CASE REPORT

Lorlatinib-Induced Pulmonary Embolism in a Patient With an *ALK*-Positive NSCLC

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The patient was a 41-year-old male ex-smoker diagnosed with advanced adenocarcinoma with malignant pleural effusion. In addition, fluorescence in situ hybridization of the cell block derived from the pleural effusion revealed anaplastic lymphoma kinase (*ALK*) gene rearrangement. Brigatinib and platinum-based pemetrexed were sequentially administered approximately 45 months after the first-line treatment with alectinib (600 mg/d); however, lymphangitis carcinomatosa and multiple asymptomatic brain metastases were found (Fig. 1*A*). Therefore, lorlatinib (100 mg/d) was administered, and a partial response was observed approximately 2 months after the initiation of lorlatinib (Fig. 1*B*).

One month after the initiation of lorlatinib, hypertriglyceridemia (grade 1: 255 mg/dL) was observed; consequently, bezafibrate 400 mg/day was administered. Nevertheless, 2 months later, hypercholesterolemia (grade 2: 353 mg/dL) was observed. In addition, the hypertriglyceridemia gradually worsened (grade 3: 656 mg/dL). Bezafibrate 400 mg/day, rosuvastatin 10 mg/day, and ezetimibe 10 mg/day were eventually needed. At that time, his performance status was zero, and he often played football (body mass index 24.5). One month after the administration of these three medications, he was admitted in the hospital for complaints of dyspnea with mild hypoxemia (SpO_2: 93%). Computed tomography revealed multiple thrombi in the pulmonary artery (Fig. 2). He was hospitalized on the same day, and lorlatinib was stopped. Although deep vein thrombosis was not observed in the legs, echocardiography revealed pulmonary hypertension, and heparin infusion was started. The hypoxemia and pulmonary hypertension were gradually improved, and his anticoagulation therapy was changed from heparin to an oral administration of rivaroxaban one week after the hospitalization. On the 28th day of hospitalization,

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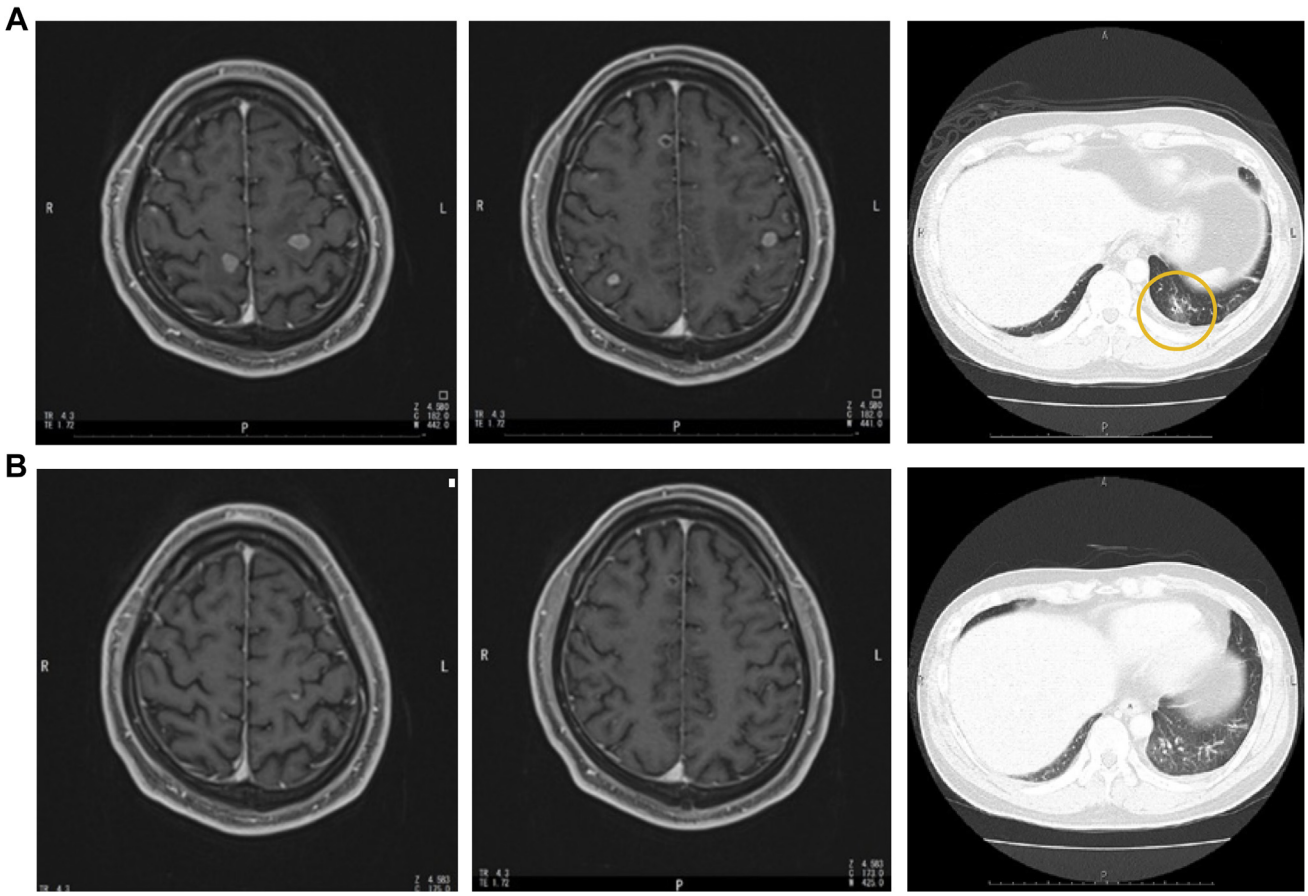

Figure 1. Multiple brain metastases and lymphangitis carcinomatosa in the left lower lobe. (*A*) Before the treatment with lorlatinib; (*B*) 2 months after the initiation of lorlatinib.

lorlatinib was restarted. One month later, computed tomography revealed that multiple thrombi in the pulmonary artery had improved considerably. Nevertheless, he died after 2 months owing to the disease progression.

