Definitive Chemoradiotherapy for Advanced Pulmonary Sarcomatoid Carcinoma

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Abstract

Pulmonary sarcomatoid carcinoma is a rare subtype of non-small cell lung cancer with a poor prognosis. We herein report on a case of pulmonary sarcomatoid carcinoma that was treated successfully by concurrent chemoradiotherapy. A 65-year-old man was diagnosed to have pulmonary pleomorphic carcinoma (clinical T4N2M0 stage IIIB). He received concurrent chemoradiotherapy (60 Gy of radiotherapy in 30 fractionations and two courses of chemotherapy with carboplatin and paclitaxel). After chemoradiotherapy, a significant reduction of the tumor size was observed. Two courses of adjuvant chemotherapy were performed. He is currently alive at 15 months after the first treatment without any recurrence or metastasis.

Key words: pulmonary sarcomatoid carcinoma, chemoradiotherapy

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Introduction

Pulmonary sarcomatoid carcinoma is a rare subtype of lung cancer which accounts for 0.3-1.3% of all lung cancers (1). It is defined as poorly differentiated non-small cell lung carcinoma that contains a component of sarcoma or sarcoma-like differentiation (1). According to the 4th edition of WHO classification of tumors of the lung published in 2015, pulmonary sarcomatoid carcinoma is used as a general term that includes pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma and pulmonary blastoma (2). In addition, pulmonary sarcomatoid carcinoma has been reported to be an aggressive disease with a poorer prognosis and higher rate of metastases than those of other types of non-small cell lung cancer (NSCLC) (3, 4).

Surgical resection is the first-choice therapy. Chemotherapy is used for inoperable cases, but there is no standard regimen of chemotherapy and a poor prognosis has been reported in those patients (5). The role of radiotherapy has not yet been established, but it is used as pre/post-operative, definitive and palliative therapy.

We herein report our findings of an unresectable case of pulmonary sarcomatoid carcinoma that showed a good response to chemoradiotherapy without any recurrence or metastasis for a long period of time.

Case Report

A 65-year-old Japanese man with hemosputum consulted a local physician in January 2014. He had a history of alcohol-induced liver cirrhosis and diabetes for 8 years. He had undergone operations for appendicitis, duodenal ulcer, pancreatic cyst and cervical hernia and had undergone endoscopic submucosal dissection for early stage esophageal cancer 4 years prior to this presentation. He was a current smoker and his Brinkman’s index was 450.

A recurrence of esophageal cancer was initially suspected, he was referred to a local general hospital and underwent a computed tomography (CT) scan. The CT scan revealed two
masses in his chest: a mass measuring 40×22 mm in size behind the main trachea (Fig. 1A) and a mass measuring 12 ×5 mm in size below the carina. At first, multiple lymph node metastases of esophageal cancer were suspected. For further examination and treatment, he was introduced to our hospital. Gastrointestinal fiberscopy revealed no lesion in the esophagus (Fig. 2A). A sputum test showed no malignancy. Bronchoscopy revealed a tumor growing from the membranous portion of the trachea (Fig. 2B), and a biopsy was conducted from that region.

