Case Report

Mucinous Adenocarcinoma of the Lung Diagnosed by Radial Endobronchial Ultrasound-guided Bronchoscopic Cryobiopsy and Presenting as Interstitial Lung Disease in a Patient with Systemic Sclerosis

CME Credits

Yan-Ting Lin[1], Chiung-Hung Lin[2], Shao-Chung Wang[3,4], Yun-Ju Huang[5], Ren-Chin Wu[6], Chung-Shu Lee[2,7], Chih-Hao Chang[2,7]*

[1]Department of Internal Medicine, Chang Gung Memorial Hospital, School of Medicine, Chang Gung University, Taipei, Taiwan, [2]Department of Thoracic Medicine, Chang Gung Memorial Hospital, School of Medicine, Chang Gung University, Taipei, Taiwan, [3]Department of Medical Imaging and Intervention, New Taipei Municipal Tucheng Hospital, New Taipei, Taiwan, [4]Department of Medical Imaging and Intervention, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan, [5]Department of Allergy, Immunology, Rheumatology, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [6]Department of Anatomic Pathology, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [7]Department of Pulmonary and Critical Care Medicine, New Taipei Municipal Tucheng Hospital, New Taipei, Taiwan

Abstract

We report a patient with systemic sclerosis who was diagnosed with advanced-stage mucinous adenocarcinoma of the lungs. The clinical presentation, imaging findings, pathological results, and molecular diagnoses are presented. A 64-year-old woman with systemic sclerosis was administered prednisolone and hydroxychloroquine sulfate to control her disease. High-resolution computed tomography (HRCT) revealed an interstitial pattern in both lungs during annual imaging. Connective tissue disease-associated interstitial lung disease (CTD-ILD) was diagnosed using blood tests, pulmonary function tests, and imaging findings. One year later, the patient underwent follow-up chest HRCT, which showed progressive lung disease. The patient underwent endobronchial ultrasound (EBUS)-guided transbronchial lung cryobiopsy and computed tomography-guided biopsy for a pathological diagnosis. The pathology reports of bilateral lungs disclosed mucinous adenocarcinoma. After tumor staging and mutation testing, the patient received chemotherapy with pemetrexed and cisplatin. The bilateral lung lesions subsided after four cycles of first-line chemotherapy. Patients with CTD and lung involvement may be diagnosed with CTD-ILD. Although histopathological results are not mandatory for ILD diagnosis, EBUS-guided transbronchial lung biopsy or lung cryobiopsy should be considered when ILD has atypical or unexplained features.

Keywords: Connective tissue disease, endobronchial ultrasound, transbronchial lung cryobiopsy

Introduction

Connective tissue disease-associated interstitial lung disease (CTD-ILD) is not rare and presents in patients with systemic sclerosis, inflammatory myositis, rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus.[1] The diagnosis of CTD-ILD is usually made by clinical presentation, serologic testing, high-resolution computed tomography (HRCT), and pulmonary function tests. However, lung biopsy is not mandatory for the diagnosis of CTD-ILD.[2] We present a case of systemic sclerosis with unexpected findings after transbronchial lung cryobiopsy (TBLC).

Received: 30-05-2022 **Revised:** 10-07-2022 **Accepted:** 09-08-2022 **Available Online:** 07-10-2022

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jmut

DOI: 10.4103/jmu.jmu_56_22

Case Report

A 64-year-old woman was diagnosed with systemic sclerosis with an initial presentation of cutaneous sclerosis 3 years ago. She received prednisolone and hydroxychloroquine sulfate to control her disease. The patient had never smoked. She underwent an examination by chest HRCT due to a

Address for correspondence: Dr. Chih-Hao Chang, No. 5, Fuxing Street, Lin-Kou Chang Gung Memorial Hospital, Guishan, Taoyuan 333, Taiwan.
E-mail: ma7384@cgmh.org.tw

How to cite this article: Lin YT, Lin CH, Wang SC, Huang YJ, Wu RC, Lee CS, *et al*. Mucinous adenocarcinoma of the lung diagnosed by radial endobronchial ultrasound-guided bronchoscopic cryobiopsy and presenting as interstitial lung disease in a patient with systemic sclerosis. J Med Ultrasound 2023;31:314-7.

