Original Article

Computed tomography (CT) characteristics and pathologic basis of ciliated muconodular papillary tumors of the lung

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Background: Ciliated muconodular papillary tumor (CMPT) is a rare pulmonary tumor with papillary architecture. Most studies have focused on the clinicopathological features of CMPT, while computed tomography (CT) characteristics have rarely been systematically described.

Methods: A cohort of 27 patients with surgically resected CMPT were identified. Clinical and demographic features were recorded. Preoperative CT images of the CMPTs and the corresponding histopathological basis were also retrospectively analyzed.

Results: All of the tumors appeared as solitary nodules. Pure ground glass, part-solid nodules and solid nodules were detected in 2/27 (7.4%), 17/27 (63.0%), and 8/27 (29.6%) patients, respectively. Twenty-one tumors (77.8%) were located in the lower lobe. The average tumor size was 1.21±0.74 (range, 0.44–3.46) cm. Eighteen (66.7%) of the 27 patients had tumors with well-defined margins and lobulated contours. Fifteen patients (55.6%) had air bronchograms in the tumor, and 19 patients (70.4%) had air-containing space. There were two patients whose tumor size was enlarged and accompanied by an increase in solid components, and one patient simply had an increase in tumor size at the preoperative follow-up duration. Notably, one patient with solid tumor components was finally diagnosed with CMPT accompanied by adenocarcinoma.

Conclusions: CMPTs of the lung mostly manifest as solitary, lobulated, well-defined tumors with air-containing spaces on CT and often occur in the periphery of the pulmonary lower lobe. When CT findings meet these criteria, the possibility of CMPT should be considered. Additionally, CMPT can coexist with adenocarcinoma. Further investigation will contribute significantly to the biological properties of CMPT and its relationship to the potential for malignant transformation.

Keywords: Ciliated muconodular papillary tumor (CMPT); pulmonary adenoma; computed tomography (CT); pathology; malignancy transformation

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Introduction

Ciliated muconodular papillary tumor (CMPT) is an extremely infrequent entity first described by Ishikawa in 2002 (1). Gradually, with the application of low-dose computed tomography (CT) and artificial intelligence, more pulmonary nodules were detected, and related case reports of CMPT increased (2,3). Recently, CMPT was introduced as a novel entity in the 2021 World Health Organization (WHO) Classification of Thoracic Tumors and considered to be a type of benign pulmonary adenoma (4). It consists of ciliated columnar cells, mucinous cells, and basal cells with distinctive papillary architecture (5). The majority of the literature has focused on the clinical and pathological features of CMPT, while CT characteristics have rarely been systematically described. Commonly, the tumor appeared as a solitary and peripheral nodule on CT scans and was easily misdiagnosed as lung cancer (6-8). In this study, we retrospectively collected a cohort of 27 patients with pathologically confirmed CMPT and analyzed CT findings of tumors and the corresponding pathological basis in these patients.

Methods

Patient cohorts

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Beijing Shijitan Hospital, and individual informed consent for this retrospective analysis was waived. We retrospectively collected and reviewed the medical records of patients with small pulmonary nodules who underwent surgical resection at the General Hospital of the People's Liberation Army and the affiliated Beijing Shijitan Hospital of Capital Medical University from January 2012 to June 2022. Patients were eligible for enrollment when they met the following criteria: (I) a surgical pathological diagnosis of CMPT and (II) received thin-slice CT scans in our institutions. Follow-up time in this study was defined as the duration from the date of the first CT examination to the last preoperative CT examination.

Radiological and histopathologic assessment

The chest CT examinations were performed with either a 64-Slice GE LightSpeed CT scanner (GE Healthcare, Beijing, China) or a Siemens SOMATOM Sensation 128-Slice CT Scanner (Siemens, Forchheim, Germany). The parameters for CT screenings were as follows: routine section thickness, 1.0–1.5 mm; section thickness after reconstruction, 0.625–1.25 mm; 80–120 kV; 200–300 mAs. These CT images were reviewed and assessed on setting the lung window (width, 1,500 HU; level, –600 HU) and mediastinal windows (width, 350 HU; level, 40 HU). Chest CT images were reviewed for tumor location, size, and external and internal characteristics. The average value of the maximum diameter on axial images was used for tumor size. Pulmonary nodules were classified into solid nodules (SNs) and subsolid nodules according to the absence of ground glass opacities (GGOs). In subsolid nodules, a pure ground glass nodule (pGGN) was defined as a nodule with only GGO, and a part-solid nodule (PSN) was defined as a nodule with both GGO and solid components. Internal characteristics of the tumor, including vascular changes (dilated, rigid, convergent, or tortuous blood vessels observed on consecutive axial, coronal, or sagittal reconstruction images), air bronchogram (branching or tubular air density surrounded by tumor tissue on CT scans and could be distinguished in consecutive multiple reconstruction images), and air-containing space (presence of round or oval air-filled spaces in the tumor with a relatively thin wall), were recorded. External characteristics, including lobulation (uneven lobular outline caused by variance in tumor growth), spiculation (radiating and tiny burr around the tumor margin) and pleural retraction, were also observed and recorded. A cardiopulmonary radiologist (J Wu) with 20 years of experience and a pulmonary radiologist (C Wu) with 15 years of experience conducted the evaluation work, and discrepancies were resolved by consensus.

