


CASE REPORT

Rifampicin mono resistant tuberculosis (RR-TB): a case report

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ABSTRACT

Introduction: Tuberculosis (TB) is a human disease caused by *Mycobacterium tuberculosis*. The bacteria is a rod-shaped and acid-resistant, hence it is also known as acid fast Bacilli. The disease mainly affects the lungs, making pulmonary disease the most common presentation of Tuberculosis. Despite advances in tuberculosis control and a decline in new cases and deaths, the disease remains a huge burden of morbidity and mortality worldwide. Diagnosis is at the forefront of TB management. Accurate diagnosis will be followed by appropriate management, thereby reducing mortality and morbidity from TB. **Case Report:** A 41-year-old male patient came to Puskesmas Kedurus after hospitalization at RSUD Dr. Soetomo after being diagnosed with TB-RO. Previously, the patient had a cough and weight loss for about 1 year, cough with greenish-yellow sputum, not containing blood. The patient began complaining about shortness of breath since 1 month ago, with the results of thorax photos and Real-Time Polymerase Chain Reaction (RT-PCR) supporting the diagnosis of Drug-resistant Tuberculosis. The patient received anti-tuberculosis drugs according to standard therapy for Multi-Drug Tuberculosis (MDR-TB) patients with a minimum treatment duration of 20 months. **Conclusion:** The risk factor for Tuberculosis in this patient was the surrounding community where the patient works daily with many coworkers who suffer from prolonged cough. The patient's prognosis is good if complaints are resolved immediately and anti-tuberculosis drugs were taken regularly. The patient still needs further education, especially regarding the cough etiquette and implementing healthy lifestyle in the household setting.



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Highlights

1. Tuberculosis is prevalent in Indonesia, and it placed Indonesia as the number 3 country with high prevalence of TB in 2020.
2. Tuberculosis spread not only from the family member, but also from the community, and drug resistance tuberculosis is still a global burden related to antibiotic medication.



BACKGROUND

Tuberculosis (TB) is a human disease caused by *Mycobacterium tuberculosis* infection. The bacteria is a rod-shaped, acid-resistant bacterium also known as acid-fast bacilli (Campbell and Bah-Sow, 2006). The disease is spread via airborne droplets, and it is estimated that 1 in 4 people had immunological response to this bacterial infection, whether in the dormant or disease form (Gill et al., 2022). TB is one of the oldest human disease which causes major mortality as more than two million people die due to this disease (Smith, 2003). Indonesia has been ranked as third country with the most frequent of TB infection worldwide, as it counts 8% of TB cases (Marliana Nurprilinda et al., 2023).

Mostly, TB affecting the lungs, manifest as pulmonary disease (Adigun and Singh, 2024). However this disease also affecting other systems, include the respiratory system, presented in the form of parenchymal or extraparenchymal disease as the primary cause of respiratory failure (Chopra et al., 2021). Other system may infected due to hematogenous and lymphogenous spread (Marliana Nurprilinda et al., 2023), such as gastrointestinal (GI) system in the form of abdominal tuberculosis (Putranto et al., 2018), lymphoreticular system (Putranto et al., 2018), skin (Nguyen et al., 2023), central nervous system (CNS) (Rock et al., 2008), musculoskeletal system (Chowdhury and Chakraborty, 2017), reproductive system (Kumar, 2008), and liver (Hickey et al., 2015).

Diagnosis of TB using interferon- γ release assay (IGRA) or tuberculin skin test (TST) is the first-line recommendation medical treatment for TB patients (Lewinsohn et al., 2017), followed by recognition of drug's resistance (Gill et al., 2022). Accurate diagnosis followed by appropriate medical management with high efficacy will reduces morbidity and mortality significantly reduces morbidity and mortality of TB severity, and prevents TB transmission (Nahid et al., 2006). Diagnosis of pulmonary TB is generally carried out by conducting clinical examinations (from the history of the patient's complaints and the results of the physical examination of the patient), and supported by the results of radiologic examination and laboratory tests (Heemskerk et al., 2015).

Drug resistance tuberculosis is one of global burden due to antimicrobial resistance, which cost healthcare budget and endemic in many country (Liebenberg et al., 2022). This condition even makes the treatment of TB is getting difficult and challenging, which leading to the death (Khawbung et al., 2021). The causes of drug resistance TB are failed or discontinued treatment and BMI less than 18.5 (Windiyarningsih and Badaruddin, 2021), smokers, diabetic, HIV, contact with MDR-TB (Iradukunda et al., 2021), poverty and vulnerability (Souza et al., 2021). The pattern of drug resistance mostly in the form of Rifampicin mono resistant (RR-TB) and Multi Drug-Resistant Tuberculosis (MDR-TB) (Simbwa et al., 2021). On both type RR-TB is the more serious type of TB than MDR-TB (Gill et al., 2022). MDR-TB defined as resistance of *M. tuberculosis* against at least rifampicin and isoniazid (Lange et al., 2018). RR-TB prevalent was 50% of global cases, but became 90% in 2018 (Fu et al., 2021). RR-TB is rare and associated with poor outcome, as it contributed to a high risk failure for TB medication (Gibson et al., 2018).

