

CASE REPORT

Small cell transformation in crizotinib-resistant ROS1-rearranged non-small cell lung cancer with retention of ROS1 fusion: A case report

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Abstract

C-ros oncogene 1 receptor tyrosine kinase (ROS1) rearrangement has been detected in patients with advanced non-small cell lung cancer (NSCLC). Although ROS1 tyrosine kinase inhibitors (TKIs) provide a survival benefit for patients with ROS1-rearranged advanced NSCLC, subsequent therapy remains limited. Small cell transformation is an important mechanism of drug resistance in epidermal growth factor receptor-mutant NSCLC. However, its significance in mediating ROS1 resistance has not been determined yet. Here, we present the case of a 63-year-old man with ROS1-rearranged advanced NSCLC who had disease progression with small cell transformation of the mediastinal lymph node after 8 months of treatment with crizotinib. More importantly, fluorescence in situ hybridization of post-progression tumor biopsy demonstrated retention of ROS1 rearrangement. Tissue biopsy remains indispensable for patients who acquire resistance to ROS1 TKIs.

KEYWORDS

adenocarcinoma, ROS1 rearrangement, small cell transformation

INTRODUCTION

ROS1 rearrangement, which was first identified in glioblastoma multiforme, is a rare driver oncogene occurring in approximately 1%–2% of the patients with advanced non-small cell lung cancer (NSCLC).¹ Although crizotinib is an effective first-line therapy for ROS1-rearranged NSCLC,² disease progression is inevitable and only about half of the patients acquire kinase domain mutations, which may be targetable by next-generation ROS1 tyrosine kinase inhibitors (TKIs).³ Data regarding resistance mechanisms in the remaining patients are limited. Small cell transformation

has been identified as an important resistance mechanism in 3%–10% of patients with epidermal growth factor receptor (EGFR)-mutant or anaplastic lymphoma kinase (ALK)-rearranged NSCLC after receiving EGFR- TKIs or ALK-TKIs.^{4–7} It is associated with poor prognosis due to its aggressiveness and poor response to systemic chemotherapy. However, reports regarding small cell transformation as a resistance mechanism in ROS1-rearranged NSCLC patients and genomic alterations after histological transformation remain limited.

Here, we describe a case of ROS1-rearranged NSCLC in which small cell transformation occurred after 8 months of treatment with crizotinib but ROS1 rearrangement was retained.

Chi-Hao Wu and Po-Lan Su contributed equally

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CASE REPORT

A 63-year-old man presented at our department with a history of intermittent chest pain. A computed tomography (CT) scan of the chest revealed a left lower lobe lung tumor with mediastinal lymphadenopathy (Figure 1a). CT-guided biopsy was performed, and poorly differentiated adenocarcinoma was diagnosed (Figure 1b). Immunohistochemical (IHC) staining of ROS1 (clone D4D6, Cell Signaling Technology) showed equivocal results (H score: 200) (Figure 1c). ROS1 rearrangement was confirmed by fluorescence in situ hybridization (FISH) using Vysis ROS1 Break Apart FISH Probe Kit (Abbott) (Figure 1d). Our multidisciplinary team concluded that the patient had cT2aN2M0, clinical stage IIIA NSCLC. Therefore, video-assisted thoracoscopic surgery (VATS) with left lower lung lobectomy was performed. The pathological stage was the same as the clinical stage (pT2aN2M0, pathological stage IIIA). Adjuvant chemotherapy followed by radiotherapy was also administered. However, an enlarged lymph node developed 13 months after surgery, and rebiopsy through endobronchial ultrasound-guided transbronchial lymph

node aspiration still revealed adenocarcinoma. The IHC stain of synaptophysin and chromogranin were both negative (Figure S1). The patient received multiple lines of chemotherapy, including cisplatin combined with pemetrexed; paclitaxel; and gemcitabine. The total treatment course was 28 months.

