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TTF-1 and Napsin a Double Staining in Diagnosing Lung Adenocarcinoma

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Introduction

Pulmonary cancer is the most commonly diagnosed cancer worldwide, and is the leading cause of cancer mortality in men [1]. Lung cancer is divided into small cell cancer and Non-Small Cell Cancer (NSCLC). NSCLC accounts for 80% of all lung cancers and is comprised of Adenocarcinoma (ADC), Squamous Cell Carcinoma (SqCCA) and large cell carcinoma [2]. In addition, 60% of NSCLCs present with locally advanced disease at the time of initial diagnosis [3]. Traditionally, the pathologic lung cancer differential diagnosis was between small cell carcinoma and NSCLC, as sub-typing NSCLC had not been shown to predict differences in patient outcomes. Recent advances in molecular biology have led to an increase in target-specific chemotherapeutic therapies that require the sub-categorization of NSCLCs. The International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society has outlined a new classification of lung ADCs based on a multidisciplinary approach. They have outlined the importance of further classifying NSCLCs as either ADCs or SqCCAs, since ADCs should be tested for Epidermal Growth Factor Receptor (EGFR) and Anaplastic Lymphoma Kinase (ALK) fusion gene mutations, as targeted chemotherapeutic agents can be used with greater efficacy [4]. Lung ADCs are often associated with EGFR mutations, and can be effectively treated with tyrosine kinase inhibitors such as gefitinib [5,6]. In addition, ADC have been shown to have improved outcomes when compared to SqCCAs when treated with pemetrexed therapy, which inhibits specific enzymes in purine and pyrimidine synthesis. Finally, the distinction between ADC and SqCCA can avoid potentially hazardous outcomes, as life-threatening hemorrhages have been rarely reported when patients with SqCCAs are treated with bevacizumab, a vascular endothelial growth factor inhibitor [7]. If the classification of NSCLCs cannot be achieved with cytologic/histologic criteria alone, Immunohistochemistry (IHC) staining should be employed. Thyroid Transcription Factor 1 (TTF-1) and Napsin A are both stains that have been proven to stain a majority of lung ADCs. TTF-1 is a nuclear stain that has been reported in 87% lung ADCs and 2% of SqCCAs [8]. Napsin A is a cytoplasmic stain that is relatively specific for ADC of the lung and reportedly stains 80% of cases [9]. A combined TTF-1 and Napsin A double stain has also been shown to be useful in the diagnosis of ADC in cell blocks from fine needle aspirates (FNAs) [10].

Discussion

In 2004, the World Health Organization (WHO) first addressed cytology in its lung cancer classification system [11]. The differentiation of NSCLC into ADC and SqCCA can be difficult when only limited tissue is present. In a series of bronchial biopsies from known lung cancer patients, only 48% of cases were found to have identifiable tumor [12]. Cytomorphologic accuracy when diagnosing ADC and SqCCA is reportedly 80% and 87%, respectively [13]. This differentiation is further confounded by ADCs adopting degenerative changes such as coagulative necrosis, lending a pseudo-keratinized appearance. Similarly, SqCCAs can develop vacuolar degeneration, mimicking features of ADC and leading to inaccurate diagnoses that directly impact patient care decisions.

It is in these difficult scenarios that IHC can be used to achieve a greater diagnostic sensitivity and specificity than cytomorphology alone. The use of IHC has clearly increased in this regard over time; in a recent study by Ocque et al. [14] before 2004, only 14% of ADCs and 8% of SqCCAs were subjected to IHC to make the definitive diagnosis, as opposed to 86% and 89% after 2004, respectively. While this increase in IHC usage has had little effect on the diagnostic accuracy of SqCCA, accuracy has increased significantly for ADC diagnoses, reflecting the difficulty in assessing heterogeneous and poorly differentiated cases based on cytomorphology alone [14].

Thyroid Transcription Factor-1 (TTF-1), a nuclear stain expressed in pulmonary alveolar lining cells and follicular cells of the thyroid, has long been shown to have diagnostic usefulness in assessing ADCs for lung origin [15]. TTF-1 reportedly stains 73% of ADCs and none of the SqCCA specimens in one series [16]. Pertaining specifically to FNA specimens, Liu and Farhood [15] showed TTF-1 positivity in 86% (12/14) lung ADCs and only 8% (1/12) SqCCAs. Additionally, TTF-1 has been shown to be highly specific for lung ADC. In a series by Hecht et al. [8] 89% (42/47) pulmonary ADCs were positive for TTF-1, while weak positivity was identified only in 1 of 50 (2%) of non-pulmonary carcinomas (a metastatic ovarian carcinoma).

Napsin A, a cytoplasmic marker identified in type II pneumocytes and alveolar macrophages, has been shown to be positive in 83% of lung ADCs while negative in all SqCCAs in one study [16]. In a study by Kim et al. [17] evaluating Napsin A and TTF-1 staining of pulmonary ADC, Napsin A had a positivity rate of 83% (44/53) compared to TTF-1 with 57% (30/53). In addition, all non-pulmonary ADCs were negative for Napsin A and TTF-1. As these studies show, TTF-1 and Napsin A are both sensitive and specific for pulmonary ADC. However, recently Napsin A has been reported expressed in renal cell carcinoma, especially the papillary and clear cell types [18].

Our group (Fatima et al. [10]) has previously evaluated the use of a TTF-1/ Napsin A double stain with Leica antibody, to increase the specificity for diagnosis of ADCs, using a cohort of 35 ADC and 24 SqCCA cell blocks. In this study, 74% (26/35) of ADCs were positive for both TTF-1 and Napsin A, with 12% (3/24) SqCCAs also staining

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positive for both, giving a sensitivity and specificity of 74% and 88%, respectively. Interestingly, when taking only the TTF-1 stain into account, 37% (9/24) of SqCCAs stained positive, lending a TTF-1 only specificity of 63%. The TTF-1 Monoclonal Antibody (MAB) used, SPT24, has been previously shown to exhibit positive staining in a high percentage of pulmonary NSCLCs of all subtypes, and is a likely cause of the decreased specificity seen in this study [19].

Aberrant TTF-1 staining has also been identified in colon cancer, and TTF-1-positivity in colon cancer metastases to the lung is a known diagnostic dilemma [20,21]. A small series by Penman et al. [20] identified focal TTF-1 nuclear staining in 4 of 7 (56%) primary colon carcinomas also using the SPT24 monoclonal antibody. Another study by Comperat et al. [21] compared the TTF-1 staining patterns using both the SPT24 and 8G7G1/1 clones. They showed 4 of 90 (5%) colorectal primary and 4 of 41 (10%) of colorectal cancer lung metastases at least focally stained with TTF-1 using the SPT24 clone; no aberrant staining was identified using the 8G7G1/1 clone. They went on to test each clone on 86 primary lung ADCs, and determined the SPT24 clone to have a higher sensitivity (84%) versus 8G7G1/1 (65%) [21]. This increased sensitivity of the Leica SPT24 clone may account for the false positive staining reported by us in SqCCAs.

In summary, TTF-1/Napsin A as a useful marker for ADC should be used in conjunction with squamous markers such as P63/Cytokeratin 5 as a double stain, and the panel of stains (positive and negative) will determine whether the tumor is ADC or SQCCA, especially in limited samples such as FNA cell blocks.

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