

## Case Report

# Pulmonary papillary adenoma with malignant transformation: report of one case and review of the literature

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Received January 30, 2020; Accepted March 6, 2020; Epub April 1, 2020; Published April 15, 2020

**Abstract:** Pulmonary papillary adenoma is a rare tumor. A total of 32 cases was studied, include 31 cases in the literature. Most of the patients were asymptomatic, and tumor was usually discovered during a routine chest roentgenogram or with other disease. Most cases demonstrated benign behavior and there have been no recurrent cases after the operation or biopsy with the follow up of 6 to 120 months. However, there was some evidence indicating it can be locally aggressive or potentially malignant. We present the first case report of cancer development in a pulmonary papillary adenoma. In our case, the imaging findings progressed from initial well-defined border, without 18F-FDG accumulation, to one side rough edge after two years of follow up. Postoperative pathology revealed a partly well-defined tumor, without a fibrous capsule, but focally infiltrated the alveoli. Our case had definite areas of papillary adenoma, with focal acinar and micropapillary adenocarcinoma area near the central fibrosis. The papillary adenoma cells were with polarity and low expression of Ki67 and C-myc, without atypia or mitosis. But the adenocarcinoma cells were obviously different from them, with high expression of Ki67 and C-myc, indicating cancer development. MYC activation may play a role in tumorigenesis, and further investigation was needed. There was no EGFR mutation in both of the components.

**Keywords:** Pulmonary, papillary adenoma, cancer development, FDG, C-myc

## Introduction

Pulmonary papillary adenoma is a rare tumor. Most of the patients were asymptomatic, and were usually discovered during a routine chest roentgenogram or with other disease. Since Spencer et al. [1] first described two cases of papillary adenoma of the lung in 1980, 31 cases have been reported worldwide. Most cases demonstrated benign behavior and there have been no recurrent cases after the operation or biopsy with a follow up of 6 to 120 months [1-25]. However, there was some evidence indicating it can be locally aggressive or have potential malignant behavior [9, 10, 21]. Mori et al. [9] demonstrated evidence of trans-bronchial dissemination and vascular invasion. Twelve-dimensional cluster analysis revealed tumor cell features similar to type II pneumo-

cyte adenocarcinoma. Motohisa et al. found a mass enlargement and lobulation to a maximum diameter from 11 mm to 18 mm with four years of follow up, and accumulation of fluorodeoxyglucose was observed by positron emission tomography (FDG-PET) [16]. Dessy et al. evaluated two cases of encapsulated papillary neoplasm with capsular invasion and, in one case, invasion of adjacent alveoli and visceral pleura [10]. Therefore, these authors tended to change the term “peripheral papillary adenoma” to “peripheral papillary tumor of undetermined malignant potential”.

In our case, the imaging findings progressed from initial well-defined border to one side rough edge after two years of follow up. Postoperative pathology revealed definite areas of papillary adenoma, with focal acinar adenocar-

cinoma area. To the best of our knowledge, this is the first case report of pulmonary papillary adenoma cancer development.

## Case presentation

A 56 year old man with history of asthma was consulted for a mass in the left lung during a routine chest roentgenogram. The radiology examination showed us a round and lobulated nodule in the subpleural margin of the inferior lobe of the left lung and fluorine-18 fluorodeoxyglucose-positron emission tomography (18F-FDG-PET) scans revealed no FDG uptake (**Figure 1A-D**). It was considered benign and a close follow-up was recommended. Two years later, the chest computed tomography (CT) revealed a well-defined homogeneous solid nodule measuring 1.5 cm in greatest dimension at the left lower lobe, which had no gradually increased size, but the upper boundary was slightly rougher than two years ago (**Figure 1E**). Cytokeratin-19-fragment in the blood was slightly higher than normal (3.67 ng/ml), and other laboratory studies and physical examinations were unremarkable. Under video-assisted thoracoscopy revealed a tumor on the boundary of S6 and S9 segment of the left lung on palpation and a wedge resection was performed. The cut surface showed a gray-white solid and well-defined nodule with a minimally invasive margin on one side. The intraoperative frozen section diagnosis was adenocarcinoma and then a left lower lobectomy with a regional lymph-node dissection was performed. No evidence of recurrence has been detected for 8 months after the operation.