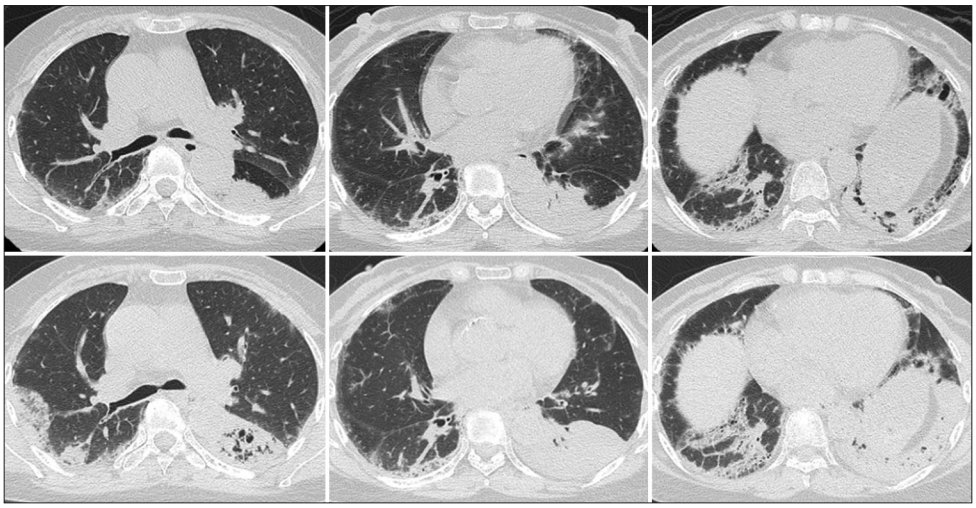

Figure 1: Transverse thin-section lung computed tomography at the level of the main bronchi, left atrium, and lower lung zone from left to right. The initial scan (top row) showed predominantly subpleural and lower lobe reticulation and ground-glass opacities with immediate subpleural sparing in the right lung. Consolidations are seen in the dependent part of the left lower lobe and traction bronchiectasis in the anterior and posterior basal left lower lungs. Follow-up scans (bottom row) 1 year later showed an increase in the extent of reticulation and consolidation. New peripheral consolidations with surrounding ground-glass opacities in the posterior right upper lobe and progressive consolidations in the left lower lobe were biopsy-proven mucinous adenocarcinomas

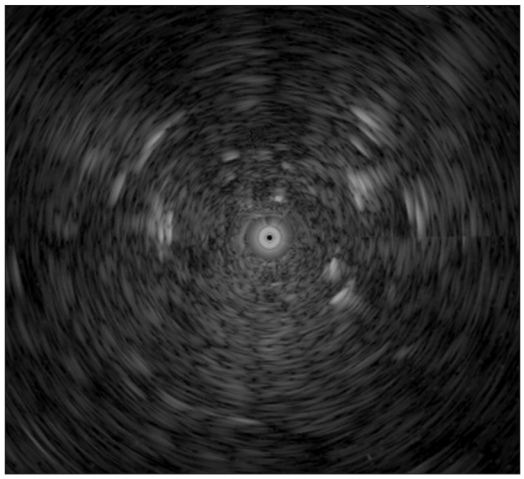

Figure 2: The radial probe EBUS showed heterogeneous echogenicity along with linear-discrete air bronchogram. The probe was within the lung lesion over the left lower lung. EBUS: Endobronchial ultrasound

chronic cough for months. The HRCT showed subpleural, peribronchovascular interstitial thickening, and ground-glass opacities in the bilateral lungs. One year later, the followed-up HRCT revealed progressive consolidations in the bilateral lungs [Figure 1].

