli were clear (magnification, x200; H&E staining); the arrows point at heterologous cells. (C-I) IHC analysis. (C) Cytoplasmic CK5/6 was positive, the arrows point at positive CK5/6 cytoplasm; (D) nuclear P40 was positive; the arrows point at positive P40 nuclear; (E) thyroid transcription factor-1 was negative; (F) Napsin A was negative; (G) nuclear EBER was positive; the arrows point at positive EBER nuclear; (H) proliferation index Ki-67 positive ~50%, the arrows point at positive Ki-67 nuclear; (I) PD-L1 detection microscopic image: Tumor proportion score=55% (magnification, x100), the arrows point at positive PD-L1 nuclear. CK, cytokeratin; PD-L1, programmed cell death ligand 1; EBER, Epstein-Barr virus-encoded small RNA; IHC, immunohistochemistry.

(negative for TTF-1 and Napsin A; if present, the diagnosis would be adenosquamous carcinoma). Serological testing revealed EBV antibody seropositivity, which is consistent with an Epstein-Barr virus infection. Together, these findings fulfill the gold-standard criteria for diagnosing pulmonary lymphoepithelioma-like carcinoma (PLELC) (1).

Postoperative staging was pT2aN0M0, stage IB (American Joint Committee on Cancer, 8th edition) (13). In January 2022, a targeted drug therapy 10 gene test (14) was performed, revealing a KRAS gene mutation (atypical driving gene). The PD-L1 expression volume was 55% [tumor proportion score: High expression (15)] (Fig. 2). Based on the patient's clinical characteristics and willingness, adjuvant chemotherapy combined with immunotherapy was planned postoperatively. Prior to the start of adjuvant chemoradiotherapy, the patient was considered to have an active HBV infection and was not treated (not given entecavir antiviral treatment). Chemotherapy combined with immunotherapy could potentially re-activate HBV, so an HBV DNA test (9.600×10^7 IU/ml) was performed in January 2022, and entecavir antiviral therapy was initiated once daily, 0.5 mg each time p.o. In February 2022, a follow-up HBV DNA test showed mild elevations in transaminase levels (AST: 75 U/l; ALT: 94 U/l) and the HBV DNA level was 9.220×10^5 IU/ml (normal, <20 IU/ml). Due to the persistent nature of the HBV, it can't be completely eradicated; therefore, long-term maintenance therapy with entecavir is required (16). The PLELC surgery was performed in November, 2021, and

an EBV DNA test was conducted in January 2022, and the result was $<4.000 \times 10^2$ copies/ml. This means that the patient's EBV DNA had become undetectable after surgery (at least 4004.000×10^2 copies/ml is required for detection). As cancer treatment, from January 2022, a penpulimab 200 mg immunotherapy combined with TC regimen (albumin-taxol 300 mg + carboplatin 500 mg, every three weeks) was initiated, and until May 2022, six cycles were given. In June 2022, a chest plain scan with enhanced CT revealed no definite signs of tumor recurrence nor metastasis, with no significant changes compared to that performed in March 2022. From June 2022 to April 2023, the patient received nine cycles of immunomodulatory maintenance therapy with penpulimab 200 mg ivgtt q3w. During the treatment, there were no significant adverse events, and there was no recurrence or metastasis of the tumor. Since April 2023, regular follow-ups have been conducted, with the last follow-up in February 2025. No recurrence or metastasis was found (representative CT images are shown in Fig. 2). The preoperative image from November 2021 shows a lesion measuring 37.21 mm, as indicated by the arrow (Fig. 2A). Before the first postoperative chemotherapy session in January 2022, the lesion was no longer visible (Fig. 2B). Following the first postoperative chemotherapy session in March 2022, no obvious recurrence or metastasis was observed (Fig. 2C). By February 2025, there remained no obvious recurrence or metastasis (Fig. 2D). For patients with pulmonary lymphoepithelioma-like carcinoma undergoing curative

