RESEARCH ARTICLE

Distribution and Characteristics of Pulmonary Neuroendocrine Tumors: Single Institution Experience in Lebanon

Carole Kesrouani[1], Claude Ghorra[1], Marc Rassy[1], Hampig Raphael Kourie[2]*, Joseph Kattan[2]

Abstract

Background: Neuroendocrine tumors represent 20% of primary lung neoplasms in some registries. According to the WHO classification of 2004, reconsidered for 2015, these lung tumors are divided into 4 groups: typical and atypical carcinoid, small cell and large cell neuroendocrine carcinomas. We report in this paper, for the first time in Lebanon, the distribution and the population characteristics of these tumors. Materials and Methods: This descriptive retrospective study concerned all the pulmonary neuroendocrine tumors (NET) with their characteristics diagnosed in Hôtel Dieu de France in Beirut, Lebanon from 2001 to 2012, with attention to features like age, gender and subgroup. Results: Of 194 patients with pulmonary NET, 12.4% were typical carcinoid tumors, 3.6% atypical carcinoid, 66.5% small cell lung cancer, 7.7% combined small cell carcinomas and 9.8% large cell neuroendocrine tumors. The mean ages of patients were respectively 51.2 years in typical carcinoid, 64 years in atypical carcinoid, 64.2 years in small cell lung cancers, 67.2 in combined small cell lung cancer and 66.9 in large cells neuroendocrine tumors. The M/F sex ratios were respectively 0.3, 1.3, 1.4, 2.7 and 2.2. Conclusions: The characteristics of lung neuroendocrine tumors in our Lebanese institution are comparable to those reported in the literature.

Keywords: Lung - neuroendocrine - carcinoid - typical - atypical - Lebanon

Asian Pac J Cancer Prev, **17 (5)**, 2579-2581

Introduction

Neuroendocrine tumors represent 20% of primary lung neoplasms (Gustafsson et al., 2008). The incidence of these tumors is increasing tremendously during the last decades (Fisseler-Eckhoff et al., 2012), the survival of these tumors depends from their subtype (Skuladottir et al, 2002). The World Health Organization (WHO, 2004, reconsidered for 2010) classifies these lung tumors in 4 major types: typical carcinoid, atypical carcinoid, small cell lung cancer and large cell neuroendocrine carcinoma, according to distinct morphological criteria (Travis et al., 2004 and Rekhtman et al., 2010). An accurate pathologic diagnosis is crucial given the fact that these different types have different prognostic implications and divergent treatment algorithms.

Typical carcinoid is defined by neuroendocrine cytology: coarsely granular ''salt and pepper'' chromatin, lack of prominent nucleoli; and neuroendocrine architectural patterns: organoid nests, trabeculae/ rosettes, prominent vascularity. Less than two mitosis per 10 high power fields (HPFs) corresponding to 2 mm^2 and no necrosis are mandatory for the diagnosis of typical carcinoid lung tumor.

Either a mitotic rate ≥2 per 10 HPFs, though not exceeding 10 mitoses per 10 HPFs, or punctuate necrosis alone is sufficient to qualify a tumor as an atypical carcinoid. No large areas of geographic necrosis- typical of high-grade NE carcinomas- are found. Concerning the cytological features, atypical carcinoid show greater nuclear pleomorphism than seen in typical carcinoid. Prominent nucleoli and nuclear membrane irregularities are seen, but they do not represent diagnostic criteria.

Small cell lung carcinomas (SCLCs) have the same morphological appearance of any other small cell carcinoma at another site. The most characteristic defining feature is nuclear appearance comprising finely granular chromatin, lack of prominent nucleoli and marked nuclear fragility and malleability manifesting as nuclear molding. Usually, the nuclear size of cells does not exceed the size of 3 small resting lymphocytes. The cytoplasm is scant and the cell borders are indistinct. High mitotic rate (at least 10 mitoses per 2 mm^2), apoptotic bodies, and large areas of geographic necrosis are typically found.