Microscopically, the tumors were partly well defined, without a fibrous capsule, but focally infiltrated the alveoli, near the central fibrosis in the tumor (**Figure 1F**). The tumor consisted of three groups. First, the papillary structures were formed with the fibrovascular stroma, lined by a single layer of uniform cuboidal to columnar cells, containing lymphocytes and interstitial hemorrhage, although many papillae had only inconspicuous blood vessels (**Figure 1G**). The second group (**Figure 1H**) had glandular structure with oncocytic features, along with amorphous eosinophilic material in the lumen. The nucleus stayed at the base of the lumen cells regularly. Both of the two groups of cells had absence of mitotic figures. The third group (**Figure 1I**) were acinar adenocarcinoma around the central fibrosis, with a small number of

micropapillary adenocarcinoma cells on one side of the tumor, which merged with the other two groups of cells. The tumor cells were cuboidal to columnar with eosinophilic cytoplasm, obvious atypia, loss of polarity and with occasional mitosis. The tumor cells invaded the peripheral alveoli. Ciliated cells were not present.

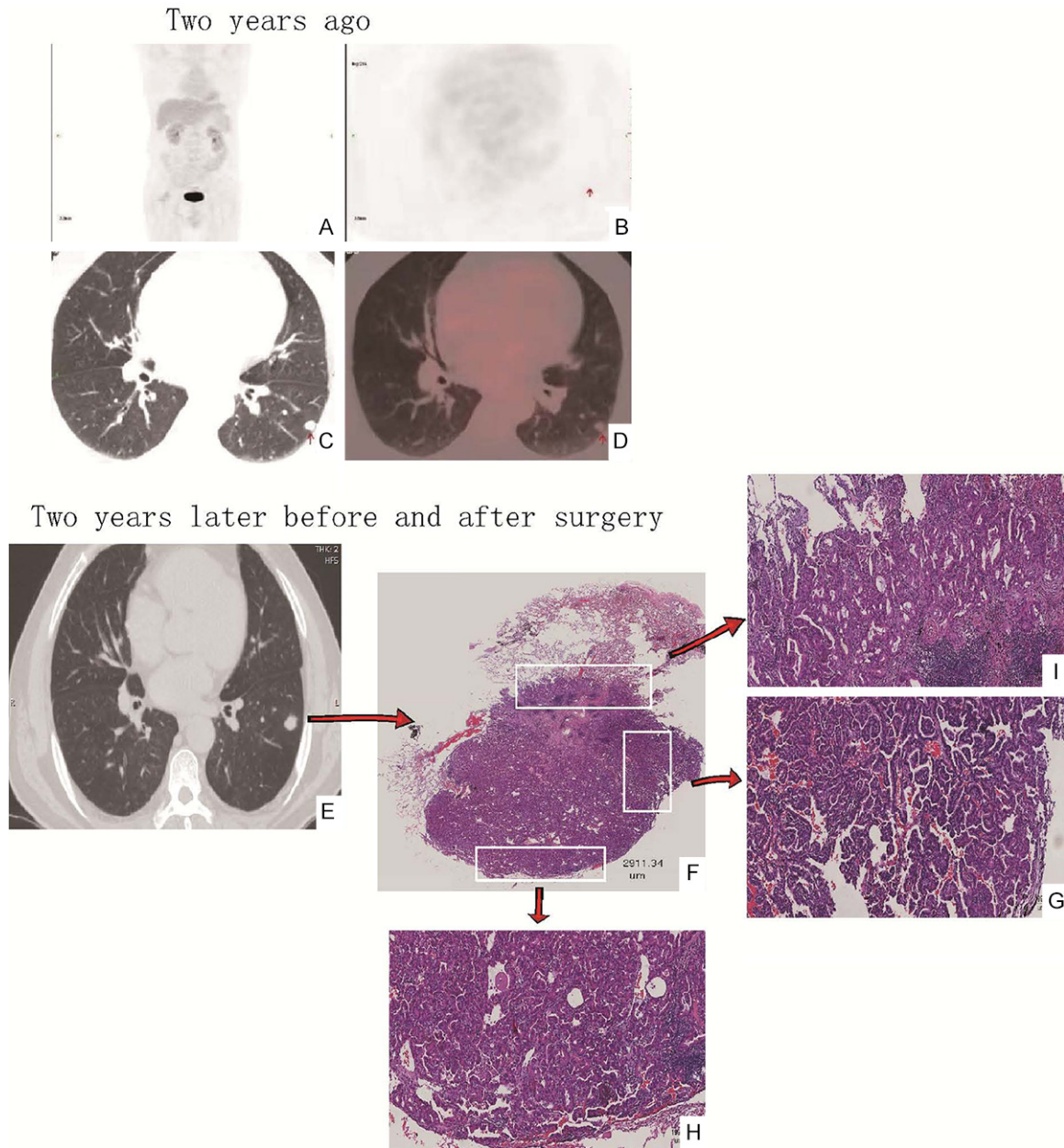
The results of the immunohistochemical studies are summarized in **Table 1**. The neoplastic cells were strongly decorated with TTF-1 (**Figure 2C, 2I, 2O**), Napsin A (**Figure 2D, 2J, 2P**), EMA (**Figure 2F, 2L, 2R**) and CK 7 in the three groups of cells. The micropapillary adenocarcinoma components were confirmed by EMA staining (**Figure 2R**), indicating the outer margin positive. Less than 2% nuclei were decorated with Ki67 in papillary cells (**Figure 2B**), about 5% in glandular cells (**Figure 2H**) and nearly 30% in adenocarcinoma cells (**Figure 2N**), which were distinct different between the benign area and the carcinoma area. C-myc nuclei expression rate was almost the same with Ki67 expression rate in the three groups of cells (**Figure 2E, 2K, 2Q**).

