Secondary Aplastic Anemia During Osimertinib Treatment for Lung Adenocarcinoma: A Case Report

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We report a case of a 79-year-old woman with epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer who developed secondary aplastic anemia during treatment with the EGFR tyrosine kinase inhibitor (TKI) osimertinib. In the 23rd week of osimertinib treatment, the patient developed pancytopenia accompanied by fatty bone marrow. Discontinuation of osimertinib and initiation of treatment with cyclosporine A (100 mg/day) and eltrombopag (25 mg/day), a thrombopoietin receptor agonist, resulted in hematological recovery. Gefitinib, a first-generation EGFR-TKI, effectively suppressed the progression of lung cancer without any recurrence of pancytopenia for four months. However, rechallenge with osimertinib upon disease progression resulted in the recurrence of pancytopenia. This case suggests that osimertinib can cause severe hematological toxicity, such as aplastic anemia, possibly through an immune-mediated mechanism independent of EGFR inhibition.

Key words: Aplastic anemia, Epidermal growth factor receptor tyrosine kinase inhibitor, Lung cancer, Osimertinib, Pancytopenia

INTRODUCTION

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) significantly improve the prognosis of patients with non-small cell lung cancer (NSCLC) harboring EGFR mutations [1]. Osimertinib, a third-generation EGFR-TKI, is widely used as first-line therapy for these patients because of its high efficacy and relatively modest adverse events [2]. Although hematologic adverse events associated with osimertinib occur in 15–28% of patients [3], they are generally mild and reversible, and severe bone marrow suppression, such as serious pancytopenia and aplastic anemia, is exceedingly rare. Here, we report a case of osimertinib-induced secondary aplastic anemia in a patient with EGFR-mutated NSCLC who was able to continue treatment with a first-generation EGFR-TKI in combination with immunosuppressive therapy and a thrombopoietin receptor agonist.

CASE REPORT

A 79-year-old woman with no history of smoking was referred to our hospital for dyspnea on exertion that had persisted for six months. She had been taking amlodipine for hypertension for more than four years. Chest radiography revealed a massive right pleural effusion, and chest computed tomography revealed a right hilar mass, enlarged mediastinal lymph nodes, and multiple ipsilateral intrapulmonary metastases (Fig. 1). Laboratory tests showed a white blood cell (WBC) count of 8,890/μL, hemoglobin (Hb) of 15.4 g/dL, and platelet count of 21.4×10^4/μL. The serum carcinoembryonic antigen level was elevated at 44.6 ng/mL. Adenocarcinoma cells with an EGFR exon 21 L858R mutation, detected by cobas® EGFR Mutation Test v2 (Roche Diagnostics K.K., Tokyo, Japan), were identified in the pleural effusion.

Osimertinib was administered at a dose of 80 mg/day, which resulted in a significant reduction in the pleural effusion after two months. Six months later, the patient developed pancytopenia with a WBC count of 1,320/μL, neutrophil count of 807/μL, Hb of 11.4 g/dL, and platelet count of 6.1×10^4/μL (Fig. 2A), prompting discontinuation of osimertinib. Two weeks after withdrawal, blood cell counts improved, and osimertinib was resumed at a reduced dose of 40 mg/day. Nevertheless, the platelet count decreased to 1.0×10^4/μL 50 days after reinitiation, and a bone marrow biopsy was performed. A histological examination of the bone marrow revealed marked hypocellularity with fatty marrow replacement (Fig. 3). No dysplastic changes of hematopoietic cells or overt malignant infiltration were observed. Chromosome analysis revealed no abnormalities suggestive of myelodysplastic syndrome, and flow cytometry of peripheral blood showed no CD55/59-deficient cells, consistent with paroxysmal

