Transbronchial Dissemination of Squamous Cell Lung Cancer

Akira Tadokoro, Nobuhiro Kanaji, Tomoya Ishii, Naoki Watanabe, Takuya Inoue, Norimitsu Kadowaki and Shuji Bandoh

Division of Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Department of Internal Medicine, Kagawa University, Miki-chō, Kita-gun, Kagawa, Japan.

ABSTRACT: We report a case of squamous cell lung cancer with transbronchial dissemination in a 73-year-old man. Bronchoscopic examination revealed multiple bronchial mucosal nodules that existed independently of one another. We reviewed 16 previous cases of endobronchial metastasis in lung cancer. All patients were men. Among the reports that described the smoking history, most patients were smokers (6/7), and the most frequent histological type of cancer was squamous cell carcinoma (11/17). Although hematogenous and lymphogenous routes have been reported as metastatic mechanisms, no previous cases involving transbronchial dissemination have been described. Transbronchial dissemination may be an alternative pathway of endobronchial metastasis.

KEYWORDS: lung cancer, endobronchial metastasis, transbronchial dissemination, E-cadherin, matrix metalloproteinase

CITATION: Tadokoro et al. Transbronchial Dissemination of Squamous Cell Lung Cancer. *Clinical Medicine Insights: Oncology* 2015:9 129–133 doi: 10.4137/CMO.S32707.

TYPE: Case Report

RECEIVED: August 05, 2015. **RESUBMITTED:** October 20, 2015. **ACCEPTED FOR PUBLICATION:** October 20, 2015.

ACADEMIC EDITOR: William C. S. Cho, Editor in Chief

PEER REVIEW: Five peer reviewers contributed to the peer review report. Reviewers' reports totaled 621 words, excluding any confidential comments to the academic editor.

FUNDING: Authors disclose no funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

CORRESPONDENCE: tadokoro@med.kagawa-u.ac.jp

Introduction

Endobronchial metastasis has been reported in various types of extrathoracic cancers, including breast, kidney, and colorectal cancers.[1–3] In one report, in which endobronchial metastasis was defined as bronchoscopically visible nonpulmonary tumors metastatic to the subsegmental or more proximal central bronchus and histologically identical to the previously examined primary tumors, the frequency of endobronchial metastasis in patients with pulmonary metastasis from extrathoracic malignant lesions was 42.1%.[4]

Three routes of endobronchial metastasis are believed to exist: lymphogenous, hematogenous, and transbronchial. Among them, metastasis by the lymphogenous route is considered to occur most often.[5] The frequency of endobronchial metastasis from lung cancer is much lower than that from extrathoracic cancers.[6] We herein report a case of squamous cell lung cancer with endobronchial metastasis due to transbronchial dissemination. We also review 16 previous reports of endobronchial metastasis from lung cancer. The hematogenous and lymphogenous routes were described as the metastatic mechanisms in these cases; however, we found no reports of the transbronchial route as a metastatic mechanism. To the best of our knowledge, the present case is the first report of transbronchial dissemination, which is an alternative pathway of endobronchial metastasis in patients with lung cancer. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Case Report

A 73-year-old man with silicosis and idiopathic interstitial pneumonia was evaluated at another hospital because of a 6-month history of progression of dyspnea on exertion and an abnormal shadow on a chest radiograph. He was treated with prednisolone at 30 mg/day for possible cryptogenic organizing pneumonia. However, his symptoms and chest radiographic findings did not improve, and he was referred to our hospital.

On admission, his right respiratory sounds were attenuated, and fine crackles were heard during auscultation in the left lung fields. He had a smoking history of 70 pack-years. The laboratory test results were as follows: C-reactive protein level, 0.80 mg/dL; white blood cell count, 14,450/L; cytokeratin 19 fragment level, 36.5 ng/mL (reference range, 0.0–3.5 ng/mL); and squamous cell carcinoma antigen level, 23.1 ng/mL (reference range, 0.0–1.5 ng/mL).