The WHO classification recognizes 2 types of SCLCs: pure SCLC and combined SCLC. The combined SCLC is defined, as SCLC in which there is a component of non–small cell carcinoma, including adenocarcinoma,

*[1]Pathology Department, [2]Hematology-Oncology Department, Faculty of Medicine, Saint Joseph University, Beirut, Lebanon *For correspondence: hampig.kourie@hotmail.com*

squamous cell carcinoma, large cell carcinoma, or uncommonly, sarcomatoid carcinoma. These components may be present as multiple scattered foci or as discrete (collision-like) areas.

Large cell neuroendocrine carcinoma (LCNEC) is defined as a high-grade tumor and characterized by high mitotic rate (greater than 10 mitoses per 10 HPFs) and large zones of necrosis in a tumor that has a neuroendocrine architecture (organoid nests, palisading, rosettes, trabeculae) , but lacking neuroendocrine cytology. In fact, cells are larger than in SCLC. They have prominent nucleoli, vesicular chromatin, abundant cytoplasm and distinct membranes. Similar to SCLC, LCNEC may be pure or combined with NSCLC.

Even though Ki-67 (MIB1) is not a diagnostic criteria in the 2004 WHO classification, several recent studies suggest that it can serve as a useful ancillary tool in the diagnosis of lung neuroendocrine tumors (Aslan et al., 2005). In typical carcinoid, Ki-67 proliferation is less than 5%. In atypical carcinoid, Ki-67 is less than 20%, while SCLC and LCNEC have Ki-67 proliferation rates significantly higher than 20%.

We aimed in this study to report for the first time in Lebanon and the Middle East the characteristics of all the pulmonary NET diagnosed at our institution.

Materials and Methods

This is a descriptive retrospective study reporting all the pulmonary neuroendocrine tumors with their characteristics diagnosed in Hôtel Dieu de France, Saint Joseph University Hospital, in Beirut, Lebanon from 2001 to 2012. The data was collected from the pathology department computerized database. All NETs were first selected, duplicated cases were removed and then NETs were distributed according to their primary site (pulmonary, digestive and others). All the pathology reports of selected patients were revised and specimens reanalyzed according to the latest WHO 2004 classification of NET tumors.

The characteristics and feature of pulmonary NET analyzed in this study were age, gender and grade. All the results were analyzed using the SPSS version 20.

Results

316 NE tumors and carcinomas were diagnosed in Hôtel Dieu de France in 12 years from 2001 to 2012. 194 pulmonary NET were identified in Hôtel Dieu de France representing 61.4 % of all NET. If only carcinoids tumors are taken into consideration, lung carcinoids represent the third (33.3%) of all carcinoid tumors (31/93).

From these 194 patients with pulmonary NET, 12.4% (24) were typical carcinoid tumors, 3.6% (7) atypical carcinoid, 66.5%(129) small cell lung cancer, 7.7% (15) combined small cell carcinomas and 9.8% large cell neuroendocrine tumors (19).

The mean age of patients according to the grade were respectively 51.2 years in typical carcinoid, 64 years in atypical carcinoid, 64.2 years in small cell lung cancers, 67.2 in combined small cell lung cancer and 66.9 in large cells neuroendocrine tumors. The M/F sex ratio of these patients according to the grade is respectively 0.3 in typical carcinoid, 1.3 in atypical carcinoid, 1.4 in small cell lung cancer, 2.7 in combined small cell lung cancer and 2.2 in large cells neuroendocrine tumors.

Table 1. Characteristics of Pulmonary NET

	N	%	Age	M/F
Typical Carcinoid	24	12.40%	51.2	0.3
Atypical carcinoid	7	3.60%	64	1.3
Small cell lung carcinoma	129	66.50%	64.2	1.4
Combined small cell carcinoma	15	7.70%	67.2	2.7
Large cell neuroendocrine carcinoma	19	9.80%	66.8	2.2

Concerning all carcinoid tumors, they represent 16% of all pulmonary NET: 77.4 % being typical carcinoid and 22.6% atypical carcinoid; male-female ratio of lung carcinoid tumors being 0.47 and the mean age of 54.09 years.

