

Peripherally Located Occult Lung Cancer with AMFR Expression

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A 67-year-old man was referred to our hospital because of positive sputum cytology. Despite detailed examination, the malignant cell source remained elusive. Twenty months later, CT revealed two nodules in the right S1 and S10 regions which were resected. A year following the operation, gastroendoscopy showed a stomach tumor. Total gastrectomy with lymph node dissection was performed. Histologically, this patient was diagnosed with double primary lung cancer with metastasis to the stomach. The tumors of the lung, stomach and tumor cells in the sputum showed the same immunoreactivities of autocrine motility factor receptor (AMFR). In our institution, of 38 occult lung cancers encountered during the past 10 years, four (10.5%) occurred in the peripheral region. The presented four cases of radiologically occult lung cancer in the peripheral region revealed bad prognosis, as three out of four patients were dead within 24 months after surgery. All of the four cases showed venous invasion, though the size of the primary tumor was small. Careful follow-up, including monitoring for distant metastasis, is necessary in radiologically occult peripheral lung cancer. (Ann Thorac Cardiovasc Surg 2003; 9: 184–7)

Key words: occult lung cancer, peripheral region, gastric metastasis, autocrine motility factor receptor (AMFR)

Introduction

Mass screening of heavy smokers by cytological examination of sputum has made it possible to detect many radiologically occult bronchogenic squamous cell carcinomas.¹⁾ In most of these cases, the carcinomas are small in extent and slight in depth of invasion, and these patients are expected to have an excellent prognosis after resection. Although radiologically occult peripheral lung cancer is rare, it does exist and awareness of its existence and careful follow-up are important. We report a case of peripherally located occult lung cancer that was detected radiologically 20 months after positive sputum cytology. A year after curative operation, this patient suffered metastasis to the stomach. We discuss the high malignancy

of radiologically occult peripheral lung cancer with a review of four cases in our institution.

Case Report

In June 1997, a 67-year-old man was referred to our hospital because carcinoma cells were detected in his sputum. However, chest X-ray, bronchoscopy, and otorhinolaryngologic examinations were normal. He had smoked 30 cigarettes a day for 45 years, and complained of a small amount of sputum. Other clinical symptoms were lacking. The results of systematic brushing of all subsegments were negative. We performed additional bronchoscopic examination four times, but brushing cytology was negative. Subsequently, he was followed up with chest roentgenograms and a computed tomography (CT) scan every three months, which produced negative results. Twenty months later (February 1999), a nodule was found by chest X-ray in the right upper segment. CT revealed two nodules, measuring 22×15 mm in diameter in the right S1 (Fig. 1a) and 18×10 mm in the right S10

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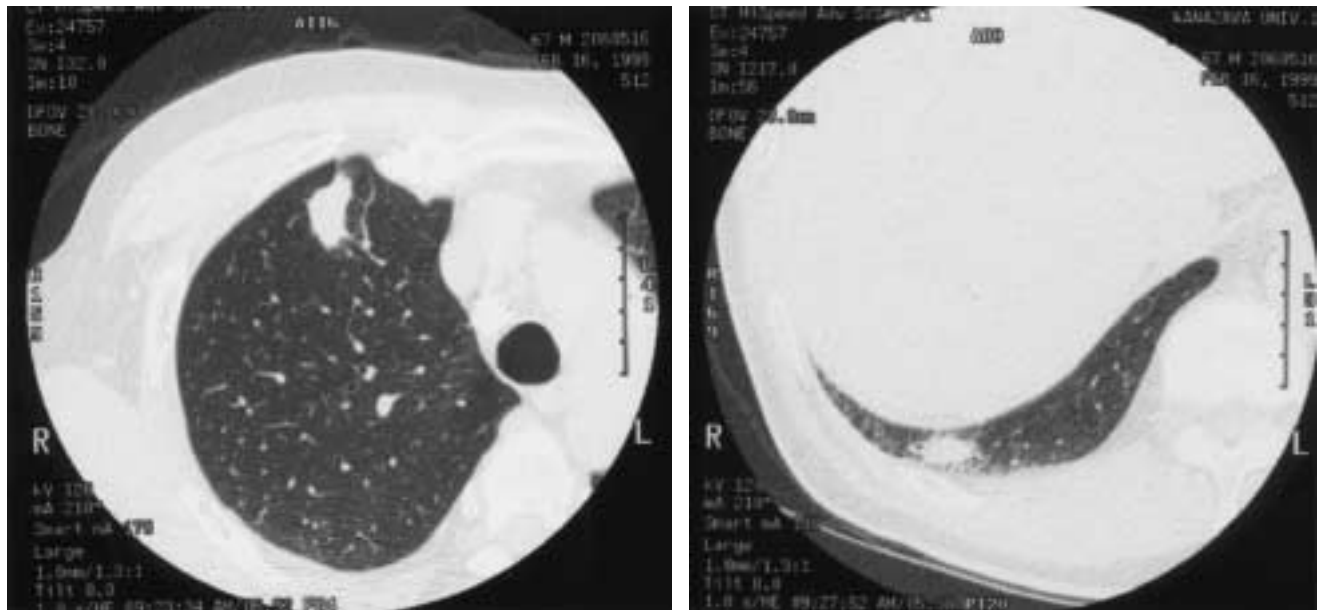


