

THE HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL DIAGNOSIS IN SMALL CELL LUNG CARCINOMA

ANA-MARIA DRĂGAN, G. SIMU, T. VAIDA

Faculty of Medicine and Pharmacy, University of Oradea

Summary. The small cells lung carcinoma (SCLC) represents 10–25% of the bronchogenic carcinomas, prevails at middle ages and is closely associated with tobacco smoke. It belongs to the group of carcinomas with neuroendocrine differentiation, the patients presenting various paraneoplastic syndromes. The study was performed on 491 patients with a clinical and radiological suspicion of bronchopulmonary cancer. In this study, the histopathological examination gives results similar to those mentioned in the medical literature for the small cells lung carcinoma, prevailing in the case of young patients. The immunohistochemical examinations are particularly precious in confirming the diagnosis, especially in the diagnosis of the lymphonodular micrometastases.

Key words: small cells lung carcinoma, histopathological exam, immunohistochemical exam.

INTRODUCTION

The small cells lung (SCLC) carcinoma is defined as a distinct non-differentiated tumor of bronchopulmonary cancer (Carter, 1983). This type comprises 20–25% of the bronchogenic carcinomas, prevails at middle ages and is closely associated with tobacco smoking; merely 1% of the patients are nonsmokers; it can also be found in some professional groups, including the miners of the uranium mines and the workers exposed to ether methylchloride.

The property of these tumors to secrete polypeptidic hormones as well as the presence of the neuroendocrine markers of the type: neuron specific enolase, parahormon-like and the production of other active hormones suggest that these tumors are derived from neuroendocrine cells of the bronchial epithelium (Cottran *et al.*, 1999).

MATERIAL AND METHODS

The study was carried out in the Bihor County Clinical Hospital from Oradea and in the Laboratory of Cytology of the Faculty of Medicine and Pharmacy of Oradea, between 2000–2002.

Casebook record: 491 patients with a clinical and radiological suspicion of bronchopulmonary cancer, aged between 32 and 84 were considered. Most of them

were men (88.87% men and 11.12% women); 86.27% were smokers. In the case of all patients, a fibrobronchoscopic examination was performed, and pathological material was scrapped in view of histopathological and partially immuno-histochemical examination.

The *histopathological* examination was made on bronchial biopsy fixed in formol 10% and stained with haematoxylin-eosin. The *immunohistochemical* examination for chromogranine was made in case of 8 patients on bronchial biopsies and for neuron specific enolase (NSE) in case of one patient in the cervical lymph nodules.

RESULTS

Out of the 491 cases examined histopathologically, 454 patients (92.46%) were diagnosed with a type of bronchopulmonary carcinoma. In 9 cases (1.83%) the result of the histopathological examination was negative while 28 patients (5.70%) were diagnosed with dysplasia (Table 1).

Table 1

Histopathological modifications on the material obtained from bronchial biopsy

Results of histopathologic exam	Number of cases	%
Negative	9	1.83
Dysplasia	28	5.70
Bronchopulmonary carcinoma	454	92.46
Total cases	491	99.99

Out of the 454 cases diagnosed with bronchopulmonary cancer, in 59 cases the diagnosis of non-differential carcinoma with small cells was set. We diagnosed plates of small or medium cells, organized in networks or isolated, with hyperchrome nuclei, with a lymphocytoid aspect (Figure 1), or of an intermediary type, with larger, spindle-like or polygonal shapes (Figure 2).

We also identified large tumor cell foci, which suggest the presence of a combined tumor of squamous carcinoma and of small cells lung carcinoma (Figure 3).

With regard to age, the small cells lung carcinoma was met at significantly higher rates in the case of young patients (23.7%) compared to those over 70 years (8.8%) ($p < 0.001$). At women, the small cells carcinoma was diagnosed in 20.6% of the cases, while with men, in 17% of the patients, the difference between sexes being not significant.

The examination for chromogranine was positive in the form of brown cytoplasm granules (Figure 4) in four cases with non-differential carcinoma with small cells, and negative in one of the five cases in which the histopathological examination identified this type of carcinoma.

On the contrary, the reaction for chromogranine was negative in all the three cases with epidermoid carcinoma (Table 2).

