Clinical Case Report

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Peripheral mucous gland adenoma of the lung with parenchymal involvement and smooth muscle in the stroma

A rare case report and literature review

Xue-Ting Zhang, MM, Man Yang, MM, Xiao-Fang Liu, MD, Xu-Yong Lin, MD*

Abstract

Rationale: Mucous gland adenoma is an extremely rare benign tumor predominately presented in central bronchus. Thus far, only six cases located in the periphery have been reported in English literature.

Patient concerns: Herein, we report a case located in periphery of the lung with parenchymal involvement in a 59-year-old female. Histologically, the tumor appeared as peripheral lobulated and solid mass with the pushing border. The tumor was composed of abundant irregular glands, mucus-filled acini and tubules lined by bland cuboidal to columnar mucus-secreting epithelial cells lacking cellular atypia and mitotic activities. Moreover, the tumor contained fibromyxoid stroma with smooth muscular bundles and prominent lymph follicles, which has not been reported in previous cases.

Diagnosis: Based on the morphological profile and immunohistochemical staining, the tumor was diagnosed as a mucous gland adenoma.

Intervention: The patient then underwent wedge resection in our hospital.

Outcomes: The patient was alive with no tumor recurrence or metastasis within 16 months of follow-up.

Lessons: We report a peculiar case of mucous gland adenoma that occurred in the periphery of the lung and involved the parenchyma. The present case reported the smooth muscular bundles presenting in the stroma, which could broaden the histologic profile of the tumor.

Abbreviations: CEA = carcinoembryonic antigen, CK = cytokeratin, CK20 = cytokeratin20, CK7 = cytokeratin7, EMA = epithelial membrane antigen, PAS = periodic acid-Schiff, SMA = smooth muscle actin, SPA = surfactant apoprotein A, TTF-1 = thyroid transcription factor 1.

Keywords: lung tumor, mucous gland adenoma

1. Introduction

Mucous gland adenoma is an uncommon benign salivary gland-type tumor that histologically comprises mucus-secreting glands resembling normal tracheobronchial glands.[1] With a presumed origin from the submucosal glands of the proximal airways, the majority of mucous gland adenomas present as an exophytic mass within the main lobar or segmental bronchi.[1–4] The patients usually manifested as signs or symptoms of airway obstruction including cough, hemoptysis, dyspnea, wheezing, and obstructive pneumonia.[1,4–6] However, it is extremely rare for this tumor to occur in the periphery of the lung.[7–10] Moreover, to our knowledge, only one previous case involved the parenchyma.[9]

We present a case of pulmonary mucous gland adenoma located in the periphery of the lung with parenchymal involvement in a 59-year-old Chinese woman. Moreover, the present case showed irregular smooth muscular bundles and prominent lymph follicles, which have not been previously reported.

2. Case presentation

2.1. Clinical history

A 59-year-old woman was referred to our hospital for evaluation of an irregular pulmonary mass incidentally detected during a routine radiological examination in another hospital. The patient did not show any signs and the physical examination failed to detect abnormal manifestations. Her laboratory studies were also all within normal parameters. Chest computed tomography revealed that there was an irregular patchy shadow measuring 1.6×0.8 cm in the left pulmonary lower lobe. There were fine burrs and proximal small bronchus truncation at the periphery (Fig. 1). Thus, a diagnosis of malignancy was not excluded. Three months later, the patient again underwent chest computed tomography and the patchy shadow was consistent with the

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Department of Pathology, the First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, Shenyang, China.

* Correspondence: Xu-Yong Lin, Department of Pathology, the First Affiliated Hospital and College of Basic Medical Sciences, China Medical University, Shenyang 110001, China (e-mail: linxuyong@hotmail.com).

