




Multiple cerebral infarctions in *ROS1*-rearranged lung adenocarcinoma

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Abstract

Rearrangements of specific tyrosine kinases are associated with an elevated risk of venous thrombosis in lung adenocarcinoma, although their effects on arterial thrombosis have not been fully elucidated. Here, we report two cases of ROS proto-oncogene 1 (*ROS1*)-rearranged lung adenocarcinoma with cerebral infarction during the peri-diagnostic period. Two cases took contrasting clinical courses: one patient could not receive targeted therapy because of a significant decline in performance status, whereas in the other patient, the performance status was maintained and targeted therapy drastically reduced the tumour size. Our cases suggest close monitoring could be considered in the selected cohort.

KEYWORDS

adenocarcinoma, arterial thrombosis, cerebral infarction, lung cancer, *ROS1*

INTRODUCTION

Thrombosis is a common complication experienced by lung cancer patients.¹ Recent advances in research such as development of tyrosine kinase inhibitors (TKIs) have markedly improved the prognosis of lung adenocarcinoma harbouring specific gene mutations, but rearrangements of specific tyrosine kinases such as ROS proto-oncogene 1 (*ROS1*) or anaplastic lymphoma kinase (*ALK*) are associated with increased risk of venous thrombosis.² However, the relationship between such gene arrangements and arterial thrombosis has not been fully elucidated. We report two cases of patients with *ROS1*-rearranged lung adenocarcinoma who developed cerebral infarction shortly after the diagnosis of lung cancer.

CASE REPORT

Case 1

A 40-year-old female ex-light smoker with a family history of lung cancer was referred to our hospital for an enlarged

left supraclavicular lymph node and low back pain. Vital signs were unremarkable. Contrast-enhanced computed tomography (CT) revealed a 65-mm mass on the left lower lobe of her lung and an enlarged left supraclavicular lymph node (Figure 1A). Tumours were also observed in her liver, right adrenal gland, body of the second lumbar vertebra and right ilium (Figure 1B). Contrast-enhanced mass was detected in the right parietal lobe. There was no observation of venous thrombosis or pulmonary embolism. Laboratory investigation showed increased white blood cells count (WBC; 15,800/ μ l) and elevated levels of C-reactive protein (CRP; 8.56 mg/dl) and D-dimer (18.6 μ g/ml). We performed transbronchial needle aspiration for enlarged left lower paratracheal (#4L) and interlobar (#11L) lymph nodes, and the patient was diagnosed with lung adenocarcinoma, cT3N3M1c (brain, liver, adrenal gland and bone metastasis), cStage IVB.

One day after bronchoscopy, the patient developed neurological symptoms. Her Glasgow Coma Scale was 10/15 (E2V3M5). She had conduction aphasia, paraphasia, left hemispatial neglect and dysarthria. Cerebral spinal fluid did not contain inflammatory cells or tumour cells. Brain