Table 2
Immunohistochemical results to cromogranine

Histopathologic exam	Number of cases	Imunohistochemical exam	
		Positive	Negative
Squamous cell lung carcinoma	3	-	3
Small cell lung carcinoma	5	4	4
<i>Total cases</i>	8	4	4

In a case with small cells lung carcinoma in the lymph nodules, a positive reaction was noticed for the neuron specific enolase (NSE), which confirms the diagnosis of neoplastic process suggested by the histopathological examination of the lymph ganglion (Figures 5 and 6).

DISCUSSIONS

The data from the professional literature concerning the treatment of the bronchopulmonary carcinoma impose dividing the disease into two major groups: small cells lung carcinoma (SCLC), and non-small cells lung carcinoma (NSCLC), (Cottran *et al.*, 1994; De Vita *et al.*, 2001).

Studies appeared in the latest ten years indicate a high rate of mixed tumors, in which endocrine and non-endocrine differentiations can be associated (Bramilla, 1999), a fact which we also signalised in the present study.

The neuroendocrine character of these tumors is set particularly by means of histochemical identification, with markers like: the neuron specific enolase, neuropeptides and neuroamines, or by means of an ultrastructural examination (the presence of secretor granules).

In our study, the small cells lung carcinoma was found in 12.01% of the cases, while some data from the professional literature (Boucher *et al.*, 1995; Wistuba *et al.*, 2001) describe this type of carcinoma to hold 10–20% of the total number of pulmonary cancers. According to other authors (Colby *et al.*, 1998), the small cells lung carcinoma holds 20–25% of the total number of pulmonary carcinomas, with a higher rate at the heavy smokers and the miners from the uranium mines. The small cells lung carcinoma used to have a higher rate at men smokers, but its incidence is growing higher at women smokers, the risk to develop a cancer being of 78% in the case of regular smokers and of merely 20% in the case of ex-smokers (Osann *et al.*, 2000).

The data of the present study, similarly to some results from the professional literature, show that the bronchial neoplasm with small cells, a type with neuroendocrine properties, can be highlighted by means of markers such as

chromogranine, NSE, or other neuroendocrine markers (Choma *et al.*, 2001). NSE equally has a pre-therapeutic prognostic value in case of the patients with non-differential carcinoma with small cells.

In this study, there was a case when the conventional microscopic examination only isolated the presence of cells with atypical mitosis, which indicates suspicion of the existence of some micro-metastases. This suspicion was confirmed by the presence of NSE in these cells, indicating the presence of the metastases of an intermediary type, with polygonal cells, of a non-differential carcinoma with small cells. Such a method could stand for the examination of the control lymph nodule of the patients with breast cancer.

Our data regarding the importance of the immunohistochemical examination for increasing the accuracy of the histopathological examination of the broncho-pulmonary carcinoma, are similar to those in the professional literature, especially of the latest years, which demonstrates the value of the immunohistochemical methods in setting a prognostic and in the therapeutic monitoring of some types of broncho-pulmonary cancer (Brambilla *et al.*, 2000; Hirashima, 1998).

CONCLUSIONS

The small cells lung carcinoma was diagnosed at a rate within the limits of the recent data from the medical literature, with a significantly higher incidence at young ages but with no significant difference between sexes.

The immunohistochemical examinations substantially increase the sensitivity of the microscopic examination, and allow the exact identification of the neuroendocrine nature of a small cells lung carcinoma or the presence of this component in other types of tumors.

Immunohistochemistry equally permits a clear-cut differentiation of a neuroendocrine tumor from a lymphocyte infiltrate of an inflammatory nature, as well as the presence of metastases in the lymph nodules, sometimes of reduced dimensions and the presence of various types of bronchopulmonary carcinoma.

At this respect, the fact that some micrometastases are highlighted in a biopsy exploring the scalene lymph nodule confers the function of control lymph nodule to this structure.

REFERENCES

- BOUCHER L.D., YONEDA K., *Cytologic characterisation of bronchial epithelial changes in small cell carcinoma of the lung*, Acta Cytol, 1995, 39:69–72.
- BRAMBILLA E., *Nouvelle classification anatomo-pathologique de l'OMS*, Rev Mal Respir, 1999, 16:3S105–3S112.
- BRAMBILLA E., LANUEJOUL S., STURM N., *Divergent differentiation in neuroendocrine lung tumors*, Semin Diagn Pathol, 2000, 17(2):138–148.

