Original Article

Primary pulmonary lymphoepithelioma-like carcinoma in Singapore

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Abstract:

BACKGROUND: Primary pulmonary lymphoepithelioma-like carcinoma (PPLELC) is a rare subtype of nonsmall cell lung cancer (NSCLC) predominantly reported in East Asia. We aimed to evaluate clinical characteristics, diagnosis, treatment, and prognosis of PPLELC in Singapore.

METHODS: Retrospective review of all patients diagnosed with PPLELC at our center between 2000 and 2014.

RESULTS: All 28 patients were Chinese, 67.9% were female, and the median age was 58 years (range37–76 years). Majority (89.3%) were never smokers and 53.6% asymptomatic at diagnosis. About 28.6% presented with Stage I/II disease, 25% had Stage III disease, and 46.4% had Stage IV disease. All patients with Stage I/II disease underwent lobectomy without adjuvant treatment. Four out of 7 patients with Stage III disease underwent surgery with or without adjuvant therapy while the rest received chemoradiation. Twelve out of 13 patients with Stage IV disease received chemotherapy with or without radiotherapy. At the end of 2016, survival data were available for all 28 patients. Two-year survival rates for Stage I/II, Stage III, and Stage IV disease were 100%, 85.7%, and 61.5%, respectively, while survival was 100%, 85.7%, and 9.6%, respectively, at five years.

CONCLUSION: The majority (46.4%) of patients presented with metastatic disease. For those with Stage I-III disease, 5-year survival for PPLELC was better than other NSCLC subtypes. Multimodality treatment including surgery could be considered in locally advanced disease. In Stage IV disease, it tended to approximate that of NSCLC.

Keywords:

Lung, lymphoepithelioma-like cancer, prognosis, stage

Primary pulmonary lymphoepithelioma-like carcinoma (PPLELC) is a rare primary lung malignancy that has been reclassified under "other and unclassified carcinomas" in the 2015 WHO histological classification of lung tumors.[1] Like nasopharyngeal carcinoma (NPC), it is an Epstein–Barr virus (EBV)-associated epithelial neoplasm that is indistinguishable from the former on histology.[2,3] Most reports are from East Asia, with only sporadic cases in the West.[4-7] Studies suggest that PPLELC is often diagnosed at an early stage and confers a better prognosis than other nonsmall cell lung cancer (NSCLC) subtypes.[4,8-11] Our center has treated a number of PPLELC cases in the last decade. Unusually, we have often noticed an advanced stage at presentation. Singapore is a small city-state in Southeast Asia, where PPLELC has curiously not been reported. Our study aimed to review clinical characteristics, diagnosis, staging, treatment, and prognosis of PPLELC in Singapore and determine if any significant differences exist in relation to published series. We also sought to evaluate if the prognosis of PPLELC is indeed better than other NSCLC subtypes in our cohort.

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Methods

Patients

All lung specimens with "lymphoepithelioma-like carcinoma (LELC)" as the primary diagnosis between 2000 and 2014 were identified from the pathology department database and reviewed. These patients were seen at our campus that comprised a tertiary 1700-bed hospital and 5 national centers (including a cancer center). LELC was diagnosed by its typical histological appearance of undifferentiated carcinoma cells with poorly defined borders, a syncytial arrangement, and a prominent reactive inflammatory infiltrate. It mimicked undifferentiated NPC, and therefore, specimens without EBV-encoded RNA (EBER) nuclear stains were excluded from the study [Figure 1]. Case files and the hospital's electronic medical records were reviewed. Patients with a history of NPC were excluded from the study. Data on clinical characteristics, diagnostic methods, staging, treatment, and outcomes were collected. Staging was in accordance to the 7th edition of the tumor, node, and metastasis (TNM) classification for lung tumors. Singhealth Centralized Institutional Review Board approved this study (CIRB Ref: 2014/544/B).

Statistical methods

Overall survival (OS) was defined as time from diagnosis (date of histology) to death from any cause. Patients were followed up to December 31, 2016. Patients still alive on December 31, 2016, were censored. Survival functions were estimated using the Kaplan–Meier method and were compared using the log-rank test. A two-sided $P < 0.05$ was taken as statistically significant. All analyzes were performed using the using the statistical package for the social sciences (SPSS) version 20 for Windows (SPSS, Chicago, IL).

