Preface

Knowledge of Pulmonary Neuroendocrine Tumors: Where Are We Now?

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Editor

Neuroendocrine tumors (NETs) of the lung are regarded as a distinct clinical subgroup of lung cancer, which share particular morphologic, ultrastructural, immunohistochemical, and molecular characteristics. According to the 2004 World Health Organization classification of tumors,[1] they are categorized into 4 major groups,[2] ranging from the low-grade typical carcinoid (TC), to highly aggressive, poorly differentiated tumors (large-cell neuroendocrine carcinoma, LCNC, and small-cell lung cancer, SCLC). Amid them, an intermediate-grade neoplasm (atypical carcinoid, AC) is characterized by a greater aggressive biological behavior, compared to TC with a poorer 5-year survival and a higher tendency to lymph-nodal involvement at presentation. TCs and ACs are categorized together as carcinoids; LCNC is considered a subgroup of large-cell carcinomas, and SCLC is an independent class of lung cancer.

NETs derive from the pulmonary neuroendocrine cells (PNECs), which are of endodermal origin, regardless of their phenotypic resemblance to neurons.[3] In the postnatal phase and later, the PNEC system represents the lung stem cells niche, which is extremely important in the airway epithelial regeneration and carcinogenesis.[4,5] In the healthy adult, the PNECs distribution is quite permeating, with approximately 1 PNEC for every 2500 epithelial cells. Although PNECs are mostly solitary, sometimes they appear aggregate in innervated PNEC clusters, intended as neuroepithelial bodies (NEBs).[6] The precise PNEC biological function remains unclear, as well as that of NEBs. Singular PNEC and NEB have a similar phenotype, because they are the site of adenosine, serotonin, and other amines storage, which play a very important role in normal lung development, growth, and repair. They have been considered to serve as airway chemoreceptors, responsive to hypoxia and thought to activate vagal nerves, participating in breath regulation.[7]

Neuroendocrine cell spread is also thought to be a rare preneoplastic condition: diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is, in fact, characterized by a widespread peripheral airway PNEC and NEBs proliferation, while Tumorlet is a nodular neuroendocrine cell proliferation that measures less than 5 mm in diameter. DIPNECHs are also considered a sort of adaptive response in persons that live at high altitudes, as well as a reactive response during lung injuries, the commonest of which are obliterative bronchiolitis and interstitial lung disease, and in patients with chronic cough.[8–10]

Genetic abnormalities have been recently detected and proposed for a better classification of lung NETs. In particular, abnormal expression or loss of heterozygosity and point mutations of the p53 locus on chromosome 17p13 were seen in approximately 4% of TCs, 29% of ACs, and 80%

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of LCNCs; this data may support the hypothesis that TC, AC, and LCNC are genetically different from each other.[11,12] Also, the p53 protein frequency was found to be 0% in TCs, 20% in ACs, and 80% in LCNCs, suggesting that this data could be used to better classify these neoplasms.[13]

The recent improvement in histologic diagnostic tools, as well as the rapid diffusion of lung cancer screening programs, resulted in a recent increase in pulmonary NETs recognition; this may explain their rapid growth in incidence, which actually accounts for approximately 30% of all NETs.[14]

Lung NETs comprise roughly 20% of all primary lung cancers; their incidence has been reported to be 1.57/100,000/year, with a median age at presentation of 64 years.

Bronchial carcinoids (both TCs and ACs) have an annual incidence comprised between 2.3 and 2.8 cases/1,000,000 people[15] and include 20% to 25% of all carcinoid tumors, but account for only 3% of all primary lung cancers. Bronchial carcinoids have an equal gender distribution; in the retrospective series, the median age of patients with TC is lower than for those diagnosed with ACs or other neuroendocrine neoplasms.

The majority of TCs are centrally located; whereas ACs and LCNCs tend to be more frequently peripheral, ACs sometimes are greater in size. Despite that patients diagnosed with SCLC and LCNC are likely to have a heavy smoking history, a clear correlation between tobacco exposure and carcinoid development has not yet been demonstrated, even if Fink and colleagues[15] and Filosso and coworkers[16] observed a higher frequency of smokers in their AC group.

Peripheral lesions tend to be asymptomatic, whereas cough, dyspnea, pneumonitis, and hemoptysis are the commonest symptoms in centrally located lesions; in addition, symptoms may be present for many years before the diagnosis, reflecting a possible slow tumor growth.

Paraneoplastic syndromes occur in less than 5% of NETs and are more frequently associated with bronchial carcinoids and SCLCs.

Cushing syndrome, due to an ectopic adrenocorticotropic hormone production and secretion, may occur in less than 2% of carcinoids, whereas less than 1% of patients with Cushing syndrome have a bronchopulmonary carcinoid.

Carcinoid syndrome, characterized by symptoms related to serotonin secretion (diarrhea, wheezing, flushing, and carcinoid heart disease), is very rare (<1% to 3% in bronchial carcinoids) and usually reflects the presence of liver metastases.

The syndrome of inappropriate antidiuretic hormone secretion is the commonest paraneoplastic syndrome in SCLC (approximately 5.5% at the time of diagnosis).[17] It is caused by the antidiuretic hormone disproportionate secretion and is characterized by reduced plasma osmolarity, concentrated urine, and euvolemic hyponatremia.

Less frequent paraneoplastic syndromes include acromegaly, hypercalcemia, hypoglycemia, and myasthenia gravis.

Bronchial carcinoids may also occur as a component (less than 5%) of the familial endocrine cancer syndrome called multiple neuroendocrine neoplasia 1 (MEN1),[18] although the majority occur as sporadic cases. MEN1 is an autosomal-dominant disease, associated with the gene locus on 11q13 and characterized by neoplasms of the pituitary gland, pancreas, and parathyroid.

Surgery is the treatment of choice for bronchial carcinoids; complete tumor resection with preservation of as much lung tissue as possible is to be achieved, whenever feasible. The conservative resection, in the case of TC, could be a sleeve resection (in the case of centrally located lesion), or a segmentectomy or lobectomy. Lobectomy/bilobectomy (depending on the tumor size and its location) may be proposed for AC. Systemic lymphadenectomy[19] must be accomplished in all cases, because lymph nodal metastases are evident in about 40% of ACs.[20]

Surgery achieves a 5- and 10-year survival rate higher than 90% for TCs and 70% and 50%, respectively, for ACs.[20] Recurrences occur in 3% to 5% of TCs, and only 15% of deaths are caused by the tumor, while in ACs the majority of deaths are due to recurrences, which occur in about 26% of cases.

The use of several various chemotherapeutic agents (doxorubicin, 5-fluorouracil, dacarbazine, cisplatin, etoposide, streptozocin, and carboplatin) has been proposed for advanced bronchial carcinoids, but it has yielded minimal and generally short-lasting results.[21] More recently, temozolamide and everolimus have been used, with promising results.

Many LCNCs/SCLCs are poor candidates for surgery, mostly due to their local or systemic spread. Lobectomy and lymphadenectomy are the treatments preferred in early-stage LCNCs, and these procedures may improve survival if no lymph nodal metastases are found. Otherwise, the reported outcome is very poor.[22,23] Recurrences and distant metastases occur early, even after a complete resection and also in stage I tumors[24]; surgery alone does not seem the appropriate treatment and should be followed by chemoradiotherapy.