The patient underwent endobronchial ultrasound (EBUS)-guided TBLC over the left lower lung. Radial probe EBUS showed heterogeneous echogenicity along with a linear-discrete air bronchogram, and the probe was within the lung lesion over the left lower lung [Figure 2]. The pathologic report of the left lower lung through bronchoscopic cryobiopsy showed wild-type mucinous adenocarcinoma [Figure 3]. The computed tomography (CT)-guided biopsy of her right lower lung was performed, and the pathology report was also mucinous adenocarcinoma. Brain magnetic resonance imaging and positron emission tomography revealed no distant metastasis. The patient was diagnosed with Stage IV mucinous adenocarcinoma. Molecular testing for epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase, and programmed death ligand-1 expression were negative [Figure 4]. She received four cycles of first-line chemotherapy with pemetrexed and cisplatin. After treatment, the follow-up CT scan showed disease in partial remission with a decrease in the size of the right lower lung lesion and the left lower lung solid component subsided.

The present study was approved by the Institutional Review Board of Chang Gung Memorial Foundation (IRB No.: 202100222B0). Owing to the retrospective study design, informed consent was not required and the Institutional Review Board approved the waiver in our institution.

Discussion and Conclusions

We demonstrated that lung biopsy might be indicated in patients with CTD-ILD when lung lesions progressively deteriorate. Mucinous adenocarcinoma lesions vary on CT scans, and CT findings are classified as solitary or pneumonic type.[3] The solid mass had a clear margin on CT. The pneumonic lesion showed alveolar consolidations, which are often confused with pneumonia. Mucinous adenocarcinomas originate from mucus-containing cells presenting a goblet or columnar cell morphology with intracytoplasmic mucin. The involved alveoli are typically filled with mucin.

Previous studies showed that 3.5% to 7% of patients with pulmonary mucinous adenocarcinoma presented with EGFR mutations.[4,5] Kirsten rat sarcoma viral oncogene homolog amino acid changes were the most frequent driver

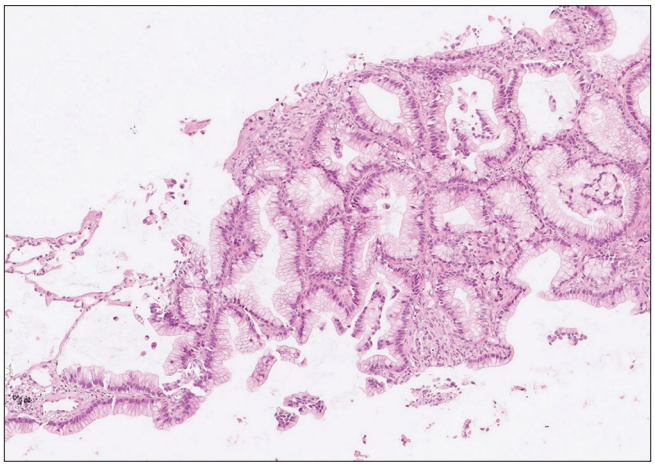

Figure 3: Left lower lung tumor cells with mucinous cytoplasm growing along the alveolar wall (lepidic pattern, and left side) or in an acinar pattern (right side) (hematoxylin and eosin stain, ×20)

mutations (up to 63%).[6] As primary pulmonary mucinous adenocarcinoma is uncommon, survival rate data are relatively limited. The 5-year survival rate for patients with mucinous and nonmucinous adenocarcinomas showed no significant difference.[6]

CTD-ILD has various features of interstitial lung abnormalities on HRCT.[7] A previous study showed that 48% of patients with rheumatoid arthritis and ILD had radiologic progression.[8] Another study reported that 23% of patients with systemic sclerosis had progression of ILD.[9] Mycophenolate, cyclophosphamide, or nintedanib is suggested to treat systemic sclerosis-associated ILD.