Results

Clinical characteristics

Twenty-eight patients were included in the analysis. Fifteen patients had to be excluded due to a history of NPC. All were of Chinese race, and 19 (67.9%) were female. The median age was 58 years (range 37–76 years). Twenty-five (89.3%) patients were nonsmokers, and 12 (42.9%) were asymptomatic at diagnosis. Chronic cough was the most common symptom (32.1%) [Table 1]. Other symptoms included cough (10.7%), hemoptysis (3.6%), chest pain (3.6%), weight loss (3.6%), and rash (3.6%). Eight patients (28.6%) had Stage I/II, 7 (25%) had Stage III disease, and 13 (46.4%) had Stage IV disease [Table 1]. Bony metastases were most commonly observed (5 patients), followed by contralateral lung (3 patients), pleura (2 patients), liver (2 patients), brain (2 patients), and adrenal gland (1 patient).

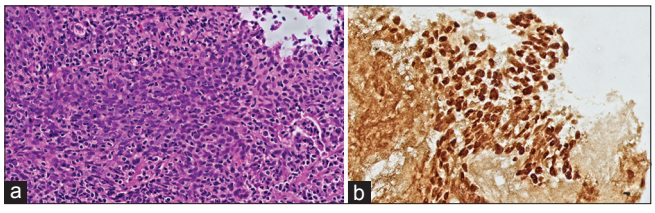

Figure 1: (a) Malignant epithelial cells with prominent nucleoli and a syncytial growth pattern infiltrated by numerous lymphoplasmacytic cells. (H and E, ×40). (b) Tumor cells stain positive for Epstein–Barr virus-encoded RNA (×40)

Radiology

The most consistent computed tomography (CT) finding was a pulmonary nodule or mass with a lobulated border, present in 18 (64.3%) patients. This was followed by mass-like consolidation 6 (21.4%) and spiculated lesion 3 (10.7%). One patient (3.6%) presented with mediastinal lymphadenopathy in the absence of any pulmonary focus radiologically. For the remaining 27 patients, 21 (77.8%) of these were centrally located, i.e., within the inner two-thirds of the lung, in proximity to the mediastinum, tracheobronchial tree, and great vessels. Two-thirds, i.e. 18 (66.7%) of the parenchymal tumors were located in the lower lobes. Heterogeneous tumor enhancement was present in 18 (66.7%) patients. Intralesional calcification and cavitation were uncommon, present in 3 patients (11.1%) and 1 patient (3.7%), respectively.

Pathology

All lung specimens demonstrated typical morphological features - epithelial cells with prominent nucleoli arranged in a syncytial pattern and separated by lymphoplasmacytic cells. Confirmatory EBER staining was positive in all specimens. Nine (32.1%) patients demonstrated prominent necrosis alongside the

Table 1: Baseline clinical characteristics and method of diagnosis (*n*=28)

Characteristic	*n* (%)
Age[a]	58 (37-76)
Female sex	19 (67.9)
Nonsmokers	25 (89.3)
Chinese race	28 (100)
Presenting complaint	
Asymptomatic	12 (42.9)
Cough	9 (32.1)
Dyspnea	3 (10.7)
Hemoptysis	1 (3.6)
Chest pain	1 (3.6)
Weight loss	1 (3.6)
Others	1 (3.6)
Stage of disease at presentation	
I-II	8 (28.6)
III A/B	7 (25)
IV	13 (46.4)

[a]Data are median (range)

typical features of PPLELC. In 7 (25%) patients, intense granulomatous inflammation was also seen.

Diagnosis

Nine patients had their diagnosis confirmed through surgical methods (8 lung resection, 1 mediastinoscopy). Surgery was performed as the first procedure in five of them for a solitary pulmonary nodule with a high pretest probability of cancer. The remaining four patients needed a surgical diagnosis due to a prior inconclusive nonsurgical diagnostic test. Nonsurgical procedures that were performed as the first diagnostic evaluation included transthoracic needle aspiration (TTNA) (eight patients), transbronchial lung biopsy (TBLB) (eight patients), endobronchial ultrasound transbronchial needle aspiration (EBUS TBNA) (six patients), and percutaneous closed needle pleural biopsy (one patient). All six patients who underwent EBUS TBNA had a conclusive diagnosis obviating further evaluation. Two out of eight patients who underwent TTNA, and four out of eight patients who had TBLB needed a second procedure due to inconclusive results.

