# Linezolid-Induced Sideroblastic Anaemia: A Reversible but Overlooked Adverse Effect


## Abstract

With the ever-evolving guidelines and changing drug regimens for tuberculosis (TB), it is paramount for treating physicians to understand the efficacy and safety profiles of the drugs being used. Linezolid is included in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB.

A 60yearold man with MDR TBwas managed with oral AKT (anti-Kochs therapy) drugs including linezolid. Six months after starting the therapy, he presented with complaints of giddiness, dyspnea on exertion and easy fatiguability. Investigations revealed severe anemia, thrombocytopenia, reticulocytopenia, leukopenia, normal liver and renal function. With Linezolid induced pancytopenia being one of the major differentials, AKT containing Linezolid was discontinued immediately. The patient was initiated on appropriate supportive care, including blood transfusions and alternative antibiotic therapy. Over the subsequent weeks, the patient's symptoms improved, and his hemoglobin levels gradually returned to the normal range.

Clinicians are habituated to treating Gram-positive infections with short courses of linezolid. This should be avoided especially in a country like India where tuberculosis burden is very high, as linezolid is an essential part of treatment of MDR TB. Regular and planned monitoring for side effects is required when linezolid is used at higher doses and longer durations, such as for the management of Tuberculosis. Further research is warranted to elucidate the pathogenesis of linezolid-induced sideroblastic anemia and identify potential risk factors for its development.

KEYWORDS: Linezolid, Ringed sideroblasts, Tuberculosis.

## Introduction

Linezolid, an oxazolidinone anti-microbial agent, is being used with increasing frequency in patients with resistant gram-positive cocci infections. It might cause myelosuppression and reversible sideroblastic anemia, which is a rare hematological disorder characterized by the impaired utilization of iron in the heme synthesis pathway, leading to abnormal mitochondrial iron deposits in erythroblasts/erythroid precursors in bone marrow. The mechanism by which linezolid induces sideroblastic anemia is by inhibition of mitochondrial protein synthesis, leading to mitochondrial dysfunction and abnormal iron metabolism in erythroid precursors.

Here, we present a case of linezolid-induced sideroblastic anemia in a patient with no prior history of hematological disorders.

## Case presentation

A 60-year-old male with a history of diabetes mellitus, hypertension, hypothyroidism (detected since 6 months), MDR TB since 6 months was admitted to the hospital with chief complaints of generalized weakness and easy fatiguability. This started after the patient was started on MDR TB regimen (containing linezolid) as previous Hemoglobin, i.e before starting AKT was 11.0 mg/dl (06/01/2023) and currently as of 24/06/2023, i.e 6 months of consuming Linezolid containing AKT his Hb is 4.0 mg/dl, with a predominant normocytic normochromic blood smear. The CBC (Hb/WBC/platelets) was 4.0/4750/170,000. PCV was 13%, MCV 99.6 fl, MCH 30.2 pg, MCHC 30.3 gm/dl and RDW of 22.1%. Stool occult blood was absent. Ultrasonography was abdomen revealed no significant abnormalities. Routine Urine examination was normal. Liver function tests were normal (Bilirubin total/direct 0.6/0.2 mg/dl, AST/ALT 26/12 IU/L). LDH was normal (214 U/L). Creatinine was 1.9mg/dl. The patient's reticulocyte count was low (0.1%) indicating ineffective erythropoiesis. There was concomitant thrombocytopenia and leukopenia indicating pancytopenia.A bone marrow aspiration and biopsy were performed to investigate the underlying cause of pancytopenia. It showed a diluted marrow with adequate erythroid maturation with mild dysplasia and 50% ringed sideroblasts, adequate myelopoeisis and few megakaryocytes consistent with a diagnosis of sideroblastic anemia.

Given the temporal association between linezolid administration and the development of sideroblastic anemia, linezolid-induced erythroid dysplasia with ringed sideroblasts was considered the likely cause.