Discussion

Neuroendocrine lung tumors represent a large and heterogenic group, since major differences related to prognosis and treatment modalities are noted between carcinoid tumors and small cell/large cell tumors. In the literature, the characteristics of each of these two subgroups of tumors (carcinoid versus small and large cell) were reported separately in different papers. Our methodology being based on all neuroendocrine tumors as starting point, and according to their primaries and to subgroups in each primary, we first presented in this paper the characteristics of all pulmonary neuroendocrine tumors. Then we described those of carcinoid and small/large cell lung cancer. Finally we considered each single entity in each group.

In a previous study, we reported that small cell lung cancer represents 13 % of all diagnosed lung cancer in our institution (Kourie et al., 2015). The characteristics of this population (frequency of this subtype, age and sex ratio) are comparable to those reported in the literature with a mean age of 64.6 years and a sex ratio M/F of 1.7.

In the carcinoid subgroup of lung tumor, the large majority of these tumors are typical carcinoid varying from 70 to 90%, while 10 to 30% only are atypical (Davini et al., 2009, Fink et al., 2001 and Herde et a., 2015). Our results are concordant with those found in the literature, where 77.4% of carcinoid tumors are typical. Carcinoid tumors are known to be more frequent in females with a sex ratio male/female going from 0.5 to 1 (Fink et al., 2001) ; in our population this ratio is 0.47. The reported mean age of patients diagnosed with these tumors is mid-fifties, which is similar to the mean age of our population 54.09 years.

In conclusion, the characteristics of the 194 patients with pulmonary NET in our Lebanese institution are comparable to those reported in the literature. The majority of these pulmonary NET are of the small cell histologic subtype (66.5%). The only subtype with a feminine predominance is the typical carcinoid (M/F sex ratio of 0.3 in our series).

References

Aslan DL, Gulbahce HE, Pambuccian SE et al (2005). Ki-67 immunoreactivity in the differential diagnosis of pulmonary neuroendocrine neoplasms in specimens with extensive crush artifact. *Am J Clin Pathol*, **123**, 874-78.

Davini F, Gonfiotti A, Comin C et al (2009). Typical and atypical carcinoid tumours: 20-year experience with 89 patients. *J Cardiovasc Surg (Torino)*. **50**, 807-11.

Fink G, Krelbaum T, Yellin A et al (2001). Pulmonary carcinoid: presentation, diagnosis, and outcome in 142 cases in Israel and review of 640 cases from the literature. *Chest*, **119**, 1647-51.

Fisseler-Eckhoff A, Demes M (2012). Neuroendocrine tumors of the lung. Cancers (Basel). 4, 777-98.

Gustafsson BI, Kidd M, Chan A, Malfertheiner MV et al (2008). Bronchopulmonary neuroendocrine tumors. *Cancer*. **113**, 5-21.

Herde RF, Kokeny KE, Reddy CB et al (2015). Primary Pulmonary Carcinoid Tumor: A Long-term Single Institution Experience. *Am J Clin Oncol*. [Epub ahead of print]

Kourie HR, Rassy M, Ghorra C et al (2015). Histologic distribution of pulmonary tumors in Lebanon: a 5-year single institution experience. *Asian Pac J Cancer Prev*. **16**, 5899-902.

Rekhtman N (2010). Neuroendocrine tumors of the lung: an update. *Arch Pathol Lab Med*, **134,** 1628-38

Skuladottir H, Hirsch FR, Hansen HH et al (2002). Pulmonary neuroendocrine tumors: incidence and prognosis of histological subtypes. A population-based study in Denmark. *Lung Cancer*, **37**, 127-35.

Travis WD, Brambilla E, Muller-Hermelink HK et al (2004). Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC