



# Ciliated muconodular papillary tumor of the lung: The risk of false-positive diagnosis in frozen section<sup>☆</sup>

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**Abstract** Ciliated muconodular papillary tumor (CMPT) is newly-defined low-grade malignant tumor, characterized as papillary tumor consisting of ciliated columnar, goblet, and basal cells. We present one case of pulmonary peripheral neoplasm misdiagnosed as mucinous adenocarcinoma. Pathologic findings showed, centrally, cystic papillary growth consisting of ciliated columnar, goblet, and basal cells, and peripherally, some tumor cells spread along the adjacent alveolar walls, in a lepidic fashion, and floating in pool of mucin. Tumor cells had bland nuclei, and no mitotic activity was observed. This had been initially misdiagnosed as mucinous adenocarcinoma in frozen section. We reviewed previous articles as well as permanent and frozen slides. In conclusion, in order to reduce the possibility of false positives, it is important to be aware that CMPT is a rare form of peripheral mucin-producing tumor with characteristic histologic findings.

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## 1. Background

Lung tumors with ciliated cells are considered benign, and most of these tumors occur in the central airway [1]. Peripheral lung neoplasms with cilia have been reported in an extremely well-differentiated adenocarcinoma [2] and solitary glandular papilloma of the peripheral lung [3]. Ciliated muconodular papillary tumor (CMPT) is peripheral lung neoplasm consisting of ciliated columnar, goblet,

and basal cells, and is considered to be low-grade malignant tumor.

Here, we report a case of CMPT misdiagnosed as mucinous adenocarcinoma in frozen section. We discuss the clinico-pathologic characteristics of CMPT as distinguished from pulmonary adenocarcinoma, and review relevant previous articles for the purpose of avoiding the potential diagnostic pitfalls in frozen section.

## 2. Case presentations

A 56-year-old man visited the emergency room with abdominal pain. While being evaluated for abdominal pain, abdominal CT showed small bowel perforation and a mass in

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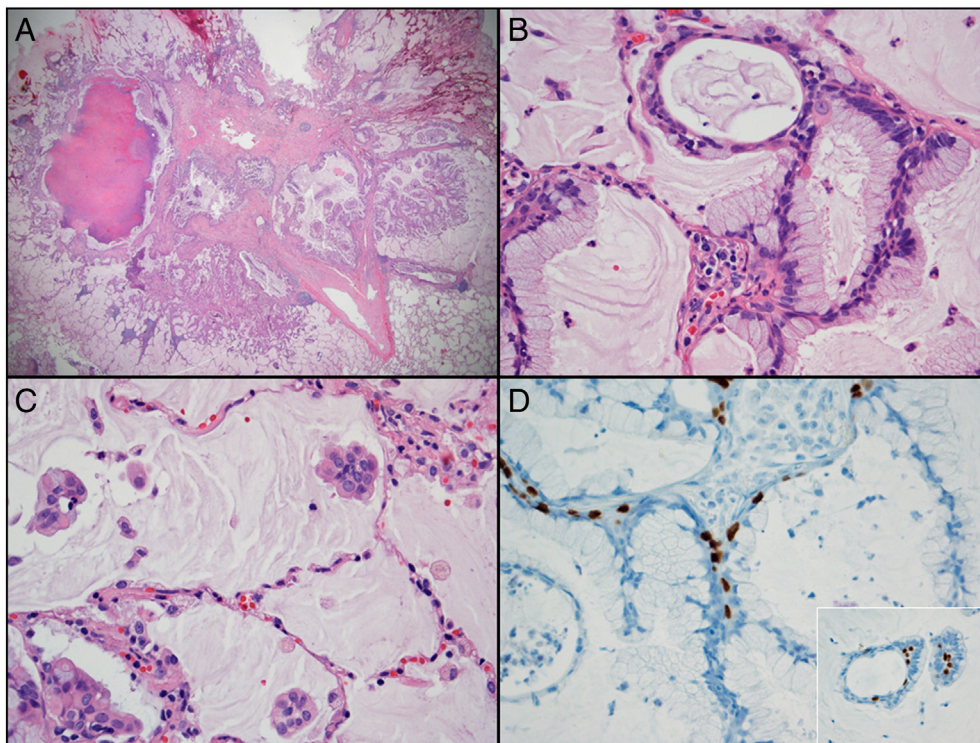
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the descending colon with multiple liver masses. Chest CT also showed an irregular, poorly enhanced, 11 mm-sized nodule in the left upper lobe, with focal mild uptake on FDG positron-emission tomography. The colon mass was diagnosed as adenocarcinoma in a biopsy specimen. A left upper lobe wedge resection was performed to determine whether primary malignancy or metastasis was present. Frozen section revealed some goblet cells along the alveolar wall and in the mucin pool. We diagnosed mucinous adenocarcinoma with presence of mucin in the resection margin. Segmentectomy and mediastinal lymph node dissection were performed to achieve a safety margin. The resected specimen showed an 8 mm, gelatinous, well demarcated, noncapsulated nodule. Microscopic examination revealed endobronchiolar and peribronchiolar papillary growing in a central cyst (Fig. 1A) consisting of different cells, including ciliated columnar, goblet, and small cells (Fig. 1B). Some tumor cells had spread to adjacent alveoli in a lepidic pattern; the mucin pool expanded the alveolar spaces and focally disrupted the alveolar septa. A few small epithelial aggregates were found to be floating in the mucin pool (Fig. 1C). Tumor cells had bland nuclei, and mitosis was not found. Immunohistochemically, the tumor cells stained positive for carcinoembryonic antigen (CEA), thyroid transcription factor-1 (TTF-1), and cytokeratin 7, but not for cytokeratin 20 or CDX2. The marker of p63 was stained

