CASE REPORT

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Ciliated muconodular papillary tumor of the lung: a case report and literature review

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Abstract

Background: Ciliated Muconodular Papillary Tumor (CMPT) was first reported in 2002, and fewer than 100 cases have since been reported. The prognosis after surgical resection is good, and recurrence has not been reported. However, it is easily misdiagnosed as adenocarcinoma. Summarizing the CT features of CMPT will help doctors better understand the disease.

Case presentation: Here, we report a rare and interesting case of ciliated muconodular papillary tumor. A 6-mm diameter solid nodule with slight lobulation, short spines, and subpleural indentation. Patients with clinical diagnosis of high-risk subpleural nodule in the left lung underwent thoracoscopic surgery. Most CMPT cases lack specific clinical manifestations and were found incidentally on physical examination or during a workup for other diseases. The disease was diagnosed through CT and biopsy, and it responded well to surgery.

Conclusions: This paper presents the detailed computed tomography features of CMPT to help prevent misdiagnosis. The typical manifestations of CMPT imaging as solid and partial nodules, nodules in subpleural or peripheral zones, and nodules contain cavities.

Keywords: Ciliated muconodular papillary tumor, Lung tumor, Computed tomography

Background

A ciliated muconodular papillary tumor (CMPT) is a rare benign tumor, with fewer than 100 cases reported in the literature. No specific clinical symptoms have been identified, and it is often diagnosed incidentally. This paper emphasizes the cytological and computed tomography (CT) features of CMPT via a case study and literature review.

In 2002, Ishikawa et al. first described a rare pulmonary nodule composed of ciliated columnar cells, mucous cells, and basal cells [1]. This disease was named CMPT. Only a few surgically confirmed cases have been reported worldwide, and more cases have been reported in East Asia than in the USA or Europe [2]. It is easily confused with adenocarcinoma and mucoepidermoid carcinoma

due to the lack of typical clinical manifestations, imaging features, and pathological features. Consequently, it is easily misdiagnosed as lung cancer and thus overtreated. In this paper, by reviewing the CT images of cases in the literature, the imaging manifestations were summarized, so as to improve the clinical and imaging doctors' understanding of the disease, reduce misdiagnosis, improve the rate of early diagnosis and early treatment, and reduce complications.

Case presentation

The patient was a 64-year-old woman with no history of smoking. She initially had persistent attacks of dull epigastric pain that became worse after eating. There is not any relevant past medical or family history. On hospitalization, there were no fevers, chills, cough, sputum, chest tightness, palpitations, or shortness of breath. Physical examination showed no chest deformity or sternal tenderness, normal thoracic breathing rhythm, chest symmetry, symmetric chest wall movement, and normal

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vocal fremitus. The lungs were hyper-resonant on percussion and while breathing. No moist rales or pleural rubs were heard.

Laboratory tests revealed elevated levels of carcinoembryonic antigen (CEA) and thyroid-stimulating hormone, no carbohydrate antigens, and an alpha-fetoprotein (AFP) level of 8.18 ng/ml (0–7 ng/ml).

On May 9, 2018, CT showed a 5-mm diameter solid subpleural nodule with a smooth margin in the outer posterior basal segment of the left lower lobe (Fig. 1). The doctor recommends that the patient have an annual review. CT on June 11, 2020, revealed a 6-mm diameter solid nodule with slight lobulation, short spines, and subpleural indentation (Fig. 2).

Diagnosis and treatment (Table 1)