A chest radiograph showed consolidation in the right lower lung field and restiform shadows in the bilateral apical portion (Fig. 1A). Chest computed tomography showed consolidation of the right lower lobe (Fig. 1B), and positron emission tomography revealed accumulation of 18F-fluorodeoxyglucose within the consolidation (Fig. 1C) and right mediastinal lymph nodes (4R) (not shown). However, there was no accumulation in the endobronchial lesions because each nodule was too small. Bronchoscopic examination revealed multiple nodules, at least eight nodules on the bronchial mucosa, which

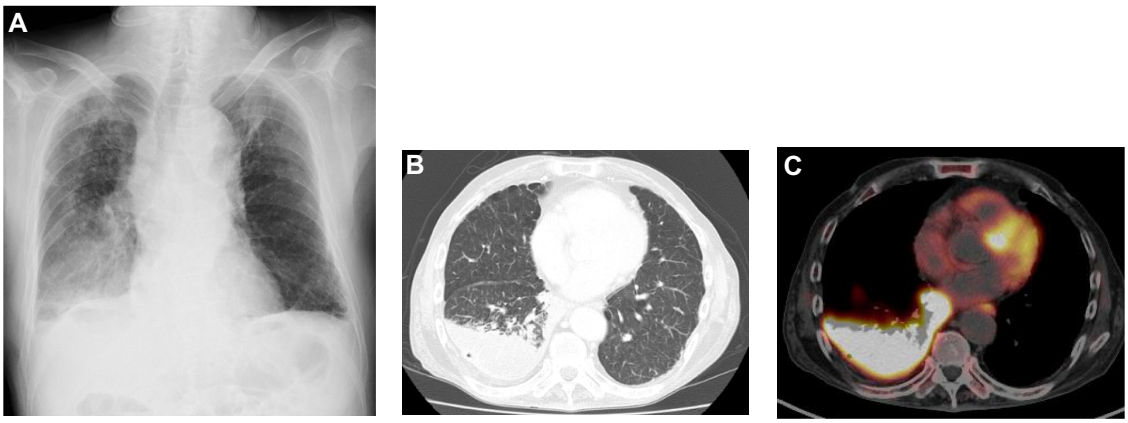

Figure 1. Chest radiograph, computed tomography scan, and positron emission tomography scan. (**A**) A chest radiograph showing consolidation in the lower area of the right lung and a restiform shadow in the bilateral apical portions. (**B**) Chest computed tomography showing consolidation of the right lower lobe. (**C**) Positron emission tomography showing 18F-fluorodeoxyglucose accumulation in the consolidation of the right lower lobe.

were not present in the submucosal lesion and not identified on the chest computed tomography (Fig. 2). The bronchoscope could not reach the right lower consolidation because of obstruction by the nodules. We performed biopsy from two locations – proximal (shown in Fig. 2, arrow) and distal nodule – under the X-ray guidance (not shown in Fig. 2). Histological examination of these nodules revealed poorly differentiated squamous cell carcinoma. Furthermore, immunohistochemical stain revealed similar stainability (Fig. 3A and B). We used CK5/6, P40, and P63 to confirm the nature of squamous cell carcinoma and CEA, CK14, EMA, CK7, and vimentin to show the equality of the tumors. CK5/6, P40, and P63 were positive in both. Furthermore, CEA, CK14, and EMA were partially positive and CK7 and vimentin were negative in both. Based on these results, we diagnosed these nodules as squamous cell carcinoma with exactly the same origin.

We consider that these nodules were developed by transbronchial dissemination, because each nodule existed independently of one another, the surface of each nodule was not covered with normal bronchial mucosa, the nodules extended from the right lower bronchus to the proximal bronchi and carina, and no nodules were present in the left bronchus.

The diagnosis was stage IV squamous cell carcinoma of the lung, clinical stage cT4N2M1a, and the patient received chemotherapy with nedaplatin and S-1 in a clinical trial. Sputum cytology examined 2 weeks after the bronchoscopic examination also showed class V squamous cell carcinoma. These findings indicated that the nodules on the bronchial mucosa were endobronchial metastases due to transbronchial dissemination.

