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Case Report

Atypical Carcinoid Tumor of the Lung: Report of a Case with Intrapulmonary Metastasis

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A 71-year-old man was noted to have a nodular opacity in S8 of the right lung. Thirteen months later, the chest CT showed a lesion "gloved finger shape" with focal calcification, and a small nodular opacity appeared in right S7. A right lower lobectomy was performed under video-assisted thoracic surgery.

The tumor filled the S8 bronchus, with invasion into the pulmonary parenchyma and S7 metastasis. Mitotic figures were seen in 5 of 10 high power fields. Positive staining for chromogranin A and synaptophysin led to the diagnosis of atypical carcinoid.

The patient has been disease-free without treatment for 9 months.

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Introduction

Carcinoid tumor is rare and accounts for less than 2% of bronchial neoplasms.[1] The most common symptoms of carcinoid tumor are cough and haemoptysis, typically related to the bronchial obstruction.[2] Pulmonary carcinoid tumors are divided into typical and atypical subtypes; the atypical subtypes show more malignant histologic and clinical features.[3]

We report a case of atypical carcinoid (AC) tumor in the right lower lobe which metastasized to the adjacent lung.

Case Report

A 72-year-old man had been followed for an abdominal aneurysm for 7 years. Past history and family history were non-contributory. The patient had been smoking 40 cigarettes a day for 50 years and drank 500 ml of Japanese liquor a day for 40 years.

At the age of 71 years, chest CT examination revealed a lobulated nodular opacity in S8 of the right lung (Figure 1a). Since a vascular lesion was considered the most likely diagnosis, the patient was followed conservatively. After 13 months, the tumor had increased in size, with intraluminal extension to the proximal portion of the right S8 bronchus on CT (Figure 1b). At the peripheral portion of the tumor, CT showed a lesion with "gloved finger shape" with focal calcification (Figure 1c). The tumor had moderate enhancement on contrast-enhanced CT, and the possibility of a vascular lesion was ruled out (Figure 1d). In addition, a new small nodular opacity appeared in S7 of the right lung (Figure 1e).

The serum CEA level was slightly elevated (5.7 μg/l, normal<5 μg/l), and CYFRA and pro-GRP levels were in the normal range. At bronchoscopy, a white mass coated with inflammatory debris was seen in the bronchus (B8b) of the right lung. Cytological examination of the material obtained at bronchoscopy showed degenerated cluster formation, which indicated class III with suspect malignancy.

Since the tumor showed enlargement, and metastasis was sus-

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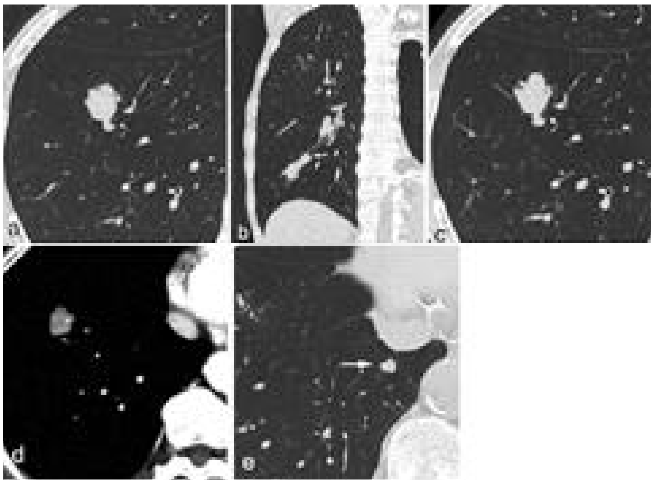

