Pulmonary Adenofibroma: A Rare Presentation of a Benign Lung Nodule – A Case Report

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Pulmonary adenofibroma is a rare primary benign mesenchymal lung tumor that has been seldom reported in the currently available literature. Unusual lung tumors constitute a broad range of histological types that unsurprisingly have a wide spectrum of imaging appearances and clinical presentations. Herein, we report a 60-year-old male who complained of low-grade fever and general malaise, and was tentatively diagnosed as having acute hepatitis and pleural effusion, accompanied with the incidental finding of pulmonary nodule on chest computed tomography (CT), which was ultimately diagnosed as pulmonary adenofibroma. The initially challenging frozen section reading raised the suspicion of malignancy, but ultimately the diagnosis was revised to benign pulmonary adenofibroma. This case can increase our awareness of this extremely rare benign lesion in the future. (Thorac Med 2014; 29: 152-159)

Key words: adenofibroma, benign pulmonary tumor, frozen section, pulmonary nodule

Introduction

Primary mesenchymal tumors of the lung are rare, with an incidence of less than 1% of all primary lung tumors according to the current literature [1], and often resemble their soft tissue counterparts. Adenofibroma is a mixed biphasic tumor with glandular and fibrous proliferation. Most adenofibromas have been reported in the ovary and breast. Pulmonary adenofibroma is an even rarer type of benign soft-tissue tumor that comprises epithelial and stromal components, both of which are histologically benign, and resembles adenofibroma of the female genital tract. To the best of our knowledge, only a few cases of pulmonary adenofibroma have been formally reported to date [2-3]. Because of the rarity and incidental finding of this tumor with its unusual histologic appearance, we face a diagnostic challenge in distinguishing this pulmonary nodule from malignancy. Herein, we report the case of a middle-aged male who initially presented with dyspnea on exertion as well as cough-related pain in

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the right subcostal region. During a later imaging survey for differential diagnosis during the patient’s hospitalization, we incidentally noted the abnormal chest CT finding of a pulmonary nodule that was ultimately pathologically diagnosed as pulmonary adenofibroma. Clinical suspicion in this case increased our awareness of this rare benign lesion.

Case Report

A 60-year-old male presented with the complaint of low-grade fever with general malaise and poor appetite for the past 1 week, associated with cough-related pain in the right subcostal region. The patient had been a social cigarette smoker for less than 5 years as a teenager and had quit smoking decades earlier. He had never experienced such discomfort before this episode, and he sought medical assistance at another hospital due to intractable cough-related chest pain with a persistent low-grade fever. He was referred to our hospital for further evaluation and management with the following initial vital signs: body temperature, 37.6°C; heart rate, 82 beats/min; respiratory rate, 18 breaths/min; and blood pressure, 120/72 mmHg. His illness history showed that he had initially suffered from poor appetite and easy satiety with normal defecation approximately 5 days earlier, followed by a low-grade fever and diarrhea along with dry cough for 2 days and eventual right subcostal region pain. His pain was dull in nature, but included intermittent sharp sensations without obvious radiation that worsened with deep breathing. There was no evidence of hereditary disease in his extended family or in the traceable recent cluster and travel history.

Physical examinations revealed the following: clear breathing sounds in the bilateral lung fields, but a rough, scratchy friction rub with basal crackles in the right lower chest, as well as local tenderness without rebounding pain at the right upper abdominal quadrant. In addition, normal active bowel sounds and a lack of skin discoloration, edematous changes in the lower extremities, and palpable lymph nodes were noted.

Laboratory examinations revealed a white blood cell (WBC) count of 5700/mm³ with a predominant neutrophil count (87%), and abnormal liver function with glutamate oxaloacetate transaminase (GOT)/glutamic pyruvic transaminase (GPT) of 311/181 U/L, and an international normalized ratio of 1.19. Urine and stool analyses revealed no specific finding.

No prior imaging studies were available for comparison. Chest radiography at presentation showed right costophrenic angle blunting, apical pleural thickening, prominent bilateral hilar vascular shadows with pulmonary vascular redistribution, and bilateral lower lung field reticulonodular infiltration (Figure 1). We performed an echocardiogram as well as chest and abdominal ultrasounds, and then a diagnostic thoracocentesis followed by closed drainage of the patient’s pleural effusion. No space-occupying lesion of the liver parenchyma or biliary tract dilatation were found. We observed preserved left ventricular systolic function with an estimated left ventricular ejection fraction of 68% in the absence of cardiac chamber dilatation. Besides, mild pulmonary regurgitation, moderate mitral valve regurgitation and mild tricuspid valve regurgitation with an estimated pulmonary artery systolic pressure of approximately 37 mmHg were mentioned in the echocardiogram report. The pleural fluid was found to be exudative in nature with a predominance of lymphocytes, (lactate dehydrogenase: 488 U/
L; protein: 3.2 g/dL; sugar: 98 mg/dL; WBC: 2140/mm$^3$; RBC: 10000/mm$^3$; differential neutrophil/lymphocyte/monocyte count ratio: 1/92/7). Hepatitis markers, including hepatitis A IgM antibody, hepatitis B surface antigen, antibody to hepatitis B surface antigen and IgM antibody to hepatitis C virus were screened with negative findings.

