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Lymphangitic carcinomatosis: A common radiographic manifestation of local failure following extended pleurectomy/decortication in patients with malignant pleural mesothelioma

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ABSTRACT

Introduction: The lymphangitic carcinomatosis (LC) pattern of metastatic malignancy is associated with a poor prognosis but is currently not well defined in malignant pleural mesothelioma (MPM). Here, we report the incidence and prognostic significance of the radiographic development of LC in MPM following extended pleurectomy/decortication (EPD).

Methods: Consecutive patients with biopsy-proven MPM undergoing EPD with intraoperative photodynamic therapy (PDT) at our institution from 2008 to 2014 were included in this retrospective study. Patients without available post-surgical clinical or imaging data for direct review were excluded. CT images were reviewed by an experienced, board-certified thoracic radiologist and confirmed by consensus review. Overall survival (OS) and progression-free survival (PFS) were calculated by Kaplan Meier methodology. Hazard ratios were compared with a cox proportional hazard model.

Results: 44 patients underwent EPD with PDT during the study period and had available clinical and imaging data. During the follow-up period (median 34 months), 17 patients (39%) developed LC at a median of 10 months after surgery (IQR 5–21 months). 16 of the 17 patients who developed LC (94%) died during the follow-up period, compared to 17 of the 27 who did not develop LC (63%). OS for the LC versus non-LC group was 53% versus 93% at 1 year and 18% versus 67% at 3 years. LC was significantly associated with a lower OS (HR 4.07; 95% confidence interval 1.44–11.48; $p = 0.008$). PFS for the LC group versus non-LC group was 8 months (IQR 5–9 months) compared to 17 months (IQR 11–24 months) ($p < 0.001$).

Conclusion: LC is a common form of failure in MPM following EPD and is associated with a poor prognosis. Thus, further studies are warranted to determine if any evidence of preoperative LC should be an absolute contra-indication to EPD and may warrant an EPP or no surgery at all.

1. Introduction

Lymphangitic carcinomatosis (LC) is a pattern of metastasis where tumor spreads along the pulmonary parenchymal lymphatics which produces a characteristic pattern of interlobular septa and axial peribronchial thickening. This pattern of metastatic disease is most typically associated with advanced disease and is observed in a range of malignancies including breast, lung, colon, and genitourinary origin. The presence of LC is usually associated with a poor prognosis and is readily detectable by computed tomography (CT) [1]. To date, there is limited data in the literature describing the occurrence of LC in MPM or its prognostic significance [2,3].

MPM typically progresses through local extension in the pleural space and through adjacent structures such as the chest wall and diaphragm. Metastasis from MPM to the regional lymph nodes is also very common; however, the extension of tumor into the pulmonary lymphatics currently is less well characterized. In a previous review of 200 patients with MPM, 13.5% displayed lymphangitic involvement of the

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lung parenchyma on pathology [4]. However, apart from this study, LC in MPM has not been well described, with no literature, to our knowledge, describing LC as a pattern of local relapse in the post-pleurectomy/decortication population.

Extended pleurectomy/decortication (EPD) is performed in MPM with the intent to achieve a gross macroscopic resection and entails stripping of the parietal and visceral pleura, leaving the uninvolved lung intact [5]. By leaving the lung intact, EPD is generally associated with a lower post-operative morbidity and possibly better overall survival compared to en block extrapleural pneumonectomy (EPP), though this is an area of active research and discussion in the MPM community [6–11]. Given the potential for increased risk of retained microscopic residual disease in EPD [12] compared to EPP, at our institution, most patients also receive intraoperative pleural photodynamic therapy (PDT) with the goal of eradicating residual microscopic disease [13]. With all therapy for MPM, the failure rate is high and an improved understanding of the predictive and prognostic implications of radiologic findings is important for disease management and prognostication [14].

In this retrospective study, we sought to characterize the incidence and prognostic significance of the appearance of the radiographic pattern of LC in MPM patients who have undergone EPD.

2. Methods

2.1. Patient population

IRB approval was obtained for this retrospective single institution study. All consecutive adult patients with a biopsy-proven diagnosis of MPM who underwent EPD [15] and intraoperative PDT [16] with either porfimer sodium or HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide) at our institution between 2008 and 2014 were included in this study. Patients were excluded from this study if they did not have post-operative clinical or CT imaging data available for direct review at our institution. They were excluded if post-operative imaging CT exams were of inadequate diagnostic quality, due to image artifact or incomplete anatomic coverage of the chest, or did not have a slice thickness of 5 mm or less. To avoid acute post-operative changes, such as edema, CT scans were excluded from review if they occurred within 30 days of surgery.