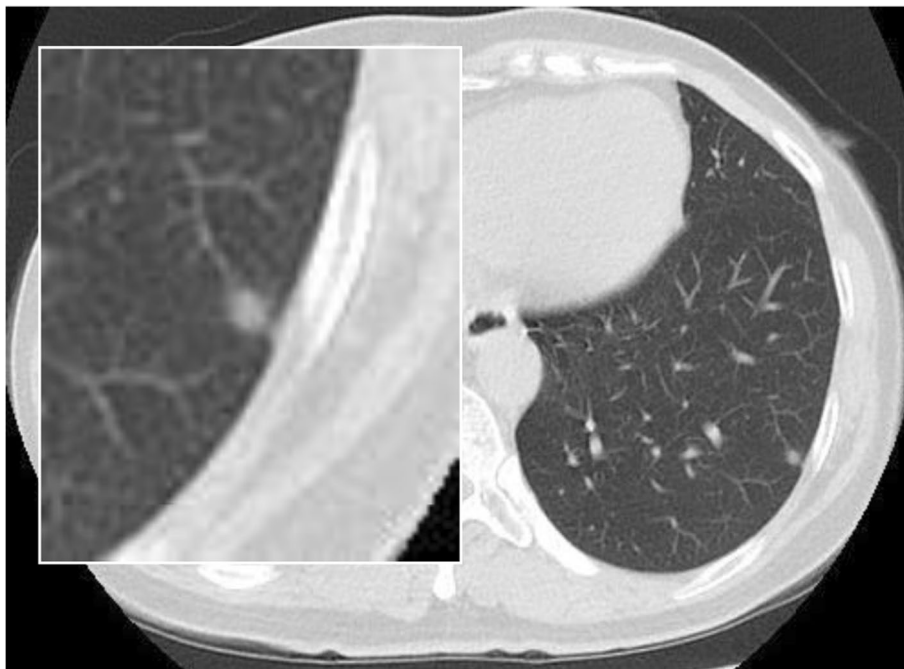The high-risk subpleural nodule in the left lung was found enlarged on CT review two years later. The nodule

Fig. 1 CT showed a round, 5-mm diameter solid, subpleural nodule. There were no spikes, lobulation, or pleural indentation
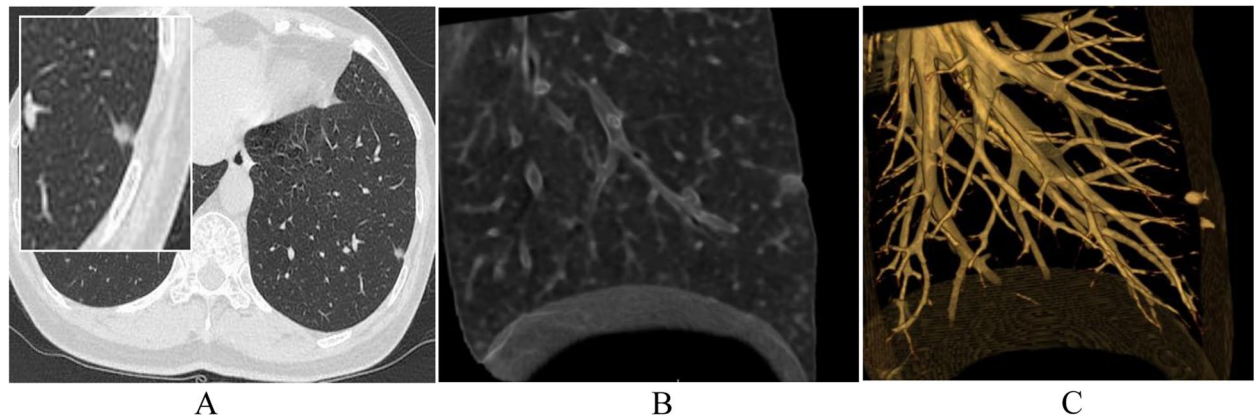

Fig. 2 A CT showed a round part solid subpleural nodule 6 mm in diameter, Lobulation, spikes, pleural indentation; three-dimensional reconstruction; and three-dimensional pulmonary reconstruction. **B** and **C** show the tumor under the pleura, with pleural indentation and thickening

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Table 1 Diagnosis and treatment