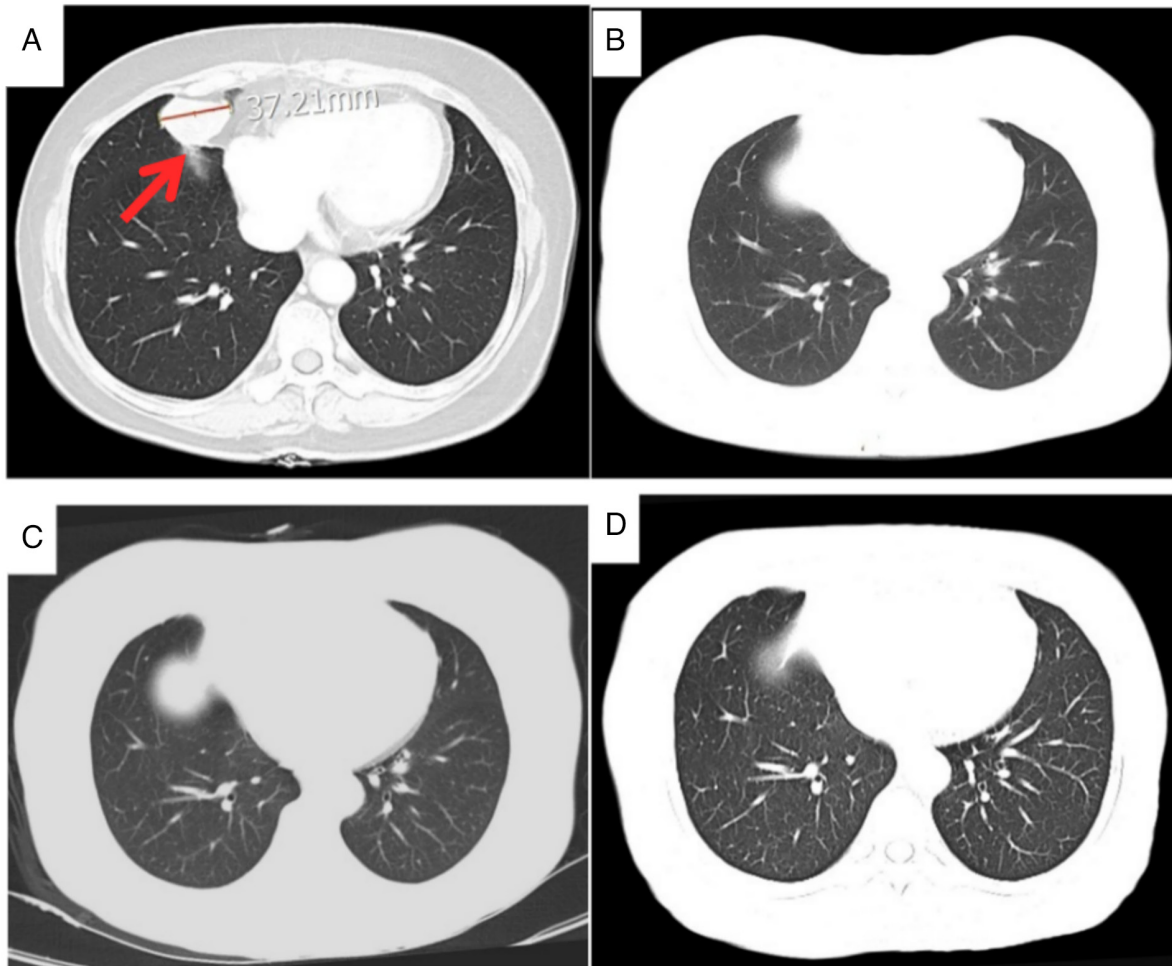


Figure 2. Chest CT images of the pulmonary lymphoepithelioma-like carcinoma patient. (A) Preoperative in November 2021 (lesion measuring 37.21 mm, arrow). (B) Before the first chemotherapy after surgery in January 2022 (the lesion is not visible). (C) After the first chemotherapy session after surgery in March 2022 (no obvious recurrence or metastasis). (D) In February 2025 (no obvious recurrence or metastasis).

treatment, long-term follow-up plans are typically based on time staging: during the first 3 years after treatment (high-risk period), a medical history review, physical examination, and enhanced chest CT scan are recommended every 6 months. Therefore, the next follow-up appointment is expected to be in October 2025, and the patient didn't complain of any abnormalities by telephone follow-up in July 2025.