OBJECTIVE

To presents a Rifampicin mono resistance tuberculosis case in a 41-years-old man with underweight and no history of TB infection in the family, but in the patient's community.

CASE REPORT

A 41-year-old man patient came to Kedurus Health Center after MRS at RSUD dr. Soetomo after being diagnosed with TB-RO. Previously, the patient had experienced cough for about 1 year, the cough was continuous, and did not improve for 1 year despite treatment. The cough was sometimes dry, sometimes with phlegm. The phlegm was greenish-yellow in color and not accompanied by blood. The patient said he had lost about 10 kg since last year. The patient stated that he did not take any medication during coughing. The patient also complained of shortness of breath since 1 month ago. After contact tracing, no source of transmission from the family was found, but based on information before the patient suffering from cough, the patient often gathered with friends at work, and some of these friends had a cough which was a possible source of transmission of TB infection. The patient has smoked since the age of 27 years, ½ - 1 pack of cigarettes per day, but stated that he has not smoked since 5 years ago. The patient sleeps in a separate room with other family members.

Physical examination of the patient found that the general condition appeared mildly ill, fully conscious, with good hygiene of clothing, hair and nails. The anthropometric examination shows that the patient's body weight is 40 kg, with a height of 160 cm, therefore the body mass index calculation result is 15.6, which means that the patient was underweight. The patient's vital signs show blood pressure of 110/80 mmHg, pulse of 92 x/min palpable strong and regular, respiratory rate of 26 x/min, temperature of 37.10C, and oxygen saturation of 98%. General status examination of the head and neck region did not find any abnormalities, in the thorax region a Water Sealed Drainage (WSD) was attached to the right chest with symmetrical breath movements on both sides, obtained faint percussion in the right hemithorax and sonor in the left hemithorax. Auscultatory examination found vesicular sound in both patient's hemithorax. Examination of the abdominal region and extremities did not reveal any abnormalities.



Figure 1. Rontgen imaging of patient's thorax region

Radiologic examination of patient's thorax region shows right pneumothorax, pulmonary TB accompanied by upper left schwarte, and subcutis emphysema in the right hemithorax region and right shoulder to right colli. RT-PCR examination which was examined at RSUD dr. Soetomo showed a positive MTB result of Rifampicin resistance.

The patient was given a combination of anti-TB drugs from the second and first line of Obat Anti Tuberculosis (OAT), which is called the OAT combination for patients with stable MDR-TB with a minimum treatment duration of 20 months. The dose was adjusted to the patient's weight of 40 kg and the patient was included in the criteria for new MDR TB and therefore was given drugs such as Kanamycin injection 625-750 mg/day for 5 days, Levofloxacin PO 1000 mg/day for 7 days, Etionamid PO 500 mg/day, Cycloserine 500 mg/day PO for 7 days, Pyrazinamide 1000 mg/day PO every 7 days, Ethambutol 800 mg/day PO for 7 days, and Isoniazid 200 mg/day PO for 7 days. All drug components were given for 8 months for the initial stage. The number of oral drugs given and swallowed is at least 224 doses and injections are at least 160 doses. For the advanced stage, it is given for 12 months without injection drugs taken once for 7 days a week with components namely Levofloxacin, Etionamid, Cycloserine, Ethambutol, and Isoniazid (8 Km5 - Lfx7 - Eto7 - Cs7 - Z7- (E)7 - (H)7 / 12 Lfx7 - Eto7 - Cs7 - Z7- (E)7- (H)7).

The number of oral medications administered and swallowed was at least 336 doses. The patient was

also given vitamin B6 at a dose of 50 mg per 250 mg of Cycloserine. In addition to medical therapy, patients also received education about MDR-TB disease and other aspects related to the treatment process and prevention of transmission of MDR-TB to the surrounding community.

The planned monitoring of the patient includes 2 consecutive sputum culture examinations with a 30-day interval to assess treatment response, laboratory examinations including GDA and hepatic function (SGOT and SGPT), clinical evaluation of the patient including evaluation of patient complaints, patient weight growth, patient vital signs, drug side effects, and patient drug compliance are also carried out to ensure optimal treatment process.

