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Case report

Successful management of a lung cancer patient harbouring both *EGFR* mutation and *EML4-ALK* fusion gene with disseminated intravascular coagulation

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ABSTRACT

Lung cancer patients harbouring driver oncogene alterations are markedly responsive to molecular target agents, such as *epidermal growth factor receptor* (*EGFR*), tyrosine kinase inhibitor (TKI), and *echinoderm microtubule-associated protein like 4 – anaplastic lymphoma kinase* (*EML4-ALK*)-TKI. We encountered an exceptionally rare case, harbouring both *EGFR* mutation and *EML4-ALK* fusion gene, and suffering from severe disseminated intravascular coagulation. In this case report, we present two notable points. First, our patient was successfully treated with a third-generation *EGFR*-TKI, osimertinib. Second, osimertinib could manage severe conditions, such as disseminated intravascular coagulation. Third-generation *EGFR*-TKIs may be a viable option for patients harbouring both *EGFR* mutations and *EML4-ALK* fusion genes, even in severe conditions.

1. Introduction

Epidermal growth factor receptor (*EGFR*) mutation and *echinoderm microtubule-associated protein like 4 – anaplastic lymphoma kinase* (*EML4-ALK*) rearrangement are well-known oncogene alterations in non-small cell lung cancer (NSCLC). They are known to have a mutually exclusive relationship. However, in rare instances, NSCLC harbours both *EGFR* mutations and *EML4-ALK* rearrangements [1,2]. Recently, molecular targeted drug therapy has achieved great success in lung cancer treatment. Third-generation *EGFR* tyrosine kinase inhibitors (TKIs), such as osimertinib, are used as the standard treatment for NSCLC with sensitive *EGFR* mutation. On the other hand, second-generation *ALK*-TKIs, such as alectinib, is used for NSCLC with *EML4-ALK* rearrangement. Controversy still exists on which of these drugs should be used as the first-line therapy for NSCLC with both *EGFR* mutation and *EML4-ALK* rearrangement.

Here, we report a case of severe advanced lung adenocarcinoma harbouring *EGFR* mutation and *EML4-ALK* rearrangement who had disseminated intravascular coagulation (DIC) and was successfully managed using third-generation *EGFR*-TKIs.

2. Case presentation

A 42-year-old woman presented with general malaise and anorexia lasting for 3 months and was admitted in early October 2020. Initial evaluation suggested advanced right upper lung cancer with multiple brain and bone metastases (Fig. 1A–E). Clinical stage of her cancer was T1bN3M1b, stage 4B. Her haematological examination showed severe anaemia (haemoglobin: 6.8 g/dL) and thrombocytopenia (4.2×10^4/μL). The clotting factor assay showed elevation of fibrin degradation products (144.4 μg/mL) and D-dimer (33.5 μg/mL). The prothrombin time-international normalised ratio was 1.87. Levels of carcinoembryonic antigen and ferritin were 7763 ng/mL and 4061 ng/mL, respectively. These suggest DIC secondary to advanced lung cancer. She received transfusion of erythrocytes and platelets, and infusion of thrombomodulin alfa. Following bronchoscopy, empirical cytotoxic chemotherapy with carboplatin and nanoparticle albumin-bound paclitaxel was initiated before pathological diagnosis due to rapid disease progression. On the 8th day after admission, histopathology revealed lung adenocarcinoma. On the 10th day (mid-October), she was transferred to our hospital to receive multidisciplinary cancer therapy. She received a

Abbreviations: NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; DIC, disseminated intravascular coagulation.

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transfusion of erythrocytes and platelets twice. Furthermore, enhanced computed tomography images revealed an asymptomatic pulmonary thromboembolism. Therefore, we started administration of heparin. Additionally, we performed a repeat bronchoscopy to obtain a larger specimen and to check exhaustive driver oncogene alterations. The mediastinal lymph node specimen obtained by endobronchial ultrasound-guided transbronchial needle aspiration demonstrated adenocarcinoma (Fig. 1F) with *EGFR* mutation (*L858R point mutation*) and *ALK* rearrangement (Fig. 1G). These driver oncogene alterations were confirmed by the Oncomine Dx Target Test. On the 14th day after initial admission, she started receiving osimertinib (80 mg/day). After administration of osimertinib, anaemia and platelet depletion stopped, and malaise gradually improved. She recovered from DIC on the 20th day. Three weeks after osimertinib induction, enhanced chest computed tomography images revealed tumour regression (Fig. 2A and B). She was switched to ambulatory follow-up care on the 30th day. Ten weeks later, we confirmed that osimertinib maintained significant reduction (>30% reduction) of her tumour. We evaluated the efficacy of Osimertinib as a partial response.

