Case Report

A case of anaplastic lymphoma kinase (ALK)-positive ciliated muconodular papillary tumor (CMPT) of the lung

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Ciliated muconodular papillary tumor (CMPT) is a rare papillary tumor that arises in the peripheral lung fields and is associated with the proliferation of ciliated and goblet cells and increased mucin production. We report a case of CMPT involving the rearrangement of the anaplastic lymphoma kinase (ALK) gene. The patient was an 84-year-old Japanese female who had exhibited a small nodular shadow on chest computed tomography during a regular checkup 10 years ago. She underwent a partial resection of segment S10 of the right lung. The cut surface of the surgical specimen revealed a well-circumscribed, jelly-like mass measuring 8 × 8 × 10 mm. Histologically, the tumor was composed of a mixture of ciliated, goblet, and basal cells arranged in a papillary pattern together with pools of mucin. A diagnosis of CMPT was made. The lung tumor cells were subjected to fluorescent in situ hybridization and highly sensitive immunohistochemical staining for the ALK protein, both of which produced positive results. CMPT usually follows a favorable course, but the exact nature of this tumor; i.e., whether it is benign or malignant, has not been established. This is the first reported case of an ALK-positive CMPT.

Key words: lung, CMPT (ciliated muconodular papillary tumor), ALK (anaplastic lymphoma kinase) gene

Ciliated muconodular papillary tumor (CMPT) is a rare mucin-producing papillary tumor that arises in the peripheral lung. It was first reported in 2002 by Ishikawa1 and is composed of a mixture of proliferating ciliated columnar cells, goblet cells, and basal cells, which produce mucin.1–6 The echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion gene has been reported to occur in about 3–5% of non-small cell lung cancers.7,8 Herein, we describe the first reported case of ALK-positive CMPT, together with a review of the literature.

CLINICAL SUMMARY

The patient was an 84-year-old Japanese female with no chief complaints. At the age of 51, she had undergone chemotherapy for uterine cervical cancer. She had a family history of lung cancer in her father, pancreatic cancer in her brother, and malignant lymphoma in her older sister. She had never smoked. Ten years ago, she had exhibited a small nodular shadow on chest computed tomography (CT) during a regular checkup. Since then, she had been followed-up with annual chest CT scans, during which time the shadow had gradually enlarged. Under a suspicion of lung cancer, she was referred to our department 10 years after the first examination.

Her levels of the tumor markers carcinoembryonic antigen (CEA), cancer antigen 19-9, cytokeratin (CK)19 fragment, and progastrin-releasing peptide were within the normal range. Plain chest CT showed a well-circumscribed lobulated nodular shadow (diameter: 8 mm) in segment S10 of the right lung beneath the visceral pleura (Fig. 1a). The patient underwent partial resection of the affected segment because the changes in her chest CT findings were suggestive of primary lung cancer. No recurrence was detected during the 10-month follow-up period after the operation.

PATHOLOGICAL FINDINGS

The cut surface of the resected specimen showed a well-circumscribed, jelly-like, lobulated mass measuring
8 × 8 × 10 mm (Fig. 1b). Histologically, proliferating tumor cells were aligned along the pre-existing alveolar septal architecture or in a papillary pattern. The alveoli around the tumor were filled with Alcian blue-positive mucin. High-power magnification showed the proliferation of a mixture of ciliated, goblet, and basal cells with little or no mitotic activity (Fig. 2a–c). Immunohistochemically, all of the tumor cells were negative for thyroid transcription factor 1 (TTF-1) and CK20, both the ciliated cells and goblet cells were positive for CK7 and CEA, the basal cells were positive for p40 and rarely positive for p53, the ciliated cells and mucin-producing cells were positive for MUC 5AC, and the ciliated cells were positive for MUC6 and rarely positive for MUC2 (Fig. 3a–d). The tumors' Ki-67 labeling index was 3.7%. A diagnosis of CMPT was made. A genetic analysis produced negative results for epidermal growth factor receptor (EGFR) and KRAS mutations. Tumor cells were negative for BRAF V600E in immunohistochemistry. Highly sensitive immunohistochemical staining of the ALK protein was performed using the HISTOFINE ALK iAEP kit (Nichirei Bioscience, Tokyo, Japan). More than 80% of the tumor cells were positive for ALK (ALK iScore 3+) (Figs. 4a, b), as was the cytoplasm of all types of epithelial cells. Formalin-fixed, paraffin-embedded, 4 µm thick tumor tissues were subjected to fluorescent in situ hybridization (FISH) analysis to detect ALK rearrangement. A break-apart probe for the ALK gene (Vysis ALK Break Apart FISH probe kit, Abbott Japan, Osaka, Japan) was used during the FISH in accordance with the manufacturer's instructions. Split signals for ALK were detected in 60% of the tumor cells (Fig. 4c), but it was difficult to identify the types of cells that exhibited split signals during the FISH analyses.

