Ancillary Studies, Including Immunohistochemistry and Molecular Studies, in Lung Cytology

Fernando Schmitt, MD, PhD, FIAC[a,b,*],
José Carlos Machado, PhD[b]

KEYWORDS

• Lung cytology • Immunohistochemistry • Molecular testing • EGFR • ALK

ABSTRACT

The importance of cytologic techniques for investigation of respiratory conditions has been recognized since the earliest days of clinical cytology. Cytology is able to detect most of mycoses and parasitic and viral infections based on the morphologic recognition of these agents. The most relevant application of lung cytology today is in the diagnosis and management of lung cancer; approximately 70% of those cancers are diagnosed at a late stage and are unresectable. This article addresses the most common ancillary techniques, such as special stains, immunocytochemistry, and molecular testing, used to refine the cytologic diagnosis of lung cancer and to guide personalized therapy.

OVERVIEW

The importance of cytologic techniques for investigation of respiratory conditions has been recognized since the earliest days of clinical cytology. The study of cellular specimens from the respiratory tract is established as a vital diagnostic procedure in the evaluation of patients with suspected lung inflammatory/infectious or neoplastic diseases. The study of sputum, bronchial washings, bronchial aspirates, bronchial brushings, bronchoalveolar lavage specimens, and fine-needle aspirates (FNAs) provides the morphologic basis for these diagnoses. Cytology is able to detect most of mycoses and parasitic and viral infections based on the morphologic recognition of these agents. The importance of the application of ancillary techniques in this field to detect some microorganisms, however, for example acid-fast special staining in tuberculosis,[1] has been recognized for a long time.

The most relevant application of lung cytology today is in the diagnosis and management of lung cancer because approximately 70% of those cancers are diagnosed at a late stage and are unresectable. Small biopsies and cytology are the primary material used for establishing diagnosis and for study of molecular markers that can drive therapy.[2–4] The identification of EGFR-positive adenocarcinomas (ADCs) permits the use of tyrosine kinase inhibitors (TKIs); and the recognition of squamous cell carcinoma (SqCC) avoids the use of bevacizumab, which has been linked to serious bleeding in this subset of lung cancer patients.[3–5] Moreover, ADC with ALK rearrangements is responsive to crizotinib,[3,6] and ADC or non–small

The authors have no relevant financial interest in the products or companies described in this article.

[a] Department of Laboratory Medicine & Pathobiology, Faculty of Medicine, University of Toronto, University Health Network Toronto General Hospital, 200 Elizabeth Street, 11E-215B Toronto, ON M5G 2C4, Canada; [b] IPATIMUP, Institute of Molecular Pathology and Immunology of Porto University, Rua Dr Roberto Frias S/N, 4200-465, Porto, Portugal

* Corresponding author. IPATIMUP, Institute of Molecular Pathology and Immunology of Porto University, Rua Dr Roberto Frias S/N, 4200-465, Porto, Portugal.
E-mail address: fernando.schmitt@ipatimup.pt

Surgical Pathology 7 (2014) 35–46
http://dx.doi.org/10.1016/j.path.2013.10.005
1875-9181/14/$ – see front matter © 2014 Elsevier Inc. All rights reserved.

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cell lung carcinoma (NSCLC), not otherwise specified (NSCLC-NOS), is more responsive than SqCC to pemetrexed.[7] This article addresses the most common ancillary techniques, such as special stains, immunocytochemistry (ICC), and molecular testing, used to refine the cytologic diagnosis of lung cancer as well as to guide personalized therapy for patients.

CYTOLOGIC DIFFERENTIAL DIAGNOSIS

The most common subtypes of lung cancer can be diagnosed on cytology if the established morphologic criteria are present.[2,3,8] Cytologically, ADCs are characterized by the presence of different architectural patterns, including cell balls, papillary fronds, and cohesive clusters with acinar structures, and the individual cells show delicate cytoplasm, varying in appearance from homogenous to extremely vacuolated. The nuclei are enlarged, with finely to coarsely granular chromatin, and show prominent and centrally placed nucleoli (**Fig. 1**). SqCC is recognized by three main morphologic characteristics: keratinization (easily recognized in Papanicolaou stain as orange or red cytoplasm), pearls, and intercellular bridges.