Treatment and outcomes

All 8 (28.6%) patients with Stage I/II disease underwent lobectomy without any adjuvant treatment. Four patients (14.3%) had Stage IIIA disease, and three (10.7%) had Stage IIIB disease. Among the four patients with Stage IIIA disease, three had lobectomy with mediastinal lymph node dissection followed by adjuvant chemoradiation. The last Stage IIIA patient received chemoradiation only. One Stage IIIB patient underwent surgery after a false-negative mediastinoscopy and subsequently declined adjuvant therapy. The other two Stage IIIB patients received chemoradiation. Among the 13 (46.4%) Stage IV patients, 12 received chemotherapy with or without radiotherapy. The last patient refused any therapy. Platinum-based chemotherapy was the first-line adjuvant or palliative regimen used for this cancer in our cancer institute. Second-line therapy, if required, was decided by the managing oncologist [Table 2].

At the end of 2016, half of 28 patients were still alive. The median follow-up was 56 months (range 6–196 months). Two-year and 5-year OS rates were 78.6% and 54.9%, respectively, for the entire cohort [Figure 2]. Survival was related to the stage of cancer [Figure 3]. Early-stage disease conferred the best OS, followed by locally advanced and metastatic disease (P = 0.002). The 2-year survival rates for early stage, locally advanced, and metastatic disease were 100%, 85.7%, and 61.5% respectively. At 5 years, the survival rates for early stage and locally advanced disease remained at 100% and 85.7%, while that of metastatic disease had fallen to 9.6% [Table 3].

Discussion

PPLELC affected the Chinese race exclusively in our cohort. The majority was never smokers, and females were more commonly affected than males. A mere 28.6% of patients presented with early-stage disease (Stage I/II) while 25% had Stage III disease and 46.4% had Stage IV disease.[5,9,12] EBUS-TBNA fared better than TTNA and TBLB. Stage of disease was the chief predictor of survival. Metastasis conferred a grave prognosis akin to NSCLC. Patients with early disease appeared to do well with surgery alone while those with locally advanced disease may benefit from surgery combined with chemoradiation.

When compared to data derived from the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project, our data suggest that the 5-year survival for patients with Stage I to III disease is higher in PPLELC than NSCLC.[13] Patients with Stage I/II PPLELC

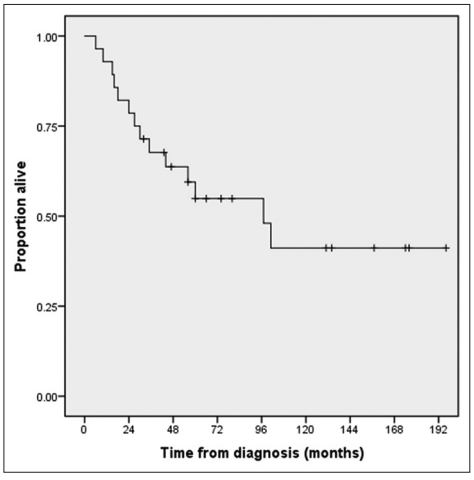

Figure 2: The overall survival rates for primary pulmonary lymphoepithelioma-like carcinoma at 2 and 5 years were 78.6% and 54.9%, respectively

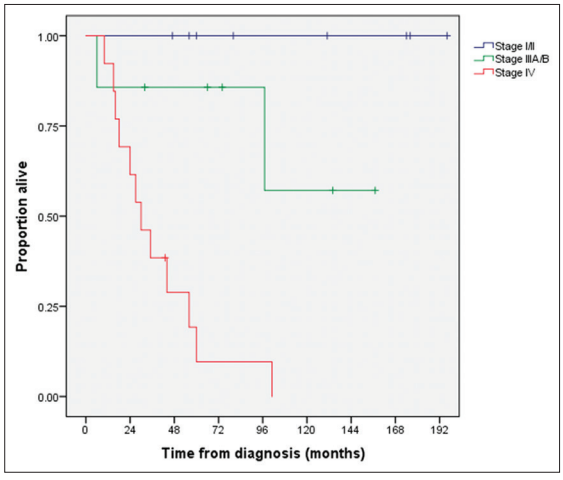

Figure 3: Overall survival for primary pulmonary lymphoepithelioma-like carcinoma was significantly associated with stage of disease

Table 2: Treatment and survival of patients with locally advanced and metastatic disease

