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The new World Health Organization classification of lung tumours

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The new World Health Organization classification of lung tumours. E. Brambilla, W.D. Travis, T.V. Colby, B. Corrin, Y. Shimosato. ©ERS Journals Ltd 2001.

ABSTRACT: Tumour classification systems provide the foundation for tumour diagnosis and patient therapy and a critical basis for epidemiological and clinical studies. This updated classification was developed with the aim to adhere to the principles of reproducibility, clinical significance, and simplicity in order to minimize the number of unclassifiable lesions.

Major changes in the revised classification as compared to the previous one (WHO 1981 [1]) include the addition of two pre-invasive lesions to squamous dysplasia and carcinoma *in situ*; atypical adenomatous hyperplasia and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. Another change is the subclassification of adenocarcinoma: the definition of bronchioalveolar carcinoma has been restricted to noninvasive tumours. There has been substantial evolution of concepts in neuroendocrine lung tumour classification. Large cell neuroendocrine carcinoma (LCNEC) is now recognized as a histologically high grade non small cell carcinoma showing histopathological features of neuroendocrine differentiation as well as immunohistochemical neuroendocrine markers. The large cell carcinoma class has been enriched with several variants, including the LCNEC and the basaloid carcinoma, both with a dismal prognosis. Finally, a new class was defined called carcinoma with pleomorphic, sarcomatoid, or sarcomatous elements, which brings together a number of proliferations characterized by a spectrum of epithelial to mesenchymal differentiation.

Immunohistochemistry and electron microscopy are invaluable techniques for diagnosis and subclassification, but our intention was to render the classification simple and practical to every surgical laboratory, so that most lung tumours could be classified by light microscopic criteria.

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Lung cancer is currently the most frequently diagnosed major cancer and the most common cause of cancer mortality in males worldwide. This is largely due to the effects of cigarette smoke. It has been 17 years since the World Health Organization (WHO) classification was updated in 1981 [1], and since this time considerable progress has been made in understanding the epidemiological histogenetic and molecular biology of lung cancer. In 1994, the WHO adopted the International Association for the Study of Lung Cancer (IASLC) pathology panel to comprise the core membership of the WHO committee, to develop a new revised classification of lung and pleural tumours. Because of the contribution of IASLC in this project, this classification is called the WHO/IASLC Histological Classification of Lung and Pleural Tumours [2] (table 1). An international

system of tumour classification is important for consistency in patient treatments and to provide the basis of epidemiological and biological studies. In developing this classification, pathologists have tried to adhere to the principles of reproducibility, clinical significance and simplicity, and to minimize the number of unclassifiable lesions. Most of this classification is based on the histological characteristics of tumours seen in surgical or needle biopsy, and is primarily based on light microscopy, although immunohistochemistry and electron microscopy findings are provided when necessary. Changes in classification were based essentially on the available published data or on the collective experience of the panel members when these data were not available. Certain time-honoured terms were retained, in order to respect their significance to the clinicians, while new concepts had

Table 1.—The 1999 World Health Organization/International Association for the Study of Lung Cancer Histological Classification of Lung and Pleural Tumours

1 Epithelial Tumours

- 1.1. Benign
 - 1.1.1. *Papillomas*
 - 1.1.1.1. Squamous cell papilloma
 - Exophytic
 - Inverted
 - 1.1.1.2. Glandular papilloma
 - 1.1.1.3. Mixed squamous cell and glandular papilloma
 - 1.1.2. *Adenomas*
 - 1.1.2.1. Alveolar adenoma
 - 1.1.2.2. Papillary adenoma
 - 1.1.2.3. Adenomas of salivary-gland type
 - Mucous gland adenoma
 - Pleomorphic adenoma
 - Others
 - 1.1.2.4. Mucinous cystadenoma
 - 1.1.2.5. Others
- 1.2. Preinvasive lesions
 - 1.2.1. *Squamous dysplasia/Carcinoma in situ*
 - 1.2.2. *Atypical adenomatous hyperplasia*
 - 1.2.3. *Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia*
- 1.3. Malignant
 - 1.3.1. *Squamous cell carcinoma*
 - Variants
 - 1.3.1.1. Papillary
 - 1.3.1.2. Clear cell
 - 1.3.1.3. Small cell
 - 1.3.1.4. Basaloid
 - 1.3.2. *Small cell carcinoma*
 - Variants
 - 1.3.2.1. Combined small cell carcinoma
 - 1.3.3. *Adenocarcinoma*
 - 1.3.3.1. Acinar
 - 1.3.3.2. Papillary
 - 1.3.3.3. Bronchioloalveolar carcinoma
 - 1.3.3.3.1. Non-mucinous (Clara/pneumocyte type II)
 - 1.3.3.3.2. Mucinous
 - 1.3.3.3.3. Mixed mucinous and non-mucinous or intermediate cell type
 - 1.3.3.4. Solid adenocarcinoma with mucin
 - 1.3.3.5. Adenocarcinoma with mixed subtypes
 - 1.3.3.6. Variants
 - 1.3.3.6.1. Well-differentiated fetal adenocarcinoma
 - 1.3.3.6.2. Mucinous ("colloid") adenocarcinoma
 - 1.3.3.6.3. Mucinous cystadenocarcinoma
 - 1.3.3.6.4. Signet-ring adenocarcinoma
 - 1.3.3.6.5. Clear cell adenocarcinoma
 - 1.3.4. *Large cell carcinoma*
 - Variants
 - 1.3.4.1. Large cell neuroendocrine carcinoma
 - 1.3.4.1.1. Combined large cell neuroendocrine carcinoma
 - 1.3.4.2. Basaloid carcinoma
 - 1.3.4.3. Lymphoepithelioma-like carcinoma
 - 1.3.4.4. Clear cell carcinoma
 - 1.3.4.5. Large cell carcinoma with rhabdoid phenotype
 - 1.3.5. *Adenosquamous carcinoma*
 - 1.3.6. *Carcinomas with pleomorphic, sarcomatoid or sarcomatous elements*
 - 1.3.6.1. Carcinomas with spindle and/or giant cells
 - 1.3.6.1.1. Pleomorphic carcinoma
 - 1.3.6.1.2. Spindle cell carcinoma
 - 1.3.6.1.3. Giant cell carcinoma
 - 1.3.6.2. Carcinosarcoma
 - 1.3.6.3. Pulmonary blastoma
 - 1.3.6.4. Others