Some authors suggest that surgical lung biopsy is seldom used and rarely provides additional information on CTD-ILD.[10] Even in cases of disease progression, surgical lung biopsy is usually not recommended. The current official clinical practice guideline has no recommendation for or against lung cryobiopsy for the diagnosis of idiopathic pulmonary fibrosis.[11] Observational studies have reported that lung cancer risk increased in patients with ILD[12,13] and CTD-ILD.[14,15]

To exclude malignancy in ILD, transbronchial forceps biopsy using endobronchial ultrasonography is acceptable.[16] However, the forceps biopsy specimen is relatively small to offer further information for ILD diagnosis. A randomized controlled trial showed that ILD diagnoses based on histopathological results from transbronchial cryobiopsy are reliable.[17] We suggest that lung cryobiopsy can be performed when ILD has atypical or unexplained features. Although the risks of lung cryobiopsy are acceptable,[18-20] an increased risk of bleeding is inevitable compared to transbronchial forceps biopsy.[21-23] Therefore, EBUS-guided bronchoscopic cryobiopsy should be performed by experienced bronchoscopists.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

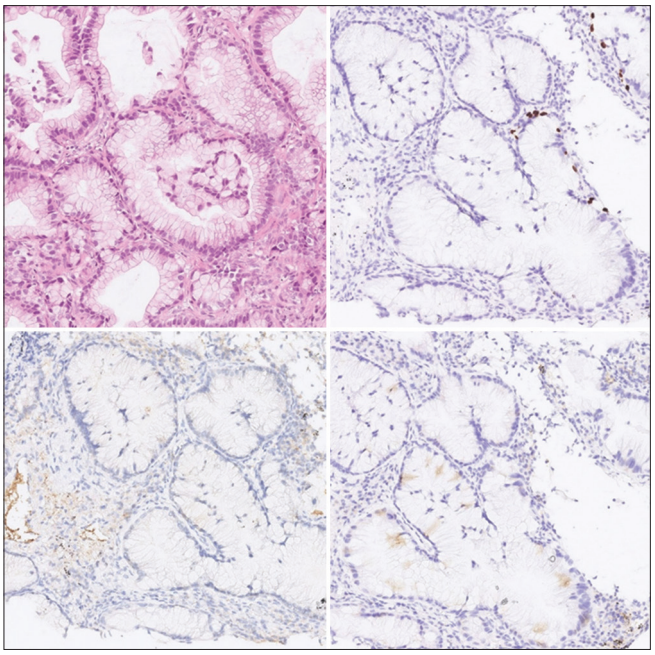

Figure 4: The left lower lung tumor cells showed mild-to-moderate nuclear atypia and abundant mucinous cytoplasm (top left). Tumor cells were negative for TTF1 immunostaining, whereas the residual alveolar epithelial cells were positive (top right). Tumor cells were negative for anaplastic lymphoma kinase (bottom left) and programmed death ligand-1 expression (bottom right) (×40). TTF1: Thyroid transcription factor-1

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, du Bois RM, *et al.* An official European Respiratory Society/American Thoracic Society research statement: Interstitial pneumonia with autoimmune features. Eur Respir J 2015;46:976-87.
2. Vij R, Strek ME. Diagnosis and treatment of connective tissue disease-associated interstitial lung disease. Chest 2013;143:814-24.
3. Watanabe H, Saito H, Yokose T, Sakuma Y, Murakami S, Kondo T, *et al.* Relation between thin-section computed tomography and clinical findings of mucinous adenocarcinoma. Ann Thorac Surg 2015;99:975-81.
4. Sun F, Wang P, Zheng Y, Jia W, Liu F, Xiao W, *et al.* Diagnosis, clinicopathological characteristics and prognosis of pulmonary mucinous adenocarcinoma. Oncol Lett 2018;15:489-94.
5. Boland JM, Maleszewski JJ, Wampfler JA, Voss JS, Kipp BR, Yang P, *et al.* Pulmonary invasive mucinous adenocarcinoma and mixed invasive mucinous/nonmucinous adenocarcinoma-a clinicopathological and molecular genetic study with survival analysis. Hum Pathol 2018;71:8-19.
6. Shim HS, Kenudson M, Zheng Z, Liebers M, Cha YJ, Hoang Ho Q, *et al.* Unique genetic and survival characteristics of invasive mucinous adenocarcinoma of the lung. J Thorac Oncol 2015;10:1156-62.

