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Case Report

Localized Papillary Adenocarcinoma of the Lung. Case report of Uncommon Tumor with Review of the Literature

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Abstract

Invasive adenocarcinoma of the lung can be classified histologically as: Lepidic, Acinar, Papillary, Micropapillary and Solid patterns with mucin production. Papillary adenocarcinoma (PA) is diagnosed histologically when >75% of the neoplasm contains papillary architecture supported by fibrovascular cores. This subtype comprises about 7.4-12% of pulmonary adenocarcinomas. Many papillary subtypes of lung adenocarcinoma have their own cytogenetic abnormalities, prognosis, and demands specific treatment modalities. We present a case of localized PA and discuss the histology, diagnostic considerations, cytogenetics, treatment, and prognosis.

Keysords: Adenocarcinoma; Papillary; Lung; Non-small cell carcinoma; Architecture

ABBREVIATIONS

PA: papillary adenocarcinoma, **NSCLC**: Non–small cell lung cancer, **ADC:** Adenocarcinoma**. IHC**: Immunohistochemistry, **OS**: Overall survival

INTRODUCTION

Lung cancer is the leading cause of cancer deaths worldwide in both men and women. [1] Approximately 80% of patients with lung cancer are diagnosed with primary non–small cell lung cancer (NSCLC), while the remaining 20% are mainly diagnosed with small cell lung cancer. The most common histologic type of NSCLC is adenocarcinoma (ADC). The recent classification of lung ADC proposed by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) emphasizes the importance of histologic subtyping. Histologic subtyping according to the recently proposed IASLC/ATS/ERS classification is an efficient discriminator for prognosis of patients with stage I to IV lung ADC. [2] Based on the new 2015 WHO classification of lung tumors, invasive adenocarcinomas with multiple different patterns should no longer be classified as "mixed adenocarcinoma", and each subtype must be assessed and reported semi-quantitatively (in 5% increments). [3] Invasive adenocarcinoma of the lung is now histologically classified as: Lepidic, Acinar, Papillary, Micropapillary and Solid patterns with mucin production. [4] The prognostic relevance of histologic subtypes is demonstrated in early stage disease, where lepidic subtype is associated with good prognosis, acinar and papillary subtypes show intermediate prognosis, whereas micropapillary and solid subtypes correlate with the worst prognosis. [5] Primary papillary adenocarcinoma (PA) is an uncommon invasive form of lung cancer where papillae replace the underlying alveolar architecture. [6] This subtype comprises about 7.4-12% of pulmonary adenocarcinomas. [4]

CASE PRESENTATION

A 53-year-old woman presented with severe dyspnea and cough including occasional episodes of hemoptysis. She had a long history of heavy smoking and chronic bronchitis with repeated episodes of exacerbated acute bronchitis. Due to absence of significant improvement in patient's condition, vigorous imaging studies were suggested, and a right upper lobe subpleural 2.8 cm mass was discovered and sampled utilizing fine needle aspiration with cellblock preparation. Cytopathology specimen showed a malignant neoplasm with papillary features. A malignant mesenchymal neoplasm could not be ruled out. A second FNA and core biopsy followed a month later. Cytomorphology recapitulated the initial hypercellular specimen: papillary growth pattern, many with complex secondary and tertiary branching structure, in addition to groups, sheets, clustered and single malignant cells, with enlarged nuclei and prominent nucleoli, vacuolated cytoplasm and atypical mitoses. The cytomorphology was consistent with a malignant neoplasm with papillary features (**Figure 1A-B**). The use of immunohistochemistry studies was essential to determine the line of cell differentiation. The tumor cells were positive for Cytokeratin AE1/AE3, CK7, TTF-1, and Napsin-A, while negative for CK20, P63, PAX-8, S-100, and Synaptophysin. IHC studies suggested a poorly differentiated

