Case Report

EBV-positive Primary Pulmonary Lymphoepithelioma-like Carcinoma Response to PD-L1 Blockade

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Clinical Practice Points

- Primary pulmonary LELC is a rare form of lung cancer; similar to NPC, it is associated with EBV infection.
- In addition, pulmonary LELC and NPC share histologic properties and regional and ethnic distributions of incidence.
- Immune checkpoint blockade has been investigated in NPC, with evidence of clinical activity comparable to that of other solid tumor types for which PD-1 and PD-L1 immune checkpoint inhibitors have been approved.
- However, little is known about the clinical activity of PD-1 and PD-L1 immune checkpoint inhibitors in pulmonary LELC, and clinical trials of this unique histologic subtype of lung cancer are unlikely owing to the rare occurrence of this malignancy.
- We have presented a patient case of the PD-L1 inhibitor atezolizumab, demonstrating clinically activity in pulmonary LELC.

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Introduction

Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare form of lung cancer that was once classified as a subtype of large cell carcinoma, a form of non–small-cell lung cancer (NSCLC). However, in the latest 2015 World Health Organization tumor classification, pulmonary LELC has been recategorized to "other or unclassified carcinoma."[1] Bégin et al[2] first discovered and described primary pulmonary LELC in 1987, recognizing its clinical similarities to nasopharyngeal carcinoma (NPC) and its association with Epstein-Barr virus (EBV). LELC shares many histologic properties with lymphoepithelioma, a subtype of NPC, and is very lymphocyte-rich, nonkeratinizing, and poorly differentiated.[3] Promising results in phase Ib and III trials have led to the approval of pembrolizumab and nivolumab for head and neck squamous cell carcinoma (HNSCC).[4,5] Our increasing understanding of immune checkpoint blockade, a method by which tumors can downregulate the immune system and escape recognition, partially mediated by programmed cell death-1 (PD-1) and its ligand, PD-L1, is being exploited with the use of anti-PD1 or anti–PD-L1 monoclonal antibodies.

Case Report

A 76-year-old never smoking woman of East Asian descent presented to her primary care clinic complaining of unrelenting cough for 2 months with occasional pleurisy, trace hemoptysis, night sweats, and a 5- to 10-lb unintentional weight loss over this time. The chest radiograph showed a lobulated mass in the lingula measuring ~5 cm in diameter and adjoining the hilum. Computed tomography (CT) of the chest showed a bulky left hilar tumor invading the left upper lobe and bulky mediastinal lymphadenopathy.

Fluorodeoxyglucose (FDG) positron emission tomography/CT showed this mass to be 6.8 × 4.8 cm with a maximum standardized uptake value of 16.4 g/mL. The mass was also intimately associated with the pericardium. Pericardial effusion without FDG activity was

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found. Significant hypermetabolic mediastinal lymphadenopathy was noted. A biopsy was performed, and immunohistochemical staining was positive for P40 and AE1/AE3. Our multidisciplinary thoracic tumor board diagnosed stage IV (T2N2M1a) NSCLC based on the tumor size, ipsilateral mediastinal lymph node involvement, and pericardial effusion. In situ hybridization for EBV-encoded small RNA expression performed on the biopsy sample showed diffuse and strong nuclear expression in the tumor cells (Figure 1). PD-L1 staining using the Ventana SP142 assay (Roche Diagnostics, Risch-Rotkreuz, Switzerland) also demonstrated TC3/IC3 expression ($\geq$ 50% PD-L1 staining in the tumor and $\geq$ 10% in the tumor-infiltrating immune cells). The findings from molecular testing were negative for mutations in *EGFR* and *KRAS* and negative for rearrangements in *ALK* and *ROS1*. Broader genomic profiling was not performed. A flexible fiberoptic examination by otolaryngology staff showed no evidence of cancer in the nasopharynx.

The first treatment regimen was carboplatin, paclitaxel, and cetuximab in a clinical trial. The patient initially responded well and achieved a partial response to the therapy. However, 4 months later, the FDG-positron emission tomography/CT scan showed an increase in the size of the primary mass and spread of tumor to her right (contralateral) supraclavicular lymph nodes. She underwent stereotactic body radiation therapy to the growing disease.