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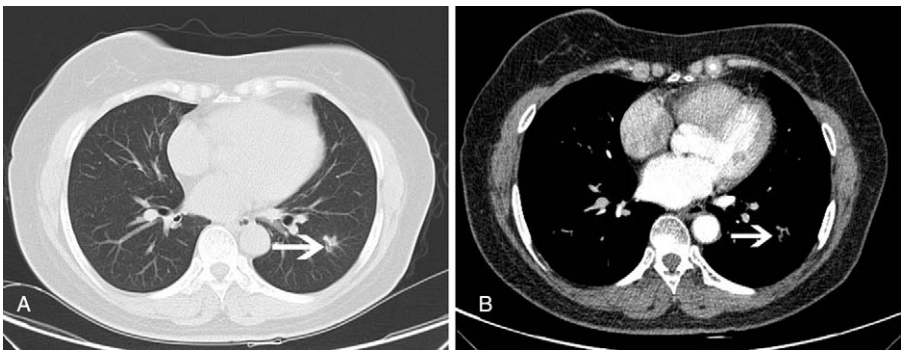

Figure 1. The chest computed tomography manifestation of the tumor. A and B, An irregular patchy shadow can be detected in the left pulmonary lower lobe (arrow). There are fine burrs and proximal small bronchus truncation at the periphery.

previous scan. The patient then underwent wedge resection in our hospital because a low grade malignant salivary type tumor could not be excluded during frozen section diagnosis.

3. Materials and methods

The resected specimens were fixed with 10% neutral-buffered formalin then embedded in paraffin blocks and cut into 4 μm-thickness slides. The slides were deparaffinized with xylene, rehydrated with graded alcohols, and incubated using antibodies against the following: cytokeratin (CK), cytokeratin 7 (CK7), cytokeratin 20 (CK20), vimentin, thyroid transcription factor 1 (TTF-1), surfactant apoprotein A (SPA), Napsin A, synaptophysin, carcinoembryonic antigen (CEA), smooth muscle actin (SMA), p63, 34βE12, CDX2, S-100, epithelial membrane antigen (EMA), p53, Ventana ALK (D5F3) and Ki-67, and 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). Appropriate positive and negative controls were used to exclude false positivity and negativity.

4. Results

Grossly, the resected lung tissue was approximately $9.5 \times 6.4 \times 3.2$ cm in size with an irregular multilobulated and solid mass measuring 1.8×0.8 cm in the central area. The mass appeared to be relatively well circumscribed. However, the capsule was absent at the periphery of the tumor. The cut face was firm and grey-white in color.

Histologically, in the absence of a fibrous capsule, the tumor straightforwardly involved the pulmonary parenchyma. It appeared that the tumor had infiltrated into the normal alveolar tissue, forming a pushing border. The tumor was predominantly composed of irregular glands, acini, and tubules lined by single-layered columnar or cuboidal cells with clear cytoplasm, basally situated nuclei, and fine chromatin. Some tubules contained pink stained periodic acid-Schiff (PAS) positive mucin. Cellular atypia and mitotic activities were absent. The peripheral myoepithelial cells were also not prominent. Moreover, several dilated tracheae were present among the glands.

The stroma of the tumor varied from myxoid changes to dense spindle cells with abundant lymphocytes and plasma cells infiltration. Focally, haphazardly distributed smooth muscular bundles could also be observed. In addition, prominent lymph follicles with marked expansion of the germinal center were distributed in the peripheral area of the tumor, forming the characteristic "cap" pattern (Fig. 2).

4.1. Immunohistochemical staining

Immunohistochemically, the epithelial cells were diffusely positive for CK, CK7, 34βE12, and EMA; focally positive for CEA; and consistently negative for TTF-1, SPA, Napsin A, ALK (D5F3), CDX2, CK20, p53, vimentin, and synaptophysin. P63 and S-100 staining highlighted the myoepithelial cells scattered at the periphery of the glands. The stroma cells including the smooth muscle bundles showed diffuse positivity for SMA. The Ki-67 index was less than 1% (Fig. 3).

4.2. Molecular mutation detection

To further exclude the possibility of adenocarcinoma, we tested for *EGFR* and *KRAS* gene mutations and did not detect any.

Based on the morphological profile and immunohistochemical staining, the tumor was diagnosed as a mucous gland adenoma.

