Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0572-17
Intern Med 57: 2709-2712, 2018
http://internmed.jp

【 CASE REPORT 】

A Rare Case of Isolated Chronic Cough Caused by Pulmonary Lymphangitic Carcinomatosis as a Primary Manifestation of Rectum Carcinoma

Minami Okayama, Yoshihiro Kanemitsu, Tetsuya Oguri, Takamitsu Asano, Satoshi Fukuda, Hirotsugu Ohkubo, Masaya Takemura, Ken Maeno, Yutaka Ito and Akio Niimi

Abstract:
A 36-year old man was referred to our hospital due to isolated chronic cough that was refractory to anti-asthma medications, including inhaled corticosteroids/long-acting β_2 agonists. Chest X-ray showed diffuse nodular and enhanced vascular shadows with Kerley lines in both lungs. A blood analysis showed elevated serum carcinoembryonic antigen (CEA) and CA19-9 levels. A transbronchial biopsy revealed well to moderately differentiated adenocarcinoma, the origin of which was immunohistochemically suspected to be the gastrointestinal tract. Colonoscopy confirmed the diagnosis of primary rectum carcinoma. Pulmonary lymphangitic carcinomatosis was therefore regarded as the origin of the cough. Lymphangitic carcinomatosis is an uncommon diagnosis but important to consider in patients with persistent cough.

Key words: chronic cough, pulmonary lymphangitic carcinomatosis, rectum carcinoma

(Intern Med 57: 2709-2712, 2018)
(DOI: 10.2169/internalmedicine.0572-17)

Introduction

Although cough is one of the most common symptoms of lung cancer (1), the frequency of lung cancer as a cause of chronic cough as the sole symptom is less than 2% (2). Among lung tumors, pulmonary lymphangitic carcinomatosis shows a poor prognosis of three to six months (3). Respiratory symptoms, such as cough, dyspnea, and hemoptysis, progress rapidly and are usually accompanied by body weight loss, appetite loss, and a fever (4, 5).

We herein report a case of pulmonary lymphangitic carcinomatosis of rectal origin, which solely presented with a chronic cough.

Case Report

A 36-year old man with no smoking history was referred to our hospital because of nighttime predominant chronic cough lasting for 2 months. He had already received a treatment of inhaled corticosteroid, long-acting β_2 agonist, and leukotriene antagonist under a tentative diagnosis of cough-variant asthma; however, the cough was refractory to such intensive anti-asthma therapies.

At the first visit, he complained of only a persistent cough, with no other symptoms, such as a fever, dyspnea, hemoptysis, body weight loss, fatigue, anorexia, abdominal pain, obstipation, diarrhea, and melena.

Chest X-ray revealed enhanced vascular shadows and bronchial wall thickening, with diffuse small nodules of both lungs. Kerley A, B, and C lines were also visible on whole-chest X-ray (Fig. 1A). Chest computed tomography (CT) demonstrated diffuse nodular shadows, thickening of the bronchovascular bundle and interlobular septa, hilar and mediastinal lymphadenopathy, and a small amount of bilateral pleural effusion (Fig. 1B). Among a number of differential diagnoses based on the radiological findings, the elevated serum levels of carcinoembryonic antigen (CEA) and carbohydrateantigen19-9 (CA19-9) strongly suggested pulmonary lymphangitic carcinomatosis (Table). A transbronchial biopsy revealed well to moderately differentiated adenocarcinoma. Immunohistochemical analyses showed posi-

Department of Respiratory Medicine, Allergy and Clinical Immunology, Nagoya City University Graduate School of Medical Sciences, Japan
Received: November 23, 2017; Accepted: February 14, 2018; Advance Publication by J-STAGE: May 18, 2018
Correspondence to Dr. Yoshihiro Kanemitsu, kaney32@med.nagoya-cu.ac.jp

