Retrospective study of clinical and pathologic features of pulmonary papillary adenoma
A rare tumor and 15 cases report
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Abstract
Pulmonary papillary adenoma is extremely rare. The limited number of published articles describing pulmonary papillary adenoma emphasize that it is always detected by physical examination, is difficult to diagnose, and has malignant potential. To further expand our understanding of this disease, we report on 15 cases of pulmonary papillary adenoma diagnosed from 2013 to 2019 in our hospital.

The clinical and pathological data of 15 cases of pulmonary papillary adenoma were collected from the medical record system of our hospital. All the clinical data were checked by 2 independent researchers. All pathology outcomes were independently reassessed by 2 pathologists. A review of the relevant literature was performed.

Of 15 patients identified, 6 were men and 9 were women, and the average age at disease onset was 61.3 years. Chest computed tomography (CT) indicated pneumonia, an isolated nodule, bronchiectasis, a mass, ground glass opacity, and local interstitial fibrosis under the pleura. Thirteen cases had benign histopathology upon microscopy and immunohistochemistry examination: a papillary morphology, grade 2 or 3 papillary branches, and a slender nipple axis composed of fibers and vessels. More than 80% of the papillary epithelial cells were columnar or cubic, and single-layered or pseudostratified, with a round nucleus at the bottom of the cell. The cytoplasm was rich in mucus and neutral mucopolysaccharides. Except the above-mentioned features, there was also local epithelial dysplasia, carcinogenesis, and interstitial infiltration in two cases. The 2 patients with a cancerous mass underwent surgical resection, whereas the other patients were kept under surveillance. While one patient with cancer is deceased, follow-up indicates that the remaining patients have experienced a good outcome.

Pulmonary papillary adenoma is very rare in clinical practice, and its clinical manifestations and CT images are not specific. Some cases may be cancerous and surgical resection should be the preferred treatment.

Abbreviations: 18F-FDG = 18F-Fluorodeoxyglucose, AB = alcian blue, COPD = chronic obstructive pulmonary disease, CT = computed tomography, FEV1/FVC = forced expiratory volume in one second/forced vital capacity, PAS = periodic acid-Schiff, TBLB = transbronchial lung biopsy.

Keywords: clinical manifestations, malignant transformation, pathological biopsy, pulmonary papillary adenoma

1. Introduction
A pulmonary papillary adenoma is extremely rare in clinical practice, with fewer than 30 cases reported in the English literature.[1–6] The clinical symptoms of pulmonary papillary adenoma are nonspecific and can manifest as cough, sputum, hemoptysis, chest pain, etc. However, patients often feel no
discomfort and are diagnosed by physical examination.\(^1\) Pulmonary papillary adenoma is thought to be a benign disease with a low malignant transformation potential, mainly appearing as a solitary pulmonary nodule on chest computed tomography (CT) images in the limited literature available\(^{15,6}\); there are no reports of cancerous cases. Owing to its rarity and atypical symptoms, its diagnosis and treatment are challenging, and the literature provides only limited guidance. This article describes the clinical and pathological features of 15 pulmonary papillary adenomas. Among them, only five had CT findings consistent with those in the literature, and 2 had both benign and malignant lesions. We present the first report on malignant pulmonary papillary adenoma, and our findings further the understanding of this disease and hence will aid in its diagnosis and treatment.

2. Materials and methods

2.1. Diagnosis

The pathological features of 15 cases of pulmonary papillary adenoma diagnosed via biopsy at our hospital from March 2013 to April 2019 were retrospectively analyzed. Eight patients underwent transbronchial lung biopsy, 3 underwent percutaneous lung biopsy, and 4 underwent surgical biopsy. The average specimens measured approximately 1 cm in length and 0.1 cm in width, and the cut surface was grayish brown and soft. All specimens were fixed in 10% formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin, Alcian blue (AB), or periodic acid-Schiff (PAS) for mucopolysaccharides. Ready-to-use primary antibodies to Ki-67, vimentin (Vim), cytokeratin 7 (CK7), cytokeratin 25/6 (CK5/6), and thyroid transcription factor 1 (TTF1) and EnVision kits were purchased from Fujian Maixin Biotechnology Development Co., Ltd. The EnVision kit was used for high-temperature, high-pressure antigen retrieval and 3,3'-diaminobenzidine color development. Cells positive for Ki-67 (i.e., proliferating cells) had brown nuclear staining, whereas cells positive for the other antigens had brown cytoplasmic staining, as visualized via light microscopy. All diagnoses were independently assessed by two pathologists. We also searched the literature from January 1, 1980, to 1 August 1, 2019, for relevant articles using the Medline (National Library of Medicine, USA), Cochrane Library (UK), CNKI (China) and SinoMed (China) databases.