A histological examination showed the presence of spindle-shaped cells, and a differential diagnosis of sarcomatoid carcinoma and synovial sarcoma was made (Fig. 3A). Immunohistochemistry was also conducted. Staining for thyroid transcription factor-1 (TTF-1, Fig. 3B) was positive, which suggested a primary lung tumor. Staining for vimentin, which is used as a marker of mesenchymal-derived cells, was partly positive (Fig. 3C). Other staining was as noted below; weakly positive for cytokeratin (CK) 5/6 and CK14, partly positive for p63, and negative for AE1/AE2, 34βE12 and cellular adhesion molecule (CAM) 5.2. Fluorescence in situ hybridization (FISH) revealed no translocation of t(X;18)(p11;q11), thus ruling out a diagnosis of synovial sarcoma. These results were therefore compatible with pulmonary sarcomatoid carcinoma. He was clinically diagnosed to have pulmonary sarcomatoid carcinoma primarily located behind the trachea and accompanied by mediastinal lymph node metastasis. The clinical stage was T4N2M0 stage IIIB according to the TNM Classification of Malignant Tumors 7th Edition. Since complete resection was judged by a surgeon to be impossible, the patient received definitive chemoradiotherapy. Six courses of carboplatin (days 1, 8, 15, 22, 29 and 36) with an area under the curve (AUC) of 6 and paclitaxel (300 mg/body). During adjuvant chemotherapy, acute adverse effects including grade 1 mucositis, grade 1 nausea, grade 1 hepatotoxicity and a grade 1 decrease in the white blood cells and neutrophils by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 were observed. After the treatment, a CT scan showed a significant reduction in both the primary tumor and the swollen lymph node (Fig. 1B), and the response was judged to be a partial response by Response Evaluation Criteria in Solid Tumours (RESIST) version 1.1. After chemoradiotherapy, he underwent two courses of adjuvant chemotherapy with carboplatin (AUC 6) and paclitaxel (300 mg/body). During adjuvant chemotherapy, acute adverse effects including grade 1 hepatotoxicity and a grade 3 decrease in the white blood cells and neutrophils (CTCAE version 4.0) were observed. A CT scan 3 months after completing chemoradiotherapy showed a further reduction of the tumor, but another tumor measuring 2 cm in size was newly detected in the liver. Ultrasoundography and dynamic enhanced CT showed the tumor to not be a metastatic tumor, but de novo hepatic cell carcinoma. He underwent radiofrequency ablation after trans-arterial embolization, and the tumor was satisfactorily controlled. He has had no recurrence of either sarcomatoid carcinoma or hepatic cell cancer for 15 months after the chemoradiotherapy (Fig. 1C), and no late toxicity has been observed.

**Discussion**

Pulmonary sarcomatoid carcinoma is a rare subtype of lung cancer that was first defined in the WHO classification in 1999 (6). Seventy-ninety percent of the patients are male and about 90% have a history of smoking (3, 4, 7-10). The mean diagnostic age is from 60-70 years. A higher rate of...
metastatic disease than that for other NSCLCs has been reported (4). Metastatic diseases arise throughout the body including the lungs, adrenal gland, brain, bone, pleura, liver, kidney, and other organs.

Pathologically, sarcomatoid carcinoma includes five subtypes: pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma (2). The WHO classification system is based on an evaluation of resected specimens, and there has been a need for a diagnostic system for biopsy or cytology specimens to decide the optimal treatment plan, namely whether to perform resection or not. According to the new WHO classification published in 2015, new criteria for making a diagnosis based small-sized biopsy specimens and cytology have been proposed (11). According to the new criteria, it is proposed that sarcomatoid carcinomas may exist if spindle cell and/or giant cell components are present. However, obtaining resected specimens is still indispensable to make a final diagnosis of pulmonary sarcomatoid carcinoma and determine the subtype of the disease, and most previous reports have been based on surgical cases. Some methods have been proposed for diagnosing pulmonary sarcomatoid carcinoma by biopsy, by using immunohistological markers including TTF-1 and vimentin. TTF-1 is an important marker which suggests that the non-small cell type tumor is derived from pulmonary epithelial tissue and it is useful to distinguish sarcomatoid carcinoma from other mesenchymal tumors (12). Vimentin is generally recognized to be expressed in mesenchymal tissues, but it is reported that pulmonary sarcomatoid carcinoma shows positive staining for vimentin and a scoring system for grading the staining pattern of vimentin is thus useful for making a diagnosis (13).

In the present case, the presence of spindle cells suggested a clinical diagnosis of sarcomatoid carcinoma, but making a definite diagnosis based on conventional histological features was difficult because only a small sample could be obtained by transtracheal biopsy. Using immunohistological methods and FISH, we decided that the tumor was compatible with sarcomatoid carcinoma. As mentioned above, new methods to diagnose sarcomatoid carcinoma by biopsy have recently been proposed. Such changes might lead to an increase in the number of patients diagnosed by biopsy, and

Figure 2. Endoscopic pictures. (A) Gastrointestinal fiberscopy revealed no lesion in the esophagus. (B) Bronchoscopy revealed a tumor growing from the membranous portion of the trachea.

Figure 3. Histological examination. (A) Hematoxylin and Eosin staining, ×200. (B) Immunohistochemistry (IHC) for thyroid transcription factor-1 (TTF-1), ×200. TTF-1 positivity suggests that the tumor is derived from lung tissue. (C) IHC method for vimentin, ×200. Vimentin positivity can be a marker for diagnosis of sarcomatoid carcinoma.
establishing a treatment method for unresectable cases might also become necessary.