The resected specimens were fixed in 4% neutral formaldehyde, embedded in paraffin, sliced at a thickness of 3–5 μm and stained with hematoxylin and eosin. Immunohistochemistry staining was performed with

Table 1 Clinical characteristics of the patients with ciliated muconodular papillary tumors

Clinical characteristics	Patients (n=27)
Age (years)	56.15±10.20 [36–71]
Sex	
Male	11 (40.7)
Female	16 (59.3)
Smoking history	
Yes/ever	5 (18.5)
No/never	22 (81.5)
Smoking index	28.3±10.5 [15–40]
Clinical symptoms	
Asymptomatic	22 (81.5)
Cough/expectoration/chest pain	5 (18.5)
Treatment	
Wedge resection	21 (77.8)
Partial resection	3 (11.1)
Lobectomy	3 (11.1)

Data are presented as the mean ± standard deviation [range] or number (%).

antibodies against thyroid transcription factor 1 (TTF-1), napsin A, p63, p40, cytokeratin 5 (CK5), cytokeratin 7 (CK7), cytokeratin 20 (CK20) and Ki-67. All pathological slices were scanned through Pannoramic MIDI digital slice scanning (3DHIESTECH, Hungary). The software CaseViewers was used to review tumors. Two experienced senior pathologists (J Gao, Y Xie) conducted histopathologic examination without being informed of the clinical information. If there was any disagreement during the evaluation, they reassessed them by consensus. The histopathological diagnostic criteria for CMPT were determined according to the 2021 WHO Classification of Lung Tumors. The mucin score could be graded into 3 categories according to the scoring system reported by a previous system (8): (I) score 1 indicates mucin amount <30%, (II) score 2 represents mucin amount within 30–70%, and (III) score 3 represents mucin amount >70%.

Statistical analysis

All data analysis in this research was performed with SPSS (version 26.0; IBM Corp, Armonk, NY). Continuous variables such as age, tumor size, and smoking index were expressed as the means ± standard deviations with ranges. Categorical variables, including sex, smoking history, symptoms and CT characteristics, were described with counts and percentages, and 95% confidence intervals (CIs) for observed variables were also expressed. The interobserver agreement for the internal and external characteristics of the tumor was investigated by using the κ statistic. A κ value of 0–0.20 was considered poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and 0.81–1.00, perfect agreement.

Results

Clinical characteristics

In this study, the final patient cohort consisted of 27 patients (mean age, 56.15±10.20 years; age range, 36–71 years) with CMPT. As summarized in *Table 1*, 11 (40.7%) of the 27 patients were men, and 16 (59.3%) were women. Only 5 (18.5%) of the 27 patients had a smoking history, and the mean pack-years among smokers was 28.3±10.5 (range, 15–40) pack-years. More than half of the cohort [22 patients (81.5%)] was asymptomatic, and the tumor was detected incidentally during physical check-up or examination for other disease processes. Five patients had clinical symptoms at presentation: coughing and expectoration of sputum in three patients and chest pain in two patients. Regarding treatment, most patients (77.8%) underwent wedge resection.

CT characteristics of CMPT

Table 2 displays the interobserver agreement for the evaluated radiological features. The κ value was perfect for category of nodule, 0.919 (95% CI: 0.762–1.076); lobulation, 0.914 (95% CI: 0.749–1.079); spiculation, 0.886 (95% CI: 0.668–1.104); vascular changes, 0.834 (95% CI: 0.616–1.052); air-bronchogram, 0.852 (95% CI: 0.658–1.046); air-containing space, 0.908 (95% CI: 0.732–1.084) and pleura retraction, 0.919 (95% CI: 0.764–1.074); and moderate to boundary of tumor, 0.647 (95% CI: 0.335–0.959).

The radiological characteristics are shown in *Table 3*. All tumors appeared as solitary nodules. pGGN, PSNs and SNs were detected in 2/27 (7.4%), 17/27 (63.0%), and 8/27 (29.6%) patients, respectively. Twenty-one tumors (77.8%) were located in the lower lobe. The average tumor size

Table 2 Interobserver agreements for radiological characteristics

Radiological characteristics	Kappa value	95% CI
Category of nodule	0.919	0.762–1.076
Lobulation	0.914	0.749–1.079
Spiculation	0.886	0.668–1.104
Vascular changes	0.834	0.616–1.052
Air-bronchogram	0.852	0.658–1.046
Air-containing space	0.908	0.732–1.084
Pleural retraction	0.919	0.764–1.074
Margin of tumor	0.647	0.335–0.959

CI, confidence interval.

was 1.21±0.74 (range, 0.44–3.46) cm. Eighteen (66.7%) of the 27 patients had tumors with lobulation contours. Only six (22.2%) tumors showed spiculation contours. Fifteen patients (55.6%) had air bronchograms in the tumor, and 19 patients (70.4%) had air-containing space. Dilated, rigid, convergent, or tortuous blood vessels were observed in the tumors of 10 patients (37.0%), and pleura retraction was observed in 18 (66.7%) patients. Eighteen (66.7%) patients had tumors with well-defined margins. Several CT features could often be seen in one patient (*Figure 1*). Seventeen patients had their previous chest CT images available. Of these 17 patients, 15 were followed up for at least 6 months. The mean follow-up period was 1.6±1.9 years, ranging from 0.3 to 8 years. During the follow-up, there were two patients whose tumor size increased and was accompanied by an increase in solid components (*Figure 2*).

Pathological basis

The postoperative histopathologic examination revealed that the tumor featured a papillary structure and was surrounded by mucus, and tumor cells floating on the 'mucoid lake' could be observed. For intratumoral mucus evaluation, 15 patients had mucin score 3, 8 patients had mucin score 2 and 4 patients had mucin score 1. The lesion area was often fairly well demarcated from the surrounding parenchyma (*Figure 3*), which correlated with the imaging finding of well-defined margins. A large amount of extracellular mucus filled and dilated the surrounding pulmonary alveoli. The papillary tumor nodule and extravasating mucus sometimes

Table 3 Radiological characteristics of patients with ciliated muconodular papillary tumors on thin-section CT

Radiological characteristics	Patients (n=27)
Category of nodule	
pGGN	2 (7.4)
PSN	17 (63.0)
SN	8 (29.6)
Location	
Right upper lobe	3 (11.1)
Right middle lobe	2 (7.4)
Right lower lobe	8 (29.6)
Left upper lobe	1 (3.7)
Left lower lobe	13 (48.2)
Tumor size (cm)	1.21±0.74
Lobulation	
Positive	18 (66.7)
Negative	9 (33.3)
Spiculation	
Positive	6 (22.2)
Negative	21 (77.8)
Vascular changes	
Positive	10 (37.0)
Negative	17 (63.0)
Air-bronchogram	
Positive	15 (55.6)
Negative	12 (44.4)
Air-containing space	
Positive	19 (70.4)
Negative	8 (29.6)
Pleura retraction	
Positive	18 (66.7)
Negative	9 (33.3)
Margin of tumor	
Well defined	18 (66.7)
Poorly defined	9 (33.3)

Data are presented as the mean ± standard deviation or number (%). CT, computed tomography; pGGN, pure ground glass nodule; PSN, part-solid nodule; SN, solid nodule.

