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Alectinib-Induced Hemolysis in a Case of ALK-Positive Metastatic Lung Adenocarcinoma: A Case Report with Review of Literature

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Abstract

This is a case report of how we tumbled upon anemia due to drug-related hemolysis, a rare side effect of alectinib, which is a primary drug used in *ALK*-positive lung cancer. A 78-year-old male patient with history of surgery and concurrent chemoradiation for a primary adenocarcinoma lung in 2013 presented with a systemic recurrence of the lung cancer in October 2022. Molecular testing of the biopsy at recurrence revealed an ALK-positive status. He was started on alectinib 600 mg twice a day, a tyrosine kinase inhibitor in November 2022. His disease had a very good response to the drug; however, he was noted to have a gradual drop in hemoglobin and a mild indirect hyperbilirubinemia. Subsequently, alectinib dosage was interrupted and investigations were performed to rule out the commonly prevalent causes of anemia, such as iron deficiency, vitamin B12, and folate, which were found to be normal. Upper and lower gastrointestinal endoscopy, Coombs test, serum lactate dehydrogenase, and haptoglobin levels were normal. The peripheral smear evaluated during his admission showed a picture of hemolysis. On reviewing literature, it was deduced that this was related to alectinib. The hemolysis in this case, like others, was occult and subclinical. This is the first such case from India, and it highlights the need for an experienced hematopathologist to clinch such a diagnosis. On follow-up, his drug has been changed to lorlatinib and his hemoglobin has recovered to normal levels.

Keywords
- alectinib
- hemolysis
- lung cancer
- case report

Introduction

Alectinib is presently one of the standard first-line target therapies for metastatic ALK-positive lung adenocarcinoma.[1] It is largely well tolerated and has drastically improved outcomes. We came across a rare side effect that was inconspicuous in presentation[2] and ultimately necessitated drug withdrawal.

Case Report

A 78-year-old male patient with no comorbidities presented to our outpatient department (OPD) in October 2022. He had a prior history of undergoing left-sided pneumonectomy for stage IIIA adenocarcinoma of the left lung. For this condition, he received presurgical radiotherapy and perioperative

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chemotherapy in 2011. He also received treatment for localized carcinoma of the prostrate in 2013 with intensity-modulated radiation therapy and brachytherapy.

We evaluated him for persistent cough in October 2022. A positron emission tomography-computed tomography (PET-CT) scan revealed deposits/recurrence in the peritoneum in the perisplenic region with a single lytic lesion in the eighth rib and mediastinal lymph nodes. The biopsy performed on the peritoneal deposit was suggestive of recurrent adenocarcinoma of the lung. Fluorescent in situ hybridization testing for a targetable mutation came positive for *ALK* rearrangement. He was started on the tablet alectinib at 600 mg twice daily in November 2022.

His complete blood count (CBC) at diagnosis was the following: hemoglobin, 15.2 g/dL (11.8–17 g/dL); total WBC count, 8,300/mL (4,000–11,000 g/dL); and platelet count, 218,000/mL (150,000–450,000 mL). The liver function test (LFT) showed a total bilirubin of 1.06 mg/dL, indirect bilirubin of 0.80 mg/dL, serum glutamic-oxaloacetic transaminase (SGOT)/pyruvate transminase (PT) of 23/19 IU/L, and albumin of 3.72 g/dL. The rest of the blood tests gave unremarkable results. Subsequent PET-CT scans (performed in January 2023 and June 2024) suggested a consistently responsive disease with continuing regression of all the disease sites.

In January 2023, his LFT showed an elevated total bilirubin of 2.60 mg/dL, with the indirect bilirubin level of 2.2 mg/dL. The CBC was unremarkable with a hemoglobin of 15.2 g/dL. The altered liver function was thought to be of drug origin, and needed a brief period of interruption. He otherwise tolerated the drug well at its full dose of 600 mg twice daily until his most recent visit to us in June 2024. The LFT showed persistence of hyperbilirubinemia, ranging between 2 and 3 mg/dL, with predominant indirect hyperbilirubinemia. His hemoglobin values through the year of 2023 were in the range of 11 to 12.5 mg/dL (►**Table 1**).

