Primary Lymphoepithelioma-like Carcinoma of the Lung in Singapore—A Rare Malignancy

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Research

Keywords: LELC, EBUS- TBNA, cancer, chemotherapy, EBV

Posted Date: February 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-240838/v1>

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Abstract

Background: Primary lymphoepithelioma-like carcinoma (LELC) of the lung is a rare histological type of lung cancer with a relatively better prognosis. It is common in Chinese population, is associated with Epstein Barr Virus (EBV), and has morphological similarities to nasopharyngeal carcinoma.

Methods: We retrospectively analysed medical records of patients with LELC at Tan Tock Seng Hospital, Singapore from November 2010 to January 2016 and evaluated baseline characteristics, staging, therapeutic interventions and survival.

Results: Ten patients were diagnosed with pulmonary LELC, all were Chinese. The median age (range) at diagnosis was 62 (42-88) years, with a female preponderance ratio of 4:1. All had Epstein-Barr virus encoded small non-polyadenylated ribonucleic acid positive status. Six (60%) patients had stage IV, 3 (30%) stage IIIA, and 1 (10%) stage IIA disease. The median overall survival was 24.2 (4.7-59.4) months; in stage II, IIIA, and IV it was 27.6, 20.7 (19.8-48.9), and 26.6 (4.7-59.4) months respectively. The 1-year, 2-year, 3-year, and 5-year survival rate was 90%, 50%, 30%, and 10% in the whole group, but 100%, 43%, 28.6%, and 14.3% in 7 patients who received chemotherapy. Gemcitabine/carboplatin was the most commonly used 1st line chemotherapy.

Conclusion: LELC is associated with Chinese ethnicity, younger age of onset, EBV, lack of smoking, advanced stage, and better prognosis than other subtypes of lung cancers. For improving outcomes, future efforts should focus on increased awareness, early diagnosis, development of an ASEAN registry and international collaboration. Options such as EBV-directed adopted immunotherapy or the role of EBV vaccine also merit evaluation.

Introduction

Lung cancer remains the cancer with highest mortality rate both globally and in Singapore causing more deaths than breast, prostate, colon, and pancreas cancer combined [1]. Histologically, adenocarcinoma is the most common subtype (41%) followed by small cell carcinoma (20%), squamous cell carcinoma (12%), large cell carcinoma and others (8.4%), and unspecified (16.3%) histology [2].

Primary pulmonary lymphoepithelioma-like lung cancer (LELC) is a rare subtype of non-small cell lung cancer (NSCLC), representing only 0.4% of all NSCLC. It is a subtype of large cell carcinoma of the lung, according to the World Health Organization histological classification [3]. However, in terms of prognosis and in contrast to other subtypes of lung cancer, LELC exhibits an improved prognosis with multimodality treatment [4, 5]. The median overall survival for *untreated* advanced NSCLC is 6 months, and if *treated* with chemotherapy or tyrosine kinase inhibitors (TKI's) is 1 year or 15.4 months respectively [6, 7]. The overall 1-year, 2-year, and 3-year survival rate in patients with advanced stage NSCLC treated with chemotherapy is 28.9%, 7.9%, and 3.3% [6, 7]. Contrary to this, median survival for advanced LELC described in the largest study of 52 patients to date is much higher at 39.1 months with 1-year, 2-year, and 3-year survival of 100%, 76%, and 61% respectively [8]; although, not quite as good as for

nasopharyngeal carcinomas (NPC) which has a 5 year overall survival in stage I and II of 90% and in metastatic stage III and IV of 60% [8, 33].

With regards to general characteristic and demographic features, while the median age of lung cancer is 70 years, LELC presents early and it is not associated with smoking. Instead, it has morphological similarities to undifferentiated carcinoma or nasopharyngeal carcinoma (NPC) shown to be associated with Epstein Barr Virus (EBV). LELC belong to the EBV-driven cancers such as NPC, Burkitt's lymphoma, post-transplant lymphoproliferative diseases (PTLDs), Hodgkin's lymphoma, and a few gastric carcinomas [9, 10]. Both its association with EBV and its incidence is more common in Asian compared to western population [11].

Despite EBV being prevalent worldwide, the geographic variation in the incidence of EBV related malignancies such as LELC in Chinese, nasopharyngeal carcinoma (NPC) in Southern Chinese people, Burkitt's lymphoma (BL) in sub-Saharan Africa, and infectious mononucleosis in teenagers and young adults in western countries, raises the possibility of genetic variation of EBV in different parts of the world [12]. In addition, Tzellos & Farrell described that a specific mutation of the EBV- EBNA3B gene (a tumour suppressor gene) may be linked to development of diffuse large B cell lymphoma (DLBCL) in a mouse model [12], demonstrating the potential different role viral genomic mutations may play in human disease around the globe.

