A Case Report: Pulmonary Tuberculosis With Rifampicin Induced Bullous Pemphigoid

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Abstract: Acute tuberculosis (TB) is a communicable disease that results from Mycobacterium tuberculosis (M.TB) infection.Although tuberculosis disease primarily impacts the lung parenchyma (pulmonary TB), this bacterium is also capable of infecting other organs (extra-pulmonary TB). Management uses a combination of several OATs over a certain period of time with treatment side effects which often become serious problems, causing patient non-compliance in taking medication. This article reports the case of a 44 year old man, who presented with multiple tense bullae on top of erythematous plaque some with crust distributed on generalized, after 2 weeks of taking OAT. Sputum examination revealed MTB detected medium, Rif Resistance Not Detected. From the chest x-ray results, it was found that there were infiltrates in the left lung field. The patient was diagnosed with a new case of pulmonary TB and bullous pemphigoid skin eruption which was suspected to be an OAT induced. The skin lesion in the form of a crusted maculo-bullous rash, based on the classification of skin lesions by the 2018 International Union Against Tuberculosis and Lung Disease (IUATLD) field guideline, is classified as grade 3 (severe). Management using the treating through method continues the administration of OAT accompanied by additional oral steroid and anti-histamine therapy, then close observation during administration of OAT. After clinical improvement, the patient will then be monitored regarding drug side effects and adverse drug reactions (ADRs) during treatment through routine monthly evaluations at the RSMH DOTS polyclinic. Adverse effects often occur during pulmonary TB treatment and affect the success rate of treatment. Only 2% of adverse drug reactions on the skin occur due to OAT when treating pulmonary TB. It is important for us to monitor ADRs to ensure safety during treatment and improve patient quality of life. Therefore, a comprehensive approach starting from providing appropriate therapy, managing side effects as well as clinical monitoring and support during treatment is very important to achieve patient recovery.

1 INTRODUCTION

Tuberculosis (TB) is a disease that can typically be prevented and cured. In 2022, tuberculosis (TB) ranked as the second most common cause of mortality worldwide caused by a single infectious agent, following coronavirus disease (COVID-19). TB caused about twice as many fatalities as Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome (HIV/AIDS). Annually, almost 10 million individuals are afflicted with tuberculosis. Prompt measures must be taken to eradicate the worldwide tuberculosis pandemic by 2030, a target that has been embraced by all Member States of the United Nations (UN) and the World Health Organization (WHO) (WHO, 2023).

Tuberculosis is a persistent contagious illness caused by the bacteria Mycobacterium tuberculosis, which is transmitted through the air when those who are infected exhale. Approximately 25% of the world's population is believed to have contracted tuberculosis (WHO, 2023).

This bacterium has a rod-shaped morphology and possesses the ability to withstand acidic conditions, so it is commonly referred to as Acid-Resistant Bacillus. The majority of tuberculosis (TB) cases primarily affect the lung tissue, resulting in pulmonary TB. However, these bacteria also possess the capability to infect several other organs outside of the lungs, such as the pleura, lymph nodes, bones, and other extra-pulmonary organs (WHO, 2023; Kemenkes RI, 2019).

In 2022, 87% of the global TB cases were found in thirty countries with a high burden of the disease. Among these countries, eight accounted for two-thirds of the total cases worldwide. These countries are India (27%), Indonesia (10%), China (7.1%), the Philippines (7.0%), Pakistan (5.7%), Nigeria (4.5%), Bangladesh (3.6%), and the Democratic Republic of the Congo (3.0%). In 2022, approximately 410,000 individuals (95% UI: 370,000-450,000) worldwide contracted multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) (WHO, 2023).

There are several factors that cause TB treatment failure, namely factors originating from TB service providers and factors originating from within the patient himself (Pradipta, 2021; Pradipta, 2022).

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Regarding factors originating from health service providers, inadequate human resources, facilities and coordination of health workers are the main problems. Apart from that, TB treatment failure is also related to TB program activities which include inadequate TB case detection, diagnosis, supply chain management and drug distribution, treatment and surveillance, case registration and reporting, as well as collaboration between the public and private sectors (Pradipta, 2021). From the patient's perspective, there are several factors that cause failure in TB treatment, namely the patient's lack of knowledge about TB disease and treatment, the emergence of stigma from the community and non-compliance with treatment.