We separated the tumor components with laser capture microsection technique, and detected EGFR gene separately by PCR. There was no EGFR mutation in all the tumor components.

This study was approved by the Ethics Committee of Qingdao Central Hospital, and Informed consents were obtained.

## Discussion

Papillary adenoma was believed to derive from primitive multipotential respiratory epithelium with bidirectional differentiation, showing type 2 pneumocytes or Clara cell differentiation [3, 7-10]. A total of 32 cases were reviewed, include 31 cases in the literature and our case. **Table 2** lists the cases reported in the literature and the present case. As seen in **Table 2**, the patients had a broad age range, from 2 months to 78 years, with an average of 40 years old. There wasn't a significant gender difference, but slightly more males (54.8%). Only 8 patients (25%) had a smoking history [3, 5, 9, 10, 20, 21, 24], indicating no correlation between smoking and the occurrence of the tumor. Most of the patients were asymptomatic and were usually discovered accidentally. One of the patients with a 4 cm nodule had 2 months his-



**Figure 1.** Imaging and pathologic findings of the tumor before and after operation. A-D. The radiology examination showed a round and lobulated nodule in the subpleural margin of the inferior lobe of the left lung and 18F FDG PET scans revealed no FDG uptake. E. Two years later, the chest CT revealed a well-defined homogeneous solid nodule measuring 1.5 cm in greatest dimension at the left lower lobe, which had gradually increased in size, but the upper boundary was slightly rougher than two years ago. F. Microscopically, the tumors were partly well defined, without a fibrous capsule, but focally infiltrated the alveoli, near the central fibrosis in the tumor (H&E×40). G. The first group, papillary structures, were formed with the fibrovascular stroma, lined by a single layer of uniform cuboidal to columnar cells, containing lymphocytes and interstitial hemorrhage (H&E×200). H. The second group had glandular structure with oncocytic features, along with amorphous eosinophilic material in the lumen. The nucleus stayed at the base of the lumen cells regularly (H&E×200). I. The third group was acinar adenocarcinoma, with a small number of micropapillary carcinoma cells on one side of the tumor. The tumor cells were cuboidal to columnar with eosinophilic cytoplasm, obvious atypia, loss of polarity, and with occasional mitosis. The tumor cells invaded the peripheral alveoli (H&E×100).

tory of cough, pyrexia, slight hemoptysis, wheezing respiration and chest pain [1], which

may be due to the local compression by the tumor. Physical examination and routine labo-

