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Feasibility of the new WHO classification of pulmonary neuroendocrine tumours

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Summary

Primary pulmonary neuroendocrine tumours present a heterogeneous group of tumours causing problems in diagnosis and treatment. The new WHO classification of lung tumours was published in 1999 in order to improve this situation by combining morphology, immunohistochemistry and clinical background for diagnosis. The aim of our study was to evaluate the feasibility of this classification and to discuss the consequences of modified diagnostic criteria. 50 cases of neuroendocrine tumours and 50 poorly differentiated lung tumours diagnosed in the years 1981–1994 were independently evaluated by three pathologists. The diagnosis of all 27 typical carcinoids (TC) was given by all authors, however, no unanimous agreement was achieved in one of three atypical carcinoids (AC) and two of four large cell neuroendocrine carcinomas (LCNEC). While typical and atypical carcinoids can be distinguished by the number of mitoses or presence of necrosis it was found that the most difficult diagnostic factor for large cell neuroendocrine carcinoma is the recognition of its light-microscopic neuroendocrine features. In consequence it must be distinguished not only from atypical carcinoid or small cell lung carcinoma (SCLC), but also from poorly differentiated carcinoma. Immunohistochemistry is important for the diagnosis of this entity but also for non-small cell lung carcinoma with neuroendocrine differentiation (of which 1 case was detected in our series) There was agreement on the diagnosis of small cell carcinomas in all but one case. The results indicate the excellent reproducibility of the WHO classification.

Key words: pulmonary neuroendocrine tumours; WHO classification

Introduction

Neuroendocrine tumours of the lung represent about 20% of pulmonary tumours and belong to a complex group of neoplasms with distinct morphology, clinical behaviour and prognosis. First diagnosed in 1928, our knowledge of the spectrum of neuroendocrine tumours in the lung has been continuously enlarged and various classifications have been published in the literature [1]. These classifications were, however, often imprecise or even contradictory. In consequence reliable reproducibility of histopathological diagnosis and a subsequent good clinical correlation were lacking.

In order to specify the spectrum of these tumours and to reduce confusions between pathologists and clinicians, the WHO classification of pulmonary neuroendocrine tumours of 1981 has been replaced in 1999 by a new one (table 1) aiming at a simple morphological, clinical and therapeutic differentiation [2].

The aim of our study was to evaluate the feasibility of this classification concerning the diagnosis of the most frequent types of neuroendocrine tumours (carcinoid, atypical carcinoid, small cell and large cell neuroendocrine carcinoma). Three different pathologists (one with particular interest in lung pathology, one general pathologist and one trainee) re-examined the neuroendocrine tumours diagnosed at the Department of Clinical Pathology, University Hospital of Geneva, Switzerland in the period 1981–1994 using histological and immunohistochemical criteria proposed by the new WHO classification (table 2). Furthermore tumours initially classified as poorly differentiated carcinoma were included in order to find cases of the newly described entity of large cell neuroendocrine carcinoma.

Finally, we discuss the pertinence and advantages in the clinical practice of this new classification as well as the importance to distinguish the different sub-types of neuroendocrine tumours.

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Table 1

Terminology for pulmonary neuroendocrine tumours (WHO 1999).