Unfortunately, disease progressed further (Figure 2a), and crizotinib was administered when the reimbursement of crizotinib as a first-line therapy was approved by Taiwan's National Health Insurance system. The best response of the primary tumor was only stable disease (Figure 2b), and disease progression with tracheal invasion developed after 8 months of treatment with crizotinib (Figure 3a). Cryobiopsy revealed poorly differentiated carcinoma with small cell transformation (Figure 3b). The IHC stain was positive for synaptophysin, but negative for chromogranin and RB1 (Figure S2). Although the IHC staining for ROS1 was negative (H score: 0) (Figure 3c), the FISH test for ROS1 rearrangement was still positive (Figure 3d). Further next generation sequencing revealed PIK3CA mutation, and no kinase domain mutation on ROS1 was found (Figure S3). Despite

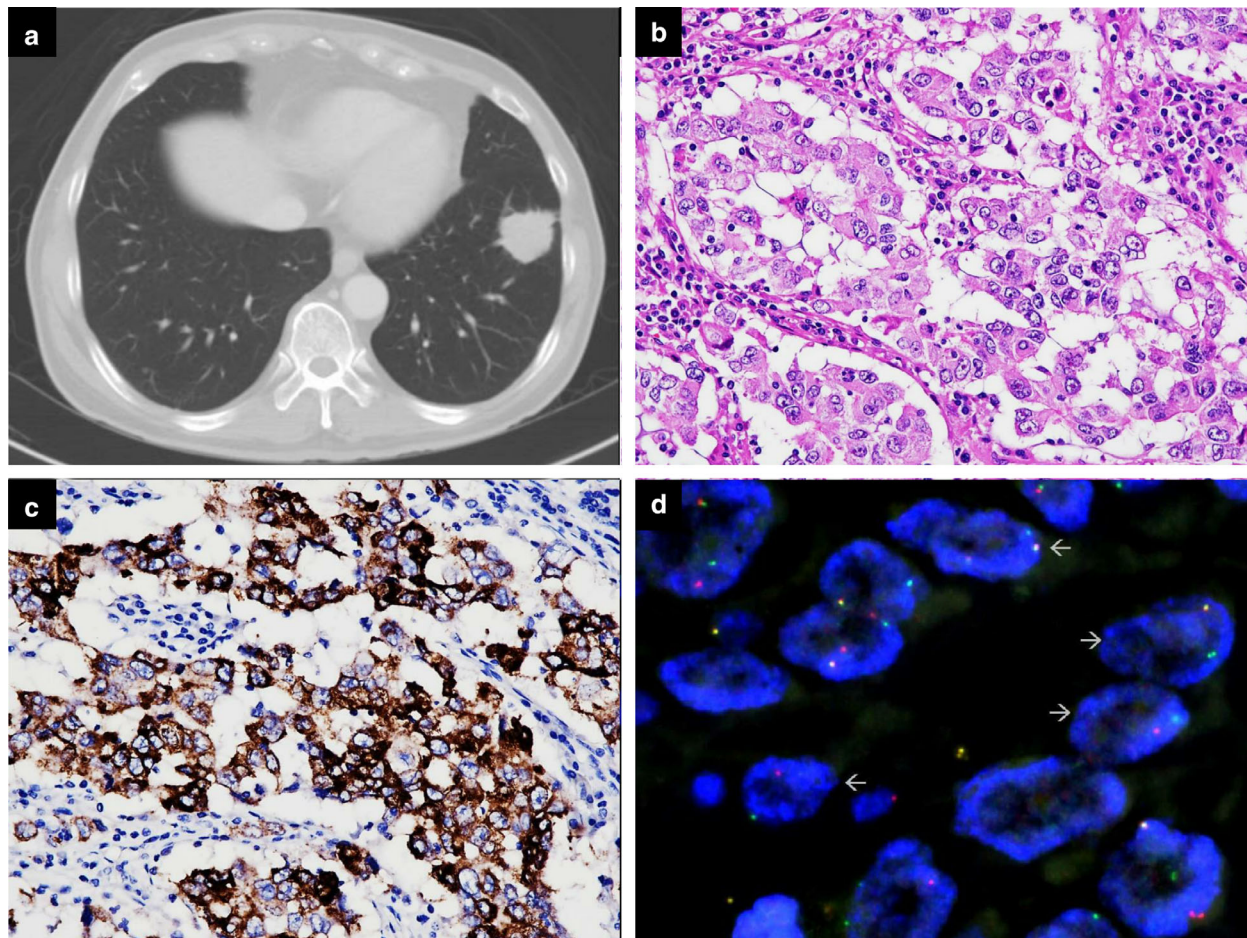


FIGURE 1 A computed tomography (CT) image of the patient's chest revealed a tumor at the left lower lobe (a). Biopsied tissue stained with hematoxylin and eosin revealed adenocarcinoma (b). Both the immunohistochemical (IHC) stain (c) and fluorescence in situ hybridization (FISH) test (d) were positive for ROS1