2.2. Electronic medical record review

The electronic medical records of the patients included in this study were reviewed for demographic and clinical data, including patient age, sex, ethnicity, histology, stage at surgery, nodal stage at surgery, date of surgery, neoadjuvant chemotherapy, adjuvant chemotherapy, number of CTs within the follow up period, and date of death. Ethnicity was defined as White, Black, Hispanic, Asian/Pacific Islander, other and unknown. Stage and nodal stage was defined based off the 7th edition of the International Association for the Study of Lung Cancer TNM classification for MPM [17] after review of the operative and pathology reports by a multidisciplinary panel of thoracic oncology experts.

2.3. CT image review

CT images for each patient were reviewed by an experienced, board-certified thoracic radiologist with over 16 years of experience in thoracic radiology (SK) for the presence of the characteristic findings of LC. CT imaging findings consistent with LC include asymmetric, regional, progressive interlobular septal thickening often accompanied by axial peribronchial thickening on the side of the EPD. Patency of the ipsilateral pulmonary veins were assessed to ensure that findings were not on the basis of pulmonary venous obstruction by tumor. Imaging deemed consistent with LC by the radiologist was then reviewed by multi-disciplinary consensus of members of the institutional mesothelioma and pleural program, including radiation oncologists and pulmonologists, both highly experienced in the imaging findings of MPM. Patients were considered positive for LC if deemed positive by consensus review. We defined upper and lower fields by the level of the left pulmonary artery. FDG avidity was not assessed on FDG-PET/CT since this modality is not typically used to follow MPM patients post EPD, limiting the number of scans available for review in this cohort.

2.4. Clinical endpoints

Overall survival (OS) was calculated as the time from the date of surgery to time of death (if applicable) as recorded in the electronic medical record. Progression-free survival (PFS) was calculated as the time (in months) from the date of surgery to clinical or radiological evidence of progression as determined by the oncologist and recorded in the electronic medical record.

2.5. Statistics

Descriptive statistics were calculated and compared with chi-squared tests for categorical variables, student's *t*-tests for continuous variables, and Wilcox rank-sum for follow-up time and number of CTs reviewed. The primary outcome was overall survival from the time of surgery as calculated by Kaplan Meier methodology. Secondary outcomes were the time-to-development of LC and progression-free-survival (PFS). Two-sided log rank tests were used to test the difference in survival between patients that developed LC and those that did not. Cox proportional hazard models were used to predict OS with variables age, sex, ethnicity, stage, histology, chemotherapy category, and development of LC. Univariate analysis was first conducted followed by multivariate analysis with all variables included simultaneously. All analyses were conducted with STATA 13.1 statistical software (STATA Corp, College Station, TX). All tests used $p < 0.05$ to determine significance.

3. Results

3.1. Study population

A total of 92 patients underwent EPD with intraoperative pleural PDT during the study period, of which 44 patients had clinical and imaging data 30 days after surgery available for review. The mean age of the cohort was 63.2 years old (standard deviation [sd] 9.9), with 78% of the patients being male. The majority of the patients had epithelial histology (37 patients; 84%) with the remainder (7 patients; 16%) found to be of non-epithelial histology at the time of surgery. A total of 33 out of 44 patients had clinical pathology reports that commented on resected adherent lung. No patients had reported evidence of lymphangitic carcinomatosis, noting that 3 patients did have microscopic foci of lymphatic or lymphovascular invasion detected on the resected samples. The median follow-up period for the cohort of 44 patients was 34 months (interquartile range [IQR] 15–46 months) following EPD with a median of 5 (IQR 3–10) postoperative CTs reviewed per patient. See Table 1 for patient demographics and clinical characteristics. Of note, only 4 patients in the LC group had FDG-PET/CT imaging available post-operatively precluding evaluation of this modality for the assessment of the LC radiographic pattern.