In June 2024, he was found to have a fall in hemoglobin (8.9 g/dL). He was referred to our hematologist, who sent tests to rule out the commonly prevalent nutritional iron and vitamin B12 deficiency anemias. His iron value was low (55 mg/dL [70–180]) in May 2024; the rest were in the normal range. He was thought to have a coexistent nutritional deficiency and anemia of chronic disease. He was admitted for evaluation of his lowering hemoglobin. He underwent upper and lower gastrointestinal endoscopy, which showed no evidence of active bleeding. He received parenteral iron therapy with 1 g of ferric carboxymaltose. His total bilirubin in June 2024 was 6.4 mg/dL, with indirect bilirubin of 5.5 mg/dL. At this point, alectinib dosage was withheld. However, his hemoglobin continued to drop in the hospital, and reached its lowest point of 7.7 g/dL on day 4 after stopping alectinib. His lactate dehydrogenase (LDH), corrected reticulocyte count, and serum haptoglobin levels were all in the normal range (►**Table 1**). The direct Coombs test (DCT) and indirect Coombs test (ICT) reports were negative.

His CBC and peripheral smear showed a considerable number of sphero-acanthocytes (►**Figs. 1** and **2**), highly characteristic of a hemolytic picture, presumed to be drug induced. The ongoing hemolysis was not picked up initially, as all his blood tests were reported from outside.

Table 1 Laboratory parameters of the patient, over time

	November 2022	January 2023	April 2023	July 2023	September 2023	December 2023	March 2024	June 7, 2024 (tablet held)	June 8, 2024	June 10, 2024
Hemoglobin (g/dL), 11.8–17	15.2	14.7	12.3	11.17	10.5	11.0	11.10	10.4	8.20	7.7
Total count (per mL), 4,000–11,000	8,300	6,500	7,500	7,840	7,200	8,900	7,900	19,840	12,330	4,100
Platelets (per mL), 150,000–450,000	217,000	218,000	295,000	335,000	307,000	345,000	310,000	306,000	256,000	267,000
Total bilirubin (mg/dL), 0.3–1.2	1.06	2.80	2.60	2.60	2.23	2.70	2.85	6.40	6.00	3.70
Direct bilirubin (mg/dL), 0–0.2	0.26	0.50	0.40	0.60	0.50	0.50	1.11	1.00	1.10	0.90
Indirect bilirubin (mg/dL)	0.80	2.30	2.20	2.00	1.73	2.20	1.74	5.40	4.90	2.80
SGOT/PT (0–0.8)	23/19	21/16	15/23	21/15	21/10	17/19	25/10	25/11	20/12	
Serum albumin (g/dL), 3.5–5.2	3.72	3.73	3.80	4.00	3.80	3.50	4.00		2.90	
LDH (IU/L), 0–248										183
Reticulocyte count (%), 0.2–2.5										3.60
Serum haptoglobin (30–200 mg/dL)										96.3
Serum iron (70–180 mg/dL)							55			

Abbreviations: LDH, lactate dehydrogenase; PT, prothrombin time; SGOT, serum glutamic-oxaloacetic transaminase.

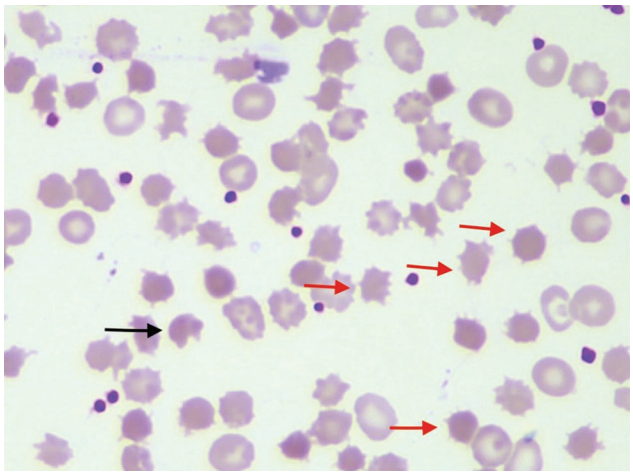

Fig. 1 Peripheral blood smear (Leishman stain, ×40) shows marked anisopoikilocytosis with normocytic normochromic cells mixed with few microcytic, hypochromic cells, polychromatic RBCs, spherocytes, acanthocytes (*red arrow*), and occasional schistocyte (*black arrow*).

