An Autopsy Case of Lepidic Pulmonary Metastasis from Cholangiocarcinoma

Yohsuke Nagayoshi¹, Kazuko Yamamoto¹, Satoru Hashimoto¹, Keiko Hisatomi¹, Seiji Doi¹, Seiji Nagashima¹, Hirokazu Kurohama³, Masahiro Ito³, Takahiro Takazono², Shigeki Nakamura², Taiga Miyazaki² and Shigeru Kohno²

Abstract

We herein report the first case of pulmonary metastasis with lepidic growth that originated from cholangiocarcinoma. A 77-year-old man was admitted to our hospital due to exertional dyspnea and liver dysfunction. Computed tomography showed widespread infiltration and a ground-glass opacity in the lung and dilation of the intrahepatic bile duct. The pulmonary lesion progressed rapidly, and the patient died of respiratory failure. Cholangiocarcinoma and lepidic pulmonary metastasis were pathologically diagnosed by an autopsy. Lepidic pulmonary growth is an atypical pattern of metastasis, and immunopathological staining is useful to distinguish pulmonary metastasis from extrapulmonary cancer and primary pulmonary adenocarcinoma.

Key words: lepidic growth, lung metastasis, cholangiocarcinoma

(Intern Med 55: 2849-2853, 2016) (DOI: 10.2169/internalmedicine.55.5972)

Introduction

The lung is a common site for metastasis. Multiple nodules or lymphangitic carcinomatosis are observed in the majority of cases of metastatic lung tumors (1-3). However, pulmonary metastasis sometimes presents uncommon radiographic features, making it difficult to distinguish the metastasis from primary lung cancer and other benign pulmonary diseases. These features include cavitation, calcification, hemorrhaging around metastatic nodules, pneumothorax, an air-space pattern, tumor embolism, endobronchial metastasis, dilated vessels within a mass, and sterilized metastasis (4). Of these radiographic features, an air-space pattern can occur when the tumor progresses along the alveolar wall, which is known as lepidic growth. Although lepidic tumor growth is typically observed in primary pulmonary adenocarcinoma, some reports have described cases of metastatic pulmonary adenocarcinoma from extrapulmonary organs, such as the gallbladder, pancreas, stomach, colon, and breast (5-7).

We herein report an autopsy case of lepidic pulmonary metastasis from cholangiocarcinoma, which was observed as a pulmonary air-space consolidation and ground-glass opacity on chest computed tomography (CT). To the best of our knowledge, this is the first case of lepidic pulmonary metastasis from cholangiocarcinoma.

Case Report

A 77-year-old Japanese man with progressing exertional dyspnea was admitted to our hospital. Prior to his first visit, the patient had been suspected to have cholangiocarcinoma according to laboratory results that included elevated transaminase, carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9) levels. Abdominal CT revealed thickening of the portal bile duct and dilation of the intrahepatic bile duct (Fig. 1A). However, no pathological evidence of carcinoma had yet been obtained at this point.

Chest auscultation revealed a fine crackle in his left lung.
oxygen saturation of the peripheral artery was degraded to 94% at room air, and the patient was afebrile. Pulmonary CT revealed a widespread air-space consolidations and ground-glass opacities (Fig. 1B). A honeycomb change was also observed, mainly in the left lower lobe. This change had been previously observed on a CT scan conducted 6 months prior to the patient's first visit, suggesting that he had subclinical interstitial pneumonia.

Laboratory data on admission are presented in Table and revealed mild increases in the C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR). However, leukocytosis was not apparent. Furthermore, (1,3)-β-D-glucan, Krebs von den Lungen-6 (KL-6), pulmonary surfactant protein-D (SP-D), and immunoglobulin G (IgG) elevation were also observed. The bronchioloalveolar lavage fluid (BALF) from the left upper pulmonary lobe exhibited increased alveolar neutrophils and lymphocytes (total: 336 cells/μL; macrophages: 38%, neutrophils: 40%, and lymphocytes: 22%). No microbes or atypical cells were detected in a BALF culture and cytological examination.

According to these findings, we initially treated the patient as having pneumocystis pneumonia and/or acute exacerbation of pre-existing interstitial pneumonia using corticosteroid and sulfamethoxazole/trimethoprim (SMX/TMP). SMX/TMP was discontinued since the elevated (1,3)-β-D-glucan level was due to a false positive result. Despite these intensive treatments, the lung infiltrates progressively expanded (Fig. 2).

Although primary lung cancer was suspected due to the pattern of the infiltrates, best supportive care for putative lung cancer was provided because the performance status of this patient had degraded rapidly. He died of respiratory failure 3 months after admission.

