



Anti-Tuberculosis Drug Allergy in a Man with Disseminated Tuberculosis

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Abstract

Background :In 2011, Indonesia had between 0.38 and 0.54 million TB cases, placing fourth after India, China, and South Africa. In 4-6 percent of TB cases, allergic responses due to ATD are one of the most common ATD side effects. **Case** : A 34-year-old male patient presented with complaints of shortness of breath, an enlarged abdomen, and a sensation of being full for two days. In the past month, there was a 10 kg weight loss, a reduction in hunger and night sweats, absence of throat pain, absence of fever, nausea, vomiting, anosmia, ageusia, and urine within normal limits. **Conclusion** : A 34-year-old male patient with pulmonary and abdominal tuberculosis who had an allergic reaction to ATD. On the fifth day of treatment, the patient acquired a rash that was reddish and itchy. Initially, the patient did not show any allergy symptoms (ATD day 15). After an allergic reaction has occurred, the entire ATD is discontinued and drug challenge testing is undertaken. The patient was discovered to have an allergic reaction to ATD caused to rifampicin. At the period of outpatient treatment, ATDs given were isoniazid 300mg every 24 hours PO (day 11), Ethambutol 750mg (day 6) every 24 hours PO, Pyrazinamide 250 mg every 24 hours PO (day 1).

3600

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Introduction

Tuberculosis, also commonly known as TB, is an infectious illness that is still an issue in today's world of medicine. There were between 0.38 and 0.54 million cases of tuberculosis reported in Indonesia in 2011, placing the country fourth on the list behind India, China, and South Africa (The Health Ministry of the Republic of Indonesia, 2013; The Health Ministry of the Republic of Indonesia, 2019). There are two types of tuberculosis: pulmonary tuberculosis and extrapulmonary tuberculosis.

Extrapulmonary tuberculosis, also known as EPTB, is a type of tuberculosis that affects organs other than the lungs, including the pleura, lymph nodes, abdomen, genitorinarian tract, skin, bones and joints, and brain membranes (Kementerian Kesehatan RI, 2013; World Health Organization, 2010). In 2010, abdominal TB accounted for approximately 2.5 percent of all TB cases in Canada, whereas in 2006, it accounted for approximately 4.9 percent of all TB cases in the United States.

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It is possible for the symptoms of abdominal tuberculosis to be confused with those of other illnesses, including malignancy and inflammatory bowel disease. This can cause diagnostic delays and lead to improper treatment. Besides, there is still a lack of understanding regarding the risk factors, presentation, and clinical path associated with abdominal tuberculosis (Chien et al., 2018).

All first-line antituberculosis drugs (ATD) have the potential to produce adverse reactions. Allergic reactions to ATD can range from moderate symptoms, such as hives and rashes, to severe and potentially fatal symptoms, such as anaphylactic shock, Steven Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN) (Nugroho & Kusmiati, 2021). In 4-6 percent of TB cases, allergic responses due to ATD are one of the most common ATD side effects (Lehloeny et al., 2011; Siripassorn et al., 2018). Chien et al discovered that skin rashes/pruritis and sensory peripheral neuropathy are the most common side effects of ATD in cases of abdominal TB (Chien et al., 2018). This case report describes an allergic reaction that occurred in a man with abdominal TB who had ATD treatment.

Case

Present History of the Disease

A 34-year-old male patient presented with complaints of shortness of breath, an enlarged abdomen, and the sensation of being full for two days. Pain throughout the abdomen and inability to defecate, coughing for one month before to hospitalization with white sputum. In the past month, there has been a 10 kg weight loss, a reduction in appetite and night sweats, and the absence of sore throat. Fever, nausea, vomiting, anosmia, and ageusia are not acquired. Urine within the normal range. The patient is transferred from an internal medicine colleague with an initial diagnostic of obstructive ileus and a differential diagnosis of Abdominal TB + Hypoalbumin (1.97) + Pulmonary TB on ATD Intensive Phase 1 + Anemia (9).

Previous history of the disease

There is no history of hypertension, diabetes mellitus, or allergies at the Class 1 State Detention Center in Surabaya where the patient is receiving TB treatment with ATD Category I Intensive Phase Day 8 3 Tab 4 FDC (since 8/9/2021).

Social History

The referral patient from the Surabaya class I detention center had been in prison since February 2020, serving a 7-year sentence, with 10 inmates to a room. The patient was unemployed, had smoked since the age of 15 (for a total of 20 years) and consumed 1 pack of cigarettes per day. The patient had a history of drug use two years prior, but denied having had close contact with COVID-19 patients. The COVID-19 vaccine's history is refuted.

Physical Examination

The overall condition is weak, Weight 45 kg at a height of 165 cm, Glasgow Coma Scale 4/5/6 for consciousness, blood pressure 101/84 mmHg, pulse 84 beats per minute regular strong lift, respiratory rate 25 beats per minute, oxygen saturation 97% with room air, and body temperature 36.7 °C. The physical examination of the head and neck revealed anemia and dyspnea, but no cyanosis or icterus. There is no distortion of the trachea, lymph node enlargement, or elevation of jugular venous pressure.

Physical chest examination and observation revealed symmetrical chest movements. On palpation, the tactile fremitus in the upper 1/3 of the right hemithorax increased. Insensitive to percussion in the upper 1/3 of the right hemithorax. Bronchovesicular auscultation in the upper 1/3 of the right hemithorax, with crackles in the upper 1/3 of the right hemithorax and 2/3 of the left hemithorax, but no wheezing was found.