DISCUSSION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* which is actually curable and preventable now, even the numbers of infected people is huge. But this disease could progress to the severe one if the diagnosis was delayed, or affecting the elderly (Silva et al., 2012). TB risk factors including those with type 2 diabetes mellitus (T2DM) and HIV (Goletti et al., 2023). Most TB bacteria affect the lungs, but also also affect other organs, so it is termed as extrapulmonary TB (Gopalaswamy et al., 2021). Active tuberculosis is a multiorgan disease caused by primary infection or as a reactivation of latent tuberculosis (Silva et al., 2012). World Health Organization (WHO) defined latent TB based on the presence of specific immune response while the clinical sign is absent (Bommart et al., 2021). MDR-TB or Multi Drugs Resistance Tuberculosis is a TB disease in which the bacteria are resistant to anti-TB treatment (Seung et al., 2015), namely isoniazid and rifampicin simultaneously, which is the most effective treatment for treating TB patients (Prasad et al., 2018). Resistance to these two drugs can be followed by resistance to other first-line drugs. MDR-TB is one of the classes of Drug Resistant Tuberculosis (DR-TB) (Chowdhury et al., 2023). The causes of DR-TB include inadequate treatment, short-term effects of chemotherapy, and community transmission of the disease (Seung et al., 2015). Prevention of TB infection includes prophylactic treatment in locations at high risk of TB transmission, prophylactic treatment of patients with MDR-TB, and vaccination (Salazar-Austin et al., 2022).

This article reports a patient who visited the Puskesmas Kedurus for the purpose of taking TB medication. The patient's complaints included a chronic progressive cough for 1 year with greenish-yellow sputum without blood. Field et al. (2018) stated that cough is common in pulmonary TB (Field et al., 2018). Sputum color plays an important role for disease determination in pulmonary disease, in which yellowish dan greenish sputum are strong predictors for acute respiratory infections which means the patient needs antibiotic medication (Altiner et al., 2009). The patient also complained of weight loss since 1 year ago, plus shortness of breath that began to appear 1 month ago. The patient was initially diagnosed with right pneumothorax and referred to an advanced health facility, only to find out that the cause of the pneumothorax was DR-TB infection. TB patients suffer from severe weight loss (Van Crevel et al., 2002). TB is a wasting disease, so body weight of the patient receiving TB medication will be fluctuated, which reflects the improvement or worsened the disease (Warmelink et al., 2011). Weight loss of 2 kg or more during the first month of medication could be the indication of toxicity, so anthropometric investigation for TB patient is crucial (Bernabe-Ortiz et al., 2011). Weight loss means of immunosuppressive and determinant of disease severity (Van Crevel et al., 2002).

Physical examination of the patient also supported the diagnosis of TB infection, with a respiratory rate of 26x/min, temperature of 37.1°C, BMI of 15.6 (underweight), and faint percussion in the right hemithorax and sonor in the left hemithorax. The supporting examination of radiologic examination and RT-PCR test also supported the diagnosis of TB infection with Resistance to Rifampicin (RR-TB). RR-TB is defined as the detection of resistance to Rifampicin using genotypic or phenotypic methods with or without resistance to other first-line anti-TB drugs. RR-TB including multidrug resistance (MDR) and polydrug resistance (Gill et al., 2022). To detect MDR-TB/RR-TB, the bacteriological evidence is the golden standard, which based on sputum smear microscopy and culture of *M. tuberculosis* along with drug susceptibility testing (DST) (Prasad et al., 2018). Prevention of TB drug resistances is important to improve the patient's outcome and reduce the diseases burden (Fu et al., 2021). Rifampicin is the main drugs for TB treatment, so resistance to this drug commonly associated with isoniazid resistance, which lead to an MDR-TB (Gibson et al., 2018). The mechanism of RR-TB including the mutation of *rpoB* gene (common in *M. tuberculosis* isolates), which located

in an 81-base-pair region of RIF resistance-determining region (RRDR), in the codons of 516, 526, and 531. Other mechanism including efflux pump mechanism (responsible for 6% of RIF resistance), and mutation in *rpoB Ile491Phe* (Malenfant and Brewer, 2021).

American Thoracic Society Centers for Disease Control and Infectious Diseases Society of America in 2003 recommended a 12–18-month medication with isoniazid, ethambutol, and a fluoroquinolone, with addition pyrazinamide for the first 2 months, and WHO guideline recommended as MDR-TB guidelines, which requires a 9-12-months of treatment, or even 18-20 months in some case. The medication needs multiple second-line anti-TB agents, including injectable agents for 4-8 months, which means increased toxicity and cost (Gibson et al., 2018). The medical therapy receiving by the patient is already in line with other (Prasad et al., 2018).