2.2. Treatment

Five patients, including two with cancerous adenomas, underwent lobectomy, whereas 10 patients received only symptomatic treatment. The comorbidities and their treatments were as follows: chronic obstructive pulmonary disease (COPD), anti-inflammatory and dilating bronchial therapy; heart failure, anti-heart failure treatment; pleural effusion, thoracentesis and drainage; diabetes, hypoglycemic therapy; sinusitis, anti-infective treatment; and chronic gastritis, anti-acid therapy.

2.3. Statistical analysis

Categorical variables were represented as number of cases (rate) and analyzed using a Chi-square test or the Fisher exact test, while continuous variables were represented as medians with an interquartile range (IQR) and compared using Mann–Whitney U tests. Statistical significance was defined as 2-sided \(P\) values < .05, and all statistical analyses were performed using the Statistical Package for the Social Sciences version 23.0 (SPSS 23.0, Chicago, IL).

3. Results

3.1. Clinical features

Among the 15 patients with pulmonary papillary adenoma, 6 were men and 9 were women. The average age at disease onset was 61.3 years (range, 39–78 years). Three patients had a history of smoking, and the average pack-year was 35. Detailed characteristics of the patients are presented in Table 1.

3.2. Comorbidities

Most patients with pulmonary papillary adenoma had multiple comorbidities. These included hypertension (5/15, 33%), diabetes (3/15, 20%), bronchiectasis (3/15, 20%), digestive diseases (3/15, 20%), chronic bronchitis (2/15, 13%), respiratory failure (1/15, 6%), COPD (1/15, 6%), and heart failure (1/15, 6%). Two (13%) patients had no comorbidities and two (13%) had a history of malignant tumors.

3.3. Clinical manifestations

Many patients had clinical symptoms not commonly associated with pulmonary papillary adenoma. Ten (67%) patients had a cough, 8 (53%) had sputum (8/15), 3 (20%) had shortness of breath, 2 (13%) had congestive heart failure, 2 (13%) had chest pain, and one (6%) had chest tightness. Four (27%) patients had no symptoms.

3.4. Chest CT findings

Among the 15 pulmonary papillary adenomas, 5 had conventional features on thorax CT: an isolated nodule (3/15, 20%) (Fig. 1A) or mass (2/15, 13%) (Fig. 1B). The remaining 10 had unexpected features: pneumonia (5/15, 33%) (Fig. 1C), bronchiectasis (3/15, 20%) (Fig. 1D), ground glass opacity (1/15, 6%) (Fig. 1E), and interstitial fibrosis under the pleura (1/15, 6%) (Fig. 1F).

3.5. Tumor markers

The following tumor markers were examined: NSE, CYFRA21-1, SCC, CEA, ferritin, CA21-1, CA125, CA72-4, and pro-gastrin-releasing peptide (proGRP). Tumor marker levels were normal in seven patients and abnormal in 5; data were not available for the remaining 3 patients. Two of the seven patients with abnormal marker levels had a history of breast cancer and esophageal cancer, respectively. There were slight increases in tumor marker levels in a patient with cancer (ferritin, CA21-1, and CA125) and a patient with a history of rectal polyps (proGRP, CA21-1, and CA72-4).