The first-choice treatment for sarcomatoid carcinoma is surgical resection. According to past reports, the 5-year overall survival rates in resectable cases ranged from 24.5-53.2% (4, 10, 14-16) (Table). Martin and colleagues reported the prognosis of sarcomatoid carcinoma in comparison to that of other NSCLCs (4). They reported 5-year overall survival rates of 24.5% for sarcomatoid carcinoma and 46.5% for other NSCLC and the median period from resection to recurrence of 11.3 months and 61.4 months, respectively. They also conducted propensity score matching and concluded that the prognosis of pulmonary sarcomatoid carcinoma is worse than that of other types of NSCLC. In resectable cases, it has been demonstrated that a small tumor size is associated with a good prognosis (10, 17).

Chemotherapy alone is generally used in inoperable cases in past reports, but the prognosis is very poor. Vieira and

Figure 4. Radiotherapy planning. (A) Plan for first course of 40 Gy. (B) Plan for second course of 20 Gy with reduction of dose to the spinal cord.
colleagues reported the outcomes in patients with stage III or IV pulmonary sarcomatoid carcinoma who received chemotherapy, and the median survival period was 6.3 months (15). They also reported that platinum-based chemotherapy is associated with a longer OS, although patients with a better performance status tended to receive platinum-based chemotherapy and no randomized controlled trial has so far been conducted. It has recently been reported that some cases have a mutation in epidermal growth factor receptor (EGFR, 15.7-28.1%), Kirsten rat sarcoma viral oncogene homolog (KRAS, 3.1-27.2%), MET (22%) and other genes (18-21). The effectiveness of inhibitors for those molecules has not yet been established, though Zou and colleagues reported that a pulmonary pleomorphic carcinoma patient with EGFR mutation showed a good response to erlotinib treatment (22).

Although most physicians today would choose chemoradiotherapy in the present case that had Stage IIIB NSCLC, there are few detailed reports on definitive radiotherapy or chemoradiotherapy for diagnosed cases of pulmonary sarcomatoid carcinoma. As discussed above, chemotherapy alone has been usually used for unresectable cases in past reports, however, the dose prescription and irradiation method has not yet been established. Considering its pathology, the same dose prescription as that used for other subtypes of NSCLC (60-70 Gy in conventional fractionation) may be reasonable. Stereotactic hypo-fractionated irradiation might be effective for local control, but there has been no report on the use of hypo-fractionated radiotherapy for pulmonary pleomorphic carcinoma. Some reports include patients who received preoperative radiotherapy (10), but the effectiveness of preoperative radiotherapy has not yet been established. Radiotherapy is also used for pain relief and other symptoms. It has also been reported that radiotherapy is effective for the local control of a remaining or recurrent tumor. Although radiotherapy is an effective local therapy, it is not sufficient for controlling all micrometastases. In surgical cases, sarcomatoid carcinoma tends to relapse earlier than other subtypes of NSCLC, and Ito and colleagues suggested that surgery followed by adjuvant chemotherapy might improve the outcomes (8). Considering the potential for an early systemic relapse of the disease, local therapy alone is not sufficient for controlling the disease. Elective nodal irradiation might also be beneficial for controlling metastases, but its effect may be limited because about half of the metastases of pulmonary pleomorphic carcinoma occur at distant sites (4). Therefore, systemic chemotherapy combined with radiotherapy may be a reasonable method to eliminate all micrometastases and improve the prognosis.

We chose definitive chemoradiotherapy for the present case of stage IIIB unsuitable for non-small lung cancer, according to NCCN Guidelines for NSCLCs and our domestic treatment guidelines. To the best of our knowledge, only one case of definitive concurrent chemoradiotherapy for pulmonary sarcomatoid carcinoma has been reported (22). Although that case showed a remarkable reduction of the primary tumor after chemoradiotherapy, distant metastases occurred soon thereafter and the patient died a few months after the therapy. In the present case, definitive chemoradiotherapy combined with adjuvant chemotherapy had a remarkable effect, and no locoregional or distant recurrence has been observed for a long period of time. Considering the aggressive features of this disease, adding adjuvant chemotherapy thus seems to be beneficial to both eliminate micrometastases and prevent recurrence.

We herein presented a case of pulmonary sarcomatoid carcinoma that was successfully treated with concurrent chemoradiotherapy followed by adjuvant chemotherapy. Further study is needed to confirm the effectiveness of this therapeutic strategy.

The authors state that they have no Conflict of Interest (COI).

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