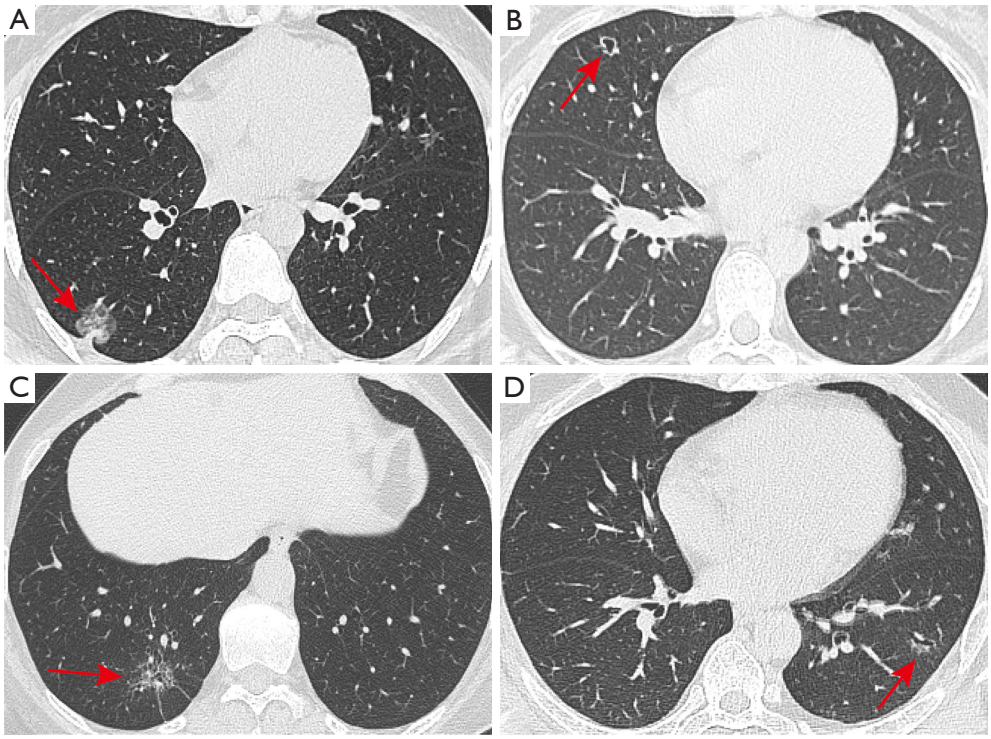

Figure 1 Axial CT images show examples of CT features of ciliated muconodular papillary tumors. (A) A 42-year-old female with a ciliated muconodular papillary tumor. CT scans show part of the solid nodule (red arrow) with lobulation contours and pleura retraction in the right lower lobe. (B) A 37-year-old female with a ciliated muconodular papillary tumor. CT scans show a well-defined nodule (red arrow) with an air-containing space in the right middle lobe. (C) A 58-year-old female with a ciliated muconodular papillary tumor. CT scans show part of the solid nodule (red arrow) with an air-containing space and pleura retraction in the right lower lobe. (D) A 58-year-old female with a ciliated muconodular papillary tumor. CT scans show part of the solid nodule (red arrow) with an air bronchogram in the left lower lobe. CT, computed tomography.

formed a double boundary (*Figure 3D*). On high-power field imaging, the tumor was composed of ciliated columnar cells, mucous cells and basal cells. The basal layer with basal cells was often observed, on top of which lay ciliated and mucous cells (*Figure 4*). Malignant invasive behavior of tumor cells, such as nuclear atypia, mitotic figures, and necrosis, was absent. However, prominent reactive changes, including lymphoid aggregates and chronic inflammation, were evident in peripheral areas of the tumor (*Figure 4A*). Immunohistochemical analysis is summarized in *Table 4*, and the proliferation index (Ki-67) was low (1–10%) (*Figure 5A*). In this research, all tumors expressed p63 and CK5 in the basal cell layer (*Figure 5B,5C*), although the area of coverage was both focal in two cases and broad in the others. TTF-1, p40, and CK7 were typically positive (*Figure 5D-5F*), while CK20 was negative in all tumors. Napsin A was weakly positive in a small portion of cells. All tumors were diagnosed as CMPTs. Notably, there is a particular case of CMPT accompanied by adenocarcinoma found in a patient. Focal adenocarcinoma manifested in partial peripheral regions (*Figure 6*).

Discussion

CMPTs are termed rare pulmonary tumors and feature papillary architecture. This tumor is reported to affect mostly middle-aged and elderly patients, but involvement in teenagers has been documented (9,10). Previous studies have reported the coexistence of peribronchiolar metaplasia with cellular components similar to CMPT and have suggested that smoking may play a role in the process of metaplasia to neoplasia (11). However, only a few cases of CMPT have been reported to have a smoking history. The pathogenesis of CMPT needs further investigation. Generally, most