Physical examination of the abdomen, including an inspection of slight distended. Tympanic beats on all four quadrants. Palpation of soepel, absence of tenderness and



hardness, absence of hepar and lien. Examination of the Inguinal Glands In the inguinal region of the decstra and sinistra, there is an enlarged lymph node with a diameter of 2 cm x 1 cm x 0.5 cm that is movable and painless. The physical examination of the extremities was obtained with a red, warm, dry accreditation, no edema, and CRT <2 seconds.

Supporting Examinations

Laboratory results (see Table 1) show Hemoglobin (9 g / dl), Granulocytosis (74.7 %), Lymphocytopeni (16.3 %), eosinophiles (0.5 %), hypoalbuminemia (1.97 g / dL), CRP (5.2 mg / dL), HCT (27.6 %), Blood gas analysis obtained pH (7.46), pCO2 (39 mmHg), pO2 (70 mmHg), HCO3 (27.7 mmol / L), BE (3.9 mmol / L), AaDO2 (31 mmHg), P / F ratio (333 mmHG), SaO2 (95%) with the results of metabolic alkalosis not compensated with mild hypoxemia.

Thoracic picture taken on September 19, 2021, photo of AP position, with insufficient exposure and inspiration. Symmetrical, soft tissues, bones, and percentdia all within normal limits. Right and left costophrenicus angles are sharp. The right diaphragm is normal. The left diaphragm seems elevated. In the pulmonary parenchim, fibroinfiltrate was obtained on 1/3 of the right hemitorax and fibroinfiltrate on the left. In the BOF AP/LLD image, there is no free air outside the bowel counter, indicating a pathological stepladder picture > 5.



Figure 1.Thoracic photo during hospital admission

Table1.Laboratory results upon hospital admission

Laboratory examination (18 September 2021)							
Hb	9 g/dl	BU N	4 mg/d L	HbsA G	NR	BGA	
WBC	5.760 uL	SK	0,3 mg/d L	HCT	27,6 %	pH	7,46
Neu	74,7 %	SGOT	33 U/L	PPT	10,4 detik (N : 9-12 s)	pCO2	39 mmHg
Lim	16,3 %	SGPT	15 U/L	APT T	28,5 detik (N : 23-33 s)	pO2	70 mmHg
Bas	0,3 %	Alb	1,97 g/dL	Na	135 mmol /L	HCO3	27,7 mmol /L
Eos	0,5 %	Bil T	0,13 mg/d L	K	4 mmol/ L	BE	3,9 mmol /L
Mon	8,2 %	Bil D	0,15 mg/d L	Cl	99 mmol/ L	AaDO2	31 mmHg
Plt	304.000 uL	CRP	5,2 mg/d L			P/F	333 mmHg
HIV	NR	GD A	112 mg/d L			SaO2	95%



Figure 2.BOF AP/LLD pictures during hospital admission





Figure 3. Patient Clinical manifestations

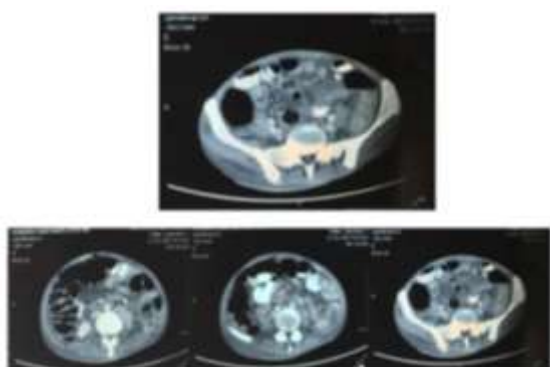


Figure 4. Abdominal CT scan

During IRD, a General Surgical Consultation is obtained based on a BOF / LLD examination: distribution of gas to the pelvic cavum and prominent fecal material on chest examination of active pulmonary TB. Suspect abdominal TB + active pulmonary TB treated with ATD for 2 weeks + anemia and hypoalbumin. CT Scan Advice Triple abdomen contrast, geneXpert sputum, and fecal examination. Planning therapy: improvement of the general condition, fasting, bowel rest, pairs of NGT open and close if diet, a gradual diet (milk -> fine porridge -> coarse porridge -> soft), installation of a central venous catheter (CVC), periodic lavement, and TB treatment according to the Pulmonary TS.

Results and Discussion

Epidemiology of Allergic Reactions due to ATD Administration in Patients with Pulmonary TB

In 4-6% of TB cases, allergic reaction to ATD is the most often documented side effect of ATD. All first-line medications are capable of causing allergic responses. The severity of an allergy ranges from mild, such as itching and redness, to severe and potentially fatal, such as anaphylactic shock, Steven Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN)(Kobashi et al., 2010; Nugroho & Kusmiati, 2021).

Allergic reactions or hypersensitivity of the drug occur in 7% of the general population and account for 15% of the entire incidence of side effects of the drug. An allergic reaction to first-line ATD was one of the reported ATD side effects in 5.7% of TB patients. After impaired liver function and gastrointestinal issues, allergic reactions to ATD are the third most common side effect of ATD (Nugroho & Kusmiati, 2021; Saravu & Pai, 2016).