Fig. 1. Chest CT showing a nodule in the right S1 (a) and right S10 (b).

a | b

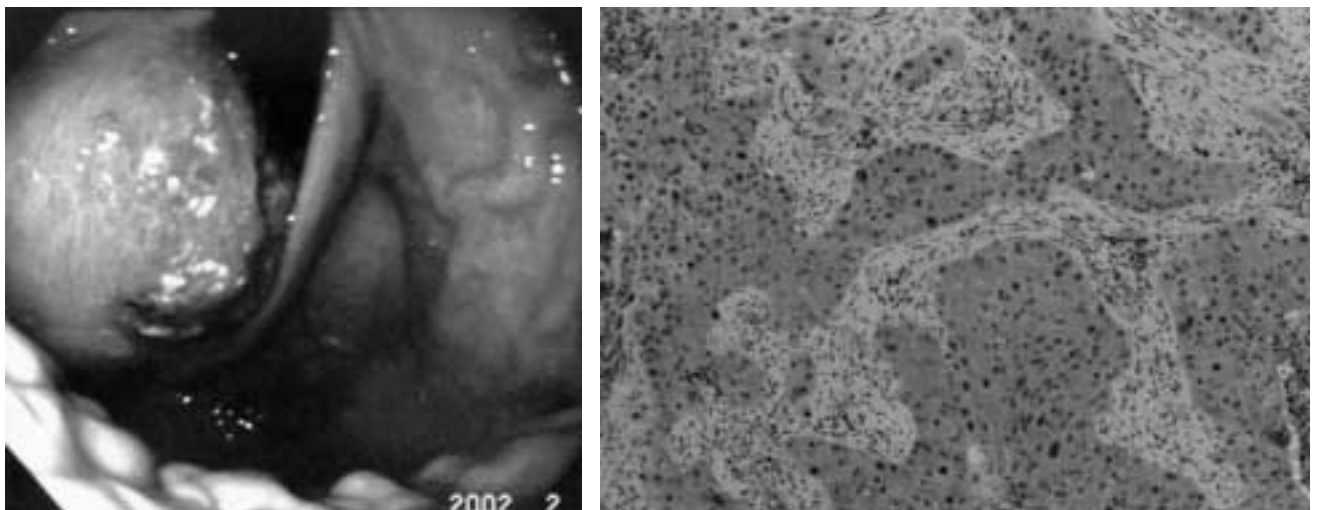


Fig. 2.

- a: Gastroscopic findings revealed a hemorrhagic tumor on the posterior wall of the cardia.
b: AMFR immunoreactivity can be observed in the metastatic stomach tumor cells.

a | b

regions (Fig. 1b). Segmentectomies were performed for each region. Histopathological diagnosis was moderately- and poorly-differentiated squamous cell carcinoma, or peripheral synchronous double primary lung cancer. There was no evidence of metastasis in the hilar or mediastinal lymph nodes. A year after the operation, the patient had hematemesis. Gastroscopy demonstrated a hemorrhagic tumor in the posterior wall of the upper stomach (Fig. 2a). Total gastrectomy with lymph node dissection was

performed. The histopathological identification of the tumor was squamous cell carcinoma (Fig. 2b), consistent with metastasis from lung cancer. The patient died six months after the second operation.

The resected specimens of the lung and metastatic gastric cancer were fixed in 10% buffered formalin, dehydrated, and paraffin-embedded. Sections with 4 μ m thickness were stained with the anti-AMFR monoclonal antibody, 3F3A diluted at 1:200. The avidin-biotin-peroxi-

