

**Title:** Red cell morphological changes associated with alectinib, a novel anaplastic lymphoma kinase inhibitor

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**Background:** Alectinib is a second generation anaplastic lymphoma kinase (ALK) inhibitor indicated for ALK mutated non-small cell lung cancer. Although the association between alectinib and anaemia was known, there were only a limited number of reports on its association with haemolytic anaemia and red cell morphological changes. Here we present a case of alectinib-induced haemolytic anaemia with prominent acanthocytosis.

**Case:** A 62-year-old man with  $\alpha$ -thalassaemia trait was diagnosed with ALK-positive lung adenocarcinoma, with liver, adrenal, pleura and bone metastasis. He was treated with alectinib. The baseline haemoglobin level was about 9 g/dL. Haematological indices 4 months after the initiation of alectinib were as follow : haemoglobin 7.2 g/dL, mean corpuscular volume (MCV) 66.9 fL, mean corpuscular haemoglobin (MCH) 23.6 pg, mean corpuscular haemoglobin concentration (MCHC) 35.2 g/dL and red cell distribution width (RDW) 22.6. There was mild reticulocytosis (2.8% of red cells). Peripheral blood smear showed significant anisopoikilocytosis with prominence in acanthocytes, presence of some microspherocytes, hypochromic microcytic red cells and occasional red cell fragments. The bilirubin, lactate dehydrogenase (LDH) and haptoglobin levels were 25  $\mu$ mol/L (5 – 27  $\mu$ mol/L), 363 IU/L (110 – 210 IU/L) and <0.10 g/L (0.30 – 2.00 g/L) respectively, which were suggestive of haemolysis. Direct anti-globulin test (DAT) was negative. Since the patient was asymptomatic, alectinib was continued with close observation of haematological indices and biochemical markers of haemolysis.

**Discussion:** To our best knowledge, this is the first reported case of alectinib-induced red cell morphological changes in a patient with underlying  $\alpha$ -thalassaemia trait. We performed literature review and found two case series on alectinib-induced haemolysis red cell morphological changes with detailed description of patient's history [1], [2]. 8 patients had been reported in the case series and 2 of them had a background of beta-thalassaemia trait. Including the case presented here, 33% of the patients (3/9) had a background of haemoglobinopathy.

The mechanisms responsible for acanthocytosis, spherocytosis and other alectinib-induced red cell morphological changes are unknown. A recent study has shown that use of alectinib is associated with reduced eosin-5-maleimide binding, suggesting that the drug could affect erythrocyte cytoskeleton [3]. We hypothesize that patients with haemoglobinopathies may be

more susceptible to the development of alectinib-induced red cell morphological changes and haemolysis due to the pre-existing impaired red cell survival.

**Conclusion:** Given the anticipated increase in utilization of alectinib in oncology patients, it is critical for haematologists to recognize the potential red cell morphological changes and haemolytic anaemia associated with this novel agent. It is suggested that examination of peripheral blood smear and monitoring biochemical markers of haemolysis should be performed regularly in patients receiving alectinib, especially in those with known haemoglobinopathies.

**References:**

- [1] Yuan Y, Mapp S, Xu W. Two cases of marked red cell anisopoikilocytosis and haemolysis with alectinib, an anaplastic lymphoma kinase inhibitor. *Br J Haematol.* 2020;190:642.
- [2] Gullapalli V, Xu W, Lewis CR, Anazodo A, Gerber GK. A multi-centre case series of alectinib-related erythrocyte membrane changes and associated haemolysis. *J Hematopathol.* 2021.
- [3] Kuzich JA, Heynemann S, Geoghegan N, Evelyn C, O'Mahoney S, Wilson S, et al. Alectinib induces marked red cell spherocanthocytosis in a near-ubiquitous fashion and is associated with reduced eosin-5-maleimide binding. *Pathology.* 2021.