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A CASE REPORT: SIDE EFFECT OF LINEZOLID IN PULMONARY RIFAMPICIN RESISTANCE TUBERCULOSIS

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Abstract: A Case Report: Side Effect Of Linezolid In Pulmonary Rifampicin Resistance Tuberculosis. *Linezolid is a very potent treatment for pulmonary tuberculosis, but it has some side effects. Patients with drug-resistant pulmonary tuberculosis may experience anemia as a side effect of taking the multidrug-resistant tuberculosis medication Linezolid. A 58-year-old man's primary complaint in one case reported to RSUD dr. H. Abdul Moeloek Lampung was a weakness. The diagnosis was made based on anamnesis, a physical examination, and supporting examinations. Treatment was given both pharmacologically and non-pharmacologically, including the intervention to discontinue Linezolid. Although linezolid-based combination therapy in program conditions is associated with favorable outcomes, side effects should be monitored closely, which may require discontinuation of the drug and taking appropriate steps to treat side effects.*
Keywords: *Anemia,Linezolid, Pulmonary TB.*

Abstrak: Laporan Kasus: Linezolid digunakan sebagai terapi pada kasus tuberkulosis paru yang resistens terhadap Rifampisin, namun penggunaan obat ini memiliki efek samping. Penderita tuberkulosis paru yang resistan terhadap obat yang menedapatkan terapi Linezolid mungkin mengalami anemia sebagai efek samping dari penggunaan obat ini. Dalam kasus ini dilaporkan bahwa seorang pria berusia 58 tahun datang ke RSUD dr. H. Abdul Moeloek Lampung dengan keluhan lemah dan lemas. Diagnosis ditegakkan berdasarkan anamnesis, pemeriksaan fisik, dan pemeriksaan penunjang. Pengobatan yang diberikan baik secara farmakologis maupun nonfarmakologis, termasuk intervensi penghentian linezolid. Meskipun terapi kombinasi berbasis linezolid sangat bermanfaat pada terapi TB, efek sampingnya harus dipantau secara ketat, karena mungkin memerlukan penghentian obat, dan diperlukan langkah yang tepat untuk mengatasi efek samping.
Kata Kunci: Anemia, Linezolid, TB Paru.

INTRODUCTION

Tuberculosis (TB) is an irresistible illness that's one of the most common causes of death worldwide. It can be cured by regulating anti-tuberculosis drugs (OAT). However, a few prove that tuberculosis patients who have completed treatment encounter tireless well-being issues after treatment. The remaining indications after tuberculosis can be characterized by anomalies within the lung parenchyma, respiratory tract, pleura/chest divider, vasculature, and mediastinum (Mustofa *et al.,* 2023).

A major public health concern, tuberculosis (TB), will kill about 1.3 million people worldwide in 2020. In 2021, the total number of TB patients climbed to 1.4 million. The WHO

estimates that 10.6 million people had tuberculosis in 2021. A major problem in TB treatment is that many patients do not follow their treatment plans, leading to less effective therapy (Marcu et al., 2023).

Pathogenic bacteria are still identified as the source of infection through isolation techniques that involve microscopy and pure culture media, followed by biochemical reactions. Nevertheless, some bacteria are challenging to isolate on pure culture media using the current methods, making it difficult to develop substitute techniques to determine the infection source (Mustofa, 2023). An estimated 10 million people globally had tuberculosis in 2019. There were 208,000 deaths from HIV that year, in addition to the 1.2 million deaths from HIV-negative people. Both men and women can get tuberculosis (TB), but in 2019, men accounted for 56% of cases, women for 32%, and children under the age of 15 for 12% of all cases. With approximately 0.5 million new cases of rifampicin-resistant TB (RR-TB), 78% of which were also resistant to multiple drugs (MDR-TB), drug-resistant tuberculosis (DR-TB) continues to be a severe threat. This resistance underscores the need for quicker, safer, and more potent treatments and poses a severe threat to the global TB epidemic (Alfenaar et al., 2017; Lin et al., 2011; Shah et al., 2017).

