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Role of Immunohistochemical Studies in the Classification of Lung Adenocarcinoma and Squamous Cell Carcinoma in Cytologic Specimens : A Review of Literature

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ABSTRACT

Primary tumours of the lung consist of four principal types; squamous cell carcinoma, small cell carcinoma, large cell carcinoma and adenocarcinoma. The results of several clinical trials identified lung tumor histologic features as a potential prognostic factor and predictor of clinical outcome and response to chemotherapy. Hence, the distinction between different subtypes of NSCLC, particularly adenocarcinoma and squamous cell carcinoma (SCC) has gained importance. Cytologic features of these tumors can overlap, and a variety of superimposed degenerative and mechanical changes can distort the cytologic appearances of the tumor cells. As a result, ancillary techniques such as immunohistochemical analysis have been frequently incorporated into the diagnostic workup of many cytologic and small biopsy specimens.CK5/6 and p63 were used as immunohistochemical markers for SCC, and TTF-1 and surfactant protein A were markers for Adenocarcinoma

KEYWORDS : Immunohistochemistry, lung tumours, Adenocarcinoma, Squamous cell carcinoma

PRIMARY LUNG TUMOURS:

Primary tumours of the lung can arise from the different tissues such as epithelium, lymphatics, mesothelium and soft tissue, and the diagnosis is based on the histological findings of biopsy seen by light microscopy. By far the most common, and exhibiting the greatest diversity are epithelial tumours.

Clinically the most important distinction is between small cell carcinomas and the others, grouped together as 'non-small cell.' This is because small cell cancers respond to chemotherapy, whereas non-small cell tumours are removed surgically if possible. Epithelial tumours consist of four principal types; squamous cell carcinoma, small cell carcinoma, large cell carcinoma and adenocarcinoma

Non small cell carcinoma

The three main subtypes of Non-small cell carcinomas are adenocarcinoma, squamous-cell carcinoma and large-cell carcinoma.[1]

Nearly 40% of lung cancers are adenocarcinoma, which usually originates in peripheral lung tissue.[2] Although most cases of adenocarcinoma are associated with smoking, adenocarcinoma is also the most common form of lung cancer among people who have smoked fewer than 100 cigarettes in their lifetimes ("never-smokers").[1][3] They may arise in relation to peripheral lung scars (scar carcinomas).A subtype of adenocarcinoma, the bronchioloalveolar carcinoma, is more common in female never-smokers, and may have a better long term survival.[4]

Squamous-cell carcinoma accounts for about 30% of lung cancers. They typically occur close to large airways. About 9% of lung cancers are large-cell carcinoma. These are so named because the cancer cells are large, with excess cytoplasm, large nuclei and conspicuous nucleoli.[2]

Small-cell lung carcinoma

In small-cell lung carcinoma (SCLC), the cells contain dense neurosecretory granules (vesicles containing neuroendocrine hormones), which give this tumor an endocrine/paraneoplastic syndrome association.[5] Most cases arise in the larger airways (primary and secondary bronchi).[6] These cancers grow quickly and spread early in the course of the disease. Sixty to seventy percent have metastatic disease at presentation. This type of lung cancer is strongly associated with smoking.[1]

Discussion:

Pathologists and oncologists have historically focused on discrimination between small cell lung carcinoma (SCLC) and non-SCLC (NSCLC) that included a large spectrum of histologically different tumor types. This was certainly a simplified view of lung cancer and reflected the clinical practice of the time and the rather limited efficacy of chemotherapy regimens for treatment of NSCLC. Hence, the distinction between different subtypes of NSCLC, particularly adenocarcinoma and squamous cell carcinoma (SCC), was considered irrelevant for the management and treatment of lung cancer.[7]