3.2. The development of the radiographic appearance of LC is a common mode of local relapse post-EPD

A total of 17 of the 46 (39%) patients developed the typical radiographic manifestation of LC in the ipsilateral lung during the follow-up period (Fig. 1), noting that two of these patients had microscopic foci of lymphatic or lymphvascular invasion in resected tumor at surgery. Two of the patients in the cohort developed diffuse LC in bilateral lungs. Five

Table 1
Patient demographics and clinical characteristics.

Variable	Overall cohort	LC	No LC	p
N	44 (100%)	17 (39%)	27 (61%)	
Age, mean (sd)	63.2 (9.9)	61.5 (11.2)	64.3 (8.9)	0.377
Sex, male	35 (78%)	15 (88%)	20 (74%)	0.257
Ethnicity				0.216
White	40 (91%)	15 (88%)	25 (93%)	
Black	0 (0%)	0 (0%)	0 (0%)	
Hispanic	2 (5%)	0 (0%)	2 (7%)	
Asian/Pacific Islander	0 (0%)	0 (0%)	0 (0%)	
Other	1 (2%)	1 (6%)	0 (0%)	
Unknown	1 (2%)	1 (6%)	0 (0%)	
Stage				0.347
Stage 1	0 (0%)	0 (0%)	0 (0%)	
Stage 2	3 (7%)	0 (0%)	3 (11%)	
Stage 3	23 (52%)	10 (56%)	13 (48%)	
Stage 4	18 (41%)	7 (41%)	11 (41%)	
Nodal Stage				0.058
N0	12 (27%)	1 (6%)	11 (41%)	
N1	4 (9%)	2 (11%)	2 (7%)	
N2	27 (61%)	14 (82%)	13 (47%)	
N3	1 (2%)	0 (0%)	1 (4%)	
Histology				0.349
Epithelioid	37 (84%)	13 (76%)	24 (89%)	
Biphasic	6 (14%)	3 (17%)	3 (11%)	
Sarcomatoid	1 (2%)	1 (6%)	0 (0%)	
Chemotherapy				0.433
None	0 (0%)	1 (6%)	1 (4%)	
Neoadjuvant	2 (5%)	2 (12%)	3 (11%)	
Adjuvant	5 (11%)	9 (53%)	20 (74%)	
Both	29 (66%)	5 (29%)	3 (11%)	
Number of CTs reviewed, median (IQR)	5 (3-10)	3 (2-6)	7 (4-10)	0.075
Follow-up in months, median (IQR)	34 (15-46)	21 (9-31)	40 (27-56)	< 0.001

(29%) patients developed localized LC while 12 (71%) developed diffuse LC. Of the 5 patients who developed localized LC, 3 were in the lower lung field, defined by the left pulmonary artery, while 2 were in the upper lung field. Characteristics of the cohort stratified by the development of LC are shown in Table 1. There were no significant differences in age, sex, or ethnicity between the LC and non-LC group. There were also no significant differences between stage, histology, number of CT exams and chemotherapy between the two groups.

The nodal stages were not significantly different between the two groups (see Table 1; p = 0.058). However, when stratifying by node positive vs. negative patients, those who developed LC were more likely

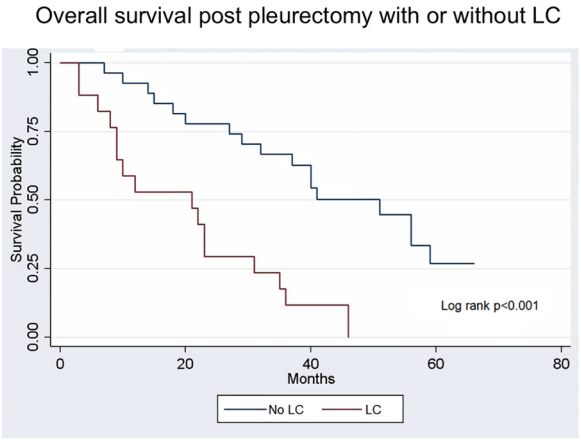

Fig. 2. Overall survival is decreased when LC manifests on CT imaging following EPD. A Kaplan Meier analysis of overall survival for all 44 patients in the cohort who underwent EPD with PDT reveals a significantly worse overall survival for patients who develop radiographic findings consistent with LC on CT. Significant differences in OS were seen between the two groups for the overall study follow-up period.

to be node positive (16/17 or 94% vs. 16/27 or 61%, p = 0.011). Patients who developed LC had a follow-up time of 21 months (IQR 9–31 months), while those who did not develop LC had a median follow-up of 40 months (IQR 27–56 months). This difference in follow-up period between the two groups was statistically significant (p < 0.001). The median time to the development LC following EPD was 10 months (IQR 5–21 months).