LELC's better prognosis, younger age of onset, an association with EBV, and lack of an association with smoking, clearly sets LELC apart from other subset of lung cancers. However, the development of optimal treatment strategies and regimen have been fraught by its extremely low incidence (< 200 cases have been described to date worldwide) and predominance in emerging economies such as China, Taiwan, and Hong Kong [5, 13, 14]. Therefore, the limited literature on optimal therapeutic management, prompted us to evaluate the disease characteristics, behaviour, staging, therapeutic interventions and outcomes of LELC in our local population.

Methods

We retrospectively analysed medical records of patients with biopsy proven LELC, at our centre from November 2010 to January 2016. Diagnosis of LELC was based on the established WHO criteria. All patients were screened for and found to be negative for co-existing NPC. Data was collected on age, gender, history of smoking, ECOG status, serum albumin levels at diagnosis, tumour size and location, mode of diagnostic investigation, staging, EBV encoded small non-polyadenylated ribonucleic acid in situ hybridization (EBER-ISH) status and sites of metastasis among stage IV disease. Staging was based on seventh edition of the American Joint Committee cancer staging system. Therapeutic modalities and outcomes were described with respect to progression free survival and median survival from time of diagnosis up to December 2016. Approval from the institutional ethics review board was obtained.

Statistical analysis

We used software (SPSS, version 17; SPSS, Chicago, Ill) for all statistical analyses. The results were compared using a Wilcoxon two-sample test. P values were two sided and considered indicative of a significant difference if less than .05. Kaplan-Meier survival analysis was performed to obtain progression free survival and overall survival.

Results

Ten patients were diagnosed with primary pulmonary LELC during the study period and all were Chinese. The median age (range) at diagnosis was 62 (42-88) years with a female preponderance ratio of 4:1. Seven patients were non-smokers. ECOG score was 0 in six and 1 in four patients. Eight of the patients had an abnormal chest radiograph at first presentation, and 1 patient had a cystic mediastinal mass detected incidentally on endoscopic ultrasound (EUS). Tumour size was > 3 cm in 9 patients. Five patients were diagnosed by endobronchial ultrasound trans-bronchial needle aspiration (EBUS-TBNA) and three by transthoracic needle aspiration of lung mass. The remaining 2 were confirmed from biopsy of a metastatic site and resected specimen. Six patients were staged as metastatic cancer, while three were stage IIIA and one was stage IIA. The commonest metastatic sites among those with stage IV disease were lymph nodes and bone. Serum albumin was noted to be low (<3.7 g/dl) in 7 patients (**Table 1**).

Seven patients with primary pulmonary LELC received chemotherapy and five of them had gemcitabine/carboplatin as first line (**Table 2**). One received gemcitabine/cisplatin, and another received cisplatin/pemetrexed/bevacizumab as the first line agents. All treated patients had progression of disease requiring second line chemotherapy and three patients required further lines of chemotherapy. The average duration of freedom from progression after first line chemotherapy was 8.4 months. Five patients received palliative radiotherapy to sites of metastases and one underwent palliative hypophysectomy for metastasis to the pituitary gland.

Three patients in total, and 2 out of 7 who received chemotherapy were alive by October 2019. One patient was diagnosed to have mediastinal LELC, and underwent surgical resection. Subsequent thoracic imaging in 13 months revealed disease free status, suggesting that curative surgery in early disease should be considered. Our cohort had a median (range) overall survival of 24.2 (4.7-59.4) months. Among all patients, the 1-year, 2-year, 3-year, and 5-year survival rates were 90%, 50%, 30%, and 10%, whilst for the 7 patients with advanced LELC treated with chemotherapy (with or without radiotherapy), the 1-year, 2-year, 3-year and 5-year survival rates were 100%, 43%, 28.6%, and 14.3% respectively.

Of the 7 patients who had died, one was deemed unsuitable for chemotherapy, while two had declined chemotherapy. Two patients treated with palliative chemotherapy progressed and died after third line therapy (**Fig. 1**).

Case Descriptions

Case summary of a representative case along with radiographic and histological images are described below to illustrate the clinical profile of this cancer. A 63-year old Chinese male, ex-smoker with ECOG-1 status, was noted to have a right lung mass on chest radiograph on admission in November 2014. Computed tomography (CT) thorax revealed a 9.7 x 7.5 x 8.5 cm right lung lower lobe mass and metastatic deposits in liver and bone. He underwent endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) for diagnostic confirmation of stage IV pulmonary LELC. He was started on palliative gemcitabine + carboplatin in Dec 2014 followed by a chemo-break and was re-challenged with gemcitabine + carboplatin in August 2015, achieving a remission until Dec 2016 (**Fig. 2**). The EBER-ISH was positive on histopathology (**Fig. 3**).

