The Histological Classification of Malignant Lung Tumors

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ABSTRACT

The gross and microscopic features of malignant lung tumors are discussed within the framework of the WHO International classification. Recent information contributed by electron microscopy is included where pertinent.

Introduction

The problem of classification of malignant tumors of the lung is, at present, only partially resolved. The lack of a uniform classification becomes apparent when an attempt is made to compare various series as to incidence, behavior, etc. of the various types of malignant tumors. Not only do the categories vary, but the criteria by which a tumor is assigned to a particular category also may vary from study to study. Not infrequently, the criteria for classification are not even mentioned, or it is merely stated that the slides were reviewed and classified by one or more pathologists. Therefore, scientists are faced with not only the problem of what are at times rather vague and subjective criteria but also the problem of intra- and inter-observer variation. This latter problem has been subjected to analysis in only a few studies.23,24

In an attempt to alleviate this situation, the World Health Organization created, in 1953, an International Reference Center for the Histological Definition and Classification of Lung Tumors. This center was located in Oslo and headed by Professor Leiv Kreyberg. At the same time, a tentative histological classification was adopted which was very similar to that used by Professor Kreyberg for a number of years. In 1967, the WHO published a slightly revised classification. Several studies have been published which found the WHO classification practical and useful. If future studies adhere to this classification or at least specify explicitly to what extent they deviate from it, the situation will be much improved.

The WHO international classification of lung tumors is shown in table I. This report will deal with groups I through XI of this classification.

Classification

GROUP I. EPIDERMOID CARCINOMAS

Epidermoid, or squamous cell carcinoma, is the most common type of primary malignant epithelial tumor of the lung, comprising approximately 50 percent of all cases. It has a decided male preponderance
TABLE I

THE WHO INTERNATIONAL CLASSIFICATION OF LUNG TUMORS

I. EPIDERMOID CARCINOMAS

II. SMALL CELL ANAPLASTIC CARCINOMAS
1. Fusiform cell type
2. Polygonal cell type
3. Lymphocyte-like ("oat-cell") type
4. Others

III. ADENOCARCINOMAS
1. Bronchogenic
   a. acinar—with or without mucin formation
   b. papillary
2. Bronchiolo-alveolar

IV. LARGE CELL CARCINOMAS
1. Solid tumors with mucin-like content
2. Solid tumor without mucin-like content
3. Giant cell carcinomas
4. "Clear" cell carcinomas

V. COMBINED EPIDERMOID AND ADENOCARCINOMAS

VI. CARCINOID TUMORS

VII. BRONCHIAL GLAND TUMORS
1. Cylindromas
2. Mucoepidermoid tumors
3. Others

VIII. PAPILLARY TUMORS OF THE SURFACE EPITHELIUM
1. Epidermoid
2. Epidermoid with goblet cells
3. Others

IX. "MIXED" TUMORS AND CARCINOSARCOMAS
1. "Mixed" tumors
2. Carcinosarcomas of embryonal type ("blastomas")
3. Other carcinosarcomas

X. SARCOMAS

XI. UNCLASSIFIED

XII. MESOTHELIOMAS
1. Localized
2. Diffuse

XIII. MELANOMAS

which varies from 75 percent to 96 percent in several reported series. This male preponderance can be explained in part by two etiologic factors: cigarette smoking and occupational exposure to carcinogenic substances, such as uranium ore and asbestos.

Epidermoid carcinomas commonly originate from large bronchi, either mainstem, lobular or major segmental bronchi. Their occurrence in a peripheral location is possible but infrequent. These tumors may occasionally grow predominantly as a bulky intrabronchial mass. More commonly, they cause gradual narrowing and eventually complete obstruction of the
bronchus. Owing to their location and mode of growth, epidermoid carcinomas are amenable to diagnosis by bronchial biopsy or the cytologic examination of sputum.

