Immunotherapy for LELC: Case Report and a Focused Review

Marie Darrason, Antoine Martin, Michael Soussan, Kader Chouahnia, Marie-Christine Pailler, Hanene Boudabous, Pierre-Yves Brillet, Guilhem Bousquet, Laurent Zelek, Boris Duchemann

Abstract

Lymphoepithelioma-like carcinoma of the lung (LELC) is a rare, Epstein-Barr virus-associated tumor. LELC occurs mostly in young, Asian nonsmokers. A few hundred cases have been reported, mostly from retrospective Asian studies. Optimal treatment has not been clearly established. Treatment options are based on surgery for early stage and on cisplatin-based chemotherapy as first-line therapy for metastatic disease. Prognosis may seem better than for other types of non–small-cell lung cancer, but it remains poor in advanced disease, with a median survival of 24 months, and new treatments options are still warranted. Immunotherapies are now key players in the treatment of non–small-cell lung cancer. However, few data are available for this rare histologic subgroup. We have reviewed the available data on LELC with a focus on the first few cases reported with a response to a programmed cell death 1 inhibitor.

Clinical Lung Cancer, Vol. 20, No. 3, e393-401
Keywords: Immunotherapy, Lymphoepithelioma-like carcinoma of the lung, NSCLC, Rare tumor, Treatment

Introduction

There are various types of lymphoepithelioma carcinoma, most of which concern the nasopharynx. However, some will involve the lung and, more exceptionally, the parotid gland,[1] ovaries,[2] and, even, the endometrium.[3] Pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare type of non–small-cell lung cancer (NSCLC) first described by Begin et al[4] in 1987. The incidence of LELC has been ~0.7% of all NSCLC cases. LELC occurs mostly in Asian women, in particular, women from Southern China, in their fifth or sixth decade, with no previous history of smoking. LELC is usually associated with Epstein-Barr virus (EBV) infection, which, at one point, was even thought to be the main etiology of LELC. However, the largest case report from non-Asian countries has demonstrated that all 6 Western patients had EBV-negative disease,[5] suggesting that no association might exist between EBV and pulmonary LELC in the Western population and that EBV is not a necessary factor in the pathogenesis of LELC.[6] However, the circulating EBV DNA level still seems to be an interesting marker for monitoring LELC in EBV$^+$ patients.[7]

Several studies have reported on the molecular profile of LELC. A fraction of LELC (2% to nearly 20%, depending on the series[8-10]) will harbor *EGFR* (epidermal growth factor receptor) mutations. Because of the small number of cases reported from Western countries, data are lacking on the *EGFR* status of patients with pulmonary LELC in those populations. Wong et al[11] analyzed the *EML4-ALK* (echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase) expression profiles in 11 patients with pulmonary LELC and observed that no patient had that fusion gene. To the best of our knowledge, only 1 case of an *ALK* translocation has been reported.[12] Thus, the relatively low rate of *EGFR* mutation and *EML4-ALK* translocation in patients with pulmonary LELC could indicate that it is a distinct type of lung cancer, especially in East Asians. Also, no *MET* amplification or mutation has been reported.[13]

Owing to its rarity, no clinical trials have been performed, and no course of treatment for LELC has been established. Only case reports and retrospective series have been reported. Most cases are diagnosed at an early stage, and most patients have undergone surgery of the primary tumor.[14] Treatment at advanced stages has usually relied on multimodal therapy, including chemotherapy and radiotherapy.[15] The response to chemotherapy and radiotherapy and the prognosis

Oncologie Médicale, Hôpitaux Universitaires Paris Seine-Saint-Denis, Hôpital Avicenne, Bobigny Laboratoire d'Oncoim, Oncology, Bobigny, France

Submitted: Aug 9, 2017; Revised: Oct 15, 2018; Accepted: Dec 10, 2018; Epub: Dec 21, 2018

Address for correspondence: Boris Duchemann, MD, Oncologie Médicale, Hôpitaux Universitaires Paris Seine-Saint-Denis, Hôpital Avicenne, Bobigny Laboratoire d'Oncoim, Oncology, 125 Route de Stalingrad, 93000 Bobigny, France
E-mail contact: boris.duchemann@aphp.fr

1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.cllc.2018.12.008

have usually been better than for most cases of NSCLC, with a 5-year overall survival (including metastatic cases) roughly estimated at ~80%. The most commonly used chemotherapy regimens have included cisplatin or carboplatin combined with 5-fluorouracil, paclitaxel, docetaxel, or gemcitabine.[16]

In this context in which few therapeutic improvements have occurred, our aim was to discuss the potential benefits of programmed cell death ligand 1 (PDL1) inhibitors to treat LELC. First, we have reported a case of a partial response and clinical improvement after pseudoprogression in a woman treated for LELC with nivolumab (Opdivo; Bristol-Myers Squibb, New York, NY) in second line. Next, we have provided a brief review of the reported data and discuss future avenues of research.