All first-line ATDS can cause rashes. Side effects in the treatment of TB range from 4.7% to 23%. The incidence of first-line ATD allergic reactions was 2.38% in pyrazinamide; 1.45% on streptomycin; 1.44% on ethambutol; 1.23% on rifampicin; and 0.98% on isoniazid(Nugroho & Kusmiati, 2021).According to research carried out by Shin et al. (2021)rifampicin is the ATD that most often causes allergies in cases of single ATD allergic reactions (47.1%) and multiple ATD allergic reactions (52.9%).Multiple ATD allergic reactions are more severe than a single ATD allergy(Shin et al., 2021).

An observational prospective study of 1011 TB patients who got ATD in India showed that as many as 14 (1.38%) patients experienced hypersensitivity during ATD therapy. Hypersensitivity was reported to be caused by isoniazid in 5 patients (0.49%), rifampicin in 6 patients (0.59%), and pyrazinamide in 3 patients (0.30%). The entire ATD is contraindicated in cases of hypersensitivity. Skin reactions were reported in 13 (1.29%) patients who received ATD therapy so that one or more ATDs were discontinued. In this study, skin reactions were reported to be caused by rifampicin, isoniazid, and



pyrazinamide in three (0.30%), seven (0.69%), and three (0.30%) patients, respectively. The inhibitory effect of rifampicin on cellular immunity can interfere with skin reactivity in intradermal tuberculosis(Imam *et al.*, 2020).

The first line ATD caused a mild allergic reaction in this patient, manifesting as a reddish rash on the chest and abdomen on the fifth day of treatment as a result of the patient returning to take the ATD FDC obtained at the previous healthcare facility against the advice or instruction of the doctor who treated the patient. After observation and drug challenging the patient was allergic to Rifampicin, therefore Rifampicin was not given to the patient.

Hypersensitivity reactions are generally characterized by allergic reactions such as pruritus, urticaria, angioedema, flu like-syndrome, shock, and shortness of breath after intermittent therapy. It is associated by antibody-mediated immune reactions or B-type reactions, which are dose-independent and can occur at any point during treatment. The metabolites monoacetyl hydrazine and desasetyl rifampicin may be responsible for some of the side effects generated by isoniazid and rifampicin. Hypersensitivity reactions to ATD might present as exantema, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), purpura-like vasculitis, acute thrombopenic purpura, joint pain, fever, and leukopenia. Such reactions can occur during combination therapy with different antituberculosis medications, making it difficult to determine which agent is responsible(Imam *et al.*, 2020).

Anti-tuberculosis drugs can cause adverse drug responses that can be categorized as type A or type B. In contrast, type B events are unpredictable, dose-independent, and account for approximately 15-20% of all ATD-related adverse drug reactions. Complications in tuberculosis treatment may result from hypersensitivity reactions caused by ATD, which may include only the skin or be part of a multisystem illness(Dheda & Lehloeny, 2012).Rashes can vary from mild, such as

maculopapular rashes, to severe and life-threatening, such as Steven Johnson Syndrome (SJS), Toxic Epidermal Necrotic (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS). Maculopapular or morbiliform rash is the most common and is reported in 95% of cases(Ban *et al.*, 2019; Nugroho & Kusmiati, 2021).

In this patient, the rash obtained is still a mild rash, namely the maculareritematous which is firmly limited and accompanied by a thin squamous in some parts, which is felt itchy by the patient.

Approximately 60% of tuberculosis patients experience adverse drug side effects, with approximately one-third of these adverse drug reactions being drug hypersensitivity reactions. Since first-line anti-tuberculosis medications cannot be administered, the simultaneous administration of numerous anti-tuberculosis drugs can induce multiple drug hypersensitivity syndrome, which can lead to treatment failure in tuberculosis. Multiple drug hypersensitivity syndrome comprises up to 48% of drug hypersensitivity reactions with symptoms of fever or maculopapular exanthem in tuberculosis patients. Ethambutol and rifampin are the most common causes of single- and multiple-drug hypersensitivity syndromes among the four first-line ATD's(Sim *et al.*, 2021).

In these patients, the cause of the skin rash is Rifampicin which is given or a challenging drug during the 10th day of treatment. Meanwhile, in other ATD administrations, patients do not get allergic reactions or side effects of drugs.

Due to variations in the design of published research, population variances, presentation of factors, erroneous reporting, and limits in case definition and disease severity, the incidence of ATD-related reactions remains unknown. It is difficult to establish the influence of ATD-related reactions on patient outcomes in the absence of sufficient evidence. Some epidemiological studies analyzing the frequency and prevalence of ATD-related adverse drug reactions do not categorize ATD-



related adverse drug reactions in detail and typically refer to them as rashes or exotanemaes(Dheda & Lehloenya, 2012).

Existing data indicate that the incidence of skin rashes attributable to ATD hypersensitivity is fairly high, despite the lack of evidence on ATD-related reactions. The incidence of skin responses due to ATD is approximately 5.7% in Malaysian hospitals, 9% in Zambian children, 20% in HIV-seropositive patients in Kenya, and 23% of the 235 Cameroonian patients who received ATD in a prospective study. In the UK, as many as 13% of HIV-infected people experience an ATD-related skin reaction, while non-HIV-infected patients who experience an ATD-related skin reaction are 8%(Dheda & Lehloenya, 2012).