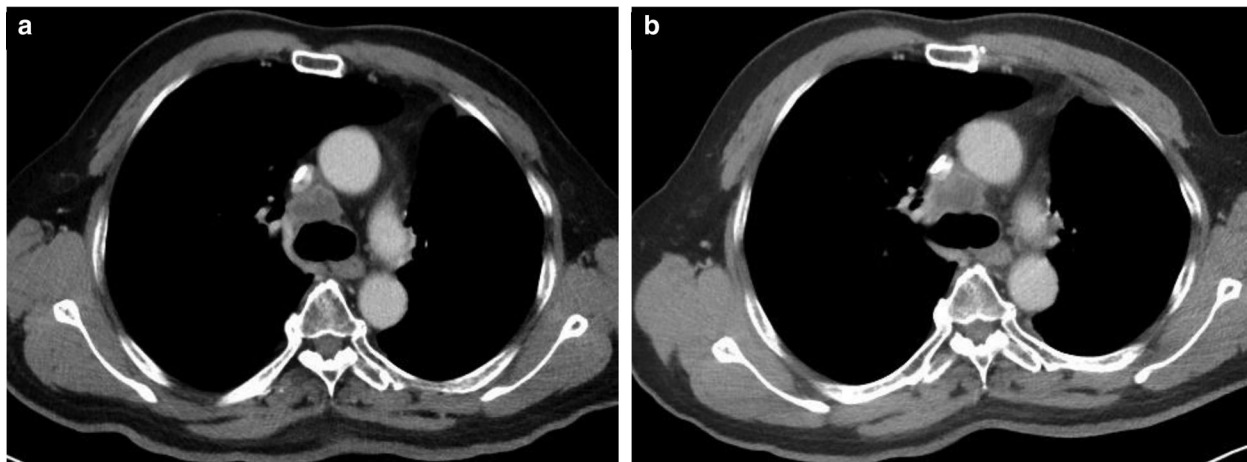


FIGURE 2 A computed tomography (CT) image of the patient's chest revealed mediastinal lymphadenopathy at baseline before (a) and 3 months after (b) the use of crizotinib

