Ciliated Muconodular Papillary Tumors of the Lung: a Clinicopathological Analysis of 10 Cases

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Abstract

Ciliated muconodular papillary tumors (CMPTs) are rare peripheral nodules of the lung first described in 2002. Because of their rarity and non-standardized diagnostic terminology, CMPTs have been poorly recognized among pathologists. To better characterize these lesions, we undertook a detailed clinicopathologic and immunohistochemical study of 10 archival cases. Ten CMPTs occurred in 7 men and 3 women with a median age of 62 years. All were small peripheral non-endobronchial nodules with a mean diameter of 1.0 cm. All but 1 tumor were incidentally detected by computed tomography-based screening, all of which were radiologically interpreted as adenocarcinomas. Although limited surgery treated all but 1 CMPT, they followed a benign course with no recurrence at a mean follow-up of 43 months (range: 2–88 months). Histologically, CMPTs showed glandular and/or papillary architecture, comprising a vaguely organized mixture of non-atypical ciliated columnar cells, mucous cells, and basal cells, often enveloped by copious intraalveolar mucin. Micropapillary tufts of ciliated cells and seemingly discontinuous growth along alveolar walls were occasionally present, mimicking adenocarcinomas. Ciliated cells and basal cells were immunopositive for TTF-1 and p40, respectively, whereas mucous cells lacked HNF4α expression. CMPTs are rare, likely benign, underrecognized processes of the lung that should be distinguished from adenocarcinomas.

Keywords: tumor, lung, mucus, diagnosis
Introduction

In 2002, Ishikawa (1) reported in Japanese literature an unusual peripheral lung nodule consisting of ciliated columnar cells, mucous cells, and basal cell proliferation. Termed “ciliated mucinous papillary tumor” (CMPT), that 1.5 cm tumor showed distinctive papillary architecture and prominent intraalveolar mucus surrounding the lesion. The tumor showed an indolent course and non-atypical cytologic properties, so the authors suspected that CMPTs represented a benign neoplasm. Only 5 similar tumors have been subsequently reported as CMPTs in the English-language literature (2-5), but its clinicopathological features have not been analyzed in a sizable series. In addition, variable terminology has been proposed for histologically similar, if not identical, tumors including “solitary peripheral ciliated glandular papillomas”, “mucinous adenomatous hyperplasia”, and “peripheral pulmonary papillary/glandular neoplasms with ciliated cells” (6-10), and their relationship to CMPTs is poorly understood. Furthermore, the great majority of these reports originated from East Asia (1-6, 8-10), and these ciliated lesions do not seem to have received global attention.

The aim of the current study was to provide a detailed clinicopathologic and immunohistochemical analysis of 10 archival CMPT cases, to better characterize this rare entity, in the hope that these distinctive likely benign tumors should be more widely recognized to avoid confusion with adenocarcinomas.
Materials and Methods

Patients and Clinicopathologic analysis

This study was approved by the institutional review board of National Cancer Center Hospital (2010-0077; Tokyo, Japan). Ten cases with characteristic features of CMPT as described in the literature (1-5) were identified between 2006 and 2014. The clinical and pathological records were reviewed, and a histological analysis of the resected specimens was performed.

Immunohistochemistry and in situ hybridization

Immunohistochemical analysis was performed on paraffin-embedded sections using the following primary antibodies: thyroid transcription factor-1 (TTF-1), hepatocyte nuclear factor 4 alpha (HNF4α), cytokeratin (CK) 7, CK 20, p40, CDX2, MUC2, MUC5AC, MUC5B, MUC6, chromogranin A, and synaptophysin. Detailed clone names, antigen retrieval methods, and antibody dilutions are listed in supplementary Table 1.

Immunohistochemical results were assessed in 3 cell types within a lesion: namely, ciliated columnar cells, mucous cells, and basal cells. The reactivity was interpreted as diffuse when $\geq 50\%$ of the cells were stained and focal when the labeled cells constituted $< 50\%$. Staining intensity was classified as strong or weak. Nuclear staining was regarded as positive for TTF-1, HNF4α, p40, and CDX2, whereas cytoplasmic staining was considered positive for CK7, CK20, MUC2, MUC5AC, MUC5B, MUC6, chromogranin A, and synaptophysin.
Human papilloma virus (HPV) infection status was determined by *in situ* hybridization using HPV probes (INFORM HPV Probe, Ventana). HPV was considered present when an episomal or integrated pattern was observed in cell nuclei.

**Results**

**Clinical findings**

As shown in Table 1, CMPTs occurred in 7 men and 3 women with a median age of 62 years (range: 56–78 years), and all were Japanese. Five patients had a history of smoking. On computed tomography (CT) imaging, all lesions were small peripheral solid or part-solid nodules with an irregular contour (Fig.1A), and they measured 1.0 cm on average (range: 0.6–1.5 cm). Three cases were accompanied by central cavities (Fig.1B). CMPTs were located in the right upper lobe (n = 1), right lower lobe (n = 5), and left lower lobe (n = 4). Nine patients were asymptomatic with the nodules being detected at CT-based medical checkups, whereas 1 presented with cough. Prior to surgery, 2 CMPTs were longitudinally followed by CT for 2 and 3 years and both showed a slight increase in size. Owing to the peripheral location and the irregularity of lesional contour, preoperative radiological diagnosis was adenocarcinoma in all but 1 case, which was not recognized before surgery.

Intraoperative frozen section diagnosis was performed in 9 cases, and the diagnoses provided were CMPT (n = 4); atypical glandular lesion, favor reactive, cannot rule out adenocarcinoma (n = 2);
muconodular tumor, favor benign (n = 1); mucinous bronchioloalveolar carcinoma (n = 1); or metaplastic lesion (n = 1). The lesions were treated by wedge resection (n = 8), segmentectomy (n = 1), and lobectomy (n = 1). The CMPT treated by lobectomy was an incidental finding in a specimen resected for a separate squamous cell carcinoma. The original final diagnoses based on permanent sections were CMPT (n = 8), unclassifiable lesion (n = 1), and metaplasia (n = 1). None of the patients experienced local recurrence or distant metastasis at a mean follow-up of 43 months (range: 2–88 months).

Gross findings

Gross descriptions were available for all cases, of which gross photographs were available for 6 cases. Most were gray-white, soft, well-circumscribed nodules with a mucinous or gelatinous quality (Fig. 1C–D). Four lesions were located adjacent to the pleura, but no plural retraction was observed. Intralesional anthracosis and fibrosis were present in 5 and 3 cases, respectively. Resection margins were negative for tumors in all cases.

Histological findings

All 10 CMPTs showed a similar spectrum of histomorphology. The nodules were not endobronchial and consisted of proliferating epithelial cells associated with mild fibrosis and chronic inflammatory cell infiltration. Overall, some lesions appeared glandular, likely conforming to the preexisting pulmonary architecture (Fig. 2A), but others showed papillary growths that could not be explainable by host microanatomy (Fig. 2B). The lesions were predominantly glandular in 5 cases and
predominantly papillary in 5 cases. Elastic staining commonly demonstrated focal loss or disruption of the alveolar elastic framework.

The epithelial components of the lesions consisted of a mixture of ciliated columnar cells, mucous cells, and basal cells. These tripartite elements proliferated in a vaguely organized manner; ciliated columnar cells lined the surface of the glandular/papillary structures, basal cells provided a scaffold in the outer layer, and mucous cells, which were interspersed between the other 2 elements, tended to form small nested structures that often protruded downwards from the papillary/glandular lining (Fig. 3A). Basal cells were uniformly present as a continuous element that was occasionally multilayered. There was no focus in which mucous or ciliated cells were proliferating without the underlying basal cells.

The relative amount of the 3 cell types differed from case to case. Basal cells were abundant in case 2 (Fig. 3B), while case 1 was predominately mucous cells (Fig. 3C). Ciliated columnar cells occasionally showed eosinophilic cytoplasm and budded focally from the glandular/papillary surface as micropapillary tufts floating in the alveolar spaces. This pattern was particularly prominent in cases 3, 4, 7, and 10 (Fig. 3D). The tumor cells completely lacked nuclear atypia, mitotic figures, and necrosis. The lesion periphery was often surrounded by copious amount of inspissated mucus filling the alveoli (Fig. 2B) Mucin was also noted in the lesional center in some cases, which correlated with the cavities observed on CT. In 6 cases, the tumor periphery harbored rare, discontinuous (“skipping”) growths of lesional cells to a minimal extent, reminiscent of invasive mucinous adenocarcinoma (Fig. 3E). The tumors were always
penetrated by large bronchioloarterial bundles or unpaired medium-sized muscular arteries (Fig. 3F), likely reflecting the peribronchiolar localization of the tumors.

**Immunohistochemistry and in situ hybridization**

Immunohistochemically, a subset of ciliated columnar cells, mucous cells, and basal cells weakly stained for TTF-1 (Fig. 4A). Strong staining of p40 highlighted the uniform continuous presence of basal cells (Fig. 4B). The mucous cells lacked staining for MUC5AC, whereas ciliated cells were focally positive for MUC5AC (Fig. 4C). In 7 cases, a small number of neuroendocrine cells immunopositive for chromogranin A and synaptophysin were interspersed among basal cells, reminiscent of bronchial Kulchitsky cells (Fig. 4D). HPV infection was not detected in any cases.

**Discussion**

The present clinicopathologic study characterized and delineated CMPTs as a distinctive entity, and provided data quite consistent with those of a small number of sporadic reports (1-5). CMPTs are small peripheral non-endobronchial lung nodules arising in middle-aged and older asymptomatic patients. Often incidentally discovered by CT screening, CMPTs commonly receive a radiological interpretation of adenocarcinoma owing to the peripheral location and irregular contour. Histologically, CMPTs are characterized by tripartite elements including ciliated columnar cells, mucous cells, and basal cells in a vaguely organized manner. One finding not emphasized in previous reports is that CMPTs may show only
inconspicuous papillary architecture, and consist predominantly of glandular proliferations, despite its name. The presence of a small number of neuroendocrine components, observed in most of this series, has not been previously documented. CMPTs consistently follow an indolent course, and no recurrences were seen in this series even after limited surgery.

From a diagnostic standpoint, CMPTs should be differentiated from several more common entities, the most important of which are adenocarcinomas. Similar to adenocarcinomas, CMPTs display a diverse growth pattern including glandular, papillary, micropapillary, and even a minimal extent of seemingly discontinuous lepidic proliferations. CMPTs also harbor fibrosis and focal loss or disruption of the alveolar elastic framework and such findings may suggest invasiveness to the unaware. However, adenocarcinomas lack the unique tripartite complements characteristic of CMPTs, namely, ciliated columnar cells, mucous cells, and continuous basal cells. In particular, the invariable presence of ciliated cells in CMPTs provides a reliable clue to suggest the benign nature of this lesion. Although exceptional cases of ciliated adenocarcinomas have been reported in the lung (11-13), it is universally accepted that the cilia and/or terminal plates are one of the most reliable findings to support a benign diagnosis (14). Furthermore, in contrast to adenocarcinomas, CMPTs always lack nuclear atypia and mitotic activity. Although mucous cells and intraalveolar mucus spillage may create the impression of invasive mucinous adenocarcinomas, basal cell and ciliated components are lacking in mucinous carcinomas, and HNF4α, a sensitive marker for invasive mucinous adenocarcinomas (15) is not expressed in CMPTs.
Another malignant tumor that is potentially confused with CMPTs is mucoepidermoid carcinoma, because the latter tumor contains mucous and basal cells. However, the distinction is readily accomplished, because this salivary-gland-type carcinoma typically arises in the central bronchus of younger individuals and lacks ciliation with rare exceptions (16).

Benign mimics of CMPTs primarily include peribronchiolar metaplasia. Indeed, vaguely organized proliferation of multiple distinct types of cells in CMPTs may be reminiscent of this common metaplastic processes. In addition, CMPTs tend to localize adjacent to the bronchiolar structure or unpaired pulmonary arteries, similar to peribronchiolar metaplasia. However, CMPTs display greater architectural distortion than peribronchiolar metaplasia. In addition, CMPTs always presented as solitary distinct nodules readily visible on CT, unlike metaplastic changes that are typically microscopic and sometimes multifocal. Further, mucous cells, a consistent finding of CMPTs, are absent in the bronchiolar lining (17), and are seldom resident in peribronchiolar metaplasia (18). Parenthetically, the mucous cells in CMPTs are immunohistochemically different from bronchiolar goblet cells; mucous cells in most CMPTs are MUC5AC-negative, while bronchiolar goblet cells are MUC5AC-positive (19). Finally, 2 of our CMPTs longitudinally followed by CT showed a slow yet seemingly autonomous growth over 2–3 years, arguing for the neoplastic nature of the process.

The relationship between CMPTs and papillomas are more complicated and require future clarification. Among 3 subcategories of papillomas (i.e., squamous cell papillomas, glandular papillomas,
and mixed papillomas (20)), the histological features of mixed papillomas resemble those of CMPTs.

Although papillary architecture is typically more conspicuous in papillomas and mucous cells of mixed papillomas are reportedly MUC5AC-positive unlike CMPTs (21), the overall arrangement of tumor cells can be otherwise similar, exhibiting a pseudostratified columnar epithelium consisting of ciliated cells, basal cells, and mucous cells (22). Given that mixed papillomas are endobronchial by definition according to the current WHO classification (20), papillomas and CMPTs might form a spectrum of the same process differing only by their locations (central vs. peripheral) and/or the association with bronchial lumens (endobronchial vs. non-endobronchial). In fact, there have been a few reports of “papilloma” in the peripheral lung (6-8), and some of them may represent CMPTs judging from the published illustrations.

CMPTs are likely benign. None of our 10 cases recurred even after limited surgery. Similar indolent clinical course was documented in all reported CMPTs (1-5). A benign nature for CMPT is readily implied histologically, not only by the constant presence of cilia, but also by bland cytology, the lack of mitotic figures, and the consistent basal cell population. Nonetheless, the long-term biological behavior of CMPTs could not be established by the present study with a limited follow-up, and further data need to be collected to draw solid conclusions. Similarly inconclusive here is whether CMPTs have any potential for malignant transformation. We are aware of 1 report (10) of “peripheral pulmonary papillary/glandular neoplasms with ciliated cells” that harbored foci interpreted as adenocarcinomas, and these might...
represent CMPTs with possible malignant alterations. However, the malignant interpretation in those cases seemed to be based solely on the papillary/micropapillary growth pattern, which would be native to CMPTs. In addition, the lesions reportedly lacked cellular atypia, and they did not recur for 29–43 months without adjuvant treatment (10). In our series, no CMPTs coexisted with contiguous adenocarcinoma components.

It is notable that all the CMPTs (1-5) and most of the cases potentially related to this entity (such as so-called peripheral papillomas) (6, 8-10) were reported in Japan and other East Asian countries. This skewed geographic distribution may reflect a frequent use of CT-based screening in Japan that facilitates detection of small peripheral nodules. Alternatively, or concomitantly, it may represent a true ethnic predisposition, perhaps associated with a differential risk to genetic changes. Future studies from Western countries may clarify the global incidence of these tumors.