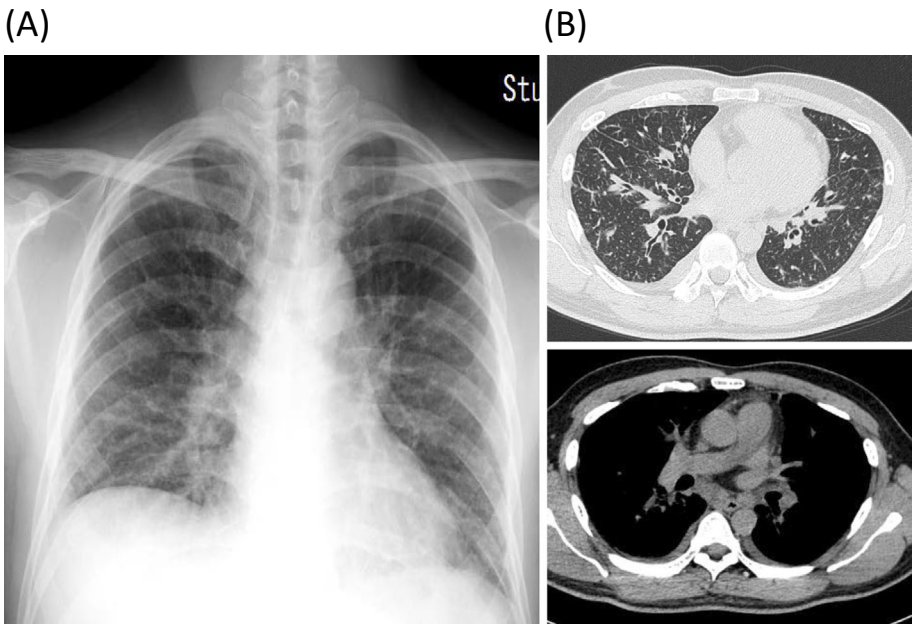

Figure 1. **Chest X-ray and computed tomography findings. (A) Chest X-ray showed enhanced bronchovascular shadow and diffuse small nodules in both lungs. Kerley A, B, and C lines were also visible on whole-chest X-ray. (B) Chest computed tomography demonstrated diffuse nodular shadows, ground-glass opacities, and thickened bronchovascular bundles and interlobular septa in the whole pulmonary area. A small amount of bilateral pleural effusion was also noted.**

Table. **The Differential Diagnosis and the Corresponding Clinical Examination Results of the Case, Based on Radiological Findings.**

Causative diseases	Clinical examinations	Results (normal ranges)
Miliary tuberculosis	Interferon-γ release assays	Negative
Sarcoidosis	Serum angiotensin-converting enzyme, IU/L	8.3 (8.3-21.4)
Malignant lymphoma	Soluble interleukin-2 receptor, U/mL	396 (145-519)
Diffuse panbronchiolitis	Paranasal sinuses X-ray	No abnormality
	Serum IgA, mg/dL	314 (100-350)
	Cold hemagglutination, folds	32 (≤128)
Pulmonary lymphangitic carcinomatosis	Tumor markers	
	Serum CEA, ng/mL	277.2 (≤5)
	Serum CA19-9, U/mL	8,500 (≤37)

tive staining for CK20 and CDX2 and negative staining for CK7, napsin A, and TTF-1 (Fig. 2), suggesting a cancer of gastrointestinal tract origin. Positron emission tomography (PET) showed a diffuse uptake of 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG) in both lungs along with an increased uptake in the intraperitoneal lymph nodes, mediastinal lymph nodes, and rectum (Fig. 3). Colonoscopy confirmed a definitive diagnosis of primary rectum cancer. The biopsy of the rectum tumor showed consistent result with those of lung biopsy including immunohistochemical analyses (Fig. 4). We therefore regarded pulmonary lymphangitic carcinomatosis as the primary manifestation of rectum carcinoma, which solely presented with chronic cough.

