CLINICAL VIGNETTE

Distinguishing Synchronous Multiple Primary Lung Cancers from Metastatic Disease

David D. Kim, M.D.

Case Report

A 68-year-old woman with a history of smoking 30 packs per year and COPD underwent further evaluation for an abnormal routine chest X-ray. CT of the chest revealed a spiculated 2.2 cm mass in the left lower lobe, consistent with lung cancer. There was a 1.4 cm heterogeneous density in the right upper lobe. The mediastinal lymph nodes were not enlarged. A PET-CT scan subsequently showed intense hypermetabolism (SUV 7.9) in the left lower lobe mass, mildly increased metabolic activity (SUV 1.0) in the smaller lesion in the right upper lobe, and no abnormal foci of hypermetabolism in the mediastinum or elsewhere in the body. Given the neoplastic nature of the right upper lobe lesion was less certain, it was biopsied under CT-guidance. Pathology showed well to moderately differentiated pulmonary adenocarcinoma.

The patient's thoracic surgeon performed a mediastinoscopy and lymph node biopsy, revealing multiple uninvolved lymph nodes in the mediastinum. A left lower lobectomy of the larger mass was performed, removing a 2.1 cm, moderately differentiated adenocarcinoma. Pathologic stage was T1b N0. The patient's case was presented at multidisciplinary tumor board, and the possibility was raised that he had two synchronous primary lung adenocarcinomas rather than metastatic disease. Definitive treatment of the second cancer was recommended. Due to her decreased pulmonary reserve, the patient underwent a wedge resection of the right upper lobe, yielding a 1.3 cm, well to moderately differentiated adenocarcinoma. Additional lymph nodes from the right paratracheal region were uninvolved. Pathologic stage was T1a N0. The pathologist compared the two cancers and reported the morphologic appearances were slightly different. Since the patient was believed to have had two primary stage I lung cancers, she was not recommended to undergo adjuvant chemotherapy. At the time of this report, the patient is alive without evidence of recurrence 5 years from her pulmonary wedge resection.

Discussion

This case highlights the importance of recognizing multiple primary lung cancers (MPLC). There is a risk of assuming metastatic lung cancer when patients present with multiple tumors in the lung and are diagnosed with lung cancer. Such patients may be offered palliative chemotherapy without being given a chance for potentially curative surgery. Patients with MPLC can be cured of their cancer as evidenced by this case report. This patient is considered to be cured of her original lung cancers as she has been cancer free for 5 years. Her outcome would not have been as good if she were offered chemotherapy without resection.

Based on the literature, the incidence of MPLC ranges from 0.2 to 20%.[1] The incidence may be rising due to earlier detection of lung cancer using computed tomography.[2] Therefore, MPLC is an entity that is not rare and practitioners have a significant chance of encountering it. MPLC can present synchronously or metachronously and can be located in the same lobe, in different lobes of the ipsilateral lung, or in contralateral lungs. The patient in this case report had synchronous primary lung cancers in contralateral lungs.

Clinicopathologic criteria for determining potential MPLC was first described in 1975 by Martini and Melamed.[3] The criteria they used consisted of the following: Tumors had to be physically distinct and separate. Histology had to be different (e.g., adenocarcinoma vs. squamous cell carcinoma). If the histology were the same, then there could be no carcinoma in the lymphatics common to both and no metastasis outside the lungs. Tumors arising from carcinoma in situ was another criteria that could be used when histology was the same. Criteria for metachronous MPLC also included being cancer free for at least 2 years. Martini and Melamed found 50 patients that met this criteria over a 20-year period at their hospital. Sixty-six percent of these patients had tumors located in different lungs and 66% had the same histology. The majority of the patients underwent resection of their tumors, consisting of pneumonectomy, lobectomy, or wedge resection. Of the 18 patients with synchronous MPLC, 20% were alive after 5 years. The authors concluded that survival in this group with synchronous MPLC treated with resection was similar to the survival of patients with single lung cancer treated with resection. Therefore, recognition of MPLC was critical.

Since the report by Martini and Melamed, there have been many more retrospective studies reporting favorable outcomes of patients surgically treated for MPLC. Chang et al[4] reported a series of 92 patients surgically treated for synchronous MPLC.

The most common operation was lobectomy for tumors in the same lobe and lobectomy with wedge resection for tumors in different lobes. Adenocarcinoma was the predominant histology for 87% of patients. The 5-year survival for these patients with synchronous MPLC was 35.3%. Multivariate analysis showed lymph node metastasis was a significant poor prognostic factor and 5-year survival for patients with and without lymph node involvement were 15.5% and 52.5%, respectively. The authors recommended complete surgical resection of node-negative synchronous MPLC. A similar study by Leyn et al[5] reported on 36 patients with bilateral synchronous MPLC who underwent bilateral resection and found a 5-year survival of 38%. Limited lung resection did not seem to have a negative impact on survival. The authors concluded that the survival rate was much higher than the historical survival of stage IV disease and recommended an aggressive surgical approach for synchronous MPLC. A larger series by Finley et al[6] of 175 patients surgically treated for synchronous MPLC reported a 3-year overall survival of 64% and a median overall survival of 67.4 months. The patients that had stage I synchronous MPLC were reported to have survival rates similar to single lung cancers matched for stage. Yu et al[7] looked at the survival of 97 patients with synchronous MPLC and a group of solitary primary lung cancer without mediastinal lymph node metastasis who underwent resection during the same time period. When matched for stage, there was no difference in overall survival. Tumor size greater than 3 cm was an independent negative predictor of survival in multivariate analysis.