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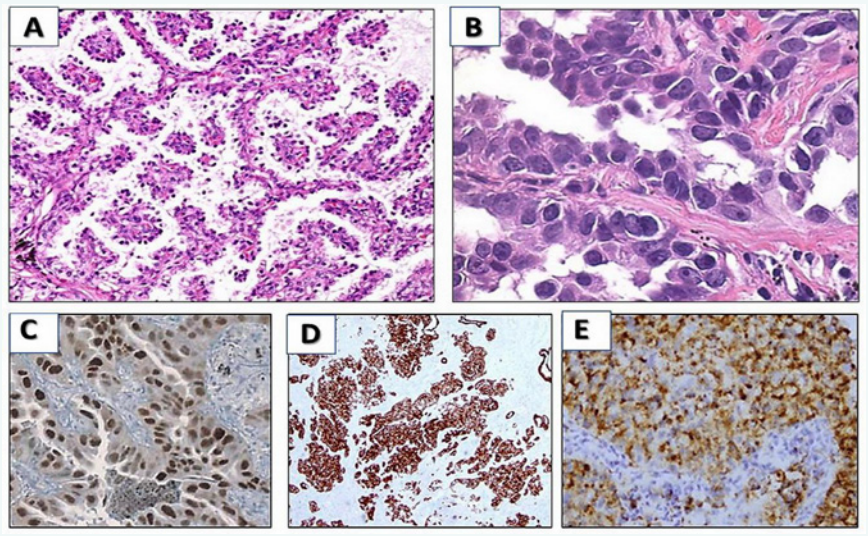

Figure 1 Histomorphology and immunohistochemistry profile of the excised papillary adenocarcinoma.
1A: Low power view of the tumor showing papillary growth pattern, many with complex secondary and tertiary branching structure, (H&E stain X20 magnification)
1B: High power view of the tumor showing clustered malignant cells layering fibrovascular cores, with enlarged nuclei and prominent nucleoli, vacuolated cytoplasm and atypical mitoses (H&E stain X40 magnification)
1C: Tumor cells positive for TTF-1
1D: Tumor cells positive for CK-7
1E: Tumor cells positive for Napsin-A.

carcinoma but none of gastrointestinal , renal, or mullerian primaries was supported (**Figure 1 C-D-E**). To rule out possible mesothelioma or metastatic Thyroid papillary carcinoma (TPC), additional IHC studies included negative calretinin, WT-1, D2-40, and thyroglobulin. The results ruled out possible mesothelioma or metastatic TPC. The proliferation index with Ki-67 was 15-20% nuclear staining.

The histomorphology with more than 75% papillary features, together with the immunohistochemistry profile were consistent with papillary adenocarcinoma of the lung, moderately differentiated with pleural involvement. No other lung masses were identified and further investigation with CT scan of chest, abdomen, pelvis and brain showed no evidence of metastasis. In addition, no lymphadenopathy was noted. Molecular testing showed negative results for EGFR mutation and showed no rearrangement of EML4-ALK gene or ROSE1 gene by fluorescence in situ hybridization method. A multidisciplinary tumor board meeting recommended surgical removal and no post-operative treatment. The mass was successfully removed with partial resection of the mass from the right upper lung lobe and adequate safe surgical margins were obtained. Patient was free of recurrence or metastasis for 14 months after which she was lost to follow up.

DESCUSSION

In 1997, Silver and Askins described a series of primary lung neoplasms, which they classified on the basis of histologic features. In this series, PA was diagnosed when more than 75% of the neoplasm contained papillary architecture supported by fibrovascular cores with complicated secondary and tertiary branches. [6,7] The more recent WHO classification supports this definition of PA as adenocarcinoma with predominance of papillary structures that replace the underlying alveolar architecture. [6] The neoplastic cells are cuboidal or columnar, with variable cytomorphological features from bland monomorphic cells, similar to papillary thyroid carcinoma, to highly pleomorphic cells, analogous to high-grade serous carcinoma of the female genital tract. Papillary structures occasionally show morules and/or psammoma bodies. [5]