Lately, this approach has been challenged after the results of several clinical trials identified lung tumor histologic features as a potential prognostic factor and predictor of clinical outcome and response to chemotherapy. Accurate distinction between small-cell and non-small cell carcinomas of the lung thus has crucial therapeutic significance. In recent years, cytologic examinations including fine needle aspiration (FNA), bronchoscopic brushing and washing, and bronchoalveolar lavage have been increasingly used for establishing the diagnosis of lung cancer and classifying the specific tumor type. [7]

However, morphologic distinction between some small-cell lung carcinomas and non keratinizing poorly differentiated pulmonary squamous cell carcinomas can be difficult. Cytologic features of these tumors can overlap, and a variety of superimposed degenerative and mechanical changes can distort the cytologic appearances of the tumor cells. In addition, the cytologic material may be limited in quantity and present only in direct smears or cytospin slides for evaluation. Therefore, the availability of reliable, sensitive, and specific ancillary techniques applicable to such cytologic preparations is desirable to supplement the cytomorphologic interpretation. [7]

As a result, ancillary techniques such as immunohistochemical analysis have been frequently incorporated into the diagnostic workup of many cytologic and small biopsy specimens. Many studies have addressed sensitivity and specificity of immunohistochemical markers in the separation of the various subtypes of NSCLC.[8-13]The interpretation of immunohistochemical studies on limited diagnostic material may be challenging, and misinterpretations are possible.CK5/6 and p63 were used as immunohistochemical markers for SCC, and TTF-1 and surfactant protein A were markers for adenocarcinoma

Table 1:

Typical immunostaining in lung cancer[1]	
Histological type	Immunostain
Squamous-cell carcinoma	CK5/6 positive CK7 negative
Adenocarcinoma	CK7 positive TTF-1 positive
Large-cell carcinoma	TTF-1 negative
Small-cell carcinoma	TTF-1 positive CD56 positive Chromogranin positive Synaptophysin positive

A study was conducted by the University of Pittsburgh Medical Center, Pittsburgh, PA, from January 2000 to January 2010 from patients who underwent surgical resection of the tumors. A total of 448 diagnostic preoperative cytologic specimens including transthoracic computed tomography–guided fine-needle aspiration (FNA) specimens, bronchial brushings, and bronchial washings of a primary lung adenocarcinoma (263 cases [58.7%]) and SCC (185 cases [41.3%] were studied.[7] Immunohistochemical and histochemical techniques were performed on all block preparations.

All adenocarcinomas showed positive staining for CK7, followed by 86.2% of cases positive for TTF-1 and 81%of cases (20/36) positive for surfactant A. Similarly, 80% of the cases were positive for PAS with diastase (69/86), but only65% were positive for mucicarmine (56/86). Surprisingly, 68% of SCC cases were reported to be positive for CK7 (28/41) and 21% for TTF-1 (9/43). In contrast, no surfactant A positivity was reported in SCCs. All of the tested cases of SCC were positive for CK5/6 and p63. The adenocarcinomas showed 21% (5/24) and 31% (13/42) positivity for CK5/6.[7]

The individual sensitivity, specificity, and positive predictive value for each marker evaluated in their study is summarized in ■**Table 2**■.[7]

Sensitivity, Specificity, and Positive Predictive Values of Immunohistochemical Markers CK5/6 and p63 for Squamous Cell Carcinoma and TTF-1, Surfactant A, Mucicarmine and PAS-D for Adenocarcinoma*

	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)
Adenocarcinoma			
TTF-1	86	73	94
Surfactant A	81	100	100
PAS-D	80	73	96
Mucicarmine	65	80	97
Squamous cell carcinoma			
CK5/6	100	79	83
p63	100	69	70

CK, cytokeratin; FN, false-negative; FP, false-positive; PAS-D, periodic acid–Schiff with diastase; TN, true-negative; TP, true-positive; TTF, thyroid transcription factor.

CONCLUSION:

There is a significant increase in the use of immunohistochemical and histochemical assays in routine cytopathology practice, leading to improved classification lung tumours. However, the interpretation of immunohistochemical studies could be challenging on the cell blocks as well as on limited diagnostic material, and misinterpretations are possible.

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