3. Discussion

We encountered an exceptionally rare case of a patient with severe lung adenocarcinoma harbouring both *EGFR* mutations and *EML4-ALK* rearrangements with DIC. *EGFR* mutations and *EML4-ALK* rearrangements have a mutually exclusive relationship [3]. Concomitant existence of these gene alterations is very rare. In previous reports, only 0.9%–1.3% of *EGFR* mutation-positive NSCLC patients showed both *EGFR* mutation and *EML4-ALK* rearrangement [1,2]. *EGFR*-TKIs and *ALK*-TKIs are theoretically effective for patients harbouring both *EGFR* mutation and *EML4-ALK* rearrangement. However, no study has compared which drug clinicians should use initially. Some case reports reported favourable response to first- or second-generation *EGFR*-TKIs [4,5]. On the other hand, other case reports reported resistance to these *EGFR*-TKIs and changed their treatment from *EGFR*-TKI to *ALK-TKI* [1,6,7]. The *EGFR* and *ALK* signalling systems are closely related. *EML4-ALK* signalling can involve resistance to *EGFR*-TKI and vice versa [1,7,8]. We speculate that there are two possible mechanisms as to why osimertinib successfully reduced the tumour in this case. First, there may a heterogeneous distribution of *EGFR*-positive and *ALK*-positive cells. If *EGFR*-positive adenocarcinoma occupies the majority of the tumour, osimertinib can reduce the majority of the tumour and any remaining