7. Yoo H, Hino T, Han J, Franks TJ, Im Y, Hatabu H, *et al.* Connective tissue disease-related interstitial lung disease (CTD-ILD) and interstitial lung abnormality (ILA): Evolving concept of CT findings, pathology and management. Eur J Radiol Open 2021;8:100311.
8. Kawano-Dourado L, Doyle TJ, Bonfiglioli K, Sawamura MV, Nakagawa RH, Arimura FE, *et al.* Baseline characteristics and progression of a spectrum of interstitial lung abnormalities and disease in rheumatoid arthritis. Chest 2020;158:1546-54.
9. Wu W, Jordan S, Becker MO, Dobrota R, Maurer B, Fretheim H, *et al.* Prediction of progression of interstitial lung disease in patients with systemic sclerosis: The SPAR model. Ann Rheum Dis 2018;77:1326-32.
10. Oliveira RP, Ribeiro R, Melo L, Grima B, Oliveira S, Alves JD. Connective tissue disease-associated interstitial lung disease. Pulmonology 2022;28:113-8.
11. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, *et al.* Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2018;198:e44-68.
12. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. Am J Respir Crit Care Med 2000;161:5-8.
13. Ozawa Y, Suda T, Naito T, Enomoto N, Hashimoto D, Fujisawa T, *et al.* Cumulative incidence of and predictive factors for lung cancer in IPF. Respirology 2009;14:723-8.
14. Onishi A, Sugiyama D, Kumagai S, Morinobu A. Cancer incidence in systemic sclerosis: Meta-analysis of population-based cohort studies. Arthritis Rheum 2013;65:1913-21.
15. Adzić TN, Pesut DP, Nagorni-Obradović LM, Stojsić JM, Vasiljević MD, Bouros D. Clinical features of lung cancer in patients with connective tissue diseases: A 10-year hospital based study. Respir Med 2008;102:620-4.
16. Ito T, Kimura T, Kataoka K, Okachi S, Wakahara K, Hashimoto N, *et al.* A pilot study of transbronchial biopsy using endobronchial ultrasonography with a guide sheath in the diagnosis of peripheral pulmonary lesions in patients with interstitial lung disease. Diagnostics (Basel) 2021;11:2269.
17. Troy LK, Grainge C, Corte TJ, Williamson JP, Vallely MP, Cooper WA, *et al.* Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): A prospective, comparative study. Lancet Respir Med 2020;8:171-81.
18. Troy LK, Hetzel J. Lung cryobiopsy and interstitial lung disease: What is its role in the era of multidisciplinary meetings and antifibrotics? Respirology 2020;25:987-96.
19. Cho R, Zamora F, Gibson H, Dincer HE. Transbronchial lung cryobiopsy in the diagnosis of interstitial lung disease: A retrospective single-center experience. J Bronchology Interv Pulmonol 2019;26:15-21.
20. Chang CH, Lee CS, Li SH, Chung FT, Wang CW, Juan YH, *et al.* Feasibility of radial endobronchial ultrasound-guided bronchoscopic cryobiopsy without fluoroscopy for lung parenchymal lesions. Can Respir J 2017;2017:7170687.
21. Hetzel J, Eberhardt R, Petermann C, Gesierich W, Darwiche K, Hagmeyer L, *et al.* Bleeding risk of transbronchial cryobiopsy compared to transbronchial forceps biopsy in interstitial lung disease – A prospective, randomized, multicentre cross-over trial. Respir Res 2019;20:140.
22. Cooley J, Balestra R, Aragaki-Nakahodo AA, Caudell Stamper DN, Sriprasart T, Swank Z, *et al.* Safety of performing transbronchial lung cryobiopsy on hospitalized patients with interstitial lung disease. Respir Med 2018;140:71-6.
23. Sharp C, McCabe M, Adamali H, Medford AR. Use of transbronchial cryobiopsy in the diagnosis of interstitial lung disease – A systematic review and cost analysis. QJM 2017;110:207-14.