Of the 157,903 cases of rifampicin-resistant tuberculosis that were reported in 2020, 25,681 of them needed further treatment because they had developed resistance to essential medications such as bedaquiline, levofloxacin or moxifloxacin, and Linezolid. The current duration of treatment for DR-TB is 9 to 24 months, and it involves several medications with potentially fatal side effects, such as problems with the heart, nerves, liver, and blood (WHO, 2020). Methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE) are two pathogens resistant to other antibiotics that can cause bacterial infections. Linezolid, an antibiotic from the oxazolidinone class, treats these infections. According to Zhang et al. (2015), when first discovered in 2001, Linezolid was used to treat pneumonia caused by Staphylococcus aureus, bacteremia caused by vancomycin-resistant enterococcus, skin infections such as gangrene, and meningitis. Linezolid has been shown over time to be a very promising medication for treating patients with drug-resistant tuberculosis (DR-TB), including multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) (Pratama, 2020).

In 2018, patients with drug-resistant tuberculosis receiving individualized therapy were to receive Linezolid, bedaquiline, and fluoroquinolones as part of Group A, per WHO guidelines. In the 2011 World Health Organization guidelines for drug-resistant tuberculosis, Linezolid was first listed as a class 5 medication. Because of inadequate safety and efficacy data, this group was not advised to be treated as a primary treatment (WHO, 2011). However, in the 2016 WHO treatment guidelines, Linezolid was included in Group C as a major second-line agent for individualized therapy (WHO, 2016). Then, in the latest guidelines of 2018, Linezolid was promoted to Group A as a drug that should be prioritized for administration (WHO, 2018).

Linezolid is a promising drug for treating drug-resistant TB, and it has shown good results in lab and animal studies. It is quickly absorbed and well-distributed in the body, effectively reaching lung tissues and stopping protein synthesis early. Mustofa (2023) states that although the long-term prognostic factors are unknown, individuals with post-tuberculosis lung disease have a reduced life expectancy and a higher risk of developing tuberculosis again. Multiple tuberculosis episodes, drug-resistant tuberculosis, delayed diagnosis, and smoking are risk factors for post-tuberculosis lung disease. Recent case reports have shown improvements in MDR-TB patients treated with Linezolid. Still, the drug can cause significant side effects like

reversible blood cell suppression and nerve damage, which are related to dosage and duration of treatment, leading to its discontinuation in some cases (H-B. Xu et al., 2012).

We describe a case of a patient with DR-TB who had adverse effects from Linezolid during the first stage of treatment.

CASE REPORT

On March 13, 2023, a 58-year-old man was admitted to the Melati ward of RSUD Dr. H. Abdul Moeloek Lampung. His primary complaint at admission was weakness, which had persisted for three days. For the previous two months, he also complained of sporadic dyspnea that got worse when he coughed. There was no correlation between the weather, cold air, body posture and the dyspnea, nor was there wheezing associated with it. Breathlessness did not cause the patient to wake up during the night. He had a productive cough with white sputum for three months before admission, but he denied coughing up blood. The patient also experienced weight loss, although he did not measure it, without a loss of appetite, and had night sweats without physical activity. He denied back pain, nausea, and vomiting and had no complaints about urination. He also denied chest pain.

The patient had undergone a rapid molecular test (TCM) at a health center on January 13, 2023, which detected Mycobacterium tuberculosis with rifampicin resistance, and he started DR-TB treatment on February 6, 2023. He had no prior history of diabetes mellitus or hypertension. Upon physical examination, the patient had a GCS score of E4V5M6 (15), appeared somewhat ill, and was fully conscious. He had a temperature of 36.5°C, a pulse rate of 110 beats per minute, a respiratory rate of 20 breaths per minute, a blood pressure of 110/70 mmHg, and an oxygen saturation of 98% on room air. His height was 156 cm, his body mass index (BMI) was 16.8 kg/m², and he weighed 40 kg.

The head and neck examination were within normal limits, but the conjunctivae were pale, the sclerae were not jaundiced, and no enlarged lymph nodes were found around the neck. The cardiac examination was normal, with no murmurs or gallops. The lung examination revealed broncho-vesicular breath sounds with rhonchi in the upper lung fields without wheezing. The abdomen was flat and soft, with normal bowel sounds, and neither the liver nor spleen was palpable. There were no ascites or tenderness. The spine examination showed no gibbous.

