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Case report

Pneumocytic adenomyoepithelioma: A case providing support for the benignity of this extremely rare pulmonary neoplasm

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ABSTRACT

Pneumocytic adenomyoepithelioma is an extremely rare and poorly understood pulmonary neoplasm, so experience with this tumor is limited. Since the initial case series where the lesion was first proposed as a distinctive entity, only one additional report has been described. We present a case of pneumocytic adenomyoepithelioma with clinical and radiologic data that provide the first long-term evidence of the benignity of this extremely rare pulmonary neoplasm. We also review the available literature surrounding pneumocytic adenomyoepitheliomas. Our case provides important new data on the behavior of this lesion, as imaging studies showed essentially stable or very slowly progressive disease over the course of approximately 9 years. Collectively, this rare and poorly described lesion appears to behave in an indolent or benign fashion, a notion that our case further supports.

1. Introduction

Benign pulmonary neoplasms are a heterogeneous and often incidentally discovered group of disparate lesions with highly variable prognostic implications [1]. Among these lesions is a group of rare neoplasms showing both epithelial and myoepithelial differentiation, most likely arising from minor salivary gland cells within the large airways of the lower respiratory tract, representing the pulmonary analogues of their far more common counterparts in the major salivary glands of the head and neck [2]. Although this family of tumors has been recognized for many years and most have been relatively well characterized, in 2007 Chang et al. described 5 cases of a distinctive and previously unrecognized pulmonary neoplasm showing not only epithelial and myoepithelial differentiation, but also evidence of pneumocytic differentiation, which they termed pneumocytic adenomyoepithelioma [3]. These tumors are extraordinarily rare and their clinical presentation and behavior remain poorly understood. Although it has been suggested that they behave in an indolent or benign fashion, no long-term clinical or radiologic evidence has been reported to support this notion and published data on this lesion are limited. Here, we present a case of pneumocytic adenomyoepithelioma with clinical and radiologic data that provide the first long-term evidence of the benignity of this extremely rare pulmonary neoplasm. We also review the available literature surrounding pneumocytic adenomyoepitheliomas.

2. Case presentation

A 63-year-old woman presented to our pulmonary clinic for evaluation of multiple bilateral pulmonary nodules. She had been recently hospitalized for a transient abdominal illness at an outside hospital, and an abdominal CT at that time detected multiple subcentimeter lesions in the bilateral lower lobes, but was otherwise unremarkable. Her past medical history was notable for hypertension, diabetes, gastroesophageal reflux, thalassemia, and remote and treated pulmonary coccidioidomycosis, which was previously identified by serology without associated x-ray findings at the time of diagnosis. She was a lifelong nonsmoker and did not have any known occupational exposures, but endorsed a passive smoke exposure in her home environment and had a family history of lung cancer.

She had also been seen in our pulmonary clinic eight years prior for incidentally detected bilateral pulmonary nodules. These nodules were initially detected in February 2008 at an outside facility. On our