Under supportive care, the patient’s constitutional symptoms greatly improved with the exception of a mild cough. We then performed sputum analysis and culture with no positive findings. We repeated the laboratory examination, and a series of liver function tests with GOT/GPT revealed a decreasing trend toward normal serum values. The follow-up CXR revealed a sharp costophrenic angle after removing the pigtail drainage. In this situation, our tentative diagnosis became acute hepatitis with reactive right-side pleural effusion, which was suspected to be related to viral infection; the differential diagnosis was acute hepatitis combined with a lymphocyte-predominant exudative pleural effusion of unknown etiology, which was suspected to be related to pulmonary tuberculosis with pleurisy or to malignancy. Chest CT scan revealed a 1-cm nodule with a well-defined and smooth margin at the right upper lobe (Figure 2A) without mediastinal lymph node enlargement, and focal ground glass opacity at the right lower lung field with minimal atelectasis (Figure 2B), likely due to the previous pleural effusion. We could not confidently define this incidental finding of a nodule as a solitary pulmonary nodule (SPN) due to the exis-
ence of the not fully explained pleural effusion. We assessed the probability of malignancy, the surgical risk and the patient’s preference, and then consulted the chest surgeon for thoracoscopic right upper lobe nodule wedge resection and pleural biopsy.

After discussing the possible etiology of the right upper lobe nodule with the patient, he agreed to go ahead with the diagnostic surgical intervention. The frozen section of the excisional biopsy of the wedge resection was originally reported to comprise a gray-white tissue, measuring $1.1 \times 1.0 \times 0.3$ cm, that was indicative of adenocarcinoma, as it contained clusters of moderately differentiated neoplastic cells in acinar and focal papillary patterns. Later, the final pathological report was revised to indicate a benign adenofibrous lesion, because a further large specimen had shown well-circumscribed features without local tissue invasion. The submitted wedge resection specimen consisted of 1 piece of tissue measuring $5.3 \times 2.2 \times 1.5$ cm in size with a white tumor that measured $1.1 \times 0.8 \times 0.7$ cm, and was 0.7 cm distant from the cut end. Hematoxylin and eosin (H&E) stain of the tumor revealed a well circumscribed but not encapsulated lesion composed of a proliferation of bland-looking epithelial cells and stroma in cleft-like and glandular patterns (Figure 3A). No mitoses, necrosis or cytologic atypia was observed (Figure 3B). The immunohistochemistry (IHC) stain of the lining epithelial cells was positive for thyroid transcription factor-1 (TTF-1) and high molecular weight cytokeratin (HMCK), and focally positive for p63. The IHC stain of the tumor cells was negative for cytokeratin 5/6 (CK 5/6), and the IHC stain of the stroma was positive for desmin and smooth muscle actin (SMA) (Figure 3C), consistent with the presence of smooth muscles (Figure 3D). The lesion met the diagnostic criteria of pulmonary adenofibroma with a smooth muscle component. In addition, the pleura excisional biopsy comprised 5 pieces of gray-white soft tissue, measuring up to $2.1 \times 1.2 \times 0.2$ cm, indicating mesothelial cell hyperplasia, acute and chronic inflammatory cell infiltration and fibrosis. Granuloma was not present. Neither mycobacteria nor fungi could be identified with the acid-fast and PAS stains. The TTF-1 stain result was negative and there was no evidence of malignancy in the examined sections.
Discussion

Pulmonary nodules [4-7] are an important problem in our daily practice. Estimates of their frequency range from 0.2% in older studies using chest radiography to approximately 40-60% in lung cancer screening trials using low-dose CT [8-11]. Possible causes of pulmonary nodules include many benign diseases, but the primary concern is bronchogenic carcinoma. Unusual lung tumors constitute a broad range of histological types that unsurprisingly have a spectrum of imaging appearances [12-13].