Discussion

The overall incidence of primary pulmonary LELC is low. The highest incidence is found in the Chinese population. In Singapore, 76% of the population is Chinese, but, as little is known about the incidence of LELC in Singapore, we sought to study the characteristics, behaviour, and outcomes of LELC in our local population.

Since first described by Begin et al in 1987, only approximately 200 cases have been reported so far globally over last 3 decades, highlighting its rarity [8, 16]. With an incidence of 1500 new cases of lung cancer every year in Singapore, the estimated incidence in our population is 0.1%.

Although the gender predilection of LELC varies, our cohort showed a female predominance with predilection for non-smokers in keeping with the published literature. Chang et al from Taiwan [17], Liang et al from China [8], and Tay et al from Singapore [26] described female predominance in their cohorts similar to ours, whereas Han et al from China described male preponderance [19].

Median age in our cohort was 62 (42-88) years. Previous studies reported the median age of LELC patients to range from 47–58 years [15, 17, 18, 20, 26]. The median age in our cohort was older than those in previous studies but still younger than the reported median age of 70 years for NSCLC, asserting the onset of LELC at a younger age. The older age of the patients in our cohort could be the reflection of the catchment area of our hospital as it lies in the district with the highest number of residents above the age of 65 years [28].

All patients in our cohort were positive for EBV-encoded small non-polyadenylated RNA (EBER), affirming the association between EBV and pulmonary LELC in keeping with the existing literature. Most LELC cases reported in the literature are positive for EBER on in situ hybridization [14, 26]. In addition, Chang et al reported that a higher EBV serology titre represented higher tumour stage and larger tumour size [17]. Due to this, primary pulmonary LELC can be histologically indistinguishable from EBV associated LELC occurring in the nasopharynx (NPC) in Asian population [14, 21]. It is therefore necessary to differentiate NPC with metastasis to lung, from an early stage primary pulmonary LELC where surgical resection is recommended. Hence, all our patients were screened and cleared by ear, nose, and throat (ENT) surgeons for any concurrent nasopharyngeal involvement.

The majority of patients (60%) in our cohort had advanced (stage IV) pulmonary LELC. This is in contrast to the reports from China, Taiwan, and Hong Kong, where the majority of patients presented with early stage and only a minority presented with stage IV disease [8, 17, 27]. However, our results are in keeping with the study from Tay et al [26]. Additionally, at our centre, all lung cancer patients are initially staged using PET/CT of the body and MRI of the brain. Although unconfirmed, one of the reasons for the more advanced stage in our cohort could have been the up-staging of these cancers. This makes a direct comparison with previous reports difficult, where less sensitive and specific imaging techniques could have been used.

LELC is reported to be chemosensitive and radiosensitive cancer [22]. Seven patients were treated with chemotherapy in our cohort out of which 5 (71.4%) received gemcitabine/carboplatin as first line chemotherapy consistent with the published literature. Although the choice of first line chemotherapy was largely an extrapolation from chemotherapy used for NPC, it had shown to offer high disease control rate. Previous studies described good outcomes in patients with multimodality treatment [23]. Ho et al noted that 5-fluorouracil (5-FU)/cisplatin (FLP) demonstrated a high tumour response rate (60% partial response), with a median survival of 23.4 +/- 4.7 months [24]. Liang et al also reported that various regimes of chemotherapy such as paclitaxel/docetaxel + cisplatin/carboplatin, pemetrexed + cisplatin, gemcitabine + cisplatin, docetaxel/paclitaxel + cisplatin + 5-fluorouracil, gemcitabine + vinorelbine in advanced pulmonary LELC had a high disease control rate (>75%) [8].

The median (range) overall survival in our cohort was 24.2 (4.7-59.4) months with 1-year, 2-year, 3-year, and 5-year survival rates of 90%, 50%, 30%, and 10% respectively. Previous reports from China, Hong Kong, Taiwan, and Singapore have described median overall survival rates of 31, 39.1, 23.4, 27.6, and 43 months [5, 8, 23, 24, 26]. In a study of 52 patients (the largest study) with advanced LELC from China receiving chemotherapy (with or without radiotherapy), 1-year, 2-year, and 3-year survival rates of 100%, 76%, and 61% were reported [8]. The 2-year and 5-year survival rates described in another study from China were 90% and 74%, whereas a Singaporean study described 2-year and 5-year survival rates of 78.6% and 54.9% [25, 26]. Worse overall survival rates were seen in patients with higher grading and more advanced tumours [25]. Although the median overall survival and 1-year survival rate in our study were similar, the 2-year and 5-year survival rate in our cohort was lower. This is likely due to the greater proportion of patients with stage IV as well as the refusal of or being unfit to receive chemotherapy in patients with early stages.