Spectrum of pulmonary neuroendocrine lesions	**other published terminology (adapted from Travis et al., Am J Surg Pathol 1991) [10]**
Neuroendocrine cell hyperplasia and tumourlets	
1. Neuroendocrine cell hyperplasia	
associated with fibrosis and/or inflammation	
adjacent to carcinoid tumours	
diffuse idiopathic NE cell hyperplasia with/without airway fibrosis/obstruction	
2. Tumourlets	
Common neoplasms with NE morphology	*common primary neuroendocrine neoplasms*
1. Typical carcinoid	1. mature carcinoid, Kulchitsky cell carcinoma-I
2. Atypical carcinoid	2. malignant carcinoid, well differentiated neuroendocrine carcinoma, Kulchitsky cell carcinoma-II, peripheral small cell carcinoma resembling carcinoid tumour
3. Large cell neuroendocrine carcinoma (LCNEC)	3. neuroendocrine carcinoma of intermediate cell type non-small cell carcinoma with neuroendocrine features
Variant	
Combined large cell neuroendocrine carcinoma	
4. Small cell lung carcinoma	4. small cell undifferentiated carcinoma small cell neuroendocrine carcinoma Kulchitsky cell carcinoma-III, oat cell carcinoma neuroendocrine carcinoma of small cell type
Variant	
Combined small cell carcinoma	
Non-small cell lung carcinoma wirh neuroendocrine differentiation (NSCLC-NE)	*atypical endocrine tumour*
(squamous cell carcinoma, adenocarcinoma or large cell carcinoma with neuroendocrine features not seen by light microscopy but detected by immunohistochemistry or ultrastructure)	large cell neuroendocrine tumour neuroendocrine differentiation in poorly differentiated carcinomas
Other tumours with NE properties	
1. Pulmonary blastoma	
2. Primitive neuroectodermal tumour	
3. Desmoplastic round cell tumour	
4. Carcinomas with rhabdoid phenotype	
5. Paraganglioma	

Table 2

Diagnostic criteria for neuroendocrine tumours.

	small cell carcinoma	**large cell neuroendocrine carcinoma**	**atypical carcinoid**	**typical carcinoid**
Growth patterns	– often grows in sheets without a specific pattern – rosettes, peripheral palisading, organoid nesting, strands, ribbons – rarely tubules or ductules	– organoid – palisading – trabecular – rosette-like	– organoid – trabecular – palisading – spindle cell – glandular – follicular – papillary (± sclerosing) – rosette-like	– organoid – trabecular – palisading – spindle cell – glandular – follicular – papillary (± sclerosing) – rosette-like
Chromatin	– finely granular – uniform	– coarsely granular or vesicular – less uniform	– finely granular (sometimes coarsly)	– finely granular
Nuclear pleomorphism	– present	– present	– present – hyperchromatism	– minimal or absent
Nucleoli	– absent or inconspicuous	– frequent	– sometimes present	– inconspicuous in most
Mitoses	>10/2 mm^2 (median of 80/2 mm^2)	>10/2 mm^2 (median of 70/2 mm^2)	2–10/2 mm^2	<2/2 mm^2
Necrosis	– abundant	– abundant	– focal or punctuate (generally small foci centrally located within organoid nests of tumour cells)	– absent
Cells	– small (ø <3 lymphocytes) – N/C ratio ↑↑ – round to spindle cells – nuclear molding – intranuclear vacuoles	– large – N/C ratio ↓↓ – polygonal shape –	– variable size – N/C ratio abnormal	– variable size – oncocytic, acinic cell-like, signet ring, mucin producing or melanocytic features
Other	– crush artefacts frequent			– ossification – dense hyaline stroma

Materials and methods

Resected specimens and biopsies of the years 1981–1994 with initial diagnosis of neuroendocrine tumours or poorly differentiated carcinoma were chosen from the files of the Department of Pathology, University Hospital of Geneva, Switzerland. After eliminating all non-representative specimens with, for example necrosis or crush-artefacts, representative tumour blocks of 100 cases were chosen. Haematoxylin-/Eosin sections of each case were reviewed and reclassified by all three investigators independently according to the 1999 WHO classification of lung carcinoma. In cases of differing diagnosis, the final decision was based on the common judgement of all three pathologists applying given diagnostic criteria.

Immunohistochemistry

Additionally , an immunohistochemical investigation using the neuroendocrine markers chromogranine A and synaptophysine was carried out on all neuroendocrine tumours and those cases of poorly differentiated carcinoma suspected of being large cell neuroendocrine carcinoma.

Sections for immunostaining were cut at 4 µm and mounted in protein-coated glass slides. After dewaxing in xylene and rehydration in a series of alcohols, the primary antibodies were applied in a humidified chamber (dilutions: synaptophysine (Dako, Denmark, 1:5) and chromogranine A (Immunotech, France, 1:400), followed by the secondary biotinylated rabbit anti-mouse IgG (dilution 1:250) and a Streptavidin Biotin Complex Peroxidase (SBC-POX) (dilution A 1:100 + B 1:100) . Subsequently the enzyme reaction was developed for 30 minutes at room temperature. Finally the sections were counterstained with haematoxylin and mounted in Kayser's glycerine gelatine. Omission of primary antibodies was used as negative, normal adrenal medulla as positive controls for chromogranine A and synaptophysine.