Our Patient

Our patient was a 51-year-old woman. She was a former smoker who had smoked < 10 packs/year without aerotoxic contaminant exposure. Her medical history was not significant. She had presented with abdominal pain from the right hypochondrium and fever. The abdominal computed tomography (CT) scan had revealed 2 nodular lesions of the liver. The subsequent fluorine-18 fluorodeoxyglucose positron emission tomography (PET)/CT scan revealed only 1 other lesion in the lung's lower right lobe (7 × 7 × 5 cm).

Liver and transthoracic needle biopsies were performed. The histologic findings from the 2 biopsy specimens found poorly differentiated tumor proliferation with a large cell component. Immunostaining showed that the tumor cells only expressed AE1/AE3 and Ber-EP4. Fluorescence in situ hybridization performed for EBV detection using an EBV-encoded RNA probe was positive for all tumor cells (Figure 1). Tests were also performed for oncogenic drivers of lung malignancy, with no mutations identified (new generation sequencing with MiSeq and Tumor Hotspot Multiplicom; Agilent Technologies, Santa Clara, CA). No mutations were found on these genes. In addition, PDL1 immunostaining of the tumor cells was negative. Finally, a sinus CT scan and sinus examination were performed without evidence of primary tumor found.

First-line chemotherapy was a combination of cisplatin and 5-fluorouracil. Her best response was stable disease at 3 cycles. After 5 cycles of chemotherapy, the LELC had progressed. At the fifth cycle, new abdominal pain had developed, and CT revealed liver and lung progression. After multidisciplinary consultation and with the patient's informed consent, we chose to treat this rare NSCLC using nivolumab, 3 mg/kg every 2 weeks (cycle 1 was in October 2015). After 1 cycle, her abdominal pain and fever had resolved. The patient experienced no toxicity. The PET/CT evaluation at the fourth treatment course revealed morphologic and metabolic progression without worsening of her symptoms. We decided to continue with nivolumab because of the clinical improvement and the suspicion for pseudoprogression. At the sixth cycle, the PET/CT scan showed dramatic improvement in the liver lesion, confirming pseudoprogression (Figure 2). She had had no side effects from the immunotherapy and no symptoms related to the tumor for 6 months. After 7 months, she had developed radiologic and clinical thoracic

Figure 1 Hematoxylin and Eosin Staining of a Bronchial Biopsy Specimen [Original Magnification (A) ×100 and (B) ×200] Showing a Sheet of Undifferentiated Carcinomatous Cells Associated With Numerous Reactive Lymphocytes. (C) Immunohistochemistry (Original Magnification ×200) Showing Tumor Cells Positive for Cytokeratin 5/6. (D) In Situ Hybridization (Original Magnification ×200) Showing Tumor Nuclei Positive for Epstein-Barr Virus-encoded RNA

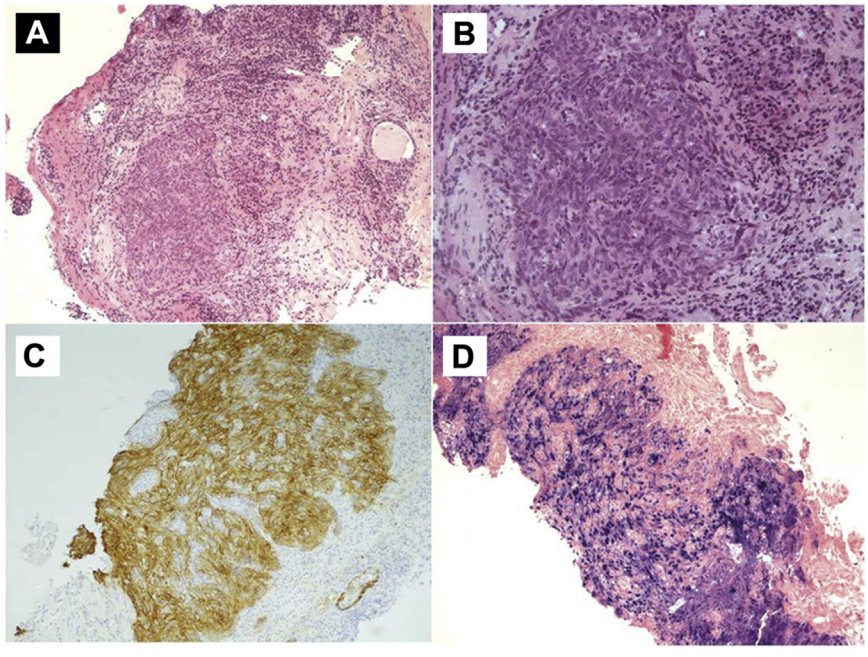
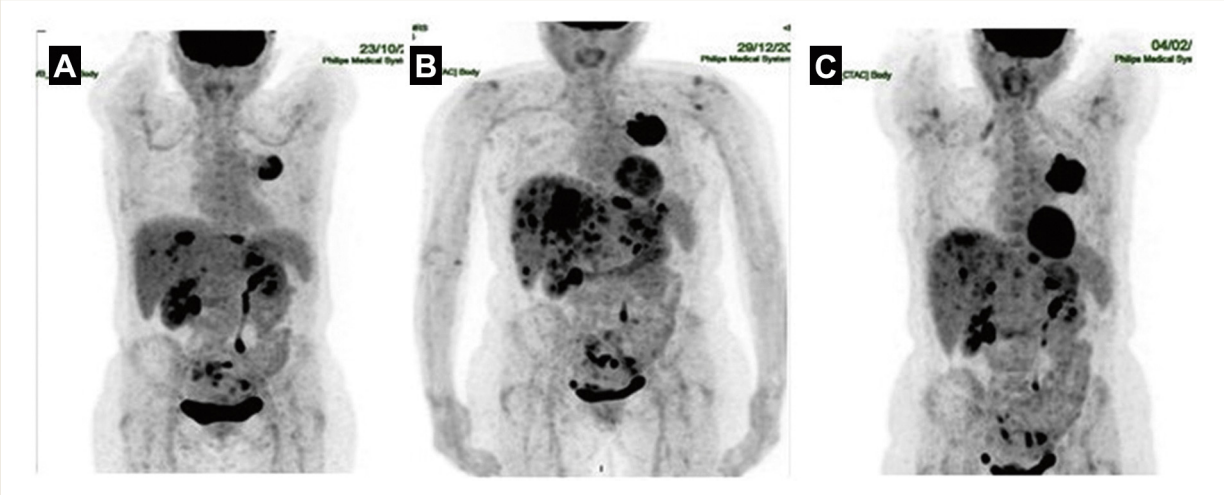