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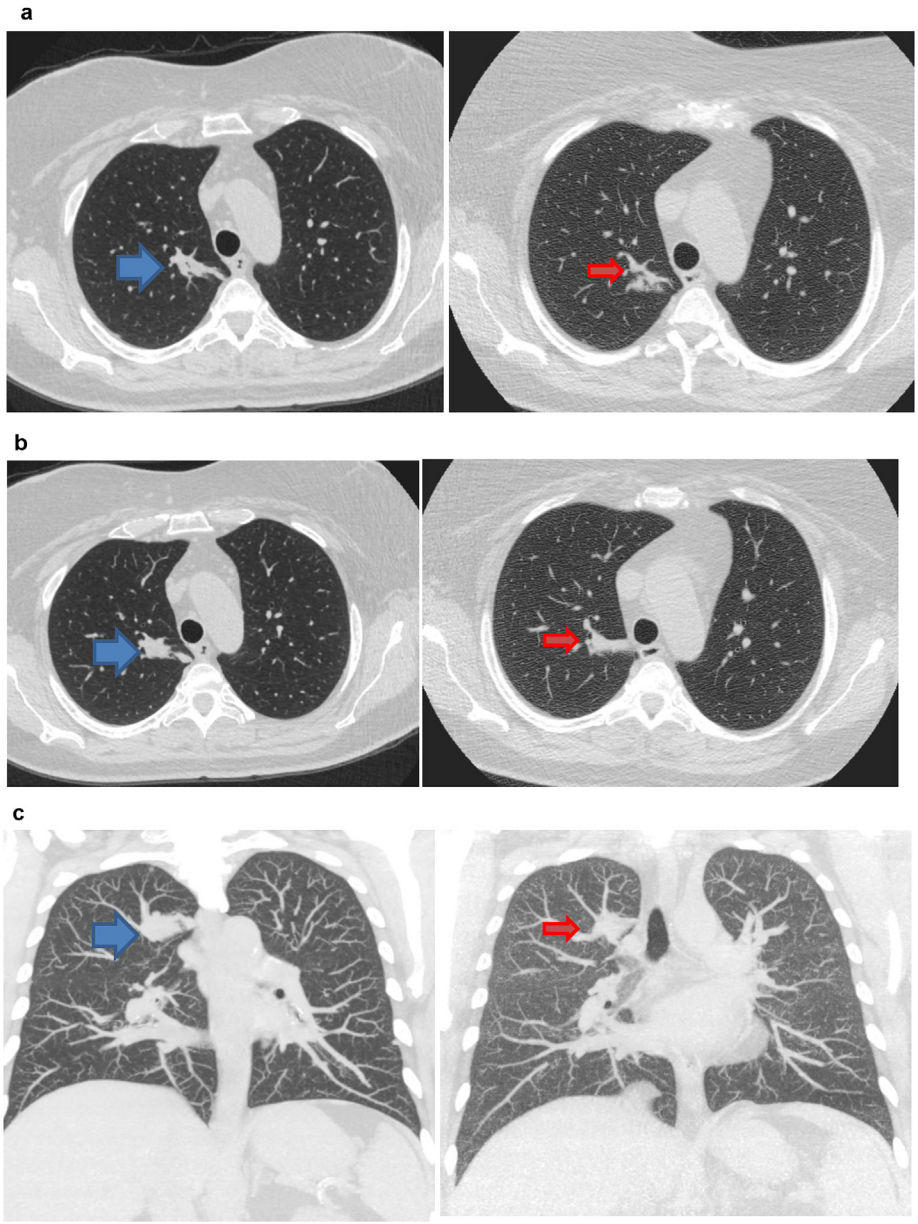

Fig. 1. a. Nodule in the right upper lobe centered around the bronchus (solid blue arrow) on September 2016 slowly growing since December 2008 (red arrow). **b**. Axial CT image slightly inferiorly shows the slowly enlarging nodule on September 2016 (solid blue arrow) as compared with December 2008 (red arrow). **c**. Coronal multiplanar reconstruction CT image shows the slowly enlarging nodule on September 2016 (solid blue arrow) as compared with December 2008 (red arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

assessment in May 2008, a chest CT without contrast showed findings radiologically consistent with several benign intrapulmonary lymph nodes and subpleural lymph nodes in the posterior portion of both lower lobes. Benign-appearing linear fibrosis was also noted in the right upper lobe apical segment medially and in the inferior lingular segment. In the right upper lobe, this abnormality was possibly associated with an endobronchial lesion (Fig. 1a), although this was not well appreciated at the time of initial evaluation and this was only recognized on subsequent review many years later when she presented again. Follow-up imaging 7 months later in 2008 was unchanged and ultimately these findings were felt to be benign without the need for subsequent imaging.

On our imaging assessment in 2016, a CT scan without contrast demonstrated a dominant slowly growing 14 mm nodule apparently centered along a subsegmental branch of the right apical segmental bronchus (Fig. 1b), in the same area where linear fibrosis was noted in 2008. The nodule appeared to be associated with airway obstruction and mucous plugging. Given the extremely slow interval growth and the fact that the lesion was centered on an airway, a typical carcinoid tumor was suspected. In addition, the patient had increasing mediastinal lymphadenopathy, predominantly in the right paratracheal region. Multiple additional subcentimeter pulmonary nodules were noted, many of which appeared to have a centrilobular distribution. Some of these nodules were stable back to 2008 and some had slightly increased in size. Additionally, there were numerous indeterminate nodules within the lungs bilaterally, as well as some new nodules along the fissures, which were new since December 2008.

Multiple prominent mediastinal lymph nodes were also noted as well as multiple indeterminate nodules along the fissures (Fig. 1c). Accordingly, bronchoscopy was pursued.