Table 1. Continued

- 1.3.7. *Carcinoid tumour*
 - 1.3.7.1. Typical carcinoid
 - 1.3.7.2. Atypical carcinoid
 - 1.3.8. *Carcinomas of salivary-gland type*
 - 1.3.8.1. Mucoepidermoid carcinoma
 - 1.3.8.2. Adenoid cystic carcinoma
 - 1.3.8.3. Others
 - 1.3.9. *Unclassified carcinoma*
- ## 2 Soft Tissue Tumours
- 2.1 Localized fibrous tumour
 - 2.2 Epithelioid hemangioendothelioma
 - 2.3 Pleuropulmonary blastoma
 - 2.4 Chondroma
 - 2.5 Calcifying fibrous pseudotumour of the pleura
 - 2.6 Congenital peribronchial myofibroblastic tumour
 - 2.7 Diffuse pulmonary lymphangiomatosis
 - 2.8 Desmoplastic small round cell tumour
 - 2.9 Other
- ## 3 Mesothelial Tumours
- 3.1 Benign
 - 3.1.1 *Adenomatoid tumour*
 - 3.2 Malignant
 - 3.2.1 *Epithelioid mesothelioma*
 - 3.2.2 *Sarcomatoid mesothelioma*
 - 3.2.2.1 Desmoplastic mesothelioma
 - 3.2.3 *Biphasic mesothelioma*
 - 3.2.4 *Other*
- ## 4 Miscellaneous Tumours
- 4.1 Hamartoma
 - 4.2 Sclerosing hemangioma
 - 4.3 Clear cell tumour
 - 4.4 Germ cell neoplasms
 - 4.4.1 *Teratoma, mature or immature*
 - 4.4.2 *Malignant germ cell tumour*
 - 4.5 Thymoma
 - 4.6 Melanoma
 - 4.7 Others
- ## 5 Lymphoproliferative Disease
- 5.1 Lymphoid interstitial pneumonia
 - 5.2 Nodular lymphoid hyperplasia
 - 5.3 Low-grade marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue
 - 5.4 Lymphomatoid granulomatosis
- ## 6 Secondary Tumours
- ## 7 Unclassified Tumours
- ## 8 Tumour-like Lesions
- 8.1 Tumourlet
 - 8.2 Multiple meningothelioid nodules
 - 8.3 Langerhans cell histiocytosis
 - 8.4 Inflammatory pseudotumour (Inflammatory myofibroblastic tumour)
 - 8.5 Organizing pneumonia
 - 8.6 Amyloid tumour
 - 8.7 Hyalinizing granuloma
 - 8.8 Lymphangioleiomyomatosis
 - 8.9 Multifocal micronodular pneumocyte hyperplasia
 - 8.10 Endometriosis
 - 8.11 Bronchial inflammatory polyp
 - 8.12 Others

emerged that would necessitate a change. An example of this is "small-cell lung carcinoma". As compared to the previous edition, changes include a better definition of pre-invasive lesion, a reclassification of adenocarcinoma, the description of two new tumour types as variants of large cell carcinoma, large cell neuroendocrine carcinoma (LCNEC) and basaloid

carcinoma, and a new class called pleomorphic carcinoma.