Results

Based on morphological criteria and immunohistochemical results, 58 tumours with neuroendocrine differentiation, consisting of 27 TC, 3 AC, 23 SCLC, 4 LCNEC, 1 non-small cell lung carcinoma with neuroendocrine features and 42 poorly differentiated carcinomas were diagnosed (see table 3).

Comparing these results with the initial diagnosis it was found that:

- 18 out of the 27 TC were correctly diagnosed, the remaining 9 cases had been classified as malignant showing spindle cells or oncocytic differentiation.
- one case of the three AC was diagnosed as malignant carcinoid (old terminology for atypical carcinoids) [7], the two others were initially diagnosed as TC respectively "oat cell carcinoma".
- 15 out of 23 cases of SCLC had been described as oat cell carcinoma, 6 as poorly differentiated carcinoma, 1 as TC vs. squamous cell carcinoma and 1 as TC.
- 3 of our 4 LCNEC were initially diagnosed as poorly differentiated carcinomas and 1 as AC
- 3 of the 42 poorly differentiated carcinomas were initially diagnosed as TC, carcinoid vs. adenocarcinoma respectively carcinoid vs. squamous cell carcinoma. In one case a non-small cell lung carcinoma with neuroendocrine features was found.

Differences in the diagnosis reached by the three investigators were observed in one of the AC and two of the four LCNEC, necessitating a review of the slides together, permitting a definitive diagnosis by using morphological criteria and immunohistochemistry according to the WHO classification.

Table 3

Reclassification of tumours 1981–1994.

Initial diagnosis	reclassification					
	typical carcinoid (n = 27)	atypical carcinoid (n = 3)	small cell lung carcinoma (n = 23)	large cell neuro-endocrine carcinoma (n = 4)	non-small cell lung carcinoma with neuro-endocrine features (n = 1)	poorly differentiated carcinoma (n = 42)
Typical carcinoid	18	1	1			1
Atypical/malignant carcinoid	9	1		1		
Carcinoid vs. Adenocarcinoma						1
Carcinoid vs. Squamous cell carcinoma			1		1	
Oat cell carcinoma		1	15			
Poorly differentiated carcinoma			6	3	1	39

Discussion

The concept and classification of neuroendocrine tumours of the lung is complex. The first pulmonary neuroendocrine tumour described was an oat cell carcinoma associated with Cushing's Syndrome [1]. In 1937 the term carcinoid was used for the first time for a lung tumour [3]. Since that time, the spectrum of these tumours has progressively grown and the diversity of terminology used, based on variable histopathological criteria, has caused problems in the diagnosis and treatment [4–9]. For example, it is known that lymphatic and lymph node involvement, as well as nuclear pleomorphism, can be seen in TC. The factors, however, do not necessarily indicate the tumour will behave in a malignant fashion.

Furthermore it was recognised that a simple classification including TC, AC and SCLC wasn't precise enough and thus in the new WHO classification a new entity, the LCNEC showing a large cell proliferation but definite neuroendocrine morphology was introduced [9, 10]. Additionally precise criteria to distinguish between TC and AC were given with respect to the prognosis for patients. However, the pathologists were not rigorous in the terminology used and missed the opportunity of replacing the terms TC and AC with more adequate ones indicating that all carcinoids are malignant.

The new WHO classification of neuroendocrine lung tumours is based on histological criteria such as neuroendocrine morphology, nuclear features, presence or absence of necrosis, and mitotic counts as well as on immunohistochemical findings (table 2, figure 1a-d). By using these criteria we revised the initial diagnoses of our cases being aware that discrepancies found might be due to diagnostic errors or changes in diagnostic criteria and standardised use of immunohistochemistry.

