[Original Research]

CHEST

Tumor Spread Through Air Spaces Identifies a Distinct Subgroup With Poor Prognosis in Surgically Resected Lung Pleomorphic Carcinoma

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BACKGROUND: Tumor spread through air spaces (STAS) has recently been reported as a novel form of lung adenocarcinoma invasion that can negatively affect survival; however, its role in pleomorphic carcinoma remains unclear. The goal of this study was to characterize tumor STAS in pleomorphic carcinoma, including its association with clinicopathologic features and prognosis.

METHODS: Tumor specimens obtained from 35 consecutive patients with pleomorphic carcinoma who underwent surgical resection between 2009 and 2015 were reviewed. Tumor STAS was defined as tumor cells spreading within the air spaces in the surrounding lung parenchyma beyond the edge of the primary tumor.

RESULTS: Fourteen patients (40%) had evidence of STAS-positive pleomorphic carcinomas. Three types of morphologic findings were observed: single cells, small tumor cell clusters, and tumor nests. Tumor necrosis tended to be more prevalent in STAS-positive tumors than in STAS-negative tumors ($P = .094$). Patients with STAS experienced significantly worse recurrence-free survival ($P = .005$) and overall survival ($P = .002$) rates than those without STAS. Moreover, multivariate analysis revealed that tumor STAS was an independent risk factor for both recurrence ($P = .014$) and poor overall survival ($P = .042$).

CONCLUSIONS: In this first study of its kind, tumor STAS in patients with pleomorphic carcinoma was shown to be associated with high recurrence rates and poor survival after surgical resection. Hence, tumor STAS can serve as a predictor of postoperative survival; this information will enable better risk stratification and more effective clinical management of patients with this rare type of tumor.

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ABBREVIATIONS: HR = hazard ratio; NSCLC = non-small cell lung cancer; OS = overall survival; RFS = recurrence-free survival; STAKS = spread through a knife surface; STAS = spread through air spaces

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Lung pleomorphic carcinoma, categorized as a subset of sarcomatoid carcinoma according to the latest World Health Organization classification,[1] is rare: it accounts for approximately 0.4% of all non-small cell lung cancers (NSCLCs).[2,3] It is widely recognized as a high-grade malignancy with a reported 5-year overall survival (OS) of only 20% to 48%, even after surgical resection.[4-7] Patients with unresectable pleomorphic carcinoma that responds poorly to conventional chemotherapy have been reported; their median OS was only 5 to 8 months.[8-10] Thus far, these tumors have not been sufficiently characterized, largely owing to their rarity. However, selecting appropriate treatment strategies requires understanding the underlying clinicopathologic features and prognostic factors associated with this malignancy.

Tumor spread through air spaces (STAS) has recently been described as an important route of tumor invasion. It also carries prognostic implications in patients with lung adenocarcinoma given that significantly higher recurrence rates, as well as poorer OS, have consistently been reported in patients with lung adenocarcinoma with STAS following surgical resection.[11-14] Moreover, a recent study revealed that STAS was prognostic in patients with squamous cell carcinoma of the lung who underwent surgical resection.[15] However, the prevalence of STAS in pleomorphic carcinoma and its association with patients' clinicopathologic characteristics and prognoses have yet to be characterized.

We therefore retrospectively investigated the clinicopathologic findings of patients with resected lung pleomorphic carcinoma and sought to characterize the significance and prognostic implications of STAS.

Patients and Methods

Patient Cohort

Q7 Our institutional review board approved this retrospective study (approval identification number YUMC 29-12), and written informed consent for using materials and clinical information was obtained from each patient. Thirty-seven consecutive patients with lung pleomorphic carcinoma underwent surgical resection at National Hospital Organization Yamaguchi-Ube Medical Center between 2009 and 2015. Following a detailed review of the medical records, two patients were excluded from the cohort; one had committed suicide 2 months following surgery, and the other had undergone tumor wedge resection for pathologic diagnosis. Therefore, 35 patients were included in the analysis. Pathologic stage was assigned according to the *TNM Classification of Malignant Tumors* (8th edition).[16] None of the patients received preoperative chemotherapy and/or radiotherapy, and each received a clinical follow-up examination at least every 6 months following surgery that included CT assessment.

Histopathologic Evaluation

Hematoxylin and eosin-stained slides of resected tumor specimens acquired from formalin-fixed paraffin-embedded tissues were microscopically reviewed and evaluated by two pathologists (S. Y. and T. M.) who were blinded to the patients' clinical features and survival outcomes; any disagreements were resolved by consensus. Pathologic diagnoses were made according to the 2015 World Health Organization classification[1] and confirmed with immunohistochemistry when necessary. Given that pleomorphic carcinoma as defined is a poorly differentiated NSCLC comprising at least 10% spindle and/or giant cells,[1] "pure" spindle cell carcinomas or giant cell carcinomas were excluded. Comprehensive histologic subtyping was performed in each case, including the evaluation of spindle or giant cell components as well as epithelial elements. Because tumor necrosis is reportedly a significant prognostic factor,[6] the presence of necrosis was also recorded.

STAS was defined as tumor cells within air spaces in the surrounding lung parenchyma beyond the edge (ie, the smooth surface clearly identified in a low-power field) of the primary tumor.[12,13,15] STAS was classified into three groups based on morphologic findings: (1) single cells, defined as the presence of only one floating tumor cell in the alveolar space; (2) small tumor cell clusters, defined as a few tumor cells floating in the same; and (3) tumor nests, which are clearly identifiable within a low-magnification field (Fig 1). The edges of tumors containing an invasive mucinous adenocarcinoma component were defined as the alveolar spaces lacking tumor mucin, because tumor clusters are often observed in alveolar spaces that are filled with mucin products.

In addition, previously described discriminative methods were used to distinguish STAS from artificially detached tumor cells arising from tumor dissection, namely "spread through a knife surface" (STAKS).[12,15,17,18] STAS was identified by the presence of tumor cells within air spaces; these were mostly contiguous but were sometimes randomly scattered across the lung tissue. Tissue fragmentations both with and without jagged edges were carefully identified and deemed to be STAKS. STAS was also distinguished from alveolar macrophages according to morphologic features; the former were characterized by a high nuclear-to-cytoplasmic ratio and nuclear atypia, whereas the latter exhibited small nuclei and foamy cytoplasm that sometimes contained faint pigments.

The distance between the edge of the tumor and the farthest STAS was measured by using an ocular WHN10X-H micrometer (Olympus Optical Co. Ltd.). The number of alveolar spaces was also counted to rule out the influence of inconsistent inflation of the lung specimens during processing. The farthest distance between the edge of the tumor and that of the circumferential lung tissue section was also measured with a ruler to determine the size of the area surrounding the pathologically examined tumor.

Statistical Analysis

The associations between STAS and clinicopathologic features were evaluated by using Fisher exact test for categorical variables and Student *t* test for numerical variables. Recurrence-free survival (RFS) was defined as the interval between the date of surgical resection and that of detection of recurrence; OS was defined as the interval between the date of surgical resection and that of death or the last follow-up visit. Survival curves to estimate RFS and OS were generated by using

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