Pulmonary papillary adenoma presenting in central portion: a case report

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Abstract
Pulmonary papillary adenoma is a very rare tumor usually presenting in periphery of the lung. Herein, we present a case of pulmonary papillary adenoma located in central portion of the lung in a 17 year-old Chinese female. A well-defined mass was incidentally detected at right pulmonary hilar region by imaging examination. Histologically, the tumor is predominantly composed of abundant papillary structures lined by columnar to cuboidal epithelial cells resembling type II pneumocytes. Immunohistochemical staining showed that the epithelial cells were diffusely positive for cytokeratin, cytokeratin7, TTF-1, EMA, surfactant apoprotein A, Napsin A, P63 and β-catenin. The Ki-67 proliferation index was approximately 2 %. Based on morphologic features and the immunohistochemical profile, the tumor was consistent with pulmonary papillary adenoma. Thus, it should be noted that pulmonary papillary adenoma was also a possible diagnosis for a central mass.

Keywords: Pulmonary papillary adenoma, Lung tumor

Background
Pulmonary papillary adenoma is a very rare tumor that first described by Fantone et al. in 1982 [1]. So far, less than 25 cases were reported in the English literature [2–16]. The reported cases predominatly occurred in periphery of the lung. In contrast, we present a case of pulmonary papillary adenoma located in the central portion of the lung in a 17 year-old Chinese female. This tumor was generally considered benign; however, some scientists thought that it might have malignant potential because of its microinvasive characteristics [9, 10]. The patient was alive with no evidence of tumor recurrence or metastasis within 12 months of follow-up.

Materials and methods
The resected specimens were fixed with 10 % neutral-buffered formalin and embedded in paraffin blocks. Tissue blocks were cut into 4-μm slides, deparaffinized in xylene, rehydrated with graded alcohols, and immunostained with the following antibodies: cytokeratin (CK), cytokeratin7(CK7), CD68, Vimentin, thyroid transcription factor 1 (TTF-1), epithelial membrane antigen (EMA), surfactant apoprotein A (SPA), Napsin A, synaptophysin, CD56, P63 and β-catenin, p53 and Ki-67. Sections were stained with a streptavidin-peroxidase system (KIT-9720, Ultrasensitive TM S-P, MaiXin, China). The chromogen used was diaminobenzidine tetrahydrochloride substrate (DAB kit, MaiXin, China), slightly counterstained with hematoxylin, dehydrated and mounted. For the negative controls, the primary antibody was replaced with PBS. This study was prospectively performed and approved by the institutional Ethics Committees of China Medical University and conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

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Results

Gross features
Grossly, the mass was approximately 3.0 × 2.9 × 2.6 cm, and was relatively well circumscribed. The cut face was firm and grey-white or grey-yellow in color (Fig. 2a).

Histologic features
Histologically, the tumor was relatively well defined, and there was a fibrous capsule around the tumor. The capsule infiltration, normal lung tissue, vessels and pleura invasion was not present in the tumor (Fig. 2b). The tumor was predominantly composed of papillary structures with fibrovascular cores (Fig. 2c). Focally, the abundant hyalinized collagen with few cells was present in the core of the papillary structure reminiscent of sclerostic pattern of sclerosing pneumocytoma. Contrastly, the stroma of papillary structure lacked the polygonal cells presenting in sclerosing pneumocytoma (Fig. 2d).

The lining cells on the papillary pattern were columnar or cuboidal with mild atypia, clear cytoplasm, fine chromatin and inconspicuous or small nucleoli. The numerous nuclear inclusions were present in the epithelial cells. The mitosis of the cells is very rare (Fig. 2f). However, focally, the cells showed florid hyperplasia, and form the micropapillary or irregular cribriform pattern, which might pose a diagnostic challenge. In addition, abundant histiocytes were present in the spaces of the tumor (Fig. 2e).

