Combined Large Cell Neuroendocrine Carcinoma and Spindle Cell Carcinoma of the Lung

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Pleomorphic carcinomas of the lung are rare malignant biphasic tumors composed of carcinomatous and sarcomatous components. The carcinomatous component is usually an adenocarcinoma or a squamous cell carcinoma, and the sarcomatous component is usually a spindle cell carcinoma. Recently, we encountered two patients who underwent surgery for pleomorphic carcinoma whose carcinomatous component was large cell neuroendocrine carcinoma.

Key words: pleomorphic carcinoma – spindle cell carcinoma – large cell neuroendocrine carcinoma – surgery – immunohistochemistry

INTRODUCTION

Pleomorphic carcinomas of the lung are rare biphasic tumors that contain both a malignant epithelial component and a sarcomatoid component (1–3). The combination of spindle cell carcinoma with other neuroendocrine carcinomas of the lung appears to be extremely rare, with only three previously reported cases (4–6). These three neuroendocrine carcinomas consisted of large cell neuroendocrine carcinoma (LCNEC), atypical carcinoid and small cell carcinoma (4–6). In this report, we describe two surgical cases of pulmonary pleomorphic carcinoma composed of spindle cell carcinoma and LCNEC.

CASE REPORT

CASE 1

The patient was a 72-year-old man. During the follow-up after surgery for hypopharyngeal cancer in the Department of Otolaryngology of our hospital, chest X-ray showed a mass shadow in the right middle lung field, and he was referred to our department (Fig. 1A). He had a history of smoking 50 cigarettes per day for 33 years. Chest computed tomography (CT) revealed a well-defined mass shadow in S3 of the right lung (Fig. 1B). Bronchoscopy biopsy showed that the tumor was composed of the fascicular proliferation of spindle-shaped atypical cells, leading to a diagnosis of spindle cell carcinoma (Fig. 1C). Chest CT showed no hilar or mediastinal lymphadenopathy. Systemic examination revealed no distant metastasis. Right upper lobectomy with hilar and mediastinal lymph node dissection was performed. The resected specimen showed a peripheral tumor measuring 61 mm in maximum diameter (Fig. 2A). The mass was soft and yellowish-tan in color. Microscopically, most of the tumor was composed of sarcomatoid areas with a fibrosarcoma-like appearance (Fig. 2B). These areas contained large spindle cells arranged in long parallel fascicles. They exhibited abundant eosinophilic cytoplasm and marked nuclear pleomorphism. Because immunohistochemical studies showed that the spindle cells were positive for cytokeratin AE1/3 and vimentin (Fig. 2C and D), this sarcomatoid area was diagnosed as a spindle cell carcinoma component. In some areas, the tumor showed an organoid pattern and was composed of solid cell nests with peripheral palisading separated by fibrovascular septa (Fig. 3A). Frequent necrosis was observed in this component. The
individual tumor cells were polygonal or round and exhibited moderate eosinophilic cytoplasm (Fig. 3B). The nuclei were vesicular and contained granular chromatin with frequent nucleoli. The tumor cells were positive for neural cell adhesion molecule (N-CAM) and synaptophysin and were partially positive for chromogranin-A (Fig. 3C–E), and this solid nested area was diagnosed as an LCNEC component. Some areas of the carcinomatous component showed a tubular structure, and these tubular areas were diagnosed as adenocarcinomatous elements (Fig. 3A). Overall, the tumor was composed of 60% spindle cell carcinoma, 20% LCNEC, 15% adenocarcinoma and 5% squamous cell carcinoma. The tumor exhibited polypoid endobronchial growth. There were no lymph node metastases (pT2N0M0, Stage IB).

According to the patient’s wishes, no postoperative adjuvant chemotherapy was performed. He died of gastric cancer of well-differentiated tubular adenocarcinoma at another hospital 8 months after the lung surgery.

CASE 2

A 79-year-old man was noted to have an abnormal shadow on chest X-ray at a regular medical checkup and was referred to our department. He had a history of smoking 20 cigarettes per day for 25 years. Chest X-ray showed a large, round mass shadow in the right middle lung field (Fig. 4A). Chest CT revealed a notched mass shadow in S6 of the right lung (Fig. 4B). Under the suspicion of lung cancer, he underwent
Figure 3. Case 1: histological findings of carcinomatous component. (A) Carcinomatous component composed of large cell neuroendocrine carcinoma (LCNEC) and adenocarcinoma. (B) Well-defined tumor nest with a neuroendocrine appearance. (C–F) Expression of neuroendocrine markers in an LCNEC area [C–E, immunostaining for neural cell adhesion molecule (N-CAM), synaptophysin and chromogranin-A, respectively].

Figure 4. Case 2: radiological and macroscopic findings. (A) Chest X-ray film. (B) Chest CT. (C) Gross appearance of the lung tumor.
right lower lobectomy with hilar and mediastinal lymph node dissection.

