Ciliated Muconodular Papillary Tumors of the Lung

Yen-Wen Lu, MD; Yi-Chen Yeh, MD

Ciliated muconodular papillary tumor (CMPT) is a rare pulmonary tumor first described in 2002 by Ishikawa.1 To date, 38 cases have been reported2–15 and the nature of the lesion is still under investigation. It is not considered a distinct entity in the 2015 World Health Organization classification.16 Thus far, the reported cases have a seemingly indolent nature, as no recurrences or metastases have been documented. Although CMPTs are rare, being aware of the lesion is important, as imaging and microscopic findings can mimic malignant processes. In this article, we review the clinical, radiologic, pathologic, and molecular findings of ciliated muconodular papillary tumors. Diagnostic pitfalls and the diagnostic considerations are discussed.

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Clinical Features

The 38 reported CMPT cases in the medical literature occurred in both women and men with a very slight female predominance (M:F ratio = 1:1.11) (Table 1). The lesion most commonly presents in the sixth to eighth decade of life (median age, 67 years); however, it has been reported in a patient as young as 19 years.2 Most of the described cases originated from Eastern Asia (34 of the 38 reported cases), with only a few cases reported from Western countries.4 Approximately 45% of the patients had a documented smoking history. Most often, the tumor was incidentally discovered during patient evaluation or follow-up for some other disease process or malignancy. Two patients with a CMPT had presented with a concurrent primary lung cancer.3,4 The described CMPT lesions were located in the peripheral lung fields. The most common location was the right lower lung followed by the left lower; upper lung fields have also been reported. The average size is 11 mm with most tumors being less than 15 mm. The largest reported lesion is 45 mm.14

IMAGING FINDINGS

Computed tomography imaging characteristics are non-specific. The lesions are typically peripherally located and can be solid, partially solid, or appear as ground glass opacities.5,6 Approximately a quarter of the reported cases have had a component of central cavitation2,5–8 and many tumors have an irregular border. A number of reported cases with follow-up imaging studies before surgical excision have shown size enlargement.3,4,7 Given the radiographic characteristics, a primary lung cancer or metastasis is often suspected.5

PATHOLOGIC FINDINGS

CMPTs are grossly well-circumscribed, grey-white, solitary nodules with a soft, gelatinous, or mucoid cut surface. Pleural retraction has not been observed in those located immediately beneath the pleural surface. Areas of anthracotic pigment deposition and fibrosis have been described.5 Low-power microscopic examination typically shows a distinct nodule with predominantly glandular or papillary structures. A discontinuous lepidic pattern can be seen at the periphery of the lesion, and adjacent alveolar spaces may contain mucin. Some tumors have central mucin accumulation, which correlates with imaging findings of central cavitation. Fibrosis and focal loss or disruption of the alveolar elastic framework is often noted. Unpaired, medium-sized muscular arteries entering the tumor can be observed, suggesting a peribronchiolar localization. High-power examination of the epithelial component shows a mixture of ciliated columnar, mucous, and basal cells. Ciliated and mucous cells (resembling goblet cells) are often intermixed and lay on top or are surrounded by a uniform layer of basal cells. Occasionally, ciliated cells bud as micropapillary tufts and appear to float in alveolar spaces.
on tissue sections. Mucous cells form small nests and protrude from glandular spaces or papillae (Figure, A through D). The proportion of ciliated and mucous cells, along with the architectural characteristics, can be variable. Nuclear atypia, mitotic activity, and necrosis are absent in lesions.4,5

Scattered neuroendocrine cells interspersed among basal cells (reminiscent of bronchial Kulchitsky cells) have been reported within the tumor.5 Reactive changes, such as chronic inflammation, peribronchiolar metaplasia, and rare nonnecrotizing granulomas, can be identified at the periphery of the tumor. One reported case occurred in a background of necrotizing bronchiolitis and acute and organizing pneumonia with neuroendocrine cell hyperplasia and multiple tumorlets.4

ANCILLARY STUDIES

Immunohistochemical analysis of CMPTs typically shows positive immunoreactivity for cytokeratin (CK) 7, carcinoembryonic antigen (CEA), and thyroid transcription factor 1 (TTF-1). There is variable expression of mucin (MUC) 1 and MUC5AC, while CK20 and caudal type homeobox 2 (CDX2) expression are negative in the tumor. The presence of continuous basal cells can be highlighted by p40 and p63 staining (Figure, E). The proliferation index (Ki-67) is less than 1%.

