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Exfoliated dermatitis and hepatitis to first line Anti-Tubercular Therapy with treatment of Drug-Sensitive Tuberculosis with second line Anti-Tubercular Therapy: a roller coaster ride

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Abstract

The Adverse Drug Reactions (ADRSs) to Anti-Tubercular Therapy (ATT) have been reported from 8% to 85% worldwide, while the prevalence of ADRSs to 1st line ATT from India reported 2.3% to 17%, with more during the intensive phase and daily regime. However, cutaneous ADRSs related to ATT are less commonly seen. Common cutaneous ADRSs are maculopapular rash, urticarial, erythema multiforme, exfoliative dermatitis, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Among the 1st line ATT, pyrazinamide is the most common cause at 2.38%, and isoniazid is reported the least at 0.98%. Exfoliated dermatitis is rarely seen with 1st line ATT therapy limited to some case reports and case series.

Introduction

The Adverse Drug Reactions (ADRSs) to Anti-Tubercular Therapy (ATT) have been reported from 8% to 85% worldwide, while the prevalence of ADRSs to 1st line ATT from India reported 2.3% to 17%, with more during intensive phase and daily regime.[1] However, the cutaneous ADRSs to ATT are less commonly seen. The most commonly seen cutaneous ADRSs are maculopapular rash, urticarial, erythema multiforme, exfoliative dermatitis, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).[1,2] Among the 1st line ATT, pyrazinamide is the most common cause seen in 2.38%, and isoniazid is reported the least, with 0.98%.[1] Exfoliated dermatitis is rarely seen with 1st line ATT therapy limited to some case reports and case series.[3,4]

The standard treatment for newly diagnosed Drug-Sensitive pulmonary Tuberculosis (DS-TB) is six months with rifampicin containing regime.[5] There are some studies showing that a TB treatment duration of less than six months also cures it, but has the risk of higher relapse. Randomized control studies of 4-month regimes with fluoroquinolones with or without rifapentine were not able to show non-inferiority.[6-8] A recent study showed that the 4-months regime was non-inferior to standard treatment in children with drug susceptible, non-severe, smear negative TB.[9] Another study with 4-months rifapentine and moxifloxacin also showed non-inferiority to standard 6-months treatment.[10] There is evidence that a shorter regime of 4-months therapy is effective in some type of Drug-Susceptible Tuberculosis (DS-TB). Here, we are reporting a case of pulmonary TB with an exfoliated dermatitis to 1st line ATT after two

months of therapy. The patient did not tolerate any single drug, even on reintroduction. He developed extrapulmonary TB after six months and again did not tolerate any 1st line ATT. Finally, a case of drug-sensitive TB was successfully treated with 2nd line ATT without relapse/recurrence for the next three years.

Case Report

A 31-year-old male presented with complaints of cough, low-grade fever, and loss of appetite for one month. There was no history of ATT in the past. He did not have any significant past medical history. His vital were within normal. The general and respiratory examination was normal. The routine blood investigations were within normal limits. Chest X-ray (Posterior-Anterior, PA, view) showed right paratracheal opacity and few nodules in the right upper zone. His sputum sample staining for Acid Fast Bacilli (AFB) was negative twice. However, *Mycobacterium tuberculosis* (*M. tuberculosis*) was detected from the sputum sample on Cartridge-Based Nucleic Amplification Test (CBNAAT), while rifampicin resistance was not detected. The Contrast-Enhanced Computed Tomography (CECT) chest showed an enlarged right paratracheal lymph node with bilateral nodular infiltrates with tree buds appearance (Figure 1). So, he was diagnosed as microbiologically-confirmed pulmonary TB with mediastinal lymphadenopathy. The treatment was started with Category-1 ATT under the national TB control program with fixed-dose combination therapy of rifampicin (R), isoniazid

(H), pyrazinamide (Z), and ethambutol (E) according to weight. He was on regular follow-ups with clinical improvement.

Nearly two months after TB treatment, he developed diffuse erythematous and scaly lesions all over the body (Figure 2). The liver enzymes were also elevated. After a clinical discussion with a dermatologist, he was diagnosed with erythroderma (generalized exfoliated dermatitis), and ATT was stopped. All other causes of erythroderma were ruled out. Symptomatic treatment along with a short course of corticosteroids was given. Sequential re-introduction of all the 1st line drugs one by one showed the reappearance of erythroderma and elevation of liver enzymes with each of the 1st line ATT, even with corticosteroids. In the process of re-introduction of one by one drug with time to resolution, skin lesions took nearly three months. He was admitted and tried to reintroduce with antihistaminic and low-dose steroids, but he did not tolerate any of the 1st line ATT. During this period, his respiratory and constitutional symptoms were resolved completely. His repeat chest X-ray showed improvement in the lesion, and the sputum smear for AFB smear and CBNAAT were negative. For further confirmation we also repeat CECT chest, which showed resolution of the mediastinal lymph node and parenchymal lesions (Figure 3). There was no evidence of disease activity for three months duration and severe adverse events with all 1st line drugs. We keep him on regular clinic-radiological follow-up.

