High-Grade Neuroendocrine Carcinoma with Bronchial Intraepithelial Tumor Spread

Possibly a New Histologic Feature of Large-Cell Neuroendocrine Carcinoma

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Introduction: During surgical resection of a peripherally located high-grade neuroendocrine carcinoma (HGNEC), we unexpectedly discovered prominent bronchial intraepithelial tumor spread up to the surgical end of the bronchus. Because bronchial intraepithelial tumor spread of peripherally located HGNEC has been rarely reported, we conducted a retrospective analysis at our hospital.

Methods: We histologically reviewed surgically resected HGNEC cases to assess bronchial intraepithelial spread of tumor cells. HGNECs with bronchial intraepithelial tumor spread were further studied by immunohistochemistry for neuroendocrine markers, and their clinicopathological characteristics were evaluated.

Results: Of 1778 cases of surgically resected lung cancer in our hospital, 47 cases of HGNEC were evaluated. Bronchial intraepithelial tumor spread was observed in nine cases (19.1%); eight of these cases were large-cell neuroendocrine carcinoma (LCNEC) or small-cell lung carcinoma with an LCNEC component. Moreover, bronchial intraepithelial tumor spread was continuous from the primary tumor to the resected end of the bronchus in four cases, and all these cases had an LCNEC component. Furthermore, HGNEC with bronchial intraepithelial tumor spread was associated with a higher recurrence rate than no bronchial intraepithelial tumor spread.

Conclusion: The results of this study suggest that bronchial intraepithelial tumor spread is commonly observed in cases of peripherally located HGNEC and may be a unique form of tumor invasion, especially tumors with LCNEC morphology. Therefore, surgeons and pathologists should be cognizant of bronchial intraepithelial tumor spread in peripherally located HGNEC, as well as its potential role as an indicator of HGNEC aggressiveness.

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Both small-cell lung carcinoma (SCLC) and large-cell neuroendocrine carcinoma (LCNEC) are classified as high-grade neuroendocrine carcinoma (HGNEC).[1,2] Centrally located SCLC usually involves tumor cells that invade along the bronchial mucosa.[3] However, bronchial intraepithelial tumor spread of peripherally located HGNEC has been rarely reported.

In our hospital, during the surgical resection of a peripherally located HGNEC, we unexpectedly discovered tumor spread along the bronchial epithelium up to the surgical end of the bronchus. Prompted by our experience with this interesting case, we histologically reviewed other cases of HGNEC to evaluate bronchial intraepithelial spread of tumor cells to determine the frequency and characteristics of this rare presentation.

PATIENTS AND METHODS

Between September 2002 and December 2012, 1778 patients underwent surgical resection for primary lung cancer at the Shizuoka Cancer Center Hospital in Shizuoka, Japan. Of these, 67 (3.8%) patients had tumors that were pathologically diagnosed as HGNEC, either SCLC or LCNEC. We histologically reviewed 47 cases of HGNEC in patients who underwent segmentectomy, lobectomy, or pneumonectomy with lymph node dissection; our focus was on the potential bronchial intraepithelial spread of tumor cells. Bronchial intraepithelial tumor spread was defined as continuous tumor invasion into the bronchus or bronchiole located outside the main tumor mass, and we excluded any tumor cell invasion of the bronchial lamina propria and submucosa or along the peribronchial soft tissue.

The histologic diagnoses of SCLC and LCNEC were based on the revised World Health Organization classification

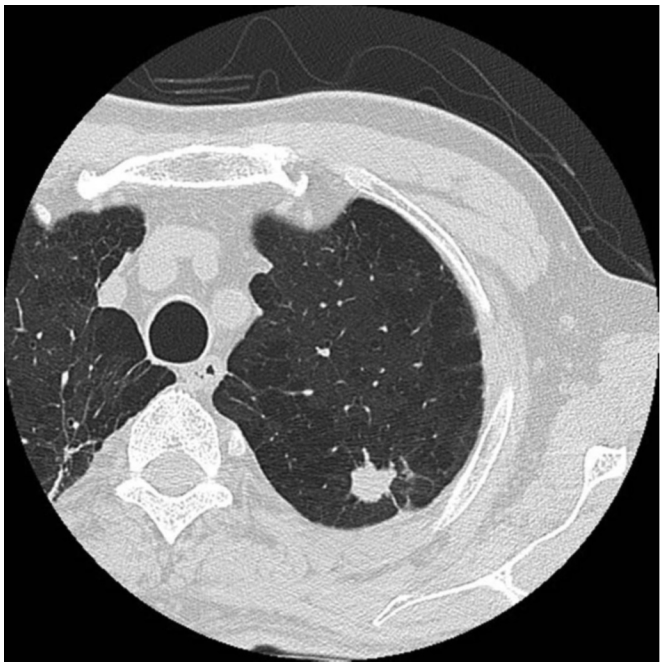

FIGURE 1. Radiographic findings of the tumor: Computed tomography of the chest reveals a well-defined and lobulated solid nodule measuring 2.4 cm in diameter in the left peripheral S^{1+2b} segment.

of lung carcinoma (2004).[2] Immunohistochemical analysis using CD56 antibodies (Nihonkayaku, Tokyo, Japan), chromogranin A (Dako, Glostrup, Denmark), and synaptophysin antibodies (Leica Microsystems, Newcastle, United Kingdom) was performed on paraffin-embedded tissue samples from all patients to confirm the neuroendocrine phenotype.