Discussion

In this report, we defined transbronchial dissemination as metastasis with the following three clinical features: each nodule exists independently, the surface of each nodule is not covered with normal bronchial mucosa, and multiple nodules on the bronchial mucosa tend to exist more prominently on the side of the chest in which the primary lesion is located. We also described an extremely rare metastatic pattern, namely transbronchial dissemination. In the present case, the nodules existed independently of one another, were not covered with normal mucosa, and extended from the primary lesion (right lower bronchus) to the proximal bronchi and carina. Generally, when the endobronchial metastasis route was lymphangenous or hematogenous, the surface of the metastatic nodules should be covered by the bronchial mucosa, at least on small nodules. Furthermore, there is a possibility of artifact that the surface of the nodules was not covered by bronchial mucosa in the pathological examination. However, the bronchoscopic findings showed that the surface of nodules was completely not covered by the mucosa. If these nodules metastasize through the lymphangenous or hematogenous route, the nodules should be covered with mucosa at least in the marginal region.

Until now, metastasis to the trachea or bronchi has been mainly reported in association with extrathoracic cancers. Only one study has reported the incidence of endobronchial metastasis of primary lung cancer.[6] The overall incidence of endobronchial metastasis including all types of metastatic routes not limited to "transbronchial dissemination" from surgically resected lung cancer, which was defined as follows in the reported histopathologically proven tracheal metastasis after surgical resection of primary lung cancer, was 0.44% (6/1372 cases) among patients with surgically resected non–small cell lung cancer. Although the frequency was very low, squamous cell lung cancer was more frequently observed than adenocarcinoma: 5/647 (0.77%) and 1/552 (0.18%) cases, respectively.[6]

We reviewed the English-language and Japanese-language medical literature reporting endobronchial metastasis from lung cancer and identified 16 cases.[4,7–14] Table 1 summarizes the clinical characteristics of these 16 cases in addition to the present case (17 cases). All cases involved men (17/17 cases). The patients were smokers in almost 90% of the reports that included a description of the smoking history (6/7 cases).