A prospective study of hospitalized patients in France found that the prevalence of skin reactions in all systemic medications was 3.6/1000 patients, with 34% of cases having severe. Skin responses to medications affect up to 1.6 out of 1000 patients in Chinese hospitals, with 0.3 out of 1000 patients experiencing severe reactions. Nevertheless, there is no widely accepted assessment of the severity of drug-induced skin reactions. The type of drug response and related fatality are frequently used to determine the severity. Severe drug-induced skin reactions include SJS, TEN, DHS, cutaneous vasculitis, and bullous fixed drug eruption. Some studies designate severity levels based on hospitalization need, therapy termination, or therapy modifications(Dheda & Lehloenya, 2012).

Currently, there is no clear data on the epidemiology of allergic reactions due to ATD in abdominal TB patients. Based on observational studies in patients with abdominal TB by Chien et al. (2018), reddish rash or pruritis is the most frequent side effect of ATD, with a prevalence of 33.3%, followed by sensory peripheral neuropathy (29.2%), GI intolerance (12.5%), and liver dysfunction (4.2%). Meanwhile, another study reported the

most common ATD side effect in abdominal TB cases is hepatitis (Mamo et al., 2013).

Risk Factors for Allergic Reactions due to ATD in Pulmonary and Extrapulmonary TB

Risk factors for drug allergic reactions can be caused by patient factors or drug factors. Patient risk factors include female gender, comorbidities (HIV, kidney disease, liver disease), ethnicity, polypharmacy, alcohol consumption, and genetics). Drug risk factors include the nature of the drug as a hapten, pro hapten, and the ability of the drug to bind to immune receptors. Topical, intramuscular, and intravenous administration of drugs is more likely to cause allergies than oral administration, this is due to the presence of antigens in the skin and high drug concentrations are achieved rapidly with intravenous administration compared to oral administration(Nugroho & Kusmiati, 2021).

In the case of this patient, there have been no risk factors that have led to the manifestation of allergic reactions. An examination using the HIV-3 method was performed on September 21, 2021, and the results were negative. On the other hand, the renal function test and the liver function test both showed normal results.

Pathophysiology of Allergic Reactions due to ATD in Abdominal Tuberculosis

Anti-tuberculosis drugs (ATD) are the third most prevalent cause of hypersensitivity syndrome to drugs characterized by fever, rash, and swollen lymph nodes, accounting for approximately 13.3% of all instances of drug-induced hypersensitivity. Hypersensitivity syndrome owing to ATD can be produced by multiple combination drugs, making it difficult to establish the causative drug and considering alternative therapy, which can result in ATD resistance and treatment failure(Wu et al., 2021).

The pathogenesis of ATD-induced hypersensitivity responses remains unclear. Various immunological processes may be involved in ATD-induced hypersensitivity reactions, and different ideas have been



proposed. According to the hapten theory, drug-like keil molecules known as hapten, which are often not antigenic or immunogenic, can be antigenic or immatogenic if they form covalent bonds with bigger proteins or peptides. Through van der Waals forces, electrostatic interactions, or hydrogen bonds, drugs that cannot bind to peptides or proteins can bind to T cell receptors or MHC molecules(Dheda & Lehloenya, 2012).There are three hypotheses of cell-mediated immunological reactions and T cell activation in drug allergies, namely: the hapten/pro-hapten hypothesis, the interaction hypothesis with immune receptors (model p-i), and the altered peptide hypothesis (Figure 1)(Nugroho & Kusmiati, 2021).

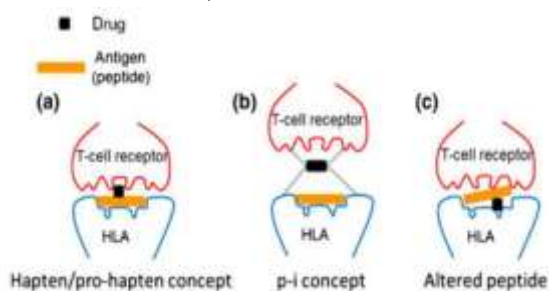


Figure 5. Pathophysiology of hypersensitivity reactions to drugs (Nugroho & Kusmiati, 2021)

Infection with tuberculosis is accompanied with several alterations in the cellular and humoral immune response. The prevalence of HLA-DR+ effectors on CD4+ T cells that are resistant to inhibition of T cell regulation may increase in tuberculosis patients. It is possible that drug hypersensitivity reactions may develop more easily in microenvironments where T cells are activated. In addition, the number of regulatory T cells has reduced in tuberculosis patients undergoing treatment, which can lead to the development of drug hypersensitivity reactions in these patients. The increased production of IgG and IgM antibodies against tuberculosis antigens and immune complexes in tuberculosis patients leads to the development of humoral immunity. Through an increase in T cells or an immune-complex-mediated hypersensitivity reaction, TB infection may contribute to the incidence of drug hypersensitivity reactions. In

addition, a higher prevalence of multiple drug hypersensitivity syndrome may be due to a combination of fixed drugs, high drug doses, and a prolonged treatment term, which can be a risk factor for the development of multiple drug hypersensitivity syndrome(Wu et al., 2021).

According to the hapten/pro-hapten hypothesis, the drug is not antigenic prior to protein binding. Entering drug molecules function as hapten (small covalent molecules that bind amino acids and proteins). Pro-hapten is a molecule that can be metabolized into hapten. Hapten and pro-hapten can produce hypersensitivity reactions as allergens, antigens, immunogens, or sensitogens (Figure 1). Covalently binding to serum proteins, including the Major Histocompatibility Complex (MHC) molecule, are drugs that function as haptens. The association with MHC will activate T cells to trigger an immune response that generates an immediate or delayed systemic reaction in the skin(Nugroho & Kusmiati, 2021).