After six months of an asymptomatic period, he developed a swelling over the sternal area, which was increasing in size progressively, with no respiratory symptoms. The swelling was

non-tender and fluctuant. (Figure 4a). The CT chest showed a well-defined, non-enhancing hypodense lesion with a thick enhancing wall over the pre-sternal area suggestive of abscess. (Figure 4b,4c) Aspiration revealed pus, and the CBNAAT report showed *M. tuberculosis* detected with rifampicin sensitivity. Line Probe Assay (LPA) of pus showed sensitivity to both H and R. He was diagnosed with extrapulmonary TB (previously treated, microbiologically confirmed) and labelled as a relapse of previously treated TB. Considering the previous history of adverse drug reactions to all drugs, ATT was started sequentially at a lower dose. But he did not tolerate any of the 1st line drugs. Similar to the previous episode, he developed exfoliative dermatitis and elevated liver enzymes with all the 1st line drugs, even with doses of corticosteroid.

So finally, it was decided to treat the patient with modified 2nd line ATT and started with the regime of kanamycin, levofloxacin, linezolid, cycloserine, and clofazimine with close monitoring for adverse effects with relevant investigations. The patient tolerated the modified ATT well. Injection kanamycin was stopped after two months and the rest of the drugs were continued for next 10 months with regular follow-up. The swelling was resolved completely. The chest Computed Tomography (CT) after completion of ATT also showed a complete resolution of the abscess (Figure 5). The patient was kept on regular follow-up with no relapse/ recurrent TB for the next three years.

Discussion

The overall ADRSs with ATT are highly variable, reported as high as in 85% of cases. Similarly, the prevalence of ADRSs to 1st line ATT is also variable, with a study reporting ADRSs in 35% of cases with a daily regime.[1,11] The common ADRSs of ATT are gastrointestinal disturbances, hepatotoxicity, peripheral neuropathy, and cutaneous adverse effects. Hepatotoxicity with ATT was seen in 11.5% of the Indian population and can occur due to more than one drug. The cutaneous ADRSs are less commonly seen. The exfoliative dermatitis can also occur with more than one of the four drugs.[1,12] The ADRS with not tolerating any 1st line drugs is very rarely seen. The exfoliative dermatitis is a rare cutaneous ADRS associated with ATT and reported mainly with H and Z. The common factors associated with ADRS are old age, Human Immunodeficiency Virus (HIV) infection, autoimmune diseases, liver or kidney dysfunction, and polypharmacy.[3,4] Dua R *et al.* reported a similar case of pulmonary TB with exfoliative dermatitis to all the 1st line ATT. They completed the duration of ATT with ofloxacin and streptomycin.[4] In the present case, the duration of the ATT gap was nearly three months, with a resolution of all symptoms with sputum conversion and completed radiological resolution of the lesion. So, we kept him on regular follow-up. Our case was a very rare case of both exfoliative dermatitis and hepatitis to all the 1st line ATT with not tolerating a single drug, even with steroids.

The recommended duration for DS-TB is six months with R containing regime.[5] A recent randomised study concluded that 4-months rifapentine and moxifloxacin was non-inferior to standard treatment.10 Another study with the HRZE regime concluded that the 4-month

duration of ATT was non-inferior to 6 months in children with DS, non-severe, smear-negative TB.9 TRUNCATE-TB Trial concluded that initial treatment with an 8-week bedaquiline linezolid regimen was non-inferior to standard treatment for TB in clinical outcomes. It was associated with a shorter total duration of treatment and with no evident safety concerns.[13] However, earlier shorter regime TB treatments were not able to show the non-inferiority of 4 months duration of ATT.[6-8] Based on the above studies, the World Health Organisation (WHO) in 2022 recommended the treatment of pulmonary TB with two four drug regimes. Our case was very rare with DS, previously treated and not tolerating any 1st line drug. All the above studies of shorter regimes were published after the treatment completion of our case. The availability and cost of rifapentine and bedaquiline were also issues. So, we treated the case with all 2nd line drugs as evidence available at that time. The case highlighted that more than two systemic adverse reactions to all four drugs can occur, and we can treat a DS-TB with 2nd line ATT in such a condition.

