World Journal of Gastrointestinal Surgery

Online Submissions: http://www.wjgnet.com/1948-9366office
wjgs@wjgnet.com
doi:10.4240/wjgs.v2.i8.270

World J Gastrointest Surg 2010 August 27; 2(8): 270-274
ISSN 1948-9366 (online)

CASE REPORT

Endobronchial metastasis from adenocarcinoma of gastric cardia 7 years after potentially curable resection

Takaaki Hanyu, Tatsuo Kanda, Atsushi Matsuki, Go Hasegawa, Kazuhito Yajima, Masanori Tsuchida, Shin-ichi Kosugi, Makoto Naito, Katsuyoshi Hatakeyama

Takaaki Hanyu, Tatsuo Kanda, Atsushi Matsuki, Kazuhito Yajima, Shin-ichi Kosugi, Katsuyoshi Hatakeyama, Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, Asahimachi-dori 1-757, Niigata 951-8510, Japan
Go Hasegawa, Makoto Naito, Division of Cellular and Molecular Pathology, Niigata University Graduate School of Medical and Dental Sciences, Asahimachi-dori 1-757, Niigata 951-8510, Japan
Masanori Tsuchida, Division of Thoracic and Cardiovascular Surgery, Niigata University Graduate School of Medical and Dental Sciences, Asahimachi-dori 1-757, Niigata 951-8510, Japan
Author contributions: Hanyu T and Kanda T drafted the manuscript; Kanda T, Matsuki A, Yajima K and Kosugi S were responsible for the patient management; Kanda T and Matsuki A were involved in follow-up of the patient; Tsuchida M played a central role in surgery of the lung tumor; Hasegawa G and Naito M made a great contribution to pathological diagnosis; Hatakeyama K coordinated the research group and supervised this study.
Correspondence to: Tatsuo Kanda, MD, PhD, Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, Asahimachi-dori 1-757, Niigata 951-8510, Japan. kandat@med.niigata-u.ac.jp
Telephone: +81-25-2272228 Fax: +81-25-2270779
Received: February 2, 2010 Revised: June 25, 2010
Accepted: July 2, 2010
Published online: August 27, 2010

Abstract

Endobronchial metastasis (EBM) is a rare form of metastasis from extrapulmonary malignant tumors, although there are few reports of EBM from gastric cancer specifically. We report the case of a 51-year-old woman who had undergone gastrectomy for advanced gastric cancer seven years previously but was diagnosed with a solitary lung tumor by follow-up computed tomography. On diagnosis of primary lung cancer, she underwent pulmonary lobectomy, but immunohistochemical examination confirmed the resected tumor to be an EBM from the gastric cancer. Six months later, she was diagnosed with peritoneal metastases and underwent chemotherapy with gastric cancer regimen. She is still alive at 33 mo after the lobectomy. Generally, the prognosis for EBM is poor although multidisciplinary treatment can lead to long-term survival. Precise diagnosis on the basis of detailed pathological and immunohistochemical evaluation can contribute to deciding the most effective treatment and improving prognosis.

Key words: Endobronchial metastasis; Immunohistochemistry; Gastric cancer

Peer reviewers: Iberto Zaniboni, MD, UO di Oncologia, Fondazione Poliambulanza, Via Bissolati 57, Brescia 25124, Italy; Giulio Melloni, MD, Department of Thoracic Surgery, San Raffaele Scientific Institute, Via Olgettina, 60, Milan 20132, Italy

Hanyu T, Kanda T, Matsuki A, Hasegawa G, Yajima K, Tsuchida M, Kosugi S, Naito M, Hatakeyama K. Endobronchial metastasis from adenocarcinoma of gastric cardia 7 years after potentially curable resection. *World J Gastrointest Surg* 2010; 2(8): 270-274 Available from: URL: http://www.wjgnet.com/1948-9366/full/v2/i8/270.htm DOI: http://dx.doi.org/10.4240/wjgs.v2.i8.270

INTRODUCTION

Endobronchial metastasis (EBM) is a rare form of metastasis from extrapulmonary malignant tumors of the lungs. Although EBM can be histologically discriminated from ordinary lung metastasis, EBM is frequently overlooked because it is rare and not widely known by clinicians. We report a case of EBM from an adenocarcinoma of the gastric cardia. In the present case, the tumor was clinically diagnosed as a primary lung carcinoma because the tumor

was solitary and the disease-free interval from the prior gastrectomy was as long as seven years. The lung tumor was surgically excised and histological examination including immunohistochemical analysis revealed it to be an EBM from the adenocarcinoma of the gastric cardia. We present herein the results of immunohistochemical analysis and discuss the clinicopathological features of EBM based on previous literature.