The main task of a pathologist in this context, is to distinguish between neuroendocrine and non-neuroendocrine tumours. In our series, however, one poorly differentiated carcinoma was initially diagnosed as carcinoid and six SCLC were not classified as neuroendocrine tumours. In the literature there are descriptions of the difficulties in making a morphological distinction between small cell lung carcinoma and non-small cell carcinoma with a non-concordance of results of 5–7% for specimens examined by pathologists specialised in lung pathology [11]. A well-known pitfall here is the small cell variant of a squamous cell carcinoma, which constitutes most of the missed cases of SCLC in our series, due to the fact that at the time of initial diagnosis immunohistochemistry was not routinely done. The case of TC which was reclassified as poorly differentiated carcinoma exhibited spindle cells, and no NE differentiation could be found by immunohistochemistry.

Concerning the diagnosis of the different entities of neuroendocrine tumours, one has to consider the influence of the size of the tissue sample on the accuracy and feasibility of the diagnosis. For example in SCLC the cell size can vary between 10–45 μm depending on the size of the biopsy and quality of fixation and processing [12]. In general the best reproducibility is found for TC and SCLC. Normally, this should cause no problem, in our series, however, one case of SCLC was initially diagnosed as carcinoid which must be considered as a diagnostic error. Pathologists as well as clini-

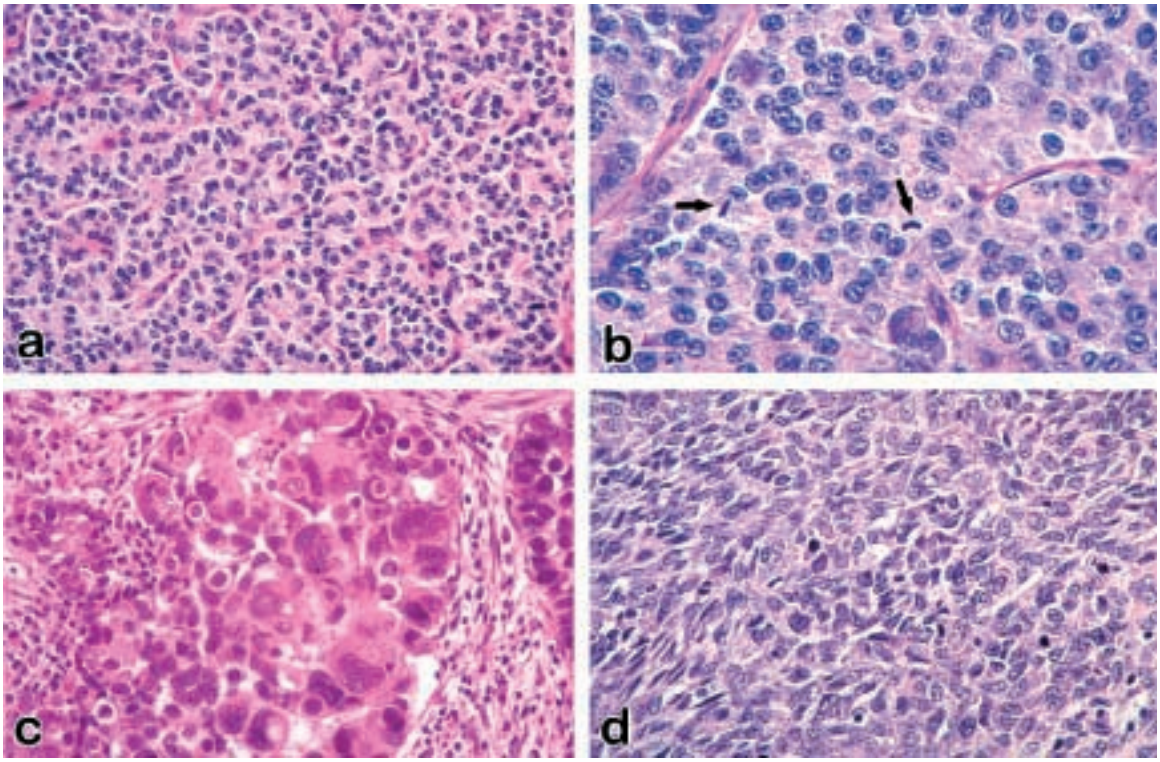

Figure 1

(HE, 40×)
a typical carcinoid characterised by organoid structures and nuclei with inconspicuous nucleoli
b atypical carcinoid with mitosis (shown by arrows)
c large cell neuroendocrine carcinoma showing organoid pattern and nuclear pleomorphism
d small cell lung carcinoma with cells lacking cytoplasm, number of mitosis >10/2 mm^2.