The algorithm for workup of potential MPLC begins when multiple nodules are found on CT scan.[6] FDG PET-CT scan is a standard part of lung cancer staging and can be used to evaluate for extrapulmonary metastasis and mediastinal lymph node involvement. Interestingly, Dijkman et al[8] showed that the FDG PET delta SUV (difference in SUV between two tumors) in synchronous MPLC was significantly greater than the delta SUV in metastatic pulmonary disease. The authors concluded that SUVs from FDG PET can be helpful in distinguishing synchronous MPLC from metastatic disease and further investigation was warranted. The patient in this case report had a PET-CT scan showing SUVs of 7.9 and 1.0. This difference in SUV was considered to be large by the reading radiologist and consistent with MPLC. If feasible, CT-guided biopsy of each nodule should be considered to confirm malignancy and determine histology. In the workup of multiple nodules, it is not uncommon for the pathology of smaller nodules to return benign.[5] Mediastinoscopy should be used to confirm that mediastinal lymph nodes are not involved. The type of resection will depend on the locations of the tumors and the patient's pulmonary reserve as determined by pulmonary function tests.

It is difficult to be certain that multiple lung cancers are different primaries rather than a primary with intrapulmonary metastasis when the histology is the same. A variety of studies have attempted to establish whether multiple lung cancers are or are not clonally related by using molecular analysis. These studies have used loss of heterozygosity, comparative genomic hybridization arrays, and mutation analysis in genes such as p53, EGFR, and KRAS in their methods.[9-13] Some of these studies reported that molecular characterization of clonality revealed a difference in outcomes, while other studies reported no difference. Gerard et al[14] reported molecular characterization contradicted Martini and Melamed criteria determination of MPLC in 32% of cases. Comprehensive histologic assessment (e.g., based on different percentages of acinar, papillary, bronchioloalveolar, and solid adenocarcinoma subtypes) was consistent with molecular characterization in 91% of cases. The authors recommended the use of comprehensive histologic assessment as a faster and more cost effective method to determine MPLC vs. metastases compared to molecular characterization. The forthcoming 8th edition of the TMN Classification for Lung Cancer allows pathologists to use comprehensive histologic subtyping and molecular analysis to make this important distinction between MPLC and intrapulmonary metastasis.[15]

In summary, MPLC may be encountered by practitioners, and it is important to recognize MPLC so that patients are considered for potentially curative surgery. Outcomes for surgically treated MPLC are generally good and more like that of resected single lung cancer rather than metastatic disease. A multidisciplinary tumor board that includes a radiologist, pathologist, thoracic surgeon, and medical oncologist should be involved in cases of multiple lung tumors so that proper evaluation and treatment of MPLC is ensured.

REFERENCES

1. **Rea F, Zuin A, Callegaro D, Bortolotti L, Guanella G, Sartori F**. Surgical results for multiple primary lung cancers. *Eur J Cardiothorac Surg*. 2001 Sep;20(3):489-95. PubMed PMID: 11509268.
2. **Trousse D, Barlesi F, Loundou A, Tasei AM, Doddoli C, Giudicelli R, Astoul P, Fuentes P, Thomas P**. Synchronous multiple primary lung cancer: an increasing clinical occurrence requiring multidisciplinary management. *J Thorac Cardiovasc Surg*. 2007 May;133(5):1193-200. PubMed PMID: 17467428.
3. **Martini N, Melamed MR**. Multiple primary lung cancers. *J Thorac Cardiovasc Surg*. 1975 Oct;70(4):606-12. PubMed PMID: 170482.
4. **Chang YL, Wu CT, Lee YC**. Surgical treatment of synchronous multiple primary lung cancers: experience of 92 patients. *J Thorac Cardiovasc Surg*. 2007 Sep;134(3):630-7. Erratum in: J Thorac Cardiovasc Surg. 2008 Aug;136(2):542. PubMed PMID: 17723810.
5. **De Leyn P, Moons J, Vansteenkiste J, Verbeken E, Van Raemdonck D, Nafteux P, Decaluwe H, Lerut T**. Survival after resection of synchronous bilateral lung cancer. *Eur J Cardiothorac Surg*. 2008 Dec;34(6):1215-22. doi:10.1016/j.ejcts.2008.07.069. Epub 2008 Oct 1. PubMed PMID: 18829338.
6. **Finley DJ, Yoshizawa A, Travis W, Zhou Q, Seshan VE, Bains MS, Flores RM, Rizk N, Rusch VW, Park BJ**. Predictors of outcomes after surgical treatment of synchronous primary lung cancers. *J Thorac Oncol*. 2010 Feb;5(2):197-205. doi:10.1097/JTO.0b013e3181c814c5. Erratum in: J Thorac Oncol. 2010 Jun;5(6):926. PubMed PMID: 20101145.

