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Pulmonary Large-Cell Neuroendocrine Carcinoma

From Epidemiology to Therapy

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Abstract: Lung neuroendocrine tumors are a heterogeneous subtype of pulmonary cancers representing approximately 20% of all lung cancers, including small-cell lung cancer (SCLC) and large-cell neuroendocrine carcinoma (LCNEC). The frequency appears to be approximately 3% for LCNEC. Diagnosis of LCNEC requires attention to neuroendocrine features by light microscopy and confirmation by immunohistochemical staining for neuroendocrine markers. Both SCLC and pulmonary LCNEC are high-grade and poor-prognosis tumors, with higher incidence in males and smokers and peripheral localization. LCNEC is very rare, and the precise diagnosis on small specimens is very difficult, so we have still too few data to define a standard of treatment for pulmonary LCNECs. Data of literature, most based on retrospective analysis, indicated a poor 5-year overall survival, with a high incidence of recurrence after surgery, even in stage I disease. Primary surgery should be the first option in all operable patients because there is no validate therapeutic approach for LCNEC due to lack of clinical trials in this setting. Neoadjuvant platinum-based regimens remain only an option for potentially resectable tumors. In advanced stages, SCLC-like chemotherapy seems the best option of treatment, with a good response rate but a poor overall survival (from 8 to 16 months in different case series). New agents are under clinical investigation to improve LCNEC patients' outcome. We reviewed all data on treatment options feasible for pulmonary LCNEC, both for localized and extensive disease.

Key Words: Lung neuroendocrine tumors, Large-cell neuroendocrine carcinoma, Pathologic characterization, Cancer treatment.

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Lung neuroendocrine tumors are a heterogeneous group of cancers originating from neuroendocrine cells in the pulmonary and bronchial epithelium and represent 20% of all lung cancers.[1]

In the 1970s, pulmonary neuroendocrine tumors were classified into three histologically defined categories: typical carcinoids (TC), atypical carcinoids (AC), usually defined as carcinoids, and the more undifferentiated entity represented by small-cell lung cancer (SCLC).[2] In 1991, Travis et al. introduced a new distinct category of lung cancer, defined as large-cell neuroendocrine carcinoma (LCNEC), which showed large cells with abundant cytoplasm, necrotic areas, a high mitotic rate, and neuroendocrine features. It shared some characteristics with SCLC, while differing because this latter presents smaller cells, with low nuclear/cytoplasm ratio and a different pattern of tissue invasiveness.[3] Later in 1999 and 2004, the World Health Organization recognizes LCNEC as a variant of large cell carcinoma (LCC), a type of non–small-cell lung cancer (NSCLC) and one of the four major types of lung neuroendocrine tumors.[4–6]

Currently, LCNECs are considered as a separate entity for clinical characteristics, histology, prognosis, and survival.

INCIDENCE AND EPIDEMIOLOGY

Pulmonary LCNECs are rare tumors of the lung: in a series of surgically resected cases, the incidence of pulmonary LCNECs appeared to be between 2.1% and 3.5%. However, the frequency appears to be higher than estimated because of difficulties in diagnosis on cytological specimens.[7]

Unlike TCs and ACs, LCNECs are often associated with male sex, older age (median age is 65 years), and heavy smoking habit[8–11] (Table 1).

CLINICAL PRESENTATION

Several characteristics differentiate LCNECs from carcinoids (TCs and ATs), indicating a more aggressive behavior. Patients with LCNECs are poorly symptomatic; cough, hemoptysis, or postobstructive pneumonia are infrequent. Sometimes, patients present an asymptomatic nodule or chest pain, nonspecific flu-like symptoms, dyspnea, night sweats, and carcinoid syndrome. Paraneoplastic syndromes are quite uncommon. At the moment of diagnosis, among pulmonary neuroendocrine tumors, LCNEC present high rate of lymph node (60%–80%) and distant metastasis (40%), similar to SCLC[8] (Table 1).

DIAGNOSIS AND STAGING

Diagnosis of LCNEC could be suggested by conventional radiograph of the chest and computed tomography scan. There are no specific findings in conventional

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TABLE 1. Main Clinicopathologic Characteristics of Pulmonary LCNECs[a]