Age	Sex	Stage	TNM	Initial treatment modality	Chemotherapy regimen	Status	OS (months)
62	Female	IIIA	T2aN2	CT + RT	CBP + TAX (SD) CBP + GEM (PR) PEM TS-1 (SD)	Alive	66
76	Female	IIIA	T2aN2	S + CT + RT	CBP + GEM (CR)	Alive	134
65	Female	IIIA	T2aN2	S + CT + RT	CBP + GEM (CR)	Alive	74
56	Male	IIIA	T2bN2	S + CT + RT	CBP + GEM (SD)	Demised	97
65	Female	IIIB	T3N3	CT	CBP + TAX (PD)	Demised	6
57	Female	IIIB	T4N2	CT	CBP + TAX (PD)	Alive	32
69	Male	IIIB	T2bN3	S + CT + RT	CBP+GEM (SD)	Alive	157
32	Female	IV	T1bN3M1b	CT	CBP + GEM (SD) NVB (PR)	Demised	56
68	Female	IV	T2bN3M1b	CT	CBP + TAX (SD) CBP + GEM (PD) XELODA (PD) TS-1 + CBP (PD) NVB (PD)	Demised	35
63	Female	IV	T2bN2M1b	CT + RT	CBP + GEM (PD)	Demised	10
52	Female	IV	T2aN3M1b				
59	Male	IV	T3N1M1b	CT	CBP + GEM (PD)	Demised	24
68	Male	IV	T2aN2M1a	CT	CBP + GEM (PD) IRESSA	Demised	18
76	Male	IV	T2bN2M1b	CT	CBP + GEM (PD)	Demised	44
45	Female	IV	T1bN1M1b	CT + RT	CBP + GEM (CR) CBP + TAX (PD)	Demised	101
74	Female	IV	T3N2M1b	CT + RT	CBP + GEM (PD)	Demised	30
41	Female	IV	T2bN2M1b	CT	CBP + GEM (PD) TS-1 (PD) NVB (PD)	Demised	43
59	Female	IV	T2bN2M1b	CT	CBP + GEM (PD) TAX (PD)	Demised	27
58	Female	IV	T2aN2M1b	CT	CBP + GEM (PD) TAX (PD)	Demised	60
49	Female	IV	T3N2M1b	CT	CBP + GEM (PD) DOC (PR)	Demised	15

TNM=Tumor lymph node metastasis classification, OS=Overall survival, CT=Chemotherapy, RT=Radiotherapy, S=Surgery, CBP=Carboplatin, DOC=Docetaxel, GEM=Gemcitabine, IRESSA=Gefitinib, NVB=Navelbine, PEM=Pemetrexed, TAX=Paclitaxel, XELODA=Capecitabine, CR=Complete remission, SD=Stable disease, PD=Progressive disease, PR=Partial remission, TS-1=Titanium silicate-1 chemotherapy

Table 3: Two-year and 5-year overall survival rates of primary pulmonary lymphoepithelioma-like carcinoma patients (*n*=28)

	Number of deaths/number of patients[+]	2-year survival, % (95% CI)	5-year survival, % (95% CI)	Log-rank *P*
All patients	14/28	78.6 (66.8-89.3)	54.9 (36.3-68.9)	NA
Stage of disease				
I/II	0/8	100	100	0.0001
IIIA/B	2/7	85.7 (32.2-98.9)	85.7 (32.2-98.9)	
IV	12/13	61.5 (40.0-82)	9.6 (0.6-30.9)	

[+]At the end of follow-up period: December 31, 2016. NA=Not available, CI=Confidence interval

had a 5-year survival rate of 100%, which is higher than NSCLC Stage IA (73%). Therefore, it could inferred that early-stage disease (Stage I/II) PPLELC fares better than early-stage NSCLC in survival. The 5-year survival for Stage IIIA/IIIB PPLELC was 85.7% (95% CI: 32.2% to 98.9%), in contrast to 24% and 9% in NSCLC Stage IIIA and IIIB, respectively. Given that these figures fall outside the 95% confidence interval (CI), it could also be inferred that 5-year survival for Stage IIIA/IIIB disease in PPLELC is superior to NSCLC. In the Stage IV group, our 5-year survival was 9.6% (95% CI: 0.6%, 30.9%) while it was 13% for NSCLC. The latter value lies within the 95% CI, suggesting that the 5-year survival in Stage IV PPLELC is not better than NSCLC.