AKT containing Linezolid was discontinued immediately in view ofsuspected linezolid induced bone marrow suppression leading to pancytopenia. The patient was initiated on appropriate supportive care, including blood transfusions. Additionally, the patient was started on alternative antibiotic therapy to manage MDR TB.
Patient was discharged once he was clinically better with a creatinine of 1.0 and with CBC 6.9/6320/131,000 with PVC of 21.1%, MCV 86.8fl, MCH 28.4pg, MCHC 32.7 gm/dl and RDW of 17.5%.
Over the subsequent weeks, the patient's symptoms improved, and his hemoglobin levels gradually returned to the normal range.

Figure-1: Bone marrow smear showing ring sideroblasts

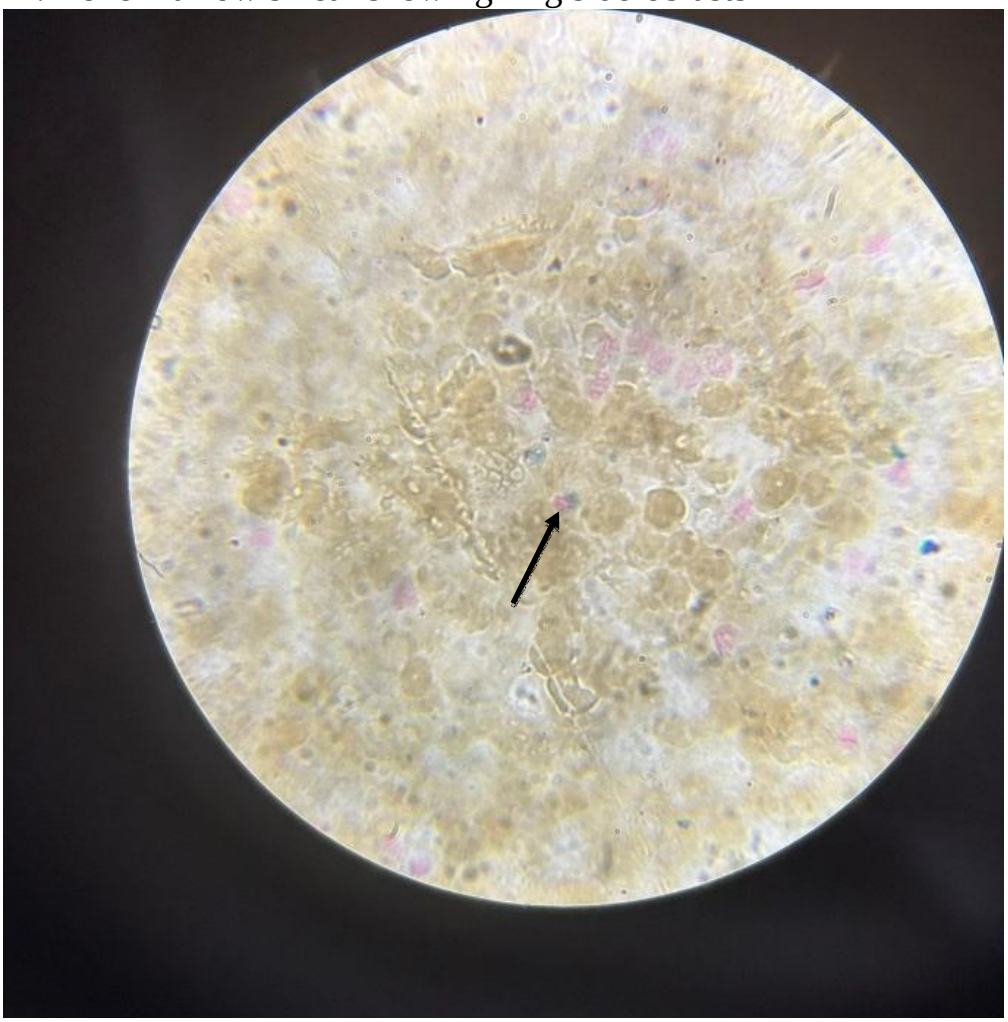

Table-1: Day-wise Laboratory findings

| | 24/06/23 | 25/06/23 | 28/06/23 | 30/06/23 |
|---|---|---|---|---|
| **Hemoglobin (gm/dL)** | 4.0 | 4.7 | 6.1 | 6.9 |
| **RBC Count (millions/cumm)** | 1.31 | 1.61 | 2.14 | 2.43 |
| **RBC** | Predominantly | Predominantly | Hypochromia | Hypochromia (+) |