Lung adenocarcinoma is seen mainly in females and non-smokers, though recently increasingly reported in patients with heavy smoking history. [4] Adenocarcinoma of the lung can occasionally present as a lung infiltrate and delay in diagnosis can be detrimental in overall patient care. [6] Patients with pulmonary PA are devoid of usual specific clinical symptoms such as cough, phlegm, fever, and failure to respond to antibiotic therapy for pneumonia in the early stage. [8] Radiologically, papillary adenocarcinoma most commonly presents as ill-defined lung nodules and can be initially confused with atypical infections. [9]

Immunohistochemistry (IHC) is invaluable for determining lung origin in both primary and metastatic, poorly differentiated carcinomas and for distinguishing the subtype of carcinoma. TTF-1 has been the predominant IHC marker used to identify lung origin and has a reported sensitivity of 75% to 80% for lung adenocarcinomas. However, TTF-1 also stains other tissues and tumors, such as thyroid tissue, some metastatic breast carcinoma, neuroendocrine tumors, such as small cell lung adenocarcinoma

and carcinoid; and, to a lesser degree, primary lung squamous cell carcinoma. [3] Stoll et al. have demonstrated that TTF-1 and napsin-A can be markers for adenocarcinomas of probable pulmonary origin. Such authors have also demonstrated that napsin-A was more sensitive, as compared with TTF-1, to differentiate the papillary subtype of adenocarcinoma (96% versus 78%, respectively). [10,11] One should be cautious to rule out mesothelioma with secondary pulmonary involvement and papillary thyroid carcinoma (PTC) with lung metastasis. Prameela and co-workers reported a 63-year-old man with a papillary carcinoma in the thyroid that originated from the lung. [4,12] Negativity for calretinin and positivity for CEA (albeit weak) can rule out mesothelioma. Meanwhile, negativity for thyroglobulin is enough to rule out PTC. [4]

Many papillary subtypes of lung adenocarcinoma have their own cytogenetic abnormalities, prognosis, and demands specific treatment modalities.[4] A 19-year-old Italian woman with papillary adenocarcinoma of the lung showed rearrangement of EML4-ALK gene by fluorescence in situ hybridization method. [4,13] Most patients with anaplastic lymphoma kinase (ALK)-rearranged or ROS proto-oncogene 1 (ROS1)-rearranged non-small-cell lung cancer (NSCLC) are sensitive to tyrosine kinase inhibitor (TKI) therapy. Crizotinib showed marked antitumor activity in patients with advanced ROS1-rearranged NSCLC. [13] Lorlatinib, a novel, highly potent, selective, and brain-penetrant ALK and ROS1 TKI with preclinical activity against most known resistance mutations, in patients with advanced ALK-positive or ROS1-positive NSCLC. [6]

Approximately 23% to 28% of patients with advanced NSCLC have a high level of programmed death ligand 1 (PD-L1) expression (defined as at least 50% of tumor cells, regardless of the staining intensity). Studies indicated that patients with advanced NSCLC and a PD-L1 tumor proportion score of 50% or greater were more likely than those with lower tumor proportion scores to have a response to Pembrolizumab, a highly selective, humanized monoclonal antibody against programmed death 1 (PD-1) that prevents PD-1 from engaging PD-L1 and PD-L2. [6]

The KRAS gene (Kristen rat sarcoma viral oncogene homolog) is located on chromosome 12p12. The gene is a member of the RAS oncogene family and encodes a GTPase. RAS proteins are involved in regulation of cell proliferation and cell survival pathways. Somatic missense KRAS are most commonly found in exons 2 and 3. KRAS mutations are detected in approximately 20-25% of non-small cell carcinoma of the lung. Therapeutic targeting of KRAS-mutant lung adenocarcinoma represents a major goal of clinical oncology. Combination targets for Trametinib, a MEK inhibitor and EGFR inhibitor combinations may lead to improved survival. KRAS mutations may predict responsiveness to anti-PD-1/PD-L1 immunotherapeutic agents, however this remains under investigation. [6]