Extremities examination revealed no cyanosis, tenderness, or hyperemia. Motor strength was normal (5/5) in both upper and lower extremities, with no edema.

Hemoglobin was measured at 7.2 g/dl, hematocrit was at 21%, leukocytes were 4,830 cells/µl, erythrocytes 2.5 million/µl, segment 81%, MCHC was at 31%, eosinophils were 0%, band neutrophils were 0%, monocytes were 9%, lymphocytes were 9%, ESR was 46 mm/hour, albumin was 2.7 g/dl, creatinine was 1.29 mg/dl, calcium was 8.0 mg/dl, chloride was 107 mmol/L, SGPT was 44 u/L, and total bilirubin was measured at 0.4 mg/dl. The levels of potassium and sodium were normal (Tables 1 & 2). A chest X-ray revealed consolidation of the right lung, the right superior intercostal space widening, and infiltrative lesions in both lungs. On echocardiography, a sinus rhythm was seen. (Figure 1).

Table 1. Blood Test

	RSAM 13/03/2023	RSAM 15/03/2023	Normal Range	
Hb	**7,2***	**10,7***	g/dL	13,2-17,3
Leukocytes	4.830	5.220	/µL	3.800 – 10.600
Hematocrit	**21***	31	%	40 - 52

Erythrocytes	**2.5***	**3.8***	Juta/µL	4.4 – 5.9
Thrombocytes	185.000	209.000	fL	150.000 – 440.000
MCV	83	81	Pg	80 - 100
MCH	29	28	g%	26 - 34
MCHC	35	35	%	32 - 36
Basophil	0	0	%	0 - 1
Eosinophil	**1***	0	%	2 - 4
Stem Cells	**0***	**0***	%	3 - 5
Segment Cells	**81***	**84***	%	50 – 70
Lymphocytes	**9***	**9***	%	25 – 40
Monocytes	**9***	7	%	2 – 8
LED	**46***	-	Mm/jam	0 – 10

Based on the anamnesis, physical examination, and supporting examinations, the working diagnosis was primary pulmonary TB confirmed bacteriologically with rifampicin resistance, far-advanced lesions, HIV-negative status, long-term treatment in the second month, normocytic normochromic anemia, and hypoalbuminemia. The patient was treated for three days, continuing his previous medication regimen consisting of bedaquiline 1x400 mg, Levofloxacin 1x750 mg, Linezolid 1x600 mg, Ethambutol 1x800 mg, Cycloserine 1x500 mg, and Vitamin B6 1x100 mg. During the hospital stay, Linezolid was discontinued for two weeks, and he received additional therapy with intravenous albumin 3x1. He also underwent non-pharmacological treatment, receiving a 400 cc PRC transfusion. A repeat blood test on March 15, 2023, showed hemoglobin 10.7 g/dl, hematocrit 31%, leukocytes 5,220 cells/µl, erythrocytes 3.8 million/µl, segment 84%, MCHC 31 g%, eosinophils 0%, band neutrophils 0%, monocytes 9%, lymphocytes 7%, and follow-up AFB and quantitative HIV tests were conducted (Table 1 & 2).

Table 2. Clinical Biochemistry

	RSAM 13/03/2023	**Normal Range**	
GDS	108	mg/dL	< 140
Ureum	39	mg/dL	17 - 43
Creatinine	**1,29***	mg/dL	< 1,20
Uric Acid	5,7	mg/dL	3,4 – 7,0
Na	137	mg/dL	135 - 147
K	3,9	mg/dL	3,5 – 5,0
Ca	**8,0***	mg/dL	8,8 – 10,0
Chlorida	**107***	mmol/L	95 - 105
SGPT	**44***	u/L	0 - 35
SGOT	5	u/L	0 - 35
Total Bilirubin	0,4	mg/dL	0,1 - 1
Direct Bilirubin	0,1	mg/dL	0,0 – 0,2
Indirect Bilirubin	0,3	mg/dL	-
Rapid Antigen	NON REAKTIF		NON REAKTIF
Albumin	**2,7***	mg/dL	3,5 – 3,2
Globulin	2,3	mg/dL	2,3 – 3,5