Discussion

LELC is a rare tumor that can occur in various locations, including the nasopharynx, tonsils, tongue, digestive system, bladder and lungs. In 2015, the World Health Organization noted that the lungs are one of the most common sites for this type of cancer, with 90% of patients testing positive for EBV (1,2,5,17). A positive EBER result in IHC is the gold standard for diagnosing this condition and serves as a key method for differentiation (1). The treatment and prognosis of the disease are influenced by several factors, including the tumor location (18) the PD-L1 expression status and the type of gene mutation (19). The case of the present study involved PLELC in the middle lobe of the right lung, similar to other types of lung cancer, with the main symptom being a cough. Due to the lack of specific imaging features (20) chest CT can

only provide a preliminary diagnosis of lung cancer. Pathology confirms the characteristics of squamous cell carcinoma, and a definitive diagnosis ultimately relies on IHC. The pathology results for the present case indicated the presence of atypical cell proliferation arranged in nests, suggesting squamous cell carcinoma. High Ki-67 expression was present, with ~50% of cell nuclei being positive. Ki-67 is a tumor growth marker and also has prognostic significance (21,22).

Currently, there is no specific treatment for PLELC. Early-stage cases are typically treated with surgery, while those in the intermediate to late stages often follow the treatment protocols for NSCLC (23). This case has certain key features: i) EBV was positive before surgery but turned negative after surgery. ii) High PD-L1 expression combined with KRAS mutation and chronic HBV infection. EBV-negative LELC has been observed in Caucasians (5), but this case differs from traditional clinical epidemiology, as it involves a middle-aged Asian woman whose EBV test was positive at the preoperative, while negative at the postoperative stage. The mechanisms of EBV infection and tumor development are not fully understood. A 2018 study suggested that the pathogenesis of related malignant tumors may be closely linked to unique epigenetic dysregulation (24). Another 2025 study found that in nasopharyngeal carcinoma, EBV infection is associated with

AKT3 signaling, but this correlation has not been confirmed in PLELC (25). Postoperative IHC confirmed EBER positivity, which helped diagnose the patient, demonstrating the competence of our pathologists and preventing misdiagnosis as common lung squamous cell carcinoma (26), which could have affected treatment. Preoperative biopsy or routine blood EBV testing for lung malignancies can reduce misdiagnosis rates and provide more reliable data for clinical practice and academic research. Studies have shown that neoadjuvant immunotherapy is a viable strategy (27), which necessitates preoperative biopsies. One of the interesting aspects of this case is the change in EBV. The clinical value of dynamic monitoring of EBV (preoperative positivity → postoperative negativity) urgently needs validation. This viral kinetic feature may reflect immune reconstitution or a reduction in tumor burden (28), but there is currently a lack of prospective studies to confirm its association with long-term survival rates. The patient's PD-L1 expression level was as high as 55%; it is a key factor in improving the prognosis of immunotherapy, which has been validated in most studies. It marks that the patient's immune system has identified and is attempting to attack the tumor (29). Common first-line immunotherapeutic agents include pembrolizumab, sintilimab and durvalumab, while second-line immunotherapy often involves Nivolumab. Combining these with chemotherapy can enhance treatment efficacy (30). Penpulimab, a novel domestic PD-L1 inhibitor (31), offers similar efficacy and better safety compared to other immunotherapeutic drugs (32). When combined with chemotherapy, it can be used as a first-line treatment for locally advanced or metastatic squamous cell carcinoma (33). To date, the patient of the present study has survived for >44 months without any significant immune-related adverse events, making it a valuable reference for the clinical application of Penpulimab in such patients. Considering the potential allergic reactions to paclitaxel and the renal toxicity of cisplatin, the patient opted for albumin-bound paclitaxel combined with carboplatin as the treatment regimen, which is the most common and effective platinum-based double-drug chemotherapy regimen for NSCLC (34).