Figure 2. Patient's house

The patient is planned to be monitored for compliance and vital signs, including weight gain and side effects. Laboratory tests to evaluate the patient's therapy included two consecutive culture tests with a 30-day interval showing negative results that were originally positive (conversion culture), as a response to successful treatment, GDA check, hepatic function check (SGPT and SGOT). Patient compliance in taking medication is also evaluated to ensure optimal TB therapy. MDR-TB/RR-TB medication is a high risk of treatment with failure and mortality, with successful rate only 56% globally (Soeroto et al., 2021). A study stated that the successful rate of MDR-TB/RR-TB treatment was 64.5%, which is associated with gender, malnutrition, history of previous TB treatment, and time of culture conversion for more than two months (Soeroto et al., 2022). The treatment of MDR-TB/RR-TB is complex arduous and long-term, as it including the second-line TB drugs, which means there were a high risk of adverse drugs reactions, poor outcomes, costly (Soeroto et al., 2022), had chronic post-infectious sequelae and loss of organ function (Makaminan et al., 2022). Compliance influencing patient's outcome, so it is important to evaluate the medication (Vernon A et al., 2019) via DOT (directly observed treatment, short course) which is recommendation strategy to control TB. DOT is direct observation of therapy done by a health worker or nominated (DOT supporter) (Munro et al., 2007). The most important outcomes of TB treatment including survival, disability and capacity for functioning in daily life. Microbiological culture of sputum is needed to evaluate the efficacy of the

treatment, in which positive culture means failure (Gler et al., 2013).

Monitoring of RR-TB medication is needed to predict the treatment outcomes. All the doctors hope the disease had improve due to the introduction of new agents (Caminero et al., 2017). The monitoring including assessing the adverse drug reaction, persistent or reappearance TB sign, including weight loss, and TB medication interruption. Weight should be monitored every month and the drug dosage should be adjusted. Weight loss during treatment is a good indicator for successful rate. Patients receiving TB medication was expected to experience weight gain, and weight loss during the first 2 month of the treatment was an indicator for treatment failure, as one of TB symptoms is weight loss (Hoa et al., 2013). Body weight change of the patients receiving TB medication was ranged from -4 kg to 20 kg, and the changes were associated with age (< 45 years old) (Vasanthi et al., 2009), men, had diabetic, and consuming alcohol (Kalva et al., 2023). Weight change monitoring during MDR-TB medication is so important as it associated with the survival rate of the patients, especially at the end of the third, fourth and fifth treatment months (Chung-Delgado et al., 2014). Hepatotoxicity is the risk for the usage of the combination OAT and Rifampicin for TB patients, and the risk is increased in elderly (aged >60 years), marked by the increment of ALT (alanine aminotransferase) during the second week of the treatment (Makaminan et al., 2022).

TB medication often left sequelae to the patients, and only a minority with successful complete medication had no side effects (Zaleskis, 2005). Complications of TB infection that can occur in patients if not treated properly include MDR-TB, pulmonary atelectasis, coughing up blood, pleuritis (pleural effusion), schwarte, and empyema, tuberculosis of other organs, post TB obstruction syndrome, cor pulmonale, hypokalemia, and pneumothorax (Behera, 2019). Pulmonary TB, even if it is treated, will be had complications, as TB is a destructive process that leads to cicatrization, alteration of parenchyma, bronchiectasis and scarring the lung, and reducing the volume of the lung so that affecting the pulmonary function. Post TB complication including relapse and re-infection, and infection other pathogens (Behera, 2019). The long-term effect of TB including fibrosis, bronchiectasis, Chronic Pulmonary Aspergillosis (CPA), air way stenosis and Chronic Obstructive Pulmonary Disease (COPD), and even lung cancer (Chakaya et al., 2016).

Contact tracing has been carried out which aims to find TB cases early by screening for TB symptoms and risk factors for all contacts of TB patients and preventing transmission to healthy contacts by providing education on clean and healthy living behavior so as to break the chain of TB transmission. TB preventive therapy including TB contact tracing to reduce the risk of TB in the community (Kadyrov et al., 2023). It defines as the method to find the person whom contacted with TB patients (UK health Security Agency, 2023), and claimed to be an efficient and targeted approach to find the cases (Dzhangaziev et al., 2020). The risk of having TB is higher in TB contacts, especially during the first three years, so investigating TB contact is the core activity for early identification of active TB (Loh et al., 2023). The findings obtained were that the patient lived in the same house with the patient's mother. The patient and the patient's mother each occupy one bedroom. Currently, none of the patient's family members show symptoms of coughing for more than 2 weeks, fever, night sweats without activity, weight loss, or enlarged lymph nodes. The patient's residence is a one-story house with adequate ventilation, and lighting, and located in a crowded neighborhood, both of which are risk factors for TB transmission. This information can serve as a basis for holistic and comprehensive management of the patient and his family.