positively in small cells of the central and peripheral area (Fig. 1D). In diagnostic pathology practice, p63 is used for diagnosing squamous cell carcinoma of the lung, but it is not a specific marker for squamous cell carcinoma. p63 immunoreactivity is found in the basal or parabasal epithelial layers of stratified epithelial tissues, and in the basal or myoepithelial cells of the glandular epithelium. Staining for p63 can confirm the presence of basal cells. The postoperative period was uneventful, and the patient has been receiving chemotherapy for colon cancer. No recurrence or metastasis was noted during a 5-month follow-up period.

### 3. Conclusions

CMPT was first reported by Ishikawa [4] in 2002. CMPT is a peripheral lung tumor characterized as a papillary tumor consisting of ciliated columnar, goblet, and basal cells. Because CMPT is newly defined, it therefore is not yet classified according to the 2004 Fourth Edition of the World Health Organization (WHO) classification pathology and genetics of tumors of the lung, pleura, thymus, and heart [5]. CMPT is an extremely rare form of tumor. Only seven cases have been reported in the literature, including our case. CMPT affects elderly patients 50–76 years of age, with no preference related to location. Most patients are smokers.



**Fig. 1** Histology and immunohistochemical staining of ciliated muconodular papillary tumor. (A) Histologic findings show endobronchial and peribronchial growth with mucin pools ( $\times 40$ ). (B) Main goblet cells spread along the adjacent alveolar wall ( $\times 400$ ), and (C) small clusters of tumor cells floated in the mucin pool ( $\times 400$ ). (D) Immunohistochemically, p63 was positive in basal cells in lepidic growth fashion ( $\times 400$ ) (inset: in floating clusters).

The size of CMPT ranges from 5 to 15 mm. Neither recurrence nor distant metastasis has been reported during 1-month to 10-year follow-up periods after surgery. The clinicopathological and immunohistochemical features are summarized in Table 1.

The malignant potential of CMPT remains unknown. According to previous reports [4,6–8], the existence of cilia, the presence of basal cells, and a low Ki-67 index are suggestive of benignity. In contrast, destroyed alveolar structures and central fibrosis, proliferation along the alveolar walls and skip lesions, lack of encapsulation, micropapillary pattern, and staining for carcinoembryonic antigen are suggestive of malignancy. The immunohistochemical staining patterns for CK7, TTF-1, and CK20 were almost identical to those of pulmonary adenocarcinoma. The present case showed both benign and malignant histologic features described above. Additionally, we reviewed previous articles related to tumor behavior. Lung tumors with ciliated cells are considered benign [1]. Pulmonary malignant tumors with developed cilia have not been reported. However, malignant tumors with cilia have been reported in other organs. Park et al. [9] proposed that normal ciliated columnar cells transitioned into mucous columnar cells, including mucous or goblet cells, through the loss of cilia, followed by dysplasia and adenocarcinoma. Therefore, mucous columnar cell changes may be a precursor lesion of pulmonary adenocarcinoma. Arai et al. [10] reported three cases showing morphology similar to CMPT with p63-positive basal cells. They diagnosed the central portion as a solitary peripheral ciliated glandular papilloma, and the periphery as a well-differentiated adenocarcinoma. Although tumor cells showed bland cytology and the presence of ciliated cells, they believed that the findings suggestive of malignancy were the decreased number of basal cells; immunohistochemistry of CEA, c-erbB2, and EGFR; and infiltrative growth, such as the destruction of the alveoli wall, proliferation along the alveolar walls, and micropapillary pattern. However, Wu et al [11] reported p63 stained focally

in precursor lesions and adenocarcinoma *in situ*, and it was negative in well-differentiated adenocarcinoma. p63-positive cells were not basal cells, but were atypical epithelial cells. Neoplastic lesions contained no basal cells.