Lorlatinib is a potent third–generation ALK tyrosine kinase inhibitor with sensitivity to most known secondary *ALK* resistance mutations. The adverse effects of lorlatinib were reported to be generally mild to moderate in severity.[1] Dyslipidemia such as hypercholesterolemia and hypertriglyceridemia was the most common adverse side effect associated with lorlatinib. This is thought to be manageable with lipid-lowering medical therapy and dose modifications. Nevertheless, the risk of dyslipidemia induced by lorlatinib is almost unknown. To our knowledge, this is the first case that suggests that pulmonary embolism with dyslipidemia may develop during a treatment using lorlatinib.

The relationship between dyslipidemia and the risk of venous thromboembolism is not well established. Nevertheless, some meta-analysis revealed a significant association between venous thromboembolism and the risk factors for atherosclerosis, such as hypercholesterolemia and hypertriglyceridemia.[2,3] In addition, it was reported that lipid-lowering medical treatment is protective against venous thromboembolism.[3,4] The clear mechanism of lipid-lowering medical treatment for such a protective effect is through improving lipid profiles, and another possibility is that such treatment may directly affect endothelial function and coagulation.[5]

Although the patient had no risk factors of venous thromboembolism, such as obesity and immobility, except for lung cancer and dyslipidemia, pulmonary embolism had developed. Strict control of lipid level might be an invaluable way to prevent venous thromboembolism during treatment with lorlatinib.

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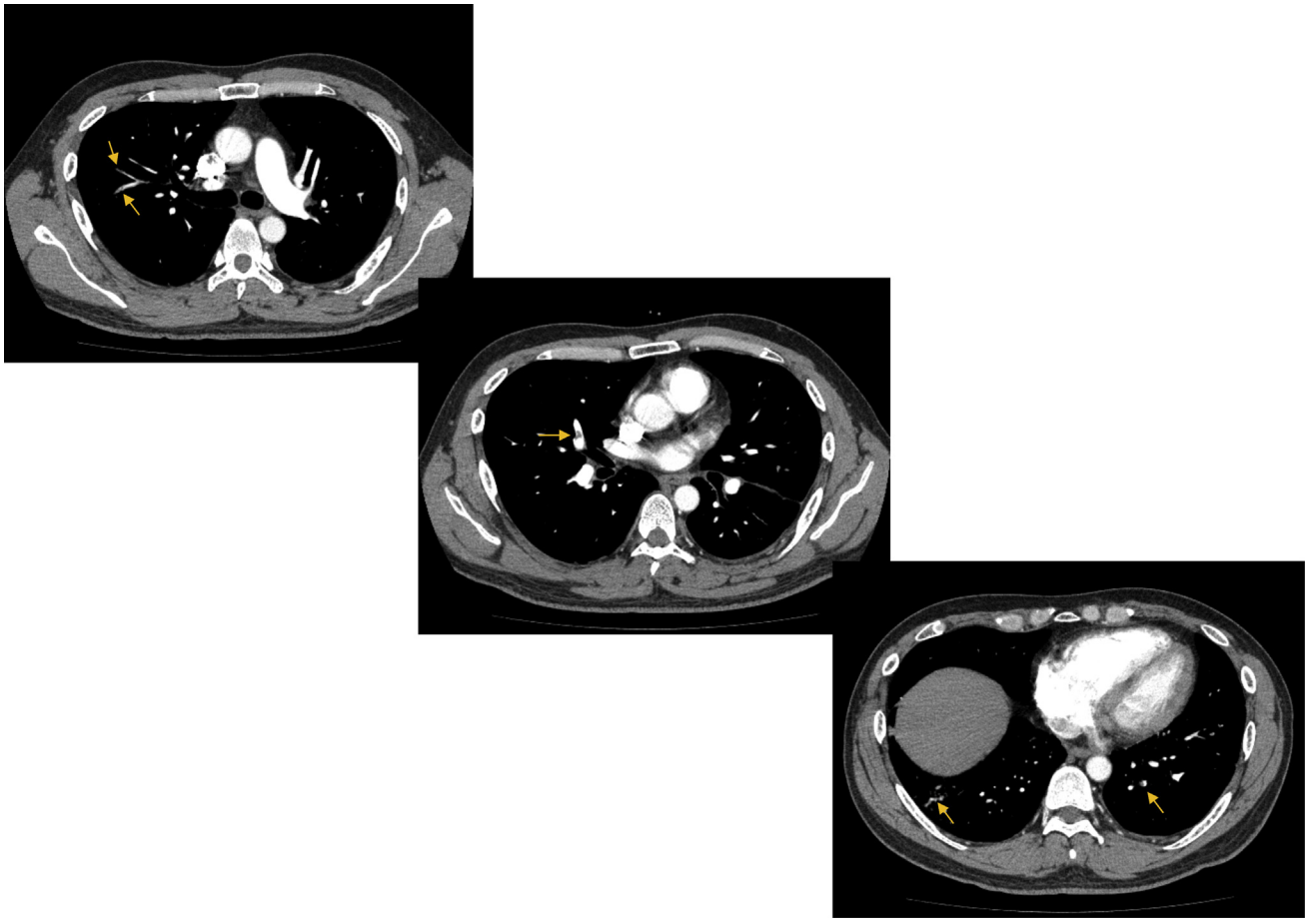

Figure 2. Multiple thrombi in the pulmonary artery (yellow arrows).

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