Discussion

Reportedly, from 8-75% of patients with lung cancer present with cough as a symptom (1). While lung cancer as the cause of isolated cough lasting for eight weeks or longer is uncommon, we believe pulmonary lymphangitic carcinomatosis is an important cause of chronic cough. Breast, stomach, and lung are the most frequent primary organs of pulmonary lymphangitic carcinomatosis, while the prevalence of rectum as the primary site is only 2% (3). In clinical practice, pulmonary lymphangitic carcinomatosis is often misdiagnosed as other diseases, such as sarcoidosis (5), miliary tuberculosis (6), and interstitial lung disease (7), particularly when patients are younger than 40 years of age, as was our case.

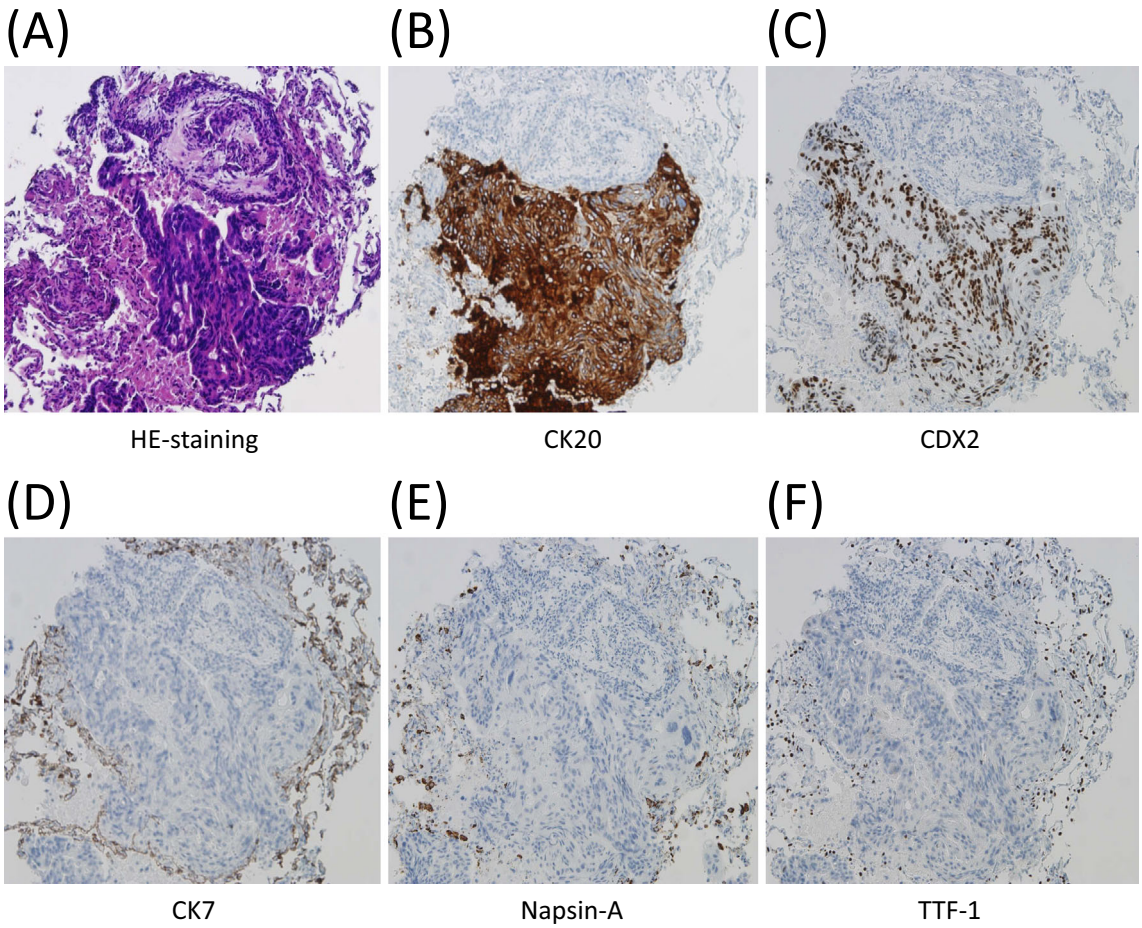

Figure 2. **Hematoxylin and Eosin (H&E) staining and immunohistochemical analyses of the transbronchial biopsy tissue. H&E staining (A) demonstrated well- to moderately differentiated adenocarcinoma. Immunohistochemical analyses showed positive staining for CK20 (B) and CDX2 (C) and negative staining for CK7 (D), napsin A (E), and TTF-1 (F), indicating a cancer of gastrointestinal tract origin. All samples were collected from the lower lobe of the left lung.**

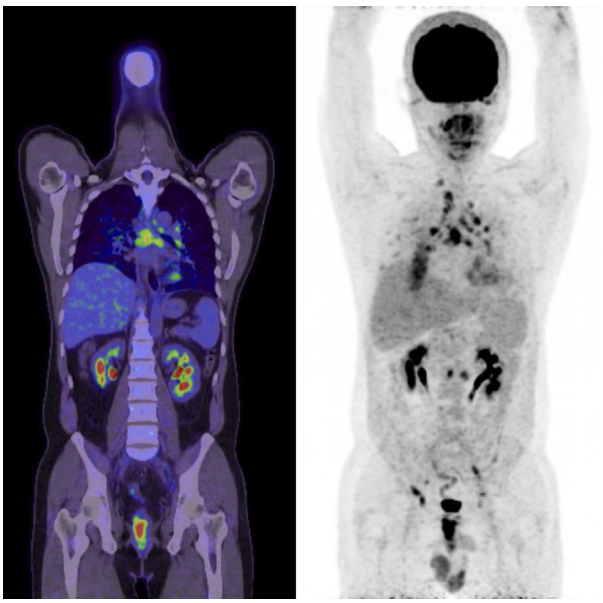