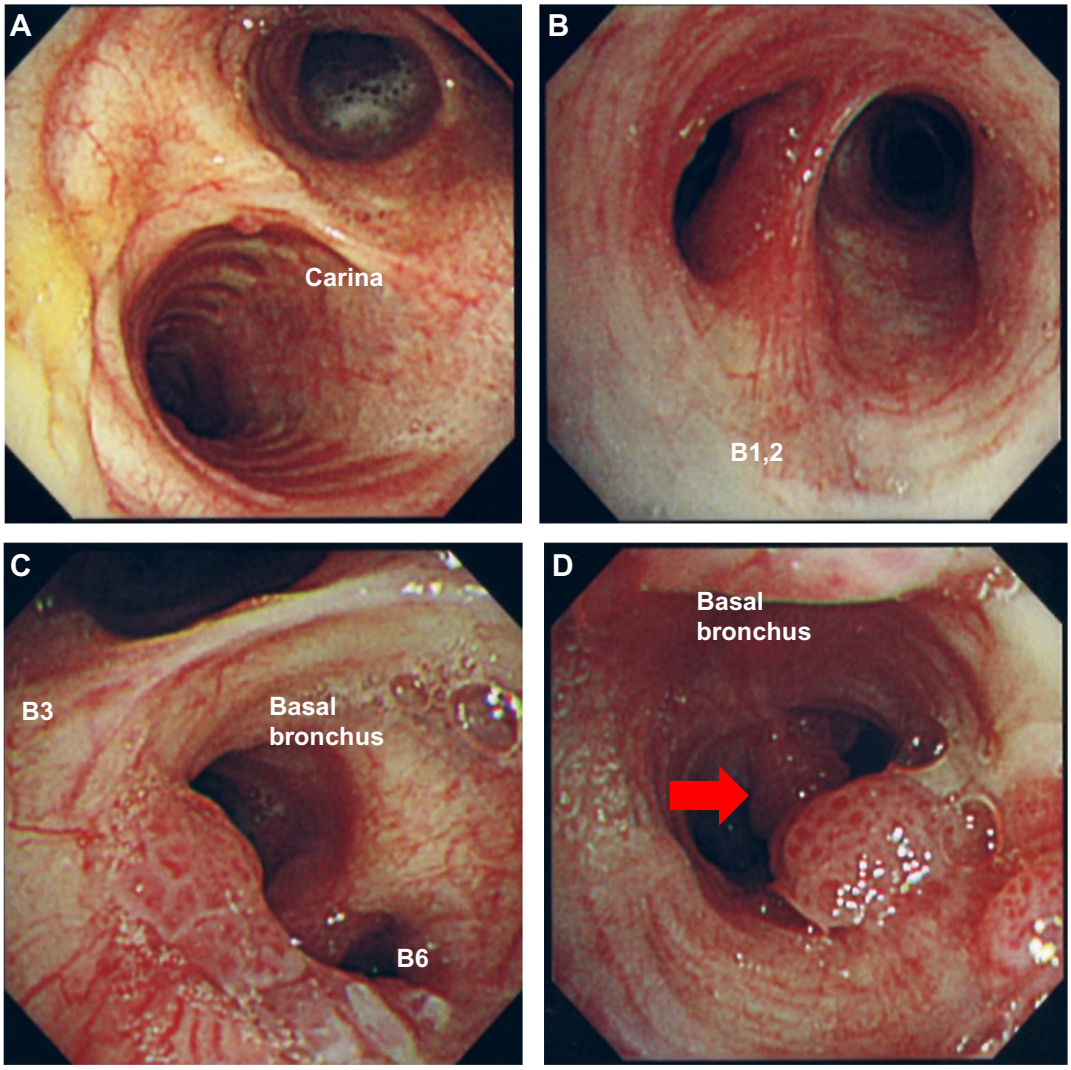

Figure 2. Bronchoscopic examination. Multiple nodules were observed on the bronchial mucosa; these nodules had not been identified on chest computed tomography. (**A**) Nodule on the left side of the carina. (**B**) Nodules on the right superior lobar bronchus. (**C**) Nodules on the intermediate bronchus. (**D**) Nodules on the basal bronchus; the arrow indicates the point of biopsy. These nodules extended from the right lower bronchus to the proximal bronchi and carina.

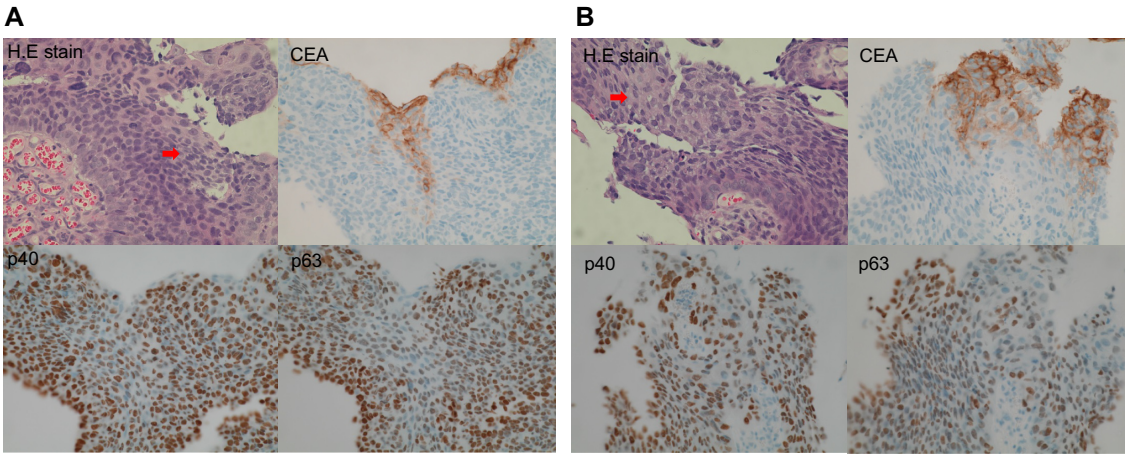

Figure 3. Pathological examination (hematoxylin and eosin stain; original magnification, ×400). (**A**) Proximal biopsy specimen and (**B**) distal biopsy specimen. Light microscopy showed poorly differentiated squamous cell lung cancer. The arrow indicates intercellular bridges. Immunohistochemical staining of CEA, p40, and p63 showed similar stainability.