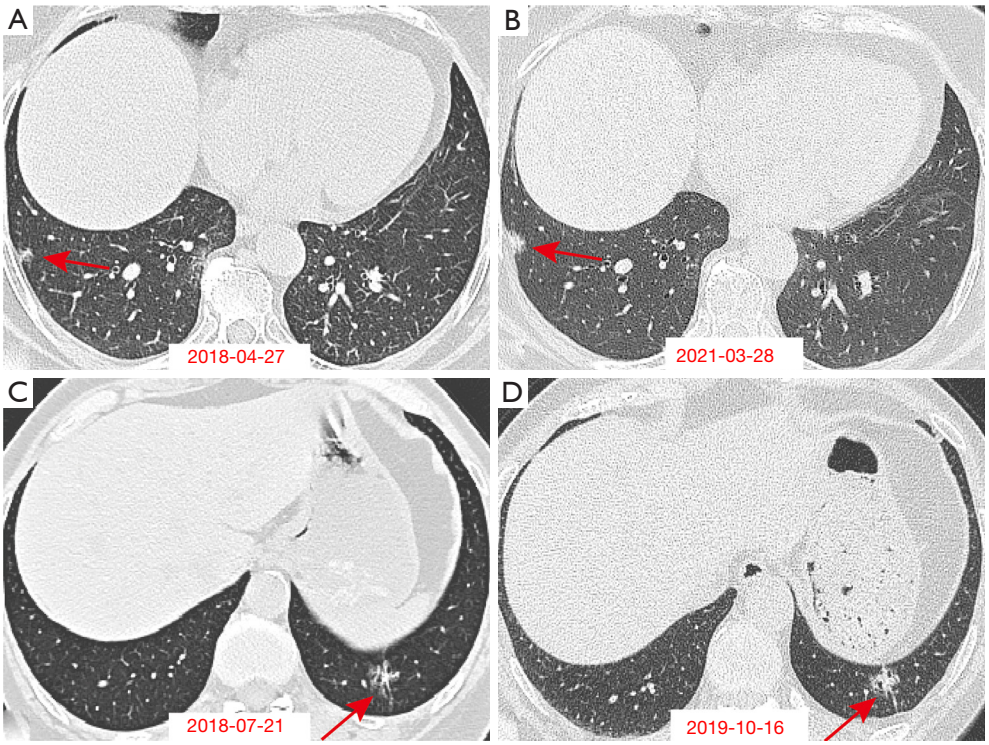

Figure 2 Axial CT images show the change in ciliated muconodular papillary tumor during follow-up. (A,B) A 68-year-old female with a ciliated muconodular papillary tumor (red arrow) in the right lower lobe. Sequential images show that the nodule increased in size and solid components enlarged. (C,D) A 63-year-old female with a ciliated muconodular papillary tumor (red arrow) in the left lower lobe. Sequential images show that solid components of the nodule were enlarged. CT, computed tomography.

CMPT cases are asymptomatic and detected incidentally via CT screening for lung cancer or medical check-up. Only 5 patients complained of cough, expectoration or chest pain in our research. All 27 patients had abnormal pulmonary shadows on pulmonary CT images and underwent tumor resection for suspicion of lung cancer, and postoperative pathology finally confirmed CMPT.

Previous studies have briefly reported that CMPT is a solitary nodule that is often located in the pulmonary lower lobes (12,13). In this research, we systematically described the radiological features of CMPT of the lung. Similarly, CMPT of the lung mostly appeared as a lobulation contour and well-defined solitary tumor. It can appear as a solitary pGGN, PSN or SN and is mostly detected at the periphery of the pulmonary lower lobe. The presence of GGO was considered to be correlated with an unfilled alveolar cavity (14,15). We thought the filled mucus containing air in pulmonary alveoli may be the explanation for GGO appearance. Additionally, the tumor was mostly found to have an air-containing space. Pathologically, in the central tumor, the alveoli were destroyed and filled with a large amount of mucus, with discharge of mucus through the bronchi, and thus, an air-containing space formed. Pleural retraction of the tumor could also be observed on CT scans, especially in those closer to the pleura. CMPT was reported to be a small tumor with a slow growth rate (8). In the present cases, the tumor size ranged from 0.44 to 3.46 cm, with an average size of 1.21 cm. This is similar to the previously reported size of 1.18 cm (16). The most important differential diagnostic consideration for CMPT is adenocarcinoma. Both of them can appear as GGO or subsolid on CT scans. It is still difficult to distinguish CMPT from adenocarcinoma by CT features. However, some malignant CT features, such as spiculation and pleural retraction, are frequently observed in lung cancer and may be helpful to differentiate CMPT and adenocarcinoma. Additionally, more cases would be beneficial to help in the differential diagnosis of CMPT in the future. During the preoperative follow-up, there were two patients with tumor size enlargement accompanied by solid component increase.