At the time of bronchoscopy, using the BCUC180F flexible fiberoptic bronchoscope, an endobronchial lesion was visualized in the right

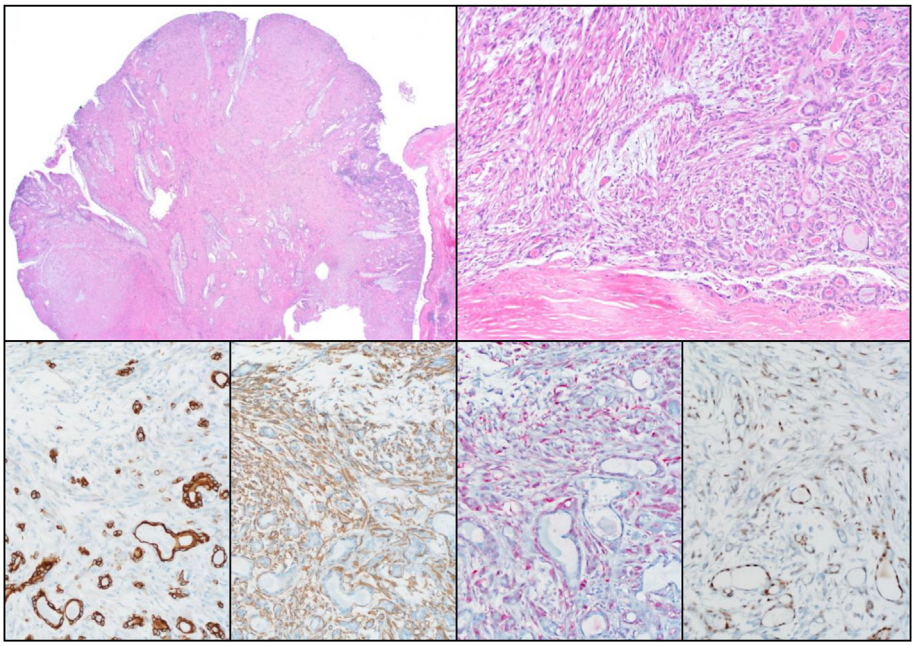

Fig. 2. Representative photomicrographs of the endobronchial tumor. At low magnification (12.5×, upper left; H&E), a polypoid submucosal proliferation projects into the lumen of a small bronchus. At medium magnification (100×, upper right; H&E), small glandular structures, cords, and spindle cells are present in a background of variably fibrotic and myxoid stroma. Two distinctive components are present, with an epithelioid ductal cell component surrounded by a clear to spindled myoepithelial component with focal overgrowth of the latter, more easily seen with immunohistochemistry (all at 100×, bottom row) that shows immunoreactivity of the ductal cell component for pancytokeratin AE1/AE3 (brown cytoplasmic pigment indicates positive reaction) and staining of the surrounding myoepithelial cell component and nearby spindle cells for smooth muscle actin (SMA, brown cytoplasmic) and S-100 protein (red cytoplasmic and nuclear). Both components display immunoreactivity for TTF-1 (brown nuclear). These features are characteristic of pneumocytic adenomyoepithelioma. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

upper lobe, at posterior subsegmental level and aspirated. An endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed using an Olympus EBUS-TBNA needle and sent for routine cytopathologic evaluation from lymph node stations 4R (lower paratracheal), 7 (subcarinal), and 10R (hilar) lymph nodes. The cytology specimen from the endobronchial lesion showed features suspicious for a low-grade spindle cell neoplasm, with small fragments of spindle cells with myxoid changes. The biopsied lymph nodes were negative for malignancy. Fungal and nocardial cultures were negative, as well as PCR testing for coccidioidomycosis. Her PET scan showed multiple hypermetabolic mediastinal and hilar lymph nodes as well as a hypermetabolic submandibular lymph node.

Collectively, this prompted us to pursue right video-assisted thoracoscopy with right upper lobectomy and mediastinal lymph node dissection. She tolerated the procedure well without complications.

Histopathologic evaluation of the lobectomy specimen demonstrated a polypoid and well-circumscribed submucosal proliferation of neoplastic cells projecting into the lumen of a small bronchus (Fig. 2). These tumor cells formed small bilayered glandular structures, cords, and small nests in a background of variably fibrotic and focally myxoid stroma. Cytologically, the neoplastic cells were bland with minimal mitotic activity, and necrosis was absent. Two distinctive components were present, with an epithelioid ductal cell component surrounded by a clear to spindled myoepithelial component. The ductal cell component displayed immunoreactivity for pancytokeratin AE1/AE3, whereas the myoepithelial cell component expressed smooth muscle actin and S-100 protein. Unexpectedly, both components displayed immunoreactivity for TTF-1, but no immunostaining was seen in either component for ALK, desmin, or CD34. These findings did not fulfill criteria for other recognized salivary gland-type neoplasms and were instead most in keeping with the reported features of pneumocytic adenomyoepithelioma.