Figure 2 Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Scans (A) at Baseline Before Nivolumab and After (B) 4 Cycles and (C) 6 Cycles. Thoracic and Hepatic Lesions Had Increased in Size and Standardized Uptake Value From Baseline to After 4 Cycles (Progression Determined Using Response Evaluation Criteria In Solid Tumors and Positron Emission Tomography Response Evaluation Criteria In Solid Tumors) Before (C) Secondary Improvement



progression, for which she underwent parietal radiotherapy and a third line of chemotherapy with docetaxel. She developed progression after 3 cycles and began a fourth chemotherapy line with gemcitabine with progression at the fourth cycle. She died in December 2016.

Review Method

We performed research with PubMed using the search terms "(lymphoepithelioma[tiab])" and "(pulmonary[tiab] or lung[tiab])" in August 2018. A total of 166 reports were retrieved and reviewed. Of these 166 reports, 27 case series reported from 1987 to 2018 were identified that had described a total of 1320 cases of LELC.

Of these 27 case series, we excluded approximately one third of the case reports because they had included < 20 patients, reducing our review to 17 case series with 1238 patients. In addition, overlapping cases from 1 case series to another were difficult to pinpoint, because they were not always reported as such. Thus, the number of cases reported in >1 study was probably underestimated, because some specialized centers treating rare cancers such as Sun Yat-Sen Hospital (Guangzhou, China) have reported on a large number of cases.

We included as many case reports reporting on the biology and clinicopathologic characteristics of LELC as those reporting on the treatment of LELC. Very few studies focused on the management of advanced LELC.[16] Also, very few case series had reported on non-Asian cases of LELC.[5,17,18] The most important case report was by Xie et al.[19]However, their focus was not so much on the treatment of LELC but on the clinical significance of plasma EBV DNA as a biomarker of pulmonary LELC.

Description of Retrospective Series

The mean age at diagnosis in these series was 57.3 years, and 48% of the patients were male (637 of 1320). Of the 27 studies that reported the percentage of ever smokers, 40% (531 of 1320) of the patients were smokers. Even when *EGFR* mutations were present, the clinical features and frequency seemed different from those in other types of NSCLC.[8,19] Most of the patients had received multimodali therapy consisting of surgery combined with chemotherapy or radiotherapy, or both. In advanced cases, palliative chemotherapy and/or radiotherapy were used. Details from these studies[6,8,16,19-32] are presented in Table 1.

PDL1 and Rationale for Immunotherapy for LELC

The main recent therapeutic progress in thoracic oncology has been with targeted therapy and immunotherapy using PD1/PDL1 inhibitors. For NSCLC, several clinical trials have led to the approval of PD1 inhibitors such as nivolumab and pembrolizumab (Keytruda; Merck Sharp & Dohme, Wilmington, DE) for second-line therapy and, more recently as first-line therapy (at least for pembrolizumab) for NSCLC.[33-37] At present, no biomarkers as strong as *EGFR* mutations are available; however, recent data have supported the use of PDL1 staining on tumor cells for patient selection.[38] Concerning PDL1 expression in LECL, few data are available; however, in a recently reported series, 75% of the 66 patients had positive immunohistochemistry findings for PDL1 with a cutoff of 5% of tumor cells.[25] In a study with > 29 cases of LELC, 12 patients had > 50% PDL1 positivity ($P < .006$) and 27 patients (93% of the cohort) had > 1% PDL1 positivity ($P < .001$).[39] In another study, Yu et al[32] tried to establish the prognostic significance of PDL1 and p53 expression in 67 resected specimens of primary LELC. Positive PD-L1 expression in the tumor cells was observed in 44 patients (65.7%), with a median H-score of 40 (interquartile range, 0-80). When defining high expression as ≥ 50% of tumor cells with moderate-to-strong staining at the membrane, the overall proportion of high PDL1 expression in the tumor cells was 41.8% (28 of 67 patients). However, positive PDL1 expression in tumor cells and positive p53 expression were both significantly associated with longer disease-free