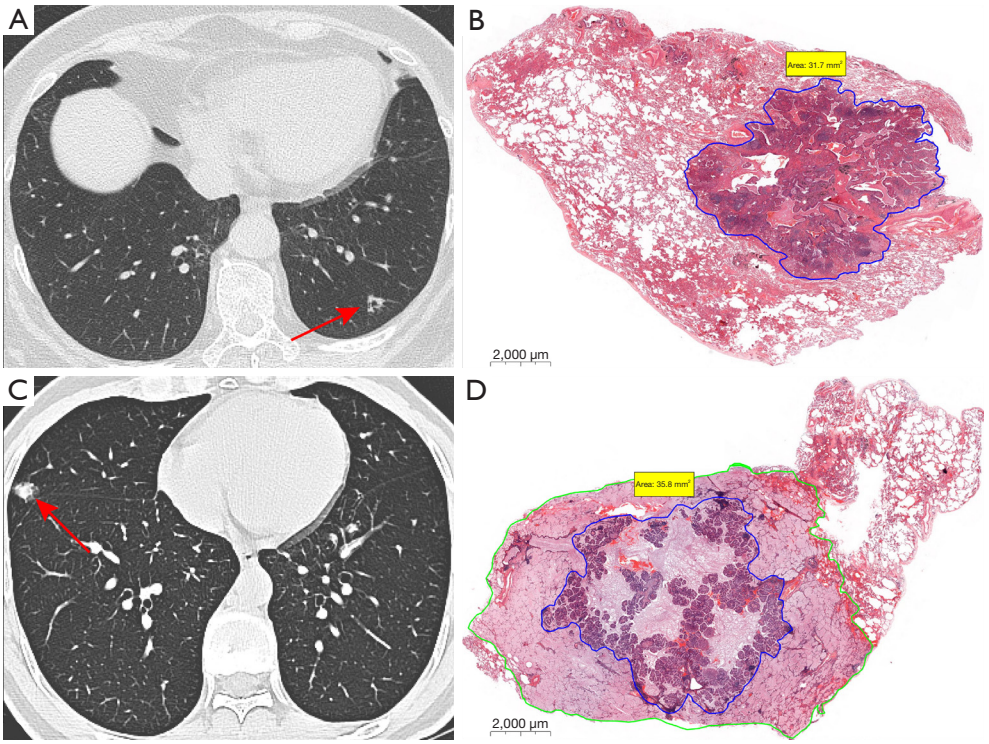

Figure 3 Axial CT images and corresponding hematoxylin-eosin-stained histologic findings in ciliated muconodular papillary tumor. (A) A 63-year-old female with a ciliated muconodular papillary tumor. CT scans show a solid nodule (red arrow) with an air-containing space in the left lower lobe. (B) Histopathological examination shows a well-defined tumor (blue outline indicates the boundary of the tumor with area of 31.7 mm^2) with extracellular mucin filling in the airspaces (HE, ×4; scale bar, 2,000 µm). (C) A 36-year-old male with a ciliated muconodular papillary tumor. CT scans show part of the solid nodule (red arrow) with pleura retraction in the right middle lobe. (D) Histopathological examination shows the papillary tumor nodule and abundant extravasating mucus form a well-defined, double boundary (blue outline indicates the boundary of the actual tumor with area of 35.8 mm2, and green outline indicates the margins of the extravasating mucus) (HE, ×4; scale bar, 2,000 µm). CT, computed tomography; HE, hematoxylin and eosin.

Notably, one patient with a solid tumor component was finally diagnosed with CMPT accompanied by adenocarcinoma.

Previous studies have discussed the nature of CMPT, but consensus has not been reached. Some studies have described CMPT as a low-grade malignant tumor (17-19). The destroyed alveolar structures, micropapillary pattern, and replacement of the alveolar epithelium by tumor cells on pathology examination and positive molecular biological characteristics indicate the malignancy of CMPT (20-22). In contrast, other studies thought CMPT to be benign due to its indolent clinical course and good prognosis after surgical resection (23-26). In the 2021 WHO Classification of Thoracic Tumors, CMPT was finally recognized as a type of pulmonary adenoma with a benign nature (4). It represents an incidental lesion and remained free of disease after surgical resection. Remarkably, previous studies reported cases of CMPT accompanied by malignant lung tumors. One CMPT accompanied by adenocarcinoma *in situ* in a 53-year-old patient and another CMPT accompanied by invasive acinar adenocarcinoma in a 79-year-old patient have been documented in the past (27,28). In addition, mucinous adenocarcinoma caused by cancerization from a ciliated multinodular papilloma tumor has also been reported (29). Similarly, there was a particular case of CMPT accompanied by adenocarcinoma in our series. Given the finite available information regarding CMPT, it is necessary to further investigate the biological properties and relationship related to the potential for malignant transformation. Surgical intervention is the optimal treatment for CMPT, and wedge resection is the mainstream choice. Similar to previous studies, the

