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Case Report

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Hyperuricemia, use of antituberculosis drugs, and liver injury: Case Report

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Abstract: Anti-tuberculous drug can cause idiosyncratic drug-induced liver injury (DILI). Considering the benefit risk, there will discontinuation therapy and rechallenge after symptom resolve. In addition to anti-tuberculosis drugs, liver injury can occur in patients with hyperuricemia. We report a 60-year-old male patient who had just used the initiation phase of OAT for 20 days experiencing hepatotoxic side effects characterized by complaints of nausea and vomiting for one week. Liver function examination results were normal with AST 23 u/L and ALT 9 u/L. OAT administration was temporarily stopped and started gradually with 150 mg rifampicin, 150 mg isoniazid and 500 mg ethambutol. The second day after using OAT again, given the full dose of 300 mg rifampicin, 300 mg isoniazid and 1000 mg ethambutol. The patient's condition improved after this modification of therapy so that therapy with three anti-TB drugs was continued until he was discharged from the hospital.

Keywords: Adverse effect, Antituberculosis, Drug induced liver injury

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis.[1] It remains a significant cause of health decline and mortality worldwide, second only to the 2019 Coronavirus pandemic (COVID-19). According to the 2021 Global Tuberculosis Report, there were 9.9 million global TB infection cases, with TB incidence decreasing from previous years, but an increase in mortality cases estimated at 1.3 million. In 2020, two-thirds of global TB cases were contributed by India, China, and Indonesia. Indonesia reported an estimated 647 TB incidents per 100,000 population.[2]

Despite successful treatment in around 85% of TB cases, drug-related side effects, including hepatotoxicity, skin reactions, gastrointestinal, and neurological

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disorders, significantly contribute to morbidity and impact treatment efficacy.[3] Drug-induced liver injury (DILI) can occur at therapeutic doses or in cases of overdose; it can be a direct effect of the drug or idiosyncratic (Kumachev & Wu, 2021). The risk of DILI side effects is higher in patients on combination regimens compared to monotherapy.[4] About 28% of DILI cases are associated with combined OAT therapy (Devarbhavi et al., 2019) and Fixed-Dose Combination (FDC) therapy.[5] Isoniazid is the most common culprit for hepatotoxicity, followed by rifampicin and pyrazinamide.[3,6,7] Apart from drug use, liver injury can also be caused by hyperuricemia conditions.[8]

The occurrence of DILI side effects undoubtedly influences drug selection and treatment regimens significantly, potentially leading to OAT discontinuation.[8] Addressing these adverse events requires intervention, including treatment modification, to prevent worsening of hepatic function and potential hepatic failure.[9] Treatment adjustments are also necessary to support medication adherence and prevent treatment failure, relapse, and drug resistance.[8,10] This case report aims to highlight a DILI case based on the patient's clinical symptoms and the management guided by clinical recommendations.

CASE REPORT

A 60-year-old adult patient, weighing 45 kg and with a height of 158 cm, was admitted to the hospital with a diagnosis of pulmonary tuberculosis (TB), functional dyspepsia, and hyperuricemia. The patient underwent a six-day hospitalization in November 2022. The patient was already on Fixed-Dose Combination Therapy (FDC-TB) for the last twenty days prior to hospitalization. There was no history of allergies, and the patient had previously worked as an intercity bus driver. The patient reported experiencing nausea since the initiation of Anti-Tuberculosis Drugs (ATDs), which persisted for 5 days. The day before admission, the patient had vomited more than 5 times within a day. Respiratory rate increased to 28 breaths per minute. Laboratory investigations revealed a slight decline in hemoglobin and serum uric acid, with liver function tests showing AST 23 IU/L and ALT 9 IU/L. Radiological assessment demonstrated active pulmonary TB based on X-ray images.

The therapeutic approach involved switching from FDC-TB to a Single Dose Combination (SDC) regimen: rifampicin 150 mg, isoniazid 150 mg, and ethambutol 500 mg. After two days on this regimen, the dosages were doubled to rifampicin 300 mg, isoniazid 300 mg, and ethambutol 500 mg. Additionally, curcumin tablets were administered 3 times daily, along with intravenous methylprednisolone 2 times daily at a dose of 62.5 mg, L-cysteine tablets 3 times daily, and sucralfate 3 times daily. Upon discharge, the patient continued with the following regimen: rifampicin 300 mg, isoniazid 300 mg, L-cysteine 1000 mg 3 times daily, allopurinol 300 mg, sucralfate 3 times daily, and domperidone 3 times daily. This case report illustrates a comprehensive therapeutic approach to managing drug-induced hepatotoxicity in a pulmonary TB patient, with multiple interventions aimed at ensuring patient well-being and effective treatment outcomes.