Pre-invasive lesions

More precise guidelines for grading squamous dysplasia in mild, moderate and severe dysplasia and to define carcinoma *in situ* are provided (fig. 1a–d). These precise criteria allowed better interobserver reproducibility [3]. In addition of the categories of squamous dysplasia and carcinoma *in situ*, two additional lesions were added to the group of pre-invasive lesions: atypical adenomatous hyperplasia (AAH) and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH).

Atypical adenomatous hyperplasia

Many studies now justify that AAH is a precursor to adenocarcinoma [4–14]. Multiple synonyms have been used for this lesion including alveolar cell hyperplasia, atypical alveolar hyperplasia, bronchioalveolar cell adenoma, alveolar atypical hyperplasia, and atypical alveolar cuboidal cell hyperplasia. AAH and nonmucinous bronchioalveolar carcinoma (BAC) are lesions located most exclusively in lung periphery and a spectrum of neoplasia exists in an AAH-BAC sequence. However, most studies have examined these lesions as incidental findings in lung specimens resected for lung cancer and few biological studies have investigated whether this lesion represents a precursor to adenocarcinoma. However, the concept that AAH is a precursor to invasive carcinoma is mainly based on the fact that they are primarily seen adjacent to adenocarcinoma and due to the fact that some are identified within the same mass in emergence with the adenocarcinoma.

Although extensive research has been made on autopsy series and the findings depend on the number and intensity of this search, it is clear that AAH are not present in each patient developing an adenocarcinoma, and their frequency goes from 2% in young people with no cancer [15] to 23.2% in autopsy series of aged people with cancer [16]. Although it was tempting to establish a morphological grading of dysplasia along the spectrum of AAH and to separate lesions into low and high grade, pathologists at the WHO/IASLC panel did not find sufficiently convincing criteria to recommend grading. AAH is defined as a proliferation of minimally atypical cuboidal type II pneumonocytes with gaps between cells; AAH generally measures <5 mm in diameter (fig. 1e, 1f). In addition to the morphology, additional data supporting the preneoplastic nature of AAH include comparative analysis of AAH and BAC showing progressive increase of a mean nuclear area by morphometry, alteration of proliferation measured by Ki-67, progressive p53 accumulation and loss of heterozygosity at 3p, 9p and 17p and K (ras mutations at codon 12) in AAH and associated BAC [5, 8, 9, 13, 17–19].

Diffuse idiopathic neuroendocrine cell hyperplasia

Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) is a very rare disorder considered a precursor of tumourlets and typical or atypical carcinoids [20] (fig. 1g, 1h). Neuroendocrine cell hyperplasia occurs most commonly as a reactive hyperplasia in the setting of airway fibrosis and/or inflammation [21–22]. Two thirds of patients with peripheral carcinoid tumours have neuroendocrine cell hyperplasia in the adjacent bronchiolar epithelium. A subset of patients with DIPNECH has associated obstructive bronchiolar fibrosis with obstructive pulmonary functions. Some patients with DIPNECH have both obstructive lung disease and multiple tumourlets/carcinoid tumours. Cytokines and growth factors secreted by neuroendocrine cells (gastrin-releasing peptide, fibroblast growth factors) suggest that these neuroendocrine cells are the cause of fibrosis [21]. A number of observations associating neuroendocrine cell hyperplasia and carcinoids suggests that this condition is a preneoplastic state for peripheral carcinoid tumours.

Adenocarcinomas

Adenocarcinoma is the predominant histological subtype of lung carcinoma in many countries [23–24]. In Europe, the incidence has increased by 10% in the last 20 yrs [25]. Adenocarcinoma is the most prevalent form of lung cancer in younger males (<50 yrs old) and in women of all ages, in never smokers, and in former smokers [26]. Differences in tobacco smoking habits (filters, light tobacco cigarettes, profound inhalation) appear to favour the development of distal bronchiolar and alveolar carcinogenesis at the expense of proximal squamous cell carcinoma [27, 28].

Difficulties in adenocarcinoma subclassification arise from the fact that adenocarcinomas are highly heterogeneous histologically, with only a minority of cases showing a pure histological pattern. Mixed pattern adenocarcinomas are more common than tumours showing a single pattern (*e.g.* acinar, papillary, bronchioalveolar, and solid adenocarcinoma with mucin formation).