Immunohistochemical staining and molecular detection
Immunohistochemical staining showed that the lining cells were diffusely positive for TTF-1, EMA, CK, CK7, SPA, P63 and Napsin A, and negative for vimentin, synaptophysin and CD56. The epithelial cells also showed a strong membranous staining for β-catenin. In addition, the cells of the stroma were negative for TTF-1, β-catenin and EMA, indicating the lack of epithelial differentiation. CD68
staining highlighted the presence of histiocytes in the tumor. Few cells showed a weak P53 staining. Ki-67 was expressed in less than 2% of all tumor cells (Fig. 3). According to the morphological and immunohistochemical findings, the tumor was consistent with papillary adenoma.

We then examined the EGFR and K-ras gene mutations, and failed to find the mutations in this tumor.

Discussion

Pulmonary papillary adenoma is a very rare tumor. So far, fewer than 25 cases were reported in the English literature [1–16]. In 1980, Spencer et al. reviewed 19 cases of papillary, non-invasive tumors arising from the bronchial epithelium, of which two cases were described as Clara cell origin [2]. In 1982, Fantone et al. used the term papillary adenoma to describe the tumor showing type 2 pneumocytes or Clara cells differentiation, as the presence of cytoplasmic dense granules and whorled lamellar membrane inclusions in the cells [1]. Subsequently, approximately 20 cases were reported [3–16]. Of them, the majority showed type 2 pneumocytes differentiation. Thus, papillary adenoma was believed to be derived from primitive multipotential respiratory epithelium with bidirectional differentiation [3, 7–10].

Histologically, the tumor comprised by the papillary structures with fibrovascular stroma. The lining cells were usually single layer, cuboidal to columnar. In our case, the cells focally showed florid hyperplasia, formed the micropapillary, sheets or irregular cribriform pattern. This might pose a great challenge, especially during the frozen section diagnosis. In addition, it was noted that the numerous nuclear inclusions were present in the epithelial cells, which was commonly present in tumors showing type 2 pneumocytes differentiation [17, 18].

If the tumor showed type 2 pneumocytes differentiation, the cells ultrastructurally contained lamellar bodies and positive for surfactant apoprotein antigen; where staining positively for a Clara cell-specific antigen indicated the differentiation towards Clara cell. The present case was

Fig. 3 Immunohistochemical staining of the tumor. a–c. The lining cells were strongly positive for CK, CK7 and EMA respectively. d. The constant and strong membranous staining for β-catenin was seen in the tumor cells. e. Ki-67 proliferative index was less than 2%. f. The CD68 staining highlighted the presence of histiocytes. g. the cells were diffusely positive for SPA. h. Scattered cells showed a weak staining for P53. i. the cells were also diffusely positive for P63. j. Napsin A was strongly and diffusely expressed in the tumor cells. k. TTF-1 was positively expressed in the lining cells in contrast to the negative expression in the cells of the stroma. l. Vimentin was expressed in the stroma rather than the lining cells.
Pulmonary papillary adenoma is an extremely rare tumor characterized by widespread papillary structures. The reported cases predominately occurred at the periphery, nevertheless, we presented the case located in central portion of the lung, indicating it should still be considered for a central mass.

Conclusion
Pulmonary papillary adenoma is a relatively rare tumor. It is characterized by proliferation of mildly to moderately type II pneumocytes with lepidic pattern along the alveolar walls. The presence of broad papillary structures could also distinguish the papillary adenoma from atypical adenomatous hyperplasia. Moreover, the lack of cellular atypia and mitosis could exclude papillary adenocarcinoma. The gene mutations of EGFR and K-ras could be involved in pulmonary adenocarcinoma, which was well documented [23]. The absence of EGFR and K-ras gene mutations in papillary adenoma might also be helpful for differential diagnosis.

Consent
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this Journal.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
LXY participated in the histopathological evaluation, performed the literature review, acquired photomicrographs and drafted the manuscript. HQ carried out the immunohistochemical stains evaluation. ZY conceived and designed the study. WEH gave the final histopathological diagnosis and revised the manuscript. All the authors read and approved the final manuscript.

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