An anaplastic lymphoma kinase (*ALK*) fusion oncogene positive metastatic sarcomatoid carcinoma of the lung with good response to crizotinib

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Abstract: Primary sarcomatoid carcinoma (SC) of the lung is a rare tumor that accounts for less than 1% of all lung cancers and compared to other non-small cell lung cancers (NSCLC) they appear more aggressive with poorer prognosis and response to treatment. Carcinosarcoma is one of the subtypes of SC. We report a case of carcinosarcoma with *ALK-EML4* fusion gene in a 50-year-old male patient with a good response to therapy with crizotinib. An *ALK* rearrangement is a rare finding in SC, but as this case demonstrates, it may occur and it is necessary to perform the *ALK* testing in these tumors to find possible targeted treatments for better outcomes.

Keywords: Sarcomatoid carcinoma (SC); lung; molecular profiling; *ALK-EML4* fusion gene; crizotinib

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Introduction

Primary sarcomatoid carcinoma (SC) of the lung is a rare and highly malignant tumor and accounts for less than 1% of all lung cancers (1-3). As recently established by the World Health Organization (WHO), the pulmonary SC is classified into carcinosarcoma, pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma and pulmonary blastoma (4).

Pulmonary SC more commonly affects men with a history of smoking and has also been described with asbestosis (5-7). The average age of diagnosis is 60 years and there is 4 times greater preponderance in men (8,9).

As long as the tumor is operable, surgery is the treatment of choice. Postsurgical radiotherapy can be well applied, especially when the resection is incomplete (10). For metastatic disease there is currently no data available and patients are usually treated with the same cytotoxic agents as non-small cell lung cancers (NSCLC), but in most cases, chemoresistance appears and this might be the reason for poor prognosis (11,12).

During the last decade, there has been an immense development of targeted and immunotherapy in the lung cancer area, which has improved the survival outcomes. Although epithermal growth factor receptor (*EGFR*)-, anaplastic lymphoma kinase (*ALK*)-, programmed death-1 (*PD-1*)- and programmed death-ligand 1 (*PD-L1*)-targeted therapies have a promising therapeutic effect in patients with typical NSCLC, especially such as adenocarcinoma, the potential clinical effect of these drugs to SC is still unknown (13-15). Therefore, we report a case of carcinosarcoma with *ALK* fusion gene with good response to therapy with crizotinib.

Case presentation

A 50-year-old male was hospitalized due to right pleural effusion for further investigation. He had complained for 2 months of progressive non-productive cough, fatigue and light pain in the right axillary region. The patient had a smoking history of 7 pack years, he had quit 5 years ago. Upon physical examination, the patient was in a stable condition, ECOG 1, with no concomitant pathologies. Lung auscultation revealed the absence of respiratory sounds in the right lower lobe.

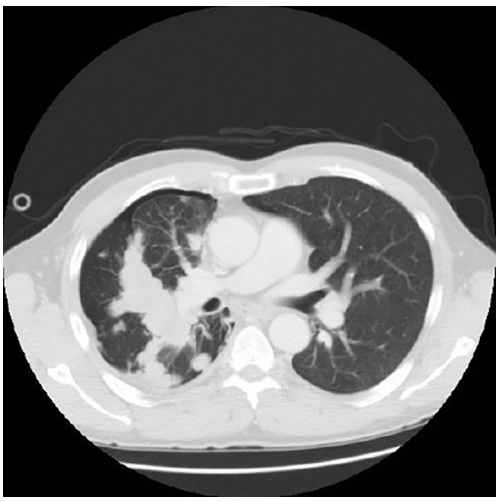

Figure 1 Baseline CT scan (January 3, 2016) of the chest shows a central tumor with a diameter of 6.5 cm from the beginning of the right main bronchus with multiple different sized metastases in the right and left lung and on the right pleura.

A CT scan was performed which showed a central tumor with multiple different sized metastases in the thorax and right pleural effusion (*Figure 1*). A chest tube instantly removed 1 liter of haemorrhagic liquid, cytologically full of atypical cells. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) found atypical cells, which were immunohistochemically characteristic to adenocarcinoma. For more accurate diagnosis biopsies were taken from the right parietal pleura. Pathohistology revealed mesenchymal tissue with spindle cells and many vascular structures (*Figure 2A*). Also, areas with epithelial component were seen (*Figure 2B*). Tumor cells were positive for vimentin (*Figure 2C*) and pan-keratin (*Figure 2D*). Histologically and immunohistochemically the pattern was primarily suggestive for carcinosarcoma. As the epithelial cells were positive for p40 and CK5/6, the epithelial component was more characteristic of a squamous cell carcinoma.

In the multidisciplinary tumor board, a palliative systemic chemotherapy was recommended and the patient received one cycle with cisplatin and docetaxel. During the 1st cycle of chemotherapy, a broad molecular profiling of the tumor tissue was performed (OncoDeepDx+ test, OncoDNA SA, Belgium). Molecular profiling showed no mutations in the common oncogenes, including *EGFR*, *BRAF*, *ERBB2*, *MET*, *MEK*, *RAS*; *PD-L1* had a low expression, but the presence of *ALK-EML4* fusion was diagnosed. Therefore, from February 9, 2016 the therapy was switched to *ALK* inhibitor crizotinib 250 mg twice daily.