The 1999 WHO classification is more restrictive in the definition of BAC; this category includes only noninvasive tumours with lepidic spread (fig. 2a, 2b). This present definition excludes cases with stromal, vascular or pleural invasion. Tumours showing these features are classified as adenocarcinoma mixed type with predominant bronchioalveolar pattern (fig. 2c, 2d). Most tumours described as BAC in the past would now be in this category. The present definition of BAC is much more restrictive than any previously used by many pathologists. Since it has been shown that patients with solitary, noninvasive BACs measuring <2.0 cm can be cured with resection [11], the current definition has a high clinical significance. Where BAC of Clara type II cells (nonmucinous) are usually solitary nodules and have very good prognosis, mucinous-type bronchioalveolar carcinomas tend to spread and form satellite tumours or

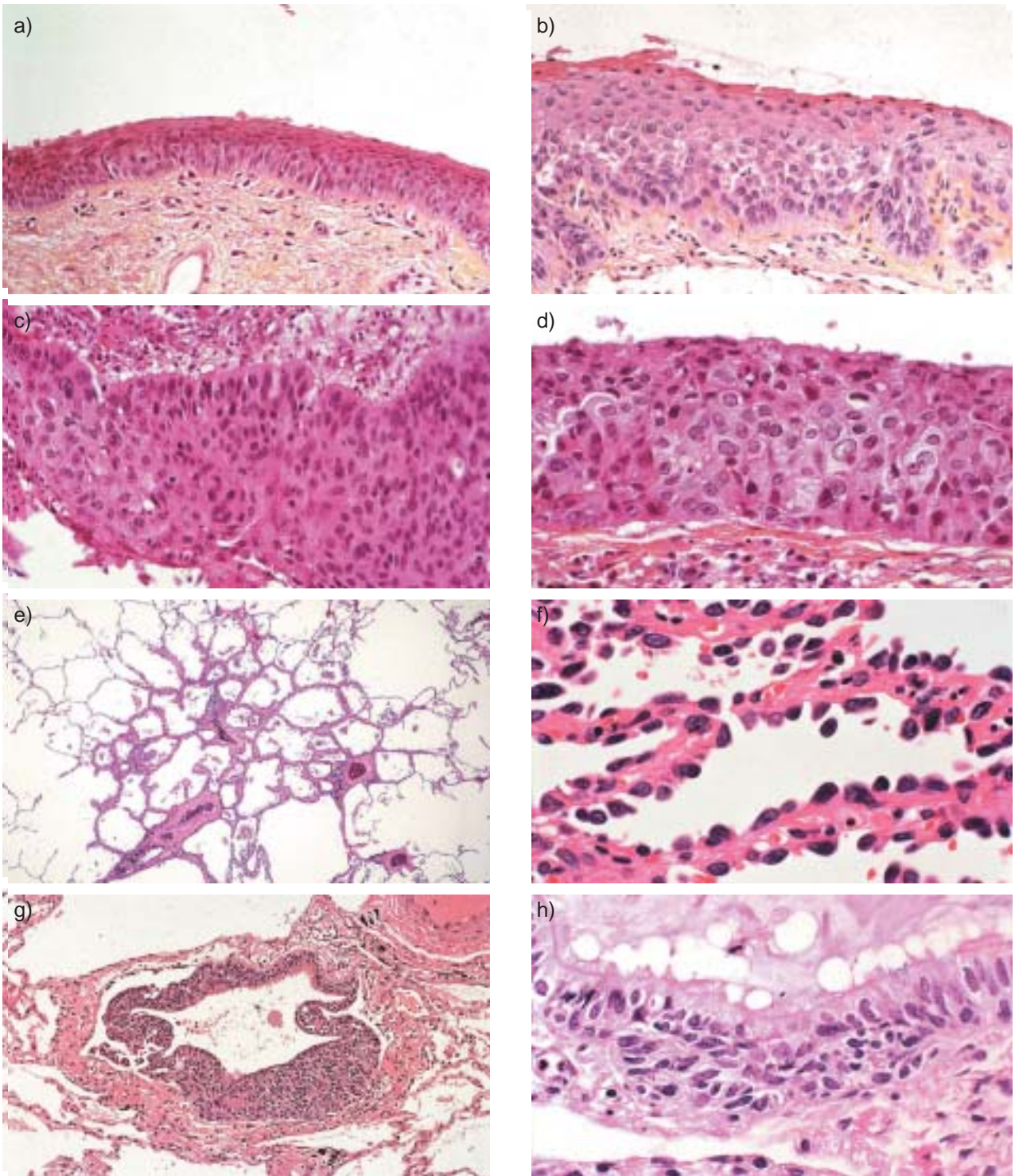


Fig. 1. – Histological patterns of significant and new entities. a) Mild dysplasia: mildly increased thickness, mild pleiomorphism, basilar zone expanded with cellular crowding in lower one-third of the epithelium, with nuclei vertically oriented, mitoses absent. b) Moderate dysplasia: moderately increased thickness, moderate anisocytosis and pleiomorphism; basilar zone expanded with cellular crowding in lower two-thirds of epithelium with nuclei vertically oriented, mitotic figures in lower third. c) Severe dysplasia: markedly increased thickness, marked anisocytosis and pleiomorphism, basilar zone expanded with cellular crowding according into upper third, little progression of maturation, irregular nuclei vertically oriented in lower third, mitosis in lower two-thirds. d) Carcinoma *in situ*: markedly increased cell size and pleiomorphism, no progression of maturation, cellular crowding throughout epithelium, no consistent orientation of nuclei, irregular nuclei with coarse, uneven chromatin, mitotic figures through full thickness. e) Atypical alveolar hyperplasia: a small millimetre-sized (<5 mm) bronchioloalveolar lesion consisting of proliferative pneumonocytes in a lepidic fashion along thin alveolar walls. f) Atypical alveolar hyperplasia: at high magnification, cuboidal type II pneumonocytes line the alveolar walls with gaps between adjacent cells (reproduced from World Health Organization (WHO) [2]). g) Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: the bronchioloalveolar epithelium is almost replaced by proliferating neuroendocrine cells (reproduced from WHO [2]). h) Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: at higher magnification, hyperplastic neuroendocrine cells form a nest at the base of the bronchiolar epithelium (reproduced from WHO [2]).