CASE REPORT

A 51-year-old woman was diagnosed with a solitary lung tumor during follow-up after surgery for adenocarcinoma of the gastric cardia (Siewert type Ⅲ)[1]. Eighty-five months earlier, the patient underwent radical surgery for gastric carcinoma. The tumor was highly advanced, invading the esophagus and the pancreas, but was completely excised by transhiatal esophagectomy, total gastrectomy, caudal pancreatectomy, and splenectomy. Histological examination revealed that the gastric tumor was a moderately differentiated adenocarcinoma, and the final stage of the disease was T4(pancreas)N2H0P0CY0M0, stage Ⅳ according to the Japanese classification of gastric carcinoma, 2nd English edition[2]. Thereafter, the patient underwent adjuvant chemotherapy with 16 cycles of weekly administration of methotrexate and 5-fluorouracil and had shown no evidence of disease recurrence in the 85 mo prior to this episode.

Computed tomography (CT) of the chest depicted an irregular nodular mass measuring 2.6 cm × 1.6 cm in size, which was associated with frosted-glass-like finding of the medial segment (S5) in the right lung (Figure 1). Serum carcinoembryonic antigen level was 3.3 ng/mL (normal range: 5.0 ng/mL or less). Other serum tumor markers, including squamous cell carcinoma related antigen, cytokeratin 19 fragment, sialyl Lewis X-I antigen, neuron-specific enolase, and progastrin-releasing peptide, also showed normal levels. The patient underwent Saccomanno's sputum cytology, which revealed adenocarcinoma cells. The patient was diagnosed with primary lung adenocarcinoma and underwent right middle lobectomy. The resected specimen indicated that the tumor measured 3.0 cm in diameter, outgrew as a polypoid in the bronchial lumen, and invaded the surrounding lung parenchyma. Histological findings revealed that the tumor was composed of well-differentiated papillary and tubular adenocarcinoma, displacing the bronchial epithelium. Therefore, the adenocarcinoma was postulated to be a primary bronchial-lung carcinoma (Figure 2).

To distinguish whether the tumor was a primary lung carcinoma or a gastric cancer metastasis, further immunohistochemical examination was performed using an antibody to human thyroid transcriptional factor (TTF)-1, a marker for lung carcinoma, and markers for gastrointestinal carcinoma, an antibody to human caudal type homeobox transcription factor (CDX)2 and an antibody against hepatocyte nuclear factor-4α (HNF4α). Unexpectedly, the lung tumor cells were negative for TTF-1 and positive for both CDX2 and HNF4α, and the same result

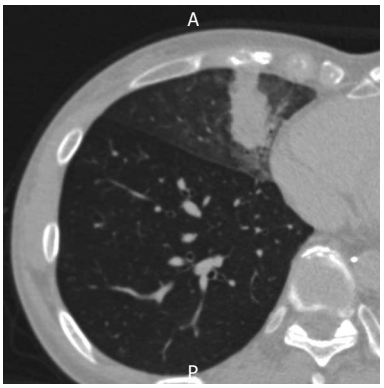

Figure 1 Chest computed tomography showing nodular shadow measuring 26 mm × 16 mm in size with frosted-glass-like shadow in right lung S5.

was obtained for the primary gastric cancer (Figure 3). In addition, the excised lung tumor was negative for CK7 expression, a conventional immunochemical marker for lung-originated tumors (data not shown). Consequently, the lung tumor in the present case was diagnosed as an EBM from the adenocarcinoma of the gastric cardia.