Figure 3. **Positron emission tomography findings. The diffuse uptake of 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG) was observed in both lungs together with multiple mediastinal lymph nodes, intraperitoneal lymph nodes, and rectum.**

Although a transbronchial biopsy is required for a definitive diagnosis of pulmonary lymphangitic carcinomatosis, characteristic findings on chest X-rays can be suggestive (5, 8). Thickened bronchovascular shadows, diffuse reticulonodular shadows, Kerley lines, hilar lymphadenopathy, and pleural effusion are observed in 20% to 50% of cases (5). However, chest X-rays show no abnormality in 30% to 50% of cased, as was a reported case by Jinnur et al. (4). They reported a patient with occult pulmonary lymphangitic carcinomatosis solely presenting with chronic cough in whom chest X-ray and high-resolution CT showed no remarkable findings (4). Body weight loss, decreased appetite, and worsening cough developed 11 weeks after initial chest CT. Follow-up chest CT four months later revealed diffused pulmonary nodules with thickening of the bronchovascular bundle in both lungs (4). This suggests that cough may be the earliest sign of occult pulmonary lymphangitic carcinomatosis among other respiratory symptoms, such as shortness of breath and hemoptysis. However, we were unable to determine whether or not cough due to pulmonary lymphangitic carcinomatosis occurred prior to the development of radiological findings, as definite interstitial patterns