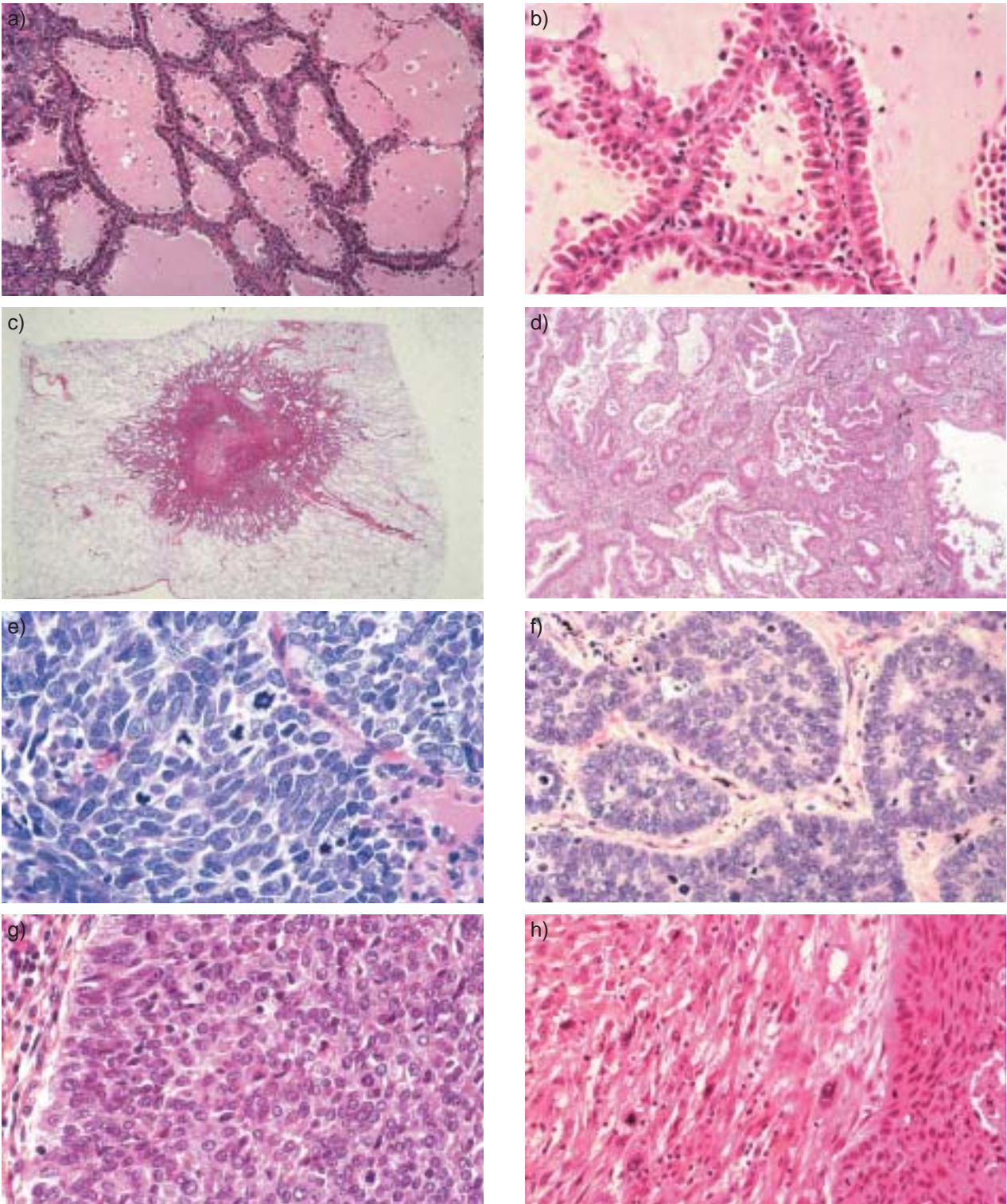


Fig. 2. – Histological patterns of significant and new entities. a) Bronchioloalveolar carcinoma, nonmucinous: the cuboidal to columnar shaped cells grow in a lepidic pattern along preexisting alveolar wall (reproduced from World Health Organization (WHO) [2]). b) Bronchioloalveolar carcinoma: cuboidal- to columnar-shaped cells (Clara cell differentiation) have basally oriented nuclei and eosinophilic cytoplasm with apical snouts (reproduced from WHO [2]). c) Adenocarcinoma with mixed subtypes: low magnification of an adenocarcinoma with a predominant bronchioloalveolar pattern that has an invasive component in a central scar. d) Adenocarcinoma with mixed subtypes: at higher magnification of the same case (c) the central scar contains an invasive acinar component. e) Small cell carcinoma: small tumour cells are densely packed, with scant cytoplasm, finely granular nuclear chromatin and absence of nucleoli. Mitoses are frequent (reproduced from WHO [2]). f) Large cell neuroendocrine carcinoma: palisading and rosette-like formation, numerous mitoses, vesicular nuclear chromatin (reproduced from WHO [2]). g) Basaloid carcinoma: palisading is conspicuous at the periphery of the nests of tumour cells. Cells are hyperchromatic with relatively scant cytoplasm and show numerous mitotic figures. h) Pleomorphic carcinoma: this tumour has a mixture of spindle and giant cell carcinoma (left) with squamous cell component (right).

pneumonic consolidation, and thus have a worse prognosis. AAH is considered a precursor for non mucinous BAC; there is no defined pre-invasive lesion for mucinous BAC.

A recent evaluation of surgically resected BAC detected in asymptomatic patients using systematic spiral computed tomography (CT) radiographic detection showed a high frequency of additional concomitant BACs, or AAH in 43% of patients [29]. It is expected that the presence of tiny multiple lesions (noninvasive and <5 mm) does not impact on prognosis [4].

Several variants of adenocarcinoma are recognized in the new WHO/IASLC classification including well-differentiated foetal adenocarcinoma, colloid carcinoma, mucinous cystadenocarcinoma, signet ring adenocarcinoma and clear cell adenocarcinoma. Since this classification work, thyroid transcription factor 1 (TTF-1) has appeared of great help in this differential diagnosis being expressed in 85% of primary lung adenocarcinoma and negative metastatic adenocarcinoma, although mucine producing primary adenocarcinoma might be TTF-1 negative.