Table 1 Case Reports and Retrospective Series of LELC Management With Conventional Multimodal Treatment (Surgery, Chemotherapy, Radiotherapy)

Investigator	Patients, n	Sex (Male %)	Age, y (Range)	Asian ethnicity, (%)	Former or Active Smokers, n (%)	Stage at Diagnosis, n	Treatment, n (%)	Outcomes, n (%)	Mutation
Han et al,[6] 2001	32	22 (68.8)	54.4 (39-72)	32 (100)	14 (43)[a] were smokers	I, 12; II, 8; III, 11; IV, 1	Surgery, 14; surgery + RT, 14; surgery + ChT, 1; surgery + ChT + RT, 3	11 (42%) died of tumor; 2- and 5-y OS rate: stage I, 75.0% and 53.5%; stage II, 100% and 62.5%; stage III and IV, 80.8% and 60.6%	NA
Chang et al,[21] 2002	23	7 (30.4)	57 (42-80)	57 (100)	6 (26.1)	I, 8; II, 3; III, 8; IV, 4	Surgery, 17; ChT alone, 3; ChT then surgery, 1; ChT + RT, 2	Died of other disease, 3, alive; 18; stage I, 6/8 alive at 11-74 mo; stage II, 2/3 alive at 26-66 mo; stage III, 7/8 alive at mean follow-up of 21 mo; stage IV, 3/4 alive at mean follow-up of 13 mo	Low *p53* and Erb2 expression
Chang et al,[8] 2011	46[b]	16 (34)	57 (40-85)	NA but Asian team	6 (13)	I, 19; II, 7; III, 15; IV, 5	Surgery, 42; neoadjuvant ChT, 9; adjuvant ChT + RT, 5	No data on PFS or OS	3 *p53* mutations, 8 *EGFR* mutations (17.4%), with 4 in exon 2, 2 in exon 20, 1 in exon 18, and 1 in exon 19
Liang et al,[22] 2012	52	29 (55.8)	51 (9-74)	52 (100)	13 (25.0)	I, 16; II, 9; III, 24; IV, 3	Surgery, 18; surgery + ChT, 19; surgery + ChT + RT, 6; ChT, 8; ChT + RT, 1	2- and 5-y OS rate for all patients: 88% and 62%; median survival for 12 patients with advanced disease receiving treatment containing ChT, 39.1 mo	In situ hybridization for EBER, 100% *EGFR*, 11; WT, 11
Huang et al,[20] 2012	21	5 (23.8)	55.6 (37-75)	21 (100)	6 (28.6)	I, 2; II, 2; III, 13; IV, 4	Surgery, 2; surgery + ChT, 6; surgery + ChT + RT, 5; ChT + RT, 6; ChT, 2	Median OS for stages I and II, NR; for stages III and IV, 3.4 y	NA
Liu et al,[23] 2014	32	11 (34.4)	50.9 (25-71)	32 (100)	7 (21.9)	I, 9; II, 6; III, 12; IV, 5	Surgery, 9; surgery + ChT, 18; ChT + RT, 1; ChT, 4	NA	In situ hybridization for EBERs, 100%; *EGFR*-targeted therapy used in 3 patients with advanced disease and 1 with distant recurrence; no obvious therapeutic effect found