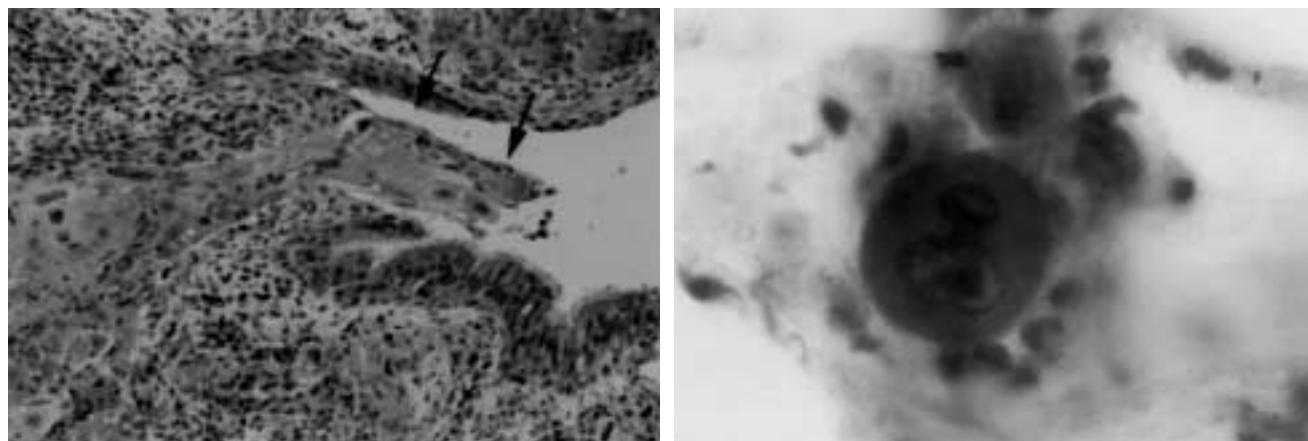


Fig. 3. Immunohistochemistry for AMFR. AMFR immunoreactivity can be observed in lung cancer tumor cells (a) and tumor cells in sputum (b). Tumor cells invading the bronchial lumen are shown by arrows (a).

a | b

Table 1. Cases of radiologically occult lung cancer in the peripheral region

Case No.	Age/ Gender	Cancer Site	Size (mm)	Histology		Time of broncho- scopy (mos)	Time interval untill detection (mos)	Method of detection	AMFR expression		Metastasis	Prognosis	
				Ly	V				Primary tumor	Cancer cell in sputum			
1	67/M	Rt S1, Rt S10	22, 18	−	+	Sq. Sq	5	20	X-P, CT	Positive	Positive	Stomach	18 mos dead
2	77/M	Lt S9	24	+	+	Sq	4	9	CT	Positive	Positive	MLN	21 mos dead
3	67/M	Rt S8	13	−	+	Ad	4	8	CT	Positive	−	−	36 mos alive
4	75/M	Rt S1	12	+	+	Sq	6	26	CT	Positive	Positive	Brain	24 mos dead

Ly, lymphatic invasion; V, vessel invasion; mos, months; AMFR, autocrine motility factor receptor; M, male; Sq, squamous cell carcinoma; Ad, adenocarcinoma; X-P, chest roentgenography; CT, computed tomography; MLN, mediastinal lymph node.

dase complex (ABC) technique was used for immunohistochemical staining. The cancer cells in the sputum were stained by the same method as above after the depigmentation of the hematoxylin-eosin stain. In the immunohistochemical examinations, most tumor cells from the lung, stomach, and in the sputum were positive for AMFR (Fig. 2b, 3).

Discussion

Sputum cytology has been effective in identifying radiologically occult lung carcinoma. Currently, it is utilized in mass screening, when lung carcinoma is suspected. Radiologically occult lung cancer occurs mainly in the larger bronchus, whereas occult tumors developing from the lung peripheral region are relatively rare. In our institution, of 38 occult lung cancers during the last 10 years, four

resions (10.5%) occurred in the peripheral region. Table 1 summarizes the assessment of these cases.

Detection of radiologically occult lung cancer in earlier stages may lead to highly effective surgical treatment and lower lung carcinoma death rates. A few reports^{2,3)} have addressed the survival rate and later outcome of patients with occult lung cancer detected by sputum cytology. The overall 5-year survival ratio, following surgical resection, was favorable at 91%,²⁾ and 93.5%,³⁾ though the location of the carcinoma was not considered in these studies. We could find no reports discussing the prognosis of occult lung cancer in the peripheral region. The present four cases of radiologically occult lung cancer in the peripheral region revealed a bad prognosis, as three out of four patients were dead within 24 months after surgery. All four showed venous invasion, even though the size of the primary tumor was small.

Autocrine motility factor (AMF) is a tumor-secreted cytokine that stimulates both random and directed cell migration by binding to its receptor, AMFR/gp78.⁴⁾ Recent studies have demonstrated that increased AMFR expression is strongly correlated with a high incidence of recurrence and decreases the survival of patients with various malignancies.⁵⁻⁸⁾ In all four cases of occult lung cancer with peripheral lesions, the primary tumors were positively stained with AMFR. Cancer cells in the sputum of three patients were also positive for AMFR expression. The high expression of AMFR in the tumor tissue and venous invasion of tumor cells in the early stage may result in bad prognosis. There is a possibility that cancer cells infiltrate into the sputum at an early stage because this type of tumor cell has high motility.

In conclusion, our finding revealed the possibility for high malignancy of peripheral occult lung cancer because of its ability to induce cell migration. Careful follow-up, including monitoring for distant metastasis, is necessary in radiologically occult peripheral lung cancer.

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