Studies have identified several molecular alterations, including BRAF mutations (7 cases: V600E mutation in 6 cases and G606R in 1 case), EGFR exon 19 deletions (3 cases, delE746-T751/S752V), AKT1 E17K mutations (2 cases), KRAS G12D mutations (1 case), and ALK gene rearrangements (2 cases).2–4,8,11,12,15 In cases with the BRAF V600E mutation, positive immunoreactivity with BRAF V600E–specific antibodies can be demonstrated.4,9,15 Similarly, in cases with ALK gene rearrangements, positive immunoreactivity with ALK antibodies (clone D5F3, Ventana; and Histofine ALK iAEP kit, Nichirei Bioscience, Tokyo, Japan) is also observed.4,8 In these cases, all 3 cell components have shown cytoplasmic staining with BRAF V600E or ALK, suggesting all 3 cell components are neoplastic (Figure, F).4

Table 1. Clinical Features of Reported Cases of Ciliated Muconodular Papillary Tumor of the Lung

| Source, y | Cases | Age, y/Sex | Smoking History | Location | Size, mm | Treatment | Outcome/Follow-up |
|-----------|-------|------------|----------------|----------|---------|-----------|------------------|
| Ishikawa,1 2002 | 1 | 50/F | Yes | RUL | 15 | Lobectomy | NED/10 y |
| Harada et al,10 2008 | 1 | 62/M | Yes | LLL | 9 | Partial resection | NED/2 y |
| Sato et al,7 2010 | 2 | 59/F | No | RLL | 5 | Partial resection | NED/18 mo |
| Hata et al,11 2013 | 1 | 76/F | Yes | RUL | 8 | Partial resection | NED/10 mo |
| Chu et al13 2017 | 1 | 56/M | N/A | LUL | 11 | Segmentectomy | NED/5 mo |
| Kamata et al,5 2015 | 10 | Median: 61.5 (range, 56–78)/M:F = 7:3 | Yes: 5 | RLL: 5 | Mean: 10 (range, 6–15)/RUL: 1 | Lobectomy: 1 | NED/mean: 43 mo (range, 2–88 mo) |
| Lau et al,2 2016 | 1 | 19/F | No | RLL | 13 | Wedge resection | N/A |
| Kon et al,6 2016 | 5 | 80/M | N/A | LLL | 7 | Wedge resection | NED/29 mo |
| Sato et al,7 2010 | 2 | 59/F | No | RLL | 10 | Wedge resection | NED/25 mo |
| Hata et al,11 2013 | 1 | 76/F | Yes | RUL | 13 | Lobectomy | NED/14 mo |
| Chu et al13 2017 | 1 | 56/M | N/A | LUL | 9 | Wedge resection | NED/5 mo |
| Ishikawa et al,14 2016 | 5 | 66/M | Yes | RUL | 13 | Lobectomy | NED/58 mo |
| 82/F | No | LLL | 10 | Partial resection | NED/55 mo |
| 77/M | Yes | LLL | 45 | Lobectomy | NED/48 mo |
| 70/M | Yes | RLL | 35 | Partial resection | NED/19 mo |
| 67/F | No | RLL | 5 | Partial resection | NED/28 mo |
| Liu et al,4 2016 | 4 | 60/M | Yes | RLL | 10 | Wedge resection | NED/7 mo |
| 83/F | N/A | RML | 4 | Lobectomy | N/A |
| 81/F | N/A | Left | 4 | Wedge resection | N/A |
| 71/F | N/A | LUL | 12 | Wedge resection | NED/10 y |
| Jin et al,6 2017 | 1 | 59/F | No | RLL | 8 | Lobectomy | NED/6 mo |
| Taguchi et al,3 2017 | 1 | 84/F | No | RLL | 10 | Partial resection | NED/10 mo |
| Udo et al,15 2017 | 4 | Median: 67/ (range, 19–84)/M:F = 18:20 | No: 4 | N/A | Median: 11 (8–25)/ | Lobectomy: 3 | N/A |
| Total | 38 | Median: 67/ (range, 19–84)/M:F = 18:20 | Yes: 13 | RLL-RUL-RML = 16:4:1 | Mean: 11 (4–45)/ | Lobectomy: 11 | NED/mean: 37 mo (range, 2 mo–10 y) |
| | | | No: 16 | LLL-LUL = 8:4 | | Wedge resection: 17 | N/A: 7 |
| | | | N/A: 9 | Left: 1, | Partial resection: 7 | | |
| | | | N/A = 4 | Segmentectomy: 3 | | |

Abbreviations: LLL, left lower lobe; LUL, left upper lobe; N/A, not available; NED, no evidence of disease; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.
A. In low-power view, ciliated muconodular papillary tumor (CMPT) of the lung shows a peripheral lesion with abundant mucin pool filling in the alveolar spaces. B. CMPT is characterized by a mixture of ciliated columnar, mucous, and basal cells in glandular, papillary, and micropapillary growth patterns. C. Discontinuous lepidic proliferation at the periphery may be observed. D. The ciliated columnar cells and interspersed mucous cells line the glandular or papillary surface. The basal cells situate beneath them. E. Continuous basal cells can be highlighted by p40 staining. F. In cases with the BRAF V600E mutation, cytoplasmic staining for BRAF V600E is present in all 3 cell components (hematoxylin-eosin, original magnifications ×20 [A], ×100 [B and C], and ×400 [D]; original magnification ×200 [E and F]).
The presence of the aforementioned gene mutations in CMPTs supports the concept that the tumor is neoplastic as opposed to a reactive or metaplastic process. These gene mutations described in CMPTs are also seen in other lesions (both benign and malignant); as such, their presence is not specific to a particular entity.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of CMPT includes both malignant and benign lesions (Table 2). Given the histologic characteristics, considerations can include well-differentiated papillary adenocarcinoma with cilia formation, mucinous adenocarcinoma, mucoepidermoid carcinoma, glandular papilloma, and even peribronchiolar metaplasia depending on the amount of tumor present on a given slide and the plane of section. Differentiating these processes on frozen section slides or on small biopsy specimens can be particularly challenging.

CMPT has to be distinguished from well-differentiated papillary adenocarcinoma with cilia formation. In general, the presence of cilia indicates a benign process; however, rare malignant tumors with ciliated cells have been reported in some organs including the endometrium, oropharynx, and lungs.\(^{15-23}\) Those reported in the lungs have been in peripheral lung fields\(^{15-23}\) and have had readily identifiable nuclear atypia, mitoses, and an infiltrative pattern of growth (findings typically associated with malignancy).\(^{15-23}\) The presence of these findings and the absence of a continuous layer of basal cells (seen in CMPT) can help one distinguish between these 2 considerations.

Other diagnostic considerations include mucinous adenocarcinoma and mucoepidermoid carcinoma. The abundant mucin pool, presence of mucous cells, and diverse growth patterns of CMPT can closely resemble invasive mucinous adenocarcinoma. However, unlike CMPT, mucinous adenocarcinoma does not contain basal cells and ciliated cells. The presence of a continuous basal cell layer and ciliated cells helps differentiate CMPT from mucinous adenocarcinoma.

Mucoepidermoid carcinoma might be confused with CMPT because both tumors contain mucous cells. In addition, the basal cells in CMPT can resemble intermediate cells in mucoepidermoid carcinoma. Mucoepidermoid carcinoma may occur in the lungs as a primary tumor or a metastatic tumor from extrapulmonary origins, such as the salivary glands. Primary mucoepidermoid carcinoma of lung is more easily distinguished from CMPT because it is usually centrally located and associated with large airways. However, metastatic mucoepidermoid carcinoma frequently appears in the peripheral lung fields, similar to CMPT. A helpful feature to distinguish CMPT from mucoepidermoid carcinoma is the lack of ciliated cells in mucoepidermoid carcinoma. Besides, cytologic atypia is usually recognizable in mucoepidermoid carcinoma, whereas no cytologic atypia is present in CMPT.\(^{4}\)

Benign mimickers include peribronchiolar metaplasia and glandular papillomas. Both peribronchiolar metaplasia and CMPT display peribronchiolar localization and contain ciliated cells. However, peribronchiolar metaplasia is typically a microscopic lesion and does not form a distinct tumor nodule. In addition, unlike CMPT, peribronchiolar metaplasia generally does not harbor mucous cells or extracellular mucin pools.\(^{5}\)

