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Case report

Roentgenological occult large-cell neuroendocrine carcinoma: Report of a long-term survivor

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ABSTRACT

A 64-year-old male patient complained of a one-month history of bloody sputum. A polypoid tumor was almost obstructing the orifice of the subsegmental bronchus (B8b) of the anterior basal segment of the right lower lobe on bronchoscopy. Biopsy specimens of the tumor surface yielded a diagnosis of undifferentiated carcinoma. Clinical staging was T1aN0M0, stage IA. Surgical resection that comprised a right upper lobectomy with systematic mediastinal and hilar lymph node dissection was performed. Histopathologically, the tumor specimen was compatible with large-cell neuroendocrine carcinoma (LCNEC) of the subsegmental bronchus. Pathological staging was T1aN0M0, stage IA. To our knowledge, few cases of central-type LCNEC have been reported in the English literature, and ours is the first report of roentgenological occult LCNEC.

1. Introduction

Large-cell neuroendocrine carcinoma (LCNEC) of the lung was proposed in 1991 by Travis et al.[1] This tumor was categorized in the spectrum of pulmonary neuroendocrine tumors such as typical carcinoid tumors, atypical carcinoid tumors, LCNEC, and small cell carcinoma. The revised WHO International Histological Classification of lung tumors considers LCNEC as a subtype of large-cell carcinoma.[2] The present case involved LCNEC, as determined by the presence of nuclei with remarkable atypia and morphology.

LCNEC is found in 2.9[3] to 3.1%[4] of resected specimens of primary lung cancer. It is a rare tumor and has a tendency to affect individuals with a smoking history[1,5] and males.[4] LCNEC typically occurs in the peripheral lung field, and only two individual cases of central-type LCNEC have been reported in the English literature.[5,6] Thus, we present a long-term survival case of central-type LCNEC, which represents the first report of roentgenological occult LCNEC.

2. Case

A 64-year-old male patient was referred for further examination because of a 1-month history of bloody sputum. The patient had no relevant medical history, but had smoked 1.5 packs of cigarettes daily from 20 to 25 years of age. His physical examination, routine laboratory test results, sputum cytology, and tumor markers were normal (CEA 2.6 ng/ml, NSE 3.8 ng/ml, Pro-GRP 19.7 ng/ml, and CYFRA 0.7 ng/ml).

Chest roentgenography and computed tomography (CT) showed no remarkable findings. On endoscopy, a polypoid tumor was found obstructing the orifice of the subsegmental bronchus (B8b) of the anterior basal segment of the right lower lobe (Fig. 1a). Biopsy specimens of the tumor surface yielded a diagnosis of undifferentiated carcinoma. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT imaging and brain magnetic resonance imaging were negative for distant and lymph node metastasis. Clinical staging was T1aN0M0, stage IA. Surgical resection that comprised a right upper lobectomy with systematic mediastinal and hilar lymph node dissection was performed.

On gross examination, there was a 1.0 × 0.9 × 0.8-cm white tumor originating from the bronchial mucosa of B8b (Fig. 1b). The tumor did not invade the pulmonary parenchyma (Fig. 1c). On histological examination, the tumor showed solid growth patterns

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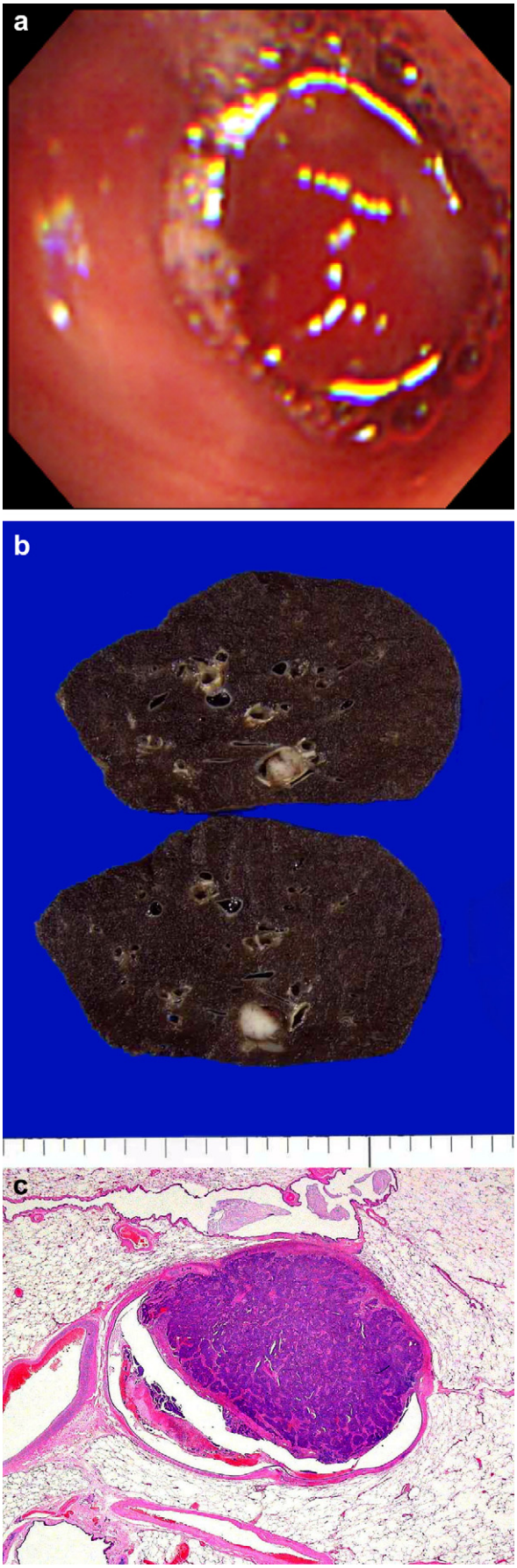

