Case report

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

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1. Introduction

Large-cell neuroendocrine carcinoma (LCNEC) of the lung was proposed in 1991 by Travis et al. 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. The present case involved LCNEC, as determined by the presence of nuclei with remarkable atypia and morphology.

LCNEC is found in 2.9 to 3.1% of resected specimens of primary lung cancer. It is a rare tumor and has a tendency to affect individuals with a smoking history. LCNEC typically occurs in the peripheral lung field, and only two individual cases of central-type LCNEC have been reported in the English literature. 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 15 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 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.
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 follows2: 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

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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).
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. 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. 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).

Fig. 3. Immunohistochemical examination shows positive staining for synaptophysin (a), chromogranin A (b), and CD56 (c).
carcinomas, and have a comparable prognosis to patients with small-cell lung cancer. 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. 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.

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