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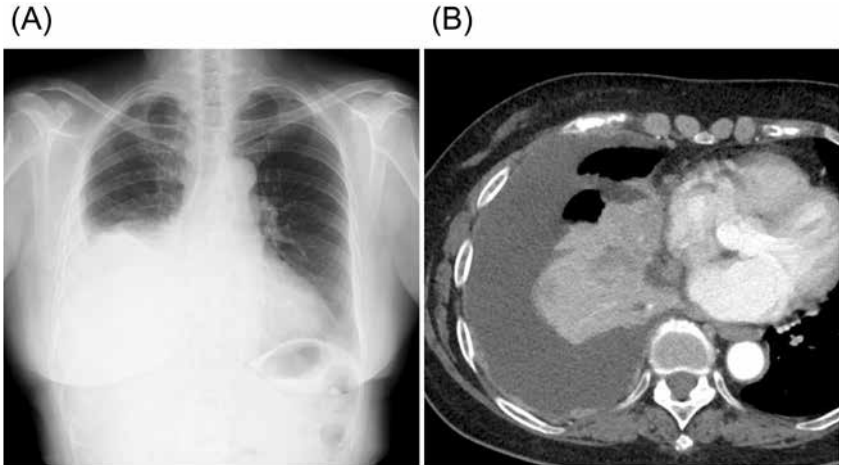

Fig. 1 Chest radiograph (A) and computed tomography (B) at diagnosis, demonstrating right pleural effusion and a right hilar mass.

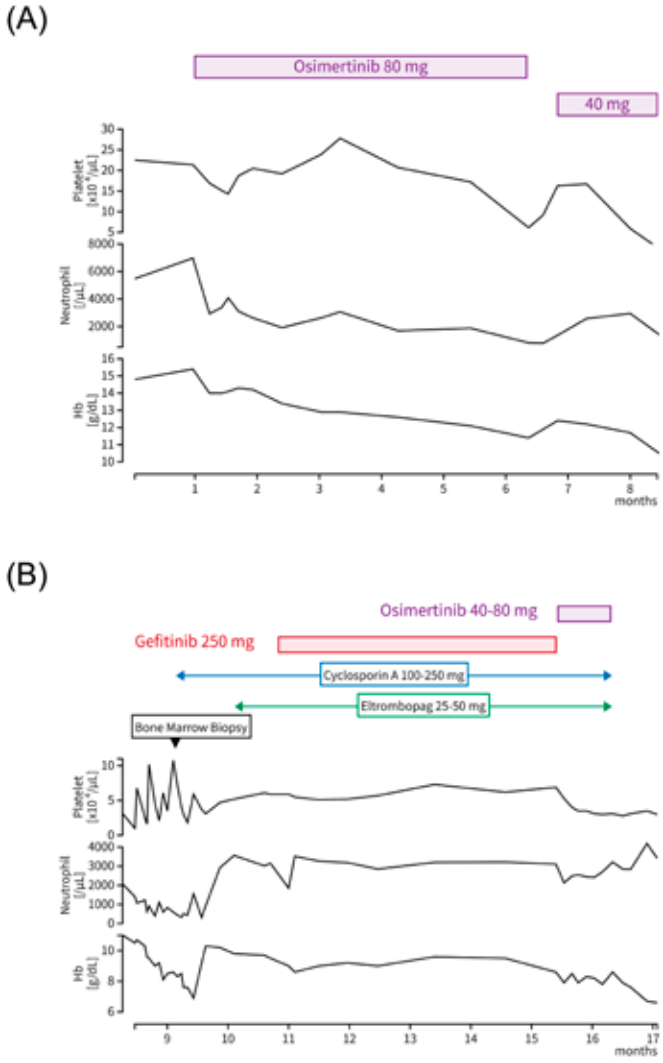

Fig. 2 Time course of peripheral blood cell counts during initial osimertinib treatment (A) and during subsequent treatment with gefitinib and rechallenge of osimertinib (B).

nocturnal hemoglobinuria. Based on these findings, the patient was diagnosed with aplastic anemia.