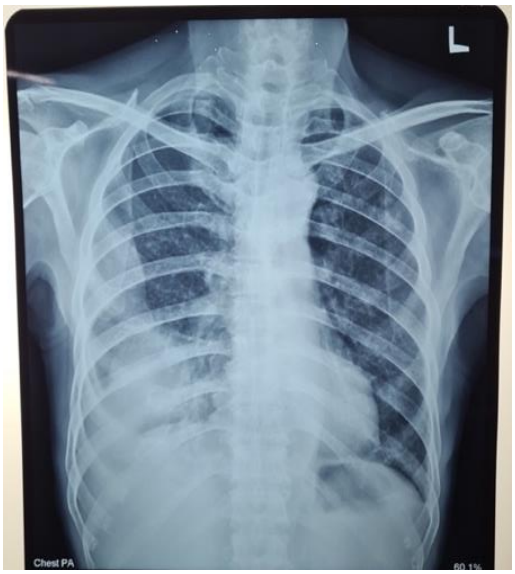

Figure 1. The Chest radiograph showed a widening of the right superior intercostal space, infiltrative lesions in both lung fields, and consolidation of the right lung.

DISCUSSION

The 58-year-old man who presented with weakness, shortness of breath, cough, and weight loss three days before admission is the subject of this case report. Sub-acute or chronic forms of active tuberculosis (TB) usually appear over weeks to months and are characterized by constitutional symptoms like fever, sweats at night, anorexia, and weight loss (Cavalhiero et al., 2020; Huang et al., 2022).

The Xpert MTB test is exceptionally touchy and particular in quickly diagnosing pneumonic tuberculosis. This strategy has critical demonstrative utility in distinguishing M. Tuberculosis in cases where smears are negative since it has shown prevalent execution compared to Ziehl-Neelsen (ZN) Recolored spread microscopy by an edge of 10-15%. This strategy can improve the recognizable proof of Mycobacterium tuberculosis by two to triple compared (Mustofa, 2023).

The patient had a history of rapid molecular testing (TCM) at a health center, which detected Mycobacterium tuberculosis with rifampicin resistance. Drug mutations that reduce drug accumulation in the bacteria or render the drug inactive are the source of drug resistance in Mycobacterium, including rifampicin resistance. These mutations may reduce the drug's binding ability to its target gene. Resistance in the bacteria can also arise when mutations elevate target gene expression to the point where the medication is unable to inhibit the target. (J.L. Khawbung et al., 2021).

Laboratory results showed decreased Hb, Ht, and erythrocytes, supporting the patient's main complaint of weakness and anemic conjunctiva, with no signs of bleeding. It is well known that TB infections harm the lungs and cause systemic inflammation. Anemia of chronic disease (ACD) is a clinical phenomenon defined by the onset of anemia in patients with neoplastic diseases, inflammatory diseases, autoimmune disorders, and infectious diseases (fungal, bacterial, or viral) such as tuberculosis. These diseases are caused by inflammation-related pathogenesis, which includes reduced erythropoietin supply or sensitivity, poor erythrocyte iron incorporation, and shortened erythrocyte lifespan. Anemia is common in most active tuberculosis

patients, most likely caused by inflammation rather than an iron deficiency. (Dasaradhan et al., 2022; Sahiratmaja et al., 2007).

A chest X-ray revealed consolidation of the right lung, the right superior intercostal space widening, and infiltrative lung lesions (Figure 1). An early and consistent finding of reactivated dormant tuberculosis needs to be more patchy and better-defined consolidation. In tuberculosis, the superior segment of the lower lobes and the apical and posterior segments of the upper lobes are highly preferred by consolidation and cavitation. Cavitation is common in chest radiography, occurring in 20% to 45% of patients. The largest dimension of a cavity can reach several centimeters, and its walls can become thick and uneven. Cavitary lesions can be multifocal and are frequently observed in areas of consolidation. (Nachiappan et al., 2017).

Anemia and rifampicin-resistant tuberculosis were the patient's diagnoses. Nevertheless, the patient had anemia even though they were receiving TB treatment without experiencing bleeding or loss of appetite. Since TB treatment is sufficient to restore Hb levels, most TB patients may experience anemia, most likely from inflammation rather than iron deficiency. Nevertheless, this patient developed anemia while receiving treatment for drug-resistant tuberculosis. Anemia in adult TB patients is associated with many risk factors, including low body mass index (BMI), HIV infection, worm coinfection, low selenium concentration, aging, high retroviral load, high IL-6 concentration, female gender, and side effects from TB drugs (Dasaradhan, 2022).