**Table 1.** Results of the immunohistochemical studies

	Ki67	TTF-1	Naspin A	CK7	C-myc
papillary cells	<2%	+	+	+	2%
glandular cells	5%	+	+	+	5%
adenocarcinoma cells	30%	+	+	+	30%

ratory studies were unremarkable with the papillary adenoma, occasionally with a slightly elevated CEA level [13]. Our patient had a cytokeratin-19-fragment in the blood slightly higher than normal. There were two patients on whom was performed positron emission tomography and CT (PET/CT) before operation, and elevated 18F-FDG accumulation were seen in the tumors [16, 18]. But there was no abnormal 18F-FDG accumulation in our case two years before operation, indicating a benign possibility then.

The tumor commonly was located in the peripheral part of the lung, but there had been described a few cases situated more centrally [6, 23]. They occurred much more in the left lung and the left lower lobe occupied the most, including our case. The tumor size ranged from 0.4 cm to 6 cm, with an average of 2.52 cm. Majority were solitary tumors with occasional multiple nodules [18]. Most of the cases were solid and well-defined nodules, but there was still one case with a partially cystic, non-encapsulated and spongy nodule [15].

The papillary adenoma displayed a branching papillary growth, and occasional cases were accompanied with micropapillary or irregular cribriform pattern [19, 23], even with some adenoid [25] and sclerotic structures [20]. The surfaces of the tumors were covered with cuboidal or columnar epithelium with occasional ciliated epithelial cells [5, 9, 15, 20], but without mucin secretion. There was almost no mitosis in papillary adenoma except in one case showing very few mitoses [1]. Our case had several kinds of structures: papillary, adenoid, acinar and micropapillary. The papillary and adenoid cells maintained polarity, without atypia and mitosis, but the acinar and micropapillary cells showed obvious atypia and occasional mitosis, indicating cancer development.

The low cellular replicative activity (Ki67<2%) in almost all the cases suggests that these tumors may have a relatively slow rate of growth. In our case, the Ki67 expression was

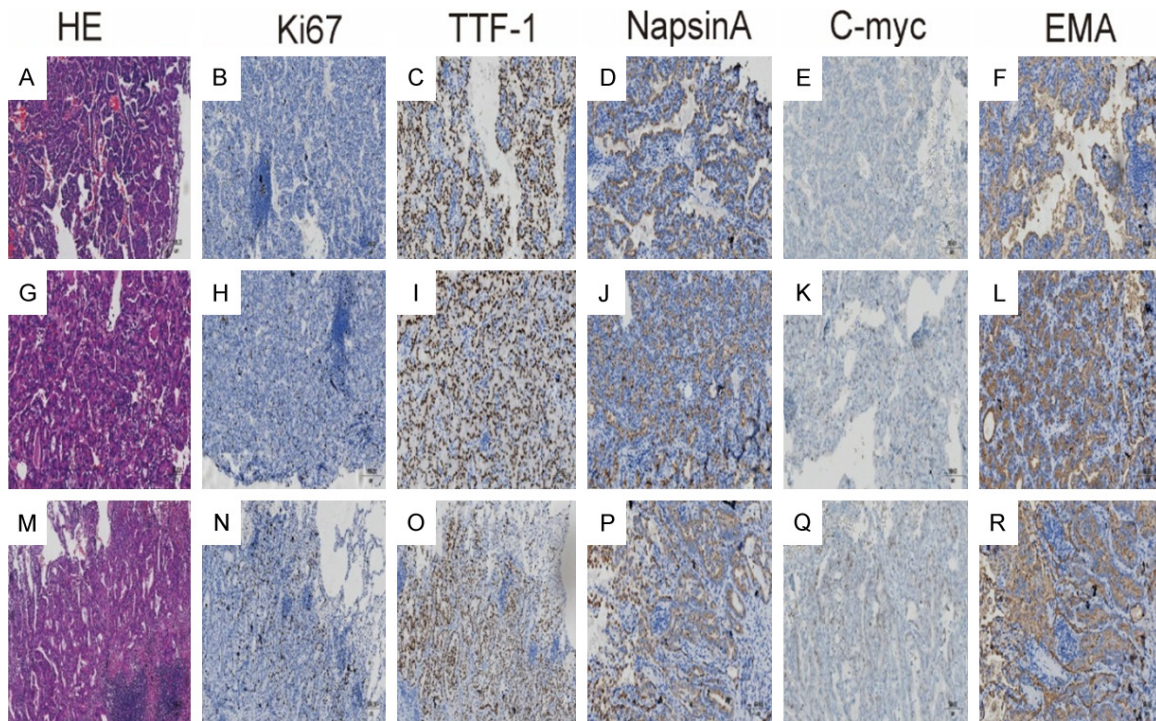
obviously different in the three groups of cells, especially higher in the cancer development area. The lining cells were immunochemically positive for Napsin A, TTF-1, CK7 [25], surfactant apoprotein A (SPA), SPB and SPC [10]. CEA was differently expressed, positive or negative [13, 17, 24, 25]. The tumor cells were negative for neuroendocrine markers [23] and UP1 [10]. Occasionally, the lining cells were nuclear positive for C-myc [21].  $\beta$ -catenin expression was either positive, or negative [21, 23]. In our case, C-myc expression also different in the malignant area than the benign area. Human pulmonary adenocarcinoma has various types of heterogeneity within the primary tumor. There was C-myc nuclear positivity research within papillary adenoma cells [21], which was an important gene during the progression of cancer. Our case had low expression in papillary adenoma cells, and high expression in adenocarcinoma cells. MYC activation may play a role in tumorigenesis, and further investigation was needed. Different immunohistochemical expression in the tumor was also evidence of cancer development of papillary adenoma.