Table 1 Continued

Investigator	Patients, n	Sex (Male %)	Age, y (Range)	Asian ethnicity, (%)	Former or Active Smokers, n (%)	Stage at Diagnosis, n	Treatment, n (%)	Outcomes, n (%)	Mutation
Mo et al,[24] 2014	35	20 (57.1)	54.7 (35-74)	37 (100)	7 (20.0)	I, 11; II, 9; III, 13; IV, 2	Surgery, 22; surgery + ChT, 10; ChT + RT, 1; ChT, 1	Median OS for all patients, NR; 2- and 5-y OS rates for all patients: 81% and 51%	NA
He et al,[25] 2015	62	36 (58.1)	65 (15-86)	NA[c]	NA[c]	I + II, 17; III, 17; IV, 7	Surgery, 41; RT, 14	All patients with LELC, 107 mo (55.2% at 5 y)	NA
Chang et al,[26] 2015	66	25 (37.9)	57.5 (39-85)	66 (100)	8 (12.1)	I, 26; II, 13; III, 20; IV, 7	Surgery, 33; surgery + ChT, 15 (neoadjuvant, 10; adjuvant, 5); surgery + RT, 1; surgery + ChT + RT, 7; ChT + RT, 5; palliative: ChT, 7; RT, 2; ChT + RT, 3	5-y OS rate: stage I, 100%; stage II, 75%; stage III and IV, 69.2%	PDL1 > 5% in 75.8%; *EGFR*, 12.1%; no *KRAS Braf, ALK, ROS1*
Fang et al,[27] 2015	113	51 (45.1)	52 (28-74)	113 (100)	32 (28.3)	I, 29; II, 24; III, 45; IV, 15	Surgery, 36; surgery + ChT, 77; neoadjuvant, 9; adjuvant, 68	5-y OS rate: stage I, 87.5%; stage II, 92.9%; stage IIIA, 64.2%; stage IIIB/IV, 36.6%	*EGFR* 2 (1.8%); no *ALK* or *KRAS*; PDL1 expression, 74.3% vs. 51.4% with negative prognostic effect
Wang et al,[28] 2016	79	39 (49.4)	52 (11-74)	79 (100)	22 (27.8)	I + II, 44; III + IV, 35	Surgery, 38; surgery + ChT or RT, 35; palliative ChT, 6	3- and 5-y OS rate: 88% and 79%; 3- and 5-y PFS: 76% and 68%	63.3 PDL1^{+} (> 5%)
Jiang et al,[29] 2016	43	18 (45)	57.3 (30-78)	NA but Asian team	6 (15)	I, 19; II, 8; III, 14; IV, 2	Surgery,43; adjuvant RT, 1; adjuvant CT, 1; adjuvant CT + RT, 10	2- and 5-y OS rates, 90% and 74%; 2- and 5-y DFS rates, 87% and 47%	ND
Lin et al,[16] 2017	23	11 (47.8)	63.7 (48-85)	NA but Asian team	9 (39.1)	I, 0; II, 0; 16, IV, 7	Surgery, 11; surgery + adjuvant ChT with or without RT, 3; neoadjuvant ChT with or without RT + surgery, 8; palliative CT with or without RT, 12	Died 9 (39.1); PFS with palliative ChT, 19.4% (cisplatin, docetaxel), 10.7% with cisplatin without docetaxel); OS for stage IIIA, NR; for stage IIIB 54%; for stage IV, 27.6%	ND
Xie et al,[19] 2017	429	177 (41)	52.5 (40.9-63.8)	NA but Asian team	330 (78)	I, 68; II, 191; III, 93; IV, 77	Surgery, 339; other treatment (ChT, RT) not described	Median OS, 4.8 y	2/429 *EGFR*; 0 *ALK*; 0 *KRAS*

Table 1 Continued

Investigator	Patients, n	Sex (Male %)	Age, y (Range)	Asian ethnicity, (%)	Former or Active Smokers, n (%)	Stage at Diagnosis, n	Treatment, n (%)	Outcomes, n (%)	Mutation
Tay et al,[30] 2018	28	9 (32)	58 (37-76)	100%	2 (10.7)	I + II, 8; III + IV, 7	I + II, 9 surgery only; III, surgery with or without adjuvant therapy, 4; ChT + RT, 3; IV, palliative ChT, 9; CT + RT, 1	2- and 5-y OS rates; stage I/II 100% and 100%; stage III, 85.7% and 85.7%; stage IV, 61.5% and 9.6%	ND (verifier)
Yu et al,[31] 2018	87	43 (49)	53 (27-72)	NA but Asian team	18 (20 22)	I, 25; II, 27; III, 35; IV, 0	Surgery, 87; adjuvant therapy, 54 (ChT, 50; RT, 4); neoadjuvant ChT, 6	5-y PFS rate, 70%; 5-y OS rate, 78.9%	ND
Yu et al,[32] 2018	67	31 (46)	52.2 (45—59)	NA but Asian team	17 (25.4)	I, 23; II, 16; III, 28; IV, 0	Surgery, 67; adjuvant ChT, 45	5 tumor-related deaths; median OS, NR; 1-, 3-, 5-y PFS, 88%, 69%, 5%; 5-y OS rate, 82%	*EGFR* and *ALK*: ND PDL1: 44% positive

Abbreviations: ALK = anaplastic lymphoma kinase; ChT = chemotherapy; DFS = disease-free survival; EBER = Epstein-Barr virus-encoded RNA; EGFR = epidermal growth factor receptor; LELC = lymphoepithelioma-like carcinoma of the lung; NA = not available or not applicable; ND = not determined; NR = not reached; OS = overall survival; PFS = progression-free survival; WT = wild-type.

[a]6 missing data.

[b]Twelve patients had been included in a previous report by the same team.[21]

[c]White, 40 (64); black, 4 (6); other, 18 (29).