The patient received initial phase DR-TB therapy, including Bedaquiline 1x400 mg, Levofloxacin 1x750 mg, Linezolid 1x600 mg, Ethambutol 1x800 mg, Cycloserine 1x500 mg, and Vitamin B6 1x100 mg. Long-term DR-TB treatment regimens (18–24 months) are given to patients who cannot receive short-term treatment regimens. Unlike short-term regimens, long-term DR-TB treatment regimens can be modified according to the patient's condition (individualized), thereby increasing the effectiveness and safety of this regimen in treating DR-TB patients (Ministry of Health RI, 2020).

During treatment, Linezolid was discontinued for two weeks due to suspected side effects causing anemia. Synthetic antibiotic linezolid (LZD) binds to rRNA on the 30S and 50S ribosomal subunits to prevent bacterial protein synthesis. Clinical studies have shown that LZD is an effective adjuvant antibiotic that can be used to treat a variety of drug-resistant strains, including extensively drug-resistant TB (XDR-TB), vancomycin-resistant enterococcus faecium (VREF), multidrug-resistant TB (MDR-TB), and methicillin-resistant S. aureus (MRSA). Among the relatively minor and transient side effects of living with zone VIII diabetes are neuropathy, hyperlactatemia, reversible myelosuppression, diarrhea, nausea, headaches, and hypoglycemia. Although extremely rare, severe hypoglycemia and anemia brought on by Linezolid may have significant adverse effects. The side effects of Linezolid include peripheral neuropathy, optic neuropathy, and bone marrow suppression, which can result in anemia and thrombocytopenia, as well as blindness and disability, which are typically irreversible. Compliance issues frequently result from gastrointestinal disturbances (Lee et al., 2012; Ramachandran, 2015).

During treatment, the patient also received a 400 cc PRC transfusion, and after a two-week discontinuation of Linezolid, it was reintroduced gradually at a dose of 300 mg per day. According to the DR-TB treatment guidelines, after addressing Linezolid side effects, such as permanent discontinuation in cases of severe myelosuppression (anemia, leukopenia, thrombocytopenia), strict patient evaluation, and investigating other causes besides Linezolid, such as bleeding or other comorbid diseases, Linezolid can be reintroduced starting at 300 mg per day (and gradually increased) if there is improvement and if LZD is one of the effective drugs. In cases of severe anemia (Hb <8 mg/dL),

the patient is hospitalized and given a blood transfusion. Anemia related to Linezolid is dose-dependent. The Linezolid dose for managing MDR-TB is 600 mg/day. A meta-analysis study by Miliard et al. stated that a Linezolid dose of 300 mg every 12 hours has the same effect as 600 mg every 24 hours with a lower risk of side effects (Ministry of Health RI, 2020; Millard et al., 2018).

CONCLUSION

A case has been reported of a 58-year-old man diagnosed with primary pulmonary TB confirmed bacteriologically with rifampicin resistance, far-advanced lesions, and HIV-negative status. The patient was in the second month of long-term treatment, presenting with normocytic normochromic anemia and hypoalbuminemia. The diagnosis was based on anamnesis, revealing weakness for three days before admission, accompanied by shortness of breath, cough, and weight loss. Lung examination revealed broncho-vesicular breath sounds with rhonchi in both lung fields. Chest radiography showed a widening of the right superior intercostal space and infiltrative lesions in both lung fields, with right lung consolidation.

Pharmacological therapy included antituberculosis drugs (OAT), definitive antibiotics, and non-pharmacological therapy, including a 400cc PRC transfusion and discontinuation of the side-effect-causing drug Linezolid. The patient's follow-up involved reintroducing Linezolid at a gradual dose after two weeks, along with follow-up AFB and quantitative HIV tests.

While Linezolid-based combination therapy in program settings is associated with favorable outcomes, side effects must be closely monitored, potentially requiring drug discontinuation, especially in the first two months. TB-resistant patients on Linezolid regimens with a history of recurrent anemia should regularly monitor their Hb levels and take appropriate steps to manage side effects.

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