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【 CASE REPORT 】

Dramatic Response to Alectinib in a Critically Ill Elderly Patient with Lung Adenocarcinoma Due to Trousseau Syndrome and Disseminated Intravascular Coagulation

Noboru Hamada, Yusaku Tada, Kazuya Hisamatsu,
Yukichika Yamamoto and Takafumi Yamano

Abstract:
Lung cancer complicated with Trousseau syndrome (TS) or disseminated intravascular coagulation (DIC) has a severe prognosis. We herein report an elderly lung cancer patient who presented with a critically ill condition due to concomitant TS and DIC and responded dramatically to alectinib. There are no rules regarding treatment indications based on the age or severity of critically ill patients. If the patient's cancer cells are positive for anaplastic lymphoma kinase rearrangement, alectinib is worthwhile to administer, even in a critically ill condition. In our patient, anticoagulation failed to suppress the TS complications. We also report how to prevent the recurrence of TS.

Key words: alectinib, performance status 4, Trousseau syndrome, disseminated intravascular coagulation

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Introduction

The treatment of non-small-cell lung cancer has recently made remarkable progress with the advent of immune checkpoint inhibitors and molecular-targeted drugs. The administration of molecular-targeted drugs is also weakly recommended even in cases with a performance status (PS) of 3-4 if the driver mutation is positive, according to the Japanese domestic guideline for lung cancer (1). However, little progress has been made in the treatment of elderly or extremely poor PS patients. No rules have been established regarding treatment indications based on the age or severity of PS 4 patients. Therefore, for extremely poor PS or elderly lung cancer patients, best supportive care is still recommended without conventional systemic chemotherapy.

Thromboembolism complicated by malignant tumors is known as Trousseau syndrome (TS) and was first reported by Trousseau in 1865 (2). It is generally recognized as a fatal condition with a poor prognosis (3). However, its pathogenesis and prevention are not well understood.

We herein report an elderly lung cancer patient who responded dramatically to alectinib, an anaplastic lymphoma kinase (ALK) inhibitor, despite having a poor PS 4 due to TS and cancer cachexia sufficient to cause disseminated intravascular coagulation (DIC). We discuss the treatment indication for elderly and poor PS lung cancer patients and the prevention of recurrence of TS.

Case Report

An 84-year-old woman was transferred to the emergency department of our hospital due to gait disturbance and impaired consciousness. The patient had been treated for rheumatoid arthritis and received edoxaban 30 mg/day as an anticoagulant for venous thrombosis associated with varicose veins of the lower extremities.

Six months ago, bronchoscopy was performed for infiltrative shadow of the left upper lung field to exclude lung cancer due to elevated tumor markers and accumulation on positron emission tomography in the infiltrative shadow. However, no malignant cells were detected. A physical examination at admission revealed right hemiplegia and expressive aphasia. Head magnetic resonance imaging (MRI)

Department of Respiratory Medicine, Okayama City Hospital, Japan
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Correspondence to Dr. Noboru Hamada, nobohamada@yahoo.co.jp

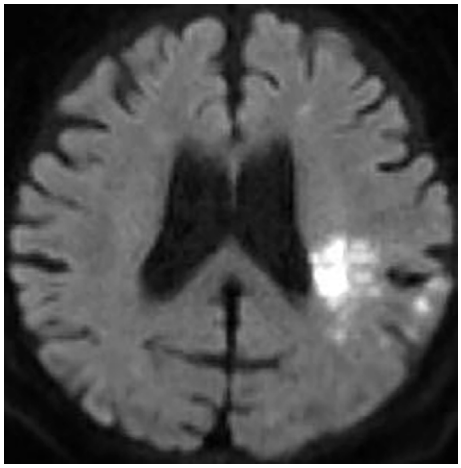

Figure 1. **Head magnetic resonance imaging showing the acute cerebral infarction inside the left temporal lobe and numerous small infarctions in the bilateral cerebral hemisphere cortex.**

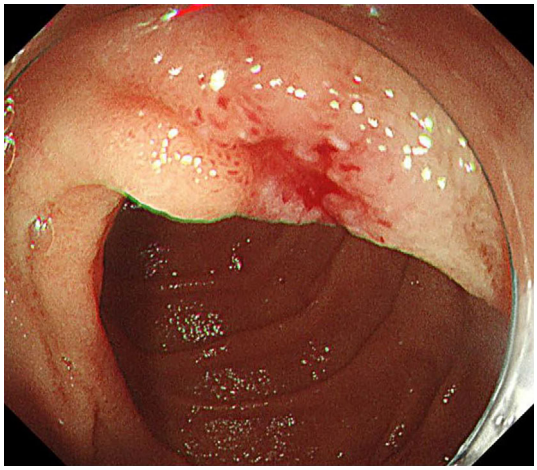

Figure 2. **Upper endoscopy showing a small bulge lesion with a slight depression in the center of the anterior wall of the duodenum.**