Table 2 Case Reports of LELC Management With Immunotherapy

Investigator	Patients, n	Sex	Age, y	Tobacco Use	Stage	First Treatment	Toxicity	Immunotherapy	Evolution	Mutation
Kim et al,[41] 2017	1	F	37		T3N2 at diagnosis, IV at recurrence	Surgery + adjuvant chemotherapy; at recurrence, first-line chemotherapy, resistance	NA	Second-line nivolumab	Best response, progression	*EFGR, ALK, KRAS,* WT
Kumar et al,[42] 2017	1	M	56 (Asian)	Former, 15 PY	T2N1M1 (liver)	Lung surgery and cisplatin, docetaxel; switched to carboplatin, paclitaxel; PR at 4th cycle; carboplatin, gemcitabine at progression; nab-paclitaxel	No	Fourth-line nivolumab	PR, April 15 to November 16; oligometastatic progression treated by stereotaxic RT	NA
Kumar et al,[42] 2017	1	F	37 (Asian)	NS	T2N2	Cisplatin, gemcitabine followed by concurrent ChT + RT with weekly carboplatin, paclitaxel, 54 Gy; radiologic progression; EBV negative; docetaxel	Pneumonitis; grade 1 rash	Third-line nivolumab	Started in April 2015, with initial radiologic progression of 24%; treatment continued followed by stable disease through December 2016 and low EBV copies; still receiving treatment in April 2017 despite progressive disease	PDL1, 5%; *EGFR, ALK* negative

Abbreviations: ALK = anaplastic lymphoma kinase; ChT = chemotherapy; EBV = Epstein-Barr virus; *EGFR* = epidermal growth factor receptor; F = female; M = male; NS = not specified; PDL1 = programmed cell death ligand 1; PR = partial response; PY = pack-years; RT = radiotherapy; WT = wild-type.

survival ($P = .037$ and $P = .011$, respectively) but not with longer overall survival ($P > .050$). In addition, the 29 patients with both PDL1$^+$ tumor cells and p53$^+$ expression had longer disease-free survival compared with the all-negative group (median, not reached vs. 21.9 months; $P = .006$). These findings are consistent with those from another study,[40] which showed that increased PDL1 expression was an unfavorable prognostic factor for NSCLC in general (hazard ratio, 1.26; 95% confidence interval, 1.05-1.52; $P = .01$) and LELC in particular (hazard ratio, 3.04; 95% confidence interval, 1.19-7.77; $P = .02$). Thus, it appears that LELC will frequently express PDL1 biomarkers, providing a rationale for the use of immunotherapy. However, none of these studies included an evaluation of the effect of immunotherapy on disease-free progression and overall survival. To date, only a few case reports have evaluated the effect of immunotherapy.

Previous Case Reports of LELC and Immunotherapy

The details of the 3 cases of LELC treated with immunotherapy are listed in Table 2.[41,42] The first case (patient 1) was a 37-year-old Asian woman who had never smoked. Localized LELC had been initially diagnosed and she had undergone chemotherapy and surgery (cisplatin and docetaxel). One year later, she experienced a relapse of the LELC with bone metastases. After initial decompressive surgery and radiotherapy (C7−T3 and L5), the patient received first-line therapy with carboplatin and pemetrexed. However, the tumor was refractory to chemotherapy, and metastases in both lungs and the liver had developed after the end of the first line. Nivolumab was then begun but was associated with rapid progression (adrenal and splenic metastases, pericardial effusion, deep venous thrombosis) and immune-related colitis.[41] Nivolumab was stopped and comfort care measures were provided, leading to the death of the patient 3 years after the initial diagnosis.

Two other cases have been reported: patient 2 had a partial response leading to stable disease and patient 3 had a partial response after pseudoprogression.

Patient 2 was a 56-year-old Asian man who was an ex-smoker. He had presented in March 2012 with a complaint of recurrent hemoptysis of 2 months' duration. The evaluation revealed T2N1M1 (liver metastasis) stage IV LELC. He underwent chemotherapy with platinum and docetaxel but experienced several side effects, including dehydration resulting from vomiting with cisplatin and mild peripheral sensory neuropathy. He experienced a partial response, followed 3 months later by a relapse with liver metastases, for which he received a second line with 5 cycles of carboplatin plus gemcitabine. The patient then received nab-paclitaxel through February 2015. However, he had to stop the treatment because of toxicity. Finally, he started nivolumab in April 2015 but multiple interruptions of several months occurred between the injections because he would return home for a few months. The only toxicity was transaminitis owing to concomitant statin treatment. Overall, the patient had stable disease and received nivolumab for 25 months.

Patient 3 was a 37-year-old Asian woman who had never smoked. She had presented in 2012 with a complaint of cough with blood-tinged sputum of several weeks duration. The evaluation revealed T2N2M0 LELC (stage IIIA), without any *EGFR* or *ALK* mutations. She received 4 cycles of chemotherapy with cisplatin and gemcitabine and experienced a partial response. She then underwent chest radiotherapy as planned with concurrent radiosensitizing chemotherapy. After progression in August 2013 with a PDL1 tumor proportion score of 5% found on the biopsy specimen, she received docetaxel as second-line therapy at 75 mg/m^2 every 3 weeks. She developed progression and was enrolled in a nivolumab trial in February 2015. After 6 cycles of nivolumab, a 24% increase in the disease extent was found using the Response Evaluation Criteria In Solid Tumors but had a good performance status. Thus, the increased disease was considered pseudoprogression. She experienced cutaneous grade 1 toxicity with a rash over her neck and forearm and then presented with pneumonitis, possibly induced by Nivolumab. Nivolumab was started again in February 2016, without any complications. After 27 months of nivolumab, she was alive and in remission.