Conclusions

Exfoliated dermatitis with hepatitis can occur to all 1st line ATT together even after two months of treatment. Shorter duration TB treatment regimes are associated with higher relapse/recurrence of TB. If not tolerating all or most 1st line ATT, DS-TB can be treated with 2nd line ATT. However the patient should be on regular follow-up for the next two years. Recent

studies have shown that moxifloxacin, rifapentine, bedaquilones, and linozolid containing regimes are effective in shorter TB treatment duration.

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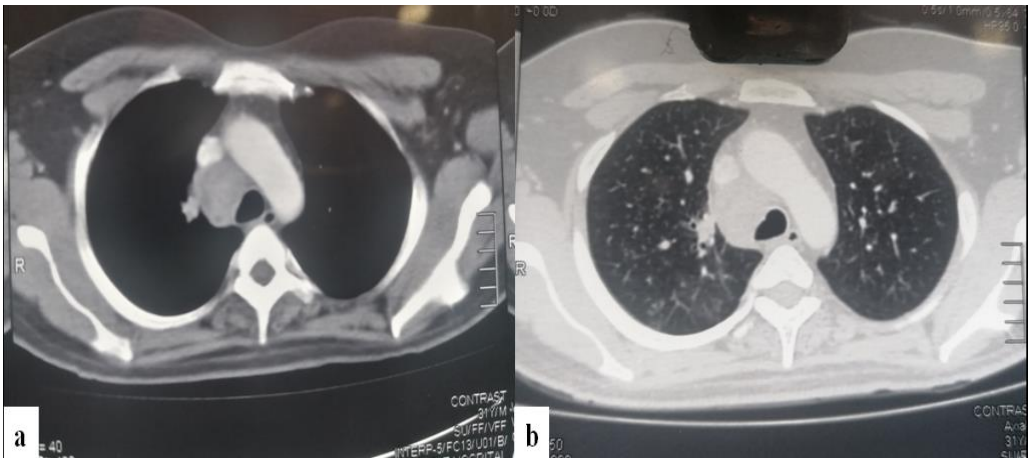

Figure 1. Contrast-Enhanced Computed Tomography (CECT) of the chest when starting Anti-Tubercular Therapy (ATT). **a)** The mediastinal window shows an enlarged right paratracheal lymph node; **b)** the lung window shows bilateral upper lobe nodular opacities.

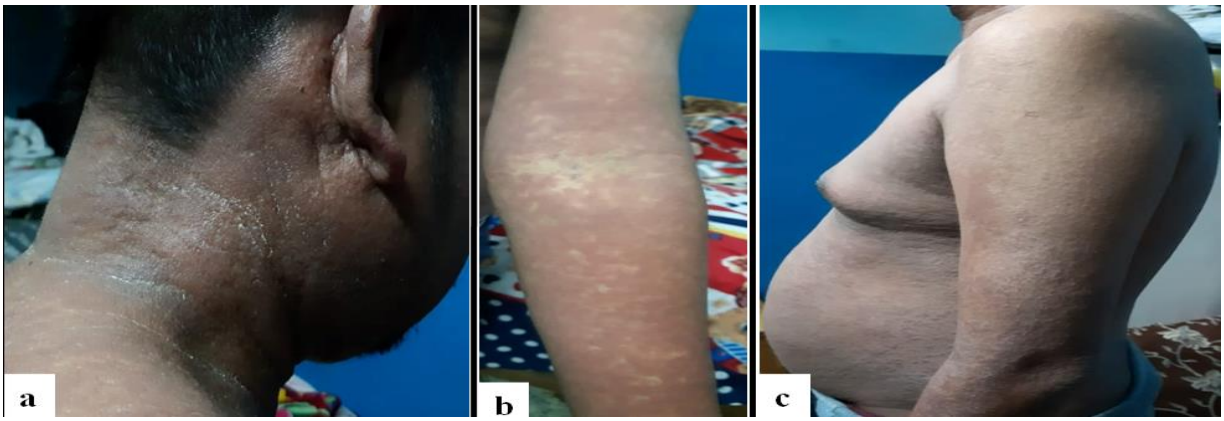

Figure 2. Extensive erythematous maculopapular lesion (morbilliform) involving most of the neck, trunk, and limbs with scaling in some areas.

