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Review

Large cell carcinoma of the lung: A tumor in search of an author. A clinically oriented critical reappraisal

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ABSTRACT

Large cell carcinoma (LCC) is a merely descriptive term indicating a subtype of lung cancer with no specific features of small-cell lung cancer (SCLC), adenocarcinoma (ADC) or squamous cell carcinoma (SQC). This diagnosis is allowed on surgical specimens only, whereas its counterpart in biopsy/cytology samples is non-small-cell lung carcinoma (NSCLC), not otherwise specified (NOS). Although these two terms do not fulfill the same concept, they can be interchangeable synonyms at the clinical level, reflecting, in different ways, the inability to define a specific subtype. Immunohistochemistry (IHC), next generation sequencing (NGS) analysis and, historically, electron microscopy have been unveiling diverse cell differentiation lineages in LCC, resulting in LCC-favor ADC, LCC-favor SQC and LCC-favor large-cell neuroendocrine carcinoma (LCNEC), the latter hopefully to be included into the neuroendocrine tumor (NET) group in the future. Paradoxically, however, the interpretation issues of LCC/NSCLC-NOS are not diminishing, but even increasing albeight an accurate diagnosis is oncologically required and crucial. Also, rare LCC/NSCLC-NOS cases exhibiting null/unclear phenotype, are difficult to classify, and this terminology could be maintained for the sake of classification (basically these tumors are serendipitous ADC, as also confirmed by the lack of p40). In this review article, seven relevant issues to LCC have been addressed by using a question–answer methodology, with final key points discussing major interpretation issues. In conclusion, most LCC/NSCLC-NOS may be eventually re-classified and addressed by exploiting IHC and/or molecular testing to satisfy the criteria of precision medicine (the right drug, to the right patient, at the right time).

1. Background

Large cell carcinoma (LCC) is probably the main controversial issue in the current lung cancer classification, clearly requiring significant changes in the next future. In this review article, we organized the discussion on LCC answering to the most frequent questions (Q) emerging from the pertinent literature and the oncologists' community.

Q1: LARGE CELL CARCINOMA EXISTENCE: TO BE, OR NOT TO BE? THAT IS THE QUESTION!

Answer: YES, it still survives to indicate lung undifferentiated non-small-cell tumors, but its own diagnostic criteria and terminology are under refinement according to improved lung cancer biology understanding. Its prevalence is destined to hopefully vanish.

Discussion: Large cell carcinoma (LCC) of the lung is an uncommitted term describing a group of primary pulmonary carcinomas having undifferentiated features, without any neuroendocrine (NE), squamous or glandular differentiation and without specific clinical characteristics [1]. LCC diagnosis is restricted to surgical specimens only, once meticulous sampling

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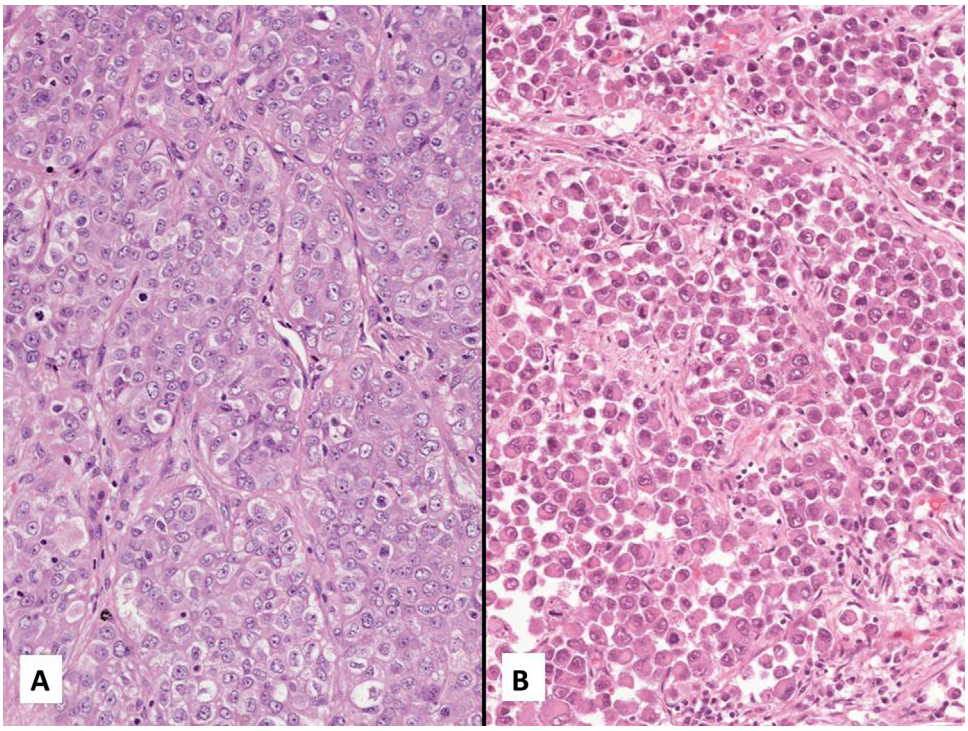