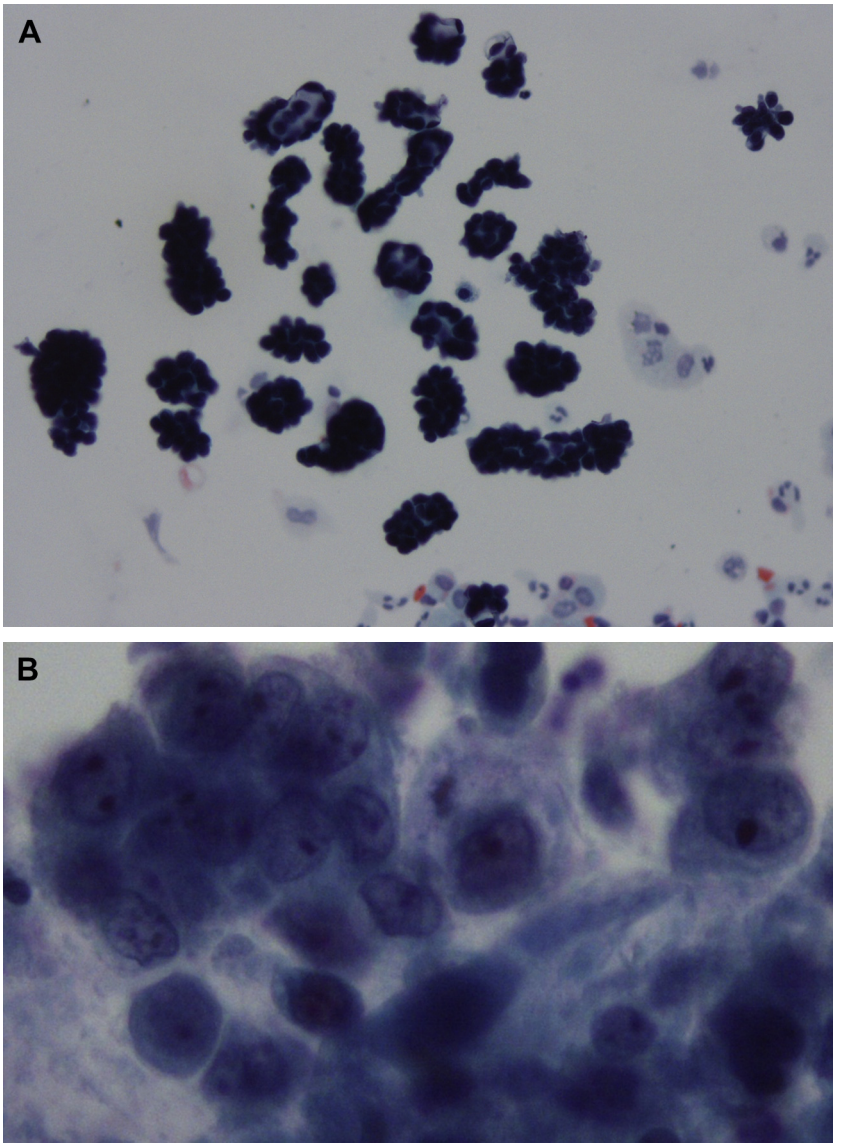

Fig. 1. ADC. (*A*) LBC preparation showing ADC cells with papillary configuration (Papanicolaou stain, original magnification ×20). (*B*) Neoplastic cells with large delicate cytoplasm and clearly malignant nuclei with prominent nucleoli (LBC preparation, Papanicolaou stain; original magnification ×60).

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