The patient has tolerated the treatment well, except for the mild augmentation of liver enzymes and the development of a light cough (grade 1) at the beginning of the therapy, which disappeared. Tumor changes are characterized in *Figure 3*. The patient has now more than a year a partial response and good tolerability to crizotinib treatment. Currently, the patient's ECOG status is 0 and the therapy with crizotinib continues.

Discussion

We report a case of an *ALK*-positive carcinosarcoma with a good response to therapy with crizotinib. Crizotinib is effective in *ALK*-positive NSCLC (16), but in the case of carcinosarcomas, such data is missing or limited.

Primary SC of the lung is a rare and highly malignant tumor and accounts for less than 1% of all lung cancers (1-3). There is no good standard therapy available for the cure of metastatic SC, patients are currently treated as NSCLC with similar chemotherapy (15). Many recent case reports and studies, which have focused on SC, have shown worse survival and outcome compared to other histological subtypes of NSCLC (17). Therefore, we can conclude that the standard treatment of NSCLC is not as effective among SC patients.

During the last decade there has been a significant development in the field of targeted therapies and immunotherapy of NSCLC with the routine use of *EGFR* and *ALK* inhibitors and more recently also *PD-1* inhibitors. Guidelines from the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association of Molecular Pathologists (AMP) recommend the analysis of either the primary tumor or of a metastasis for *EGFR* and *ALK* for all patients whose tumor contains an element of adenocarcinoma, regardless of the clinical characteristics of the patient (18,19), but the approach in SC is less clear.

Targetable genetic aberrations in NSCLC have also been investigated in SC.

One of these targets is *EGFR* (20). A study by Italiano *et al.* analyzed *EGFR* and *KRAS* mutational status among 22 cases of primary lung SC, where *KRAS* mutation was found in eight cases, no *EGFR* mutation was detected (13). Also, Terra *et al.* analyzed molecular characterizations of lung SC in 33 cases and didn't find *EGFR* mutations, but in 20% of cases a *KRAS* mutation was detected (14). These

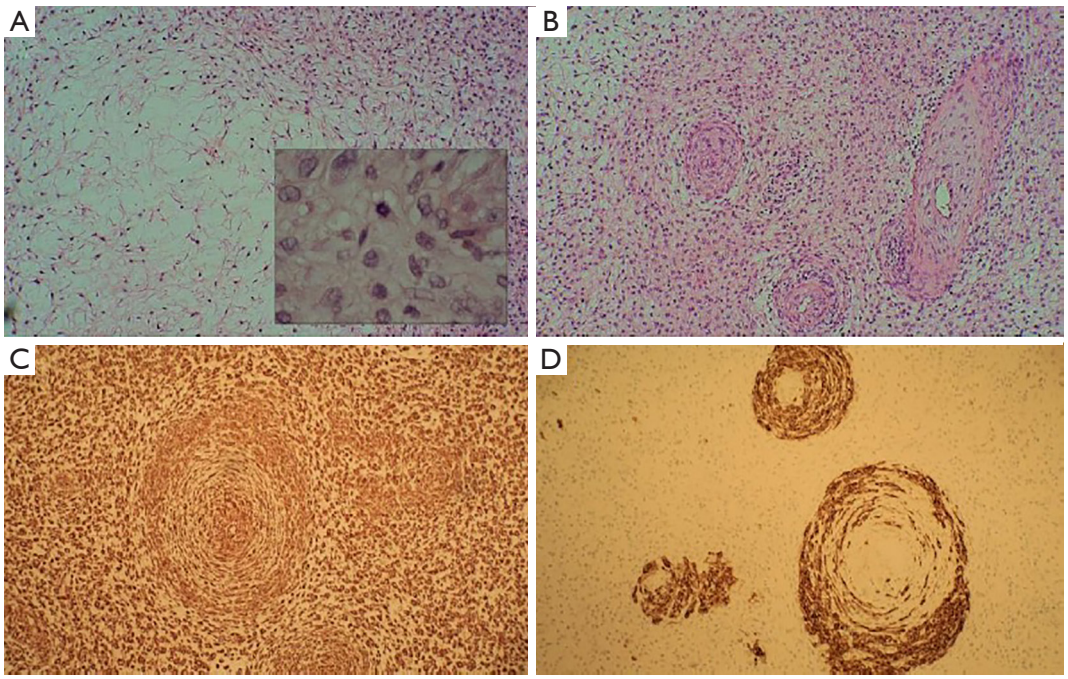

Figure 2 Pathohistology. (A) Sarcomatoid component (H&E, ×100, ×1,000); (B) epithelial component (H&E, ×100); (C) widespread positivity in the sarcomatous cells with vimentin (immunohistochemical staining, ×100); (D) positivity of epithelioid cell groups with pan-keratin (PK) (immunohistochemical staining, ×100).