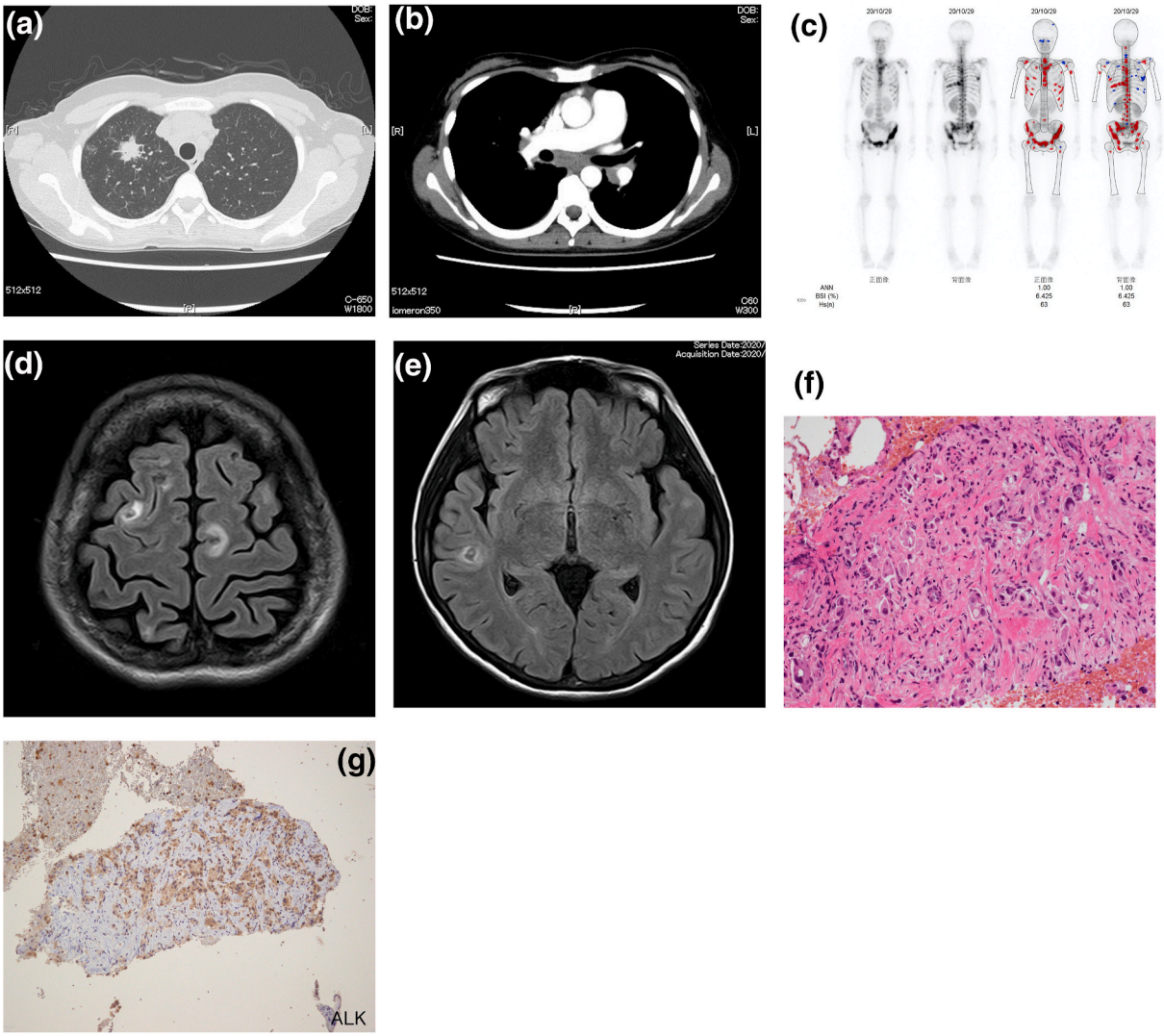

Fig. 1. Computed tomography shows right upper nodule (A) and balky mediastinal lymphadenopathy (B). Bone scintigraphy (C) and brain magnetic resonance imaging (D, E) show multiple bone and brain metastases. Histopathology of a lymph node revealed adenocarcinoma (F, ×200 haematoxylin and eosin). Immunohistochemistry shows positive staining of *ALK* fusion gene (G, ×100).

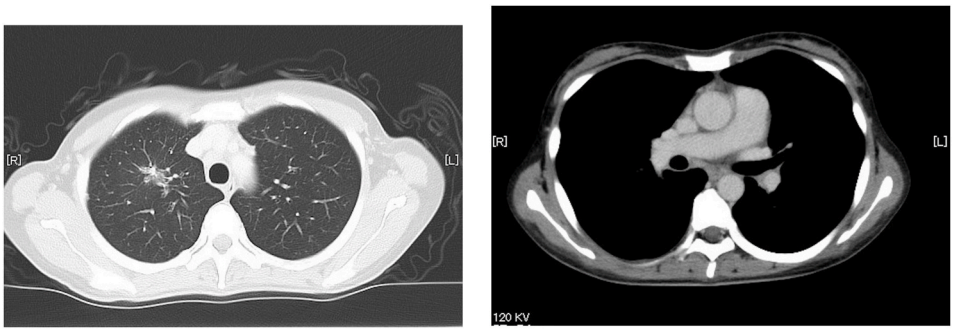

Fig. 2. Computed tomography shows remarkable remission of right upper nodule (A) and mediastinal lymphadenopathy (B) after osimertinib induction.

tumour may consist of *ALK*-positive adenocarcinoma. Second, a recent study suggested that osimertinib can inhibit the phosphorylation activity of both *EGFR* and *ALK* in a human adenocarcinoma cell line with *EML4-ALK* under experimental conditions [9]. This phenomenon may partially explain the favourable clinical response in our case. Furthermore, that study [9] and another case report [10] also suggest that the combined use of *EGFR*-TKI and *ALK*-TKI can favourably manage lung adenocarcinoma harbouring both *EGFR* mutations and *ALK* rearrangements.

Our case had two notable points. First, Osimertinib, a third-generation *EGFR*-TKI, showed a favourable tumour response. Despite the controversy regarding the use of *EGFR*-TKI as first-line treatment, our patient benefitted from its use. Second, osimertinib could quickly overcome severe conditions as represented by the DIC in this patient. In general, clinicians often hesitate to induce cytotoxic chemotherapy for lung cancer patients with severe DIC because these patients are thought to have no tolerance. Molecular targeting agents such as *EGFR*-TKIs and *ALK*-TKIs are good choices for patients with severe clinical conditions.

In conclusion, we encountered a patient with severe lung adenocarcinoma harbouring both *EGFR* mutations and *EML4-ALK* rearrangements. Even in severe conditions, third-generation *EGFR*-TKIs may be indicated for patients with multiple sensitive driver oncogene alterations.

Author contributions

KF, MN, TI, OK, KN, and KM cared for the patient. TM supervised the patient's care. KF drafted this case report. MN, OK, KM, KN, and TM supervised the manuscript. All authors approved this case report.

Declaration of competing interest

All authors have no conflict of interest to declare.

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