

Received: 2021.03.19

Accepted: 2021.07.15

Available online: 2021.08.02

Published: 2021.09.07

Acute Lower Extremity Arterial Thrombosis Associated with Osimertinib-Induced Erythrocytosis

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This work has been presented in the 234th meeting of the Japanese Respiratory Society, Kanto Branch, and the abstract was published online in Japanese (https://www.jrs.or.jp/modules/basicauth/index.php?file=190527_234kaikigo.pdf)

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Conflict of interest: None declared

Patient: Male, 70-year-old
Final Diagnosis: Drug induced polycythemia
Symptoms: Sural pain
Medication: —
Clinical Procedure: Endovascular treatment
Specialty: Oncology • Pulmonology

Objective: Unusual or unexpected effect of treatment
Background: Osimertinib is an oral third-generation epidermal growth factor receptor (*EGFR*)-tyrosine kinase inhibitor (TKI) approved as first-line therapy for advanced non-small cell lung cancer (NSCLC) with positive *EGFR* mutation. Rashes, nail toxicity, and diarrhea are common adverse events. Hematological adverse effects, including anemia, thrombocytopenia, and lymphocytopenia, have been reported. However, erythrocytosis has not been reported as an adverse event. To the best of our knowledge, we report the first case of acute lower extremity thrombosis presumably caused by osimertinib-induced erythrocytosis.

Case Report: A 70-year-old man with epidermal *EGFR*-mutant advanced NSCLC presented with acute left sural pain. The patient's left foot was cold, and peripheral arterial Doppler signals were absent. He had developed erythrocytosis of unknown etiology during osimertinib therapy. Hemoglobin (Hb) and hematocrit were 22.6 g/dL and 62.5%, respectively. Contrast-enhanced computed tomography showed thrombotic occlusion of the popliteal artery. Other than erythrocytosis, there was no possible cause of arterial thrombosis. Osimertinib was discontinued immediately because the NSCLC started to resist treatment and was presumed to be the cause of erythrocytosis. He received endovascular treatment (EVT). Following serial EVT and debridement, his fourth toe was amputated for necrosis. Erythrocytosis persisted 8 months during osimertinib therapy. Hb levels decreased to 15.4 mg/dL due to blood loss complicated with catheter thrombectomy and remained normal for 20 months after osimertinib discontinuation. The patient died of cancer progression.

Conclusions: This case suggests the erythrocytosis was possibly caused by osimertinib. We may need to monitor Hb levels during osimertinib therapy and be alert to thrombosis once Hb starts to rise.

Keywords: Antineoplastic Agents • Carcinoma, Non-Small-Cell Lung • Embolism and Thrombosis • Long Term Adverse Effects • Molecular Targeted Therapy • Polycythemia

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/932252>

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Background

The recent development of tyrosine kinase inhibitors (TKIs) has dramatically improved the prognosis of patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (*EGFR*) gene mutations [1-4]. Osimertinib is an oral third-generation *EGFR*-TKI specifically designed to inhibit *EGFR*-sensitizing mutations and acquired *T790M* mutations [5]. It is an approved first-line therapy for *EGFR*-mutant advanced NSCLC [6]. Rashes, nail toxicity, and diarrhea are common adverse events of the drug [1,7]. Hematological adverse events such as anemia, thrombocytopenia, and lymphocytopenia have also been reported [7]. However, erythrocytosis has not been previously reported as an adverse event of osimertinib. To the best of our knowledge, we report the first case of acute lower extremity thrombosis caused by osimertinib-induced erythrocytosis.

Case Report

A 70-year-old man with a history of hypertension and hyperuricemia was diagnosed with *EGFR*-mutant advanced NSCLC and underwent treatment with afatinib. Twelve months later, disease progression was observed, and a second biopsy of the lung tumor was taken to investigate the resistant mutation in *EGFR*. A *T790M* mutation was identified and we began osimertinib therapy. A partial response was observed. Four months later, erythrocytosis developed. The patient's hemoglobin (Hb) levels increased to 18 g/dL over 5 months (Figure 1). He did not report vomiting or diarrhea, and there were no other clinical signs of volume contraction, such as reduced skin turgor or tachycardia. His bone marrow smear, pathological examination, and serum erythropoietin levels were normal and *JAK2V617F* was not mutated, ruling out polycythemia vera. The patient had quit smoking 10 years prior and did not have a history of sleep apnea syndrome; polysomnography also showed no evidence of sleep apnea syndrome. The tumor continued to respond to osimertinib therapy. Low-dose aspirin was administered to prevent thrombosis. Since the cause of erythrocytosis was unclear, we continued osimertinib therapy. Eight months later, the patient presented with acute left sural pain. His Hb level and hematocrit were 22.6 g/dL and 62.5%, respectively, with a mean corpuscular volume of 105.0 fL and mean corpuscular Hb of 38.0 pg.

The patient's vital signs on admission were as follows: body temperature, 36.7°C; blood pressure, 164/96 mm Hg; heart rate, 113 beats/min (regular); respiratory rate, 15 breaths/min; and oxygen saturation of 98% in ambient air. On examination, the patient's left foot was cold, and the peripheral arterial Doppler signals were absent. The remaining complete blood cell count results revealed a white blood cell count of 3500/ μ L and a