Discussion

LELC is a rare lung tumor with clinicopathologic characteristics distinct from those of other types of NSCLC. It is probable that some molecular heterogeneity exists between white and Asian patients. However, the number of non-Asian patients is far too few to establish this point. The response to chemotherapy and multimodal systemic treatment have seemed better than the response in patients with traditional NSCLC; however, new therapies are still warranted.

In this uncertain therapeutic scheme, the rationale for using immunotherapy has relied on the frequent positivity of LELC tumor cells for PDL1. However, many questions remain regarding the clinical relevance of the mutational burden, a biomarker that seems more and more important for predicting immunotherapy efficiency in other types of NSCLC. Finally, a clinical trial testing immunotherapy for LELC would be warranted before this line of treatment could be suggested as a new standard of care for advanced LELC.

Conclusion

We have been among the first to report cases of response after initial pseudoprogression with nivolumab for LELC. Specific trials of immunotherapy for rare lung cancer cases are still warranted.

References

1. Ambrosio MR, Mastrogiulio MG, Barone A, et al. Lymphoepithelial-like carcinoma of the parotid gland: a case report and a brief review of the western literature. *Diagn Pathol* 2013; 8:115.
2. Ambrosio MR, Rocca BJ, Onorati M, et al. Lymphoepithelioma-like carcinoma of the ovary. *Int J Surg Pathol* 2011; 19:514-7.
3. Ambrosio MR, Rocca BJ, Mourmouras V, et al. Lymphoepithelioma-like carcinoma of the endometrium. *Pathologica* 2010; 102:57-61.
4. Begin L, Eskandari J, Joncas J. Epstein-Barr virus related lymphoepithelioma-like carcinoma of lung. *J Surg Oncol* 1987; 36:280-3.
5. Castro CY, Ostrowski ML, Barrios R, et al. Relationship between Epstein-Barr virus and lymphoepithelioma-like carcinoma of the lung: a clinicopathologic study of 6 cases and review of the literature. *Hum Pathol* 2001; 32:863-72.
6. Han A, Xiong M, Zong Y. Association of Epstein-Barr virus with lymphoepithelioma-like carcinoma of the lung in Southern China. *Am J Clin Pathol* 2000; 114:220-6.
7. Ngan RKC, Yip TTC, Cheng WW, et al. Clinical role of circulating Epstein-Barr virus DNA as a tumor marker in lymphoepithelioma-like carcinoma of the lung. *Ann N Y Acad Sci* 2004; 1022:263-70.
8. Chang Y-L, Wu C-T, Shih J-Y, Lee Y-C. Unique p53 and epidermal growth factor receptor gene mutation status in 46 pulmonary lymphoepithelioma-like carcinomas. *Cancer Sci* 2011; 102:282-7.
9. Tam IYS, Chung LP, Suen WS, et al. Distinct epidermal growth factor receptor and KRAS mutation patterns in non-small cell lung cancer patients with different tobacco exposure and clinicopathologic features. *Clin Cancer Res* 2006; 12:1647-53.