Most of the nodules were well circumscribed, without a fibrous capsule around the tumor, but there were still some tumor cells extending to the bronchial lumen [9, 13, 15, 16] or infiltrated with alveoli [1, 3, 10], vascular [9], capsule or visceral pleura [10], indicating the malignant potential of the mass. Nearly half of the patients received lobectomy of the lung because lung cancer could not be ruled out clinically, and the other half underwent wedge resection. After the operation, all of the patients remained with no recurrence or metastasis with 6 to 120 months of follow up [1-25]. In our case, the imaging findings progressed from initial well-defined borders to one side rough edges after two years of follow-up. Postoperative pathology revealed the tumor cells partly invaded the alveoli, indicating the process of malignant transformation.

Nakano et al. [18] reviewed previously reported 16 cases and their one case of pulmonary papillary adenoma. Four cases of theirs had a description of intraoperative consultation by the frozen section or imprint cytology. Only one case was diagnosed as papillary adenoma on frozen section, while the possibilities of malig-



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**Figure 2.** The IHC outcome of the three components. (A, G, M) H&E stain of the three group tumor cells (H&E×200). (C, I, O) The three components were strongly decorated with TTF-1 (IHC×200). (D, J, P) The three components were strongly decorated with Napsin A (IHC×200). (B, H, N) The three components were nuclear stained with Ki67, and the expression rates were less than 2%, about 5% and nearly 30%, respectively (IHC×200). (E, K, Q) C-myc nuclei expression rates were almost the same with Ki67 expression rate in the three group cells (IHC×200). (F, L, R) The three components were positive with EMA, and the micropapillary adenocarcinoma components were confirmed by EMA staining (R), indicating the outer margin was positive (IHC×200).