Date	Diagnosis and treatment process
2018-05-09	A 5-mm-diameter nodule was found in the left lower lobe on CT
2019-08-09	Hospitalized for coronary heart disease, but no chest abnormalities were found
2020-06-11	Hospitalized for abdominal pain, and gastric polyps were resected
2020-6-11	Chest CT showed a 6-mm diameter nodule in the left lower lobe, which was slightly lobulated and had spikes and pleural indentation.
2020-6-17	Resection of the pulmonary nodule

has the characteristic: slightly nodule lobules, spikes, and pleural indentation. Thus, the patient underwent thoracoscopic surgery six days later. The incision was made in the fifth intercostal space in the left anterior axillary line. No pleural effusion or adhesions were found, and the lung was well differentiated. Local protuberant nodules were seen at the posterolateral basal segment of the left lower lobe. The surrounding area was slightly red and swollen, but no nodules were found on the parietal pleura or diaphragm. A cut was made along the base of the tumor, and a frozen section suggested a micro-invasive adenocarcinoma with acinar cells; the nodule was approximately 6 mm in diameter.

A wedge-shaped slice of tissue was removed for pathological examination. The tissue contained a 4-mm diameter gray-white nodule with a clear margin and no envelop. Microscopically, glandular tubular and papillary structures were seen. The glandular cavity and papilla were covered with two layers of the epithelium. The inner layer contained basal cells and the outer layer mostly ciliated cells. A few cells were mucinous, and mucinous secretions could be seen in the glandular cavity. The cells were regular in shape and size, and no mitosis or necrosis was observed. The tumor was not connected to the bronchus. There was an area of perivascular cell proliferation in the tumor (Fig. 3).

Immunohistochemistry showed positivity for TTF-1 (clone SPT24) in epithelial and basal cells, partial positivity for napsin A in epithelia, positivity for CK7 in epithelia, positivity for P40 in the basal layer, positivity for P63, positivity for CK5/6, negativity for Syn, negativity for CgA, negativity for CD56, 1% positivity for Ki67, partial positivity for CEA, and negativity for CK20(Fig. 4).

Follow-up and outcomes
Pathologically, distal-type CMPT was diagnosed. There has been no disease recurrence, and no treatment such as chemotherapy or radiotherapy was required. On February 19, 2021, CT scan showed no recurrence.

Discussion
In this study, an extensive literature search of PubMed and Web of Sciences was conducted on 20 August 2020 to include all published studies. A total of 18 CMPT articles were published and 87 cases, 35 cases of which contained CT images. There were 36 CT images, including that from our case. The reported images were evaluated by two senior radiologists for the respiratory system. CT findings were summarized in Table 2. The 36 images
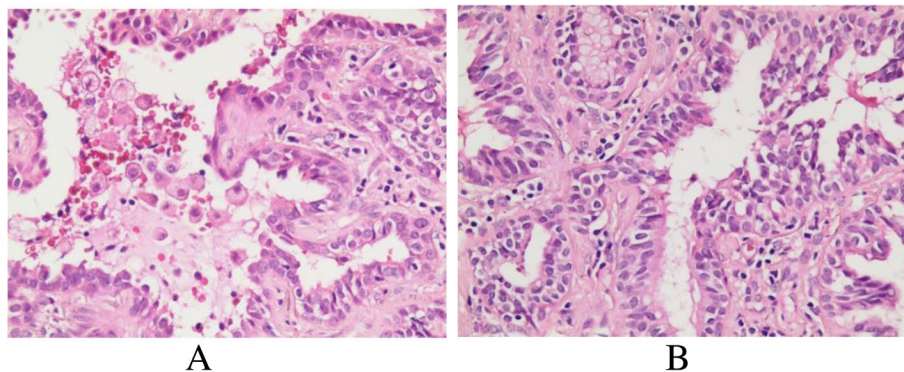

Fig. 3 A Hematoxylin and eosin staining (H&E) of loupe image. **A** Tumor cells are proliferating along the alveolar walls, surrounded by mucous lakes, **B** Tumor cells are proliferating along the alveolar walls, consisting of ciliated columnar cells and goblet cells with basaloid
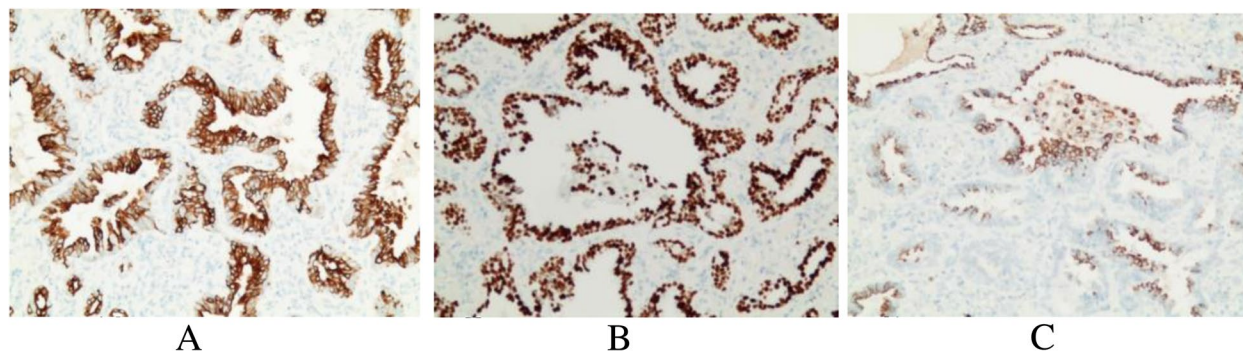
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Fig. 4 A Ciliated cells, mucous cells, and basal cells positive for CK7 (EnVision, ×100). **B** TTF-1 is weak to moderately positive in the basal cells but negative in the luminal cells. **C** Cells lining the cavity are positive for CEA (EnVision, ×100)

showed 18 solid nodules (50.0%), 11 partially solid nodules (30.5%), three GGNs (8.3%), two inflammatory solid lesions (5.56%), and two hollow lesions (5.56%). Subdividing the lungs into the inner, middle, and outer parts, there were 22 subpleural nodules (61.1%), 13 peripheral lesions (36.1%), and 2 central lesions (5.6%). Of the lesions, 15 showed air bronchograms (41.6%), 20 showed spikes (55.6%), 19 showed lobulation (52.8%), 15 showed pleural indentation (41.6%), 11 were subpleural nodules with cavities (30.6%), and 4 in the lung periphery had cavities (11.1%). Imaging manifestations of typical CMPT nodules are as follows: elderly people, solid or partially solid nodules, located under the pleura or peripheral zone, the nodules contain cavities, and pleural depression, air bronchograms, spikes.

In this study, all of the articles containing CT images had pathology. In a literature search, we found 87 cases in 18 articles in addition to our case (a total of 88 cases). The average age of the patients was 64.8 (range 31 to 82) years. The ratio of males to females was 42:46. The ratio of lesions in the left lung to those in the right lung was 30:36 (in 21 cases, the affected lung was not reported). There was a history of smoking in 21 of 64 (32.8%) patients, and the smoking history was not known in 24 patients. Table 3 shows the average tumor diameter 6.91 mm.

We found articles related to the CT findings of CMPT in 18 publications from 2002 to 2020 [3–20], but none provided a detailed description of the CT findings. Most CMPT cases lack specific clinical manifestations and are found incidentally on physical examination or during a workup for other diseases. A summary of the CT manifestations of CMPT would give doctors a better understanding of this disease, thereby reducing misdiagnosis, missed diagnosis, and especially overtreatment. Qiang Zheng summarized the CT imaging features of CMPT for 11 typical pathological and 10 atypical pathological

cases [20]. CMPT are more likely to develop in the elderly and females, The lesion diameter averaged 7 (range 4–20) mm. Small pseudocavitation was found in 64% of the typical cases but only 10% of the atypical cases, In this paper, the ratio of male to female is 1:1. This article summarizes typical CMPT image characteristics based on CMPT image performance. Onishi et al. summarized the CT imaging features of 16 lesions, of which 9 were in the right lung and 7 in the left lung. Ten lesions were subpleural, while six were 3–18 mm from the pleura. One case had ground-glass nodules (GGNs), seven had partial GGNs, and nine had solid nodules; the average diameter was 9.1±2.4 mm [13]. The sex of these patients was unknown, our study further summarizes the nodules lobules, pleural indentation, spikes, and air bronchograms, summarizes the most characteristic imaging manifestations of subpleural nodules with cavities.