Metastasis commonly occurs first in the hilar and then in the mediastinal and supraclavicular lymph nodes. Since they are more accessible, the supraclavicular nodes are sometimes biopsied as an adjunct to diagnosis. The occurrence of more distant metastases seems to correlate with the degree of differentiation, frequently occurring later in the better differentiated tumors.

By light microscopy the typical features are stratification of cells, whorl formation, intracellular bridges and keratinization. Areas of necrosis are not infrequent and, indeed, this process may on rare occasions be so extensive that the tumor presents as a cavitory lesion on X-ray.

Less well-differentiated epidermoid carcinomas, in which keratinization and intracellular bridges are inconspicuous, may maintain a semblance of stratification and assume a transitional pattern. In some such cases, cuboidal or columnar cells may line the periphery of clumps of tumor cells, giving the appearance of a basilar layer. In these less well-differentiated tumors, it is sometimes helpful to examine the bronchial mucosa adjacent to the tumor for evidence of intraepithelial malignant change.

Epidermoid carcinomas may rarely have areas where the majority of the cells assume a spindle shape (figure 1). This change may be so pronounced that the tumor appears sarcomatous. This histologic variation probably accounts for many of the tumors that have been classified as carcinosarcomas in the past.

By electron microscopy tonofibrils in bundles and abundant, well-developed desmosomes are the most significant organelles (figure 2). These two structures are intimately associated at the intercellular bridges which are numerous. These organelles become noticeably scarce as the tumor de-differentiates.

**Group II. Small Cell Anaplastic Carcinomas**

The WHO classification recognizes four sub-groups under this heading: (1) fusiform cell type, (2) polygonal cell type, (3) lymphocyte-like ("oat-cell") type and (4) other. Of these the oat-cell carcinoma

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**Figure 1. Photomicrograph of a spindle cell variant of epidermoid carcinoma of bronchial origin. Hematoxylin and eosin. (×200)**
is by far the most widely recognized and will be discussed as a prototype of the group. The other categories serve to accommodate what appears at present to represent significant histologic variations from this pattern.

Oat-cell carcinoma comprises approximately 20 percent of all malignant epithelial lung tumors. It also has a decided male preponderance, probably for much the same reasons as are proposed for epidermoid carcinoma. Kreyberg\textsuperscript{13} has divided carcinomas of the lung into two groups: group I composed of epidermoid and oat-cell carcinoma and group II consisting of adenocarcinomas and some much rarer types of tumors, i.e., carcinoids. Group I has a much higher percentage of males and shows an increasing risk of developing lung cancer with increasing numbers of cigarettes smoked. Group II shows much less of a male preponderance and many more non-smokers or light smokers.

The majority (approximately 70 percent) of oat-cell carcinomas arise from main bronchi. In contrast to epidermoid carcinomas, they do not typically form bulky intrabronchial masses but tend to spread along submucosal lymphatics causing an irregular thickening of the mucosa. Not uncommonly, the primary focus is relatively small but has produced extensive metastases, i.e., to mediastinal lymph nodes. It was probably this characteristic, in addition to the histologic appearance of the tumor, that accounted for the early designation of this tumor as mediastinal sarcoma. The epithelial origin of oat-cell carcinoma was first recognized in 1926 by Barnard.\textsuperscript{2} Subsequently, it was considered an anaplastic (possibly epidermoid) carcinoma. Origin from "reserve cells" of bronchial epithelium was also postulated.

The true nature of this tumor was established in several stages. Azzopardi\textsuperscript{1} and others made the first step by delineating its unique histologic appearance by light microscopy. After the histologic characteristics became well established, oat-cell carcinomas began to be associated with cer-
tain clinical features, such as a generally poor prognosis and occasional endocrine activity.

The final step in delineating the origin of this tumor was an ultrastructural study by Bensch which demonstrated the presence of neurosecretory-type granules in oat-cell carcinomas similar to those seen in bronchial carcinoids. He had previously identified Kultschitzky-like (argentaffin) cells in normal bronchial epithelium and postulated that oat-cell carcinoma and bronchial carcinoid might be, respectively, the malignant and locally malignant form of tumors derived from these cells. A recent study by Hattori et al has shown good correlation between the number of neurosecretory-type granules and the level of serotonin in the serum and in the tumor.