| **Morphology** | normocytic, normochromic, occasionally macrocytic | normocytic, normochromic, occasional macrocytes, few pencil cells and tear drop cells, few fragmented RBCs seen | (+) Microcytosis (+) Anisocytosis (+) Occasional Macrocytosis Polychromasia (+) Occasional Tear Drop Cells | Microcytosis (+) Anisocytosis (+) Macrocytosis (+) Pencil Cells (+) Polychromasia(+) Tear Drop Cells(+) |
|---|---|---|---|---|
| **PCV (%)** | 13 | 14.5 | 17 | 21.1 |
| **MCV (fL)** | 99.6 | 90.0 | 89.8 | 86.8 |
| **MCH (pg)** | 30.2 | 29.3 | 29.1 | 28.4 |
| **MCHC (gm/dL)** | 30.3 | 32.5 | 32.7 | 32.7 |
| **RDW (%)** | 22.1 | 20.5 | 20 | 17.5 |
| **Total Leucocyte count (10^3/µL)** | 4.75 | 4.97 | 4.62 | 6.32 |
| **Platelet (10^3/µL)** | 170 | 147 | 142 | 131 |
| **Erythrocyte sedimentation rate** | 85 | | | |
| **Sr. Bilirubin – Total (mg/dL)** | 0.6 | | | |
| **Sr. Bilirubin – Direct (mg/dL)** | 0.2 | | | |
| **Sr. Bilirubin – Indirect (mg/dL)** | 0.4 | | | |
| **Sr. Aspartate Transaminase [AST]/ GOT (IU/L)** | 26 | | | |
| **Sr. Alanine Transaminase [ALT]/ GPT (IU/L)** | 12 | | | |
| **Sr. Alkaline Phosphatase (IU/L)** | 121 | | | |
| **Total Sr. Protein (gm/dL)** | 5.6 | | | |
| **Sr. Albumin (gm/dL)** | 2.9 | | | |
| **Sr. Globulin (gm/dL)** | 2.7 | | | |
| **Sr. Creatinine (mg/dL)** | 1.9 | 1.5 | | 1.0 |
| **Sr. Calcium (mg/dL)** | 7.5 | | | |
| **Sr. Phosphorus (mg/dL)** | 4.9 | | | |
| **Sr. Uric Acid (mg/dL)** | 9.1 | | | |
| **Urea nitrogen** | 54 | | | |

| | | | | |
|---|---|---|---|---|
| **serum (mg/dl)** | | | | |
| **Sr. Sodium (mEq/L)** | 142 | 145 | | 143 |
| **Sr. Potassium (mEq/L)** | 4.4 | 4.3 | | 3.8 |
| **Sr. Chloride (mEq/L)** | 109 | 111 | | 109 |
| **Lactate Dehydrogenase Serum (LDH) (U/L)** | | 214 | | |
| **Reticulocyte Count (%)** | | 0.1 | | 0.2 |
| **Routine Urine Examination** | Pus Cells – 1-2/hpf<br><br>Epithelial Cells – 2-4/hpf | | | |
| **Routine Stool Examination** | Pus Cells – 1-2/hpf<br><br>Epithelial Cells – 1-2/hpf | | | |

## Discussion

Sideroblasts are found in normal bone marrow, in the nucleated red cell precursors. They contain granules with non-heme iron.
Sideroblastic anemias are a heterogeneous group of disorders characterized by ring sideroblasts in the peripheral blood and impaired heme biosynthesis. The ring sideroblast(RS) is a pathological erythroid

precursor that contains excessive deposits of nonheme iron in the mitochondria. They are erythroid precursors with mitochondrial iron accumulation appearing as perinuclear granules on bone marrow (BM)smears.These cells are identified on Prussian blue staining of the bone marrow aspirate, in which bluish-green inclusions (siderosomes) can be seen as a “ring” around the nucleus.