7. **Yu YC, Hsu PK, Yeh YC, Huang CS, Hsieh CC, Chou TY, Hsu HS, Wu YC, Huang BS, Hsu WH**. Surgical results of synchronous multiple primary lung cancers: similar to the stage-matched solitary primary lung cancers? *Ann Thorac Surg*. 2013 Dec;96(6):1966-74. doi: 10.1016/j.athoracsur.2013.04.142. Epub 2013 Sep 7. PubMed PMID: 24021769.
8. **Dijkman BG, Schuurbiers OC, Vriens D, Looijen-Salamon M, Bussink J, Timmer-Bonte JN, Snoeren MM, Oyen WJ, van der Heijden HF, de Geus-Oei LF**. The role of (18)F-FDG PET in the differentiation between lung metastases and synchronous second primary lung tumours. *Eur J Nucl Med Mol Imaging*. 2010 Nov;37(11):2037-47. doi: 10.1007/s00259-010-1505-2. Epub 2010 Jun 10. PubMed PMID: 20533031; PubMed Central PMCID: PMC2948164.
9. **Wang X, Wang M, MacLennan GT, Abdul-Karim FW, Eble JN, Jones TD, Olobatuyi F, Eisenberg R, Cummings OW, Zhang S, Lopez-Beltran A, Montironi R, Zheng S, Lin H, Davidson DD, Cheng L**. Evidence for common clonal origin of multifocal lung cancers. *J Natl Cancer Inst*. 2009 Apr 15;101(8):560-70. doi: 10.1093/jnci/djp054. Epub 2009 Apr 7. PubMed PMID: 19351924.
10. **Girard N, Ostrovnaya I, Lau C, Park B, Ladanyi M, Finley D, Deshpande C, Rusch V, Orlow I, Travis WD, Pao W, Begg CB**. Genomic and mutational profiling to assess clonal relationships between multiple non-small cell lung cancers. *Clin Cancer Res*. 2009 Aug 15;15(16):5184-90. doi: 10.1158/1078-0432.CCR-09-0594. Epub 2009 Aug 11. PubMed PMID: 19671847; PubMed Central PMCID: PMC2892178.
11. **Arai J, Tsuchiya T, Oikawa M, Mochinaga K, Hayashi T, Yoshiura K, Tsukamoto K, Yamasaki N, Matsumoto K, Miyazaki T, Nagayasu T**. Clinical and molecular analysis of synchronous double lung cancers. *Lung Cancer*. 2012 Aug;77(2):281-7. doi: 10.1016/j.lungcan.2012.04.003. Epub 2012 May 3. PubMed PMID: 22560922.
12. **Takamochi K, Oh S, Matsuoka J, Suzuki K**. Clonality status of multifocal lung adenocarcinomas based on the mutation patterns of EGFR and K-ras. *Lung Cancer*. 2012 Mar;75(3):313-20. doi: 10.1016/j.lungcan.2011.08.007. Epub 2011 Dec 29. PubMed PMID: 22209037.
13. **Schneider F, Derrick V, Davison JM, Strollo D, Incharoen P, Dacic S**. Morphological and molecular approach to synchronous non-small cell lung carcinomas: impact on staging. *Mod Pathol*. 2016 Jul;29(7):735-42. doi: 10.1038/modpathol.2016.66. Epub 2016 Apr 15. PubMed PMID: 27080983.
14. **Girard N, Deshpande C, Lau C, Finley D, Rusch V, Pao W, Travis WD**. Comprehensive histologic assessment helps to differentiate multiple lung primary nonsmall cell carcinomas from metastases. *Am J Surg Pathol*. 2009 Dec;33(12):1752-64. doi: 10.1097/PAS.0b013e3181b8cf03. PubMed PMID: 19773638.
15. **Detterbeck FC, Franklin WA, Nicholson AG, Girard N, Arenberg DA, Travis WD, Mazzone PJ, Marom EM, Donington JS, Tanoue LT, Rusch VW, Asamura H, Rami-Porta R; IASLC Staging and Prognostic Factors Committee; Advisory Boards; Multiple Pulmonary Sites Workgroup**. The IASLC Lung Cancer Staging Project: Background Data and Proposed Criteria to Distinguish Separate Primary Lung Cancers from Metastatic Foci in Patients with Two Lung Tumors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol*. 2016 May;11(5):651-65. doi: 10.1016/j.jtho.2016.01.025. Epub 2016 Mar 2. PubMed PMID: 26944304.

Submitted July 6, 2016