- CARTER D., *Small cell carcinoma of the lung*, Am J Surg Pathol, 1983, 7:787–795.
- CHOMA D., QUANTIN X., LAMY P.J., GRENIER J., *Pro-gastrin releasing peptide, neuron specific enolase et chromogranine A, come marqueurs sériques du cancer bronchique a petites cellules*, Rev Mal Respir, 2001, 18:17S.
- COLBY T.V., WISTUBA J.L., GATDAR A., *Precursors to pulmonary neoplasia*, Adv Anat Pathol, 1998, 5(4):205–215.
- COTTRAN S.R., KUMAR V., COLLINS L.S., Bronchogenic carcinoma, In: *Robbins' Pathologic Basis of Disease*, 5th edition, WB Saunders Company, Philadelphia, 1994, 720–727.
- COTTRAN S.R., KUMAR V., COLLINS L.S., Bronchogenic carcinoma, In: *Robbins' Pathologic Basis of Disease*, 6th edition, WB Saunders Company, Philadelphia, 1999, 741–748.
- DE VITA V.T., HELLMAN S., ROSENBERG S.A., Epidemiology and aetiology of lung cancer, In: *Principles and Practice of Oncology*, Lippincott-Williams and Wilkins, 2001, 917–1010.
- HIRASHIMA T., TAKADA M., KOMIYA T. *et al.*, *Prognostic significance of CYFRA-21-1 in non-small cell lung cancer*, Anticancer Res, 1998, 18(6B):4713–4716.
- OSANN K., LOWERY J., SCHELL M., *Small cell lung cancer in women: risk associated with smoking, prior respiratory disease, and occupation*, Lung Cancer, 2000, 28(1):1–10.
- VIGNAUD J.M., *De la dysplasie au cancer: aspects cytologiques, histopathologiques et moléculaires*, Rev Mal Respir, 1999, 16:3507–3510.
- WISTUBA I.I., GAZDAR A.F., MINNA J., *Molecular genetics of small cell lung carcinoma*, Semin Oncol, 2001, 28(2 Suppl. 4):3–13.

Received: 4 October, 2004

Accepted: 22 November, 2004

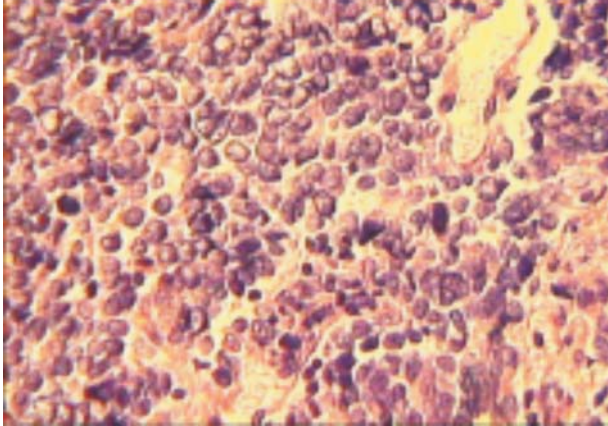


Figure 1 – Small cell lung carcinoma (oat cell carcinoma) in bronchial biopsy (H-E, $\times 400$)

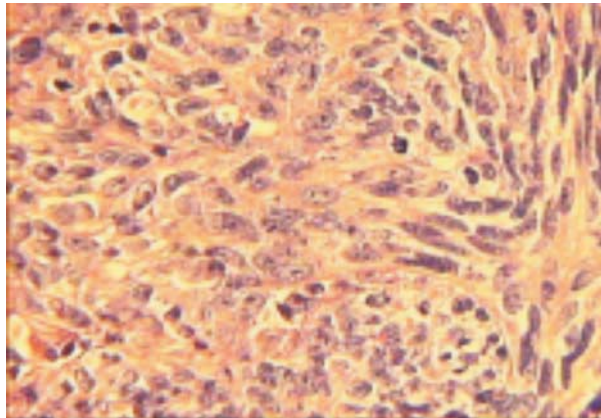


Figure 2 – Small cell lung carcinoma, intermediate cell type, bronchial biopsy (H-E, $\times 400$)