Glandular papilloma is another benign mimic of CMPT. It contains the 3 cell elements, that is, ciliated columnar, mucous, and basal cells, arranged in a similar way to those in CMPTs. Glandular papillomas usually arise in the bronchial surface and are centrally located. However, they can arise in peripheral bronchioles in rare circumstances. In the literature, various terminologies have been used for these exceptional lesions, including solitary peripheral ciliated glandular papillomas, peripheral pulmonary papillary/glandular neoplasms with ciliated cells, and mucinous adenomatous hyperplasia.\(^{20,23-26}\) The relationship between these lesions and CMPTs is intriguing and remains to be determined. The age distribution of these lesions is similar to that of CMPTs; all of them occur most commonly in the sixth to eighth decade of life. Slight male predominance (M:F ratio = 1.5:1) is observed in these lesions, which is a bit different from the slight female predominance (M:F ratio = 1:1.11) in CMPTs.\(^{23-25}\) Although peripheral glandular papillomas show more conspicuous endobronchial intraluminal growth and papillary architecture than CMPTs, their microscopic appearance is otherwise quite similar. The possibility that these entities might belong to a spectrum of the same disease process has been proposed.\(^{9}\) Further comparison of the molecular characteristics between CMPTs and these histologically similar lesions might assist in clarifying their relationship.\(^{9}\)

PROGNOSIS AND TREATMENT

CMPTs have overlapping microscopic features with benign and malignant processes. For example, the benign nature is implied by the constant presence of ciliated and basal cells, bland cytology, lack of mitotic figures, and absence of necrosis. On the other hand, the concern of possible malignant potential in CMPTs comes from focally destroyed alveolar structures, central fibrosis, proliferation along the alveolar walls, the existence of skip lesions, the lack of encapsulation, the presence of a micropapillary

### Table 2. Differential Diagnoses of Ciliated Muconodular Papillary Tumor and Other Entities

| Similarities With CMPT | Differences From CMPT |
|------------------------|-----------------------|
| ADC with cilia formation | Ciliated cells forming glands or papillae | More nuclear atypia and mitosis; infiltrative growth; no continuous basal cells |
| Mucinous ADC | Abundant mucin pool; presence of mucous cells | No ciliated cells; no continuous basal cells |
| Mucoepidermoid carcinoma | Presence of mucous cells; intermediate cells might resemble basal cells | Primary tumor usually centrally located; no ciliated cells; more cytologic atypia |
| Peribronchiolar metaplasia | Peribronchiolar location; presence of ciliated cells | Not forming distinct nodules; generally no mucous cells and mucin pool |
| Glandular papilloma | Similar microscopic appearance (presence of ciliated, mucous, and basal cells); might belong to a spectrum of the same disease | |

**Abbreviations:** ADC, adenocarcinoma; CMPT, ciliated muconodular papillary tumor.
pattern, and positive immunostaining for CEA.\textsuperscript{6,10–12} Besides, because mutations in oncogenes such as \textit{EGFR} and \textit{KRAS} have been shown to occur early in the pathogenesis of lung adenocarcinoma, the presence of \textit{EGFR} and \textit{KRAS} mutations in CMPTs had raised the hypothesis that CMPT may be a precursor lesion of lung adenocarcinoma by some investigators (Lau et al\textsuperscript{2} and Udo et al\textsuperscript{15}).

The reported cases of CMPT have had an indolent clinical course. In 11 of 38 reported cases, lobectomy had been performed; remaining cases were treated with wedge resection or segmentectomy. Regardless of the type of surgical intervention, no recurrences or metastasis has been reported with up to 10-year follow-up. Although the optimal treatment for CMPTs has not been established, complete resection with wide, free margins seems to be sufficient.

**SUMMARY**

CMPT is a rare pulmonary tumor often found incidentally in older adults with an average age of 67 years. Computed tomography imaging studies show a small, peripheral ground glass opacity or solid nodule with occasionally central cavities. The presence of ciliated, mucous, and basal cells with bland cytologic characteristics and lack of mitotic figures and necrosis help distinguish it from malignant lesions. Described molecular alterations include \textit{BRAF} mutations, \textit{EGFR} exon 19 deletions, \textit{AKT1} E17K mutations, \textit{KRAS} G12D mutations, and \textit{ALK} gene rearrangements. These molecular findings support the tumor being a true neoplasm. The lesion is felt to be indolent, as no recurrences or metastases have been reported to date. With increasing applications of chest computed tomography, CMPTs may be encountered more frequently hereafter. Future studies will help to clarify its exact disease nature and relationship with histologically similar tumors.

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