Zhang et al. further found that surgical treatment could provide an expressively prolonged survival time for pulmonary PA patients (35.8 months vs 14.3 months). With regard to surgical categories, patients who received lobectomy or bilobectomy had significantly superior outcomes than those managed by pneumonectomy ($P < 0.01$ for both). [8]

Sica et al. proposed a grading system for lung adenocarcinomas based exclusively on histologic pattern, with grade 1 corresponding to lepidic growth, grade 2 to acinar and papillary, and grade 3 to solid and micropapillary. The two prevalent grades were combined into a score, which proved to predict prognosis in a large series of lung adenocarcinomas. Kadota et al. and von der Thusen et al. proposed two different grading systems, both combining histologic pattern and mitotic count. The best grading system for lung adenocarcinoma is yet to be determined. [5,14-16].

Overall, the papillary subtype of ADC has an intermediate prognosis, with some variability in survival rates among different studies, with a 5-year disease free survival of about 50-70% for Stage I- III. [6] According to the univariate analysis of prognostic factors, patients with older age; bilateral and larger lesions located in the main bronchus; poor pathological differentiation; lymph node invasion and remote metastasis; as well as chemotherapy subjected with undesirable prognosis. Inversely, surgical intervention and radiation therapy were conducive to improving the mean overall survival (OS) ($P<0.05$ for all). [8] In 26 cases of predominantly papillary adenocarcinoma, the five-year survival reached 71%. As a comparison is made with other invasive adenocarcinoma subtypes, for example, it is observed that in 14 cases of the predominantly micropapillary subtype, the five-year survival reached 38%. [10,11]

Zhang et al. found that the OS of the total 3391 pulmonary PA patients was 32.6 months (95% CI 31.2-33.9 months), with no significant difference in clinical prognosis between pulmonary PA patients and counterparts with non-PA adenocarcinoma. [8] Yaldiz et al. investigated five-year survival rates of papillary predominant histological subtype in comparison to lepicidic, acinar and mucinous subtypes, grouped as “LAM” subtypes. Five-year survival was 40.5% in the papillary predominant histological pattern, while this rate was 70.9%, 59.0%, and 66.6% in LAM, respectively. Papillary subtype showed significantly poor survival compared to lepidic ($p=0.002$), acinar ($p=0.008$), and mucinous subtypes ($p=0.048$). Therefore, PA patients may be candidates for adjuvant treatment modalities even in the earlier stages of disease. [17].

Our patient was lost to follow up after 14 months of free recurrence or metastasis. We expect our patient to have a favorable prognosis. She is not of older age; the tumor was unilateral localized and not in the main bronchus; was not of poor pathological differentiation; and there was no evidence of lymph node metastasis. In addition, the tumor was completely resected with adequate safe margins. The lack of molecular abnormalities in our case, mutation or re-arrangement may be due to very early stage of the carcinoma and being small localized mass. The intent of this case report is to further expand the body of investigation available on primary papillary adenocarcinoma of the lung, aiding in the understanding, diagnosis and treatment of this type of cancer.