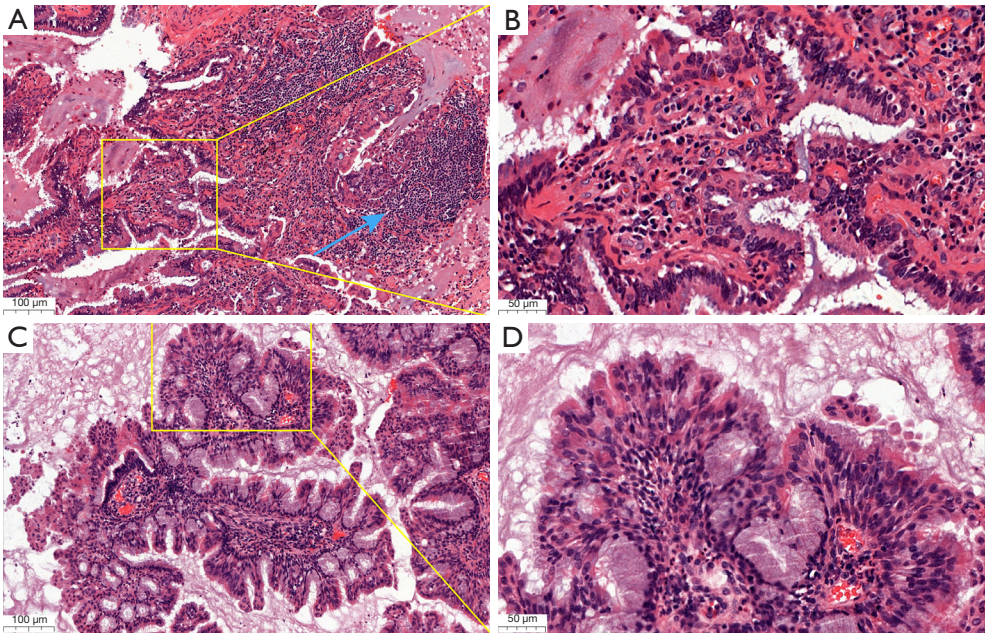

Figure 4 Hematoxylin-eosin-stained histologic findings of ciliated muconodular papillary tumor on high power field. (A,B) The tumor featured papillary structures composed of a mixture of ciliated columnar cells, mucous cells, and underlying basal cells (A: HE, ×12; B: HE, ×40). Reactive changes, such as lymphoid aggregates, were observed (blue arrow). (C,D) The tumor also featured papillary structures composed of a mixture of ciliated columnar cells, mucous cells, and underlying basal cells (C: HE, ×12; D: HE, ×40). HE, hematoxylin and eosin.

Table 4 Immunohistochemistry analysis of the CMPT cases

Outcome	TTF-1	p63	p40	CK5	CK7	CK20	Napsin A
Positive	21 (77.8)	27 (100.0)	17 (63.0)	27 (100.0)	22 (81.5)	0	10 (37.0)
Negative	6 (22.2)	0	0	0	0	27 (100.0)	7 (26.0)
NA	0	0	10 (37.0)	0	5 (18.5)	0	10 (37.0)

Data are presented as numbers (frequencies). CMPT, ciliated muconodular papillary tumor; TTF-1, thyroid transcription factor 1; CK5, cytokeratin 5; CK7, cytokeratin 7; CK20, cytokeratin 20.

patient with CMPT accompanied by adenocarcinoma in this research also received adjuvant therapy after surgery. Although no recurrence or metastasis has been reported, long-term follow-up is still warranted.

There are several limitations in this study. First, the number of patients in this retrospective study was small. However, to our knowledge, this study is the first to systematically describe the detailed radiological features of CMPT. Second, a comprehensive molecular test was not conducted, and driver mutation analysis was not provided. Further investigation of the research will be continued.

Conclusions

CMPTs of the lung mostly manifest as solitary, lobulated, well-defined tumors with air-containing spaces on CT and occur in the periphery of the pulmonary lower lobe. When CT findings meet these criteria, the possibility of CMPT should be taken into consideration. Additionally, CMPT can coexist with adenocarcinoma. Further investigation