cians have to be aware that there is a grey-zone concerning the differential diagnosis of TC versus AC, LCNEC versus SCLC as well as AC [13]. In our series one AC was initially diagnosed as TC. This can be explained by the changing of diagnostic criteria for this entity. While Arrigoni et al. defined AC as a carcinoid with increased mitotic activity (5–10 mitosis/2 mm^2) Travis et al. redefined it by correlation of the mitotic activity with the survival data [5, 14]. According to the new classification a mitotic activity ranging from 2–10 mitosis per 2 mm^2 or the presence of necrosis is accepted [2].

In former times AC was presenting a great diversity of tumours with variable clinical outcome. Thus, in 1991, Travis et al. suggested to add an entity, the large cell neuroendocrine carcinoma, which had already been described by Hammond et al in 1985 [9, 10]. This tumour is quite uncommon with a reported prevalence of 3% in surgically resected lung cancers [15]. Earlier this entity has been described as AC, large cell carcinoma or small cell carcinoma. A similar observation was made in our series with initial diagnoses of one AC and three poorly differentiated carcinoma. By recognition of the characteristic morphology and the immunohistochemical proof of the neuroendocrine differentiation, the diagnosis of LCNEC was reached in these cases. LCNEC and basaloid carcinoma (BC) may show an overlap in their morphology, although BC normally presents small cells with hyperchromatic nuclei and inconspicuous nucleoli. In difficult cases the use of immunohistochemistry, essential the fact that expression of TTF-1 excludes BC and 34βE12 excludes pure LCNEC, helps to distinguish both entities [16].

The same finding was observed in the one case of non-small cell lung carcinoma with neuroendocrine features. This entity was described for the first time in 1988 and can not be diagnosed without using immunohistochemistry [17–19]. According to the literature, there is a frequency of 10–20% of neuroendocrine features in NSCLC. The fact that we just found one single case can be explained by the observation that neuroendocrine features are mainly found in adenocarcinoma and squamous cell carcinoma [19].

While given histological criteria are quite precise, the application of immunohistochemistry may cause problems. It is known that neuroendocrine markers are very useful for determining the neuroendocrine phenotype of diverse tumours [20, 21]. These markers are quite numerous, the results of the immunohistochemical investigation, however, are dependent on the material (open biopsy vs. transbrochial biopsy) and the entity of tumour investigated reflecting the spectrum of these tumours.

According to literature and our own results the most useful neuroendocrine markers for SCLC in formalin-fixed, paraffin-embedded tissue sections are chromogranine A (positivity in 60% for open lung biopsy vs. 47% transbrochial biopsy) and synaptophysin (5% vs. 19%) followed by the rather unspecific markers Leu-7 (40% vs. 24%) and NSE (60% vs. 33%) [22]. LCNEC stain with NSE (100%), chromogranine A (80%), Leu-7 (40%) and synaptophysin (40%) [10]. In TC, chromogranin A is the most useful immunohistochemical marker, followed by synaptophysin and Leu-7 showing a positivity in about 100% of tumour cells [10]. Another marker, however not specific for neuroendocrine tumours, is the thyroid-transcription factor-1 (TTF-1) which can be found in about 95% of SCLC, 70% of LCNEC, 100% of AC and 35% of TC but not in basaloid carcinoma (BC) or basaloid variant of squamous cell carcinoma [16, 23].

One result of our study is the demonstration of the good inter-observer correlation due to precise diagnostic criteria which are relatively easy to apply. The diagnosis of the 27 TC was presented by all three authors as straight forward (100%), one of three AC (33%) was diagnosed by one of the pathologists as TC but this was not justified due to the presence of necrosis. One of four cases LCNEC was diagnosed as AC, however, more than 10 mitoses/2 mm^2 were found and agreement on diagnosis was obtained. A second case of LCNEC was presented as differential diagnosis LCNEC vs. SCLC due to crush artefacts. After review of slides respecting strictly the proposed criteria diagnosis of large cell neuroendocrine carcinoma was performed.