Sex	Primarily in male patients (M:F = 17:1)
Median age (yr)	Older (median age, 65 yr)
Smoking status	Heavy smokers
Incidence	2.1%–3.5% (in surgically resected cases)
Five-year and median survival	
Resectable stage I, %	33
Stage II, %	23
Stage III, %	8
Stage IV (median survival months)	9.2–12.6
Symptoms	
Infrequent	Cough
	Hemoptysis
	Postobstructive pneumonia
Sporadic	Asymptomatic nodule
	Chest pain
	Dyspnea
	Night sweats
	Carcinoid syndrome
Uncommon	Paraneoplastic syndromes
Lung location	Peripheral or midzone
Differentiation grade	High
Neuroendocrine markers	Chromogranin A
	Neuron-specific enolase
	Synaptophysin
	Somatostatin
Mitotic count per 2 mm^2 field	>11 mitoses/10 high power field
Necrosis	Extensive
Cell histology	Large cells
	Low nuclear/cytoplasm ratio
	Significant nuclear pleomorphism
	Atypical nucleoli
Growth pattern	Organoid growth pattern
	Extensive areas of necrosis
	Cellular palisading pattern or rosette-like areas
Lymphatic metastases at diagnosis	60%–80%
Distant metastases at diagnosis	40%
Treatment	Surgery and neoadjuvant or adjuvant chemotherapy and/or RT for early stages (I to II)
	Multimodal treatment (stage III)[1]
	Chemotherapy for advanced stage (IV)[b]

[a]Multimodal treatment includes computed tomography and/or RT.
[b]Chemotherapy includes etoposide- and platinum-based regimens.
LCNECs, large-cell neuroendocrine carcinomas; RT, radiotherapy.

radiographic examination; LCNECs often are peripherally located expansively growing lesions with irregular margins, with unspecific calcifications in 10%.[12] Bronchoscopy and staging are recommended. International Association for the Study of Lung Cancer suggested application of tumor, node, metastasis (TNM) staging to predict prognosis for neuroendocrine tumors.[13]

Because neuroendocrine tumors frequently express somatostatin receptors (SSTR), mostly type 2 (68%),[14] SSTR scintigraphy diagnostic techniques have been used for their imaging work-up. In particular, OctreoScan (indium 11-tagged diethylenetriaminepentaacetic acid pentreotide scintigraphy) targets with high-affinity SSTR2, SSTR3, and SSTR5, whereas 111In-DOTA-TOC (111In-DOTA-DPhe1-Tyr3-octreotide) and 111In-DOTA-LAN (111In-DOTA-lanreotide) targets, especially, with SSTR2 and SSTR5. These imaging procedures have been proposed to be used in preoperative staging and in postoperative follow-up of LCNEC, but there is still no evidence supporting their use in clinical practice, as it is for F-18 fluorodeoxyglucose positron emission tomography imaging, which is still controversial. Indeed, in neuroendocrine tumors, F-18 fluorodeoxyglucose positron emission tomography can have a minor sensitivity than 111In-DOTA-TOC and 111In-DOTA-LAN in detecting metastatic lesions, expecially for those located in mediastinum.[15]

Pulmonary LCNECs diagnosis often requires immunohistochemical staining and sometimes electronic microscopy to identify clear marks of neuroendocrine differentiation, which are difficult to perform on small biopsies or cytology specimens. Consequently, diagnosis is rarely enunciated without surgery.[5]

PATHOLOGIC CHARACTERIZATION

Histologic features of pulmonary LCNEC include large cell size (similar to three or more lymphocytes), areas of abundant necrosis, low nuclear/cytoplasm ratio, neuroendocrine differentiation growth pattern such organoid nests, trabecular, rosette and palisading features, a variably granular pattern of chromatin, clear or atypical nucleoli, and high mitotic rate (11 or more mitoses per 10 high-power fields)[16–19] (Table 1).

Foci of squamous or adenomatous differentiation sometimes coexist in these tumors, creating mixed pathologic entities called "*mixed LCNEC*." Although prospective data seem to be uncertain, mixed LCNEC exhibit an aggressive behavior, with a 5-year overall survival (OS) of 30%, quite similar to "*pure LCNEC*."[20]

LCNEC and AC share some pathologic features, such as growth patterns and necrosis, so differential diagnosis may be challenging. For instance, AC presents fewer mitotic figures and LCNEC exhibit much more necrosis.[18] Indeed, a mitotic rate of 11 mitoses or more per 10 high-power fields is a key factor to differentiate LCNEC and SCLC from AC.[21] Moreover, with respect to basaloid carcinoma, it presents more often comedo-like necrosis compared with the abundant one of LCNEC, and in addition, it does not express generally neuroendocrine markers.[18]

To achieve a more precise diagnosis, a careful pathologic review is recommended because it is quite easy to mistake an LCNEC for a poorly differentiated NSCLC, an AC and even an SCLC. The diagnosis of LCNEC is difficult on small biopsy or cytological samples and often described as non–small-cell lung carcinomas-not otherwise specified: these two terms referred to two different entities, not interchangeable expecially for treatment.[22]