CASE REPORT

An autopsy case of rapid progressive atypical carcinoid of the lung discovered with multiple nodular shadows

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Abstract : We report an autopsy case of rapid progressive atypical carcinoid of the lung discovered as multiple nodular shadows. The patient was an 82-year-old man with non-productive cough. Both chest radiography and computed tomography revealed multiple nodules in both the lung and pleural effusion. Multiple metastases to bone and liver were also noted. Samples from the wall-side pleural lesion were obtained by video-assisted thoracoscopic surgery under local anesthesia, and histological examination led to a diagnosis of atypical carcinoid. Treatment was ineffective and the patient died on day 39 after admission. The primary site was identified as the lung after autopsy. We believe that early detection is crucial in the treatment of atypical carcinoid due to poor prognosis. J. Med. Invest. 55 : 142-146, February, 2008

Keywords **:** *atypical carcinoid, lung, computed tomography, video-assisted thoracoscopic surgery*

INTRODUCTION

Carcinoid tumors comprise 1-2% of all lung tumors (1). Although carcinoid tumors are generally considered to represent a low-grade malignancy, an atypical variant exists that exhibits more virulent behavior and less favorable prognosis. The first description of atypical carcinoid tumor appeared in 1944, when Engelbreth-Holm described two cases of bronchial carcinoids with atypical features (2). Treatment for carcinoid tumors involves complete surgical removal, while a more aggressive approach is required in the treatment of atypical carcinoid tumors. The case of atypical carcinoid tumor described herein was discovered as multiple nodular shadows and pleural effusion on chest radiography, and was diagnosed by video-assisted thoracoscopy. Aggravation of the condition was rapid and the patient died shortly after admission. Autopsy was performed. We describe an unusual case of atypical carcinoid tumor of the lung and review the relevant literature.

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CASE REPORT

An 82-year-old man was referred to our hospital from his local physician due to dry cough, dyspnea and abnormal chest shadows on chest radiography. He had never smoked. On admission to our hospital, no abnormalities were identified other than weakness of breath sounds in the left chest. Laboratory blood examination revealed decreases in both hemoglobin and total protein levels (Table 1). Erythrocyte sedimentation rate and levels of C-reactive protein and lactate dehydrogenase were elevated. In addition, serum levels of neuron-specific enolase (NSE), a tumor marker, were markedly

Table 1. Clinical examination test on admission

WBC	6900/μl	GOT	19IU/L
Neutro	63.1%	GPT	22IU/L
Eos.	5.1%	LDH	230IU/L
Baso.	1.2%	T-Bil	0.46mg/dl
Mono.	6.1%	γ-GTP	62IU/L
Lymph.	24.5%	TP	6.2g/dl
RBC	391× 10^4/μl	BUN	20.3mg/dl
Hb	11.9g/dl	Cre	0.97mg/dl
Ht	35.7%	Na	141mEq/L
Plt	21.1× 10^4/μl	K	4.40mEq/L
ESR	50mm/hour	Cl	109mEq/L
CRP	0.85mg/dl	NSE	57ng/ml
		Pro-GRP	17.4pg/ml
		CEA	3.3ng/ml

increased (normal : <10 ng/ml). Conversely, carcinoembryonic antigen and progastrin-releasing peptide levels were within normal ranges.

Radiography and computed tomography (CT) of the chest reveled multiple nodules in bilateral middle and lower lobes, and bilateral pleural effusion (Figs. 1, 2). Multiple metastases to the bone and liver were also noted. Although bronchoscopy was performed, a definitive diagnosis could be identified.

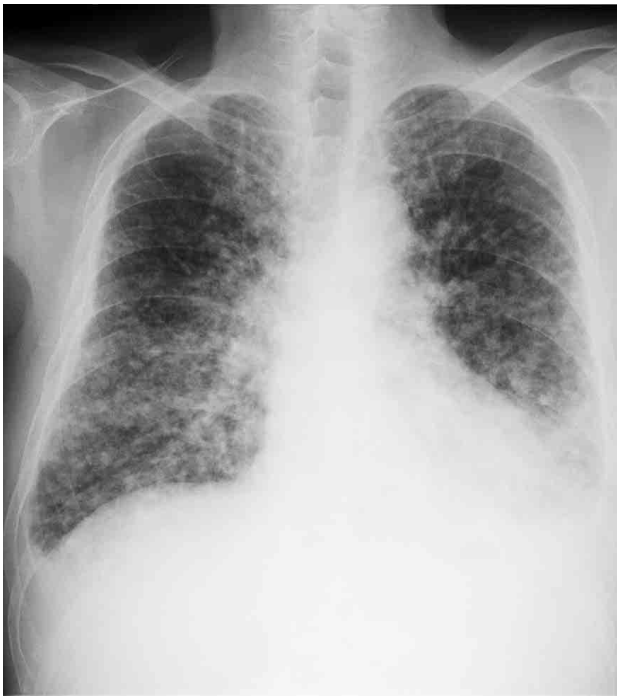

Fig. 1 Chest radiography on admission showing multiple nodules in both lungs.