These results were quite unexpected by us showing a distinct reduction of cases with divergent diagnosis in comparison to literature [12]. This may be due to the fact that we were working with a selected collective of cases without artefacts and considered to be representative for the tumour. Another cause might be the exhaustive use of immunohistochemistry in all cases where neuroendocrine differentiation was suspected.

Different entities of neuroendocrine tumours of the lung have different prognosis and therapeutic approaches. Regarding literature a five-years survival of 94% for TC is given, 55% for AC, 9% for SCLC and 27% for LCNEC. 5 to 15% of TC show local lymph node metastases at the time of diagnosis accompanied rarely by distant metastases, while in AC about 40 to 48% show local lymph node metastases and 20% metastases at distance [14]. The most aggressive form, the SCLC is characterised by 90% local lymph node metastases and metastases at distance. Due to the relative small number of large cell neuroendocrine carcinoma diagnosed with documented follow-up, we have only little information permitting determination of the differences in terms of survival and therapy between this entity and AC or SCLC.

These data stress the need for accurate and reproductive diagnostic criteria in order to allow clinicians appropriate treatment of neuroendocrine lung tumours. Implications for the patients in our collective concern those cases where treatment due to initial diagnosis is different from

the treatment which should have been applied according to the revised diagnosis. In our series one case of AC was initially diagnosed and treated as SCLC. The interpretation of this superficial biopsy was hampered by the presence of small cells and necrosis. The revised diagnosis is supported by the fact that the patient is still alive after 8 years. One case of SCLC was initially diagnosed and treated as TC, and a second as TC vs. squamous cell carcinoma. In both cases operation was performed and diagnosis had to be revised. Concerning the cases of LCNEC which were diagnosed as AC, or poorly differentiated carcinoma, appropriate treatment is not quite clear, resection is recommended whenever possible [10]. This entity also poses most problems in diagnosis due to the fact that it is rare. Immunohistochemistry is important in these cases. Not only in these cases but in general the role of immunohistochemistry for diagnosis should not be underestimated. The case of non-small cell lung cancer with neuroendocrine features could not be found without immunostaining with chromogranine A and synaptophysin (positive in both cases). The meaning of neuroendocrine differentiation in these tumours concerning prognosis and survival is divergent and doesn't implicate changing the treatment [24, 25].

In conclusion we confirm in this study the feasibility of the WHO-classification, allowing pathologists with different backgrounds to obtain excellent inter-observer correlation. We are convinced that other pathologists are not confronted with more problems than we were in this study. The reproducibility of this classification will have implications in the treatment of patients and also result in a more appropriate comparison of different studies respectively treatment protocols of different entities of neuroendocrine tumours of the lung.

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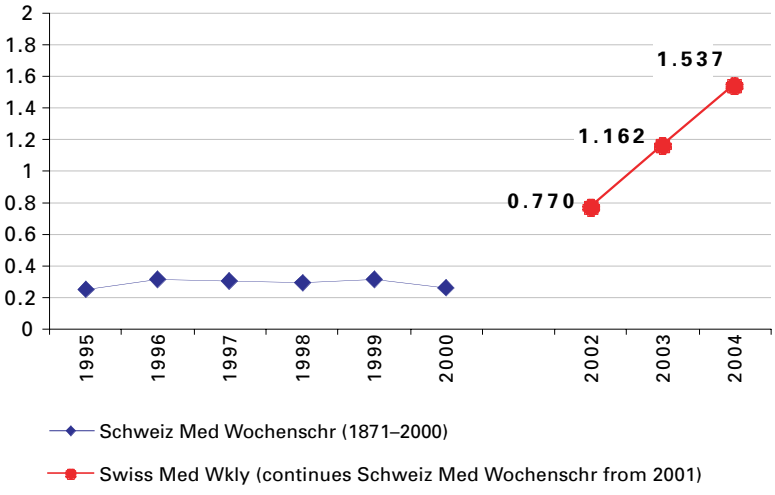

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