Table 1. Reported cases of lung cancer with endobronchial metastasis

CASE(REFERENCE)	AGE/SEX	TISSUE TYPE	SMOKING HISTORY (PACK-YEAR)	ENDOBRONCHIAL METASTASIS	METASTATIC PATTERN
1(4)	60/M	Ad	Unknown	After operation	Unknown
2(4)	68/M	Sq	Unknown	After operation	Unknown
3(4)	53/M	Sq	Unknown	After operation	Unknown
4(4)	66/M	Sq	Unknown	After operation	Unknown
5(4)	53/M	Sq	Unknown	After operation	Unknown
6(4)	64/M	Sq	Unknown	After operation	Unknown
7(15)	68/M	Sq	36	After operation	Unknown
8(16)	36/M	Ad + Sq	Non-smoker	First diagnosis	Hematogenous
9(17)	71/M	Ad	62	After operation	Lymphangenous
10(18)	85/M	Sq	90	After operation	Unknown
11(19)	65/M	Sm	17	After diagnosis	Hematogenous
12(20)	61/M	Sm	Unknown	After diagnosis	Unknown
13(20)	73/M	Sq	Unknown	After diagnosis	Unknown
14(20)	66/M	Sq	Unknown	After diagnosis	Unknown
15(21)	55/M	Ad	26	First diagnosis	Unknown
16(22)	65/M	Ad	Unknown	After operation	Lymphangenous
The present case	73/M	Sq	70	First diagnosis	Transbronchial

Abbreviations: M, male; Sq, squamous cell carcinoma; Ad, adenocarcinoma; Sm, small cell carcinoma.

The most frequently observed histological type of cancer was squamous cell carcinoma (11/17 cases). In 3 of the 17 cases, endobronchial metastasis was recognized at the first diagnosis of lung cancer. In most cases, endobronchial metastasis was diagnosed as postoperative recurrence. In these cases, two metastatic pathways were described: hematogenous and lymphogenous metastasis. However, no previous reports described transbronchial dissemination, which was observed in the present case, as the pattern of endobronchial metastasis.

Although the exact mechanism of transbronchial dissemination is unknown, various mechanisms have been suggested. First, several cell adhesion molecules might be implicated in this type of dissemination. E-cadherin and catenins are essential molecules in the tight junctions between cells.[15] According to a previous report, reduced expression of E-cadherin and/or catenins is correlated with atypical grades of bronchial squamous metaplasia, and expression of E-cadherin and catenins is reduced in 100% of squamous cell carcinomas.[16] Decreased expression of these adhesion molecules in squamous cell lung cancer may contribute to an increased ability of the tumor to disperse.

Second, matrix metalloproteinases (MMPs) might be important in transbronchial dissemination. MMP-2 and MMP-9 can degrade type IV collagen and are believed to play important roles in tumor invasion and metastasis.[17–19] The importance of MMP-2 and MMP-9 in intrapulmonary tumor implantation has been confirmed by intrabronchial orthotopic propagation.[20] Interestingly, higher levels of MMP-2 and MMP-9 were observed in smokers than in control subjects.[21] Additionally, the expression of both MMP-2 and MMP-9 tended to be higher in squamous cell carcinoma than in adenocarcinoma.[22]

Based on these studies, low expression of E-cadherin and high expression of MMP-2 and MMP-9 in squamous cell lung cancer might be associated with transbronchial dissemination as well as hematogenous and lymphogenous metastasis.

In summary, we have reported the first case of squamous cell lung carcinoma with transbronchial dissemination. Our literature review shows that endobronchial metastasis is mostly observed in smokers and in patients with squamous cell carcinoma.

Author Contributions

Conceived and designed the experiments: AT, NK. Analyzed the data: AT, NK. Wrote the first draft of the manuscript: AT. Contributed to the writing of the manuscript: All authors. Agree with manuscript results and conclusions: All authors. Jointly developed the structure and arguments for the paper: All authors. Made critical revisions and approved final version: All authors. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Braman SS, Whitecomb ME. Endobronchial metastasis. *Arch Intern Med*. 1975;135:543–7.
2. Salud A, Porcel JM, Rovirosa A, Bellmunt J. Endobronchial metastatic disease: analysis of 32 cases. *J Surg Oncol*. 1996;62:249–52.