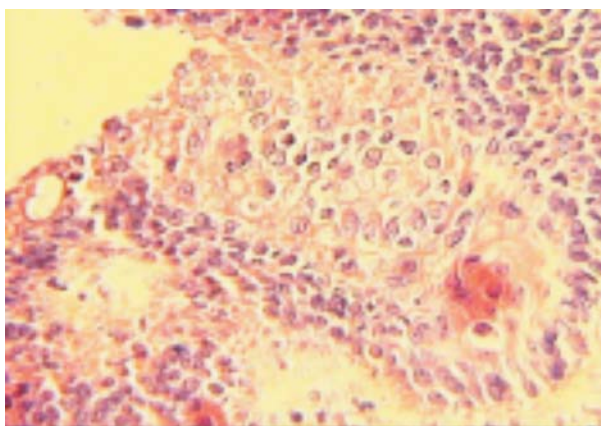


Figure 3 – Small cell lung carcinoma combined with squamous cell carcinoma, bronchial biopsy (H-E, $\times 400$)

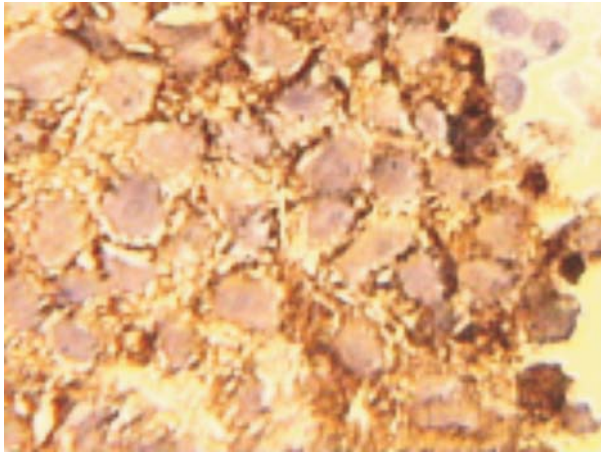


Figure 4 – Small cell lung carcinoma.
Cromogranine positive,
bronchial biopsy, $\times 400$

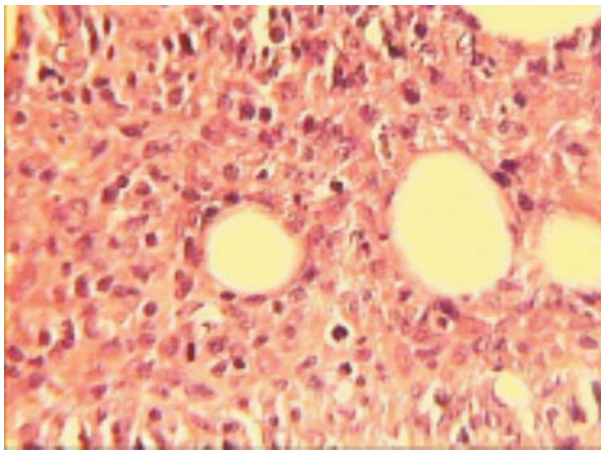


Figure 5 – Metastatic lymphoid
ganglia with small cell carcinoma,
intermediate cell type (H-E, $\times 400$)

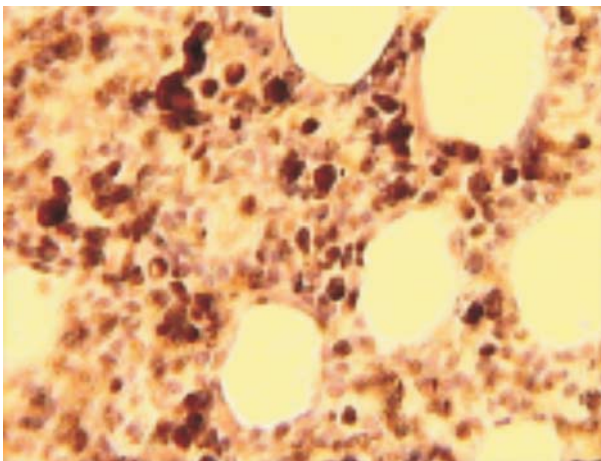


Figure 6 – Metastatic lymphoid
ganglia with small cell carcinoma,
intermediate cell type. Neuron
specific enolase positive, $\times 400$