**DISCUSSION**

Ciliated muconodular papillary tumor is a rare lung tumor and was first reported by Ishikawa in 2002 in the Japanese
It arises in the peripheral lung fields in middle-aged or older asymptomatic patients and follows an indolent course. Histologically, it is composed of papillary proliferations of a mixture of ciliated cells, goblet cells, and basal cells and displays marked mucin production. A similar tumor was named extremely well-differentiated papillary adenocarcinoma by Nakamura et al. in 1992, which was shown to be a low-grade malignant tumor.

The differential diagnoses of CMPT include primary and metastatic adenocarcinoma and other benign papillary lesions. Carcinomas demonstrate malignant cytological features, but usually lack basal and ciliated cells (Appendix)

Figure 3  Immunohistochemistry for (a) CK7 (positive), (b) CK20 (negative), (c) TTF-1 (negative), (d) p40 (positive in basal cells), (e) CEA (positive in ciliated cells), (f) MUC2 (rarely positive in ciliated cells), (g) MUC5AC (positive in ciliated cells), and (h) p53 (rarely positive in basal cells)

Figure 4  (a) Highly sensitive immunohistochemical staining of ALK (positive) x20. (b) Highly sensitive immunohistochemical staining of ALK (positive) x40. (c)All types of epithelial cells were positive for ALK. (d) ALK-FISH: split signals for ALK were detected (arrows: translocation-positive, arrowhead: normal gene)
S1). Among benign papillary lesions, glandular papillomas are the most difficult to differentiate from CMPT.11 Glandular papillomas, like CMPT, are composed of ciliated columnar cells, mucin-producing cells, and basal cells. The main difference between these lesions is that papillomas often arise in the trachea, main bronchus, and segmental bronchi, and rarely in the subsegmental bronchi or more distal locations,11 whereas CMPT originates in the periphery of the lung. Ciliated glandular papilloma of the lung has been reported to occur in the periphery of the lung in rare cases, but most proliferations are located along bronchioles, and proliferations within alveolar structures are only seen in a limited area during pathological examinations.12 The current World Health Organization (WHO) classification does not recognize CMPT as a distinct entity; instead, it is included under glandular papilloma. However, CMPT might be classified as a new entity in the near future.

There have been a few reports about CMPT, which included 16 cases.1–6 The clinical and immunohistochemical findings and mutation statuses of these 16 cases are summarized in Table 1. The mean age of the affected patients was 63.8 years, and the male to female ratio was 10 to 6. The right and left lungs were affected in 10 and 6 cases, respectively. The lesion was located in the upper lobe in 4 cases, whereas it arose in the lower lobe in 12 cases. The tumors ranged in size from 5 mm to 15 mm. Immunohistochemically, CMPT tumor cells are always positive for CK7. However, the outcomes of staining for TTF-1 and MUC5AC varied between reports. Alveolar type II cells in the normal lung also exhibit positivity for TTF-1(Appendix S1). The degree of the differentiation of the tumor cells into alveolar type II cells might differ from case to case. Similarly, the epithelial cells in normal bronchioles display variable positivity (from cell to cell) for MUC proteins so the kinds of mucin produced by CMPT cells seem to differ from case to case according to the types of cells present within the tumor(Appendix S1).