Osimertinib was discontinued again, and treatment with cyclosporine A (100 mg/day) and eltrombopag (25 mg/day), a thrombopoietin receptor agonist, was initiated, resulting in a stable condition with no blood transfusions required (Fig. 2B). Two and a half months after osimertinib discontinuation, the right pleural effusion with adenocarcinoma cells increased. Gefitinib (250 mg/day), a first-generation EGFR-TKI,

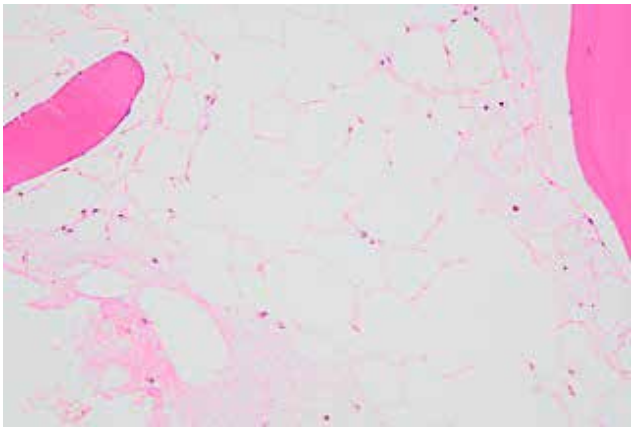

Fig. 3 Pathological findings of bone marrow after treatment with osimertinib for six months.
The bone marrow contained few hematopoietic cells and was replaced with adipose tissue. Hematoxylin and eosin staining; magnification × 200.

successfully suppressed the increase in pleural effusion without any recurrence of pancytopenia (Fig. 2B) until four months later, when she presented with pleural dissemination and bone metastases.

Given the patient's advanced age, frailty, and performance status, the anticipated toxicity of cytotoxic chemotherapy was deemed unacceptable. Best supportive care was also discussed. After shared decision-making with the patient and her family, we elected to rechallenge with osimertinib at a dose of 80 mg/day, which caused thrombocytopenia ($3.1 \times 10^4/\mu L$) and was discontinued (Fig. 2B). The patient developed multiple brain metastases and died of the progressive disease.

DISCUSSION

We report a case of NSCLC with an EGFR mutation treated with osimertinib. The patient developed secondary aplastic anemia accompanied by pancytopenia and bone marrow hypoplasia with fatty marrow replacement. Rechallenge with osimertinib, but not with gefitinib, resulted in the recurrence of aplastic anemia.

Bone marrow examination revealed fatty or empty bone marrow, and there was no history of underlying hematological disorders or use of other potentially myelotoxic agents. Furthermore, pancytopenia improved after discontinuation and worsened after rechallenge with osimertinib, suggesting that osimertinib induces secondary aplastic anemia. Previous studies have reported severe hematological adverse events in patients treated with osimertinib [4–8]. The interval from the start of osimertinib administration to the onset of pancytopenia was 19–31 weeks in patients with advanced metastatic lung cancer [4–6], consistent with 23 weeks in this case.

Another important observation in this case was that gefitinib, a first-generation EGFR-TKI, did not induce pancytopenia as observed during osimertinib treatment. According to the Food and Drug Administration Adverse Event Reporting System [9] and a comprehensive search of the PubMed database, there have been no reports of gefitinib-induced aplastic anemia. Considering both the available evidence and the clinical course in this patient, we attribute the development of aplastic anemia to osimertinib itself rather than to EGFR inhibition common to all EGFR-TKIs.

Although the mechanism of drug-induced aplastic anemia remains unclear, several possible mechanisms, such as direct cytotoxicity and immune-mediated destruction, have been postulated [10]. Although no definitive immunological abnormalities, such as autoimmune involvement or infectious triggers, were identified, the administration of cyclosporine A improved and maintained blood cell counts in the present case, suggesting an immune-mediated mechanism rather than direct hematological toxicity. Furthermore, the recurrence of cytopenia upon rechallenge with osimertinib provides additional evidence for a causal relationship between the drug and immune-mediated marrow failure.

In conclusion, osimertinib treatment can cause severe hematopoietic disorders such as aplastic anemia through a mechanism independent of EGFR inhibition. Although rechallenge with osimertinib should be avoided, other EGFR inhibitors, such as gefitinib, may be used based on individualized, shared decision-making. Further studies are required to elucidate the mechanism underlying osimertinib-induced secondary aplastic anemia, and appropriate treatment strategies are needed.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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