Oat-cell carcinomas are typically composed of small, ovoid cells, most of which are slightly larger than lymphocytes and have scant cytoplasm and hyperchromatic nuclei. These cells are distributed in irregular sheets and cords, mitoses are frequent and areas of necrosis may be present. Some of these tumors may show areas where the cells are arranged in ductules or rosette formations. In such areas, mucin-like material may be identified by means of special stains. Small foci of epidermoid differentiation may also be present. None of these features invalidates the diagnosis of oat-cell carcinoma. These tumor cells are fragile and areas showing crush artifact are commonly seen in biopsy material.

The salient ultrastructural features of oat-cell carcinoma are angulated nuclei with coarsely clumped chromatin, scant cytoplasm with few organelles, and variable numbers of neurosecretory-like granules. These granules have electron-dense homogeneous round cores, are bound by a single membrane and vary in size from 50 to 240 microns. They are often aggregated in pseudopod-like processes of the cell.

**GROUP III. ADENOCARCINOMAS**

Adenocarcinomas make up approximately 20 percent of malignant epithelial lung tumors. They do not show a marked predilection for either sex, but most series have a slight male predominance. Many adenocarcinomas arise in a more peripheral location and a significant number are associated with scars.

The WHO classification recognizes two principal categories of adenocarcinoma: (1) bronchogenic and (2) bronchioloalveolar. The bronchogenic category is further subdivided into (a) acinar and (b) papillary types, both of which may or may not form mucin. The bronchogenic adenocarcinomas, as the name implies, originate from a bronchus, either from the surface epithelium or rarely from bronchial glands. By light microscopy, the better differentiated tumors are composed of columnar or cuboidal cells that resemble bronchial epithelial cells and are in continuity with a bronchus where transition to normal appearing epithelium may be demonstrable. Some mucus secreting cells are almost always present and they may be numerous. Less well-differentiated tumors have a less obvious glandular pattern, but some of these cells usually contain intracytoplasmic mucin. It remains a debatable point as to whether or not a small amount of intracytoplasmic mucin is sufficient justification for classifying an otherwise undifferentiated tumor as adenocarcinoma.

By electron microscopy, features common to tumors of glandular derivation are observed in pulmonary adenocarcinoma. There are usually rich networks of rough endoplasmic reticulum and vacuoles containing secretory products including mucin. Typically there is a well developed juxtanuclear Golgi apparatus. The apical surface often displays microvilli. In a well-differentiated cell there is often polarization of cytoplasmic organelles so that a "secretory pole" is recognizable. Neighboring cells
exhibit terminal bars at the level of the secretory pole. Desmosomes are present but tonofibrils are not.

Bronchiolo-alveolar carcinomas typically originate in the peripheral portions of the lung beyond a grossly recognizable bronchus and tend to grow on the walls of pre-existing alveoli. A papillary pattern is often present and the alveoli are lined by cylindrical cells which may show evidence of mucin production. A clear-cut separation from other adenocarcinomas may at times be difficult and a primary tumor in other sites, such as the gastrointestinal tract or ovary, must always be excluded.

Several recent reports on the electron microscopy of bronchiolo-alveolar carcinoma appear to have at least partially resolved the controversy concerning the cell of origin.\(^6\)\(^{15}\)\(^{17}\) The cells comprising these tumors typically have numerous microvilli over their free borders. Although granular endoplasmic reticulum and Golgi complexes are prominent as in adenocarcinomas, secretory vacuoles are usually absent. The most distinctive feature, however, is the presence in variable numbers of lamellated cytosomes thought to contain surfactant. The tumor cells thus bear a strong resemblance to the granular or type 2 pneumocytes. It has been suggested by several investigators that these are the cells of origin.