When analysed by stage, the median survival in stage II, IIIA, and IV was 27.6, 20.7 (19.8-48.9), and 26.6 (4.7-59.4) months respectively. This is higher compared to NSCLC, where the median survival for stage III and IV is 13.7, and 4 months respectively [29, 30]. The stage by stage comparison with survival data for LELC from other studies showed that our median survival was lower but still significantly higher than the corresponding stages for NSCLC as a whole.

Thus, our cohort demonstrated similarities and differences from other existing literature which may be due to our study limitations. It is a retrospective, single centre study with a small sample size. However, in

view of the rarity of this subtype of lung cancer, our study highlights the biological characteristics of LELCs and demonstrated the better survival of these patients, adding to the growing body of evidence and understanding of this rare condition. The biology of LELCs appears to be similar to NPC patients and it is therefore reasonable to consider therapeutic options available for NPC. One such consideration would be the use of adoptive immunotherapy once the results of the on-going phase III trial re-infusing EBV-specific autologous cytotoxic T-lymphocytes are known [31]. The publication of this trial is eagerly awaited. Another consideration would be to use EBV vaccination against virulent EBV antigens such as LMP2 potentially together with other treatment modalities [32].

In conclusion, comparing our study to the reports from China, Hong Kong, and Taiwan, our cohort was similar in terms of low incidence of LELC, Chinese preponderance, association with EBV, lack of smoking, younger age of onset and improved survival compared to other subtypes of lung cancer. Our study differed in terms of older patients, patients with more advanced stage disease, and henceforth an inherent poorer survival. For improving outcomes, future efforts should focus on increased awareness, early diagnosis, development of an ASEAN registry and international collaboration. Options such as EBV-directed adopted immunotherapy or the role of EBV vaccine also merit evaluation.

Abbreviations

LELC: lymphoepithelioma-like carcinoma; EBV: Epstein Barr Virus; EBER: Epstein-Barr virus encoded small non-polyadenylated ribonucleic acid; ASEAN: Association of Southeast Asian Nations; NSCLC: Non-small cell lung cancer; TKI: Tyrosine kinase inhibitor; NPC: Nasopharyngeal carcinoma; PTLT: Post-transplant lymphoproliferative diseases; BL: Burkitt's lymphoma; DLBCL: Diffuse large B cell lymphoma; ECOG: Eastern Cooperative Oncology Group; EBUS-TBNA: Endobronchial ultrasound guided transbronchial needle aspiration; LMP2: Latent membrane protein 2.

Declarations

Ethics Approval: Approval from the institutional review board, domain specific review board (DSRB) was obtained. DSRB Ref 2019/00955

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest: J.D., D.Y.H.T., J.S., S.K.G., A.C.K., Y.K.Z., D.C., S.J.W., O.K.C., and A.V. have no competing financial interests to disclose.

Funding: This study was retrospective and hence did not receive any funding.

Contribution of authors: Conceptualisation : AV & JS. Data collection & analysis: JD & AV. Drafting the manuscript : DYHT, SKG, ACK, YKZ, DC, JWS. Critical review and revision of the manuscript : DYHT, YKZ, DC, SJW, OKC.

Acknowledgment: Authors would like to thank Dr. Chua Khoon Leong, and Ms. Ivy Yu Ling Ling, for their valuable contribution in preparing the figures and the administrative work.

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Tables

Table 1. Baseline characteristics of the pulmonary LELC patients

Variable	Category	N (%)
Patients	Total number	10
Age at diagnosis	Years	62 (42-88)
Gender	Male	2 (20)
	Female	8 (80)
Race	Asian	10 (100)
Smoking	Yes	2 (20)
	No	7 (70)
	Unknown	1 (10)
ECOG status	0	6 (60)
	1	4 (40)
Tumour Size	< 3 cm	1 (10)
	> 3 cm	9 (90)
Stage	I	0 (0)
	II A	1 (10)
	III A	3 (30)
	IV	6 (60)
Primary site	Lung, NOS	3 (30)
	Upper lobe, lung	1 (10)
	Middle lobe, lung	0 (0)
	Lower lobe, lung	6 (60)
Mode of diagnostic investigation	EBUS- TBNA	5 (50)
	TTNA	3 (30)
	Biopsy of non-pulmonary metastatic Site	2 (20)
Therapeutic modality	Palliative chemotherapy	7(70)
	Radiation therapy (Isolated or in combination with chemo)	5(50)
	Declined chemotherapy	2(20)