Patient compliance with the treatment being undertaken is an important factor in the recovery of TB patients. There are several factors that influence patient treatment compliance, one of which is the side effects of OAT. Non-compliance resulting from the side effects of TB drugs can result in treatment resistance which results in low treatment success rates, thereby increasing the burden of treatment costs and the occurrence of complications (Pradipta, 2022).

Adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as an unexpected drug response or adverse effect, which occurs at normal doses administered to humans. The most common ADR is a skin eruption (cutaneous adverse drug reaction/CADR), which is around 30-45% of all ADRs and 2-7% of them are serious drug eruptions (Grando, 2014).

Bullous pemphigoid (BP) is an autoimmune dermatological subepidermal blistering disease that mainly affects the elderly population. Bullous pemphigoid manifests with tense blisters or bullae over the trunk and extremities accompanied by intense pruritus. Mucosal involvement is rarely reported (Alina, 2023).

Bullous pemphigoid is mostly caused by autoantibodies that circulate or bind to tissues, targeting either bullous pemphigoid antigen 1 or bullous pemphigoid antigen 2, or both. This condition is more prevalent in women (Cohen, 2020).

Bullous pemphigoid can be caused by medications and other factors. Currently, there are no specific tests available to distinguish between Bullous pemphigoid (BP) and DIBP. DIBP are caused by variety of medicines includes, antihypertensives, nonsteroidal anti-inflammatory drugs, diuretics, antiarrhythmics, antidiabetics, antirheumatics, antibiotics, tumour necrosis factor inhibitors, vaccines, and other agents (Moro, 2020).

However, anti-tuberculous medications precipitating BP have been reported rarely (WHO, 2023).

2 CASE PRESENTATION

A 44 year old man, presented with multiple tense bullae on top of erythematous plaque some with crust distributed on generalized, after 2 weeks of taking anti tuberculosis drugs therapy come to Emergency room. There no co-morbidities disease from medical history. There was no history of any significant skin rashes.

A-44 year old man with history of lung tuberculosis on anti tuberculosis drugs therapy come to the emergency department with multiple tense bullae all over his body. This was associated with fever, he start noticing skin eruptions as early as 2 weeks after intake of anti tuberculosis drugs therapy. He denied any history of allergy or any previous similar lesion. He did not have any history of hypertension or diabetes mellitus.

According to his chest radiograph results, there were infiltrates in the left lung field. Sputum examination revealed MTB detected medium, Rif Resistance Not Detected. Anti-tuberculous therapy was commenced with a world health organization (WHO) defined standard category 1 treatment comprising Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol according to body weight.

Anti-tuberculous therapy was commenced according to the world health organization (WHO) defined standard category 1 treatment comprising Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol according to body weight. Other than anti tuberculosis multi drug therapy, he denied ingestion of any other medication including over the counter drugs and medications related to traditional or alternative medicine. There was no past experience of drug or food allergy.

We evaluated these patients utilizing the Naranjo score. The purpose of developing this scale was to establish a standardized method for assessing causality in all adverse drug reactions, rather than primarily targeting drug-induced liver harm. Naranjo score was calculated: 9 (definite ADR) (NIH, 2019).

Two weeks after intake of MDT he developed a generalized erythematosus rash involving the palms, soles of the feet, upper limbs, neck and trunk. We reffered to the Dermatovenereology department and upon examination there was a multiple tense bullae on top of erythematous patches and plaque, some with erosions, hemorrhagic crust measuring

0.8x1.5cm to 1x2cm distributed on the upper trunk, back, upper and lower extremities. (Figure.1A,B).

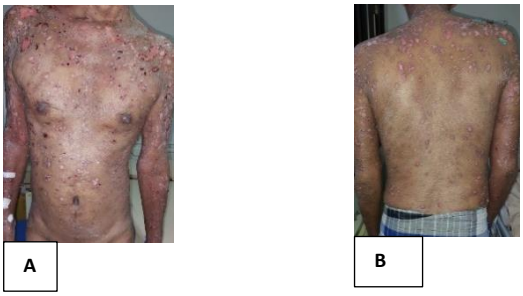

Fig.1A,B Dermatologic manifestation.

Further dermatological examination there were negative Asboe-Hansen and Nikolsky sign. Blood examination revealed increase of total white count of 16700/mm3 with 73% of neutrophils. Blood sugar, renal and liver function tests were within the normal range.

Dermatovenerology department initially diagnosed as drug induced bullous pemphigoid. All anti-tuberculous medications were stop immediately patient was planned for a biopsy and to be given oral and topical medication. After skin biopsy were done patient was given oral prednisolone 20mg daily, cetirizine 10 mg daily, and topical Clobetasol propionate to apply twice daily.