“Ring sideroblasts are mainly observed in myelodysplastic syndromes (MDS) particularly refractory anemia with ring sideroblasts (RARS) and less often in several types of inherited sideroblastic anemia”.[1] “RARS is defined by both the presence of dyserythropoiesis and 15% or more RS among the erythroid precursors”.[2] “Molecular mechanisms leading to RS in RARS are not well understood”.[3] “Recently, mutations of *SF3B1*, a gene implicated in the spliceosome machinery, were found in up to 60–75% of RARS”.[4] “Altered function of SF3B1 protein seems responsible for the phenotype observed in RARS”.[5]

Sideroblastic anemia may be secondary to drugs (i.e., chloramphenicol, busalfan, pyrazinamide, D-penicillamine, and progesterone), toxins (alcohol, arsenic and lead), nutritional deficiencies (copper and pyridoxine), myelodysplastic syndrome, or idiopathic in origin. A rare form of sideroblastic anemia is an inherited X-linked deficiency of ALA synthase.

“Linezolid, an oxazolidinone antibiotic approved for the treatment of respiratory tract and skin infection caused by Gram-positive bacteria, is known to have mitochondrial toxicity”.[6] Mitochondrial toxicity is explained by linezolid’s specific binding to mitochondrial ribosomes, leading to inhibition of mitochondrial protein synthesis.[7]

“The anti-bacterial mechanism of action of Linezolid is the disruption of protein synthesis by the binding of the drug to the 70S initiation complexes in the bacterial ribosomes”.[8]“However, the same mechanism also allows it to bind to human mitochondria and inhibit protein synthesis, resulting in failure to make protoporphyrin. Therefore, iron accumulates in mitochondria resulting in Ring sideroblasts.The mechanism is similar to that of

chloramphenicol (inhibition of mitochondrial translation, induction of reversible sideroblastic anemia after a median exposure of 2 weeks). Thrombocytopenia is attributed to the suppression of the final step of platelet release from mature megakaryocytes, as well as immune-mediated platelet destruction".[9]

"Linezolid has emerged as a viable option for the treatment of resistant TB.According to the National TB Elimination Program guidelines,linezolid is an important drug in the regimen of MDR and XDR-TB.However, there are reports of variation in safety profiles related to dosage and duration of therapy".[10] The spectrum of adverse effects is hematological (anemia, leukopenia, and thrombocytopenia), neurological and gastrointestinal."Hematologic abnormalities were consistent with mild, reversible, duration-dependent myelosuppression. Thrombocytopenia and a slight increased risk for anemia were evident at ≥2 weeks of linezolid treatment[11]. linezolid produced time- and dose-dependent reversible myelosuppression with doses up to 1,000 mg/kg of body weight/day"[11].Though the adverse events are common following prolonged Linezolid use, the occurrence of sideroblastic anemia is rare.

## Conclusion

Patient case reports are valuable resources of new and unusual information that may lead to vital research.
Treatment regimen recommended for resistant tuberculosis consists of various drugs and these drugs are prescribed for 18-20 months. Such a

long duration therapy and high dose of antibiotics result in adverse drug reactions (ADRs). ADRs may lead to various complications in disease management like replacement of drugs, dose increment, therapy withdrawal, etc.

Hematologists should reconsider about diagnosing MDS as RARS in case of recent or concomitant linezolid treatment.

Linezolid is one of those drugs, practiced as an anti-mycobacterial agent and it is an important member of drug regimen for MDR and XDR tuberculosis. This case emphasizes the need for clinicians to be vigilant for hematological adverse effects during linezolid therapy, particularly when linezolid is used at higher doses and longer durations. Early recognition and prompt discontinuation of the offending agent are crucial for optimal patient outcomes. Further research is warranted to elucidate the pathogenesis of linezolid-induced sideroblastic anemia and identify potential risk factors for its development.

## Ethical Approval:

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

## Consent

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

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Details of the AI usage are given below:

1.

2.

3.

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