Based on the classification of Coombs and Gell, hypersensitivity reactions can be divided into four types based on the speed and mechanism of the immune reaction, namely hypersensitivity reactions of fast type (type I), cytotoxic (type II), hypersensitivity of slow type (type III), and immune complex hypersensitivity (type IV) (type IV). Type I (rapid type) reactions are mediated by immunoglobulin (Ig)E, which can cause anaphylactic reactions, urticaria, and angiodema. Type I (rapid type) reactions manifest very rapidly, and urticaria/angiodema can persist for several weeks after the treatment is discontinued. Type II is a cytotoxic mechanism mediated by antigen responses, IgG, and complements to erythrocytes, leukocytes, and other hematological progenitor cells. While type III is an immune complex reaction that manifests as vasculitis on the skin and drug-induced autoimmune disorders, type II is characterized by vasculitis on the skin. The final kind is type IV (slow type), which is mediated by T cells



with modest to severe clinical symptoms(Wu et al., 2021).

The most frequent type of allergic reaction due to ATD is a type I reaction. Type 1 hypersensitivity reactions in TB patients are associated with IgE levels. Total specific IgE levels in TB patients are known to be higher than in healthy people. It can be attributed to *M.tuberculosis* infection, which stimulates the work of T-helper 2 (Th2) to produce interleukin-4 (IL-4), which stimulates B cells to produce IgE. Allergic desensitization is an important treatment for type 1 hypersensitivity(Cernadas & Cernadas, 2019; Nugroho & Kusmiati, 2021)

According to other findings, the majority of antituberculosis drug-induced allergy reactions are of the slow-type hypersensitivity variety (type IV)(Wu et al., 2021).In contrast, hypersensitivity reactions mediated by immune complexes (type III) or T cell hypersensitivity (type IV / slow type) are typically responsible for the signs of fever or maculopapular exantema in ATD-exposed patients. There was no difference between type III and type IV hypersensitivity reactions in the frequency of pharmacological causes, risk factors, or other clinical features(Sim et al., 2021).

Clinical Symptoms and Severity of Allergic Reactions due to ATD in Abdominal Tuberculosis

Clinically, there are two categories of drug allergies: immediate and delayed. Immediate reaction occurs 1 to 6 hours following drug administration (most often in the first hour). Local erythema, urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, gastrointestinal problems, or anaphylactic shock are among the symptoms. Immediate drug hypersensitivity reactions are mediated by IgE (type 1 hypersensitivity reactions). Hypersensitivity reactions of delayed type usually appear after the first 6 hours of drug administration. Common symptoms include maculopapular exantema and slow-type urticaria; often associated with slow-type T

cell-dependent allergic mechanisms (type IV hypersensitivity reactions)(Nugroho & Kusmiati, 2021; Shin et al., 2021).

In these cases, an immediate type allergic reaction is present since clinical signs develop within six hours of ATD administration, but the patient is not subjected to an IgE test, which is an essential component for diagnosing type I hypersensitivity reactions.

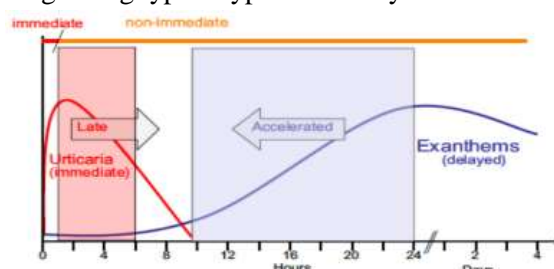


Figure 6. Distribution of hypersensitivity reactions by onset (Nugroho & Kusmiati, 2021)

Allergic reactions to ATD include morbiliform rashes, erythema multiforme, urticaria, lichenoid eruptions, exfoliative dermatitis, and SJS. Pirazinamide was the most common cause of allergies (2.38%), followed by Streptomycin 1.45%, Ethambutol 1.44%, Rifampicin 1.23%, and Isoniazid 0.98%(Piubello et al., 2018).Kutaneus reactions that can arise include Stevens–Johnson syndrome (SJS), drug hypersensitivity syndrome, kutaneus vasculitis, likenoid drug eruptions, and acute generalisata exostulosis(Dheda & Lehloenya, 2012).The severity of allergic reactions due to ATD can be assessed based on recommendations from the International Union of Tuberculosis Lung Disease (IUATLD) (Table 1)(Nugroho & Kusmiati, 2021; Piubello et al., 2018).

Table 2. Severity of skin manifestations of allergic reactions due to ATD (Piubello et al., 2018)

Degree	Clinical symptoms
1 st Degree	Itching or reddish rash
2 nd Degree	Extensive maculopapular rash with or without itching
3 rd Degree	Popular, vesicular, or wet rash Purpura
4 th Degree	Skin or mucosal ulcers SJS (<i>Steven Johnson syndrome</i>) Febrile erythroderma TEN (<i>toxic epidermal necrolysis</i>)



In 95% of cases, morbiliform and maculopapular drug eruptions are the most prevalent drug-induced skin reactions. Macular and erythematous papules begin in the center and extend to the periphery 7-14 days after initial exposure to the causative drug. In severe instances, the lesion becomes confluent, leading in erythroderma. In the vast majority of instances, the eruption caused by morbiliform medicines will heal on its own, and treatment can continue uninterrupted. Even so, maculopapular exantema can be the early manifestation of more serious reactions, including SJS and DHS. A worsening rash, accompanied by systemic symptoms or mucositis, is typically an early sign of a serious hypersensitivity reaction requiring therapy discontinuation (Dheda & Lehloenya, 2012).