Histopathology result demonstrated a subepidermal split with eosinophils which in line with the diagnosis of a suspected case of bullous pemphigoid. However, since bullous pemphigoid was rarely reported in association with first line anti-tuberculous medications, he was re-commenced on isoniazid, rifampicin, ethambutol and pyrazinamide once the blisters were resolved. Oral prednisolone were continued further.

After a week, the patient presented with recurrent new blisters on the forearms. Once again all anti-tuberculous drugs were removed. Upon gradually starting rifampicin he developed similar eruptions on the body. Therefore rifampicin was stopped and isoniazid and pyrazinamide were introduced to the regimen slowly without recurrence of the eruptions. The oral steroid was continued for about 1 month and slowly tailed off. He has continued the total duration of anti-tuberculous therapy without further recurrence.

3 DISCUSSION

According to the World Health Organization (WHO), around 10 million individuals across the globe were afflicted with Mycobacterium tuberculosis by 2019, resulting in 1.4 million fatalities due to tuberculosis (TB).(1) Prompt identification and timely intervention of tuberculosis (TB) are crucial for achieving efficient TB management. The standard treatment for tuberculosis (TB), known as anti-TB treatment (ATT), is quite effective. However, one of the major obstacles to achieving success with ATT is effectively managing the toxicity of TB medications (Fla, 2022).

Effective treatment of tuberculosis requires a combination of multiple antituberculous medications given for several months for complete eradication. Antituberculous medications are classified into 5 groups according to WHO, in which group 1 is considered as the first line medications which include isoniazid, rifampicin, ethambutol and pyrazinamide. These first line medications are highly effective in treating WHO defined new and re-treatment cases of tuberculosis in the absence of drug resistance, thereby forming the core of tuberculosis management.

Adverse drug reactions (ADR) to first line antituberculous medications are considered common. The prevalence of ADR varies widely from 8- 85% according to studies conducted globally . Though the majority of first line antituberculous medication associated ADR are mild; serious hepatic, cutaneous, renal, rheumatological and neuropsychaitric manifestations may develop leading to significant morbidity and potential mortality unless recognized earlier (Singh, 2015).

Adverse drug responses (ADR) are characterized as "unintended and harmful reactions to medication that occur at typical human dosage levels." This study categorized adverse drug reactions (ADR) based on the specific organ or system affected, using the Adverse Reaction Terminology and outlined in the Supplementary Methods. The causation of ADR was evaluated using the Naranjo Scale, which categorizes the relationship as implausible, conceivable, probable, or definitely related (NIH, 2019).

The cutaneous adverse drug reactions associated with antituberculous medications encompass a wide range of symptoms, varying from mild to moderate

reactions such as itching, rash resembling measles, rash resembling lichen, localized skin reactions, inflammation of the blood vessels in the skin, and hives, to severe and potentially life-threatening conditions including drug hypersensitivity syndrome (DHS), widespread rash with pustules, Stevens-Johnson syndrome (SJS), and Toxic epidermal necrolysis (TEN).Thirteen It is acknowledged that a single antituberculous medication can cause several types of skin reactions, while multiple medications can lead to a specific reaction (Manchanda, 2018).

Bullous eruptions as a cutaneous adverse reaction of first-line antituberculous medications have been reported exceedingly rare. Two cases of rifampicin induced bullous pemphigoid have been reported by Garrido-Colmenero et al. and SA Ibn et al. earlier (Garrido-Colmenero, 2016; IbnSellam, 2011). Similar like our patient developed a reaction of bullous pemphigoid possibly due to rifampicin. Akrout reported a rare case of ethambutol induced bullous and lichenoid skin eruption in an elderly woman. However, our patient developed a reaction of bullous pemphigoid due to isoniazid. K Vinitha et al. (2016) reported a case of bullous eruption due to isoniazid.

Therefore, in clinical practice, gradual treating through with careful monitoring for the recurrence of cutaneous reaction is an accepted protocol for precise identification of the culprit drug.

4 CONCLUSIONS

First line antituberculous medications including rifampicin are commonly utilized in clinical practice and mild cutaneous adverse reactions are frequently encountered. Serious cutaneous reactions are rare, however can lead to significant morbidity and potential mortality. Drug induced bullous pemphigoid is a rare form of serious drug eruption reported in association with rirampicin. Early recognition and termination of therapy followed by gradual treating through re-introduction is the key to the identify suspected medication.

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