In conclusion, this study confirmed that CMPTs are distinctive small peripheral lung nodules that occur in middle-aged and older patients, and consist of a vaguely organized mixture of non-atypical ciliated columnar cells, mucous cells, and basal cells. CMPTs are likely benign with no or negligible risk of recurrences even after limited surgery, and they should be distinguished from adenocarcinomas. Although solitary presentation and distinctive histology strongly supports neoplastic process, understanding the pathogenesis of CMPTs requires future studies including molecular analysis.
Acknowledgements

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REFERENCES


FIGURE LEGENDS

Figure 1

CMPTs are radiologically identified as small peripheral nodules, some of which show central cavities (high-resolution CT, A: case 10, B: case 6, Arrows mark the nodules.) Grossly, CMPTs are gray-white, soft, well-circumscribed nodules with a mucinous or gelatinous quality (C: case 7, D: case 8).

Figure 2

At low power, CMPTs show overall growth patterns ranging from predominantly glandular (A, case 3) to papillary (B, case 1).

Figure 3

The lesions are surrounded by copious amount of mucus, and consist of ciliated columnar cells, mucous cells, and basal cells in varying proportions. Most cases harbor a relatively balanced mixture of the 3 cell types (A, case 3), while a few show unbalanced combination such as the case with predominant basal cells (B, case 2) and that with predominant mucous cells (C, case 1). Notice the vaguely organized arrangement of the 3 cell types and the lack of nuclear atypia. Micropapillary tufting of the ciliated cells with eosinophilic cytoplasms are a characteristic feature seen in 4 cases (D, case 3). A few cases show discontinuous (“skipping”) growth of lesional cells to a minimal extent (E, case 9). CMPTs are consistently penetrated by larger bronchioloarterial bundles or unpaired medium-sized muscular arteries, reflecting the peribronchiolar localization (F, case 2).

Figure 4
The immunophenotype of CMPTs. A: TTF-1 stained ciliated and basal cells (case 3). B: p40 stained continuous basal cells (case 5). C: mucous cells generally lacked staining for MUC5AC, while ciliated cells were focally positive for MUC5AC (case 8) (inset: higher-magnification view of ciliated cells). D: a few chromogranin A-positive cells are interspersed between basal cells (case 3).
Table 1. Clinicopathologic findings of CMPTs

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>Size (cm)</th>
<th>Predominant Architecture</th>
<th>Treatment</th>
<th>Outcome (months)</th>
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<tr>
<td>1</td>
<td>61</td>
<td>M</td>
<td>RUL</td>
<td>1.0</td>
<td>Papillary</td>
<td>WWR</td>
<td>NED (76)</td>
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<tr>
<td>2</td>
<td>60</td>
<td>F</td>
<td>LLL</td>
<td>1.5</td>
<td>Glandular</td>
<td>WWR</td>
<td>NED (33)</td>
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<td>3</td>
<td>78</td>
<td>M</td>
<td>RLL</td>
<td>0.9</td>
<td>Glandular</td>
<td>Segmentectomy</td>
<td>NED (66)</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>M</td>
<td>RLL</td>
<td>1.1</td>
<td>Papillary</td>
<td>Lobectomy</td>
<td>NED (63)</td>
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<tr>
<td>5</td>
<td>75</td>
<td>M</td>
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<td>0.6</td>
<td>Papillary</td>
<td>WWR</td>
<td>NED (44)</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>F</td>
<td>LLL</td>
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<td>WWR</td>
<td>NED (45)</td>
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<tr>
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<td>M</td>
<td>RLL</td>
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<td>Papillary</td>
<td>WWR</td>
<td>NED (4)</td>
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<td>9</td>
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<td>NED (88)</td>
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<tr>
<td>10</td>
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<td>WWR</td>
<td>NED (2)</td>
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M indicates male; F, female; RUL, right upper lobe; LLL, left lower lobe; RLL, right lower lobe; WWR, wide wedge resection; NED, no evidence of disease.
**Supplementary Table 1. Summary of antibodies**

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