10. Wang L, Lin Y, Cai Q, et al. Detection of rearrangement of anaplastic lymphoma kinase (ALK) and mutation of epidermal growth factor receptor (EGFR) in primary pulmonary lymphoepithelioma-like carcinoma. *J Thorac Dis* 2015; 7: 1556-62.
11. Wong DW-S, Leung EL-H, So KK-T, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. *Cancer* 2009; 115:1723-33.
12. Ose N, Kawai T, Ishida D, Kobori Y, Takeuchi Y, Senba H. Pulmonary lymphoepithelioma-like carcinoma with echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion gene: pulmonary LELC with EML4-ALK fusion gene. *Respirol Case Rep* 2016; 4:e00200.
13. Tong JH, Yeung SF, Chan AWH, et al. MET amplification and exon 14 splice site mutation define unique molecular subgroups of non-small cell lung carcinoma with poor prognosis. *Clin Cancer Res* 2016; 22:3048-56.
14. Lin Z, Situ D, Chang X, et al. Surgical treatment for primary pulmonary lymphoepithelioma-like carcinoma. *Interact Cardiovasc Thorac Surg* 2016; 23:41-6.
15. Chan AT, Teo PM, Lam KC, et al. Multimodality treatment of primary lymphoepithelioma-like carcinoma of the lung. *Cancer* 1998; 83:925-9.
16. Lin C-Y, Chen Y-J, Hsieh M-H, Wang C-W, Fang Y-F. Advanced primary pulmonary lymphoepithelioma-like carcinoma: clinical manifestations, treatment, and outcome. *J Thorac Dis* 2017; 9:123-8.
17. Morbini P, Riboni R, Tomaselli S, Rossi A, Magrini U. EBER- and LMP-1-expressing pulmonary lymphoepithelioma-like carcinoma in a Caucasian patient. *Hum Pathol* 2003; 34:623-5.
18. Ferrara G, Nappi O. Lymphoepithelioma-like carcinoma of the lung: two cases diagnosed in Caucasian patients. *Tumori* 1995; 81:144-7.
19. Xie M, Wu X, Wang F, et al. Clinical Significance of plasma Epstein-Barr virus DNA in pulmonary lymphoepithelioma-like carcinoma (LELC) patients. *J Thorac Oncol* 2018; 13:218-27.
20. Huang C-J, Feng A-C, Fang Y-F, et al. Multimodality treatment and long-term follow-up of the primary pulmonary lymphoepithelioma-like carcinoma. *Clin Lung Cancer* 2012; 13:359-62.
21. Chang Y-L, Wu C-T, Shih J-Y, Lee Y-C. New aspects in clinicopathologic and oncogene studies of 23 pulmonary lymphoepithelioma-like carcinomas. *Am J Surg Pathol* 2002; 26:715-23.
22. Liang Y, Wang L, Zhu Y, et al. Primary pulmonary lymphoepithelioma-like carcinoma: fifty-two patients with long-term follow-up. *Cancer* 2012; 118: 4748-58.
23. Liu Q, Ma G, Yang H, et al. Lack of epidermal growth factor receptor gene mutations in exons 19 and 21 in primary lymphoepithelioma-like carcinoma of the lung: lack of EGFR mutations in LELC of lung. *Thorac Cancer* 2014; 5:63-7.
24. Mo Y, Shen J, Zhang Y, et al. Primary lymphoepithelioma-like carcinoma of the lung: distinct computed tomography features and associated clinical outcomes. *J Thorac Imaging* 2014; 29:246-51.
25. He J, Shen J, Pan H, Huang J, Liang W, He J. Pulmonary lymphoepithelioma-like carcinoma: a Surveillance, Epidemiology, and End Results database analysis. *J Thorac Dis* 2015; 7:2330-8.
26. Chang Y-L, Yang C-Y, Lin M-W, Wu C-T, Yang P-C. PD-L1 is highly expressed in lung lymphoepithelioma-like carcinoma: a potential rationale for immunotherapy. *Lung Cancer* 2015; 88:254-9.
27. Fang W, Hong S, Chen N, et al. PD-L1 is remarkably over-expressed in EBV-associated pulmonary lymphoepithelioma-like carcinoma and related to poor disease-free survival. *Oncotarget* 2015; 6:33019-32.
28. Wang L, Jiang L, Li P, et al. Positive expression of programmed death ligand-1 correlates with superior outcomes and might be a therapeutic target in primary pulmonary lymphoepithelioma-like carcinoma. *OncoTargets Ther* 2015; 8:1451-7.
29. Jiang W-Y, Wang R, Pan X-F, et al. Clinicopathological features and prognosis of primary pulmonary lymphoepithelioma-like carcinoma. *J Thorac Dis* 2016; 8:2610-6.
30. Tay CK, Chua YC, Takano A, et al. Primary pulmonary lymphoepithelioma-like carcinoma in Singapore. *Ann Thorac Med* 2018; 13:30-5.
31. Yu X, Wen Y, Qin R, et al. Prognosis and distribution of lymph nodes metastases in resectable primary pulmonary lymphoepithelioma-like carcinoma: a large cohort from a single center: pulmonary lymphoepithelioma-like carcinoma. *Thorac Cancer* 2018; 9:360-7.
32. Yu X-Y, Zhang X-W, Wang F, et al. Correlation and prognostic significance of PD-L1 and P53 expression in resected primary pulmonary lymphoepithelioma-like carcinoma. *J Thorac Dis* 2018; 10:1891-902.
33. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non—small-cell lung cancer. *N Engl J Med* 2018; 378:2078-92.
34. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1—positive non—small-cell lung cancer. *N Engl J Med* 2016; 375:1823-33.
35. Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; 387:1540-50.
36. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non—small-cell lung cancer. *N Engl J Med* 2015; 373:1627-39.
37. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; 373:123-35.
38. Ilie M, Hofman V, Dietel M, Soria J-C, Hofman P. Assessment of the PD-L1 status by immunohistochemistry: challenges and perspectives for therapeutic strategies in lung cancer patients. *Virchows Arch* 2016; 468:511-25.
39. Chan AWH, Tong JHM, Kwan JSH, et al. Assessment of programmed cell death ligand-1 expression by 4 diagnostic assays and its clinicopathological correlation in a large cohort of surgical resected non-small cell lung carcinoma. *Mod Pathol* 2018; 31:1381-90.
40. Zhang M, Li G, Wang Y, et al. PD-L1 expression in lung cancer and its correlation with driver mutations: a meta-analysis. *Sci Rep* 2017; 7:10255.
41. Kim C, Rajan A, DeBrito PA, Giaccone G. Metastatic lymphoepithelioma-like carcinoma of the lung treated with nivolumab: a case report and focused review of literature. *Transl Lung Cancer Res* 2016; 5:720-6.
42. Kumar V, Dave V, Harris J, Huang Y. Response of advanced stage recurrent lymphoepithelioma-like carcinoma to nivolumab. *Immunotherapy* 2017; 9: 955-61.