including trabeculae (Fig. 2a) and pseudorosettes (Fig. 2b). Focal necrosis was also seen (Fig. 2c), and at a higher magnification, the neoplastic cells showed remarkably atypical and pleomorphic nuclei and finely granular chromatin (Fig. 2d). A mitotic rate of up to 134 mitoses per 10 high-power fields was observed. In immunohistochemical studies, the neoplastic cells were found to be positive for synaptophysin (Fig. 3a), chromogranin A (Fig. 3b), and CD56 (Fig. 3c). Based on the histopathological and immunohistochemical features, typical carcinoid and non-small-cell lung carcinoma with neuroendocrine features were ruled out. These findings were compatible with LCNEC from the subsegmental bronchus, T1aN0M0, stage IA.

The patient's postoperative course was uneventful, and he was discharged on postoperative day five. The patient was doing well without recurrence 70 months after the operation and is being followed as an outpatient.

3. Discussion

Reports of central-type LCNEC are very rare. The difference between central- and peripheral-type LCNEC remains unknown. As described above, LCNEC is positioned within the spectrum of neuroendocrine tumors. Interestingly, however, the clinical features in our case, such as central-type, smoker, and male, are similar to those of squamous cell carcinoma, most cases of which have a smoking history and male tendency and are located in the segmental bronchi or centrally in approximately two-thirds of cases. These features are more characteristic of squamous cell carcinoma than of LCNEC.

We found only two individual reports on roentgenological occult large-cell neuroendocrine carcinoma in the English literature. Megyesi et al.[6] reported a 58-year-old patient with LCNEC involving an endobronchial location, which was removed by right middle lobectomy. The authors suggested some similarities to atypical carcinoid, such as endobronchial growth, non-smoker, good prognosis (36-month survival), and carcinoid-like morphology. However, the presence of up to 20 mitoses per 10 high-power fields allowed for a diagnosis of LCNEC. They then proposed a redefinition of the histologic criteria to allow a higher mitotic rate for classification as an atypical carcinoid. Tokuyasu et al.[7] admitted the similarity to Megyesi's case,[6] but stated that there were differences from an atypical carcinoid tumor because of the high mitotic rate and morphology and from small cell carcinoma because of the cytological features.

In 1980, pulmonary neuroendocrine tumors were categorized as typical carcinoids, atypical carcinoids, and small cell carcinomas.[8] However, some authors indicated that a fourth category may exist between atypical carcinoids and small cell carcinoma in prognosis.[9,10] In 1991, Travis et al.[1] proposed a new category for LCNEC and reported that the prognosis of LCNEC fell between atypical carcinoids and small cell carcinoma.[1] In 1998, Travis et al.[11] reported further LCNEC cases. The histological LCNEC criteria proposed by the WHO in 1999 are as follows[2]: 1) a tumor with neuroendocrine morphological features (organoid nesting, palisading, rosettes, and trabeculae); 2) a high mitotic rate of $\geq$11 mitoses per 2 mm^2; 3) necrosis (often in large zones); and 4) cytological features of non-small-cell carcinoma; i.e., large cells, low nuclear/cytoplasmic ratio, vesicular or fine chromatin, and/or

Fig. 1. Flexible bronchoscopy demonstrates a polypoid tumor almost obstructing the orifice of the subsegmental bronchus (B8b) of the anterior basal segment of the right lower lobe (a). Gross examination shows a 1.0 × 0.9 × 0.8-cm white tumor originating from the bronchial mucosa of B8b (b). The tumor is not invading the pulmonary parenchyma (c).