Under the guidance principle of precision tumor treatment, targeted therapy is a necessary consideration. The patient had a KRAS mutation and the possibility of targeted therapy exists. However, in clinical practice, drugs targeting KRAS mutations are not satisfactory in terms of efficacy and safety (35), which may be due to the widespread and complex metabolic changes caused by the reduction of guanosine triphosphate activity of the KRAS gene (36). He *et al* (37) compared 22 studies and found that chemotherapy combined with immunotherapy can serve as the first-line treatment for KRAS-mutated NSCLC, and the combination with anti-angiogenesis may offer better outcomes. Currently, KRAS inhibitors (targeting G12C) are in clinical trials, such as the GFH925 study (38), the LY3537982 study (39) and the AseBreaK 101 study (40). As clinical trials progress, it is possible that KRAS inhibitors could become the first-line treatment for KRAS-mutated NSCLC and potentially for PLELC. The patient refused targeted therapy due to personal reasons. As a clinical physician, it is also important to consider the impact of HBV on treatment and prognosis. Research data indicate that immunotherapy can indeed lead to the reactivation of the HBV in certain HBsAg seropositive

patients (41); even for neoadjuvant immunotherapy, it is essential to first screen for HBsAg. Recently, researchers have developed a model to predict the prognosis of PLELC (42). This model showed that positivity for HBsAg is significantly associated with overall survival (hazard ratio=2.028, P=0.023), making it an independent risk factor. The study also highlights that immunotherapy is a significant option for improving the prognosis of PLELC. The patient in question had a high DNA load of HBV infection, which was controlled after treatment, but continued monitoring is necessary in subsequent treatments. Unfortunately, current clinical studies generally lack patient cohorts that simultaneously have KRAS mutations, high PD-L1 expression (≥50%) and HBsAg+. The immune treatment response for this triple-feature population has remained to be clearly defined, and there is an urgent need for prospective large-scale trials to verify its safety and efficacy.

In summary, the present study reported a case of PLELC with KRAS mutations, high PD-L1 expression and concurrent HBV infection. The patient received adjuvant immunotherapy plus chemotherapy and maintenance immunotherapy post-surgery, achieving an ongoing progression-free survival of >44 months. This suggests that adjuvant immunotherapy plus chemotherapy, along with maintenance immunotherapy, could be an option for treating such patients. To date, one study has been conducted (43), but more data and individualized treatment are still needed.

Acknowledgements

Not applicable.

Funding

This work was financially supported by the National Natural Science Foundation of China (grant no. 82202976) and the Dr Pioneer Foundation of North Sichuan Medical College (grant no. CBY21-QD18).

Data availability statements

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

Authors' contributions

JinZ was responsible for methodology, investigation [the systematic collection, collation, and analysis of the clinical data for this case report (including medical history, laboratory tests, imaging, and pathological data), participation in clinical discussions regarding the case, and review of relevant literature to provide the core data and rationale for the report], language editing, obtaining materials, visualization and writing-original draft. QX, JiaZ, RZ and YZ were involved in methodology, investigation [the systematic collection, collation, and analysis of the clinical data for this case report (including medical history, laboratory tests, imaging, and pathological data), participation in clinical discussions regarding the case, and review of relevant literature to provide the core data and rationale for the report] and obtaining materials, writing-original draft, language editing and providing general supervision. ZL performed investigation

[the systematic collection, collation, and analysis of the clinical data for this case report (including medical history, laboratory tests, imaging, and pathological data), participation in clinical discussions regarding the case, and review of relevant literature to provide the core data and rationale for the report], methodology, supervision, writing-original draft and writing-review & editing, and obtained funding. All authors have read and approved the final manuscript. All authors have verified and confirmed the authenticity of the original data.

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (Nanchong, China; approval no. 2025ER426-1).