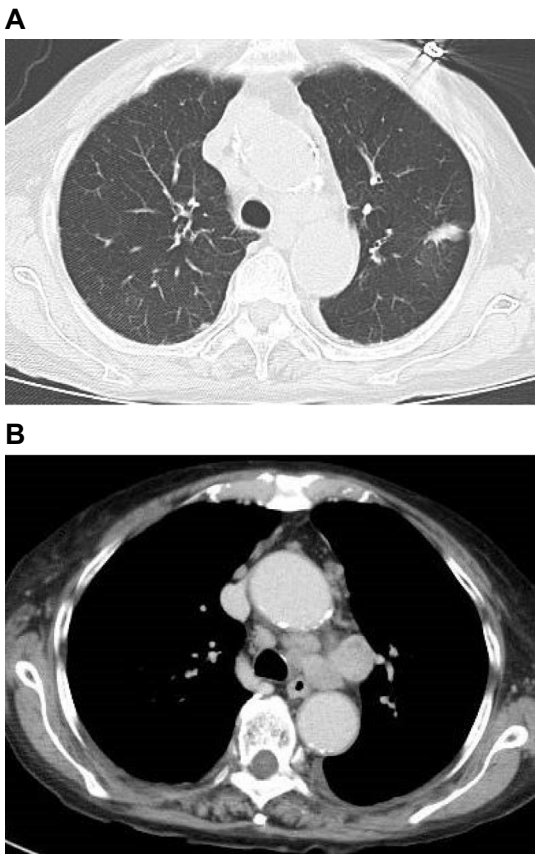

Figure 3. **(A) Chest computed tomography showing the enlarged tumor in the upper left lung field. (B) Chest computed tomography also showing the swelling of many supraclavicular, mediastinal, and intraperitoneal lymph nodes.**

showed an acute cerebral infarction inside the left temporal lobe and numerous small infarctions in the bilateral cerebral hemisphere cortex and bilateral cerebellar hemispheres, mainly indicating occlusion of the left middle cerebral artery region (Fig. 1). The neurosurgeon did not perform thrombectomy because more than 12 hours had passed since the onset of symptoms. The neurosurgeon gave the patient rivaroxaban 10 mg/day orally and edaravone 30 mg ×2/day by injection.

On the 10th hospital day, tarry stool and anemia suddenly occurred. Emergent upper endoscopy revealed a small bulging lesion with a slight depression in the center of the anterior wall of the duodenum (Fig. 2), and bleeding from the same area was noted. The endoscopist performed endoscopic clipping immediately and succeeded in stopping the bleeding. Later, poorly differentiated adenocarcinoma was detected by a tissue biopsy from the edge of a small, raised lesion. A blood transfusion temporarily stopped the progression of anemia, but thrombocytopenia progressed further. According to the laboratory data at that time, the platelet count was 2.5×10^4/μL (normal range, 13-35×10^4/μL), the international standardization ratio of prothrombin time was 1.85 (normal range, 0.9-1.13 international normalized ratio), the fibrinogen level was 81 mg/dL (normal range, 150-340 mg/dL), fibrinogen degradation product level was 187.8 μg/mL (normal range, 0-8 μg/mL). The patient's DIC score reached 10 points (Japanese Society on Thrombosis and Hemostasis Criteria, 2017). We consulted with the Department of Hematology, and the patient was diagnosed with DIC.

Computed tomography (CT) from the neck to the pelvis was performed to search for the malignant disease that had caused the DIC, and an enlarged mass was found in the upper left lung field (Fig. 3A) along with many supraclavicular, mediastinal, and intraperitoneal lymph nodes (Fig. 3B). A biopsy of the supraclavicular lymph nodes was performed for a diagnosis. Adenocarcinoma was detected in addition to the histological findings from the duodenal lesion. Primary lung adenocarcinoma (cT1cN3M1c stage IVB) was considered based on the thyroid transcription factor-1-positive and p63-positive findings on immunostaining. Therefore, the cerebral infarction on admission was diagnosed as cerebral infarction associated with lung cancer - namely TS.