Large cell carcinoma and neuroendocrine tumours

Large cell carcinoma now includes five variants in addition to large cell carcinoma defined as undifferentiated malignant epithelial cells. Two variants are recognized, both with dismal prognosis, LCNEC and basaloid carcinoma.

The concept of neuroendocrine tumours has been examined as a spectrum extending from low grade typical carcinoid to intermediate grade atypical carcinoid to high grade neuroendocrine tumours including large cell neuroendocrine carcinoma and small cell lung carcinoma (SCLC). Because of differences in clinical behaviour, therapeutic implications, and epidemiological context, these tumours have been presented separately in the WHO revised classification.

Typical and atypical carcinoid have been more precisely defined and clearly differentiated from each other with more objective criteria. Typical carcinoids have <2 mitotic figures per 2 mm², and have no necrosis. The presence of necrosis, or a mitotic count between 2–10.2 mm⁻², allows separation of atypical carcinoid from typical carcinoid. A mitotic count >10.2 mm⁻² is seen in LCNEC. Using only very objective criteria (mitosis and necrosis), there is substantial interobserver reproducibility for subclassification of pulmonary neuroendocrine tumours; the most common disagreement involves LCNEC *versus* SCLC, followed by typical carcinoids *versus* atypical carcinoids. Subclassification of neuroendocrine tumours has been shown to be of strong prognostic implication on survival, allowing high significantly different survival rate between typical and atypical carcinoids ($p < 0.0001$), and between atypical carcinoids and LCNEC ($p < 0.0001$). There is no significant survival differential rate between LCNEC and SCLC when stratified by stage [30–31]. LCNEC may be pure or combined, the latter if at least 10% of the tumours presents another non-small cell histology.

The diagnosis of LCNEC is based on recognition of both neuroendocrine morphology (organoid pattern) and the immunohistochemical demonstration of at least one specific neuroendocrine marker (fig. 2f). Among these specific neuroendocrine markers are chromogranin, synaptophysin and neural cell adhesion molecule (NCAM).