**Table 2.** Cases review of the pulmonary papillary adenoma

Case	Sex/age (years)	Site	Diameter (cm)	Extension to BL	invasion	Operation	Follow up (months)	Ref.
1	F/26	LUL	4			Lobectomy	ND	1
2	M/7	LLL	ND		alveoli	Lobectomy	ND	1
3	F/15	RLL	2.5			ND	120	2
4	M/57	RML	1.5		alveoli	lobectomy	96	3
5	F/28	left lobe	ND				ND	4
6	M/23	RUL	1.8			lobectomy	120	5
7	F/56	RLL	1.8			Wedge resection	24	5
8	F/25	RLL	2.5			Lobectomy	108	6
9	M/60	RUL (central)	2.4			Lobectomy, LN	24	6
10	F/52	RUL (central)	1.2			Lobectomy, LN	11	6
11	M/26	RLL	2			wedge resection	16	7
12	F/2 month	RUL	2			wedge resection	24	8
13	M/35	LLL	2	+	vascular	Lobectomy, LN	36	9
14	M/15	LUL	2.5		capsule	wedge resection	108	10
15	M/27	RLL	2.4		alveoli and visceral pleura	lobectomy, LN	24	10
16	M/9	left lobe	0.4			wedge resection	ND	11
17	F/35	peripheral	3			ND	ND	12
18	M/50	LUL	2.5	+		segmentectomy	35	13
19	ND/66	LLL	3			multiple segmentectomy	ND	14
20	M/61	LLL	1.5	+		partial excision	84	15
21	M/70	LLL	1.8	+		partial resection	36	16

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22	M/75	TBNA biopsy	1.5		FNAC+cell block	ND	17
23	M/52	LLL	1.8		Wedge resection	46	18
24	F/16	LLL	3		lobectomy	ND	19
25	M/45	LLL	2		Wedge biopsy	ND	20
26	M/24	LUL	6		wedge resection	6	21
27	F/68	left lobe	2.5		wedge resection	ND	22
28	F/17	right lobe (central)	3.13		wedge resection	12	23
29	F/78	RUL	3.8	minimal adjacent invasion in CT	FNAC+Core biopsy	26	24
30	F/64	RUL	1.5		lobectomy	6	25
31	F/41	left lobe	2		wedge resection	ND	25
32	M/56	LLL	1.5		lobectomy	10	present

Abbreviations: BL: bronchial lumen; M: male; F: female; LUL: left upper lobe; LLL: left lower lobe; RUL: right upper lobe; RML: right middle lobe; RLL: right lower lobe; LN: regional lymph-node dissection; ND: not described.

nancy were not excluded in other three cases. According to our statistics-nearly half of the patients (12/27) were performed lobectomy for the potential malignancy. However, the other patients, who were performed wedge resection (13/27) or segmental resection (2/27), all had no recurrence or metastasis, proving that complete resection of pulmonary papillary adenomas was definitive treatment.

Electron microscopy of the epithelial cells revealed secretory granules of high electron density and osmiophilic lamellar bodies. Ultrastructural features favored type II alveolar epithelium and Clara cell differentiation. Hence, the tumor is also known as Clara cell adenoma, bronchiolar adenomas, and type II alveolar papillary tumor [3, 5, 6-10, 19].

The differential diagnosis includes alveolar adenoma, sclerosing pneumocytoma, glandular papilloma and papillary adenocarcinoma. Alveolar adenoma has a characteristic multicystic histology and often resembles the normal lung parenchyma. Pulmonary sclerosing pneumocytoma may have the same origin with papillary adenoma. The presence of polygonal cells in pulmonary sclerosing pneumocytoma, which also showed positivity for TTF-1, was a peculiar feature for differential diagnosis. The peripheral type of glandular papilloma also can be considered due to papillary fronds, but its epithelial lining consists of a stratified columnar or cuboidal epithelium and mucous cells with varying proportion. The lack of cellular atypia and mitosis exclude papillary adenocarcinoma.

With the development of targeted drugs, gene testing is becoming more popular. EGFR gene mutations are early and common events in pulmonary adenocarcinoma. EGFR, K-Ras, or BR-

AF gene mutations were not found in the reported pulmonary papillary adenoma cases [21, 23, 25]. There was also no EGFR mutation in all the components of our case.

Relatively little is known regarding genetics about these tumors. Masunaga et al. recently determined, based on the increased degree of detectable fibroblast growth factor receptor, that the production of FGFR2 plays an important role in tumor development [19]. FGFR2 is one of the tyrosine-kinase receptors causing cellular proliferation, and migration, which has been shown to be associated with lung adenocarcinoma. This is a genetic proof of the possibility of cancer development of papillary adenoma.

Thus, we provide the first case of pulmonary papillary adenoma cancer development. We have a certain understanding of this tumor, and more work is needed in the future to show the molecular nature of this tumor.

### Disclosure of conflict of interest

None.

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