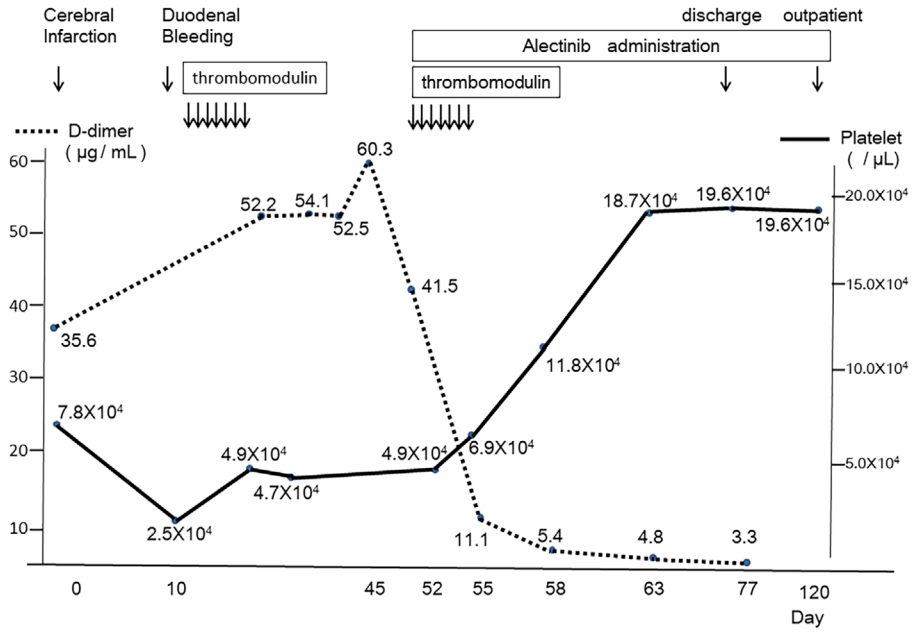

Figure 4. Changes in laboratory test results, including the platelet count and D-dimer level. There were no significant differences in platelet counts or D-dimer levels after the thrombomodulin injection. However, there was a decrease in the D-dimer level and an increase in the platelet count after the alectinib administration.

A search for gene mutations in the tumor cells revealed that ALK gene rearrangement was positive by high-sensitivity immunohistochemical staining. The patient's condition was determined to be PS 4 due to TS and cancer cachexia sufficient to cause DIC, indicating a critically ill condition for the treatment.

After fully explaining the side effects of alectinib to the patient and her family, she agreed to begin treatment with alectinib. Her platelet counts began to increase on the 5th day after starting treatment, and on the 28th day, the other laboratory test findings for the congealing fibrinogenolysis systems returned to the normal range, and the DIC state was relieved (Fig. 4). No serious side effects were observed. Follow-up CT showed the shrinkage of the primary lung tumor and systemic lymph nodes. Upper endoscopy showed scarring of the duodenal lesions.

Thereafter, administration of direct oral anticoagulants (DOACs) was resumed to prevent the venous thrombosis associated with varicose veins of the lower extremities. Since head MRI showed no recurrence of cerebral infarction, we plan to change the drug to a subcutaneous heparin injection or the combined administration of an anticoagulant and an antiplatelet drug to prevent recurrence of TS if the tumor progresses in the future.

The patient was discharged two months after the start of treatment. She has now recovered to PS 2 because of her recovery from cancer cachexia with alectinib and improvement of her motor paralysis with rehabilitation. She is now able to live at home with little help and continues oral therapy with alectinib as an outpatient.

Discussion

We identified two clinical issues. First, to our knowledge, our case is the first to show a dramatic response to alectinib in an elderly patient with ALK gene rearrangement-positive lung adenocarcinoma despite a poor PS 4 due to TS and cancer cachexia sufficient to cause DIC. Second, a DOAC is insufficient for the prevention of TS, which is cancer-related arterial thromboembolism, although the combination of an anticoagulant and an antiplatelet drug may be effective. The Japanese domestic lung cancer practice guidelines weakly recommend the use of ALK inhibitors if the ALK gene rearrangement is positive, even in cases with PS 3-4 (1). However, on checking the details of the references in the clinical practice guidelines. The number of patients with PS 2, 3, and 4 was 12, 5, and 1, respectively, and the details of the medical condition of the single PS 4 patient were not well-described in the reference report (4).

Only two cases of ALK-positive lung cancer patients with PS 4 complicated with only DIC in which an ALK inhibitor was markedly effective have been reported (5, 6). Although both patients had a poor PS, their ages were quite young at 29 and 43 years old, and they seemed to have a sufficient ability to recover from the illness. However, our patient was 84 years old, so her ability to recover from the illness was considered poor. Furthermore, our patient was in a more serious condition due to the combination of DIC and TS. According to a survey of 716 patients with lung cancer, thromboembolism was identified in 16 (2.2%) patients, and DIC was identified in 5 patients (0.7%), with 2 patients showing

both conditions concomitantly. The median survival time after the onset of DIC was 13 days (7). Systemic chemotherapy, especially a molecular-targeted drug, such as epidermal growth factor receptor tyrosine kinase inhibitors, which have few side effects, has been reported to contribute to the improvement of the survival rate (8). Our patient was positive for ALK gene rearrangement. To our knowledge, this is the first report of an elderly lung cancer patient who recovered from a critically ill condition due to DIC and TS with a dramatic response to alectinib.