Pulmonary adenofibroma is a very rare benign tumor that appears on chest radiograph as a SPN, a well-defined soft-tissue nodule that is detected incidentally in middle-aged adults. The most common causes of benign SPN were healed or nonspecific granulomas, which account for 25% of all benign nodules. Another 15% of benign nodules were caused by active granulomatous infections, including tuberculosis, coccidioidomycosis, histoplasmosis, cryptococcosis, and aspergillosis. Hamartomas comprised an additional 15% of benign lesions. Less common miscellaneous causes of benign nodules included nonspecific inflammation and fibrosis, lung abscesses, round pneumonia, round atelectasis, bronchogenic cysts, healed pulmonary infarcts, focal hemorrhages, hemangiomas, and arteriovenous malformations. The border characteristics of a nodule in CT imaging can also be used to help estimate the probability of malignancy. Nodules with irregular, lobulated, or spiculated borders are associated with a progressively higher probability of malignancy than those with a smooth border [14]. Furthermore, nodules with a purely ground-glass or semisolid appearance have a higher probability of malignancy than purely solid lesions [15]. Benign calcification patterns (diffuse, central, laminated, or popcorn patterns) and intranodular fat density are associated with an extremely low probability of malignancy. Stippled and eccentric calcification patterns do not exclude malignancy, and thus further work-ups are required.

Adenofibroma is a mixed biphasic benign tumor with glandular and fibrous proliferation. Most adenofibromas have been reported in the ovary and breast. Even rarer cases of uterine endometrium adenofibroma [16], uterine cervical
adenofibroma [17], paratesticular adenofibroma [18], biliary adenofibroma of the liver, and pulmonary adenofibroma have been formally reported, but to the best of our knowledge, these are extremely rare in the current literature. To make the diagnosis of pulmonary adenofibroma, there should be a histological finding of dominant pseudopapillae covered by bland cuboidal epithelium and bland spindle cell-rich sclerotic stroma, as well as findings of positive cytokeratin and TTF-1 epithelium stains and negative cytokeratin and S-100 stroma stains.

With regard to our patient, the initial report from the frozen section obtained during intraoperative sampling was adenocarcinoma, moderately differentiated; however, the final report was revised after the larger specimen was sampled and the examination was completed. We attempted to determine the possible cause of such an extreme difference, and concluded that careful specimen sampling with an adequate margin from the cut end and delicate high-power field reading with a better resolution are crucial when diagnosing this rare benign tumor.

Pulmonary nodules are frequently first diagnosed by frozen section, immediately followed by lobectomy or other procedures. The frozen section diagnoses of pulmonary nodules can be difficult, since inflammatory and fibrotic lesions can be confused with malignancies, thus creating intraoperative dilemmas for pathologists and thoracic surgeons [19]. The discrepancies between the frozen section and the permanent section were mainly due to the interpretation error, and sampling errors and technical artifacts, and partly due to a lack of interdepartmental communication. The causes of the false positive diagnosis were the interpretation error and the unavoidable freezing artifacts. The sampling error was the main reason for the false negative diagnosis. In a few cases, the diagnosis has been deferred to the permanent section, mainly due to a lack of adequate clinical information and inadequate material. In our case, delicate structures such as ciliated epithelial cells devoid of cytologic atypia, which were not definitively observed in the frozen section due to freezing artifacts, were identified in the permanent section, and thus the final pathological report was revised to a benign adenofibrous lesion.

In summary, advanced imaging modalities combined with clinical information and histopathological findings assisted by IHC staining are still needed for the definite diagnosis. Adequate preoperatively diagnostic imaging-guided or intraoperative sampling with careful readings may facilitate diagnoses and decisions regarding whether to perform major surgery. Finally, pulmonary adenofibroma should be taken into consideration when encountering a lung tumor that comprises bland stromal and epithelial cells in the microscopic examination, and should be carefully distinguished from pulmonary harmartoma, leiomyoma, pulmonary blastoma, intrapulmonary solitary fibrous tumor, and metastases from soft tissue and visceral sarcoma.

References


肺腺纖維瘤：罕見良性肺部結節－病例報導

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肺腺纖維瘤是一種非常罕見的良性間葉細胞瘤，在目前的文獻資料庫裡只有極少數的臨床病例報告。不常見的肺部腫瘤由各種不同組織型態的細胞所構成，也會有不同的影像學表徵以及臨床表現。我們報導了一位六十歲男性以輕微發燒及全身倦怠就診，初步理學檢查及配合實驗室和影像學診斷為急性肝炎及右側肋膜積液，肋膜積液抽吸檢查顯示淋巴細胞為主的滲出液；進一步安排胸部電腦斷層檢查發現右上肺一個邊緣清楚的結節。經手術取得檢體冰凍切片初步報告為中度分化的肺腺癌，然而最終病理報告修正為良性腫瘤。藉由此病例報告讓臨床醫師增加對此良性肺腫瘤的了解。(胸腔醫學 2014; 29: 152-159)

關鍵詞：腺纖維瘤，良性肺腫瘤，冷凍病理切片，肺結節