3. Shepherd MP. Endobronchial metastatic disease. *Thorax*. 1982;37:362–5.
4. Kiryu T, Hoshi H, Matsui E, et al. Endotracheal/endobronchial metastases: clinicopathologic study with special reference to developmental modes. *Chest*. 2001;119(3):768–75.
5. Shoenbaum S, Viamonte M. Subepithelial endobronchial metastases. *Radiology*. 1971;101(1):63–9.
6. Chong S, Kim TS, Han J. Tracheal metastasis of lung cancer: CT findings in six patients. *Am J Roentgenol*. 2006;186(1):220–4.
7. Oyama T, Suito T, Fujimoto H, Kudo H, Amakawa K, Yoshizu A. Tracheal sleeve resection for endotracheal metastasis after left pneumonectomy for lung cancer. *Jpn J Lung Cancer*. 2007;47:47–51. [in Japanese].
8. Yokoba N, Nishii Y, Hagiri S, Tanimura S, Honma K. Endobronchial metastasis from slow-growing lung cancer: a rare case report and review of the literature. *Respir Med CME*. 2008;1:107–10.
9. Hayashi Y, Matsuura T, Kato M, Takeuchi T. A case of adenocarcinoma of the lung with endotracheobroncheal metastasis. *J Jpn Soc Bronchol*. 1989;11(2):164–9. [in Japanese].
10. Kobayashi K, Oda M, Nishijima H. Brachytherapy and placement of a Dumon tube for a patient with tracheal stenosis due to recurrent primary lung cancer. *J Jpn Soc Bronchol*. 2004;26(2):149–53. [in Japanese].
11. Yamamura J, Waku M, Koyama A. A case of small cell carcinoma with endotracheal metastasis. *J Jpn Soc Bronchol*. 1987;9(1):72–7. [in Japanese].
12. Miura T, Tanaka K, Cyujo M, et al. Three cases of postoperative tracheal metastasis from lung cancer. *J Jpn Soc Bronchol*. 1997;19(5):422–5. [in Japanese].
13. Fujiwara N, Miwa C, Iwai Y, et al. A case of signet-ring cell adenocarcinoma with endotracheal and endobronchial metastasis, with the lungs suspected as the primary origin. *J Jpn Soc Respir Endosc*. 2013;35(5):493–8. [in Japanese].
14. Segawa M, Kusajima Y, Nakamura H, Sugihara M, Saito K. Postoperative endotracheal metastasis of the peripheral adenocarcinoma of lung. A case report with review of the Japanese literature. *Jpn J Lung Cancer*. 2000;40:633–7. [in Japanese].
15. Watabe M, Nagafuchi A, Tsukita S, Takeichi M. Induction of polarized cell-cell association and retardation of growth by activation of the E-cadherin-catenin adhesion system in a dispersed carcinoma line. *J Cell Biol*. 1994;127(1):247–56.
16. Kato Y, Hirano T, Yoshida K, et al. Frequent loss of E-cadherin and/or catenins in intrabronchial lesions during carcinogenesis of the bronchial epithelium. *Lung Cancer*. 2005;48(3):323–30.
17. Wilhelm SM, Collier IE, Marmer BL, Eisen AZ, Grant GA, Goldberg GI. SV40-transformed human lung fibroblasts secrete a 92-kDa type IV collagenase which is identical to that secreted by normal human macrophages. *J Biol Chem*. 1989;264:17213–21.
18. Collier IE, Wilhelm SM, Eisen AZ, et al. H-ras oncogene-transformed human bronchial epithelial cells (TBE-1) secrete a single metalloprotease capable of degrading basement membrane collagen. *J Biol Chem*. 1988;263:6579–87.
19. Fridman R, Toth M, Peña D, Mobashery S. Activation of progelatinase B (MMP-9) by gelatinase A (MMP-2). *Cancer Res*. 1995;55(12):2548–55.
20. Mase K, Iijima T, Nakamura N, et al. Intrabronchial orthotopic propagation of human lung adenocarcinoma – characterizations of tumorigenicity, invasion and metastasis. *Lung Cancer*. 2002;36(3):271–6.
21. Gonzalez AG, Delgado J, Mendosa-Posada DA, et al. Differences in plasma MMPs and TIMPs protein expression and chemotherapy response in patients with tobacco- or wood-smoke-induced lung cancer. *Respiration*. 2013;85(4):281–8.
22. Shah SA, Spinale FG, Ikonomidis JS, Stroud RE, Chang EI, ReeD CE. Differential matrix metalloproteinase levels in adenocarcinoma and squamous cell carcinoma of the lung. *J Thorac Cardiovasc Surg*. 2010;139(4):984–90.