In this patient, an allergic reaction manifested as an erythematous macula with a firm limit and itching; the reaction occurred within the first six hours after drug administration (immediate reaction); and, based on the severity of the reaction, it was determined that rifampicin was the cause of the hypersensitivity reaction, as determined by drug challenging administered on the 10th day of treatment.

Drug rash with eosinophilia and systemic symptoms (DRESS) is a severe skin reaction that can result in up to 10% mortality. It is characterized by a long latent period (>3 weeks), fever, edema (especially facial and accrual), lymphadenopathy, leukocytosis, eosinophilia, and/or atypical lymphocytomics, and hepatitis. Eruptions in DRESS are generally urticaria and maculopapular, however vesicles, pustules, kesylitis, purpura, targetoid lesions, and erythroderma have also been reported. The severity of the skin reaction is not always reflective of the systemic diseases involved. Anti-tuberculosis drugs that have been reported to cause DRESS include isoniazid, rifampicin, streptomycin, and pyrazinamide. Meanwhile, ATD reported to cause SJS (Steven Johnson syndrome) and TEN (Toxic Epidermal Necrolysis) include

rifampicin, pyrazinamide, isoniazid, ethambutol, streptomycin, cycloserine, and fluoroquinolones. Rifampicin and fluoroquinolones are reported to cause fixed drug eruption. Meanwhile, isoniazid, pyrazinamide, and ethambutol are reported to cause the eruption of likenoid drugs (Dheda & Lehloenya, 2012)

In these cases, skin allergic reactions do not cause fever, edema (particularly facial and accumulation), lymphadenopathy, leukocytosis, eosinophilia, and / or atypical lymphocytomic, and hepatitis. With urticaria and maculopapular skin symptoms, as well as vesicles, pustules, keilitis, purpura, targetoid lesions, and erythroderma. Furthermore, there is simply an erythematous macula with clear boundaries and itching, hence the patient's allergic reaction is of degree II and not Drug rash with eosinophilia and systemic symptoms (DRESS).

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Management of Allergic Reactions due to ATD in Abdominal TB

All first-line ATDs can cause allergic reactions. An assessment of the severity of allergies is essential to determine further management, including referrals to more complete health facilities. ATDs that cause allergic reactions from the lowest to the highest risk are Isoniazid, Rifampicin, Pyrazinamide, Ethionamide, Cycloserine, Ethambutol, Para-aminosalicylic acid (PAS), and Streptomycin (Nugroho & Kusmiati, 2021; Piubello et al., 2018).

a. ATD allergic reactions without rashes

If the patient complains of itching without rashes and there is no other reason, antihistamines (diphenhydramine 25-50 mg or cetirizine 5-10 mg before ATD consumption) and moisturizers for dry skin are recommended treatments. If there is no improvement, topical or oral corticosteroids (prednisolone 10-20 mg per day) may be administered. ATD can be continued with monitoring, and symptoms usually disappear within a few weeks (Nugroho & Kusmiati, 2021; Piubello et al., 2018;




Saravu & Pai, 2016)

b. ATD allergic reaction with rash

All ATDs should be temporarily discontinued if a rash develops. As recover, TB treatment must be completed to the fullest; consequently, efforts can be undertaken to determine which ATD is causing the skin reaction utilizing a drug-challenging method. The drug challenge begins with isoniazid, the medicine with the lowest allergy risk, and ends with streptomycin, the antibiotic with the highest (Table 2)(Cernadas & Cernadas, 2019; Menteri Kesehatan Republik Indonesia, 2019; Nugroho & Kusmiati, 2021)

Table 3. Drug challenging of ATD (Nugroho & Kusmiati, 2021)

ATD	Start course	Day 1	Day 2	Day 3
Isoniazid	 The most common cause	50 mg	150 mg	300 mg
Rifampicin		70 mg	300 mg	Full dose
Pyrazinamide		250 mg	1 gram	Full dose
Ethambutol		100 mg	500 mg	Full dose
Streptomycin		125 mg	500 mg	Full dose

Once the reaction can be overcome, ATDs are given back gradually one by one starting with ATDs which are less likely to cause a reaction. Each of the drugs is administered with a dose that increases gradually over 3 days, from a small dose to a larger dose, so that when the drug is suspected as a cause it is reintroduced with a small dose so that no serious side effects occur. Side effects may occur as soon as a small dose is administered but are expected to be milder than full dose administration. A well-tolerated drug is immediately administered with a full dose followed by the subsequent administration of the drug starting small doses with the same procedure(Kementerian Kesehatan RI, 2013; Menteri Kesehatan Republik Indonesia, 2019). If no reaction occurs, the procedure is repeated with the addition of another ATD. If a skin reaction develops following administration of a certain ATD, this suggests that the supplied ATD is the cause of the reaction. If the ATD causing the skin reaction is identified, treatment can proceed without ATD (Kementerian Kesehatan RI, 2013; Menteri

Kesehatan Republik Indonesia, 2019).

If possible, a different drug can be replaced for pyrazinamide, ethambutol, or streptomycin if they produce allergic reactions. In some cases where rifampicin or INH is the source of the reaction, desensitization may be performed if possible, with the exception of HIV-positive patients due to the severe toxicity of these drugs(Kementerian Kesehatan RI, 2013; Menteri Kesehatan Republik Indonesia, 2019).Research demonstrates the efficacy and safety of ATD desensitization therapy for ATD-induced allergic reactions(Ban *et al.*, 2019).