DISCUSSION

Hepatotoxicity is a side effect that most frequently reported on patients undergoing therapy with anti-tuberculosis drugs such as isoniazid, rifampin and pyrazinamide.[11] Drug-Induced Liver Injury (DILI) remains a critical concern during tuberculosis (TB) treatment, with varying definitions and management approaches across guidelines.[12] The World Health Organization's Adverse Drug Reaction Terminology (WHO-ART) defines DILI grades based on alanine aminotransferase (ALT) levels: grade 1 (mild) <2.5 times the upper limit of normal (ULN), grade 2 (mild) 2.5–5 times ULN, grade 3 (moderate) 5–10 times ULN, and grade 4 (severe)

>10 times ULN.[13] Additionally, American Thoracic Societies (ATS) and British Thoracic Societies (BTS) guidelines define DILI due to anti-tuberculosis drugs as ALT elevation of 3-5 times ULN with or without symptoms.[14] DILI because of OAT occurred within 2 months after administration and the highest incidence occurred in the first 2 weeks of therapy.[15]

Several studies reveal that DILI symptoms include nausea, vomiting, and jaundice.[3,5,16] TB patients with hepatotoxicity often report symptoms such as nausea and vomiting, fatigue, and jaundice, occurring 8-56 days after the intensive phase of TB therapy.[17] Notably, liver damage due to anti-tuberculosis drugs occurs within the initial 2 weeks of treatment.[18,19]

Isoniazid plays a role in metabolism pathway via N-acetyltransferase 2 (NAT2) and microsomal enzyme cytochrome P4502E1 (CYP2E1) which will convert isoniazid to acetyl diazine which is a toxic metabolite. Next, acetyl diazine will be broken down to activate acetyl onium ion, acetyl radical and ketene which will bond covalently with hepatic macromolecule triggering liver injury. Beside that, isoniazid inhibits glutathione peroxidase which is an antioxidant against free radicals. There are other mechanisms regarding the hepatotoxicity of isoniazid, the presence of immune mediated idiosyncrasy as a response mechanism liver adaptation to isoniazid and hepatotoxicity.[20,21]

Rifampicin activates CYP3A4 increase in metabolism Isoniazid produces toxic metabolites and cause hepatotoxicity. Rifampicin also induces isoniazid hydrolase, which causes thereby increasing hydrazine production increase toxicity when combined with isoniazid. Additionally, rifampicin able to inhibit bile salt exporters pump (BSEP) thereby causing conjugate hyperbilirubinemia.[20,21] Pyrazinamide inhibits activity CYP450 and disrupt levels nicotinamide – acetyl dehydrogenase (NAD) thus producing free radicals mediates hepatotoxicity.[20]

To manage DILI, a patient's treatment regimen might be modified or alternative therapies introduced. International Union against Tuberculosis and Lung Disease and WHO recommend temporarily halting treatment until liver function returns to normal, followed by reinitiating therapy.[17] ATS and BTS guidelines suggest gradual reintroduction starting with the safest drug, rifampicin, and progressively adding others like isoniazid.[17,22,23] National Institute for Health and Care Excellence (NICE) guidelines propose discontinuing treatment until ALT is below twice ULN and then reintroducing full-dose therapy, beginning with ethambutol or isoniazid.[24]

Despite the approaches mentioned, there is no evidence-based treatment to support the comparison of full-dose versus gradual reintroduction of anti-tuberculosis drugs.[14,25] A retrospective study employing gradual dose escalation reported high regimen completion rates (75.2%).[14] Mechanisms underlying pirazinamid – induced hepatotoxicity are complex, involving dose-dependent effects and metabolic pathways.[26–28]

In conclusion, managing DILI during TB treatment requires vigilant monitoring, dose adjustments, and careful drug selection. An integrated approach considering various guidelines, patient characteristics, and evolving evidence can effectively address DILI, ensuring optimal TB treatment outcomes and patient safety.

CONCLUSION

DILI side effects due to the use of OAT can occur at the beginning of treatment. Management of OAT-DILI is temporarily stopping the use of OAT until normal liver function and reusing the treatment regimen. A two-drug hepatotoxic regimen with gradually increasing doses was adopted in the management of this case. The use of hepatoprotectors such as curcuma can be done.

AUTHORS' CONTRIBUTIONS

Vina Yuwantari took research data and wrote this journal. Nur Oktafiyani, Nurmelinda Hadi Ningrum, M. Hari Pristantiningtyas, Herya Putra Dharma and Muhammad Muchlis chose cases in the hospital that could be used as case reports, as well as guiding the writing of this journal. Jainuri Erik Pratama, Fauna Herawati, Adji Prayitno Setiadi and Marisca Evalina Gondokesumo reviewed and supervised the journal. All authors have read and approved the final journal.

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DISCLOSURE STATEMENT

The views and opinions expressed in this journal are those of the authors after reviewing various literatures and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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