Figure 1. CT imaging
a. Axial image of high-resolution CT at the time the tumor was initially noted. A Lobulated nodular opacity is seen in S8 of the right lung.
b. Oblique-coronal reconstruction image of high-resolution CT at 13-month follow-up.
The tumor increased in size with intraluminal extension into the proximal portion of the right S8 bronchus (arrow).
c. Axial image of high-resolution CT at 13-month follow-up.
The peripheral portion of the tumor has a "gloved finger shape" with focal calcification.
d. Axial image of contrast-enhanced CT at 13-month follow-up.
The tumor has moderate enhancement in the early phase. Focal calcification is also evident.
e. Axial image of high-resolution CT at 13-month follow-up. (Lower level of the main tumor shown in Figure 1c)
A new, small, nodular opacity is seen in S7 of the right lung (arrow).

pected, the lesion was considered to be malignant. Therefore, right lower lobectomy under video-assisted thoracic surgery was performed. Intraoperative pleural washing cytology was negative. The aspiration biopsy cytology of the lesion revealed AC or well-differentiated adenocarcinoma. Right lower lobectomy with regional lymph node resection was carried out.

White tumor filled the bronchial lumen at the cut surface. There also was a small nodule at S6, which was suspected to be metastasis (Figure 2). Histopathologically, the tumor filled and expanded the S8 bronchial lumen, with partial invasion into the pulmonary parenchyma (Figure 3a, b). The tumor formed nests and showed a trabecular or rosette pattern without gland formation (Figure 3c). The tumor cells had uniform nuclei with uniformly round to oval shapes. An area in the tumor showed large and strongly oncocytic morphology (Figure 3a, c). The elastic stain revealed suspicious area of vessel invasion (Figure 3d). Mitotic figures were counted in 5 of 10 high power fields (HPF). Immunohistochemical staining was positive for chromogranin A and synaptophysin (Figure 4). Based on these findings, the lesion was diagnosed as AC.

The right S7 nodule showed atypical epidermal cell proliferation with foam cell infiltration and degenerative change. Immunohistochemical staining was positive for chromogranin A and synaptophysin, which confirmed the diagnosis of metastasis.

Both of the primary and metastatic tumor showed negative reaction for CEA. The serum CEA level also didn't change after surgery.

Nine months after surgery, the patient has been free from disease with no further treatment.

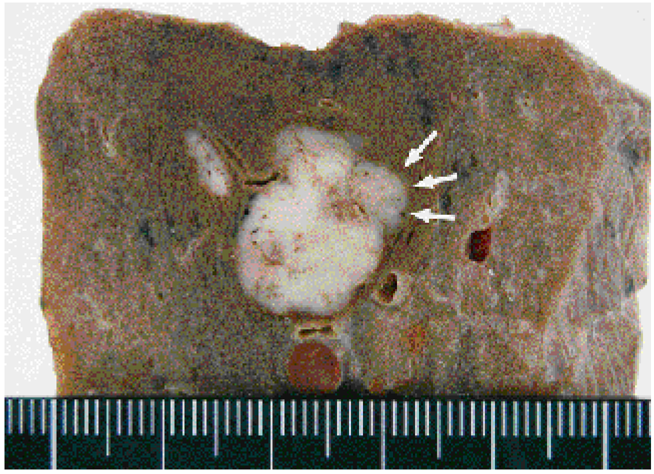

Figure 2. Cut surface of the tumor.
A white tumor fills the bronchial lumen. Infiltration to the lung parenchyma is suspected (arrows).