Follow-up CT performed 5 mo after the pulmonary lobectomy revealed massive ascites accompanied by an enlargement of the left ovary. Paracentesis revealed adenocarcinoma cells in the ascites. The patient was diagnosed with peritoneal and ovarian metastases and underwent chemotherapy with paclitaxel (100 mg/body administered weekly for 3 wk per 4-wk cycle). After 8 cycles, the ascites disappeared and ovary size became normal. The patient is continuing this regimen and complete clinical response has been achieved for 19 mo so far.

DISCUSSION

The lungs are often involved in extrapulmonary malignancies, although EBM is uncommon. EBM is clinically characterized by obstructive bronchial symptoms and chest X-ray findings, such as atelectasis. To date, there have been cases where secondary bronchial involvement from mediastinal lymph node, hilar lymph node, or parenchymal metastases has been included in EBM. Currently, EBM is defined as a metastasis developing on the tracheobronchial wall, occupying the mucosal epithelium, growing into a polypoid mass in the bronchial lumen, and invading pulmonary parenchyma. EBM is clearly discriminated from ordinary pulmonary metastases that occur in alveolar parenchyma, and its frequency is estimated to be from 2% to 13% of pulmonary metastases, based on data from cancer autopsy series or bronchoscopic bronchial biopsy series[3-5].

The most common primary tumors associated with EBM are breast, renal, and colorectal carcinomas. Others include tumors of the bladder, skin, thyroid, pancreas, ovary, testis, uterus, melanoma, and various sarcomas[3,5-9]. Many of the pulmonary involvements from gastric cancer appear as carcinomatous lymphangitis or pleuritis. Moreover, solitary pulmonary metastasis was found in only 0.1% to 0.5% of patients who underwent surgery for

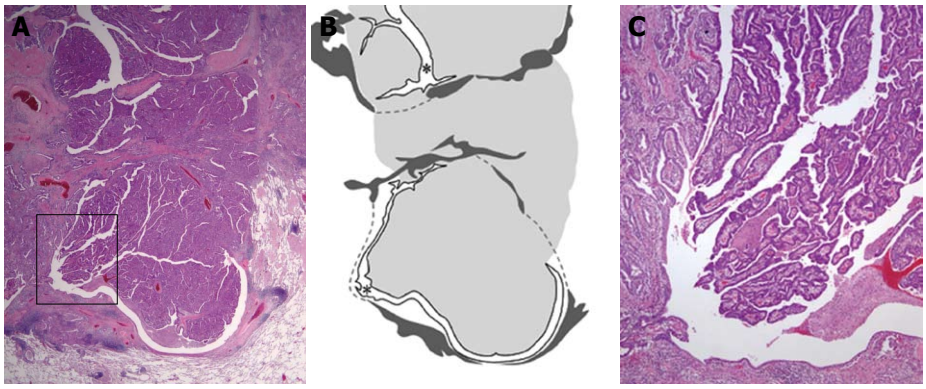

Figure 2 Pathological findings of resected lung tumor (HE staining). The illustration (B) depicts the location and growth pattern of the tumor. A tumor arose from the bronchial wall and grew endoluminally. The tumor, forming a polypoid mass, almost completely obstructed the middle lobe bronchus. The tumor measured approximately 3 cm in diameter. The extent of the tumor is illustrated in light gray. Dark gray areas indicate smooth muscle layers of the bronchial wall. Asterisks indicate the remaining original bronchial lumen. Histologically, the tumor was a well-differentiated papillary and tubular adenocarcinoma. Figure 2C is a magnification of the part enclosed by a grid in Figure 2A. The tumor cells displaced the bronchial mucosal epithelium. Original magnification: ×10 (A), ×40 (C).