On the other hand, some bronchiolo-alveolar carcinomas have ultrastructural features resembling those of adenocarcinoma.\(^8\)\(^{19}\) It is thus possible that some tumors classified as alveolar type are glandular in origin, while others are of true alveolar origin. Whether establishing this histogenetic difference will have any bearing on prognosis is not yet known.

**Group IV. Large Cell Carcinomas**

The WHO classification currently recognizes four subgroups of large cell carcinoma: (1) solid tumors with mucin-like content, (2) solid tumors without mucin-like content, (3) giant cell carcinomas, and (4) “clear” cell carcinomas. Together they constitute approximately 10 percent of all carcinomas of the lung. The most widely recognized of these is the third type, giant cell carcinoma. This entity was first described by Nash and Stout in 1958.\(^{16}\)

Histologically, giant cell carcinomas are composed of large, extremely pleomorphic cells. Bizarre, multinucleated tumor cells are a prominent feature. Phagocytosis is sometimes exhibited by the tumor cells. It is extremely important in making the diagnosis of giant cell carcinoma to exclude the possibility of a primary adrenal tumor.

Although these tumors lack distinctive features by electron microscopy, with the possible exception of the multinucleated cells, they have typically been found to possess abundant rough endoplasmic reticulum, Golgi zones, and secretory vacuoles. It is thus possible that at least some of these represent a poorly differentiated form of adenocarcinoma, but this relatively uncommon tumor’s histogenesis remains controversial.

**Group V. Combined Epidermoid and Adenocarcinomas**

If one adheres to strict diagnostic criteria, this type of tumor is rare, representing less than one percent of all malignant epithelial tumors of the lung. Prerequisite for the diagnosis are areas with well-developed epidermoid and glandular features. Electron microscopy simply confirms the presence of organelles characteristic of each cell type.

**Group VI. Carcinoid Tumors**

Carcinoid tumors were originally classified as bronchial adenomas along with adenoid cystic carcinomas. Carcinoid tumors comprised about 90 percent of this group. For some time, carcinoids were regarded as benign, largely because of their
favorable prognosis compared to the more common types of carcinoma of the lung. As larger numbers of these tumors were collected, controversy arose over their true nature. They are now generally regarded as malignant.\textsuperscript{5,10} Though typically slow growing, they are capable of local destruction and metastasis. Carcinoid tumors characteristically occur as polypoid submucosal growths projecting into the lumen of a major bronchus. The more aggressive ones may have only a small intrabronchial component with the majority of the tumor protruding into the pulmonary parenchyma. Carcinoids may occur in the more peripheral branches of the bronchial tree in which case they are usually quite small. The pathology, symptomatology and clinical course of the bronchial carcinoids share many common features with intestinal carcinoids, including the secretion of serotonin.

Histologically, these tumors are composed of uniform cells with pale eosinophilic cytoplasm and rounded nuclei arranged in trabecular, acinar or alveolar formations. Special stains may reveal mucous production or argentaffin cytoplasmic granules. Some tumors, especially those located more peripherally, may be composed of spindle-shaped cells similar to those seen in oat-cell carcinoma.

By electron microscopy the most characteristic feature is the presence of neurosecretory granules previously described in the section on oat-cell carcinomas (figure 3).

**Group VII. Bronchial Gland Tumors**

Bronchial gland tumors are divided by the WHO classification into (1) cylindromas, (2) mucoepidermoid tumors and (3) others. Cylindromas, or adenoid cystic carcinomas, arise from the mucus glands adjacent to large bronchi. This type of tumor more frequently occurs in the major and minor salivary glands.

Its mode of presentation and growth is similar to that of bronchial carcinoids but it usually behaves in a more aggressive manner. If not widely excised, it is likely to recur and may metastasize to regional lymph nodes or distant organs.