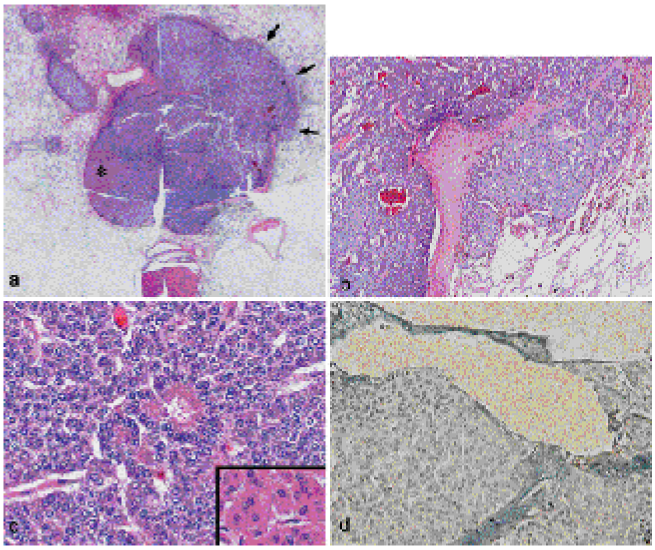

Figure 3. Microscopic findings.
a. Scanning view.
The tumor occludes the bronchial lumen and invades the pulmonary parenchyma (arrows).
There is an eosinophilic area. (*)
b. The invasive area.
The tumor infiltrates the alveolar space, breaking through the bronchial wall. (HE, x40)
c. High power view.
The tumor cells have regular nuclei and rather basophilic granular cytoplasm, and rosette formation is seen. (HE, x200) Inset: High power view of the oncocytic area observed in Figure 3a. The tumor cells are rich in eosinophilic granular cytoplasm. (HE, x200)
d. Elastic stain finding.
The tumor cells invade the vessel wall with elastic fiber, directly contacting the subendothelial area, suggesting the possibility of vascular metastasis. (EVG, x100)

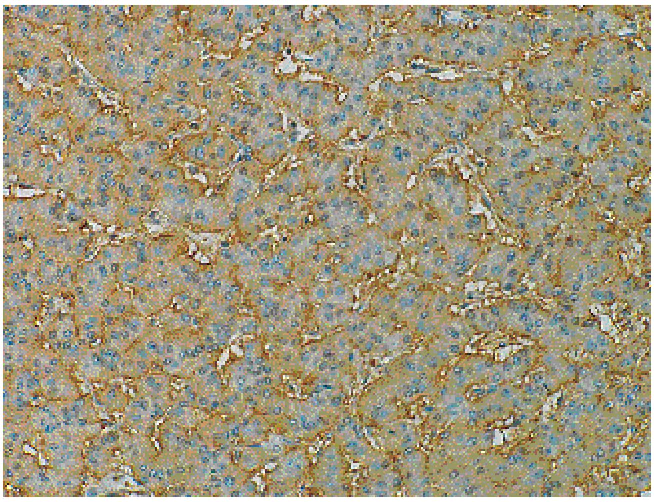

Figure 4. Immunohistochemical staining.
The tumor cells are positive for chromogranin A. (x200)

Discussion

Hamperl first used the term carcinoid in 1937 for a lung tumor with low-grade malignancy and a good prognosis.[4] In 1944, carcinoid was further subclassified into typical and atypical carcinoid tumors by Engelbreth-Holm,[5] based on the presence of aggressive behavior in some cases.

In 1999, Travis et al. defined the typical carcinoid (TC) as a carcinoid tumor with fewer than 2 mitoses per 2 mm^2 and lacking necrosis, while, on the other hand, AC is a carcinoid tumor with 2-10 mitoses per 2 mm^2 and/or foci of necrosis. This proposal was adopted in the classification of lung tumors by the World Health Organization.[2] Immunohistochemically, positivity for neuroendocrine markers such as chromogranin A, synaptophysin, Leu-7 (CD57), and N-CAM (CD56) makes the diagnosis of carcinoid tumor definite.[2] In the present case, chromogranin A and synaptophysin were positive in both the main tumor and in the metastatic focus, confirming the diagnosis of carcinoid with metastasis.

Compared with TC, AC has significant differences in the occurrence of distant metastases and patient survival. At presentation, it has been reported that 10-15% of TC cases had already metastasized and had regional lymph node involvement, and 5-10% of cases eventually will metastasize to distant sites such as liver or bone. However, 40-50% of AC cases were reported to have metastasized to the regional lymph nodes, and the tumor progressed further in approximately 20% with Stage Ⅱ, 15% with Stage Ⅲ, and 10% with Stage Ⅳ,[6] with rare reports of skull or pituitary metastases.[7,8] The present case had already metastasized to the lung parenchyma at the time of presentation, when the tumor was Stage Ⅳ, which is concordant with the aggressive behavior of AC.