3.6. Pulmonary function

Five patients were examined for lung function. The FEV1/FVC (forced expiratory volume in 1 second/forced vital capacity) was less than 70%, 43%, and 69% in 3 patients, respectively. The residual volume/total lung capacity ratio was high in 2 patients (69 and 54 respectively). After calibration, the diffusing capacity of the lungs was low in 2 patients (69% in both). The remaining 10 patients had normal lung function.
3.7. Pathology outcomes

In 13 cases, examination of the tumor tissue showed benign features: papillary morphology, mostly grade 2 or 3 papillary structure, and a slender papillary axis composed of fibers and vessels. More than 80% of the Papillary epithelial cells were columnar, partially cubic, or flat and single-layered or pseudo-stratified, with a round or oval nucleus at the bottom of the cell (Fig. 2A). The cytoplasm was rich in mucus and neutral mucopolysaccharides, and mucus retention was observed between the nipples (Fig. 2B). Staining was positive for AB (Fig. 2C and D) and PAS (Fig. 2E), and CK7, Vim, CK20, and TTF1 (Fig. 2F) were expressed. The Ki-67 proliferation index was less than 3%. The pathological diagnosis of these cases was a pulmonary papillary adenoma.

Two cases involving lobectomy had malignant manifestations (Fig. 3A and B), including tumor cell dysplasia and short, flat, or tubular nipples. The tumor cells had different sizes and a disorderly and uneven arrangement. The nuclei were strongly stained with HE (Hematoxylin-eosin), mitotic figures were easy to see, and some tumor cells had infiltrated between the interstitial regions. Fibrous tissue hyperplasia, lymphocytic infiltration, and carbon deposition were observed in and around the tumors, as is the case for inflammatory pseudotumors. The Ki-67 proliferation index in heterotypic regions was more than 25% (Fig. 3C and D).

### Table 1
The Clinical features of 15 cases of pulmonary papillary adenoma.

| Num. | Gender | Age | Smoking history (Pack-year) | Comorbidity | Respiratory symptoms | CT chest performance | Tumor markers | Diagnosis method | Treatment | Follow-up |
|------|--------|-----|-----------------------------|-------------|----------------------|---------------------|---------------|-----------------|------------|-----------|
| Case 1 | Female | 62  | NO                          | Diabetes, Hypothyroidism, Hypertension | Cough, Sputum | GGO (LUL) | Ferritin† | TBLB | NO | Good |
| Case 2 | Male   | 60  | NO                          | Hypertension, LDH | Cough, Chest pain | Nodule (1.1cmX0.7cm, LLL) | Normal | SB | SR | Good |
| Case 3 | Female | 65  | NO                          | Breast cancer, Esophageal cancer, Hypertension | Cough, Sputum, Heart tired | Exudation | CA21-1†, CA72-4†, ProGRP†, SCC†, NSE† | PCNB | NO | Good |
| Case 4 | Male   | 64  | NO                          | Rectal polyp | Cough, Sputum, Dyseania | Exudation | CYFRA21-1† | PCNB | NO | Good |
| Case 5 | Female | 62  | NO                          | Breast cancer | Cough, Sputum | Nodule (1cmX1cm, RML) | Cytoplasm, Nodule | SB | SR | Good |
| Case 6 | Female | 72  | NO                          | No            | Cough, Sputum | Exudation | Normal | SB | SR | Good |
| Case 7 | Male   | 47  | 30                          | Diabetes, CB, RF, Emphysema | Cough, Sputum | Exudation | Consolidation | NA | TBLB | NO | Good |
| Case 8 | Female | 78  | NO                          | Diabetes, Hypertension, IP | No | Mass | NA | TBLB | NO | Good |
| Case 9 | Female | 68  | NO                          | Diabetes, Hypertension | Cough, Sputum, Dyseania | BE | Normal | TBLB | NO | Good |
| Case 10| Male   | 48  | NO                          | Vitiligo, BE, CB, Heart failure | Cough, Sputum, Heart tired | BE | Normal | TBLB | NO | Good |
| Case 11| Female | 63  | NO                          | COPD, Lung bubble, BE, Heart failure, Pleural effusion | Cough, Sputum, Dyseania | BE | Normal | TBLB | NO | Good |
| Case 12| Female | 39  | NO                          | COPD, Lung bubble, BE, Hypertension | Cough, Sputum | Exudation | Consolidation | NA | PCNB | NO | Good |
| Case 13| Female | 76  | NO                          | Hypertension | Cough, Sputum, Chest pain | Mass | CA21-1†, CA125†, Ferritin† | SB | SR | Dead |
| Case 14| Male   | 70  | 50                          | Hypertension | No | Mass | NA | TBLB | NO | Good |
| Case 15| Male   | 45  | 25                          | Esophagitis, Chronic gastritis, BE | Cough, Sputum, Chest tightness | BE | Normal | TBLB | NO | Good |