Interestingly, sections of the lymph nodes showed no evidence of metastasis, but extensive non-necrotizing granulomatous lymphadenitis was identified with morphologic features consistent with sarcoidosis, and Gomori methenamine silver, Ziehl-Neesen acid-fast, and auramine-rhodamine stains were all negative for microorganisms. Sputum cultures grew 1+ normal flora. From the bronchoalveolar lavage, Pneumocystis Smear, Legionella PCR, Legionella Culture, Fungal Smear, Fungal Culture, Nocardia Smear, Coccidioides PCR, and Mycobacterium Culture were all negative. It was felt that her noncaseating granulomatous lymphadenitis likely represented a reactive sarcoidosis, we elected not to treat with steroids. Of the few reported cases of pneumocytic myoepithelioma, associated sarcoidosis has not been reported.

On follow-up imaging 2 months later, her bilateral pulmonary nodules were stable without evidence of interval change and she felt well overall. Pulmonary function tests were also obtained, which were unremarkable.

3. Discussion

Pneumocytic adenomyoepithelioma is an extremely rare and poorly understood pulmonary neoplasm, so experience with this tumor is limited. Since the initial case series where the lesion was first proposed as a distinctive entity, only one additional report has been described [3,4]. The pathogenic drivers are not understood, though TTF-1, one of the characteristic markers for this tumor which is responsible for surfactant production, has been reported as a possible proto-oncogene [5]. The initial report of pneumocytic adenomyoepithelioma by Chang et al. encompassed cases from five separate hospitals, and only 3 had available clinical data regarding their presentation [3]. Of these 3 patients, 2 presented with incidentally discovered lung nodules and the third presented with pleuritic chest pain. In a subsequent case reported by Krishnamurthy et al. the patient presented with a history of recurrent submandibular pleomorphic adenoma along with a lung mass, but a careful review of this report leaves the final diagnosis of pneumocytic adenomyoepithelioma in question, as the lung lesion was incompletely immunophenotyped (including no interrogation of TTF-1 expression). Thus, the possibility of metastatic pleomorphic adenoma was not acknowledged, which could show a very similar if not identical morphologic appearance (but no TTF-1 expression) and would probably be more likely in that setting. Of the patients reported by Chang et al. all of these patients were female between 52 and 62 years of age and lesions ranging from 0.8–2.6 cm in size. In 4 of these 5 cases, there was no prior history of malignancy and there were only solitary pulmonary lesions (2 in the right upper lobe and 2 in the right middle lobe). In one of the other cases, the patient had a history of ameloblastoma of the jaw and had bilateral lung nodules on initial evaluation, of which the largest lesion was resected from the left upper lobe.

The clinical course of the 5 available patients by Chang et al. was largely favorable. In 4 of the patients, there was no evidence of

recurrence 13–78 months later, and in the patient with multiple nodules, the other lung nodules did not change in appearance on repeat imaging after 5 months. Our case provides important new data on the behavior of this lesion, as imaging studies showed essentially stable or very slowly progressive disease over the course of approximately 9 years. Collectively, this rare and poorly described lesion appears to behave in an indolent or benign fashion, a notion that our case further supports. However, data on this tumor remains limited, and long-term follow-up is still warranted. The significance of granulomatous lymphadenitis in our case and its relationship to her tumor was unclear. Although it is possible that this represented a secondary sarcoid-like reaction to the tumor, this has not been reported with salivary gland tumors, and it is equally plausible or perhaps more likely that this represented the coincidental presence of an entirely separate and unrelated systemic granulomatous inflammatory disorder such as sarcoidosis.

In summary, our case provides additional evidence supporting the benignity of pneumocytic adenomyoepithelioma. Although this tumor is extremely rare, it should be included in the differential diagnosis of endobronchial tumors. The underlying pathogenic drivers behind this unique tumor have yet to be elucidated, and future studies are needed in order to better characterize and understand this unusual pulmonary tumor.

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