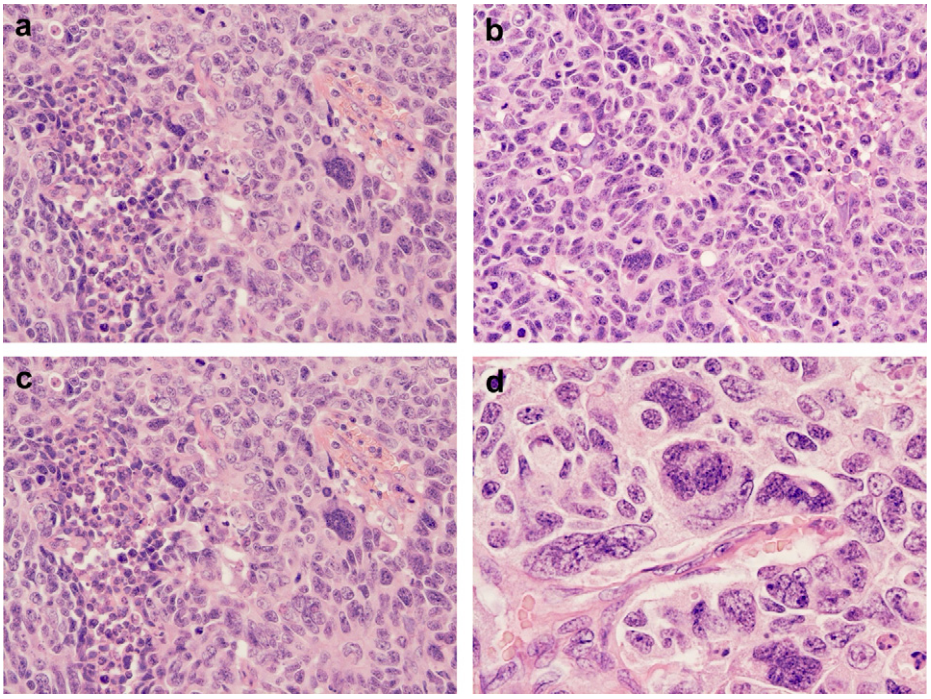

Fig. 2. Histological examination shows solid growth patterns including trabeculae (a) and pseudorosettes (b). Focal necrosis is also seen (c), and at a higher magnification, the neoplastic cells are large and polygonal and have a low nuclear-to-cytoplasmic ratio and finely granular chromatin (d).

frequent nucleoli. By definition, LCNECs are positive for one or more neuroendocrine markers such as chromogranin, synaptophysin, and neural-cell-adhesion-molecule as assessed by immunohistochemistry, or they contain neuroendocrine granules as detected by electron microscopy. To date, LCNEC is classified as a variant of large cell carcinoma in non-SCLC. LCNEC shows characteristic cytomorphological arrangements such as palisading or rosettes with necrosis. In contrast, classic large cell carcinomas show bizarre cells with inflammatory cell infiltration. The morphometry analysis showed significantly different tumor cell sizes between LCNEC and classic large cell carcinoma.[12] Our case is compatible with the criteria of LCNEC.

In general, patients with stage I LCNEC have a significantly poorer prognosis than those with other stage I non-small-cell lung

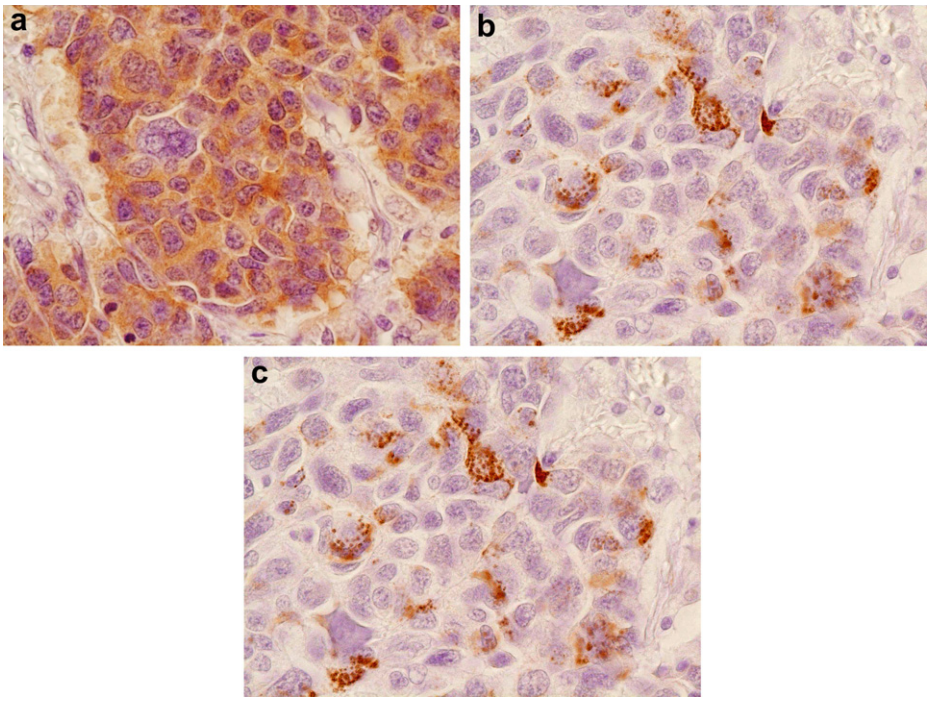

Fig. 3. Immunohistochemical examination shows positive staining for synaptophysin (a), chromogranin A (b), and CD56 (c).