BE = bronchiectasis, CA125 = carbohydrate antigen 125, CA21-1 = carbohydrate antigen 21-1, CA72-4 = carbohydrate antigen 72-4, CB = chronic bronchitis, CI = cerebral infarction, COPD = chronic obstructive pulmonary disease, CYFRA21-1 = cytokeratin fragment 21-1, F = female, IP = interstitial pneumonia, LDH = lumbar disc herniation, LLL = left lower lobe, LUL = left upper lobe, M = male, NA = not available, NSE = neuron specific enolase, PCNB = percutaneous needle biopsy, ProGRP = pro-gastrin releasing peptide, RF = respiratory failure, RLL = right lower lobe, RML = right middle lobe, SB = surgical biopsy, SCC = squamous cell carcinoma associated antigen, SR = surgical resection, TBLB = transbronchial lung biopsy.
4. Discussion
A pulmonary papillary adenoma is an extremely rare, seemingly benign tumor. Spencer et al were the first to describe 2 cases of peripheral papillary adenoma of the lung. In both the cases, the tumor cells were pathologically similar to Clara cells. In one case, that of a 7-year-old child, the tumor cells approached the alveoli, but there were no malignant features. Fantone et al published a case of “lung papillary adenoma” in a 25-year-old woman. The tumor cells contained lamellar bodies and dense electronic particles resembling those of type II alveolar cells and Clara cells. In 1992, Xu et al presented two cases of pulmonary papillary adenoma in China. As shown via electron microscopy, the tumor...
cells contained abundant eosinophilic lamellar bodies, which suggest that they were alveolar type II epithelial cells.\(^1\) Thus far, there are fewer than 30 reports of pulmonary papillary adenoma in the English literature.

The clinical manifestations of pulmonary papillary adenomas are non-specific, and patients are often diagnosed by physical examination.\(^4\) These tumors most often occur in men, with age at onset varying from 2 months to 75 years (average, 34 years).

**Figure 2.** On Hematoxylin-eosin staining, the tumor was papillary, with a single and pseudo-stratified layer, the nucleus was at the bottom of the cell (Fig. 2A ×20; Fig 2B ×40); On Alcian blue, the tumor cell cytoplasm was rich in mucus (Fig. 2C ×20; Fig 2D ×40); On Periodic acid-Schiff staining, the tumor cell cytoplasm was rich in mucus (Fig. 2E ×20); Staining was positive for TTF (Fig. 2F ×20).
years.\(^{[5,6]}\) Chest CT usually shows an isolated nodule or mass of 1 to 6 cm with a smooth edge and round or oval shape,\(^{[5–8]}\) The lesion is typically located in the periphery of the lungs, most commonly the left lower lobe,\(^{[5,6]}\) Lesions in the central part of the lung (e.g., the hilar region and main bronchus) have also been observed on occasion.\(^{[9,10]}\) Tumors that block the airway can cause coughing and asthma owing to poor ventilation. To the best of our knowledge, there have been no reports of malignant transformation of pulmonary papillary adenoma. We described 15 cases of this disease in this article, 6 in men and 9 in women, with an onset age of 39 to 78 years. Chest CT revealed a nodule or mass lesion in 5 cases, as expected based on the existing literature. However, the other 10 cases had novel features on CT, including pneumonia (5 cases), bronchiectasis (3 cases), ground glass opacity (1 case), and interstitial fibrosis under the pleura (1 case). These features may be related to the loose structure of the tumor tissue, which hinders the formation of a dense mass.

