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**CASE REPORT** 

# **Endobronchial Large Cell Neuroendocrine Carcinoma**

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Lung tumors with neuroendocrine morphology include typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma, and small cell carcinoma. The World Health Organization emphasizes the importance of mitotic count in differentiating these tumors. We studied the case of a 58year-old male nonsmoker with recurrent pneumonia and an endobronchial mass, which was removed by right middle lobectomy. The patient was alive with no recurrent disease at 36-month follow-up. Histologically, the tumor showed welldeveloped neuroendocrine morphology but con-

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#### Introduction

The differential diagnosis for lung tumors with neuroendocrine morphology includes typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma, and small cell carcinoma.<sup>1</sup> The revised World Health Organization (WHO) International Histological Classification emphasizes the importance of mitotic count in differentiating these tumors.<sup>1</sup> Typical carcinoid tumors exhibit fewer than 2 mitoses per 10 high-power fields (HPFs). Similar tumors with 2 to 10 mitoses per 10 HPF or necrosis are diagnosed as atypical carcinoids. A neuroendocrine lung tumor with more than 10 mitoses per 10 HPF is categorized as a large cell neuroendocrine carcinoma or a small cell carcinoma, depending on other histologic features. By definition, large cell neuroendocrine carcinomas are also reactive for 1 or more neuroendocrine markers by immunohistochemistry or contain neuroendocrine granules by electron microscopy.

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tained up to 20 mitoses per 10 high-power fields and was therefore diagnosed as a large cell neuroendocrine carcinoma. However, several features, including the carcinoid-like morphology and endobronchial location of the tumor, absence of smoking history, and promising clinical course, were more characteristic of an atypical carcinoid than of a large cell neuroendocrine carcinoma. It may be necessary to redefine histologic criteria to allow a higher mitotic rate for classification as an atypical carcinoid. (Pathology Oncology Research Vol 9, No 3, 198–200)

Small cell carcinomas are distinctive tumors with characteristic cytologic features, frequent mitoses, and extensive necrosis.

We report a case of an unusual neuroendocrine lung tumor that showed several features of an atypical carcinoid but was diagnosed as a large cell neuroendocrine carcinoma because of an increased mitotic rate.

## Report of a Case

A 58-year-old man with no significant past medical history presented with right-sided chest pain and productive cough. He denied a history of smoking. Pneumonia was diagnosed and treated with antibiotics. Healing occurred with residual right middle lobe consolidation. Four months later, the symptoms recurred and included intermittent hemoptysis. The patient's temperature was subfebrile. Chest radiographs and computed tomographic scans showed right middle lobe atelectasis and mild hilar lymphadenopathy. Bronchoscopy revealed a round yellow mass that occluded the orifice of the right middle lobe bronchus. Bronchial biopsies were performed, followed by right middle lobectomy and hilar lymph node sampling. At latest follow-up, 36

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*Figure 1.* Low-magnification view of the endobronchial tumor showing organoid nesting growth pattern. The surface is covered by metaplastic squamous epithelium. (HE; ×40)



Figure 2. High-magnification view showing a pseudorosette. (HE;  $\times$ 400)

months after surgery, the patient was asymptomatic. Follow-up bronchoscopy and imaging studies revealed no recurrent disease.

Gross examination of the right middle lobectomy specimen revealed an endobronchial, yellow-white polypoid mass measuring 2.5 cm in greatest dimension. The lesion occluded the lumen of the right middle lobe bronchus, and the pulmonary parenchyma distal to the lesion was atelectatic. Histologically, the tumor showed well-developed neuroendocrine growth patterns, including organoid nesting, trabeculae, and pseudorosettes (Figure 1 and 2). Focal necrosis was also seen. At higher magnification, the neoplastic cells exhibited abundant amphophilic cytoplasm, moderately pleomorphic nuclei, and finely granular chromatin. A mitotic rate of up to 20 mitoses per 10 HPF was noted (*Figure 3*). The respiratory epithelium overlying the lesion showed squamous metaplasia. The hilar lymph nodes showed anthracosis and no evidence of malignancy. In paraffin immunoperoxidase studies, the neoplastic cells were strongly reactive for neuron-specific enolase and chromogranin A (*Figure 4*). These results were similar to those in the biopsy specimen taken before the lobectomy.

### Discussion

The case presented here did not show cytologic features of a small cell carcinoma, and the presence of necrosis excluded a typical carcinoid. Therefore, the differential diagnosis was narrowed down to atypical carcinoid or large cell neuroendocrine carcinoma. Because of the increased mitotic rate (more than 10 mitoses per 10 HPF), a diagnosis of large cell neuroendocrine carcinoma was made.

A review of computerized tomography studies showed that approximately one-third of carcinoid tumors are located centrally, one-third peripherally, and one-third in the mid portion of the lung.<sup>2</sup> Central carcinoids frequently exhibit a large endobronchial component.<sup>2,3</sup> Large cell neuroendocrine carcinomas may be central or peripheral and may extensively replace the lung.<sup>2,4</sup> However, to our



**Figure 3.** High-magnification view with numerous mitoses. (HE; ×400)



*Figure 4.* Paraffin immunoperoxidase study showing reactivity for chromogranin A. (×200)

knowledge, predominantly endobronchial large cell neuroendocrine carcinoma has not previously been described.

Atypical carcinoids and large cell neuroendocrine carcinomas are both malignant neoplasms, but atypical carcinoids are intermediate grade and large cell neuroendocrine carcinomas are high grade. Whereas the survival rate for atypical carcinoids is 56% at 5 years and 35% at 10 years, it is 27% at 5 years and 9% at 10 years for large cell neuroendocrine carcinomas.<sup>5</sup> Survival for large cell neuroendocrine carcinoids after stratification for stage.<sup>5,6</sup> Furthermore, the majority of large cell neuroendocrine carcinomas relapse with distant metastases within 6 months after surgery.<sup>7,8</sup> Our patient is alive without recurrence of the tumor 36 months after surgery. Thus, his clinical course seems to be unusual for a patient with large cell neuroendocrine carcinoma.

The mitotic activity criteria used to diagnose an atypical carcinoid have changed over time. In 1972, Arrigoni et al<sup>9</sup> suggested that atypical carcinoids contained 1 mitotic figure per 1 to 2 HPF, or 5 to 10 mitoses per 10 HPF. In 1998, Travis et al<sup>5</sup> analyzed 200 neuroendocrine lung tumors using statistical methods and redefined the mitotic criteria for atypical carcinoids as 2 to 10 mitoses per 10 HPF. These criteria were incorporated in the new WHO classification of lung tumors.<sup>1</sup>

The tumor presented here was diagnosed as large cell neuroendocrine carcinoma because of the increased mitotic rate. However, several features of the case were more characteristic of an atypical carcinoid, including the welldeveloped neuroendocrine morphology, endobronchial location of the tumor, absence of smoking history, and promising clinical course. If similar cases are identified in the future, it may be necessary to adjust the mitotic criteria to allow a somewhat higher mitotic rate in diagnosing atypical carcinoids.

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