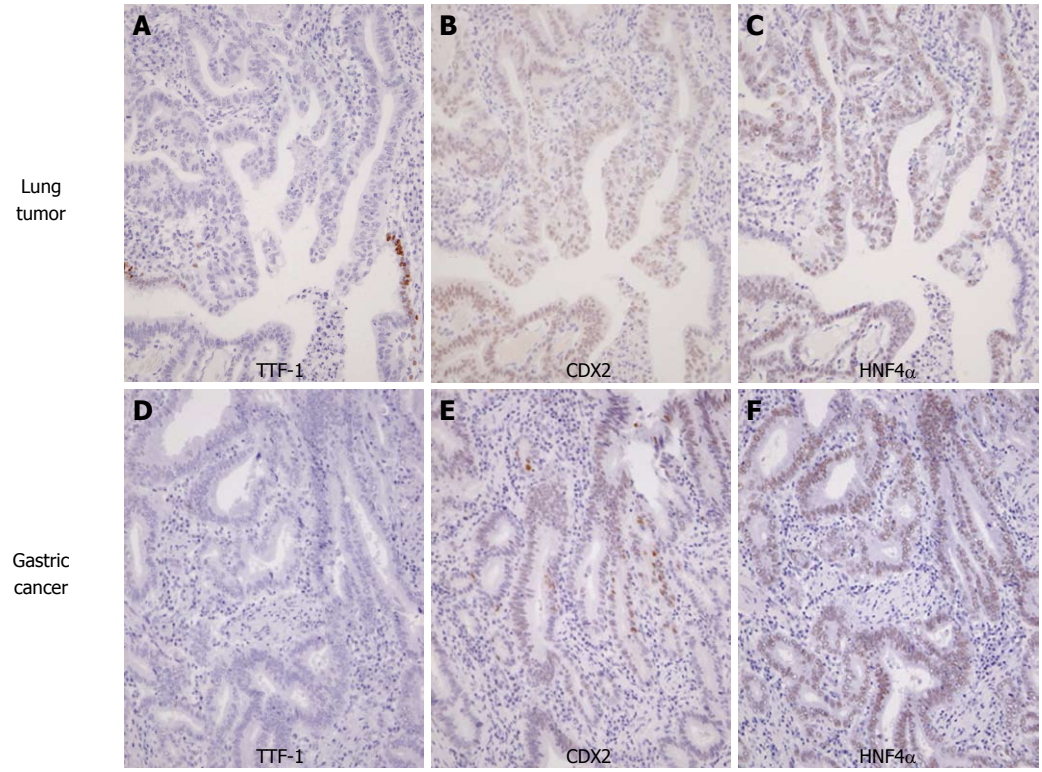

Figure 3 Lung tumor was immunohistologically negative for thyroid transcription factor-1 (A) and positive for caudal type homeobox transcription factor 2 (B) and hepatocyte nuclear factor-4α (C), the primary gastric carcinoma showed the same immunoreactivity (D-F) (Original magnification × 200). Thyroid transcription factor (TTF)-1: NCL-TTF-1 (Novocastra, UK, 1/100 dilution). Caudal type homeobox transcription factor (CDX)2: NCL-CDX2 (Novocastra, UK, 1/100 dilution). Hepatocyte nuclear factor-4α (HNF4α): mouse mAb H1415 (recognizing a wider range of HNF4α isoforms) (Perseus Proteomics, Tokyo, Japan, 1/100 dilution)

gastric cancer[10-12]. Thus, EBM from gastric cancer is very rare from the viewpoint of the primary tumor and the metastatic pattern. To our knowledge, only five cases have been described and detailed information is available only in three[13-15] (Table 1). Of the four EBM patients including ours, two were diagnosed synchronously with the time of diagnosis of the primary tumors and were associated with respiratory symptoms. The two patients died shortly after diagnosis. On the other hand, in the remaining two patients, the tumors were diagnosed as EBM by histological examination of surgically resected specimens. It should be noted that EBM appeared long after gastrectomy and the patients were alive for more than one year after lobectomy for EBM in both cases.

To devise an appropriate treatment strategy, it is vital to differentiate EBM from primary lung cancer although this is usually difficult. In metachronous cases, it was often that EBM occurred after long disease-free intervals; the average intervals were from 3.8 to 5.0 years[5,8,16], indicating that this disease is characterized by relatively slow progres-