Pathological examination is the gold standard for diagnosis of pulmonary papillary adenoma. When visualized under low magnification, the tumor tissue is typically intact with a papillary and glandular tubular arrangement and cubic or columnar epithelial cells.\(^{[11–13]}\) In rare cases, squamous epithelial components and papillary of various sizes and shapes can be seen.\(^{[12]}\) When visualized under high magnification, a single layer of adenoid, papillary, and agglomerate alveolar epithelial cells and fibrous interstitial cells is apparent. The nuclei are round or elliptical and lightly stained, with no mitoses or other abnormalities.\(^{[13]}\) CKs, TTF1, surfactant, carcinoembryonic antigen, p63, epithelial membrane antigen, and napsin A are always expressed in the epithelial cells, but never in the interstitial cells, and the Ki-67 proliferation index is approximately 2%.\(^{[8,14]}\) The pathological findings in our cases were mostly almost consistent with these descriptions. However, 2 cases in our study, both involving lobectomy, had malignant manifestations,

Figure 3. On Hematoxylin-eosin staining, The tumor cell was dysplasia, short, and flat, the nuclei were deeply stained with HE, the tumor cells had different sizes and a disorderly arrangement (Fig. 3A ×20; Fig 3B ×40); The Ki-67 proliferation index in heterotypic regions was more than 25% (Fig. 3C ×20; Fig 3D ×40).
including tumor cell dysplasia and short, flat, or tubular nipples. Pulmonary papillary adenoma needs to be differentiated from sclerosing hemangioma, bronchioalveolar adenocarcinoma, atypical adenomatous hyperplasia, micronodular pneumocyte hyperplasia, and papillary adenocarcinoma, etc.

Accurate diagnosis requires experienced pathologists to make a decision. At present, the pathogenesis of pulmonary papillary adenoma is unknown. Some scholars believe that pulmonary papillary adenoma is derived from pluripotent stem cells that have the potential to differentiate into respiratory ciliated epithelial cells, Clara cells, and type I and type II alveolar cells. Others suggest that it originates in Clara cells or type II alveolar cells. It may also be related to the overexpression of fibroblast growth factor receptor 2-IIIb: in the case of a 16-year-old girl reported by Masunaga et al., FGFR2 mRNA expression was 350% higher in adenoma versus that in normal lung tissue. Genetic mutations may also be involved: a mutation in exon 2 of the KRAS gene in lung papillary adenoma tissue has been reported. Most investigators currently believe that pulmonary papillary adenomas are benign tumors with a good prognosis and a low malignant potential. Only 2 cases of benign pulmonary papillary adenoma with invasive growth behavior have been reported, both by Dessy et al. In 1 case, the tumor cells approached the capsule, whereas, in the other, the adjacent alveolar structure and pleura were affected. The results reported herein show for the first time that pulmonary papillary adenomas can be malignant. In agreement, Mori et al. suggest that these tumors resemble alveolar cell type adenocarcinomas, which are thought to have malignant potential.

Since pulmonary papillary adenomas can be cancerous, it is best to perform radical surgery after diagnosis. For tracheobronchial lesions, bronchoscopy-guided intervention therapy is effective if surgery cannot be tolerated. Fang et al. used laser to remove a papillary adenoma in the trachea; blood gas irregularities and dyspnea symptoms were immediately relieved after surgery, with no recurrence for at least 360 days. For patients unable or unwilling to undergo surgery or interventional therapy, routine monitoring and symptomatic treatments are available. In our study, five patients underwent surgical resection, and ten received symptomatic treatment only. Three patients were hospitalized several times for acute exacerbation of COPD, heart failure, and pulmonary infection, respectively; the patient with heart failure had received surgery. There were no changes in the appearance of the lesions in other patients. After all, this article is a retrospective study, so the acquisition of clinical and pathological data can only be based on what is recorded in the medical record system. These may be biased due to inconsistencies between different doctors. In the future, a prospective design to improve the quality of evidence is needed.

5. Strengths and limitations of this study

1. The 15 cases of pulmonary papillary adenomas reported in this article are the largest single-center case reports at present.
2. This article firstly and comprehensively analyzes the clinical manifestations, imaging findings, pathological features, diagnosis, treatment, and follow-up of pulmonary papillary adenoma.
3. This article is a retrospective analysis and cannot prospectively detect the tumor mutation genes and other indicators.