3.3. The development of radiographic LC is associated with poor overall survival

During the 40-month follow-up period, 33 of the 44 patients (75%) died. A total of 16 of the 17 (94%) who developed LC died during the follow-up period. In comparison, a total of 17 of the 27 (63%) patients with no evidence of LC died during the study period. The difference in overall survival between the LC and non-LC groups during the follow-up period was statistically significant (p < 0.001, Fig. 2). The median OS in the non-LC group was 51 months (IQR 27-remains alive) and 21 months (IQR 9–31) in the LC group.

This survival difference was also seen at 1 year following EPD where there was 93% survival for the non-LC group (95% CI 74%–98%) and 53% survival in the LC group (95% CI 28%–73%). At 3 years following EPD, survival in the non-LC group was 67% (95% CI 46%–81%)

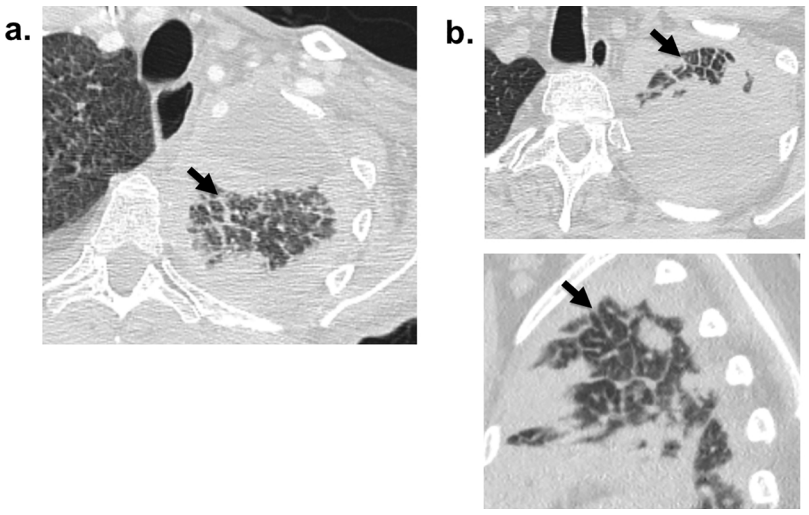

Fig. 1. Appearance of MPM lymphangitic carcinomatosis on computed tomography (CT). (a.) An axial image of a unenhanced CT (lung windows) in a 61 year old male and (b) axial and sagittal images in a 62 year old male both demonstrating extensive interlobular septal thickening typical of LC. Both patients have biopsy proven MPM s/p EPD on the left with recurrent disease.

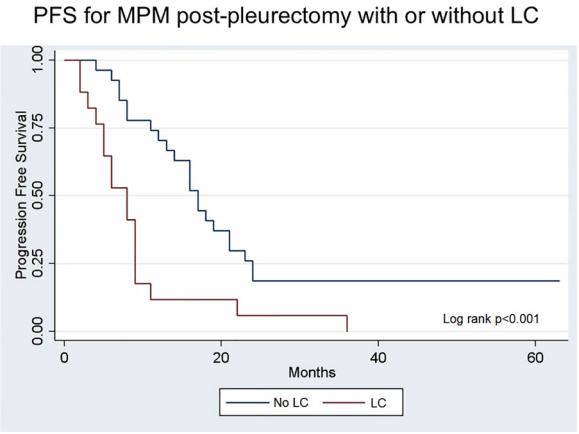

Fig. 3. Disease-free survival is decreased when LC manifests on CT imaging following EPD, relative to patients without LC. A Kaplan Meier analysis of progression-free survival for all 44 patients in the cohort who underwent EPD with PDT reveals a significantly worse overall PFS for patients who develop radiographic findings consistent with LC on CT. Significant differences in PFS were seen between the two groups for the overall study follow-up period.

compared to 18% (95% CI 4%–38%) in the LC group. At 5 years, survival in the non-LC group was 27% (95% CI 10%–47%) compared to 0% in the LC cohort. On multivariable analysis using the cox proportional hazard model, the development of LC was significantly associated with OS (Hazard ratio [HR] 4.07; 95% confidence interval [95% CI] 1.44–11.48; $p = 0.008$).