5. Follow-up

The patient was alive with no tumor recurrence or metastasis within 16 months of follow-up.

6. Discussion

Truly benign pulmonary adenoma is relatively uncommon, including papillary adenoma, alveolar adenoma, glandular papilloma, sclerosing pneumocytoma, and salivary gland type adenoma. Of these, it is likely that papillary adenoma, sclerosing pneumocytoma, and alveolar adenoma show type II pneumocytes differentiation.[11–13] Mucous gland adenoma is thought as a salivary gland type tumor, which is presumed to arise from submucosal seromucous glands of the bronchus. Consequently, the majority of the tumors presented as an intraluminal exophytic mass of the proximal airways.[1] To the best of our knowledge, only 6 cases located in the periphery of the lung have been reported in the English literature.[1,6–10] Moreover, among these, only 1 case has been reported to involve the pulmonary parenchyma, rather than be located inside the bronchus.[9] The current case also mainly involved the parenchyma and occurred in the periphery.

Clinically, most of the patients present with signs or symptoms of airway obstruction including cough, hemoptysis, dyspnea,

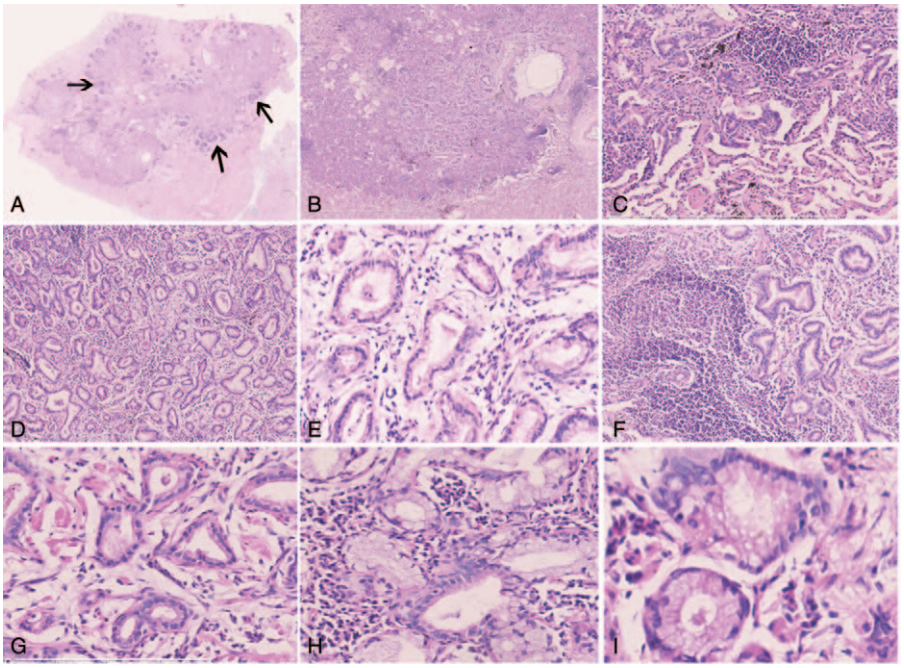

Figure 2. Morphological changes of the tumor. A, Lower magnifications show the mass is solid, multilobulated, and relatively well circumscribed. Prominent lymph follicles can be observed at the periphery (arrow). B, The tumor lacks a fibrous capsule and involves the lung parenchyma with several normal bronchi intermingled in the tumor. C, The normal lung tissue appears to be infiltrated by the tumor due to the lack of a fibrous capsule. D, The tumor is composed predominantly of irregular glands, acini, and cysts containing pink stained mucin. Abundant lymphocytes and plasma cells are in the stroma. E, Focally, the stroma shows obviously myxoid changes. F, A lymph follicle with marked expansion of the germinal center can be seen at the periphery of the tumor. G, Randomly distributed smooth muscle tissue is in the stroma. H, The nuclei of some cells is squeezed because of the presence of cytoplasmic mucin. I, The lining cells are columnar or cuboidal with mild atypia and basally situated nuclei. Mitosis is absent.

wheezing, and obstructive pneumonia because of the predominately central location of the tumor. However, the patient in our case did not show any symptoms because the lesion was located peripherally.