6. Conclusion

Pulmonary papillary adenoma has a good prognosis, but it can cause malignancy in some cases. Therefore, these tumors should be surgically removed as soon as possible after diagnosis. Additional case reports are needed, as are studies addressing mechanisms.

Author contributions

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References

[1] Spencer H, Dail DH, Arneaud J. Non-invasive bronchial epithelial papillary tumors. Cancer 1980;45:1486–97.
[2] Fantone JC, Geisinger KR, Appelman HD. Papillary adenoma of the lung with lamellar and electron dense granules. An ultrastructural study. Cancer 1982;50:2839–44.
[3] Xu Y, Zhang ZY, Liu H, et al. Report of two cases of pulmonary papillary adenoma and literature review. Chin J Tuberc Respir Dis 1992;15:296–7. (reported in chinese).
[4] Chiu IH, Han J, Moon JW, et al. A rare case of pulmonary papillary adenoma in old aged woman: a brief case report. Korean J Pathol 2014;48:66–8.
[5] Cornejo KM, Shi M, Akalin A, et al. Pulmonary papillary adenoma: a case report and review of the literature. J Bronchology Interv Pulmonol 2013;20:52–7.
[6] Yamamoto T, Horiguchi H, Shibagaki T, et al. Encapsulated type II pneumocyte adenoma: a case report and review of the literature. Respiration 1993;60:373–7.
[7] Aida S, Ohara I, Shimazaki H, et al. Solitary peripheral ciliated glandular papillomas of the lung: a report of 3 cases. Am J Surg Pathol 2008;32:1489–94.
[8] Shomura S, Suzuki H, Sawada Y, et al. Surgery of papillary adenoma: report of a case. Kyobu Geka 2019;72:720–3.
[9] Lin XY, Han Q, Wang EH, et al. Pulmonary papillary adenoma presenting in central portion: a case report. Diagn Pathol 2015;10:190. Published 2015 Oct 17.
[10] Wohlschläger J, Wehrt S, Stamatis G, et al. Glandulares Papillom des rechten Hauptbronchus. Nachweis einer Exon-2-Mutation des KRAS-Gens (c.35G>A) [Glandular papilloma of the right main bronchus. Detection of an exon 2 mutation of the KRAS gene (c.35G>A)]. Pathologie 2013;34:338–42.
[11] Wang FH, Li N, Yang JH. Clinicopathological observation of pulmonary papillary adenoma. J Mod Oncol 2011;19:58–9.
[12] Minami Y, Morishita Y, Yamamoto T, et al. Cytootechnic characteristics of pulmonary papillary adenoma. A case report. Acta Cytol 2004;48:243–8.
[13] Nakano T, Yokose T, Hasegawa C, et al. Papillary adenoma of the lung with a peculiar raw macroscopic feature. Pathol Int 2011;61:475–80.
[14] Wang XL, Jiang GJ, Zhang XZ, et al. Pulmonary papillary adenoma: report of two cases. J Coll Physicians Surg Pak 2017;27:582–3.
[15] Masunaga A, Nagashio R, Iwamoto S, et al. A case of pulmonary papillary adenoma: possible relationship between tumor histogenesis/tumorgenesis and fibroblast growth factor receptor 2. Pathol Int 2012;62:640–5.
[16] Dessy E, Braidotti P, Del Curto B, et al. Peripheral papillary tumor of type-II pneumocytes: a rare neoplasm of undetermined malignant potential. Virchows Arch 2000;436:288–95.
[17] Mori M, Chiba R, Tezuka F, et al. Papillary adenoma of type II pneumocytes are malignant potential. Virchows Arch 1996;428:195–200.
[18] Fang BM, Huang WN, Lv L, et al. The clinical features of endotracheal papillomatous and treatment of it with holmium: YAG laser under the electron-bronchoscope A report of one case. Zhongguo Linchuan Baqian Zazhi 2007;3:244–6. (reported in chinese).