An autopsy was subsequently performed. In the hepatic hilus, 15 mm of solid mass was observed around the root of the left hepatic duct. Microscopically, atypical cells grew along the surface of the intrahepatic bile duct (Fig. 3A) and showed stromal invasion forming irregular tubular structures with or without papillary projection (Fig. 3B and C). Exfoliation of tumor clusters was evident in the lumens (Fig. 3C). The tumor showed positivity for cytokeratin 7 (CK7; Fig. 3D) and cytokeratin 20 (CK20; Fig. 3E) on immunostaining. These findings suggested a diagnosis of cholangiocarcinoma, as had been previously suspected. Adenocarcinoma was also observed in the bilateral pulmonary lobes. Atypical cells were observed along the alveolar wall in most pulmonary areas (Fig. 4A and B). In resemblance with a liver tumor, stromal invasion of the carcinoma forming irregular tubular structures with or without papillary projection (Fig. 4C and D) was also found in the lung specimen. Additionally, a large number of tumor clusters were found in the alveolar cavity, suggesting transbronchial spread of adenocarcinoma (Fig. 4B). Although these findings were similar to those of primary pulmonary adenocarci-
no evidence supported the existence of an active fungal infection, including *Pneumocystis jirovecii*, in the lung specimen.

According to these histopathological findings, we finally diagnosed the patient with lepidic pulmonary metastasis from cholangiocarcinoma.

**Discussion**

Lepidic growth of cancer cells is a common pathological feature of primary pulmonary adenocarcinoma. However, pulmonary metastasis can also show lepidic growth, although it is rare. The lepidic growth of metastatic cancer is associated with radiological findings such as air-space nodules, consolidation containing an air bronchogram, focal or

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**Table. Laboratory Findings on Admission.**

| Blood examination | Cre | 0.7 mg/dL |
|-------------------|-----|----------|
| WBC 5,600 /μL     | Na  | 132 mEq/L|
| Neutrophils 46.2 %| K   | 4.6 mEq/L |
| Eosinophils 1.1 % | Cl  | 98 mEq/L  |
| Basophils 0.2 %   | CRP | 2.99 mg/dL|
| Monocytes 5.0 %   | CEA | 10.0 ng/mL|
| Lymphocytes 47.5 %| CA19-9 | 372.3 U/mL|
| RBC 434×10^6 /μL | KL-6| 578 U/mL  |
| Hb 12.4 g/dL      | SP-D| 256 ng/mL |
| Plt 11.4×10^4 /μL | IgG | 3,460 mg/dL|
| TP 9.5 g/dL       | IgA | 661 mg/dL  |
| Alb 3.4 g/dL      | IgM | 195 mg/dL  |
| Total bilirubin 1.4 mg/dL | (1,3)-β-D-glucan | 218.2 pg/mL |
| Direct bilirubin 0.6 mg/dL | ESR (60 min) | 62.0 mm |
| AST 68 IU/L       | ESR (120 min) | 74.0 mm |
| ALT 78 IU/L       | BALF examination |
| LDH 174 IU/L      | total cells | 336 /μL |
| ALP 1,167 IU/L    | macrophages | 38 % |
| GGT 465 IU/L      | neutrophils | 40 % |
| BUN 17.2 mg/dL    | lymphocytes | 22 % |

**Figure 2.** A chest radiograph obtained on admission (A) and 3 months after admission (B). The rapid progression of bilateral infiltrative opacity is observed.
extensive ground-glass opacities, and nodules with halo signs (4). These radiological features of lepidic metastasis also resemble those of primary pulmonary adenocarcinoma that shows lepidic growth.

Some case reports have described lepidic pulmonary metastasis from adenocarcinoma of extra-thoracic organs, such as the gallbladder, pancreas, stomach, colon, and breast (5-8). In addition to the pulmonary metastasis of adenocarcinoma, the pulmonary metastasis of malignant melanoma can also show pathologically lepidic growth in the lung (9). In a previous case series, approximately 10% of cases with an air-space pattern on a chest CT scan were identified as metastatic adenocarcinomas. However, that series only included 1 case in which pancreatic carcinoma was pathologically shown to have undergone lepidic pulmonary metastasis (8).

In the present case, metastatic lung cancer from cholangiocarcinoma was strongly suspected because the pathological features observed in the lung tumor were closely related to those observed in the bile duct tumors. For the purpose of further examination, several immunostainings were performed. Immunostaining with CK7 and CK20 is commonly used to estimate the origin of carcinoma. A previous report has demonstrated that 90% of pulmonary adenocarcinomas show a CK7/CK20 pattern, whereas 43% of cholangiocarcinoma show a CK7/CK20 pattern (10). Furthermore, TTF-
The authors state that they have no Conflict of Interest (COI).

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