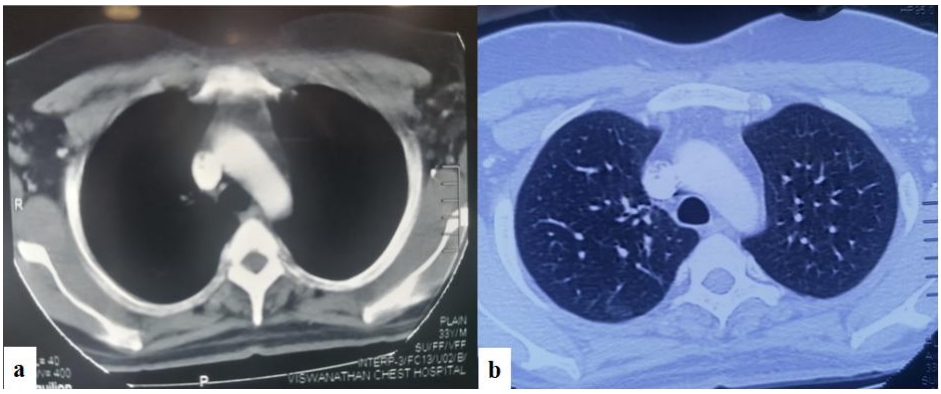

Figure 3. Computed Tomography (CT) scan of the chest after five months showed complete resolution of the mediastinal lymph node and parenchymal lesions.

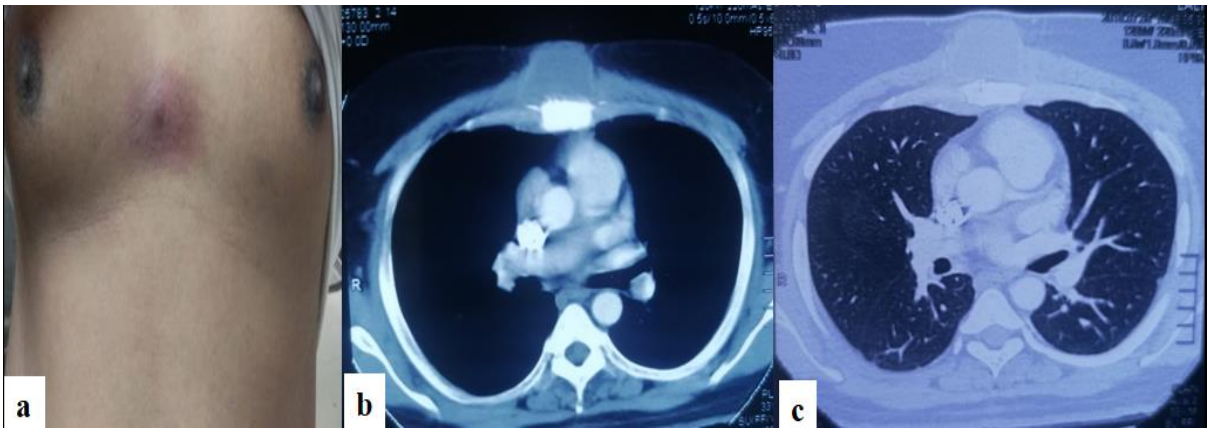

Figure 4. a) Swelling over the anterior chest wall; **b)**, **c)** sternal area. Chest Computed Tomography (CT) scan showing well defined non enhancing hypodense lesion with thick enhancing wall over pre-sternal area suggestive of abscess.

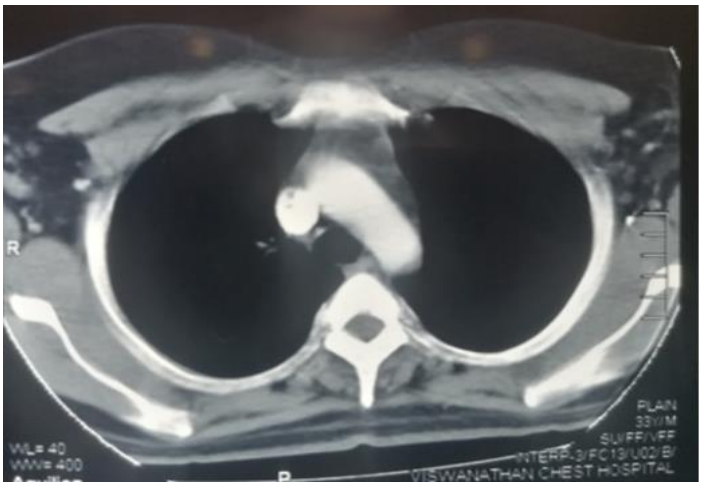

Figure 5. Computed Tomography (CT) of the chest shows complete resolution of anterior chest wall swelling.