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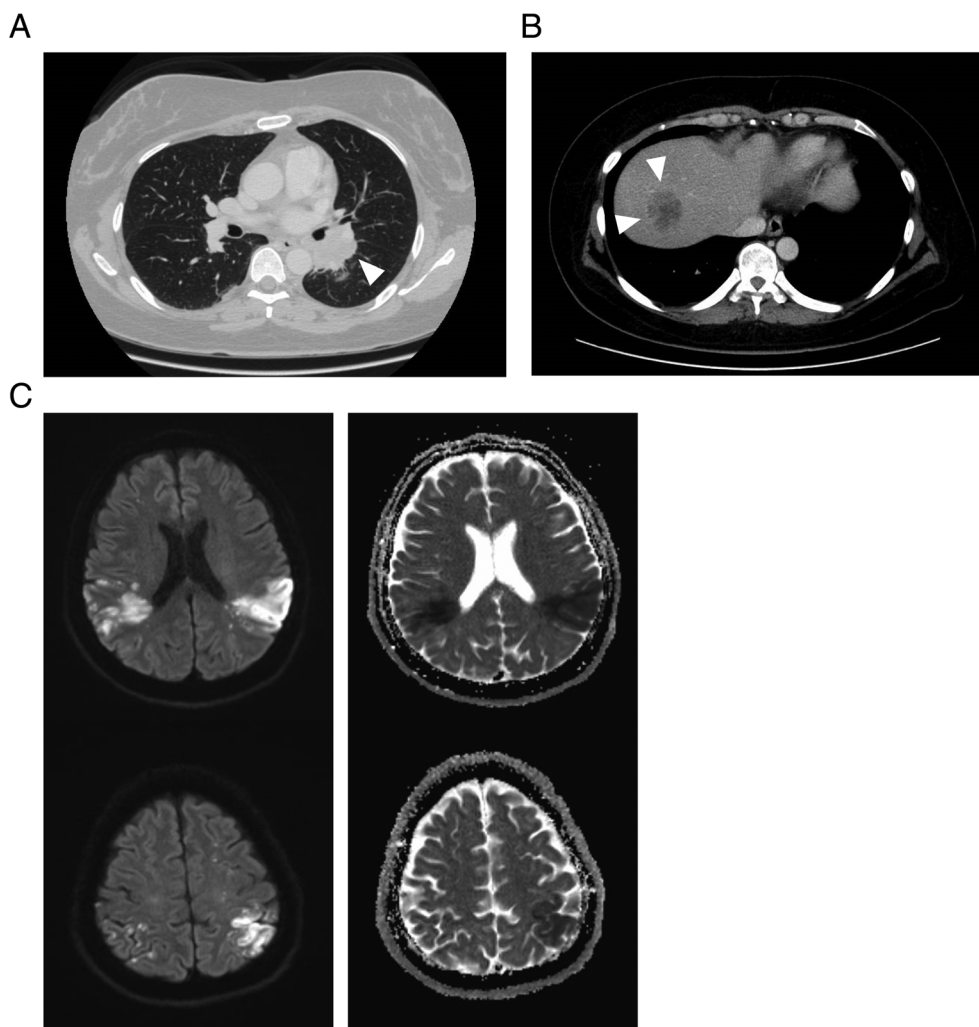


FIGURE 1 Clinical course of Case 1. A computed tomography scan at the time of diagnosis revealed a mass on the left lower lobe of the lung (A, arrow head) and liver metastasis (B, arrow heads). One day after bronchoscopy, brain magnetic resonance imaging revealed an increase in diffusion-weighted signal intensity (C, left) and decrease in apparent diffusion coefficient level (C, right) in the bilateral parietal and temporal lobes

magnetic resonance imaging (MRI) revealed an increase in diffusion-weighted signal intensity and a decrease in apparent diffusion coefficient level in the bilateral parietal and temporal lobes, which indicated acute cerebral infarction (Figure 1C). Heparin was initiated, and despite the absence of additional neurological symptoms, performance status was not improved (Eastern Cooperative Oncology Group performance status 4). Thirty-two days after the first referral to our hospital, the patient died of respiratory failure. We received results of next-generation sequencing analysis (the Mutation Investigator using Next-era Sequencer: MINtS)³ of her tumour after she died, which revealed rearrangement of the *ROS1* gene (fusion with *SDC4* gene) in the tumour cells.

Case 2

A 50-year-old male ex-light smoker with no significant medical history was referred to our hospital because of an

abnormal chest x-ray image acquired during his annual health check-up. His vital signs were unremarkable, and a physical examination revealed left leg oedema. Contrast-enhanced CT demonstrated a right hilar mass surrounded by infiltrates and atelectasis in the right middle and lower lobes (Figure 2A). We also observed enlargement of bilateral hilar, mediastinal and para-aortic lymph nodes. Furthermore, we detected left deep venous thrombosis (DVT; Figure 2B). No brain metastasis was observed. Laboratory investigation indicated increased WBC (9300/ μ l) and elevated levels of CRP (5.78 mg/dl), D-dimer (44.7 μ g/ml) and carcinoembryonic antigen (80.9 ng/ml). The patient received apixaban for DVT. We performed transbronchial biopsy of the tumour in the right middle lobar bronchus, and the patient was diagnosed with lung adenocarcinoma, cT4N3M1c (contralateral lung and lymph node metastasis), cStage IVB. Amoy real-time polymerase chain reaction analysis revealed rearrangement of the *ROS1* gene in the tumour cells. Based on that result, we initiated