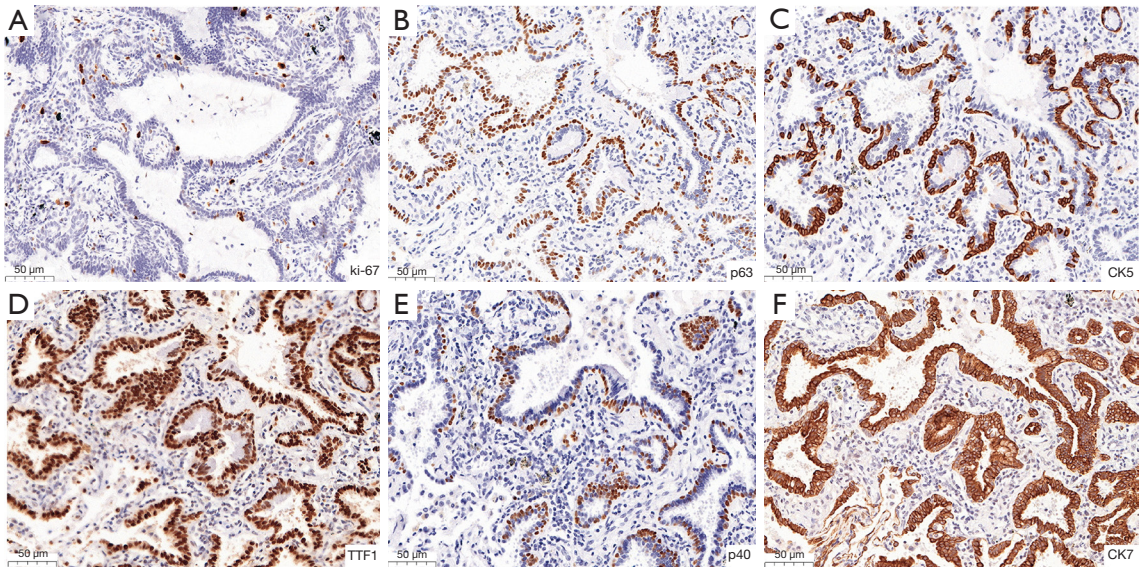

Figure 5 Immunohistochemical staining of antibodies in tumor cells. (A) Low labeling index of Ki-67 (IHC, ×20); (B) p63 (IHC, ×20); (C) CK5 (IHC, ×20); (D) TTF1 (IHC, ×20); (E) p40 (IHC, ×20); (F) CK7 (IHC, ×20). CK, cytokeratin; IHC, immunohistochemistry; TTF1, thyroid transcription factor 1.

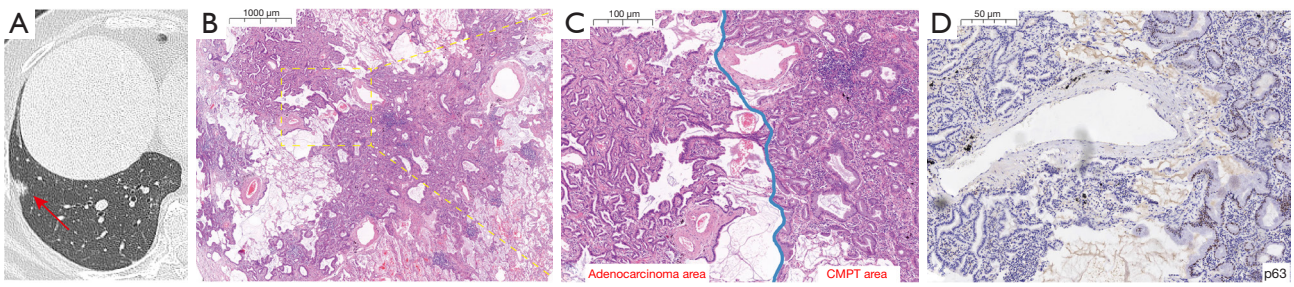

Figure 6 Axial CT images and corresponding hematoxylin-eosin-stained histologic findings in a particular case of a ciliated muconodular papillary tumor accompanied by adenocarcinoma. (A) A 68-year-old female with a ciliated muconodular papillary tumor (red arrow) in the right lower lobe. (B) Histopathological examination shows that the adenocarcinoma was in the periphery of the ciliated muconodular papillary tumor structure (HE, ×4). (C) The higher power field shows the junction (blue outline) of the ciliated muconodular papillary tumor area and adenocarcinoma area (HE, ×12). (D) Immunohistochemical staining of p63 was negative in the adenocarcinoma area but positive in the CMPT area (IHC, ×20). CT, computed tomography; HE, hematoxylin and eosin; CMPT, ciliated muconodular papillary tumor; IHC, immunohistochemistry.

will contribute significantly to the biological properties of CMPT and its relationship to the potential for malignant transformation.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.

amegroups.com/article/view/10.21037/qims-22-1258/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Beijing Shijitan Hospital, and individual informed consent for this retrospective analysis was waived.

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