Two months later, CT imaging demonstrated significant progression of disease. Her right supraclavicular lymphadenopathy had now formed a confluent focal mass, palpable by physical examination. Subsequently, the patient was administered atezolizumab 1200 mg IV every 21 days. After 2 cycles, her cough and sputum production had improved significantly. The CT scan highlighting improvement in the burden of disease after 4 cycles is shown in Figure 2. The primary mass had decreased by 78% using the Response Evaluation Criteria In Solid Tumors, version 1.1, guidelines, and the lymphadenopathy had improved. She did not experience any immune-related adverse events. Four months later, after completing her sixth cycle of atezolizumab, the patient began experiencing worsening of her cough. A CT scan showed increasing perihilar consolidation and a new consolidation in the right middle lobe. Biopsy showed this to be a progression of her disease. Her therapy was subsequently switched to docetaxel and then to gemcitabine. She survived her primary pulmonary LELC for another 18 months.

Discussion

In the present case, we have described the oncologic history of a patient with stage IV primary pulmonary LELC. A case report of 2 patients with LELC responding to the PD-1 antibody was recently reported.[6] To the best of our knowledge, the present case is the first report of primary pulmonary LELC responding favorably to blockade with a PD-L1 antibody. Our patient experienced a partial response to atezolizumab, an anti–PD-L1 antibody, for 6 cycles that lasted 4 months. During this time, her tumor burden had decreased significantly, and the therapy had offered her some respite from her pulmonary symptoms and improvement of her functional status with minimal side effects.

Pulmonary LELC is a rare malignancy, estimated to represent 0.15% to 3.6% of all lung malignancies and frequently overlooked in the differential diagnosis.[7] It is more commonly found among specific ethnic and geographic groups, including people of Chinese, Japanese, Taiwanese, and Eskimo origin, and most cases have been reported in Southeast Asia, specifically Hong Kong, Taiwan, and Guangdong.[8] Thus, most studies have come from these regions, rather than from the west. The patients included in the reported studies have been younger, nonsmoking patients. In addition, a strong association has been found between LELC and positive EBV serology in Asian populations.[3,9-11] The present patient was from

Figure 1 (A) Hematoxylin and Eosin and (B) Programmed Cell Death Ligand 1 (SP142 Assay) Staining and (C,D) Epstein-Barr Virus In Situ Hybridization of Tumor

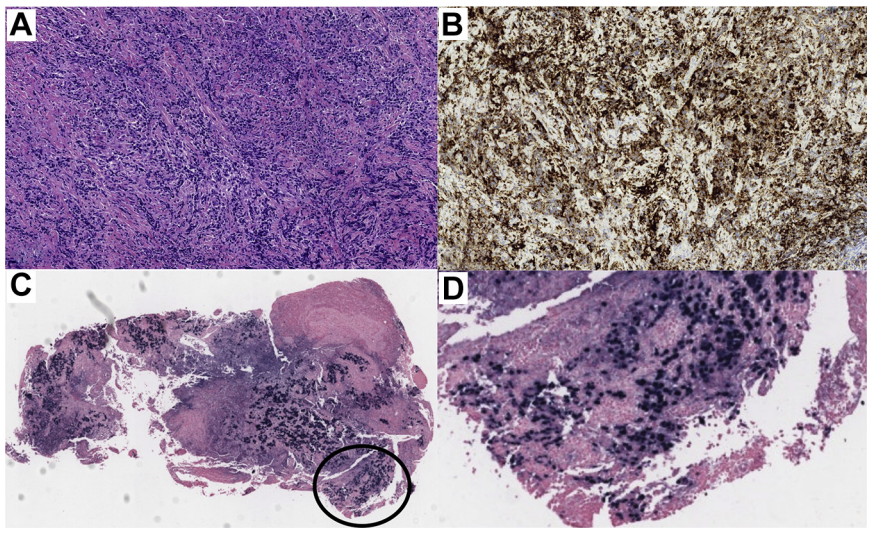
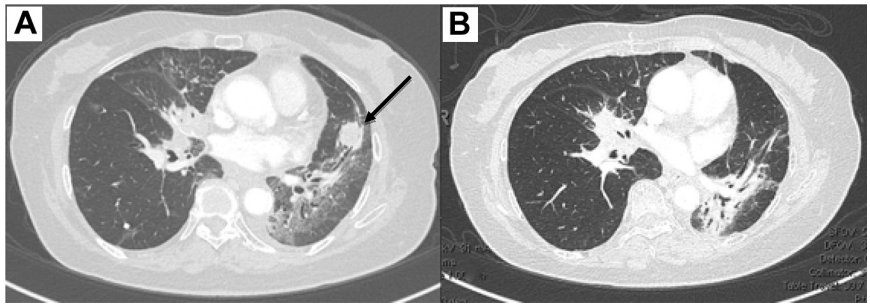