In essence, the ATD desensitization protocol based on the Philadelphia Protocol defined in the Guidelines for the Management of Adverse Drug Reaction of Antimycobacterial Agents begins with the administration of ATD according to the first day's drug challenge drug dose. If a reaction develops following drug administration, the drug should be discontinued and desensitization should begin on the first day after the reaction subsides. Thereafter, a double dose is administered every hour until the daily therapeutic dose is reached. Continue treatment in divided doses for three days after reaching the therapeutic dose, subsequently switch to a single dose (for example, Isoniazid 2x150 mg for three days, then 300 mg for a single dose). Whenever an allergy occurs during desensitization, the dose should be lowered to the prior, allergy-free level and then increased gradually(Cernadas & Cernadas, 2019; Lawrence Flick Memorial Tuberculosis Clinic Philadelphia Tuberculosis Control Program, 1998; Nugroho & Kusmiati, 2021).

Table 4. Isoniazid and Rifampicin desensitization protocols(Lawrence Flick Memorial Tuberculosis Clinic Philadelphia Tuberculosis Control Program, 1998; Nugroho & Kusmiati, 2021)



Time	Isoniazid (mg)	Time	Rifampicin (mg)
07:00	0.1	07:00	0.1
07:15	0.5	07:15	0.5
07:30	1	07:30	1
07:45	2	07:45	2
08:00	4	08:00	4
08:30	8	08:15	8
09:00	16	08:30	16
09:30	32	08:45	32
10:30	50	09:15	50
12:30	100	10:15	75
14:30	150	12:15	100
15:00	150	16:15	150
12:30	Continue 150 mg every 12 hours	12:15	Continue 300 mg every 12 hours

Desensitization or re-exposure of patients with ATD hypersensitivity carries a significantly increased risk. Given the lack of in vitro and in vitro evaluation to identify the causative drug, desensitization techniques involving sequential re-introduction of ATD are often used. A prospective observational cohort research in Korea involving individuals with hypersensitivity reactions to first-line antituberculosis drugs revealed an 80.7% desensitization success rate. In Thailand, desensitization was successful in 78.9% of individuals with ATD hypersensitivity, with a median desensitization period of 18 days, according to retrospective studies involving patients aged 18 and older. Another retrospective study in Singapore revealed a 92% desensitization success rate(Thong et al., 2020).

The patient has been drug-challenged according to the above table, with the results showing that the patient is allergic to the administration of Rifampicin given in the H-10 treatment, whereas in other ATD treatments, namely isoniazid, pyrazinamide, and ethambutol, which were given until the full dose, no adverse drug effects were observed. Because the patient is forcibly discharged, a complete dose of pyrazinamide could not be administered, and rifampicin desensitization must be repeated.

Tuberculosis Lymphadenitis

TB lymphadenitis is the most prevalent sign of extrapulmonary tuberculosis related to M. tuberculosis infection(Hegde et al., 2014; Mathiasen et al., 2019; Salvador et al., 2015)In several counties, the overall incidence of pulmonary tuberculosis cases is decreasing,

while the proportion of extrapulmonary infections is rising. In the United States, of the 9945 cases of tuberculosis diagnosed in 2012, 846 (8.5%) cases were lymphadenitis. In Spain, 6762 cases of tuberculosis were reported in 2011 (14.7 cases/100,000 person-years) and 1785 (26.4%) cases were extrapulmonary tuberculosis(Salvador et al., 2015).In Denmark, in 2017 there were 275 patients diagnosed with TB and 22.2% of them had TB lymphadenitis(Mathiasen et al., 2019). In most cases, tuberculous lymphadenitis was more common in women than men with a ratio of 1.4:1. This ratio is different from pulmonary tuberculosis, where pulmonary tuberculosis is more common in men. TB lymphadenitis was previously more common in children, but is now more common in patients aged 30-40 years. In non-TB endemic countries, the majority of patients are foreign-born immigrants with cases of reactivation of TB(Fontanilla et al., 2011; Salvador et al., 2015).

The pathogenesis of tuberculous lymphadenitis can occur either by hematogenous spread after primary TB or as a local extension of tuberculous infection of the tonsils or adenoids. M. tuberculosis can migrate from the main site of infection (lungs) to the lymphatic system and bloodstream. To migrate from the lungs to the lymph nodes and bloodstream, the bacilli must penetrate the alveolar epithelium. Bacteria within alveolar macrophages or dendritic cells can be transferred by phagocytes to lymph nodes and blood. Bacteria can also invade and cause lysis of epithelial cells after infecting epithelial cells. From regional lymph nodes, the organism can continue to spread through the lymphatic system to other nodes or it can pass through the gland and reach the bloodstream in small amounts, where it can spread to almost any organ in the body.This form of lymphatic and hematogenous spread is generally self-limited and more than 90% of primary infections resolve without symptoms, but in the remaining 10% the infection progresses to



clinical significance(Cataño & Robledo, 2016).