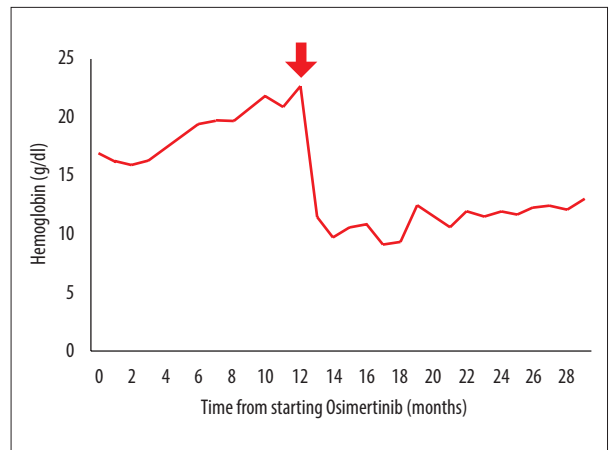


Figure 1. The trend of hemoglobin (Hb) level. The trend of Hb level from the initiation of osimertinib therapy is shown. The arrow indicates the timepoint at which acute arterial thrombosis developed and osimertinib was discontinued.

platelet count of $110 \times 10^3/\mu$ L. The blood chemistry and coagulation panel results were as follows: blood urea nitrogen, 16.9 mg/dL; serum creatinine, 0.79 mg/dL; aspartate aminotransferase, 39 U/mL; alanine aminotransferase, 27 U/mL; activated partial thromboplastin time, 40.5 s; and prothrombin time-international normalized ratio, 1.24. His lipid profile and HbA1c were within the reference ranges. Contrast-enhanced computed tomography (CT) and urgent angiography revealed thrombotic occlusion of the left popliteal artery. Progression of the tumor was also identified during CT. There was no evidence of severe atherosclerosis, aneurysm, or shunt in the pulmonary circulation. An electrocardiogram on presentation showed sinus tachycardia. The systolic function was normal, and cardiac defect or intracardiac thrombus were not noted on the trans-thoracic echocardiogram. Other than erythrocytosis, there was no possible cause of arterial thrombosis. Endovascular treatment (EVT) was successful, and the blood flow to the toe improved. Osimertinib was discontinued immediately because the lung cancer started to resist treatment and was presumed to be the cause of erythrocytosis.

The patient's Hb levels decreased to 15.4 mg/dL due to blood loss complicated with catheter thrombectomy. Following serial EVT and debridement, his fourth toe was amputated because of necrosis. Anticoagulation therapy and wound care were continued.

On admission day 10, the patient was discharged. We initiated platinum-based combination chemotherapy in an outpatient setting. After the discontinuation of osimertinib, there was no recurrence of erythrocytosis or thrombosis (Figure 1). The cancer progressed, and the patient died 20 months after the thrombotic event.

Discussion

We reported the first case of arterial thrombosis associated with erythrocytosis caused by osimertinib therapy. Erythrocytosis increases the red blood cell (RBC) mass, leading to hyperviscosity and increased risk of both arterial and venous thrombosis [8]. In the present case, erythrocytosis was considered the most probable cause of acute lower extremity thrombosis because other possible causes of arterial thrombosis, such as atrial fibrillation, myocardial ischemia, severe arteriosclerosis, or paradoxical embolism through intracardiac or intrapulmonary shunt, were not identified. However, it could not be excluded that the cancer also led to the development of arterial thrombosis, in view of its progression [9]. Erythrocytosis is classified as either absolute or relative erythrocytosis [10]. The former is due to increased RBC production and the latter is due to decreased plasma volume [11]. Based on the patient's medical history, physical examination, and normal blood urea nitrogen/creatinine levels, relative erythrocytosis (eg, dehydration) was excluded. Absolute erythrocytosis is further categorized into primary and secondary erythrocytosis [12]. The former includes polycythemia vera and other myeloproliferative neoplasms. According to the 2016 WHO classification, the patient did not meet the diagnostic criteria of polycythemia vera and other myeloproliferative neoplasms owing to the absence of hypercellularity of bone marrow and *JAK2* gene mutation [13]. Secondary erythrocytosis occurs when RBC production is induced by increased erythropoietin [14]. The differential diagnosis of secondary erythrocytosis includes hypoxia-associated erythrocytosis and tumor-associated erythrocytosis. Chronic hypoxia could result from tobacco use, cyanotic heart disease, chronic obstructive pulmonary disease, carbon monoxide exposure, and sleep apnea syndrome [14]. These factors were not identified in the present case. Autonomous production of erythropoietin by various tumors, such as renal cell carcinoma, hepatocellular carcinoma, and hemangioblastoma, can cause secondary erythrocytosis [14]. They were also ruled out based on imaging studies, and the tumor continued to respond while the patient was receiving osimertinib therapy. Furthermore, he did not have any history of using anabolic steroids or exogenous erythropoietin that could be a pharmacological cause for erythrocytosis [15].

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Erythrocytosis persisted for 8 months during osimertinib therapy. The patient's Hb levels continued to be normal for 20 months after discontinuing osimertinib, even though the tumor progressed. This suggested that erythrocytosis was probably caused by osimertinib and was not a paraneoplastic effect. Previous clinical trials have not reported that erythrocytosis is associated with osimertinib therapy [1,7]. Vascular endothelial growth factor (*VEGF*-TKIs, such as sunitinib, sorafenib, and pazopanib, have been reported to cause secondary erythrocytosis [16-19]. *VEGF* tyrosine kinases cause erythrocytosis, without elevating serum erythropoietin. Although the precise mechanism remains unclear, it is hypothesized that *VEGF* inhibition may sensitize erythropoietin or modulate the erythropoietic pathway [16]. Osimertinib is an *EGFR*-TKI and does not block the *VEGF* signaling pathway; therefore, osimertinib may cause erythrocytosis through a different mechanism. Further studies are required to investigate the association and mechanism of osimertinib-induced erythrocytosis.

Conclusions

We reported a case of arterial thrombosis which was probably due to osimertinib-induced erythrocytosis. We may need to consider monitoring Hb during osimertinib therapy and remain alert for thrombosis once Hb level starts to rise.

Conflicts of Interest

None declared.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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