Microscopically, these tumors are composed of nests of small cells with scant cytoplasm and hyperchromatic nuclei. Within these clumps of cells are round to ovoid acellular spaces which typically con-
tain hyalinized or mucinous material. It is the unique appearance of these acellular spaces that led Billroth\(^4\) to describe these tumors as cylindromas.

Electron microscopy has so far not been of help in solving the problem of the histogenesis of this tumor.\(^21\)

Mucoepidermoid tumors are rarely encountered as primary pulmonary neoplasms, being much more commonly of salivary gland origin. They may be present as polypoid intrabronchial growths and sometimes show infiltration. They are characterized by masses of epidermoid cells among which are scattered collections of extracellular mucus as well as epithelial cells containing intracytoplasmic mucus. Variable numbers of indeterminate cells which cannot be definitely classified as epidermoid or glandular may also be present.

It may at times be difficult to separate these tumors from group V (combined epidermoid and adenocarcinomas). This differentiation is important because of the more favorable prognosis of mucoepidermoid tumors. The principal distinction is that in combined epidermoid and adenocarcinomas there are separate areas of unequivocal epidermoid and adenocarcinoma, a feature not shared by the typical mucoepidermoid carcinoma.\(^9\)

Electron microscopy only confirms the presence of both types of cells and is usually not otherwise contributory.

**Group VIII. Papillary Tumors of the Surface Epithelium**

These are divided into (1) epidermoid, (2) epidermoid with goblet cells and (3) others. This group of tumors has been singled out, not because of unique histologic characteristics, but because they have a much better prognosis than the bronchogenic carcinomas. They are frequently located near the carina of the trachea and may be radiosensitive.

**Group IX. “Mixed” Tumors and Carcinosarcomas**

This group is divided into: (1) “mixed” tumors, (2) carcinosarcomas of embryonal type (“blastomas”), and (3) other carcinosarcomas. As a group, these tumors are rare and consequently rather poorly understood. Many of them occur in children and young adults, and the prognosis, although usually better than for bronchogenic carcinoma, is difficult to predict.

“Mixed” tumors are similar to their counterparts in salivary gland. Carcinosarcomas of embryonal type are situated peripherally in the lung and are circumscribed though not necessarily encapsulated. They often contain areas of hemorrhage and necrosis. Histologically they consist of tubules resembling fetal bronchioles embedded in immature connective tissue. Spencer has called these tumors blastomas and thinks they are the pulmonary counterpart of Wilms’ tumor of the kidney.\(^20\)

**Group X. Sarcomas**

Although there have been rare reports of most types of sarcomas occurring as primary lung tumors, only leiomyosarcomas and lymphomas are sufficiently frequent to warrant discussion here. Leiomyosarcomas of the lung do not differ significantly, either grossly or microscopically, from those arising elsewhere. They may be either central or peripheral in location. Those that involve major bronchi often present as polypoid endobronchial growths. In this regard, they must be differentiated from polypoid epidermoid carcinomas exhibiting a spindleled or pseudosarcomatous type of pattern. Metastatic leiomyosarcoma must be ruled out, especially in adult women where the uterus may contain an occult primary.

Primary malignant lymphomas are rare, having an estimated incidence of 0.45 percent of bronchial carcinomas. Of the slightly more than 100 cases reported, 80 percent have been lymphosarcomas. Most
of the remainder were reticulum cell sarcomas with Hodgkin's disease being extremely rare.

Papioannou and Watson defined pulmonary lymphomas as primary if the tumor is confined to one lung, with or without involvement of hilar lymph nodes, but without mediastinal spread. Jenkins and Salm considered this definition too narrow and felt it should be broadened to include bilateral pulmonary involvement.

These tumors tend to grow slowly, metastasize late and have a more favorable prognosis than lymphosarcomas in general with the exception of some gastrointestinal lymphosarcomas which may also be cured by radiotherapy, surgery or both.

Group XI. Unclassified

This category is included for those primary lung tumors that cannot be placed in any of the type categories described.

References