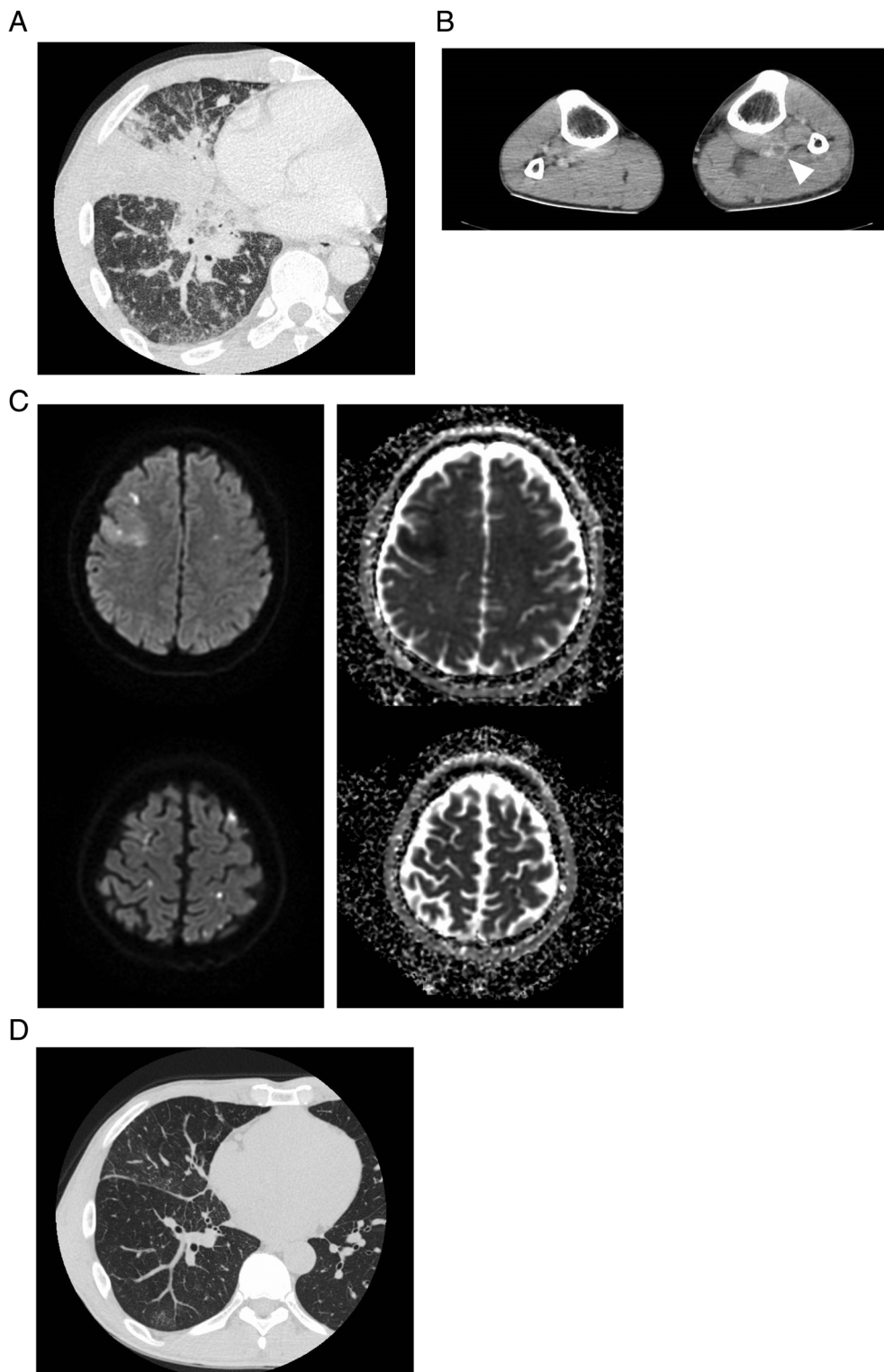


FIGURE 2 Clinical course of Case 2. A computed tomography (CT) scan at the time of diagnosis showed a right hilar mass surrounded by infiltrates and atelectasis in the right middle and lower lobes (A). Deep venous thrombosis occurred in the left leg (B, arrow head). Brain magnetic resonance imaging on Day 3 of crizotinib revealed an increase in diffusion-weighted signal intensity (C, left) and decrease in apparent diffusion coefficient level (C, right) in the right frontal lobe. A CT scan on Day 27 of crizotinib showed a significant decrease in tumour size (D)

administration of crizotinib (500 mg/day) as the first-line therapy. After crizotinib initiation, the D-dimer level decreased to 17.5 µg/ml.

Two days after starting crizotinib treatment, the patient experienced drooling from the left side of his mouth. Brain MRI revealed increased diffusion-weighted signal intensity

and decreased apparent diffusion coefficient level in multiple sites, including the right frontal lobe, indicating acute cerebral infarction (Figure 2C). Echocardiography did not show any cardiac shunt and his electrocardiogram showed normal sinus rhythm. Based on the diagnosis of cerebral thrombosis, we started heparin administration in place of apixaban. Additional neurological symptoms did not occur, and he continued to receive crizotinib treatment, which resulted in drastic effects on the tumour (Figure 2D).