To analyze the clinicopathological characteristics of HGNEC, clinical and pathological information was collected from the medical records. This study was approved by the Shizuoka Cancer Center Institutional Review Board.

The clinicopathological features of patients were compared using the Fisher's exact test or the chi-square test. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using JMP 9 software (SAS Institute, Cary, NC).

RESULTS

A Representative Case

Herein, we describe the details of the case that prompted us to perform this study, as a representative case. The patient was a 66-year-old man who was admitted to our hospital with an abnormal shadow on a chest radiograph. Chest computed tomography revealed a well-defined and lobulated solid nodule measuring 2.4 cm in diameter in the left peripheral S^{1+2b} segment (Fig. 1). Transbronchial lung cytology yielded a pathological diagnosis of non-SCLC, and bronchoscopy showed normal epithelium of the B^{1+2} bronchus and the left upper bronchus. The clinical stage was T1bN0M0 (stage IA), and a left upper lobectomy was performed. The resected tumor was $1.6 \times 1.5 \times 1.5$ cm. Microscopically, the tumor contained a vast necrotic area in the center and variably sized tumor nests around the necrotic area (Fig. 2*A*). Tumor nests were a mix of small cells with fine hyperchromatic oval- to spindle-shaped nuclei and large cells with large round nuclei, distinct nucleoli, and scant cytoplasm (Fig. 2*B*). The tumor cell border was clear, and many rosette-like structures were observed. Immunohistochemical analysis revealed that the cells were diffusely positive for CD56 (Fig. 2*B*, inset), partially positive

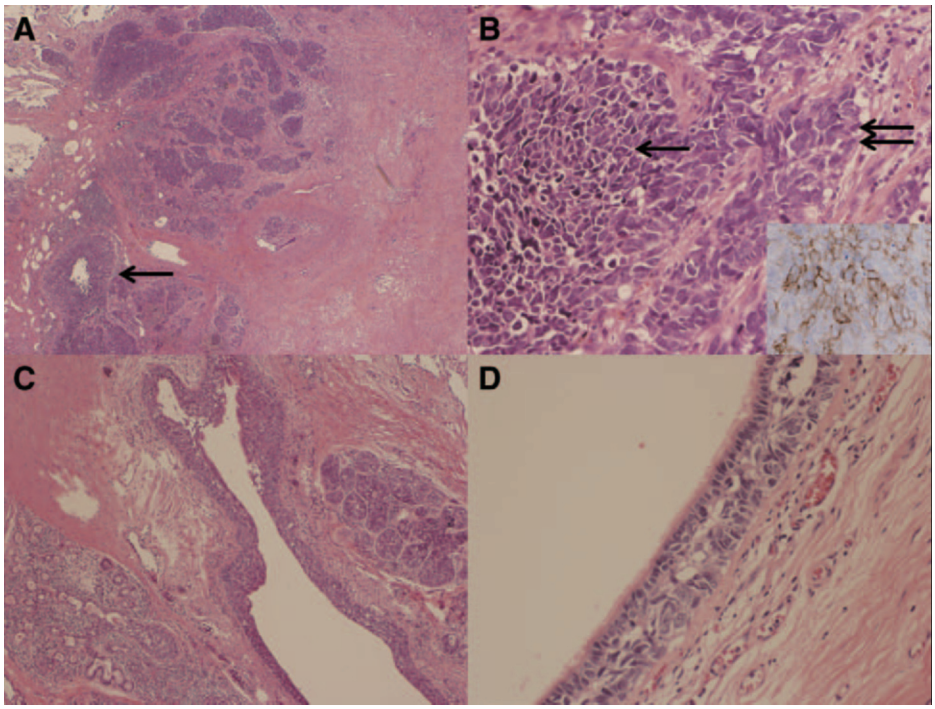

FIGURE 2. Microscopic findings of high-grade neuroendocrine carcinoma: The tumor has a vast necrotic area in the center (right side) and variably sized tumor nests around the necrotic area. Bronchiole is completely replaced by tumor cells (single arrow) and vascular invasion is seen in the center (*A*). The tumor nests are a mix of small cells (single arrow) with fine hyperchromatic oval- to spindle-shaped nuclei and large cells (double arrows) with large round nuclei, small nucleoli, and scant cytoplasm (*B*). The tumor cells are positive for CD56 (*B*, inset). Apart from the primary tumor, the bronchial epithelium and bronchial glands in the B^{1+2b} region have tumor cell invasion (*C*). Two to three layers of tumor cells occupying the basal bronchial epithelium and normal respiratory epithelial cells are present on the surface at the resected end of the left upper bronchus (*D*).