Differential diagnosis includes papilloma, peribronchiolar metaplasia, and malignant tumor. Pulmonary papillomas are histologically divided into three types: squamous cell, glandular, and mixed types, and are locationally divided into central endobronchial and peripheral bronchiolar types (PBT) [12]. Most PBTs are histologically glandular types similar to CMPT, and immunohistochemical details and malignant characteristics are unclear [3]. Peribronchiolar metaplasia is a common histologic finding in various interstitial lung disorders characterized by fibrosis and bronchiolar epithelial proliferation, affecting the peribronchiolar alveolar septa and terminal bronchioles. Neoplasms containing a mucin-producing epithelium growing within the alveolar spaces in the absence of a preexisting inflammatory or fibrosing condition may be considered to be adenocarcinoma as the first diagnostic possibility.

The present case was misdiagnosed as mucinous adenocarcinoma in the frozen section. This frozen section showed some goblet cells along the alveolar wall and mucin pool. The permanent slides for remnant tumor showed central papillary growth with peripheral spreading along the alveolar wall. The tumor was composed of ciliated columnar, and basal cells, as well as goblet cells. The presence of basal cells was confirmed by p63 immunostaining. Upon review of the frozen slide, this slide was similar to the periphery of the tumor. We could not exclude the possibility of adenocarcinoma. This was due to our belief that mucin-producing cells were not normally present in the alveolar wall and that neoplasms consisting of mucin-producing cells along the alveolar wall may be mucinous adenocarcinoma. Additionally, our case did not reveal interstitial lung disorders in clinical, histologic, and radiologic findings. The most characteristic findings of CMPT compared with adenocarcinoma may be central papillary growth and the presence of

**Table 1** Clinical findings of reported and present cases.

Author	Age/ sex	Smoking	Location	Size	IHC					Treatment	Follow-up
					CEA	TTF-1	CK7	CK20	P63		
Ishikawa [4]	50/F	+	RUL	15 mm	+	n/a	n/a	n/a	n/a	Lobectomy	10 yr NED
Harada [6]	62/M	+	LLL	9 mm	+	–	+	–	n/a	Partial resection	2 yr NED
Sato [8]	67/M	+	RUL	8 mm	+	+	+	–	n/a	Partial resection	10 mo NED
	59/F	–	RLL	5 mm	+	+	+	–	n/a	Partial resection	16 mo NED
Hata [7]	76/F	n/a	LUL	7 mm	n/a	n/a	n/a	n/a	n/a	Lobectomy	2 yr NED
Chuang [13]	68/M	+	RLL	12 mm	Focal, +	+ <sup>a</sup>	+	–	+ <sup>b</sup>	Wedge resection	4 yr NED
Present case	56/M	+	LUL	11 mm	+	+	+	–	+ <sup>b</sup>	Segmentectomy	5 mo NED

+, positive result; –, negative result; CEA, carcinoembryonic antigen; TTF-1, thyroid transcription factor 1; CK, cytokeratin; GGO, ground glass opacity; IHC, immunohistochemistry; LLL, left lower lobe; LUL, left upper lobe; mo, month; yr, year; n/a, not applicable; NED, no evidence of disease; RUL, right upper lobe; RLL, right lower lobe.

<sup>a</sup> Positive in some basaloid cells.

<sup>b</sup> Positive in basaloid cells.

ciliated columnar and basal cells. When we repeated our review of the frozen slide, it was difficult to recognize cilia and basal cells in the small floating cells. If the growth of the central papilla and ciliated cell are not included, it may be difficult to distinguish CMPT from adenocarcinoma.

In conclusion, as the use of CT increases, the small mucinous lesions described in this paper may become more readily detected. In daily practice, we can pose diagnostic problems in case we first diagnose small mucinous lesion by frozen section. In order to reduce the possibility of false positives, we believe that it is important to be aware that CMPT is one form of peripheral mucinous neoplasm with characteristic findings including central papillary growth consisting of ciliated columnar, goblet, and basal cells.

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