Macroscopically, mucous gland adenoma appeared as a round, smooth, exophytic mass. However, the current case showed a peripheral multilobulated solid tumor outside the bronchial lumen, which was not described in the previous cases.

Histologically, this type of tumor contains glands, acini, tubules, and even dilated mucus-containing cysts. Occasionally, a papillary pattern can be observed.[1] The lining cells vary from cuboidal cells to tall columnar cells with mild cellular atypia. Stratified epithelia are not prominent and papillary proliferation is absent. The tumor often protrudes into the bronchial lumen and is coved by the normal tracheal epithelia. Although these tumors commonly involve the normal tracheal wall, it is extremely rare for them to extend into lung parenchyma.

In our case, the tumor predominately occurred in the lung parenchyma rather than inside the bronchial lumen, which might pose a great diagnostic challenge, especially for frozen section diagnosis. Although the cells in our case appeared to lack cellular atypia and nuclear mitosis, we still could not exclude malignant tumors during the frozen section diagnosis, as the tumor showed parenchymal involvement and alveolar infiltration. The stroma of mucous gland adenoma may be hyalinized or contain dense spindle cells with prominent lymphocytes and plasma cell infiltration, which may be a diagnostic clue. Lee et al[8] reported a case of mucous gland adenoma with prominent fibromyxoid stroma. In addition, we noted focal myxoid in our case, which indicated the varying histologic change in the stroma. The myxoid to sclerosing stroma forming the characteristic "organoid" pattern might be useful for differential diagnosis. Douglas et al[1] reported that the infiltrative lymphocytes were commonly limited to the surface of the tumor. Coincidently, in the current case, prominent lymph follicles with marked expansion of the germinal center could be easily found, and they were mainly distributed in the peripheral areas of the tumor, forming the characteristic "cap" pattern. In addition, randomly distributed smooth muscular bundles were focally found in the stroma, and these have not been described in previous reports. We think the presence of smooth muscular bundles indicates the tumor originated from a submucosal gland of the bronchus, because smooth muscle tissues are also present in the bronchial wall. It also should be noted that in our case, several normal dilated bronchial tissues were distributed among the neoplastic glands. We think this characteristic may be helpful in differential diagnosis.

The immunohistochemical staining of the tumor in our case was well-documented. As the tumor originated from submucosal glands of the airway, the neoplastic cells showed reactivity for CK, EMA, and high molecular weight CK, which is thought to be a useful marker for salivary gland-type tumors of the bronchus,[14] and it did not express the markers of pneumocytes, such as napsin A, surfactant apoprotein antigen, or TTF-1. We then performed staining for CK7 and CK20, and found reactivity for CK7 but not CK20, and p63 and S-100 staining in scattered myoepithelial cells at the periphery of the glands, but not in the stroma cells.

Clinically, mucous gland adenoma is generally believed to be a benign tumor. Nevertheless, some authors believe that it might have malignant potential.[15] In our case, because the tumor straightforwardly involved the lung parenchyma and lacked a