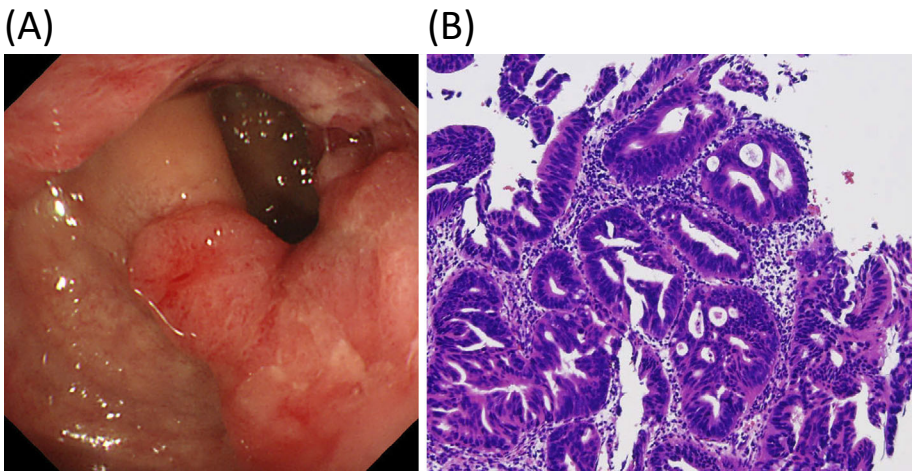

Figure 4. Colonoscopy findings. Colonoscopy showed full-circumference constriction of an ulcer mass in the lower rectum (A). The biopsy specimens from the rectum tumor showed findings consistent with those from the lung (B).

were found on chest X-ray at the initial consultation.

Thomas et al. described a patient with metastases to the intraperitoneal lymph nodes, mediastinal lymph nodes, and both lungs but not to the liver (Fig. 3) (5). This presentation accounts for 9% of cases of rectum cancer (9). Vascular endothelial growth factor (VEGF)-C and its receptor VEGFR-3, which are both lymphangiogenesis factors for such tumors, are associated with lymph node metastases including lymphatic dissemination to the lung (10). Although we were unable to evaluate his condition because he was referred to another hospital to receive chemotherapy, an intensive chemotherapeutic regimen including VEGFR inhibitors may be effective for treating cough via the attenuation of lymphangitic dissemination.

Conclusion

Based on our observation, pulmonary lymphangitic carcinomatosis should be considered as a cause of isolated chronic cough along with common causes, including asthma, especially because of its potentially life-threatening outcome, despite the absence of other symptoms, such as dyspnea, hemoptysis, and body weight loss.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We thank Ms. Jennifer Maries G Yap (Nagoya City University) for proofreading the English of our manuscript.

Minami Okayama and Yoshihiro Kanemitsu equally contributed to this work.

References

1. Spiro SG, Gould MK, Colice GL, Physicians ACoC. Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest **132**: 149S-160S, 2007.
2. Kvale PA. Chronic cough due to lung tumors: ACCP evidence-based clinical practice guidelines. Chest **129**: 147S-153S, 2006.
3. Bruce DM, Heys SD, Eremin O. Lymphangitis carcinomatosa: a literature review. J R Coll Surg Edinb **41**: 7-13, 1996.
4. Jinnur PK, Pannu BS, Boland JM, Iyer VN. Occult pulmonary lymphangitic carcinomatosis presenting as 'chronic cough' with a normal HRCT chest. Ann Med Surg (Lond) **6**: 77-80, 2016.
5. Thomas A, Lenox R. Pulmonary lymphangitic carcinomatosis as a primary manifestation of colon cancer in a young adult. CMAJ **179**: 338-340, 2008.
6. Welch J, Welsh G. Lymphangitis carcinomatosis mimicking miliary tuberculosis. N Z Med J **121**: 123-125, 2008.
7. Gilchrist FJ, Alton H, Brundler MA, Edwards L, Plunkett A, Rao S. Pulmonary lymphangitic carcinomatosis presenting as severe interstitial lung disease in a 15-year-old female. Eur Respir Rev **20**: 208-210, 2011.
8. Trapnell DH. Radiological appearances of lymphangitis carcinomatosa of the lung. Thorax **19**: 251-260, 1964.
9. DeVita VT Jr, Hellman S, Rosenberg SA. Cancers of the gastrointestinal tract. In: Cancer: Principles and Practice of Oncology. 6th ed. Lippincott Williams & Wilkins, Philadelphia (PA), 2001: 1229-1230.
10. Podgrabinska S, Skobe M. Role of lymphatic vasculature in regional and distant metastases. Microvasc Res **95**: 46-52, 2014.