Figure 2 Computed Tomography Images Demonstrating (A) Baseline and (B) Maximal Response After 4 Cycles of Atezolizumab



Guangzhou, the capital of the province of Guangdong in Southern China and was a never smoker.

Because pulmonary LELC is rare, only 12-case series with a total of 501 cases have been described since its discovery in 1987, and definitive treatment strategies have yet to be established.[6] Tumors that are histologically similar to NPC have been reported to indicate a more favorable prognosis.[8,11] Studies of immunotherapy for NPC and other HNSCCs have yielded positive results. In the KEYNOTE-012 study, a phase 1b trial, pembrolizumab, an anti−PD-1 therapy, was well tolerated and produced an overall response rate in 18% of patients with HNSCC. The response rate for nivolumab, another anti−PD-1 antibody, was 13.3% compared with 5.8% for the standard therapy group in the CheckMate 141 study, a phase III trial, comparing nivolumab and single-agent systemic therapy (methotrexate, docetaxel, or cetuximab). A multicenter study of 44 patients with NPC treated with nivolumab showed promising results, demonstrating an objective response rate of 20.5%, with 1 patient having a complete response and 8 patients showing a partial response.[12]

Atezolizumab is an engineered human monoclonal antibody of an IgG1 subtype against PD-L1. Disruption of the interaction between PD-1 on activated T cells and PD-L1 on tumor cells mediates immune escape by downregulating T-cell activation and the production of proinflammatory cytokines.[13] Checkpoint antibodies have been demonstrated to be safe and effective in many patients. In a meta-analysis that included 9 studies evaluating the safety and efficacy of anti−PD-1/PD-L1 for NSCLC, the odds ratio for total adverse events compared with receiving docetaxel was 0.36.[14] The phase III OAK study (a study of atezolizumab compared with docetaxel in participants with locally advanced or metastatic non−small-cell lung cancer who have failed platinum-containing therapy), comparing atezolizumab to docetaxel for advanced NSCLC, found the median overall survival to be longer in the immunotherapy intention-to-treat group (13.8 vs. 9.6 months).[15]

Unlike other non−smoking-associated NSCLC types, the driver mutations in pulmonary LELC are rare. In a retrospective study of 66 patients with biopsy-confirmed LELC, only 8 patients (12.12%) carried an *EGFR* mutation. No patient had *KRAS* or *BRAF* mutations or rearrangements of *ALK* and *ROS1*. However, in the same cohort, 50 patients (75.8%) had positive immunohistochemical staining of PD-L1, defined as > 5% positive staining of malignant cells.[16] Many cancers, including pulmonary LELC, NPC, NSCLC, renal cell carcinoma, melanoma, and others, have been shown to upregulate PD-L1. The present patient's pulmonary LELC was TC3/IC3, indicating high PD-L1 expression (Figure 1). These patients have seemed to benefit the most in terms of the clinical efficacy from atezolizumab.[15] It is also believed that EBV infection in those with pulmonary LELC results in progression and evasion of host immune attacks.

Conclusion

We have reported the case of a patient with metastatic EBV-positive primary pulmonary LELC, a rare form of lung cancer with similarities to NPC with TC3/IC3 expression in the tumor. Our patient responded well to checkpoint antibody therapy with atezolizumab (anti−PD-L1 antibody). Owing to the rarity of this type of cancer, the diagnosis can be difficult. In addition, treatment strategies have not been established and have generally followed the NSCLC guidelines. Although the effectiveness of checkpoint inhibition in pulmonary LELC will be difficult to assess owing to the low incidence rate, the findings from the present case report indicate that EBV-positive pulmonary LELC can derive benefit from PD-1/PD-L1 blockade. It is unclear why our patient's duration of response was short. However, further studies should aim to investigate the reasons for resistance to PD-L1 inhibition in EBV$^+$ LELC and NPC.

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