The imaging findings of CMPT have been differentiated from those of adenocarcinoma [21]. Compared with adenocarcinomas, CMPT are usually found in older patients, are smaller, and contain pseudocavitation in the nodules. In a study that classified the nodules as central or peripheral [21], the nodules were peripheral in 36 cases (97.2%) and were round or oval in most cases (see Table 4).

On gross pathology, the nodules are usually pale or grayish brown, soft, and well-recognized, with a mucinous or gelatinous substance [17]. The tumors are composed of ciliated columnar cells, mucous cells, and basal cells. The ciliated columnar cells are on the surface of adenoids and papilla-like structures. The basal cells act as a scaffold in the outer layer, whereas the mucous cells are scattered. Microscopically, there was no obvious atypia, mitotic figures (mitosis), or necrosis of the tumor cells. A large amount of mucus was found in the alveolar space or around the tumor. Some of the tumor epithelium grew discontinuously along the alveolar wall, and there was no surrounding envelop. Irregular bronchial walls or

Table 2 Analysis of the CT imaging features of reported cases

Author	Cases	Cases with CT images											
		Subpleural	Lung periphery	Central lung	Spike	Lobulation	Air bronchogram	Pleural indentation	Solid	Partial solid	Ground-glass	Inflammatory solid	Hollow-type
Kosuke Miyai [3]	1	1										1	
Mitsuhiro Tachibana [4]	1	1	1		1		1	1		1			
Miyuki Abe [5]	1	1	1		1	1							
Florence MF Cheung [6]	1	1	1		1		1		1	1			
Toshiyuki Harada [7]	1	1							1				
Yoshinobu Hata [8]	1			1	1	1			1				
Masashi Ishikawa [9]	5	5	1		3	2	1	1	3		1	1	
Yan Jin [10]	1	1			1		1	1		1			
Tetsuo Kon [11]	5	3	1	1	1	3	2	2	3	1			1
Masashi Mikubo MD [12]	1	1			1	1	1	1	1				
Yasuyuki Onishi [13]	4	4			1	4	2	4	1	2	1		
Yasuyuki Onishi [14]	1	1			1	1	1	1		1			
Shuichi Sato [15]	2	1	1		2	1	1			2			
Kang Shao [16]	2	2	2							1	1		
Tsugumasa Kamata [17]	2	2	2		2				1				1
Tsuyoshi Uchida [18]	1	1				1	1	1		1			
XiaojunYao [19]	1	1			1		1		1				
Qiang Zheng MD [20]	4	2	2		3	3	1	2	4				
Present case	1	1			1	1	1	1	1				

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Table 3 Basic characteristics of reported cases

Reference	Age (years)	Sex		Site		Size	Smoking history
		Man	Female	Left lung	Right lung		
Kosuke Miyai [3]	66		1		1	20mm	1
Mitsuhiro Tachibana [4]	77		1		1	8mm	NO
Miyuki Abe [5]	76	1			1	14mm	1
Florence MF Cheung [6]	61	1			1	10mm	1
Toshiyuki Haradaa [7]	62	1		1		9mm	1
Yoshinobu Hata [8]	76		1	1		7mm	N0
Masashi Ishikawa1 [9]	72.4 (66–82)	3	2	2	3	21.6mm (5–45 mm)	3
Yan Jin [10]	59		1		1	8mm	NO
Tetsuo Kon [11]	71.2 (66–80)	3	2	2	3	9.4mm (7–13 mm)	Not known
Masashi Mikubo MD [12]	69	1		1		13 mm	No
Yasuyuki Onishi [13]	70.7(57-82)	10	6	7	9	9.1mm ±2.4mmm	7
Yasuyuki Onishi [14]	70.4 (60–80)	8	7	7	8	9mm (7–14mm)	Not known
Shuichi Sato [15]	67, 59	1	1	0	2	9mm, 7mm	1
Kang Shao [16]	58, 66		2	1	1	8mm, 6mm	Not known
Sugumasa Kamata [17]	62 (56–78)	7	3	6	4	10mm (6–15mm)	5
Tsuyoshi Uchida [18]	78		1		1	19mm	Not known
Xiaojun Yao [19]	67		1	1		12mm	Not known
Qiang Zheng [20]	55 (31–78).	6	15	Not known	Not known	7mm (4–20mm)	1
Present case	67		1	1		6mm	NO

