



# Papillary Adenocarcinoma of the Lung. Case Report of Uncommon Tumor and Review of the Literature

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## Abstract

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). Papillary adenocarcinoma (PA) is a subtype of invasive adenocarcinoma defined by presence of papillary structures with true fibrovascular cores replacing the alveolar lining or present within the alveolar spaces. Pure lung papillary adenocarcinoma represents about 7.4-12% of lung adenocarcinomas. We report a case of papillary lung adenocarcinoma presenting as a small solitary nodule, and we discuss diagnostic features, differential diagnosis, molecular changes, treatment, and prognosis.

**Keywords:** Papillary, Micropapillary, Adenocarcinoma, Differential diagnosis, Molecular

## ABBREVIATION

**PA:** Papillary adenocarcinoma, **CECT:** Contrast enhanced computed tomography, **IHC:** Immunohistochemistry, **BAC:** Bronchoalveolar carcinoma

## INTRODUCTION

Primary Papillary Adenocarcinoma (PA), is an uncommon invasive subtype of adenocarcinoma of the lung with a predominance of papillary structures that replace the underlying alveolar architecture (1). PA comprises about 7.4-12% of pulmonary adenocarcinomas (2) but has considerably worse morbidity and mortality and poorer response to chemotherapeutic agents (3) compared to other sub-types of adenocarcinoma. PA has a peak incidence ranging from 50 to 60 years old (4) and occurs predominantly in female and nonsmokers (5). PA has been associated with paraneoplastic syndromes such as Evans syndrome (6) and autoimmune hemolytic anemia (7), and numerous metastatic sites such as the choroid (8), pericardium (9), thyroid (10), and brain (11). Clinically, patients are often devoid of specific symptoms of malignancy such as cough, phlegm, fever, and weight-loss in the early stages of the cancer, so are often discovered incidentally on imaging (4). Distinguishing PA from other subtypes of adenocarcinoma of the lung have prognostic and therapeutic implications (5) since PA has its own

prognosis and cytogenetic abnormalities, demanding specific treatment modalities (2). We present an uncommon case of PA.

## CASE PRESENTATION

A 37-year-old woman presented with cough and chest pain. Patient was a non-smoker with no other risk factors for malignancy. Chest X-ray showed a small poorly defined infiltrating left lung tumor mass. Contrast enhanced computed tomography thorax (CECT) revealed a mass lesion measuring 1.8 cm x 1.2 cm in the left lower lobe of the lung. Computed tomography-guided large biopsy was performed, and histopathology examination revealed malignant tumor dispersed in irregular glandular and papillary architecture with scattered micropapillary changes. The glands were lined by atypical columnar cells displaying loss of polarity, moderate nuclear polymorphism, hyperchromatic nuclei, prominent nucleoli, and large eosinophilic cytoplasm. Scattered psammoma bodies were also identified. The tumor cells were seen arranged in multiple layers around true fibrovascular cores. Some papillary clusters were seen floating in the alveolar spaces suggesting focal micropapillary changes but estimated to be less than 5% of the entire tumor. (**Figure 1A and 1B**)

A metastatic workup was done including contrast enhanced computed tomography of the head, chest, and abdomen which did not reveal any other lesions. Immunohistochemistry (IHC) studies included positive TTF-1 (**Figure 1C**), Napsin-A (**Figure 1D**), CMA 5.2 and CK7, while negative for P63, PAX8, CDX2, and CD20. Studies to rule out possible TPC included TSH, fT3, fT4 within normal limits; and thyroid ultrasound showed with no evidence of any thyroid nodules. The immunoprofile was in support of a primary papillary lung adenocarcinoma. Proliferation index MIB-1(Ki-67) showed 10-20% nuclear staining of the tumor cells in support of well to moderately differentiated tumor.