DISCUSSION

We report two cases of patients with *ROS1*-rearranged lung adenocarcinoma who developed arterial thrombosis shortly after the diagnosis of lung cancer. Both of these two patients had smoking history. In Case 1, multiple cerebral infarctions resulted in significant decline of her performance status, preventing chemotherapy. In Case 2, apparent neurological symptoms were limited to facial nerve paralysis, and heparin suppressed cerebral infarction progression and maintained performance status. The patient could receive targeted therapy, which led to a significant reduction in tumour size.

Thrombotic complications as represented by Trousseau's syndrome are the second leading cause of death in cancer patients.⁴ Lung cancer has one of the highest incidence of thromboembolic events (~15%), occurring throughout the disease course.¹ Some studies suggested that patients with some genomic subtypes of lung cancer might be at increased risk of developing thromboembolic events, particularly those with rearrangements of *ROS1* or *ALK*.^{2,5} Those studies reported that 30%–50% of patients with *ROS1*-rearranged lung cancer experienced venous thrombosis throughout the disease course. Recent meta-analysis⁶ revealed that the total (arterial and venous) thromboembolism incidence rate was 32.1 (95% CI: 24.6–39.6) per 100 patient-years for *ROS1*-rearranged lung cancer, which was greater than that for *ALK*-rearranged lung cancer (17.4, 95% CI: 15.3–19.5). Although the relationship between such gene arrangements and arterial thrombosis has not been fully elucidated, one study reported that *ROS1*-rearranged lung cancer had a significantly increased odds ratio (2.12, 95% CI: 1.09–4.14) for arterial thromboembolism compared to *EGFR*-mutated and *KRAS*-mutated non-small cell lung cancer.^{2,6} Of note, patients with driver mutation-negative lung cancer were not included in this study.

Considering the prolonged median overall survival of patients suitable for targeted therapies, it may not be surprising that these patients experience arterial or venous thrombotic events during the course of the disease. However, our two patients developed arterial thrombosis during the peri-diagnostic period, which could suggest an inherent procoagulant status underlying *ROS1* rearrangement. Some reports have suggested that *ROS1* rearrangement is associated with higher expression of extracellular mucin,⁵ which could activate aggregation of platelets and increase the risk

of thrombosis, although further analysis is required to uncover the underlying mechanisms.

Because of the high control rates and durable responses achieved with targeted therapy (e.g., TKIs), maintenance of performance status and therapy continuation are key to prolonging the survival of patients with *ROS1*-rearranged lung cancer. Arterial thrombosis is relatively rare in *ROS1*-rearranged lung cancer but can lead to a drastic decline in patients' performance status, affecting their prognosis and ability to receive targeted therapy, as typified by our contrasting two cases.

The role of primary thromboprophylaxis has been investigated in solid tumours. The AVERT study included lung carcinoma⁷ and demonstrated a significant reduction in the incidence of venous thromboembolic events in patients treated with apixaban, but the incidence of major bleeding increased. However, the effect of anticoagulants on arterial thromboembolic events has not been fully investigated. Although he took apixaban, Case 2 developed cerebral infarction. Furthermore, apixaban did not improve overall survival in unselected patients in the AVERT study. Findings of previous studies on *ROS1*-rearranged lung carcinoma and in our cases suggest that close monitoring and increased awareness by the treating physicians and patients could be considered in selected cohorts.

We reported two cases with *ROS1*-rearranged lung adenocarcinoma who developed cerebral infarction during the peri-diagnostic period. Neurological symptoms may significantly change the patients' performance status, which can affect the continuation of effective targeted therapy. Although further studies will be required to clarify prophylactic strategies for arterial or venous thrombosis in patients with *ROS1*-rearranged lung carcinoma, our cases indicate the importance of careful follow-up for neurological symptoms.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

Hiroaki Ikushima and Yoshihisa Hiraishi prepared the data and drafted the manuscript. Kanto Toriumi and Takahiro Ando supported data collection. Hiroyuki Tamiya, Junichi Ishida, Yosuke Amano, Hidenori Kage, Goh Tanaka and Takahide Nagase revised and edited the manuscript. All authors read and approved the final manuscript.

ETHICS STATEMENT

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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