Neuroendocrine differentiation has been found immunohistochemically or ultrastructurally in 5–10% of NSCLC that do not display any neuroendocrine (organoid) morphology. The presence of neuroendocrine markers without neuroendocrine morphology does not allow a specific classification and is collectively referred to as "NSCLC with neuroendocrine differentiation" [32–35]. There is controversy over whether these tumours are associated with a worse or a better survival rate. Their clinical and therapeutic significance is not firmly established.

Although, IASLC had proposed to recognize a variant form of SCLC called mixed small cell-large cell carcinoma [36], this variant was not retained in revised WHO classification. Instead, SCLC is now described with only one variant: "SCLC combined", when at least 10% of the tumour bulk is made of an associated non-small cell component. SCLC presents a proliferation of small cells (<4 lymphocytes in diameter) with unique and strict morphological features, scant cytoplasm, ill-defined borders, finely granular "salt and pepper" chromatin, absent or inconspicuous nucleoli, frequent nuclear molding, and a high mitotic count (fig. 2e). The category of combined small cell carcinoma includes cases with a mixture of small cell and large cell or any other non-small cell component. Importantly for the clinical significance of the diagnostic signature, any cases showing at least 10% of SCLC is diagnosed as SCLC combined, even if the tumour has a heterogeneous sarcomatous component. SCLC alone is reserved to tumours with pure SCLC histology. SCLC associated with LCNEC is diagnosed as SCLC combined with LCNEC.

In addition, LCNEC comprise rare tumour types such as lymphoepithelioma-like carcinoma (Epstein-Barr virus-dependant epithelial proliferation) [37, 38], clear cell carcinoma [39], and large cell carcinoma with rhabdoid phenotype [40]. Large cell carcinoma with rhabdoid phenotype as well as blastoma and desmoid round cell tumours, primitive neuroendocrine tumour (PNET) and paraganglioma belong to the category of non-neuroendocrine tumours that may display neuroendocrine markers.

Basaloid carcinoma

Basaloid carcinoma is now defined as a variant of large cell carcinoma [41, 42]. Basaloid carcinoma presents with relatively small cells forming lobular pattern with a high rate of mitosis (15–100.2 mm⁻²), peripheral palisading and comedo-type necrosis (fig. 2g). They represent 3% of non-small cell lung carcinoma (NSCLC) in Europe. In their pure type, they should not be confused with poorly differentiated squamous cell carcinoma, because they bear

significantly poorer prognosis at stage I–II [42]. Thirty per cent of basaloid carcinoma disclose rosettes, but they are distinguished from LCNEC on the basis of tumour cell size, nuclear features and absence of immunohistochemical neuroendocrine markers. Like other NSCLC, basaloid carcinoma may display one or two neuroendocrine histochemical markers in a small proportion (<10%) of the tumour cells. A specific set of cytokeratins (CK 1, 5, 10, and 14 recognized by the 34 β E12 monoclonal antibody) is consistently absent in neuroendocrine tumours including LCNEC, and consistently expressed in basaloid carcinoma [43]. When a basaloid carcinoma shows squamous differentiation, the designation as basaloid variant of squamous cell carcinoma is appropriate (table 1). The basaloid variant of squamous cell carcinoma and pure basaloid carcinoma share the same dismal prognosis with a median survival time of 20 months [41, 44]. Interestingly basaloid carcinoma disclose a higher frequency of p53 mutation and p53 protein aberrant expression, a higher rate of p16^{INK4} inactivation with loss of protein expression and higher Bcl2:bax ratio than squamous cell carcinoma and other NSCLC [45, 46].

Carcinoma with pleomorphic, sarcomatoid, or sarcomatous elements

These tumours are defined as a group of poorly differentiated nonsmall cell carcinoma that contains a component of sarcoma or sarcoma-like elements. They have been described under a variety of names including sarcomatoid carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, blastoma and others. They are rare tumours and few pathologists have the opportunity to study very many of them. Spindle and giant cell carcinoma and carcinosarcoma comprise only 0.4% and 0.1% of all lung malignancies, respectively [23]. The tumours described under which name represent overall a continuum of epithelial and mesenchymal differentiation [47, 48]. Whether these tumours have a worse prognosis than other NSCLC is intuitively likely, but has not been firmly demonstrated on large series.

The great majority of carcinoma with components of spindle cells and/or giant cell carcinoma is histologically heterogeneous. Pleomorphic carcinoma shows carcinomatous as well as spindle and/or giant cell components (fig. 2h). Using antibodies against a large panel of cytokeratins, the epithelial nature of the spindle or giant cell component in these tumours can almost always be demonstrated. The epithelial markers might be negative on the spindle cell component, but an obvious carcinoma associated in the tumour allows the diagnosis of pleomorphic carcinoma in these cases. Pure spindle cell or giant cell carcinomas are extremely rare if the tumour has been widely sampled.