Patient consent for publication

The patient provided written informed consent for the publication of the clinical data and images.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, an AI tool, Yuanbao v2.57.10.150 (<https://yuanbao.tencent.com>), was used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

- Qin Y, Gao G, Xie X, Zhu Z, Guan W, Lin X, Xie Z, Ming O, Chen R, Zhong N, *et al.*: Clinical features and prognosis of pulmonary Lymphoepithelioma-like carcinoma: Summary of Eighty-five cases. *Clin Lung Cancer* 20: e329-e337, 2019.
- Lin Z, Fu S, Zhou Y, Zhang X, Chen C, He LN, Li H, Wang Y, Chen T, Zhang L and Hong S: First-line platinum-based chemotherapy and survival outcomes in locally advanced or metastatic pulmonary lymphoepithelioma-like carcinoma. *Lung Cancer* 137: 100-107, 2019.
- Zhang J, Lin L, Li W and Guo J: Role of the 'inflammation-immunity-abolism' network in non-small cell lung cancer: A multi-omics analysis. *Discov Oncol* 16: 847, 2025.
- Chen J, Gu C, Chen X, Dai C, Zhao S, Xie H, Fei K and Chen C: Clinicopathological and prognostic analyses of 86 resected pulmonary lymphoepithelioma-like carcinomas. *J Surg Oncol* 123: 544-552, 2021.
- Chen M, Chen Y and Fang X: Clinical features and treatment outcome of lymphoepithelioma-like carcinoma from multiple primary sites: A population-based, multicentre, real-world study. *BMC Pulm Med* 22: 360, 2022.
- Hu Y, Ren S, Liu Y, Han W and Liu W: Pulmonary Lymphoepithelioma-Like Carcinoma: A Mini-review. *Onco Targets Ther* 13: 3921-3929, 2020.
- Zhang M, Li G, Wang Y, Wang Y, Zhao S, Haihong P, Zhao H and Wang Y: PD-L1 expression in lung cancer and its correlation with driver mutations: A meta-analysis. *Sci Rep* 7: 10255, 2017.
- Sasaki A, Kato T, Ujiie H, Cho Y, Sato M and Kaji M: Primary pulmonary lymphoepithelioma-like carcinoma with positive expression of Epstein-Barr virus and PD-L1: A case report. *Int J Surg Case Rep* 79: 431-435, 2021.
- Zhong YM, Yin K, Chen Y, Xie Z, Lv ZY, Yang JJ, Yang XN, Zhou Q, Wang BC, Zhong WZ, *et al.*: PD-1/PD-L1 combined with LAG3 is associated with clinical activity of immune checkpoint inhibitors in metastatic primary pulmonary lymphoepithelioma-like carcinoma. *Front Immunol* 13: 951817, 2022.
- Yin K, Feng HB, Li LL, Chen Y, Xie Z, Lv ZY, Guo WB, Lu DX, Yang XN, Yan WQ, *et al.*: Low frequency of mutation of epidermal growth factor receptor (EGFR) and arrangement of anaplastic lymphoma kinase (ALK) in primary pulmonary lymphoepithelioma-like carcinoma. *Thorac Cancer* 11: 346-352, 2020.
- Sok M, Zavrl M, Greif B and Srpčič M: Objective assessment of WHO/ECOG performance status. *Support Care Cancer* 10: 3793-3798, 2019.
- Becnel D, Abdelghani R, Nanbo A, Avilala J, Kahn J, Li L and Lin Z: Pathogenic role of Epstein-Barr virus in lung cancers. *Viruses* 13: 877, 2021.
- Kutob L and Schneider F: Lung cancer staging. *Surg Pathol Clin* 13: 57-71, 2020.
- Wu YX, Zhang WL, Wang TM, Liao Y, Zhang YJ, Xiao RW, Jia YJ, Wu ZY, Deng CM, Yang DW, *et al.*: Genomic landscapes of Epstein-Barr virus in pulmonary Lymphoepithelioma-Like carcinoma. *J Virol* 96: e0169321, 2022.
- Zhao X, Bao Y, Meng B, Xu Z, Li S, Wang X, Hou R, Ma W, Liu D, Zheng J, *et al.*: From rough to precise: PD-L1 evaluation for predicting the efficacy of PD-1/PD-L1 blockades. *Front Immunol* 13: 920021, 2022.