Education provided to patients includes diagnosis, therapy, and prevention of TB transmission to the surrounding community, which includes methods of the disease process, TB transmission, and therapy that will be carried out, routine control schedules that must be followed by patients are also educated to ensure the eradication of TB bacteria. TB is one of communicable disease that can be prevented via health education. The program with lecture method and group discussion using flipchart and video as the media could be used to change the attitude of the audience, such as taking medicine regularly and on-time, so that reduced the prevalent of MDR-TB in the society (Malini et al., 2021). Health education given to the patients, family and patient's community was expected to increase the knowledge and awareness about MDR-TB, as it is the crucial aspect for effective prevention (Octaviana et al., 2019). A study showed that with the structured education of TB was significantly affected the knowledge, attitude, and the prevention of TB transmission (Astuti et al., 2019). The education for the patients including: coughing etiquette, recommendations for wearing masks, prohibition of sputum littering carelessly, prohibition of sleeping with other people for 2 weeks, ensuring ventilation and air

circulation at home, and education to put the clothes and bedding directly under the sun to prevent transmission of TB disease to the surrounding community. In addition, patient was also provided with information that TB is a disease that can be completely cured with proper therapy, to encouragement the patients and their families to be cured of tuberculosis.

In addition, the patient is also taught about the diet and nutrition needed by the patient to recover optimally, which is a calorie requirement of 40 kcal/kg/day. Adjusted to the patient's ideal body weight, protein as much as 1.5 - 2.5 g/kg/day, sufficient fat 10-25% of total energy needs, high vitamins and minerals, especially vitamins A (carrots, tomatoes, pumpkin, mango), B₁₂, C, E, folate, calcium, magnesium, zinc selenium, sufficient fiber, derived from vegetables and fruits, sufficient fluids, according to the patient's condition. Malnutrition and TB are both problems which interacted each other, malnutrition increases the risk of TB infection, and TB causes malnutrition. Malnutrition is frequent in TB patients, and lead to secondary immunodeficiency that increases the host's susceptibility to infection. While TB leads to appetite reduction, malabsorption and metabolism alteration, and cause wasting (Gupta et al., 2009). Diet is important for TB treatment, as it is a daily nutrition fulfillment consisting macro- and micronutrient (Yani et al., 2018). Several study recalling dietary need of TB patients showed that more than 50% TB patients had lower nutrient intake than their daily nutritional requirements (Gurung et al., 2018), especially micronutrients such as vitamin D (Yani et al., 2018), magnesium, calcium zinc, water soluble and fat soluble vitamins (Hung et al., 2023). Study in Chinese found that protein intake of TB patients was lower than DRI (Ren et al., 2019). Dietary counselling is needed for patients with TB, especially during treatment period as the nutritional status was easily fall due to inadequate nutritional intake, as TB causes loss of appetite and nausea/vomiting (Bacelo et al., 2017). Dietary counselling could improve TB patient's BMI, protein intake and albumin levels (Sharan kumar et al., 2022).

STRENGTHS AND LIMITATIONS

Further analysis is needed in the aspect of family compliance and tracing, especially in the vulnerable groups, such as children, pregnant women, etc.

CONCLUSION

A case of drug-resistant tuberculosis (DR-TB) was reported. The patient's diagnosis was bacteriologically confirmed pulmonary TB (with RT-PCR) with rifampicin resistance. The risk factor for the occurrence of Tuberculosis disease in this patient is the patient's environment whereas patient often gathered with coworkers which some of them was suffer from chronic cough which was a possible source of transmission of TB infection. The patient's prognosis is good if complaints are treated immediately and anti-tuberculosis drugs are taken regularly. The patient still needs further education, especially regarding the coughing etiquette and implementation of healthy lifestyle in the household setting.

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CONFLICT OF INTEREST

None declared.

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AUTHOR CONTRIBUTION

The authors contributed to all processes in this study, including preparation, data gathering and analysis, drafting, and approval for the manuscript's publication.

PATIENT CONSENT FOR PUBLICATION

Written and verbal informed consent to present this case report was obtained from the responsible parties, which in this case, was the patient herself and his/her guardian.



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