Although no recurrent lesions arose in the previously reported cases of CMPT, the exact nature of this tumor; i.e., whether it is benign or malignant, has not been established. The previously reported features of this tumor that suggest malignancy include: (i) the destruction of alveolar structures and aggregation of elastic fibers; (ii) the replacement of the alveolar epithelium by tumor cells; (iii) the presence of skip lesions (raising a suspicion of intrapulmonary metastasis); (iv) the absence of a capsule; (v) CEA positivity; and (vi) the presence of a micropapillary pattern.1–6 On the other hand, the following clinicopathological features suggest that CMPT is benign: (i) marked differentiation of the tumor cells into ciliated cells; (ii) the absence of mitotic figures; (iii) the absence of KRAS mutations; and (iv) the absence of reported cases of recurrence (although all reported patients underwent partial pneumonectomy, segmentectomy, or lobectomy).1–6 To date, detailed genetic analyses have been performed in 12 CMPT patients (Table 1). Chuang analyzed one CMPT for EGFR mutations and another for EGFR and KRAS mutations, with all of the results being negative.5 Recently, Kamata et al. genetically analyzed 10 cases of CMPT using next-generation sequencing and found high rates of BRAF and/or EGFR mutations.13 The high prevalence of driver gene mutations in CMPT suggests that these lesions are neoplastic. However, no previous studies have examined ALK mutations. This is the first reported case of an ALK-positive CMPT. The ALK fusion gene was originally found in anaplastic large-cell lymphoma.14 The ALK fusion gene has also been found in ALK-positive large B-cell lymphoma(Appendix S1) and renal cell carcinoma (Appendix S1) both of which are malignant tumors. Soda et al. reported in 2007 that the EML4-ALK fusion gene was present in about 3–5% of non-small cell lung cancers and exhibited strong carcinogenicity and proliferative activity.7,15 It is interesting that many ALK-positive adenocarcinomas and CMPT exhibit mucin production. Although the EML4-ALK fusion gene is the predominant ALK fusion gene in lung cancer, several other partner genes of ALK have been detected, including kinesin family member 5b (KIF5B),16 fibroblast growth factor receptor 3 (FGFR3),17 huntingtin-interacting protein 1 (HIP1), (Appendix S1) kinesin light chain 1 (KLC1), (Appendix S1) striatin (STRN), protein tyrosine phosphatase, nonreceptor Type 3 (PTPN3) (Appendix S1) and translocated promoter region (TPR) (Appendix S1). In the present case, the partner gene of ALK was not clarified because no polymerase chain reaction analysis of the fusion gene was performed. ALK rearrangement is mostly associated with an acinar pattern (including cribriform morphology) and signet ring cell features in lung cancer6 (Appendix S1). ALK rearrangements are non-overlapping with other oncogenic mutations in majority of cases of non-small cell lung cancer. The present case was also ALK-positive and BRAF negative.18

On the other hand, no cases of ALK-positive, benign lung tumors have been reported to date although epithelioid fibrous histiocytoma of the skin has been reported to harbor vinculin (VCL)-ALK and sequestosome 1 (SQSTM1)-ALK fusion genes (Appendix S1). However several studies have described cases of ALK-positive inflammatory myofibroblastic tumor (IMT) involving low-grade atypia19(Appendix S1). IMT is a distinctive lesion composed of myofibroblastic spindle cells that demonstrates a small degree of atypia accompanied by inflammatory infiltrates, which are usually mainly composed of plasma cells and lymphocytes. About 50% of cases, particularly those involving children or young adults, exhibit ALK gene rearrangement. Although IMT is indolent, complete resection is advocated to avoid recurrence and metastasis19 (Appendix S1).