- Shi M, Sun WL, Hua YY, Han B and Shi L: Effects of entecavir on hepatitis B virus covalently closed circular DNA in hepatitis B e antigen-positive patients with hepatitis B. *PLoS One* 10: e0117741, 2015.
- Bégin LR, Eskandari J, Joncas J and Panasci L: Epstein-Barr virus related lymphoepithelioma-like carcinoma of lung. *J Surg Oncol* 36: 280-283, 1987.
- Samaras MG, Koufopoulos NI, Mitsos S, Dylja E, Monokrousou A, Tomos P, Panayiotides IG and Goutas D: Lymphoepithelial carcinoma of the lung: A case report and review of the literature. *Cureus* 16: e70309, 2024.
- Zhai X, Liu J, Lu D and Zhou Q: Demographics, clinical features, and prognosis of rare lymphoepithelioma-like carcinoma across different anatomic sites. *J Egypt Natl Canc Inst* 34: 5, 2022.
- Mo Y, Shen J, Zhang Y, Zheng L, Gao F, Liu L and Xie C: Primary lymphoepithelioma-like carcinoma of the lung: Distinct computed tomography features and associated clinical outcomes. *J Thorac Imaging* 29: 246-251, 2014.
- Sun X and Kaufman PD: Ki-67: More than a proliferation marker. *Chromosoma* 127: 175-186, 2018.
- Menon SS, Guruvayoorappan C, Sakthivel KM and Rasmi RR: Ki-67 protein as a tumour proliferation marker. *Clin Chim Acta* 491: 39-45, 2019.
- Zhang L, Zheng J, Fang LJ, Zhang L and Zhou JY: Efficacy analysis of PD-1/PD-L1 inhibitors in the treatment of advanced primary pulmonary lymphoepithelioma-like carcinoma: 6 case reports and literature review. *Zhonghua Zhong Liu Za Zhi* 46: 590-594, 2024 (In Chinese).
- Li L, Ma BBY, Chan ATC, Chan FKL, Murray P and Tao Q: Epstein-Barr Virus-induced epigenetic pathogenesis of Viral-associated Lymphoepithelioma-like carcinomas and natural Killer/T-cell lymphomas. *Pathogens* 7: 63, 2018.
- Tan B, Xu K, Lyu Y, Liang Y, Liang R, Lei K, Liang J, Huang J, Wang K, Wu D, *et al.*: Single-cell analysis reveals transcriptomic features and therapeutic targets in primary pulmonary lymphoepithelioma-like carcinoma. *Commun Biol* 8: 394, 2025.
- Yin CJ, Wang GJ, Su XM and Li D: Primary pulmonary lymphoepithelioma-like carcinoma misdiagnosed as lung squamous cell carcinoma: A case report. *World J Clin Cases* 11: 7876-7880, 2023.
- Chen J, Fan L, Deng H, Li L and Li S: Neoadjuvant immunotherapy-a promising strategy for primary pulmonary lymphoepithelioma-like carcinoma. *World J Surg Oncol* 22: 338, 2024.
- Li W, Yang C, Lv Z, Li J, Li Z, Yuan X, Wu S, Yuan Y, Cui L, Lu J, *et al.*: Integrating pre- and post-treatment plasma Epstein-Barr virus DNA levels for better prognostic prediction of Nasopharyngeal Carcinoma. *J Cancer* 9: 2715-2722, 2021.
- Tang L, Chen N, He W, Zhou J, Zhang J, Lin Z, Wang Z, Hao J and Lin F: The clinicopathological features and prognosis of primary pulmonary lymphoepithelioma-like carcinoma: A systematic review and meta-analysis. *PLoS One* 15: e0240729, 2020.
- Zhou Y, Huang J, Lan J, Hu H, Yuan Z, Dong L, Deng H, Yue LA, Xiao Y and Yang X: Comparison of first-line immunotherapy efficacy between advanced lung squamous cell carcinoma and pulmonary lymphoepithelioma-like carcinoma: A propensity score matching multicenter study. *J Cancer Res Ther* 19: 1011-1018, 2023.