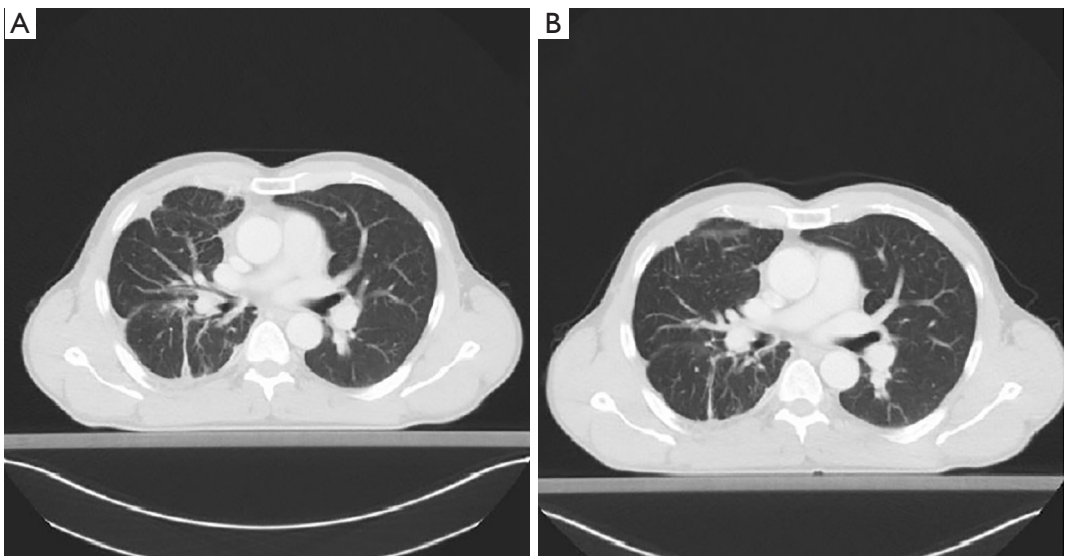

Figure 3 Tumor changes in dynamics. (A) CT scan (May 20, 2016) of the chest 3 months after starting the treatment with crizotinib shows positive dynamics—peribronchial infiltration around the right main bronchus and mediastinal lymph nodes has decreased, multiple metastases in the right and left lung have disappeared; (B) currently, the last CT scan (September 26, 2017) of the chest 19 months after starting the therapy shows the continuation of partial response.

findings may suggest that the overexpression of *EGFR* protein and high rate of *KRAS* mutation could be the reason for poor prognosis compared to other types of NCSLC.

SC may benefit from therapies targeting *PD-1* protein and *PD-L1* (21). A study by Velcheti *et al.* found that SC have higher *PD-L1* levels than NSCLC. They analyzed two large retrospective lung cancer cohorts, where 9 of 13 patients with SC were positive for *PD-L1*. This study supports the potential clinical effect of using anti-*PD-1*/*PD-L1* targeted therapies in the treatment of metastatic SC (15). Our patient had low expression of *PD-L1*.

In a recent study by Terra *et al.* (14), they analyzed almost 2,800 mutations in 33 cases of lung SC by next-generation sequencing. Twenty-four of 33 cases had at least 1 abnormality. The most common were *TP53* mutations (19 cases), which were followed by *KRAS* mutations (10 cases), *AKT1*, *JAK3*, *BRAF*, *NRAS* and *PIK3CA* mutations (1 case in each), no *EGFR* mutations were found. *ALK* rearrangement, which has been a rare finding among SC so far, occurred in one case and currently we have potential targeted treatment for this mutation. However, a study by Chen *et al.* showed that the incidence of *ALK* rearrangement (5/141, 3.5%) in SC is similar to other subtypes of NSCLC and more often among young patients with no smoking history (22).

Those studies show the importance of testing SC also for targetable mutations to find potential therapeutic options (14). Chen *et al.* have reported a case of *ALK*-positive pleomorphic carcinoma with partial response to crizotinib (23). Our patient with metastatic carcinosarcoma had *ALK* rearrangement and is currently receiving crizotinib with good response and has stable disease for more than 1 year.

Conclusions

Pulmonary SC is a rare and aggressive tumor, which is partly pathomorphologically and molecularly different from other types of NSCLC. In metastatic disease, chemoresistance appears fast and so far, there is no comprehensive data about potential targeted therapies in SC. An *ALK* rearrangement is a rare finding in SC, but as the current clinical case demonstrates, it may occur and with currently available treatment with crizotinib there might be a good response and a better outcome. SC should be evaluated for potentially targetable mutations in the same manner as other NSCLC, especially adenocarcinoma. Broad molecular profiling or at least *EGFR* mutation, *ALK*, *ROS1* and *PD-L1* testing should be a standard of care among SC patients to better understand molecular characteristics and to find a possible treatment.

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None

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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