Fig. 1. Examples of undifferentiated LCC with a solid (A) and discohesive (B) growth pattern.

and immunophenotyping has been conducted to exclude the presence of areas featuring ADC or SQC differentiation. A diagnosis of LCC cannot be made on biopsies or cytological samples, where non-small-cell lung cancer (NSCLC) lacking any specific morphologic criteria must be diagnosed as NSCLC-NOS [2,3]. Although the term LCC was adopted in lung cancer classifications to compensate the impossibility of further classifying undifferentiated NSCLC [1,4–6], most LCC are probably more related to lung ADC than SQC, at least from a clinical viewpoint [7]. At light microscopy, LCC is basically a tumor featuring large, atypical, polygonal cells, arranged in cohesive or even discohesive sheets or nests with vesicular nuclei and prominent nucleoli, and a moderate amount of cytoplasm, in the absence of specific signs of differentiation (Fig. 1). Before drawing such a diagnostic conclusion, mucin histochemistry (Alcian-blue/PAS stain, PAS-diastase, Kreyberg or mucicarmine stain) is required to exclude the "solid with mucin production" variant of ADC. Apart from the entirely undifferentiated LCC, the current 2004-WHO classification recognizes five different variants of LCC, namely clear cell carcinoma (CCC), lymphoepithelioma-like carcinoma (LELC), LCC with rhabdoid phenotype (LCC-R), basaloid carcinoma (BC) and large cell neuroendocrine carcinoma (LCNEC) [1]. In our and others' views [5–12], this sub-classification of LCC is a source of confusion, because BC shows a SQC lineage and should be classified accordingly, LELC should be restricted to Epstein–Barr virus-related neoplasms with SQC lineage (as seen in the relevant head & neck tumors), most LCC-R and at least two third of CCC are definitely poorly-differentiated ADC, and LCNEC belongs to the spectrum of NET. A rare subset of LCC do not react with any of the specific lineage markers ("null phenotype") or shows immunohistochemistry (IHC) negativity for ADC markers in the presence of only focal positivity for squamous or NE markers ("unclear phenotype") and remain part of the LCC-NOS category when dealing with surgical specimens, and of the NSCLC-NOS group in the case of cytology/biopsy samples, provided that metastatic or other uncommon pulmonary tumors (e.g., sarcomatoid or NUT midline carcinomas) have been reasonably excluded (Fig. 2).

KEY MESSAGES: *(A) The LCC (on surgical specimens only) category should be reduced as much as possible, subtyping all undifferentiated (mucin-negative, and NE marker negative) carcinomas by IHC and reporting cases defined by immunophenotype in the relevant category with the terminology "LCC-NOS, favor adenocarcinoma" or "LCC-NOS, favor squamous cell carcinoma". (B) Immunohistochemically negative or ambiguous cases ("null/unclear phenotype") should enter in the group of LCC/NSCLC-NOS, hopefully not exceeding 5% in the routine practice.*

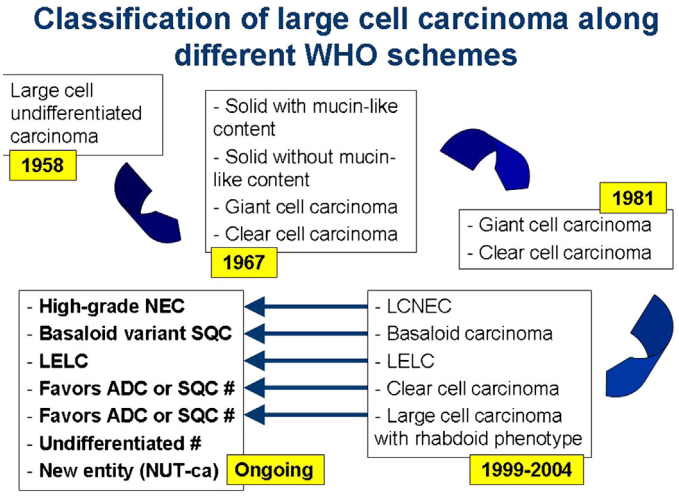

Fig. 2. A summary of the previous and ongoing classifications of large cell carcinoma of the lung according to the WHO schemes (#, after immunostains and molecular investigations).