Carcinosarcoma is arbitrarily defined as a biphasic tumour with both carcinomatous and sarcomatous components, with the latter demonstrating heterologous elements such as malignant bone, cartilage, or skeletal muscle. It is controversial whether

carcinosarcoma really exist. Most of the studies examining the presence of keratin in chondrosarcomatous or osteosarcomatous elements associated with epithelial components in these tumours have shown the presence of cytokeratin expression, favouring classification as a carcinoma with sarcomatoid elements, rather than carcinosarcoma. Consistent with this, molecular studies have demonstrated the same molecular and genetic abnormalities in both the epithelial and sarcomatoid components [49–53].

Pulmonary blastoma is considered as part of the spectrum of carcinomas with a pleomorphic sarcomatoid or sarcomatous element, based also on clinical pathological and molecular data. It is a biphasic tumour containing a primitive epithelial component resembling well-differentiated foetal-type adenocarcinoma and a primary mesenchymal stroma. Well-differentiated foetal adenocarcinoma is now included as an histological variant of adenocarcinoma and should not be regarded as a "monophasic" pulmonary blastoma, since the former has a much better prognosis and lacks p53 mutations in the latter. Pulmonary blastoma are observed in adults, whereas pleuropulmonary blastoma is a cystic and/or solid sarcoma (included in soft tissue tumours) arising in children <6 yrs old.

Other tumours arising in the lung

A number of tumours arising in the lung as the primary site are not described in details in the WHO classification of lung tumours because they have no specific features in the lung.

Carcinomas of salivary-gland type are described in detail in the WHO Histological Classification of Tumours of the Salivary Gland [54]. Mucoepidermoid carcinoma of high grade malignancy should be differentiated from adenosquamous carcinoma and from low grade mucoepidermoid carcinoma, which has a better prognosis. Adenoid cystic carcinomas predominantly arise in the trachea and large bronchi. Acinic cell carcinoma, epimyoeplithelial carcinoma and malignant mixed tumours arising from bronchial glands are also described.

Soft tissue tumours are defined and classified in WHO Histological Typing of Soft Tissue Tumours [55]. Among these, some merit mention for their frequency in the lung: localized fibrous tumour (formerly called benign fibrous mesothelioma); epithelioid haemangioendothelioma (previously called intravascular bronchioloalveolar tumours); pleuropulmonary blastoma (which occurs in children and is distinguished from pulmonary blastoma which occurs in adults); chondroma (which mostly occurs in early childhood); calcifying fibrous pseudotumour of the visceral pleura); congenital peribronchial myofibroblastic tumours, diffuse pulmonary lymphangiomyomatosis (not to be confused with lymphangiomyomatosis) and; desmoplastic round cell tumour.

Lymphomas primary in the lung are mentioned briefly and the WHO Classification of leukaemia and lymphoma is now available for details [56]. Pleural

mesothelial tumours are described briefly in WHO 1999 with no changes from previous classification [57].

Role of immunohistochemistry and electron microscopy

Immunohistochemistry and electron microscopy are indeed valuable techniques for diagnosis and subclassification of lung tumours; however, the authors have attempted to establish a classification that is simple, practical, and able to be used even in surgical pathology laboratories where these techniques are not available.

Nevertheless, immunohistochemistry and/or electron microscopy are required for diagnosis of LCNEC (specific neuroendocrine markers are chromogranin, synaptophysin, NCAM) and for the differential diagnosis between malignant mesothelioma and metastatic adenocarcinoma to the pleura (specific positive markers are calretinin and cytokeratin 5, 6). These markers are necessary for the differential diagnosis between malignant mesothelioma and peripheral mesothelioma-like adenocarcinoma, but have been developed further to the WHO classification. The distinctive immunostaining characteristics of certain tumours are also very useful, such as HMB-45 positivity in clear cell tumours and lymphangioleiomyomatosis. Epidermic membrane antigen and TTF-1 immunostaining in sclerosing haemangiomas are of great help. In addition, TTF-1 has been shown to recognize specifically lung adenocarcinoma (85% of the cases positive), whereas metastatic adenocarcinoma in the lung are always TTF-1 negative.

Molecular studies

The advent of molecular biology has also allowed a new depth of insights into the understanding of many lung tumours. For example, the molecular demonstration of the neoplastic nature of alveolar adenoma, chondroid hamartoma, and inflammatory pseudotumours (inflammatory myofibroblastic tumour) has been provided. Molecular and genetic abnormalities have highly contributed to the concept of bronchial or alveolar pre-invasive lesion as compared to invasive lung tumours.

Conclusion

Most lung tumours can be classified on the basis of light microscopy only, which provide a potential widespread and worldwide application of this classification system. Future studies should clarify some of the difficult problems in lung tumour classification, especially for pre-invasive lesions, adenocarcinoma subtyping, and carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements.

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