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Hematology Quiz – Case 68

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2024, 41(6):860–861

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A 26 year-old woman treated for an ALK-positive metastatic pulmonary adenocarcinoma with alectinib, an anaplastic lymphoma kinase (ALK) inhibitor since two years, in stable disease, presented to her routine consultation with sclerar icterus and mild fatigue. Her biological investigations showed a macrocytic anemia (Hb 11 g/dL, MCV 100.6 fL). Of note, macrocytosis occurred one year after alectinib initiation.

Biochemical tests were suggestive of hemolysis with a total bilirubin of 96 μmol/L, unconjugated bilirubin at 83 μmol/L, LDH at 374 IU/L and haptoglobin as low as 0.13 g/L. Transaminases were normal (AST 38 IU/L, ALT 53 IU/L).

The patient's personal history was free of alcohol abuse, hypothyroidism or vitamin B deficit and there was no documented hereditary hematological disease.

The blood smear, revealing five morphological abnormalities, is shown on figure 1.

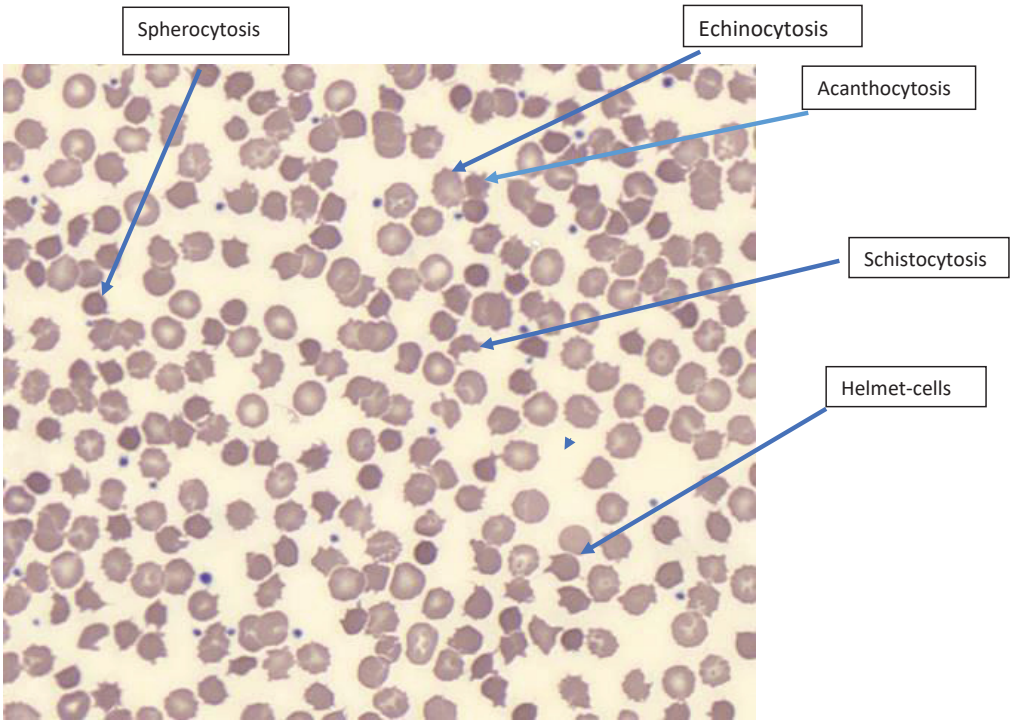

Figure 1.

Comment

Few studies have so far described red-cell abnormalities on patients treated with alectinib.[1,2] Blood smears reveal the presence of spherocytes, acanthocytes, spheroacanthocytes/spiculated spherocytes, echinocytes and irregularly contracted cells resembling schistocytes.[1] In a study of 43 cases, mild polychromasia was evident in only 30% of films, supported by the reticulocyte count results available.[1] Of note, two thirds of patients developed anemia, though definite new hemolysis was present in only 11%.[1]

Published data on alectinib treated patients show a decrease in Eosin-5-maleimide (EMA) binding. EMA is a fluorescent dye which intercalates with a number of erythrocyte cytoskeletal proteins, including band-3 and Rh-related proteins; staining is typically reduced in erythrocytes from patients with hereditary spherocytosis (HS), hereditary pyropoikilocytosis and south-east Asian ovalocytosis. In a case study reporting spherocytosis on an elderly patient treated with alectinib[2] flow cytometry test showed a 60% decrease in fluorescence intensity compared to a control subject, this being even more decreased than in hereditary spherocytosis (HS), which is typically around 20% decreased. The mechanisms behind red cell abnormalities in the setting of alectinib treatment remain unclear.

ALK is not presently implicated in erythropoiesis or in genes related to the development or function of the red cell membrane. Moreover, these morphological abnormalities have not been observed on patients treated with other ALK inhibitors,[1] suggesting that alectinib-induced membrane abnormalities are probably due to an off-target, non-ALK related effect specific to alectinib. An effect on hepatic function and lipid levels is a possible alternative explanation. Published data show that most patients did not have abnormal liver function testing, as is the case of this patient. Added to that, there was no hypercholesterolemia and hypertriglyceridemia observed in alectinib clinical trials.[3,4]

In the authors view, it is important to detect these morphological findings on alectinib-treated patients in order to avoid unnecessary extensive investigations in favor of an alternative pathology. Of course, prompt detection of clinically significant anemia and hemolysis is of undoubted clinical importance. In the case of this patient, as she presented with compensated anemia along with satisfying oncological response on alectinib, treatment was continued, and a regular hematology follow up was instaured.

References

1. KUZICH JA, HEYNEMANN S, GEOGHEGAN N, EVELYN C, O'MAHONEYS, WILSON S ET AL. Alectinib induces marked red cell spheroacanthocytosis in a near-ubiquitous fashion and is associated with reduced eosin-5-maleimide binding. *Pathology* 2021, 53:608–612
2. LEGLAND EP, DEJEAN A-M, PLANTAMURA J, ARNOUX I, PALEIRON N, LOOSVELD M, ET AL. Acanthocytosis in an alectinib-treated patient. *Br J Haematol* 2022, 197:131
3. HIDA T, NOKIHARA H, KONDO M. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet* 2017, 390:29–39
4. PETERS S, CAMIDGE DR, SHAW AT; ALEX TRIAL INVESTIGATORS. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med* 2017, 377:829–838

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