thick-walled vessels were found in most cases [22]. The diagnosis of CMPT is based primarily on morphology; cilia, mucus, and papilla are often seen in this disease, although all three components may not be present in some cases. The latter cases are known as atypical CMPT, which needs to be validated by more studies.

Immunohistochemically, CEA and CK7 were highly positive in the three cell types of CMPT, whereas TTF-1 was weakly positive, and Ki-67 expression was low (≤10%). CK20 and MUC2 expression was negative. p40, p63, and CK5/6 were highly positive in basal cells. MUC5AC was not expressed in mucous cells but was expressed in some ciliated cells [23].

Many gene mutations are detected in CMPT. Among 18 cases, BRAF-V600E mutations were detected in six cases, EGFR exon 19 deletions in three cases, KT1-E17K mutations in two cases, and BRAF-G606R and KRAS-G12D mutations in one case each. Given the few cases reported and lack of research on gene mutations in CMPT, cancer driver genes have yet to be identified. Although Udo E and Kamata T thought CMTP was an inflammatory lesion, they did not use anti-inflammatory treatment before surgery, which was consistent with our study [24, 25].

Initially, CMPT were thought to be malignant [7], but with increasing knowledge, these tumors now tend to be classified as benign. No recurrence has been reported in any case undergoing surgical resection after long-term follow-up. Cilia were found in all cases, while only a few malignant tumors have cilia. There was an absence of atypia, mitotic figures, and necrosis and a presence of low Ki-67 expression, and high BRAF expression; the opposite features indicate malign lesions [25]. More importantly, no ciliated or goblet cells were seen in these tumors. The differential diagnosis based on pathological findings includes squamous metaplasia, intrabronchial papilloma, mucoepidermoid carcinoma, and well-differentiated adenocarcinoma. Well-differentiated papillary adenocarcinoma has been reported [26], and its pathology is similar to that of CMPT, except that the cells are heterogeneous.

In summary, CMPT has the characteristic of typical pulmonary nodules, the nodules lobules, pleural indentation, spikes, and air bronchograms, comprise the most characteristic imaging manifestations of subpleural nodules with cavities. Regular review can be performed. When nodules become enlarged, surgical treatment should be performed. The diagnosis of CMPT is based primarily on morphology; cilia, mucus, and papilla are often seen in this disease, The atypical CMPT is missing one of these components, CMPT is easily misdiagnosed to lung adenocarcinoma on CT, The former nodule is small (with an average diameter of 6 mm), while the latter is 24mm. The former is mostly located in the peripheral

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Table 4 Differentiation between CMPT and adenocarcinoma

Mutation	Sex	Cases of M	(ratio)	Maximum tumor diameter (mm)	Site Central	Site Peripheral	Spike	Round to oval	Irregular	Groud glass	Part solid	Solid	Others
CMPT	64.8	34 (43%)	38 (57%)	6.91	2.8%	97.2%	55.6% 41.6%	75%	25%	8.3%	30.5%	50%	11.1%
Adenocarcinoma [21]	59.2	129 (43%)	147 (43%)	24.7	34.8%	65.2	11.6% 5.8%	67.8%	32.2%	12.3%	37.7	50%	0

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zone, about 97.2%, while the latter is located in the middle and inner zone, 34.8%. Moreover, lung adenocarcinoma has vessel convergence, air bronchiologram (irregularity, disruption, or dilatation) (Table 4).

Conclusion

Few cases of CMPT have been reported, and this disease has no specific clinical manifestations. The CT imaging features, pathological and immunohistochemical features, and possible gene mutations in the disease were discussed. This paper should give radiologists, thoracic surgeons, and pathologists a better understanding of CMPT to help them avoid misdiagnosis.

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