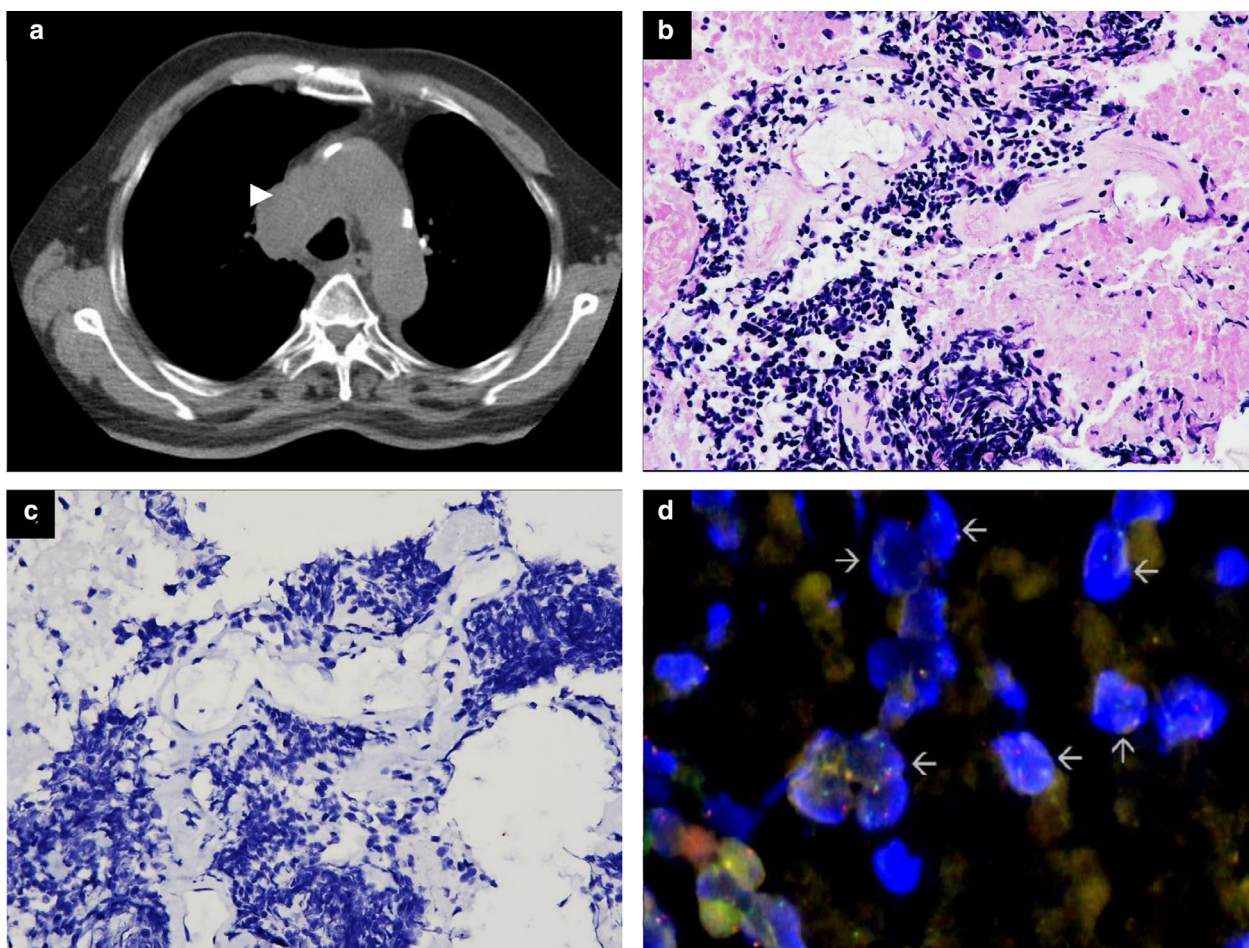


FIGURE 3 A computed tomography (CT) image of the patient's chest revealed an enlarged mediastinal lymph node with tracheal compression (a). Biopsied tissue stained with hematoxylin and eosin revealed small cell transformation (b). Immunohistochemical (IHC) stain was negative for ROS1 (c), but the fluorescence in situ hybridization (FISH) test was positive (d)

undergoing further chemotherapy with cisplatin and etoposide, the patient did not respond to the treatment. A massive pericardial effusion with cardiac tamponade

developed, and the patient died due to progressive respiratory failure. The total disease course was approximately 60 months.

DISCUSSION

Small cell transformation has been widely reported as a mechanism of resistance in patients with *EGFR*-mutant or *ALK*-rearranged NSCLC.^{4–7} However, the frequency of small cell transformation has been reported to be very low after acquired resistance to crizotinib or lorlatinib in patients with ROS1 positive NSCLC.⁸ Recently, the autopsy of a patient with ROS1-rearranged NSCLC who failed to respond to all available ROS1 inhibitors and chemotherapy confirmed the development of small cell transformation in post-mortem pathological assessment at all metastatic sites.⁸ The genomic test of the patient highlighted the importance of genomic change; except for the inactivation of TP53 and RB1, which have been reported as markers for small cell transformation,⁸ ROS1 fusion was retained throughout the evolutionary trajectory of the tumor as confirmed by FISH. However, its expression was lost at the RNA and protein levels in the transformed tumors at autopsy. Our case showed similar results, in which the best response to crizotinib was only stable disease. Although the FISH test showed the presence of ROS1 rearrangement, IHC staining of ROS1 was negative (H score: 0). These findings suggest that TKI-resistant small cell transformation and the preceding adenocarcinoma share a common clonal origin, and loss of ROS1 protein expression may implicate the diminished activity of the promoter gene of ROS1 rearrangement and poor response to ROS1 TKIs. A previous study on *EGFR*-mutant NSCLC also revealed the loss of *EGFR* expression in patients with small cell transformation after the use of *EGFR*-TKI,⁹ which implies diminished activity of original oncogenic signaling. These findings suggest small cell transformation may have occurred in patients harboring ROS1 rearrangement who suffer from disease progression after the use of ROS1 TKIs, and the genomic test of progressive tumors may still reveal ROS1 rearrangement. Currently, the guidelines regarding the need of rebiopsy after acquired resistance to crizotinib remains controversial.^{10,11} Given the limitation of liquid biopsies in capturing tumor histology changes,^{12,13} repeated tissue biopsies should be considered if it is feasible, following disease progression with ROS1 inhibitors.

Here, we report the case of a patient with ROS1-rearranged NSCLC who developed small cell transformation but retained ROS1 rearrangement. Tissue biopsy remains indispensable for patients who acquire resistance to ROS1 TKIs.

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The patient involved in this case report gave his informed consent authorizing use and disclosure of his health information.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

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