In the present study, a DOAC was insufficient for preventing cancer-related arterial thromboembolism, such as TS. In our case, there was no recurrence of deep vein thrombosis in the lower extremities because the patient was taking an oral DOAC, but only TS developed. This is the second case report in our research of a DOAC failing to prevent arterial thromboembolism (9). The efficacy of DOACs for the treatment and prevention of cancer-related venous thromboembolism has been reported to be comparable to that of heparin (10). However, arterial thromboembolism in patients with cancer is caused by both the upregulation of coagulation and the activation of platelets (11, 12). DOACs alone are expected to be insufficient to suppress TS. Therefore, the standard treatment for TS is heparin (13). However, the present patient and her husband were too old to self-administer heparin at home. For this reason, the addition of antiplatelet drugs to anticoagulants may be effective in preventing the recurrence of TS in patients with lung cancer due to the mechanism of action of heparin on TS.

However, attention should be paid to the fact that the combination of both antiplatelet agents and anticoagulants may promote a local bleeding. There is still insufficient evidence supporting the use of both of these drugs. Further studies are needed to verify the validity of using both drugs.

Conclusion

We experienced an extremely rare case of a dramatic response with alectinib on ALK gene rearrangement positive lung adenocarcinoma with fairy severe PS 4 due to TS and cancer cachexia enough to cause DIC. Adding antiplatelet drugs to anticoagulants may prevent recurrence of TS. Fortunately, the treatment was successful in our case without major complications, but we would like to verify in the future that this treatment is safe and effective for patients with similar critically ill conditions.

The authors state that they have no Conflict of Interest (COI).

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References

1. Akamatsu H, Ninomiya K, Kenmotsu H, et al. The Japanese Lung Cancer Society Guideline for non-small cell lung cancer, stage IV. Int J Clin Oncol **24**: 731-770, 2019.
2. Trousseau A. Phlegmasia alba dolens. In: Clinique Medicale de l'Hotel-Dieu de Paris. 2nd ed. JB Bailliere, Paris, 1865: 654-712.
3. Lee AY, Levine MN. Venous thromboembolism and cancer: risks and outcomes. Circulation **107**: 117-121, 2003.
4. Iwama E, Goto Y, Murakami H, et al. Alectinib for patients with ALK rearrangement-positive non-small cell lung cancer and a poor performance status (Lung Oncology Group in Kyushu 1401). J Thorac Oncol **12**: 161-166, 2017.
5. Yoshida T, Hida T, Yatabe Y. Rapid and dramatic response to alectinib in an anaplastic lymphoma kinase rearranged non-small-cell lung cancer patient who is critically ill. Anticancer Drugs **27**: 573-575, 2016.
6. Toyokawa G, Takenoyama M, Watanabe S, et al. Dramatic response to crizotinib in an ALK-positive adenocarcinoma patient with disseminated intravascular coagulation. J Thorac Oncol **8**: 96-98, 2013.
7. Kanaji N, Mizoguchi H, Inoue T. Clinical features of patients with lung cancer accompanied by thromboembolism or disseminated intravascular coagulation. Ther Clin Risk Manag **14**: 1361-1368, 2018.
8. Inoue A, Kobayashi K, Usui K, Maemondo M, Okinaga S, Mikami I. First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. J Clin Oncol **27**: 1394-1400, 2009.
9. Nakao S, Masuda T, Sakamoto S, et al. Cerebral embolism during edoxaban administration for venous thromboembolism in a patient with lung adenocarcinoma. Medicine **98**: 1-3, 2019.
10. Vedvan MC, Germini F, Agnelli G, et al. Direct oral anticoagulants in patients with VTE and cancer: a systemic review and meta-analysis. Chest **147**: 475-483, 2015.
11. Varki A. Trousseau syndrome: multiple definitions and multiple mechanisms. Blood **110**: 1723-1729, 2007.
12. Gon Y, Sakaguchi M, Takasugi J, et al. Ischemic stroke in cancer patients treated with direct oral anticoagulants for venous thromboembolism. Thromb Res **154**: 16-18, 2017.
13. Lyman GH, Bohlke K, Khorana AA, et al.; American Society of Clinical Oncology. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. J Clin Oncol **33**: 654-656, 2015.