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REFRENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015 Mar;65(2):87-108. doi: 10.3322/caac.21262. Epub 2015 Feb 4. PMID: 25651787.
2. Nitadori J, Bograd AJ, Kadota K, Sima CS, Rizk NP, Morales EA, Rusch VW, Travis WD, Adusumilli PS. Impact of micropapillary histologic subtype in selecting limited resection vs lobectomy for lung adenocarcinoma of 2cm or smaller. J Natl Cancer Inst. 2013;105(16):1212. Epub 2013 Aug 7.
3. Sheplay K, Nicholas J, Lombard A, Funk C, Aziz M, et al. (2021) Papillary Adenocarcinoma of the Lung. Case Report of Uncommon Tumor and Review of the Literature. SM J Pulm Med 5:4.
4. Ramezani M, Heydari R, Amirian F, Sadeghi M. Papillary Adenocarcinoma of the Lung in a Young Man: A Case Report. IJBC 2020; 12(2): 64-66.
5. Kuhn E, Morbini P, Cancellieri A, Damiani S, Cavazza A, Comin CE. Adenocarcinoma classification: patterns and prognosis. PATHOLOGICA. - ISSN 1591-951X. - 110: 1 (2018 Mar), pp. 5-11.
6. Madan N, Patel V, Escobar CP (2019) Non-Resolving Lung Infiltrate: A Rare Case of Papillary Adenocarcinoma of the Lung. Med Case Rep Vol.5 No.3:127.
7. Silver SA, Askin FB (1997) True papillary carcinoma of the lung: a distinct clinicopathologic entity. Am J Surg Pathol 21: 43-51.
8. Zhang Y, Xie H, Zhang Z, Zhang P, Chen P, Wang X. The Characteristics and Nomogram for Primary Lung Papillary Adenocarcinoma. Open Med (Wars). 2020;15:92-102. Published 2020 Feb 20. doi:10.1515/med-2020-0014
9. Gupta A, Palkar A, Narwal P. Papillary lung adenocarcinoma with psammomatous calcifications. Respir Med Case Rep. 2018 Jul 24;25:89-90. doi: 10.1016/j.rmcr.2018.07.004. PMID: 30094154; PMCID: PMC6080217.
10. Bispo IGA, Nascimento DT, Ferreira KO, Fakhouri R, Godinho AS, Ferrão TO. Brain metastasis as initial presentation of papillary adenocarcinoma of the lung: case report. Radiol Bras. 2013 Set/Out;46(5):313–316.
11. Stoll LM, Johnson MW, Gabrielson E, et al. The utility of napsin-A in the identification of primary and metastatic lung adenocarcinoma among cytologically poorly differentiated carcinomas. Cancer Cytopathol. 2010;118:441–9.
12. Prameela CG, Ravind R, Sruthi K. Nonthyroidal metastatic lesion in thyroid: A missed diagnosis and a lesson learnt. J Can Res Ther. 2019;15:665-8. doi: 10.4103/jcrt.JCRT_1043_16. PubMed PMID: 31169237.
13. Polo V, Zago G, Frega S, Canova F, Bonanno L, Favaretto A, et al. Non-Small Cell Lung Cancer in a Very Young Woman: A Case Report and Critical Review of the Literature. Am J Case Rep. 2015; 16:782–789. doi:10.12659/ajcr.894426. PubMed PMID: 26525068.
14. Sica G, Yoshizawa A, Sima CS, et al. A grading system of lung adenocarcinomas based on histologic pattern is predictive of disease recurrence in stage I tumors. Am J Surg Pathol 2010;34:1155-62.
15. Kadota K, Suzuki K, Kachala SS, et al. A grading system combining architectural features and mitotic count predicts recurrence in stage I lung adenocarcinoma. Mod Pathol 2012;25:1117-27.
16. von der Thusen JH, Tham YS, Pattenden H, et al. Prognostic significance of predominant histologic pattern and nuclear grade in resected adenocarcinoma of the lung: potential parameters for a grading system. J Thorac Oncol 2013;8:37-44.
17. Yaldız D, Acar A, Örs Kaya Ş, Aydoğdu Z, Gürsoy S, Yaldız S. Papillary predominant histological subtype predicts poor survival in lung adenocarcinoma. Turk Gogus Kalp Damar Cerrahisi Derg. 2019 Jun 21;27(3):360-366. doi: 10.5606/tgkdc.dergisi.2019.17284. PMID: 32082885; PMCID: PMC7021432.