The resected specimen showed a peripheral tumor measuring 54 mm in maximum diameter (Fig. 4C). The mass was soft and grayish-tan in color. Microscopic examination revealed a predominantly sarcomatous tumor composed solely of the fascicular proliferation of spindle-shaped cells (Fig. 5A). The spindle-shaped cells had oval or pleomorphic nuclei and abundant elongated cytoplasm (Fig. 5B). Because immunohistochemical staining showed intense immunoreactivity for cytokeratin AE1/3 and vimentin, the sarcomatous component was diagnosed as spindle cell carcinoma. Some areas of the tumor contained a squamous cell carcinoma component showing distinctly stratification and keratinization (Fig. 5C and D). The carcinomatous component with a neuroendocrine appearance was also admixed with the sarcomatous component. In this area, tumor cells which have sparse cytoplasm and fine nuclear chromatin were arranged in trabeculae (Fig. 5E). Areas of necrosis were frequently observed in this component. The tumor cells were positive for N-CAM and were partially positive for synaptophysin and chromogranin-A, leading to a diagnosis of LCNEC (Fig. 5F). Overall, the tumor was composed of 40% spindle cell carcinoma, 35% squamous cell carcinoma, 20% LCNEC and 5% adenocarcinoma. Metastatic carcinoma was present in the subcarinal lymph nodes, and intrapulmonary...
metastases were found microscopically in the same lobe (pT4N2M0, Stage IIIB).

Post-operative adjuvant chemotherapy was not performed due to the patient’s refusal. Twelve months after surgery, the patient developed pleural dissemination and died 22 months post-operatively. Autopsy was not performed.

DISCUSSION

Pleomorphic carcinoma is defined as a tumor that combines spindle or giant cell carcinoma with any of the more usual patterns of non-small cell carcinoma (1–3). In pleomorphic carcinomas, the most common carcinomatous element consists of conventional adenocarcinoma and squamous cell carcinoma and less commonly undifferentiated large cell carcinoma (1–3). The combination of spindle cell carcinoma with other neuroendocrine carcinomas appears to be uncommon in the lung.

On the other hand, LCNEC is defined as a large cell carcinoma demonstrating neuroendocrine architectural features and immunohistochemical or ultrastructural evidence of neuroendocrine differentiation (7). Jiang et al. (8) described the presence of conventional squamous cell carcinoma and adenocarcinoma in four of their 22 cases of LCNEC, but no spindle cell differentiation was reported. Similarly, no sarcomatoid elements were reported in the series by Rusch et al. (9) or Travis et al (7).

In our cases, the diagnosis of LCNEC was supported by characteristic light microscopic features in conjunction with positive immunohistochemical staining for neuroendocrine markers. The epithelial nature of the spindle cell carcinoma was supported by positive staining for cytokeratin. The co-expression of vimentin and cytokeratin in the spindle cell component of the tumors reported herein is consistent with the idea that spindle cell carcinoma represents a form of mesenchymal differentiation in lung carcinoma. Our observation of combined LCNEC/spindle cell carcinoma is consistent with the concept that primary lung cancer is derived from a multipotent stem cell and can differentiate into virtually any combination of the known histologic subtypes of carcinoma. Spindle cell carcinomas and LCNEC may represent additional forms of histologic heterogeneity in conventional non-small cell lung cancers where the tumor differentiates in mesenchymal and neuroendocrine directions, respectively (1,10,11). Thus, the combination of spindle cell carcinoma and LCNEC observed in our cases appears to exemplify an unusual manifestation of histologic heterogeneity. We speculate that since conventional non-small cell lung cancer is very unlikely to simultaneously differentiate in mesenchymal and neuroendocrine directions, spindle cell carcinoma may occur more frequently in combination with non-neuroendocrine rather than neuroendocrine carcinomas.

Patients (one man and two women; 54, 62 and 52 years of age, respectively, with a mean of 56 years) with pleomorphic carcinoma composed of spindle cell carcinoma and neuroendocrine carcinoma were previously reported by Khalifa et al. (4), Tsubota et al. (6) and Rainosek et al. (5). Our two patients were males in their 70s. These five patients, including ours, had a long history of smoking. In the three previously reported patients, the neuroendocrine carcinoma component was LCNEC, small cell carcinoma and atypical carcinoid, respectively. Except for the bronchogenic tumors reported by Tsubota et al., the previously reported tumors of pulmonary origin were large (8.0 or 9.0 cm in long diameter) and were in contact with the chest wall. The tumors in our patients were also large (54 or 61 mm in long diameter) and were adjacent to the chest wall. The polypoid endobronchial tumor growth in Case 1 was a feature previously described in spindle cell carcinoma (12). All patients, including ours, underwent surgery, but the prognosis is uncertain due to the small number of cases reported. However, many studies have reported a poorer prognosis for LCNEC and spindle cell carcinoma than for conventional non-small cell lung cancer (2,3,13,14), which indicates that the prognosis of patients with tumors showing a mixture of both components, as in our patients, is poor. The identification of a spindle cell component and an LCNEC component in the tumor described herein may indicate that conventional non-small cell lung cancer underwent multidirectional differentiation into an undifferentiated type of carcinoma as a whole.

Conflict of interest statement

None declared.

References

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