In a report that included 252 carcinoid cases, TC showed significantly better survival than AC; 10-year survival was 93% in TC and 64% in AC.[9] The recurrence rate was also significantly different between TC (3.4%) and AC (17.9%).[9] Therefore, it is important to differentiate these two subtypes.[9,10] In AC, a higher mitotic rate, tumor size of 3.5 cm or greater, female gender and presence of rosettes are independent predictors of worse patient survival.[6]

About 1% of patients with pulmonary carcinoid present with carcinoid syndrome, including symptoms such as acute diarrhea, flushes, palpitations, and asthma-like symptoms (wheezing) caused by the release of vasoactive substances into the systemic circulation by the tumor.[11] In addition, 2% of pulmonary carcinoid tumors have been reported to release ACTH and cause Cushing's syndrome.[11,12] Pulmonary carcinoid tumors that secrete ACTH are considered to be aggressive.[12] Bronchopulmonary carcinoid tumors are the most frequent cause of ectopic ACTH secretion.[12] There are also reports of GHRH secretion,[11,13] which resulted in acromegaly[13] and was successfully treated with somatostatin analog therapy.[13] In the present case, the tumor did not secrete any hormones.

The radiologic findings of TC and AC are very similar.[14] About 80% of bronchial carcinoids arise centrally in the main, lobar or segmental bronchi, and show no specific lobar distribution.[15] In cases of centrally located lesions, chest radiographs and CT scans often show a v-shaped or w-shaped tubular opacity due to intraluminal extension of the tumor and/or mucoid impaction, which is called "gloved finger opacity".[14] In the present case, the tumor also presented as a "gloved finger opacity" on CT, and intraluminal extension of the tumor was evident pathologically. When the lobar bron chus is completely obstructed by the tumor, atelectasis or obstructive pneumonia commonly occurs.[15] However, in the present case, since the tumor was located in the segmental bronchus, atelectasis or obstructive pneumonia was not produced because of collateral air drift from surrounding pulmonary tissue. With respect to the differential diagnosis of AC, large cell neuroendocrine carcinoma and small cell lung carcinoma, which are neuroendocrine tumors with a higher degree of malignancy, are important. However, these tumors are easily distinguished by their higher mitosis rate (greater than 10/2 mm^2).[2]

Treatment for pulmonary carcinoid can be bronchoscopic or surgical. Most cases are treated surgically with pulmonary lobectomy, as in the present case.[3] Initial bronchoscopic treatment can be used to improve the presurgical condition, to obtain tissue samples for proper histological classification, and to enable less extensive parenchymal resection;[16] however, bronchoscopic resection is limited to cases with very early phase tumors that are confined to the bronchus. Radical mediastinal lymphadenectomy is recommended in patients with nodal involvement to improve their survival.[10,17]

Patients with either locally-advanced/unresectable or metastatic carcinoid tumor are usually treated with chemotherapy and/or radiotherapy.[18] Streptozocin, 5-flourouracil (5-FU), paclitaxel, alpha-interferon, etoposide, cisplatin and their combinations have been used as chemotherapy. Until recently, only a few small-scale older studies describing combination anticancer drug therapy were available.[19-21] It has been reported that combined-modality treatment with paclitaxel resulted in partial response.[11] Alpha-interferon treatment has also been reported to stabilize the disease in 4 of 27 patients (median duration 15 months), while 23 patients showed progressive disease. Streptozocin and 5-fluorouracil were reported to result in progressive disease in 7 of 7 patients.[22] One report has suggested that there is no role for streptozocin-based therapy.[18] Thus, chemotherapy has not been reported to be effective in pulmonary carcinoid tumor.

Although the present patient had an intrapulmonary metastasis, the tumor was curatively resected, and there was no lymph node metastasis. Therefore, no further treatment has been performed, and the patient is being followed. Although the patient has been disease-free for 9 months, careful follow-up for recurrence is necessary, since the patient has already had a metastasis.

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