Table 1 Reported cases of endobronchial metastasis from gastric cancer

Year	Author	Age/Sex	Primary cancer			Endobronchial metastasis			
			Histological type	Stage (TNM)	Surgery	Opportunity	Interval	Therapy	Outcome
1999	Park *et al*[13]	27/F	por, muc, sig	-	None	Dry cough	Synchronous	Chemotherapy	3 mo dead
2000	Scala *et al*[14]	57/F	por, sig	T4NxMx	TG	Dry cough, dyspnea	Synchronous	No therapy	2 mo dead
2005	Yoshioka *et al*[15]	76/M	tub2	T2N0M1	DG + Hepatectomy	Medical examination	59 mo	Resection	15 mo alive
2009	Present case	51/F	tub2, tub1	T4N1M0	EG + TPS	Follow CT	85 mo	Resection	33 mo alive

por: Poorly differentiated adenocarcinoma; muc; Mucinous carcinoma; sig: Signet-ring cell carcinoma; tub2: Moderately differentiated adenocarcinoma; tub1: Well differentiated adenocarcinoma; TG; Total gastrectomy; DG: Distal gastrectomy; EG: Esophagectomy; TPS: Total gastrectomy with pancreaticosplenectomy; CT: Computed tomography.

sion. Similarly, in our case it took seven years from surgery of the primary tumor to recognize the pulmonary lesion as a malignancy. This was why the tumor in our case was initially diagnosed as a primary lung cancer.

When a metastatic tumor resembles a primary lung cancer histologically, no absolute criteria are available to differentiate primary tumor from metastasis. In such cases, immunohistochemistry should be considered. Park *et al*[17] reported the use of immunohistochemistry in differentiating a primary tumor from a metastatic adenocarcinoma. Su *et al*[18] reported the important role of immunohistochemistry in distinguishing primary lung adenocarcinoma from metastatic lung adenocarcinoma. Cytokeratin (CK)7 and CK20 have been used as markers for this purpose. However, the low specificity of these markers remains problematic. Recently, new organ-specific markers have been reported. The application of these molecular markers is improving the ability of pathological diagnosis. CDX2 expression was found in 93.9% of colorectal cancer cases and 60.9% of gastric cancer cases, but not in any primary lung cancer cases[17]. Tanaka *et al*[19] reported that HNF4α could be a novel diagnostic marker for metastases of unknown primary origin particularly in cases of gastric-origin: HNF4α expression was exclusively found in metastasis from gastric carcinoma[19,20]. Meanwhile, TTF-1 expression was noted in 72.5% to 88.0% of lung adenocarcinoma cases but not in any extrapulmonary adenocarcinoma cases[17,18]. In our case, the lung tumor was immunohistochemically negative for TTF-1 and positive for CDX2 and HNF4α. The immunoreactivity for the three biomarkers was very similar to that of the gastric tumor that was surgically excised seven years earlier and consequently the lung tumor was finally diagnosed as an EBM from the gastric cancer. Furthermore, the disease recurred as a Krukenberg tumor after the lung tumor was excised, supporting the belief that the lung tumor was a metastasis from the gastric cancer despite the long disease-free interval.

Treatments for EBM include surgical resection, local radiotherapy, chemotherapy, and bronchoscopic disobstruction. EBM is essentially a manifestation of the disease at a far advanced stage and has poor prognosis[4,6,16]. Therefore, systemic treatment, i.e. chemotherapy, is recommended in most cases. Distinguishing EBM from primary lung cancer is vital to the selection of the appropriate chemotherapeutic regimen and could be critical for the selection of molecularly targeted drugs. In our case, surgical resection was chosen because the diagnosis could not be made before resection. The patient had peritoneal metastases thereafter and underwent systemic chemotherapy with gastric cancer regimen.

Generally, the survival time from the diagnosis of EBM is short, averaging 9 to 19 mo[4-6,16]. The prognosis for EBM from gastric cancer is unclear because we have data from only a few case reports. In our review of literature, we found that two patients surviving for a long periods were those who underwent lobectomy for metachronous EBM. Although publication bias should be taken into consideration, surgical resection could be the treatment of choice when the target lesion is single and resectable, no extrapulmonary metastasis is found, and the disease-free interval is long. In addition, as patients who underwent resection of EBM face a high risk of recurrence, they should be carefully followed up.

In summary, we have reported a rare case of EBM from gastric cancer, in which immunohistochemical analysis was useful for diagnosis and selection of the appropriate chemotherapeutic regimen. The patient in the present case is alive at 33 mo after the lobectomy. Our findings suggest that precise diagnosis and multidisciplinary treatment of EBM are important, and these could be achieved by detailed pathological analysis, including immunohistochemical evaluation of the tumor.

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S- Editor Wang JL **L- Editor** Hughes D **E- Editor** Yang C