Variable	Category	N (%)
	Surgical resection	1 (10)

Data presented as number (%) or median (range)

ECOG: Eastern Cooperative Oncology Group, NOS: Not otherwise specified, EBUS-TBNA: Endobronchial ultrasound guided Transbronchial needle aspiration, TTNA: Transthoracic needle aspiration

Table 2. Clinical information of 10 patients with pulmonary LELC.

Case no. /sex/age years/race	Smoking history	Tumour location	Size in cm	TNM stage	EBER	Treatment	Outcome (Alive/Deceased)
1/F/53/C	No	RLL	3.0x4.0	IVB (T3 N3 M1c)	+	ChT (GP x6, PC x6) +RT	Alive, 59.4 months
2/M/63/C	Yes	RLL	9.3x7.4	IVB (T4 N2 M1c)	+	ChT (GP x14)	Deceased, 32.4 months
3/F/65/C	No	LLL	8.0x5.0	IIIA (T3 N0 M0)	+	ChT (GP x6, C x6) +RT	Deceased, 20.7 months
4/M/52/C	Yes	BLN	2.0x1.4*	IVA (T1b N2 M1a)	+	ChT (GP x6, N x3, D x3) +RT	Deceased, 20.8 months
5/F/49/C	No	LSH	6.2x5.3	IVA (T3 N2 M1b)	+	ChT (GP x6, Pac x4, D x3)	Deceased, 16.9 months
6/F/42/C	No	RUL	6.4X6.3	IVA (T3 N2 M1a)	+	ChT (PPB x6, G x6)	Alive, 49.5 months
7/F/73/C	Unknown	MS	6.9x4.7	IIIA (T3b N1 M0)	+	SG, RT, declined ChT.	Alive, 48.9 months
8/F/88/C	No	RLL	5.0x4.8	IIA (T2b N0 M0)	+	RT, unfit for ChT/SG	Deceased, 27.6 months
9/F/67/C	No	RLL	9.1x8.9	IVB (T4 N2 M1c)	+	Declined treatment	Deceased, 4.7 months
10/F/61/C	No	LLL	4.6x3.9	IIIA (T2b N2 M0)	+	ChT (GP x6, N x2, D x1)	Deceased, 19.8 months

TNM, tumour-node-metastasis; F, female; M, male; C, Chinese; RLL, right lower lobe of lung; LLL, left lower lobe; BLN, bilateral lung nodules; LSH, left suprahilar; RUL, right upper lobe of lung; MS, mediastinal; RH, right hilum; +, positive; SG, surgery; ChT, chemotherapy; RT, radiotherapy; EBER, Epstein-Barr virus-encoded

RNA; D, docetaxel; PPB, pemetrexed + cisplatin+ bevacizumab; GP, gemcitabine + carboplatin/cisplatin; P, cisplatin/carboplatin; C, Capecitabine; LELC, lymphoepithelioma-like carcinoma N; Nivolumab, Pac; paclitaxel. * largest among multiple nodules.

Figures

Figure 1

A) Kaplan-Meier Survival Curve for the 10 patients with LELC. B) Kaplan-Meier survival curve for the 7 patients with advanced LELC who received palliative chemotherapy.

Figure 2

A) Chest radiograph with right lower zone consolidation. B) Computed tomography with large right lower lobe mass lesion. C) Endoscopic image of right main bronchus with no Endobronchial lesions. D) EBUS – TBNA of station 4R Lymph node.

Figure 3

Epstein-Barr virus encoded small non-polyadenylated ribonucleic acid in situ hybridization (EBER-ISH) was positive in all cases. The histopathological representation of some of the patients in this cohort is shown below. A) Biopsy from lung revealing clusters of elongated epithelial cells with prominent nucleoli in some areas associated with a desmoplastic stroma. (H&E, original magnification x200). B) Tumour cells decorated by antibody against high molecular weight cytokeratin CK5/6. (Optiview detection kit, Ventana. Original magnification x200). C) Diffuse positive signals within nuclei of tumour cells on EBER-ISH. (Iview blue detection kit, Ventana. Original magnification x400). D) Lymph node affected by metastatic lymphoepithelioma like carcinoma. Note the indistinct cytoplasmic borders and prominent nucleoli. (H&E, original magnification x400).