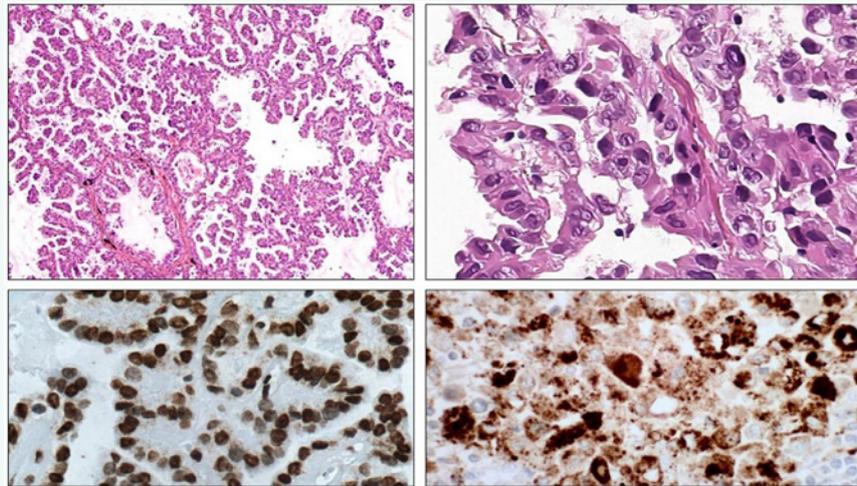
Patient was treated with wedge resection and adequate safe surgical margins were obtained. Patient did not receive post-operative chemotherapy or radiation and showed no evidence of recurrence or metastasis for 18 months after which she was lost to follow up.

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**Figure 1** Microscopic examination of the lung tumor mass

Figure 1A: Low power view displaying malignant tumor dispersed in irregular glandular and papillary architecture with scattered micropapillary changes (H&E stain X20)

Figure 1B: High power view showing the glands are lined by atypical columnar cells displaying loss of polarity, moderate nuclear polymorphism, hyperchromatic nuclei, prominent nucleoli, and large eosinophilic cytoplasm (H&E stain X60)

Figure 1C: Tumor cells showing positive nuclear staining with TTF-1

Figure 1D: Tumor cells showing positive cytoplasmic staining with Napsin-A

## DISCUSSION

Lung carcinoma is the second most common cancer in both men and women and the leading cause of cancer related mortality in the United States and of the world. The main sub-types of lung cancer are non-small cell lung carcinoma (NSCLC) and small cell carcinoma (SCLC). About 85% of lung cancers are NSCLC, of which more than 50% are adenocarcinomas (12). Invasive adenocarcinoma of the lung is histologically classified as: Lepidic, Acinar, Papillary, Micropapillary, and Solid patterns with mucin production. Definite subtyping is necessary for precise diagnosis and determination of prognosis (2).

Recognizing papillary subtype of adenocarcinoma is difficult because of its histological complexity. To date, three pathological criteria have been proposed for defining PA of lung. Silver and Askin defined PA in an adenocarcinoma with >75% papillary structures supported by fibrovascular cores with complicated secondary and tertiary branches (13). Noguchi et al. classified lung adenocarcinoma subtypes based on tumor growth patterns. In their classification, PA was defined as Type F small adenocarcinoma of lung (14). The WHO classification defines PA as adenocarcinoma with predominance of papillary structures that replace the underlying alveolar architecture. PA needs to be further distinguished from another entity labeled as Micropapillary Adenocarcinoma. These tumors are adenocarcinomas with areas resembling the micropapillary features seen in other tumors such as of the ovary, breast, and bladder. The presence of a micropapillary component in PA presents at a frequency of 74% (15) and is associated with a nonsmoker status, early lymph node metastasis, intrapulmonary metastasis, and a significantly lower 5-year survival rate (5).

Histopathologically, PA can be divided into PA-A and PA-B. PA-A resembles Bronchioloalveolar Carcinoma (BAC) histologically, with the peripheral BAC growth pattern, collapsed fibrosis and proliferating tumor cells composed of atypical alveolar type II cells. The presence of the BAC structure is a significant feature in PA-A, compared with PA-B. Since PA-A and BAC are so similar histologically, PA-A is often misdiagnosed as an adenocarcinoma with mixed papillary subtypes. By contrast, PA-B is composed of tall columnar tumor cells and exhibits compressive and destructive growth (15). PA-B is similar to the type F tumor proposed by Noguchi et al (14). Radiologically, PA may appear as poorly or well-defined lung nodules/masses which may be associated with hilar lymphadenopathy. The masses may show internal bubble lucencies, surrounding areas of ground glass opacities and satellite micronodules (5).