Tuberculous lymphadenitis generally manifests as painless slowly progressive swelling of a single group of lymph nodes. The duration of symptoms is usually 1-2 months, but can vary from 3 weeks to 8 months. In the Indian study, the mean duration of symptoms was significantly longer in men than in women. The median diameter of lymph nodes in tuberculous lymphadenitis is 3 cm, but can reach 8-10 cm. Patients generally do not complain of significant pain and tenderness only occurs in 10%-35% of cases. Unilateral involvement of 1-3 nodes is reported in 85% of cases. Cervical node involvement is the most common and is reported in 45%-70% of cases, with 12%-26% of cases being in the supraclavicular region and 20% of cases bilateral. A study of 104 HIV-negative patients with tuberculous lymphadenitis reported fever in 19% of patients and weight loss in 16% of patients. While other studies report fever and weight loss in 40%-60% of HIV-negative patients. Systemic symptoms were reported more frequently in HIV-positive than in HIV-negative patients, ie 76% versus 12%. Concomitant pulmonary tuberculosis is reported in 18%-42% of patients. HIV-positive patients with TB lymphadenitis usually have higher rates of disseminated disease than HIV-negative patients(Deveci, 2016; Fontanilla *et al.*, 2011).

In this patient, the right and left inguinal lymph nodes were enlarged with a diameter of ± 2 cm, mobile, painless, which was suspected as TB lymphadenitis. However, the patient refused to undergo FNAB supporting investigations to confirm the diagnosis.

Some clinical manifestations of nonspecific TB lymphadenitis may overlap with other infectious and non-communicable diseases(Salvador *et al.*, 2015).The differential diagnosis of TB lymphadenitis includes lymphadenitis due to other infections including nontuberculosis mycobacteria (*M. scrofulaceum*, *M. avium*, and *M.*

haemophilum), toxoplasmosis, bartonellosis, and fungi. Noninfectious causes of lymphadenitis include neoplasms, sarcoidosis, Castleman disease, drug reactions, and nonspecific reactive hyperplasia(Deveci, 2016; Fontanilla *et al.*, 2011).

The presence of *M. tuberculosis* is demonstrated by culture or polymerase chain reaction (PCR) to validate the conclusive diagnosis of tuberculous lymphadenitis. The gold standard for diagnosing tuberculous lymphadenitis is a culture, although results can take up to four weeks. A positive acid-fast bacillus (BTA) stain shows the presence of mycobacterial infection, although the sensitivity is between 5 and 38 percent lower than that of culture. In patients with a negative smear and/or culture, histopathological features, such as granulomas with or without caseous necrosis, may support the diagnosis of tuberculous lymphadenitis(Deveci, 2016; Fontanilla *et al.*, 2011; Salvador *et al.*, 2015).

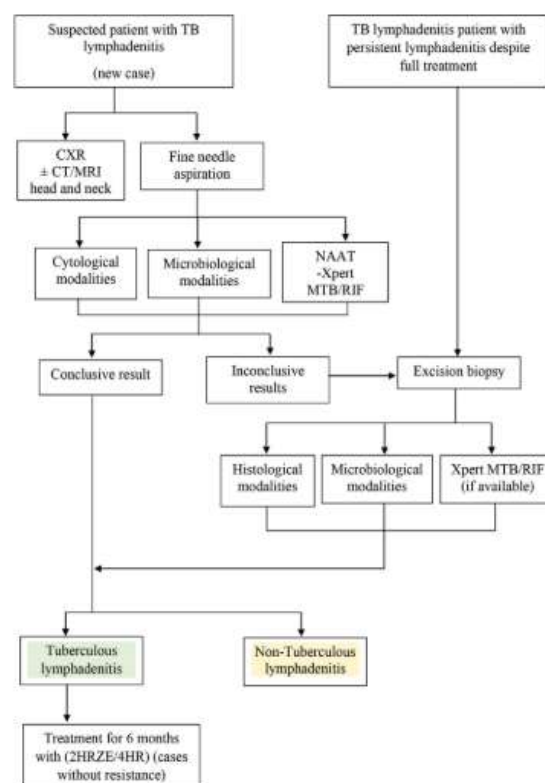


Figure 7. Flowchart for Diagnosing TB Lymphadenitis (Sivaratnam *et al.*, 2020)

The Infectious Disease Society of America (IDSA) advises antiretroviral drug treatment for 6 months for TB lymphadenitis sensitive to



first-line drugs, including isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for an additional 4 months. Studies indicate that there is no significant difference in cure or recurrence rates between 6 and 9 months of ATD, hence supporting the recommendations for treatment with 6 months of ATD. In 20% of cases, tuberculous lymphadenitis responds slowly to standard antibiotic treatment. Surgical management is only advised under special circumstances, such as paradoxical upgrading reaction (PUR) or ATD therapy failure. Recommendations urge patient follow-up during treatment to reassure patients and alleviate patient suffering. To enhance the efficacy of traditional antibiotic therapy, further research is needed to establish any other alternative treatments (Fontanilla et al., 2011).

Conclusions

There have been reported cases of a 34-year-old male patient with pulmonary and abdominal tuberculosis who had an allergic reaction to ATD. On the fifth day of treatment, the patient acquired a rash that was reddish and itchy. Initially, the patient did not show any allergy symptoms (ATD day 15). After an allergic reaction has occurred, the entire ATD is discontinued and drug challenge testing is undertaken. The patient was discovered to have an allergic reaction to ATD caused to rifampicin. At the period of outpatient treatment, ATDs given were isoniazid 300mg every 24 hours PO (day 11), Ethambutol 750mg (day 6) every 24 hours PO, Pyrazinamide 250 mg every 24 hours PO (day 1).

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