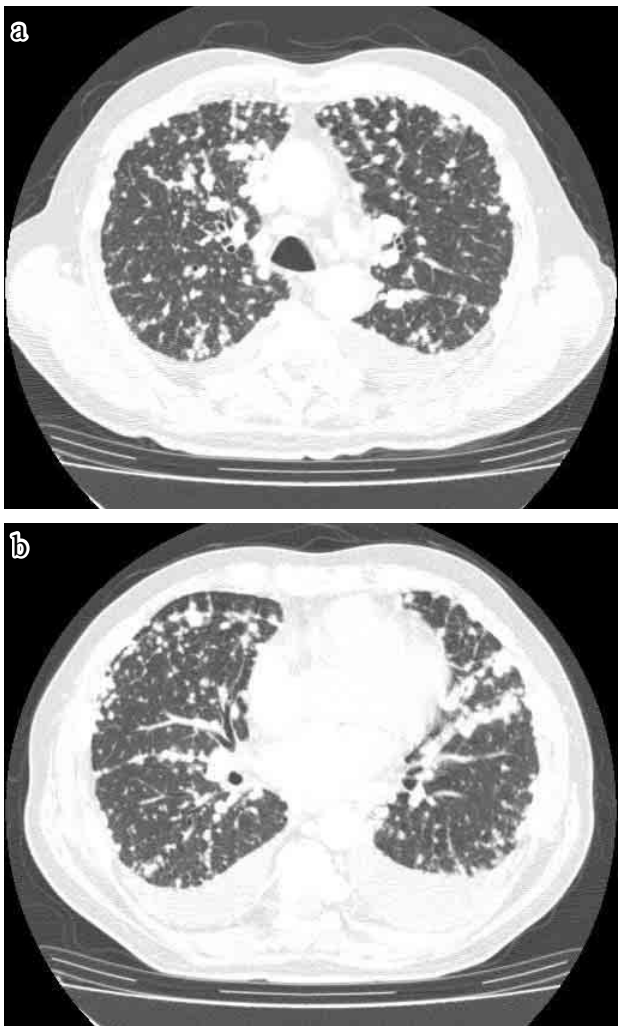

Fig. 2 a, b) Chest CT on admission, demonstrating multiple shadows in both lung fields.

Specimens for histological examination were obtained from the pleural wall lesion by video-assisted thoracoscopic surgery under local anesthesia. Thoracoscopic findings showed multiple nodules at the pleural surface. Histological findings demonstrated that tumor cells displayed small, round nuclei with increased levels of chromatin and a low nucleus/cytoplasm (N/C) ratio. Cells displayed a nested, nodular arrangement and numerous mitotic figures, and intracellular connections were weak. Blood vessels were included diffusely inside tumors and necrotic lesions were also occasionally observed in high-power fields (Fig. 3). Immunohistochemistry revealed that tumor cells were positive for chromogranin A, NSE and synaptophysin (Fig. 4), and negative for AE 1/3, CK7, CK20, EMA, CEA and thyroid transcription factor (TTF)-1 (data not shown). MIB-I index was >10%. Histological diagnosis was

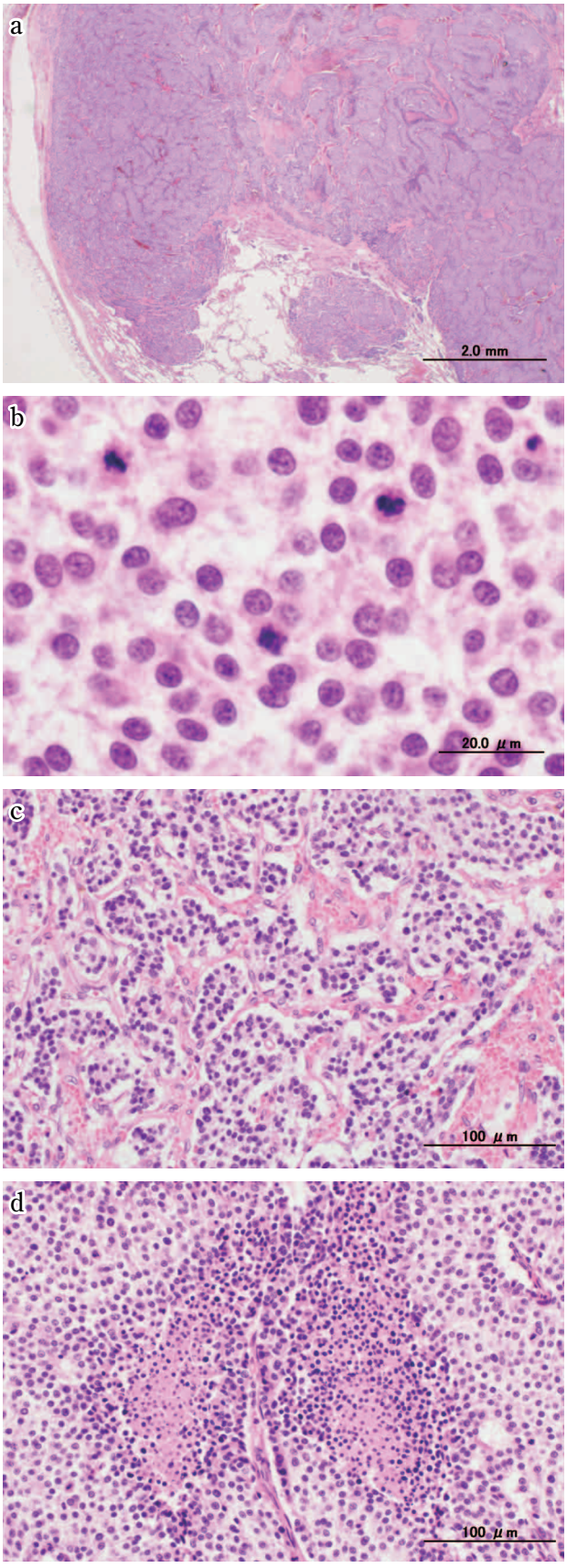

Fig. 3 a-d) The specimen obtained from the wall side of the pleural lesion using thoracoscopy showed small nuclei and small deep stained round nuclei with many nuclear division (b), with weak intercellular connections but infiltrative growth with alveolar structures containing vessels. Several areas appeared rosette-like (c). Necrotic areas were identified (d).

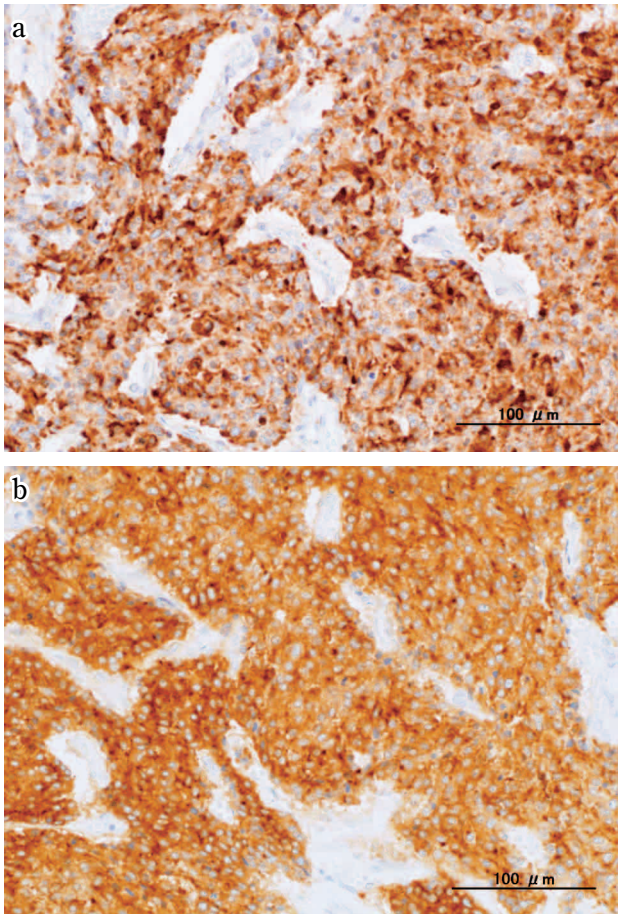

Fig. 4 a, b) Immunohistochemical findings show positive staining of tumor cells for synaptophysin and chromogranin A.

atypical carcinoid, not small cell carcinoma, based on the following findings : tumor cells showed low N/C ratio, presence of clear, big nuclei compared with those in small cell carcinoma, positivity for chromogranin A, and overly extensive synaptophysin. Tendency of infiltration to organs was weak, and cells formed clumps (Table 2). Given the anatomical location of the tumor, atypical carcinoid was diagnosed.

For control of pleural effusion, local combination chemotherapy comprising hypotonic cisplatin treatment using 250 ml distilled water, cisplatin 10 mg, OK432 10KE, and 100 mg minocycline was initiated according to a modification of the method described by Ichinose, *et al*. (3). This treatment had no effect. Disease progressed rapidly and the patient died on day 17 after initiation of treatment. Autopsy was performed, and no lesion of atypical carcinoid could be confirmed in the digestive organs, although >80% of carcinoid tumors develop in the wall of the hollow organs of the gastrointestinal tract (4). The tumor was thus identified as atypical carcinoid tumor arising from the lungs.

Table 2. Clinicopathological characteristics between typical, atypical carcinoid large cell neuroendocrine carcinoma and small cell carcinoma

Clinicopathological Features	TC	AC	LCNEC	SCLC
Mitoses	Absent or rare	5 to 10 per 10 HPF	More than 10 per 10 HPF (average, 75 per 10 HPF)	More than 10 per 10 HPF (average, 75 per 10 HPF)
Necrosis	Uncharacteristic	Frequent, usually punctate	Frequent, usually infarct-like	Frequent, usually infarct-like
Nuclear,pleomorphism, hyperchromatism	Uncommon	Sometimes	Frequent	Cells are usually small, large pleomorphic cells are rare unless mixed SC/LC
N/C ratio	Moderate	Moderate	Low	High
Nucleoli	Occasional	Common	Very commom	Absent or inconspicuous
Nuclear chromatin	Finely granular	Finely granular	Usually vesicular,can be finely granular	Finely granular
Histological grade	Low	Intermediate	High	High
5-y survival(%)	87-100	37-71	15-44.8	10-20*, 0-5**

Abbreviations : HPF, High-power fields ; N/C, Nuclear to cytoplasmic ; SC/LC, Mixed small-cell/large-cell carcinoma ; *Liimited disease
**Extensive disease

DISCUSSION

Carcinoid tumors constitute approximately 1-2% of all lung tumors (5). These are low-grade malignancies that belong to the amine precursor uptake decarboxylase group of tumors. The bronchopulmonary tract has a rich and complex complement of neuroendocrine cells (6), and bronchial carcinoids appear to share a common neuroectodermal stem cell origin with small cell carcinoma of the lung (7).

The clinical presentation of carcinoid tumors largely depends on location and size. Tumors usually cause symptoms only after growing large enough to restrict the airways. Moreover, carcinoid syndrome appears in patients with carcinoids (7). However, the present patient showed neither signs nor symptoms suggestive of carcinoid syndrome.

Carcinoids can be divided into typical and atypical types, the difference being first defined by the histopathological criteria of Arrigoni, *et al*. and later modified by Travis, *et al*., eventually resulting in the generally accepted classification (8-10). Carcinoids are almost equally distributed between males and females (9). Mean age of onset is approximately 47 years, but atypical carcinoid tumors occur in significantly older patients (11-13). Although this theory is speculative, such age differences might be due to smoking as a risk factor. Several studies support the hypothesis that smoking may represent a risk factor in the development of atypical carcinoid tumor (14-15), but the present patient was a non-smoker.

In accordance with the classification of typical carcinoids and atypical carcinoids on pathological and clinical grounds, molecular studies have also shown differences between typical and atypical carcinoids and between atypical carcinoids and other neuroendocrine tumors (16-20). Based on these reports, abnormalities in tumor-suppressor genes and oncogenes are seen more frequently in atypical than in typical carcinoids.

Chest imaging is widely recognized for detecting mean lesion sizes of approximately 3 cm (although much larger lesions are also frequent), mostly centrally located, with only approximately one-third located in peripherally (21). In this case, chest radiography showed multiple nodules in both lungs. To the best of our knowledge, pulmonary atypical carcinoid with multiple nodules in bilateral lung fields on diagnosis is very rare. Metastasis was observed more frequently with atypical carcinoid tumors than for other bronchopulmonary carcinoids (22). The multiple nodules in our case were considered pulmonary metastases of atypical carcinoid tumor. Although the primary site in this case was unclear, we did not identify atypical carcinoid cells in the digestive organs, which are the most common primary organ after autopsy. We thus consider that the primary organ in this case was the lungs.

In conclusion, we have presented an autopsy case of rapid progressive atypical carcinoid of the lung discovered as multiple nodular shadows and a rare clinical course involving no carcinoid syndrome signs. Furthermore, the outcome following chemotherapeutic treatment was fatal. In this regard, early diagnosis is important for more successful surgical treatment.

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