Abstract. Pulmonary sarcomatoid carcinoma (PSC) is a rare histological subtype of non-small cell lung cancer, and the available studies on the response to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) is limited. In the present study, a 73-year-old female presented with a large mass in the lower right lung, which was diagnosed as a PSC on biopsy. An amplification-refractory mutation system (ARMS) test revealed that the patient possessed the wild-type EGFR gene, and the patient subsequently underwent radiotherapy (60 Gy) and four 21-day cycles of chemoradiotherapy (1,600 mg gemcitabine, days 1 and 8; 30 mg, cisplatin, days 1-3). Following radiotherapy and chemoradiotherapy treatment, a CT scan revealed complete remission of the mass in the lower right lung, however, metastases were identified in the para-aortic lymph node, bilateral iliac fossa and the right gluteal region. Notably, an EGFR exon 21 L858R gene mutation was identified in the mass of the right gluteal metastasis. Therefore, treatment with erlotinib was initiated. The patient continued to experience progression-free survival for six months following the initiation of erlotinib therapy. However, multiple metastases were then identified, and all lesions possessed the wild-type EGFR gene, as identified by the ARMS test. The findings suggest that erlotinib is a viable therapeutic option for the treatment of PSC patients that possess an EGFR mutation. The spatio-temporal evolution of EGFR mutation heterogeneity in PSC may result in drug-resistance, which challenges EGFR-TKI therapy and EGFR gene mutation diagnosis.

Introduction

Pulmonary sarcomatoid carcinoma (PSC) is a rare and heterogeneous pulmonary tumor in which carcinomatous and sarcomatous elements occur, and accounts for 0.1-0.4% of all pulmonary malignant tumors (1). PSC predominantly affects males and smokers, with a median age of 51.4 years and a male to female ratio of 2.12-6:1 (2-4). Erlotinib, which is one of the highly promising epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), is administered orally once daily for the treatment of patients with non-small cell lung cancer (NSCLC). The present study reports the first case of PSC successfully treated with erlotinib. The spatio-temporal evolution of EGFR mutation heterogeneity between the primary lesion and metastasis, as well as between metastases, was also analyzed in the present study. Written informed consent was obtained from the patient's family.

Case report

A 73-year-old female was admitted to the Department of Oncology at Xiangya Second Hospital of Central South University (Changsha, China) in November 2012 due to violent coughing for 1 month. A computed tomography (CT) scan revealed a 5.2x4.5 cm mass in the lower right lung (Fig. 1), and a pulmonary needle biopsy revealed carcinomatous and sarcomatous components within the lesion (Fig. 2A and B). Immunohistochemically, the tumor cells were positive for the expression of creatine kinase (CK; Fig. 2C), epithelial membrane antigen (EMA; Fig. 2D), vimentin (Fig. 2E) and Ki-67 (Fig. 2F), and did not express thyroid transcription factor-1 (TTF-1), smooth muscle actin (SMA) or S100. An amplification-refractory mutation system (ARMS) test revealed that the lesion possessed the wild-type EGFR gene. These findings were consistent with the features of PSC and clinical tumor-node-metastasis (cTNM) stage IIIa (cT3N2M0). The patient refused surgery and underwent four 21-day cycles of chemotherapy, comprising a regimen of gemcitabine (1,600 mg, days 1 and 8) and cisplatin (30 mg, days 1-3) combined with intensity-modulated radiotherapy (2 Gy/30 fractions). In December 2012, positron emission tomography/CT (Fig. 3) revealed that the right lower
mass of the lung was in complete remission, but metastases had arisen in the paraaortic lymph node, bilateral iliac fossa and the right gluteal region. Notably, an EGFR exon 21 L858R mutation was identified in the right gluteal metastatic lesion using the ARMS test. Therefore, treatment with 150 mg of erlotinib once daily was initiated. However, six months subsequent
to targeted therapy, CT (Fig. 4) revealed that the right iliac fossa metastases had decreased in size, but metastases were identified in the right gluteal region, right groin and the right chest wall of the right-lower abdomen. Biopsy of the right iliac fossa, right gluteal tumor and the right chest wall, the right abdominal subcutaneous nodules were all revealed to be metastatic sarcomatoid carcinoma, and all were revealed to also possess wild-type EGFR without the T790M mutation by performing an ARMS test (Fig. 6). The patient was therefore treated with two 21-day cycles of pemetrexed (800 mg, day 1), instead of erlotinib. In September 2013, CT re-examination revealed multiple organ metastases to the liver, pancreas and left adrenal gland. The patient received nutritional support, but succumbed to the disease in October 2013.

Discussion

According to the 2004 World Health Organization classification (5), PSC can be divided into five subtypes, consisting of pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma and pneumoblastoma. Overall, PSC runs an aggressive clinical course, with the five-year survival rate for patients with PSC being only 24.5%, which is a worse rate compared with other forms of NSCLC (6,7). In addition, distant metastasis can be identified in the early stages of the disease (8).

Surgery is currently considered to be the best option for the treatment of PSC (9) alongside chemoradiotherapy, which mainly refers to the chemotherapy regimens for NSCLC treatment (10). The effect of EGFR-TKIs on PSC remains unclear, and the available studies on the expression of EGFR are also limited. Italiano et al (11) tested the EGFR status of 22 PSC patients and the results revealed that none presented with EGFR mutation. However, Leone et al (12) retrospectively tested the EGFR status of 23 patients and the results revealed an EGFR exon 19 deletion in two patients. Ushiki et al (13) reported one patient who did not receive therapeutic effect from the administration of gefitinib. However, the autopsy of this patient revealed an EGFR exon 19 deletion, and a T790M drug-resistant mutation. In this case, the patient was a female with no smoking history. An EGFR exon 21 L858R mutation was identified in the metastatic lesion. In the present study, the patient experienced progression-free survival for the six months following the initiation of erlotinib therapy. However, resistance emerged finally, which may have been caused by EGFR mutational heterogeneity.
EGFR mutation heterogeneity is a common phenomenon in pulmonary carcinoma tissue (14,15). Numerous studies have supported that the NSCLC primary and metastatic lesions also exhibit EGFR mutation heterogeneity (16-19). However, no study has yet reported EGFR mutation heterogeneity in PSC lesions. The present patient was identified as possessing EGFR mutation heterogeneity between the primary and metastatic lesions, as well as between the metastases, which demonstrated the double characteristics of temporal and spatial evolution. In the present study, the pulmonary primary lesion was EGFR wild-type, but in the first group of metastases, the lesion in the right gluteal region possessed a EGFR mutation and the lesion in the left iliac fossa was wild-type. Within the second group of metastases, the paraaortic lymph node and right iliac fossa...
metastases possessed EGFR mutations, according to the clinical response. Among the second array of metastases, all four lesions were wild type. With the exception of the pulmonary primary lesion, which was able to be well-controlled post-chemoradiotherapy, the therapeutic response of the metastatic lesions overall conformed to that expected due to the EGFR status. To the best of our knowledge, the spatio-temporal heterogeneous evolution of tumors has only been previously reported by Gerlinger et al (20) and Sequist et al (21).

In summary, the present study is the first case report of PSC successfully treated using erlotinib. The findings suggest that erlotinib is a viable therapeutic option for patients with PSC that possesses an EGFR mutation. However, the spatio-temporal evolution of EGFR mutational heterogeneity in PSC may result in drug-resistance, which challenges EGFR-TKI therapy and the diagnosis of EGFR gene mutation. Therefore, multiple biopsies may be necessary in cases exhibiting EGFR mutational heterogeneity.

References