The distinction of squamous and non-squamous cell carcinoma, including adenocarcinoma and large cell carcinoma, can be made in most patients through cytopathology. However, in certain patients, the distinction cannot be made by assessment of morphology alone, most often in poorly differentiated carcinomas in later stages due to the lack of specific architectural and cytomorphologic characteristics. Under these circumstances, immunohistochemistry (IHC) is invaluable for determining lung origin in both primary and metastatic, poorly differentiated carcinomas and for distinguishing the subtype of carcinoma. Thyroid transcription factor-1 (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, metastatic breast carcinoma, neuroendocrine tumors, such as small cell lung carcinoma and carcinoid; and, to a lesser



degree, primary lung squamous cell carcinoma. In addition, its expression reportedly decreases inversely in relation to the degree of tumor differentiation. Several studies in the literature indicate that Napsin-A, an aspartic proteinase involved in the maturation of the surfactant protein B, has a sensitivity equal to or greater than that of TTF-1 in well to moderately differentiated lung adenocarcinomas (96% versus 78%, respectively). Therefore, its use has been advocated in conjunction with TTF-1 in the differential diagnosis of lung adenocarcinomas (16). PA is also positive for CK7, CK19, CEA, surfactant apoprotein A (SP-A), CAM 5.2, epithelial membrane antigen, and pulmonary surfactant apoproteins (detected by PE10 monoclonal antibody) (2).

The differential diagnosis of papillary pulmonary lesions should include sclerosing hemangioma, metastatic adenocarcinoma to the lung, mesothelioma with secondary pulmonary involvement, and papillary carcinoma of the thyroid with lung metastasis (5). To differentiate, metastatic adenocarcinoma to the lung is TTF-1 negative, mesothelioma is negative for calretinin and positive for CEA (albeit weak), and PTC is negative for thyroglobulin (2).

Surgical intervention is the optimal treatment and first-line therapy for PA patients. Most studies show that lobectomy, followed by segmentectomy/wedge resection and pneumonectomy contributed to an excellent prognosis. Pneumonectomy often has a much more undesirable clinical prognosis than lobectomy or resection, due to the extensive loss of pulmonary function (4). The impact of chemotherapy on patients with lung papillary adenocarcinoma is still controversial. Multiple studies have shown that chemotherapy had no significant benefit for pulmonary PA patients (4, 17). Other studies, however, have shown the effectiveness and significance of surgical intervention in combination with chemotherapy (6, 7). PA patients might also benefit from postoperative radiotherapy (PORT) (18).

Current conventional chemoradiation therapies have begun to reach their plateaus of effectiveness; thus, increasing efforts have been made to develop and use novel targeted or personalized therapies that potentially may lead to improved survival and prognosis (16). One of the most significant changes in latest edition of the 2015 World Health Organization Classification of Lung Tumors was to involve a new emphasis on genetic studies, in particular, integration of molecular testing to help personalize treatment strategies for advanced lung cancer patients (25). The most common mutations associated with PA are EGFR, PD-L, KRAS, MEK, ROS1, and ALK. Patients with major papillary morphology had a higher rate of EGFR mutations (55%) than did those with nonpapillary morphology (5%), in adenocarcinomas of the lung, which includes micropapillary pattern. Somatic mutations in the kinase domain of EGFR strongly correlates with increased responsiveness to EGFR tyrosine kinase inhibitors Erlotinib, Gefitinib, and Trametinib, which also inhibits MEK. Response to EGFR-TKI therapy is generally predicated on EGFR copy number or mutational status (19, 20). Gefitinib has also shown to be effective against adenocarcinoma with a micropapillary component. Approximately 23% to 28% of patients with advanced non-small-cell lung cancer has a high

level of programmed death ligand 1 (PD-L1) expression and have had a great response to Pembrolizumab, a highly selective, humanized monoclonal antibody against programmed death 1 (PD-1) (21). KRAS mutations are detected in approximately 20-25% of non-small cell carcinoma of lung and have been a recent target of clinical oncology. KRAS mutations may even predict responsiveness to anti-PD-1/PD-L1 immunotherapeutic agents, however this remains under investigation (22). Most patients with anaplastic lymphoma kinase- rearranged or ROS proto-oncogene 1 (ROS1)-rearranged NSCLC are sensitive to tyrosine kinase inhibitor therapy such as Crizotinib (23) and Lorlatinib, which also targets ALK (12, 24).

Our hope is that this case report will add to the repertoire of research on this topic and provide clinicians and pathologists with more insight about Primary Papillary Adenocarcinoma of the lung, allowing for appropriate diagnosis and informed management decisions.

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