Except for ALK, various fusion genes have been detected in both malignant and benign tumors. Among malignant salivary gland tumors, CREB-regulated transcription
| Author      | Age/gender | Smoking | Location   | CT finding     | Size (mm) | Treatment          | Immunohistochemical findings | Mutation status | Outcome (months) |
|------------|------------|---------|------------|----------------|-----------|---------------------|------------------------------|-----------------|------------------|
| Ishikawa¹  | 50F        | +       | RUL        | nodule         | 15        | Lobectomy          | n/a n/a n/a n/a n/a         | n/a n/a n/a n/a | 120 alive        |
| Harada²    | 62M        | +       | LLL        | nodule         | 9         | WR                  | + - - + n/a n/a n/a          | n/a n/a n/a n/a | 24 alive         |
| Sato³      | 67M        | -       | RUL        | nodule with GGO | 8         | WR                  | + + + 10% n/a n/a            | n/a n/a n/a n/a | 10 alive         |
| Hata⁴      | 59F        | -       | RLL        | GGO with cavity | 5         | WR                  | + - - 3% n/a n/a n/a         | n/a n/a n/a n/a | 18 alive         |
| Chuang HW⁵ | 76F        | n/a     | LUL        | nodule         | 7         | Lobectomy          | n/a n/a n/a n/a n/a          | NM n/a n/a n/a | 24 alive         |
| Kamata⁶    | 68M        | +       | RLL        | nodule         | 12        | WR                  | + n/a + <1% <1% n/a          | NM NM n/a n/a | 48 alive         |
| 61M        | -          | RUL     | nodule     | 10             | WR        | n/a n/a n/a n/a n/a | n/a n/a n/a n/a n/a          | NM n/a M n/a | 76 alive         |
| 60F        | -          | RLL     | nodule     | 15             | WR        | n/a n/a n/a n/a n/a | n/a n/a n/a n/a n/a          | M n/a NM n/a | 33 alive         |
| 78M        | +          | RLL     | nodule     | 9              | Segmentectomy | n/a n/a + n/a n/a | n/a n/a n/a n/a n/a          | NM n/a M n/a | 66 alive         |
| 63M        | +          | RLL     | nodule     | 11             | Lobectomy | n/a n/a n/a n/a n/a | n/a n/a n/a n/a n/a          | NM n/a M n/a | 63 alive         |
| 75M        | +          | RLL     | nodule     | 6              | WR        | n/a n/a n/a n/a n/a | n/a n/a n/a n/a n/a          | NM n/a NM n/a | 44 alive         |
| 62F        | -          | RLL     | nodule with cavity | 13 | WR | n/a n/a n/a n/a n/a M n/a NM n/a | n/a n/a n/a n/a n/a          | 45 alive         |
| 57M        | +          | RLL     | nodule     | 12             | WR        | n/a n/a n/a n/a n/a | n/a n/a n/a n/a n/a          | NM n/a NM n/a | 7 alive          |
| 56M        | -          | RLL     | nodule     | 11             | WR        | n/a n/a n/a n/a n/a | n/a n/a n/a n/a n/a          | NM n/a M n/a | 4 alive          |
| 66M        | -          | RLL     | nodule     | 7              | WR        | n/a n/a n/a n/a n/a | n/a n/a n/a n/a n/a          | M n/a NM n/a | 88 alive         |
| 61F        | -          | RLL     | nodule     | 6              | WR        | n/a n/a n/a n/a n/a | n/a n/a n/a n/a n/a          | NM n/a M n/a | 2 alive          |
| Present case | 84F      | -       | RLL        | nodule         | 8         | WR                  | + + + 3.7% <1% n/a          | NM NM NM M     | 10 alive         |

GGO, ground-glass opacity; LLL, left lower lobe; LUL, left upper lobe; M, mutated; n/a, not available; NM, not mutated; RLL, right lower lobe; RUL, right upper lobe; WR, wedge resection
coactivator 1/3–mastermind-like 2 (CRTC1/3-MAML2), (Appendix S1) ETS variant 6-neurotrophic tyrosine kinase receptor, type 3 (ETV6-NTRK3), (Appendix S1) and v-myb avian myeloblastosis viral oncogene homolog-nuclear factor 1 b-type (MYB-NFIB) Appendix S1 have been detected in mucoepidermoid carcinoma, mammary analogue secretory carcinoma, and adenoid cystic carcinoma, respectively. In addition, the pleomorphic adenoma gene 1-high-mobility group AT-hook 2 (PLAG1-HMGA2) fusion gene20 has been found in pleomorphic adenoma, which is the most common type of benign salivary gland tumor.

This present case is the first reported case of ALK-positive CMPT, which is a tumor that displays a small degree of atypia, an indolent clinical course, and a low risk of recurrence. Further studies are needed to investigate whether CMPT has malignant potential or is a precancerous lesion that leads to adenocarcinoma.

DISCLOSURE STATEMENT

None declared.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher’s website.

APPENDIX S1 Additional reference.