No more than 200 cases of PPLELC have been reported since Begin *et al.* first reported it some three decades ago.[14,15] In case series from China, Taiwan, and Hong Kong, 48.1%, 56.5%, and 31.6% of their patients had Stage I/II disease at presentation while only 5.8%, 10.9%, and 26.3% had Stage IV disease at diagnosis, respectively.[5,9,12] Interestingly, half (46.4%) in our series had metastatic disease at presentation [Table 4]. PPLELC may perhaps possess more potential for metastasis than what was previously thought or perhaps due to later presentation and diagnosis. When compared to NSCLC, the 5-year survival rate for PPLELC was more favorable stage for stage, with the sole exception of Stage IV.[13] However, our 5-year survival rate was not worse despite having more metastatic patients, and this could be attributed to the better survival outcomes of Stage III patients in our study.[9] We postulate that our improved survival might be related to a higher proportion of Stage IIIA/B patients (4 out of 7) having undergone surgical resection.[9] The authors acknowledge that this statement could represent a departure from standard guidelines in NSCLC and may not be standard practice in other centers. However, PPLELC patients with Stage IIIA or IIIB disease may possibly benefit from a multimodality approach (i.e., surgery with chemoradiation) rather than chemoradiation alone.

There are several limitations to our study. First, its retrospective nature and small cohort size mean that result relating treatment and prognosis remain inconclusive and could not be generalized. Unfortunately, small patient numbers are not unavoidable in any rare disease. Second, as standardized treatment guidelines currently do not exist, therapeutic options are up to the discretion of the managing oncologist. However, this is mitigated by the fact that a platinum-based regimen was the first-line chemotherapy used in all instances. Third, the long duration over which the cohort was derived meant that variability in staging practices (e.g., increasing use of PET, practice shifts in mediastinal staging from mediastinoscopy to EBUS-TBNA, etc.) was inevitable.

The significantly higher proportion of Stage IV disease (46.4%) in our study was surprising.[5,9,12] A plausible reason is the varying practices in staging workup, which are bound to exist in real-world clinical practice. This notwithstanding, delayed detection is unlikely to be cause in our cohort as our proportion of asymptomatic patients was higher than published series.[9] Another postulation is the unknown interaction of tumor biology, genetic factors, and the environment.[16] The "Chinese race" is not a single, homogeneous ethnicity, despite 90% of Chinese worldwide being classified as Han Chinese.[17] Some 56 ethnic minority groups exist in China. Although the majority of Chinese in Singapore are of immigrant ancestry from southern China, differences may have developed in our cohort as a result of different geography and milieu.

The majority of patients with PPLELC were asymptomatic and detected incidentally through health screening or opportunistic medical check-ups. With more CT scans being performed for lung cancer screening and coronary artery calcification scoring, it is likely that the incidence of PPLELC would rise.[18-21] In terms of diagnosis, the central location of this tumor within the mediastinum renders EBUS-TBNA, a useful tool in diagnosis and staging.[22-25] The authors believe that this is the first report documenting the potential use of EBUS-TBNA in PPLELC diagnosis. Finally, care must be taken to discern PPLELC from three differential diagnoses that exhibit similar morphologies on cytology: poorly differentiated carcinoma, malignant melanoma, and malignant lymphoma.[26] Fortunately, core biopsies could be obtained with EBUS-TBNA and potentially circumvent this problem. However, accurate interpretation hinges on prior awareness of this rare cancer.[15,27] It must be reiterated that sampling of coexisting necrosis or granulomatous inflammation (both of which could be intense) could easily lead to misdiagnosis.[26,28] *In situ* hybridization for EBER in cytological or histological samples remains crucial to diagnosis as it is present in more than 90% of Asian patients with PPLELC.[29]

Conclusion

PPLELC may possess a metastatic potential not unlike other NSCLC subtypes even though published studies report a low prevalence of metastases. Patients with Stage I to III disease have a better 5-year survival than other NSCLC subtypes except those with Stage IV disease, who tend to have similar survival to metastatic NSCLC.[30] Unlike NSCLC, patients with locally advanced PPLELC

Table 4: Proportion by disease stage of East Asia and Singapore Cohorts

Stage of disease	SGH data Singapore (*n*=28)	Liang *et al*.[9] China (*n*=52)	Chang *et al*.[12] Taiwan (*n*=46)	Ngan *et al*.[5] Hong Kong (*n*=19)
I/II (%)	28.6	48.1	56.5	31.6
III A/B (%)	25	46.1	32.6	42.1
IV (%)	46.4	5.8	10.9	26.3
IV (*n*)	13	3	5	5

SGH: Singapore General Hospital

regardless of substage classification may benefit from a more aggressive multimodality approach, i.e., surgery with chemoradiation. No standardized treatment regimens currently exist for this rare tumor. International collaborations through clinical trials are needed in order for physicians to gain a deeper scientific insight into the natural history and optimal therapy for each disease stage. This is with the eventual hope of standardizing treatment in the future.

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Conflicts of interest

There are no conflicts of interest.

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