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Original contribution

Spindle cell and pleomorphic ("sarcomatoid") carcinomas of the lung: an immunohistochemical analysis of 86 cases☆

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Summary Spindle cell and pleomorphic carcinomas are currently grouped among sarcomatoid carcinomas of the lung. Because of their unusual occurrence, these tumors have not been properly assessed by immunohistochemistry. We performed a comprehensive immunohistochemical analysis of 86 of these tumors. Seventy-four pleomorphic carcinomas (57 with differentiated elements) and 12 spindle cell carcinomas were subjected to immunohistochemistry with CAM5.2, cytokeratin (CK) 7, thyroid transcription factor 1, napsin A, CK5/6, p40, desmocollin 3, Sox2, calretinin, and D2-40. The percentage of positive tumor cells as well as the staining intensity were evaluated and scored. The spindle/giant elements were positive for CAM5.2 (93%), CK7 (79%), thyroid transcription factor 1 (41%), napsin A (20%), calretinin (20%), Sox2 (13%), CK5/6 (9%), p40 (8%), D2-40 (6%), and desmocollin 3 (3%). Of 29 cases in which immunohistochemistry was performed on spindle/giant cell and corresponding differentiated elements, 21 (72%) showed a consistent staining pattern in both components, whereas in 8 cases (28%), the immunophenotype in the spindle/giant cells was less lineage-specific than in the differentiated component. Therefore, we consider that 42% of neoplasms otherwise classified as sarcomatoid carcinoma can be reclassified as adenocarcinoma and 14% as squamous cell carcinoma, while the remaining 44% failed to show a more specific immunophenotype. The use of a comprehensive immunohistochemical panel allows reclassification of the majority of sarcomatoid carcinomas as poorly differentiated variants of adenocarcinoma or squamous cell carcinoma. Such reclassification will facilitate clinical management and allow molecular testing and pursuit of targeted treatment strategies. Application of immunohistochemistry should become the standard in the workup of pulmonary sarcomatoid carcinomas.

1. Introduction

Pulmonary spindle cell and pleomorphic carcinomas are unusual non–small cell lung carcinomas (NSCLCs). These tumors are characterized by the presence of spindle cell elements (spindle cell carcinomas) or a mix of spindle and giant cells

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(pleomorphic carcinomas). Pleomorphic carcinomas may also contain differentiated elements in the form of adenocarcinoma, squamous cell, or large cell carcinoma [1], whereas spindle cell carcinomas "consist of an almost pure population of epithelial spindle cells, with no differentiated elements," according to the latest World Health Organization (WHO) classification of lung tumors [2]. There continues to be sufficient confusion about these neoplasms due to a lack of uniformity in terminology and diagnostic criteria because in the WHO classification, these lesions have been consistently grouped along entities such as carcinosarcomas or pulmonary blastomas resulting in a very heterogeneous tumor category [2,3]. However, there appears to be little disagreement that, as a group, these tumors are associated with a poor clinical outcome [4-8].

Sarcomatoid carcinomas of the lung are very uncommon tumors with an incidence estimated between 2% and 3% of all lung malignancies [1,3-13]. These tumors not only create diagnostic difficulties but also provide a challenge for clinicians treating such patients. The lack of research focusing on these tumors has prevented the development of specific treatment strategies. This becomes a particular problem in an era where personalized medicine becomes increasingly important and treatment of lung tumors is highly dependent on most accurate tumor classification. Similar debate has long surrounded tumors classified as large cell carcinomas of the lung [14,15], and for similar reasons, current criteria now mandate the use of immmunohistochemistry in the workup of those neoplasms [2]. Such requirement, however, is currently not in place for sarcomatoid carcinomas. However, the results of our study clearly indicate that the immunohistochemical profiles of these tumors should be taken into account to establish proper lines of treatment.

2. Materials and methods

Eighty-six cases of spindle cell (n = 12) and pleomorphic carcinomas (n = 74) were identified in the files of the Department of Pathology, MD Anderson Cancer Center, in Houston. Histologic material was derived from surgical resection specimens including wedge resections, lobectomies, or pneumonectomies. All cases were primarily parenchymal-based lesions; diffuse pleural disease as commonly seen in mesotheliomas was not identified in any of the tumors. An average of 9 hematoxylin and eosin–stained sections was available for review in each case (range, 3-30).

For practical purposes, spindle cell carcinomas were defined as tumors composed entirely (100%) of epithelial spindle cell elements. Pleomorphic carcinomas were defined as tumors containing at least 10% spindle and/or giant cells and varying proportions of differentiated elements in the form of adenocarcinoma (n = 21), squamous cell carcinoma (n = 5) or large cell carcinoma (n = 31), or tumors entirely composed of spindle and giant cells (n = 17) as identified by light microscopy. Pure giant cell carcinomas were not included in this study, as they already formed the subject of another recent report [16]. Immunohistochemical studies were performed on the spindle/giant cell (undifferentiated) elements of all cases; in 29 cases, a differentiated component was included in the same section. Immunostaining was performed on formalin-fixed, paraffin-embedded tissue using a horseradish peroxidase–labeled polymer system. Tissue sections were incubated with antibodies directed against CAM5.2, cytokeratin 7 (CK) 7, thyroid transcription factor 1 (TTF-1), napsin A, CK5/6, p40, desmocollin 3, Sox2, calretinin, and D2-40 (Table 1). 3,3′-Diaminobenzidine was used as a chromogen for antigen localization. Adequate positive and negative controls were run for all antibodies tested. The immunostaining was scored on a sliding scale of 0 to 4+ according to the percentage of reactive cells (0, negative; 1+, 1%-25%; 2+, 26%-50%; 3+, 51%-75%; 4+, 76%-100%). The staining intensity was graded as weak (1), intermediate (2), or strong (3). Cases were considered positive for any marker if the percentage score was at least 1+. The study was approved by the institutional review board.

3. Results

3.1. Immunohistochemical findings

The immunohistochemical findings are summarized in Table 2.

3.2. CAM5.2

Expression of CAM5.2 was identified in the spindle and/or giant cell component of 80 (93%) of 86 cases, in most cases in a strong and diffuse pattern. In 6 cases that were negative, positive staining for other markers of epithelial differentiation (CK7, TTF-1, p40, Sox2, or a combination thereof) was present. Among the 29 cases containing differentiated elements and in which immunohistochemistry was performed, all were positive for CAM5.2 in the differentiated component, whereas in 3 cases, the dedifferentiated component remained negative. The latter 3 cases, however, did show expression of Sox2 in 2 cases and TTF-1/CK7 in the third.

3.3. CK7

The spindle/giant cell component of 68 cases (79%) showed a positive reaction with CK7, predominantly in a strong and diffuse fashion. Among the differentiated elements, strong and diffuse staining was seen in nearly all cases (26/29; 90%). Twenty-four of these cases showed concurrent reactivity for CK7 in the undifferentiated elements, whereas 2 cases were negative in this component. A single case that was CK7 positive in the spindle/giant cells was negative in the concurrent differentiated component (adenocarcinoma).