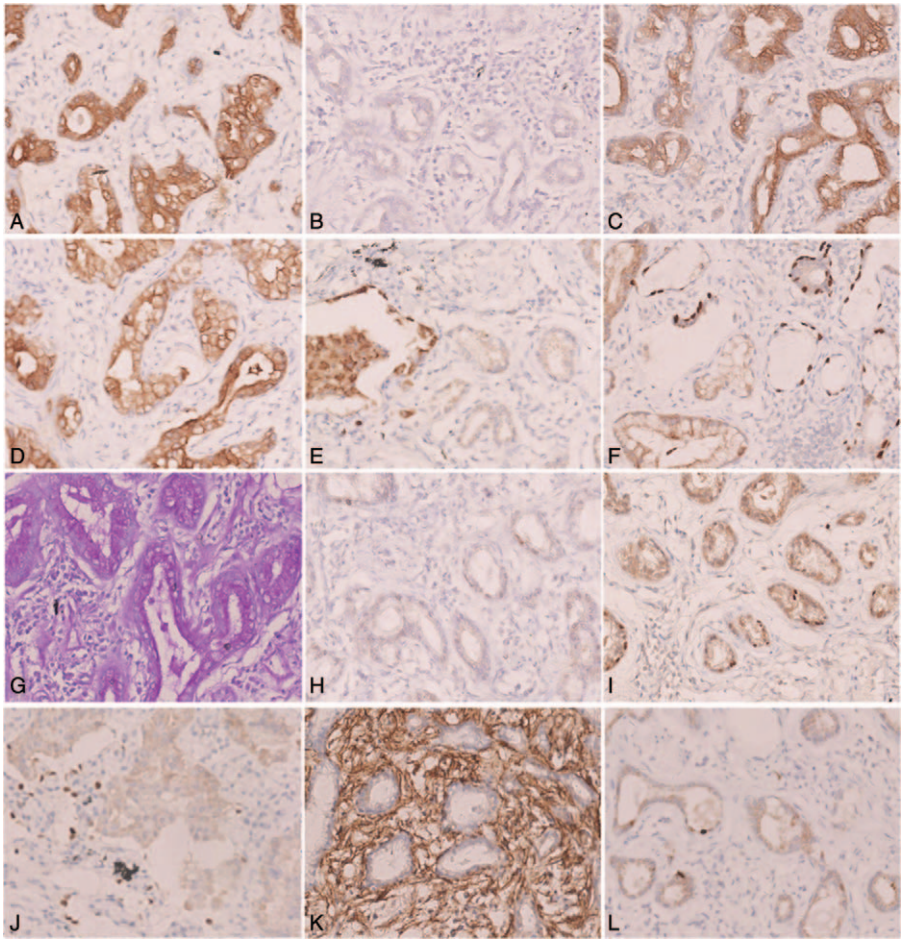

Figure 3. Immunohistochemical staining of the tumor. A, The glands are diffusely positive for CK. B, The glands are negative for CK20. C, D, The tumor is strongly positive for CK7 and 34βE12, respectively. E, The tumor cells are consistently negative for napsin A. F, The p63 staining highlights the presence of peripheral myoepithelial cells. G, The lining cells of the gland are positive for PAS staining. H, Synaptophysin is not expressed in the tumor. I, S-100 also stained the myoepithelial cells. J, TTF-1 is not expressed in the tumor, but is expressed in the normal pneumocytes. K, SMA is diffusely expressed in the stroma rather than the lining cells. L, the Ki-67 proliferative index is less than 1%.

fibrous capsule, a complete excision and a longer follow-up were necessary.

The differential diagnosis of the tumor included pulmonary sclerosing pneumocytoma, papillary adenoma, alveolar adenoma, pleomorphic adenoma, low grade mucoepidermoid carcinoma, and primary mucous adenocarcinoma. Pulmonary sclerosing pneumocytoma, papillary adenoma, and alveolar adenoma are tumors with type II pneumocytes differentiation. Napsin A, surfactant apoprotein antigen, and TTF-1 staining were useful for differential diagnosis. Pleomorphic adenoma is characterized by epithelial and modified myoepithelial elements intermingling with myxoid stroma. The lack of prominent myoepithelial elements could be used to exclude pleomorphic adenoma. Similarly, low grade mucoepidermoid carcinoma was also excluded because of the absence of squamous cells and intermediate type cells. Although the tumor infiltrated the parenchyma, the lack of cellular atypia and mitosis and the presence of myoepithelial cells were helpful to rule out mucous adenocarcinoma.

7. Conclusion

We report a peculiar case of mucous gland adenoma that occurred in the periphery of the lung and involved the parenchyma. Moreover, the tumor contained fibromyxoid stroma with smooth muscular bundles and prominent lymph follicles, which has not been reported in previous cases. This report serves to widen the histologic spectrum of mucous gland adenomas.

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