Progression-free survival (PFS) was also significantly different between the two groups (Fig. 3, $p < 0.001$). The median PFS in the non-LC group was 17 months (IQR 11–24) compared to 8 months (IQR 5–9 months) in the LC group. PFS for the non-LC group at 1 year was 74% (95% CI 53%–87%), compared to 12% (95% CI 2%–31%) in the LC group. At 3 years, PFS in the non-LC group was 19% (95% CI 7%–34%) compared to 6% (95% CI 0.4%–24%) in the LC group.

4. Discussion

Pulmonary LC is a pattern of tumor metastasis that has been described for a range of primary malignancies [18], most commonly breast cancer, lung cancer and cancers of gastrointestinal origin. The incidence of LC has been estimated at approximately 6–8% in some cancers [19] and generally portends a worse prognosis. There is little published literature describing the incidence of LC in MPM. To the best of our knowledge, this is the first report characterizing the incidence of this pattern of metastasis in MPM patients who have undergone lung-sparing EPD. When LC occurred in our cohort, it presented in the ipsilateral lung, possibly a consequence of the disrupted pleural barrier to local extension of disease in the pleurectomy space into the lung. Bilateral disease occurred in 2 patients with diffuse LC.

Here we have demonstrated that the LC pattern of metastasis is a common pattern of failure in the post-EPD setting with the radiographic appearance of LC in patients (39%) who undergo EPD with intraoperative PDT for MPM. This is in keeping with the reported incidence of 44% lymphatic invasion in a population of epithelioid diffuse MPM reported by Kadota et al [3]. This suggests that the performance of EPD, at least when performed together with PDT, does not result in an increased incidence in LC compared to the non-surgical population. However since PDT is intended to destroy microscopic tumor after macroscopic resection [20](5), it is possible that the use of this intraoperative technique in our population may have decreased the rate of LC and increased OS and PFS in our cohort compared to patients that do not undergo PDT.

As has been reported in other malignancies, we found that the appearance of the radiographic characteristics of LC on post-surgical follow-up CT was associated with a statistically worse OS and PFS compared to patients that did not develop radiographic evidence of LC on CT. In our cohort of 44 patients status post EPD, the median overall survival in those that developed LC was 21 months compared to 51 months in patients that did not develop LC. Kadota et al. [3] reported an OS of 11 months for patients with lymphatic invasion compared to 21 months for patients that did not develop invasion in their population of patients with MPM. Other studies have demonstrated a prognostic significance for the development of LC. For example, a reported 2–4% 2-year survival in breast cancer [21] and mean survival of 13 months in lung cancer in patients that developed LC [22]. Harold et al reported a 3-month survival for patients with cancer that developed LC [23].

Our study has several limitations to be considered. As this data was not collected prospectively, clinical variables that may influence the manifestation of LC on imaging cannot be controlled for including surgical and PDT factors. Our results may not be generalizable to patients that do not undergo EPD with intraoperative PDT. In addition, due to the retrospective nature of this study, surgical pathology was not collected prospectively for direct review. As a result, while none of the clinical surgical pathology reports described the presence of LC in resected specimens, the presence of LC in resected specimens at surgery can not be assessed for specifically, though felt to be unlikely. Finally, the diagnosis of LC was made based on radiographic changes on computed tomography (CT) rather than histologic confirmation since none of the patients who developed LC had available biopsy or autopsy data. However, while LC is a histologic diagnosis, it manifests with a characteristic radiographic pattern on CT [24] that has a reported diagnostic accuracy of 85% [25]. Since CT is the primary imaging modality used for therapeutic surveillance in MPM, it remains important to understand the prognostic implications of this radiographic pattern on CT imaging, even in the absence of histological correlation.

In conclusion, for the first time, we report LC as a common pattern of failure in MPM patients who have undergone EPD and that the manifestation of LC portends a poor prognosis. Awareness of the implications of this radiographic pattern on CT is useful for therapy surveillance and prognostication in this patient population. It would also be interesting to explore FDG-PET/CT as a modality for characterization of LC in the patients with MPM following EPD since this modality has shown value in detection of LC [26]. Further studies are warranted to determine if any evidence of preoperative LC should be an absolute contraindication to EPD and may warrant alternative consideration of either EPP or non-surgical management.

Conflict of interest statement

The authors have no conflicts of interest to disclose related to this work.

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