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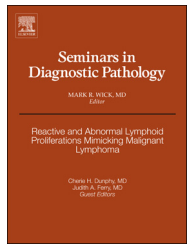

Large cell carcinoma of lung: On the verge of extinction?

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ABSTRACT

Pulmonary large cell carcinoma is a tumor whose existence as a defined entity has been challenged in recent years in the wake of advances in techniques to subtype lung cancer. Large cell carcinoma has been defined in the past as a tumor that lacks morphologic evidence of either glandular or squamous differentiation. This rather vague definition and the inclusion of more specific entities such as large cell neuroendocrine carcinoma, basaloid carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, and large cell carcinoma with rhabdoid phenotype as subtypes of large cell carcinoma has not only diluted the homogeneity of this entity but has also contributed to its use as a "wastebin" category for tumors lacking a definitive morphologic pattern. Today, there is increasing evidence that a large proportion of these tumors can be subtyped further using modern immunohistochemical and molecular methods. This is of special value not only from a diagnostic point of view but becomes increasingly important in terms of treatment choice since the selection of therapeutic modalities is often based on specific tumor histology. When viewed in this light, large cell carcinoma of the lung—as defined today—appears to be an outdated entity that needs to be reevaluated taking into account not only light microscopic findings but also the results of adjunct techniques such as immunohistochemistry and molecular profiling so that patients can benefit from more targeted therapies. This review examines the entity of pulmonary large cell carcinoma from these aspects and tries to delineate a practical diagnostic approach until further redefinition of this tumor is in place.

Introduction

Non-small cell lung carcinoma has historically been divided into 3 broad categories: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Large cell carcinoma is the least common among these tumors and accounts for 3–9% of all primary pulmonary lung cancers.[1,2] The 2004 World Health Organization (WHO) classification of lung tumors defines large cell carcinoma as an "undifferentiated non-small cell carcinoma that lacks the cytologic and architectural features of small cell carcinoma and glandular or squamous differentiation."[1] For practical purposes this includes any tumor in which the line of differentiation cannot be established by light microscopy. At the same time, this definition implies that the term is reserved for resection specimens that contrary to surgical biopsies or cytology preparations are not limited by incomplete sampling or poor cell preservation. In addition to the classic form of large cell carcinoma, the WHO currently recognizes 5 further variants: large cell neuroendocrine carcinoma, basaloid carcinoma,

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lymphoepithelioma-like carcinoma, clear cell carcinoma, and large cell carcinoma with rhabdoid phenotype.

In the last few years, there has been increasing controversy about whether large cell carcinoma of the lung represents a unique clinicopathological entity or as a group combines the most poorly differentiated form of various non-small cell lung carcinomas. The latter theory has received increasing support in the last decade with the advent of specific and sensitive immunohistochemical antibodies that can be used to distinguish between different types of lung cancer and molecular techniques that allow to search for gene expression patterns that are specific for either squamous cell or adenocarcinoma.[3–5] Using these approaches, it has been shown that the majority of large cell carcinomas can be subtyped more accurately.[6–10] This is of particular interest since recent advances in cancer treatment have moved away from standardized cytotoxic chemotherapy and are increasingly directed towards personalized or targeted medical therapies. These novel therapies directed against specific molecular alterations require more precise histologic diagnosis, especially distinction between adenocarcinoma and squamous cell carcinoma, in order to identify the correct approach to molecular testing and to select the appropriate targeted agent. The use of specific therapies for large cell carcinoma has not been investigated sufficiently, which is largely to blame on the relative rarity of this diagnosis, although the latest recommendations suggest to include large cell carcinoma with the adenocarcinoma group for the purpose of treatment and molecular testing.[11]

Historical aspects of large cell carcinoma classification

The history of pulmonary large cell carcinoma dates back to the middle of the 20th century when Liebow[12] used the term "anaplastic carcinoma" to encompass small and large cell carcinomas of the lung. These tumors were separated in the subsequent WHO nomenclature of lung tumors of 1958 into small cell carcinoma and large cell undifferentiated carcinoma; the latter designating a carcinoma without any differentiation precluding inclusion into any of the other categories of lung tumors[13] (Table 1). When in 1967, the first edition of the WHO classification of carcinomas of the lung was published,[14] 4 subtypes of large cell carcinoma were recognized: (1) solid tumors with mucin-like content, (2) solid tumors without mucin-like content, (3) giant cell carcinomas, and (4) clear cell carcinomas (Table 2). In the WHO second edition published in 1981,[15] solid tumors with mucin-like content were included in the adenocarcinoma category after recognition that mucin-producing cells belong to the adenocarcinoma spectrum reducing the category of large cell carcinoma to the classic variant as well as giant cell and clear cell carcinomas (Table 3). In 1999, the large cell carcinoma class was extended to include several more variants: large cell neuroendocrine carcinoma (and combined large cell neuroendocrine carcinoma), basaloid carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, and large cell carcinoma with rhabdoid phenotype[16] (Table 4). Large cell neuroendocrine

Table 1 – WHO nomenclature of lung tumors (1958).

Cell group
Squamous cell carcinomas
Highly differentiated
Moderately differentiated
Slightly differentiated
Small cell carcinomas
Oval cell structure
Polygonal cell structure
Adenocarcinomas
Acinar
Papillary
Chiefly "large cells"
Large cell undifferentiated carcinoma
Combined epidermoid and adenocarcinomas

Table 2 – WHO classification of lung carcinomas (1967).

Cell group
Epidermoid carcinomas
Small cell anaplastic carcinomas
Fusiform type
Polygonal cell type
Lymphocyte-like ("oat cell") type
Others
Adenocarcinomas
Bronchogenic
Acinar
Papillary
Bronchioloalveolar
Large cell carcinomas
Solid tumors with mucin-like content
Solid tumors without mucin-like content
Giant cell carcinomas
Clear cell carcinomas
Combined epidermoid and adenocarcinomas

Table 3 – WHO classification of lung carcinomas (1981).

Cell group
Squamous cell carcinoma
Variant: spindle cell
Small cell carcinoma
Oat cell carcinoma
Intermediate cell type
Combined oat cell carcinoma
Adenocarcinoma
Acinar adenocarcinoma
Papillary adenocarcinoma
Bronchioloalveolar cell carcinoma
Solid carcinoma with mucus formation
Large cell carcinoma
Variants:
Giant cell carcinoma
Clear cell carcinoma
Adenosquamous carcinoma