carcinomas,[3] and have a comparable prognosis to patients with small-cell lung cancer.[4] A published surgical series report on LCNEC mentioned that the 5-year survivals for overall and stage I LCNEC are 21.2–57% and 27–67%, respectively.[13,14] Even patients with tumors diagnosed at an early stage do not have a good prognosis. On the other hand, the present patient had a good prognosis. We believe that that central-type LCNEC has a better prognosis than peripheral-type LCNEC simply because the clinical symptoms, such as cough, bloody sputum, or pneumonia, tend to occur in the endobronchial location.

This patient underwent complete resection with early success. Roentgenological LCNEC has not been reported to-date, and the prognosis is not known in detail. Although this patient achieved a long period of health, we believe that close follow-up is mandatory.

Conflict of interest policy

The authors have no commercial associations or sources of support that may pose a conflict of interest.

References

1. Travis WD, Linnoila RI, Tsokos MG, Hitchcock CL, Cutler GB, Nieman L, et al. Neuroendocrine tumors of the lung with proposed criteria for large cell neuroendocrine carcinoma: an ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. *Am J Surg Pathol* 1991;**15**:529–53.
2. World Health Organization Classification of Tumours, Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC, et al., editors. *Tumours of the lung, pleura, thymus and heart: pathology and genetics*. Lyon, France: International Agency for Research on Cancer Press; 2004.
3. Jiang SX, Kameya T, Shoji M, Dobashi Y, Shinada J, Yoshimura H. Large cell neuroendocrine carcinoma of the lung: a histologic and immunohistochemical study of 22 cases. *Am J Surg Pathol* 1998;**22**:526–37.
4. Takei H, Asamura H, Maeshima A, Suzuki K, Kondo H, Niki T, et al. Large cell neuroendocrine carcinoma of the lung: a clinicopathologic study of eighty seven cases. *J Thorac Cardiovasc Surg* 2002;**124**:285–92.
5. Jung KJ, Lee KS, Han J, Kwon OJ, Kim J, Shim YM, et al. Large cell neuroendocrine carcinoma of the lung: clinical, CT, and pathologic findings in 11 patients. *J Thorac Imaging* 2001;**16**:156–62.
6. Megyesi M, Berta M, Khoor A. Endobronchial large cell neuroendocrine carcinoma. *Pathol Oncol Res* 2003;**9**:198–200.
7. Tokuyasu H, Sakaguchi Y, Isowa N, Izumi H, Takeda K, Miura H, et al. Large cell neuroendocrine carcinoma arising from the left main bronchus. *Intern Med* 2011;**50**:2003–6.
8. Arrigoni MG, Woolner LB, Bernatz PE. Atypical carcinoid tumors of the lung. *J Thorac Cardiovasc Surg* 1972;**64**:413–21.
9. Hammond ME, Sause WT. Large cell neuroendocrine tumors of the lung. *Cancer* 1985;**56**:1624–9.
10. Warren WH, Faber LP, Gould VE. Neuroendocrine neoplasms of the lung: a clinicopathologic update. *J Thorac Cardiovasc Surg* 1989;**98**:321–32.
11. Travis WD, Rush W, Flieder DB, Falk R, Fleming MV, Gal AA, et al. Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. *Am J Surg Pathol* 1998;**22**:934–44.
12. Iyoda A, Baba M, Hiroshima K, Saitoh H, Moriya Y, Shibuya K, et al. Imprint cytologic features of pulmonary large cell neuroendocrine carcinoma: comparison with classic large cell carcinoma. *Oncol Rep* 2004;**11**:285–8.
13. Veronesi G, Morandi U, Alloisio M, Terzi A, Cardillo G, Filosso P, et al. Large cell neuroendocrine carcinoma of the lung: a retrospective analysis of 144 surgical cases. *Lung Cancer* 2006;**53**:111–5.
14. Paci M, Cavazza A, Annessi V, Putrino I, Ferrari G, De Franco S, et al. Large cell neuroendocrine carcinoma of the lung: a 10-year clinicopathologic retrospective study. *Ann Thorac Surg* 2004;**77**:1163–7.