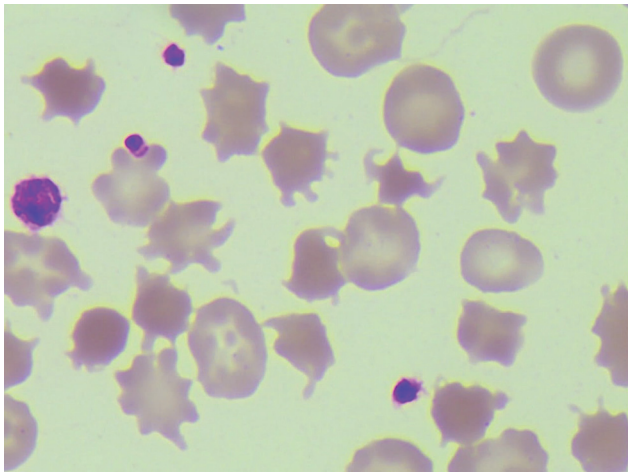

Fig. 2 Peripheral blood smear (Leishman stain, ×100) shows anisopoikilocytosis with numerous spherocytes and acanthocytes. A macroplatelet is also noted in the field.

After 6 days of stopping alectinib, his hemoglobin stabilized. He went home on a steady hemoglobin of 8.7 g/dL and a total bilirubin of 3 g/dL. He was advised to change his medication to tablet lorlatinib. His hemoglobin as of June 17, 2024 (day 11 after drug interruption) was 9.9 g/dL. His last follow-up was with us in September 2024, and the hemoglobin level noted was 13.2 g/dL.

Discussion

Alectinib-related anemia has been reported to be as high as 22%, in its trials.[1] However, drug-related hemolysis has not been described in them. Alectinib-related hemolysis is a rare event, but has been more frequently reported as solitary events or as case series[2–5] in the last decade, in its post-marketing surveillance. Most cases reported have been from Japan and Europe. On our review of literature, we have found that this is the first case report from India.

On reviewing our patient's hemoglobin levels, we noted a steady and asymptomatic decline, from grade 1 to 2 anemia over the past year, with a marked decline in the fortnight to grade 3 (lowest level of hemoglobin: 7.7 g/dL). This is similar to other case reports,[2–5] which have described anemia as subacute (with onset ranging from as early as 14 days up till a year), subclinical, and as an occult presentation.

There are hypotheses postulating that steep hemoglobin drops are more common in patients who have coexistent hemoglobinopathies. An enzyme deficiency named eosin-5′-maleimide, which causes inherent red blood cell (RBC) membrane defect, has been associated with alectinib-related hemolysis.[3,4] We proposed performing an osmotic fragility test on his peripheral blood sample and sending a panel for hereditary hemoglobinopathy evaluation. The patient refused to do both tests.

Immune and nonimmune mechanisms have been used to explain the causation of such hemolysis.[3,5,6] Cases reported in the literature have mentioned both direct antiglobulin test (DAT) positive and negative hemolytic anemias.[3,5,6] They have mentioned cases with normal reticulocyte count and serum haptoglobin as in our case. We presume that given that the DAT was negative in this patient, the mechanism is non–immune related, and that hence steroids and/immunosuppressants have a limited role and benefit. The DAT-negative hemolytic anemia also supports the subacute course of his anemia.[6,7]

The patient's anemia improved as early as within 1 week of follow-up, with a reduction in bilirubin levels as early as 5 days after discontinuation of the drug. The peculiar aspect of his hemolysis was that barring the peripheral smear, which clinched the hemolytic picture, other parameters such as LDH, corrected reticulocyte count, and serum haptoglobin were normal.

Nutritional deficiencies are the most common causes of anemias that we see in India, along with anemia caused due to chronic disease/cancer. As this patient had ongoing malignancy with mildly reduced iron levels, this was the initial hypothesis, given the normal LDH levels and reticulocyte count. However, the peripheral smear repeat test of the patient confirmed the diagnosis of alectinib-induced hemolytic anemia. Similar reports in the literature further clinched the diagnosis. This case highlights the importance of a peripheral smear reported by a good hematopathologist.

We hope this case report alerts more clinicians to alectinib-related hemolysis, which is drug specific. The decision to change, or rechallenge the drug at the same/lower dose, should be done depending on the symptoms, degree, and lowest point of anemia, jointly with the patient.[8] We prescribed a change in tyrosine kinase inhibitor (TKI) to tab lorlatinib 100 mg once daily, as we suspect his hemolysis would be severe if reinitiated on alectinib. As alectinib-related hemolysis is drug specific and not class specific, lorlatinib should not potentially cause hemolysis in the patient.[8]

Conclusion

Alectinib-related hemolysis is a rare drug-specific and not class-specific side effect, and not part of common working

knowledge of this drug. This experience taught us the importance of thorough evaluation of even commonly seen adverse events such as anemia and underscored the need for an experienced hematopathologist to clinch such diagnosis.

Patient's Consent

Written informed consent was obtained from the patient prior to the study.

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Conflict of Interest

None declared.

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