31. Song Y, Zhou K, Jin C, Qian Z, Hou M, Fan L, Li F, Ding K, Zhou H, Li X, *et al*: Penpulimab for relapsed or refractory classical Hodgkin lymphoma: A multicenter, Single-Arm, pivotal phase I/II Trial (AK105-201). *Front Oncol* 12: 925236, 2022.
32. Huang Z, Pang X, Zhong T, Qu T, Chen N, Ma S, He X, Xia D, Wang M, Xia M and Li B: Penpulimab, an Fc-Engineered IgG1 Anti-PD-1 antibody, with improved efficacy and low incidence of Immune-Related adverse events. *Front Immunol* 13: 924542, 2022.
33. Kaplon H, Chenoweth A, Crescioli S and Reichert JM: Antibodies to watch in 2022. *Mabs* 14: 2014296, 2022.
34. Zhou C, Wu L, Fan Y, Wang Z, Liu L, Chen G, Zhang L, Huang D, Cang S, Yang Z, *et al*: Sintilimab plus platinum and gemcitabine as First-Line treatment for advanced or metastatic squamous NSCLC: Results from a randomized, Double-blind, Phase 3 trial (ORIENT-12). *J Thorac Oncol* 16: 1501-1511, 2021.
35. Tamiya Y, Matsumoto S, Zenke Y, Yoh K, Ikeda T, Shibata Y, Kato T, Nishino K, Nakamura A, Furuya N, *et al*: Large-scale clinico-genomic profile of non-small cell lung cancer with KRAS G12C: Results from LC-SCRUM-Asia study. *Lung Cancer* 176: 103-111, 2023.
36. McCormick F: KRAS as a therapeutic target. *Clin Cancer Res* 21: 1797-1801, 2015.
37. He Q, Liu X, Jiang L, Liu P, Xuan W, Wang Y, Meng R, Feng H, Lv S, Miao Q, *et al*: First-line treatments for KRAS-mutant non-small cell lung cancer: Current state and future perspectives. *Cancer Biol Ther* 26: 2441499, 2025.
38. Gregorc V, González-Cao M, Salvagni S, Koumariou A, Gil-Bazo I, Maio M, Viteri S, Majem M, Gutiérrez V, Bernabe Caro R, *et al*: KROCUS: A phase II study investigating the efficacy and safety of fulzerasib (GFH925) in combination with cetuximab in patients with previously untreated advanced KRAS G12C mutated NSCLC. *J Clin Oncol* 42: LBA8511, 2024.
39. Burns TF, Dragnev KH, Fujiwara Y, Murciano-Goroff YR, Lee DH, Hollebecque A, Koyama T, Cassier PA, Italiano A, Heist RS, *et al*: Efficacy and safety of olomorasib (LY3537982), a second-generation KRAS G12C inhibitor (G12Ci), in combination with pembrolizumab in patients with KRAS G12C-mutant advanced NSCLC. *J Clin Oncol* 42: 8510, 2024.
40. Kuboki Y, Fakhri M, Strickler J, Yaeger R, Masuishi T, Kim EJ, Bestvina CM, Kopetz S, Falchook GS, Langer C, *et al*: Sotorasib with panitumumab in chemotherapy-refractory KRASG12C-mutated colorectal cancer: A phase 1b trial. *Nat Med* 30: 265-270, 2024.
41. Zhang X, Zhou Y, Chen C, Fang W, Cai X, Zhang X, Zhao M, Zhang B, Jiang W, Lin Z, *et al*: Hepatitis B virus reactivation in cancer patients with positive Hepatitis B surface antigen undergoing PD-1 inhibition. *J Immunother Cancer* 7: 322, 2019.
42. Chen X, Liu T, Mo S, Yang Y, Chen X, Hong S, Zhou T, Chen G, Zhang Y, Ma Y, *et al*: A Novel Inflammation-Marker-Based prognostic model for advanced pulmonary Lymphoepithelioma-Like carcinoma. *J Inflamm Res* 18: 2433-2445, 2025.
43. Yang X, Xiao Y, Zhou Y, Hu H, Deng H, Huang J, Liang M, Yuan Z, Dong L and Huang S: Efficacy and safety of immunotherapy in locally advanced or metastatic pulmonary lymphoepithelioma-like carcinoma: A multicenter retrospective study. *Ther Adv Med Oncol* 17: 17588359251316099, 2025.



Copyright © 2026 Zhu et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.