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Toxidermia Secondary to Anti-Tubercular Therapy: A Cross Sectional Study

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ABSTRACT

Introduction: Tuberculosis (TB) is a major global public health problem and leading cause of death among communicable diseases in India. Anti tubercular therapy (ATT) is associated with various adverse drug reactions including diverse presentation of cutaneous adverse drug reactions (CADRs) also known as toxidermia, ranging from mild to life threatening sequelae. Re challenge remains the only option to restart the therapy safely with other primary ATT drugs.

Objectives: To study the epidemiological profile, various CADRs, histopathological features, identify the offending drug and reinstitution of safe ATT.

Materials and Methods: This was a cross-sectional study conducted at tertiary care centre. Patients who were diagnosed with tuberculosis of any type and on ATT with CADRs were included in the study. Data collection included demographic characteristics, type of TB, ATT regimen, pattern of drug rash, offending drugs, histopathological features, laboratory parameters and reinstitution of ATT after re challenge.

Results: Among 32 adult patients, male to female ratio was 1:1.3 and mean age was 45 years. Clinical diagnosis of CADRs was confirmed histopathologically. The most common type of TB observed was Pulmonary, (n= 21, 65.6%) followed by extra pulmonary (n=11, 34.4%). Among 32 cases of CADRs, Maculopapular rash was the most common 15(46.87%) type of cutaneous eruptions followed by lichenoid drug rash in 6(18.75%), urticarial in 5(15.63%), 4(12.5%) had generalised xerosis and 2(6.25%) had severe CADRs in the form of erythema multiforme1(3.15%) and DRESS syndrome1(3.15%). Patients with milder forms of CADRs were continued ATT with concomitant topical treatment for cutaneous lesions. Re-challenging was performed as per the institution's protocol in 8 patient who gave consent. Ethambutol was the most common 6(75%) offending drug followed by other first line anti tubercular drugs in 2(25%) patients.

Conclusion: CADRs to ATT is like a poisoned chalice, as stopping ATT and treating CADRs with systemic steroids can aggravate underlying TB. Re-challenge with ATT will help in sniffing out the culprit drug and reintroduction of safer alternative regimen.

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Introduction

Tuberculosis (TB) is preventable and usually curable disease. TB is major global public health problem and leading cause of death among communicable diseases accounting to 1.4 million cases globally and 4.94 lakh in India [1,2]. Incidence of TB cases globally accounts to 8.2 million, out of which 3 million are from India in 2023 [1,2]. First line anti-tubercular (Anti-TB) therapy (ATT) with rifampicin (R), isoniazid (INH), pyrazinamide (Z) and ethambutol (E) remains the mainstay of treatment. After the advent of National TB Elimination Program (NTEP) availability of diagnostic centres and hence newly diagnosed cases have significantly surged [2]. India has the one of the best estimates (>80%) of treatment coverage with ATT among 30-high burden countries. Owing to this, the incidence of adverse drug reactions (ADRs) has also raised [2]. Cutaneous adverse drug reactions (CADRs) secondary to ATT also known as toxidermia accounts to majority of ADR cases. Diverse clinical presentation, ranging from mild to life threatening sequelae. Re-challenging and desensitization remains the only option to restart the therapy safely with other ATT drugs. Currently very few studies are in the literature. Hence this study was conducted in 32 TB patients presenting with CADRs secondary to ATT. However, ATT was still continued in all the patient after rechallenging.

Aims and Objectives

To study the epidemiological profile, various CADRs, histopathological features, identify the offending drug and reinstitution of safe ATT.

Materials and Methods

This was the prospective cross-sectional study conducted in the department of dermatology, venereology and leprosy of tertiary care centre. Patients aged >18years and diagnosed with tuberculosis of any type and on ATT with CADRs secondary to ATT were included in the study. Study period was from January 2023 to August 2024. Data collection included demographic characteristics, complete history and general physical examination including risk factors, co-morbidities and drug history. Data on type of TB, ATT regimen, pattern of drug rash and offending drugs was also gathered. Laboratory parameters like complete hemogram with absolute eosinophil count, liver function test (LFT), renal function test (RFT), chest radiography and serology. Skin biopsy was also done and sent for histopathological examination. Patients were rechallenged with ATT as per the institution's protocol [modification of European Academy of Allergology and Clinical Immunology guidelines [3]. After identifying the culprit drug and excluding it, patients were reinitiated with safer and alternative ATT regimen. Institution ethical committee (IEC) clearance has been obtained before starting this study. Data was entered in the Excel master sheet and Statistical Package for the Social Sciences (SPSS)- Version 26 was used for statistical analysis. The data was expressed in the form of frequency, percentage, mean, percentage, tables and graphs.

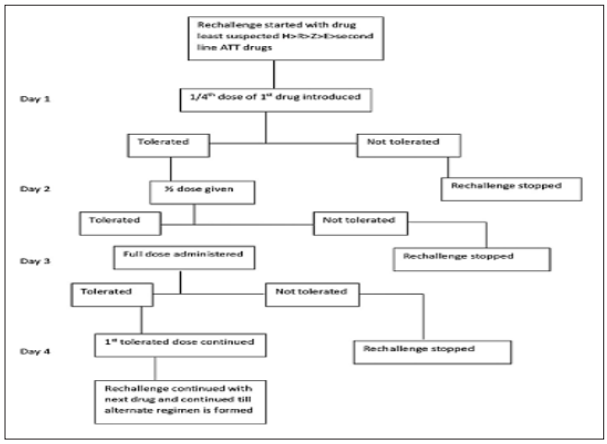

Figure 1: Algorithm for Drug Rechallenge Protocol

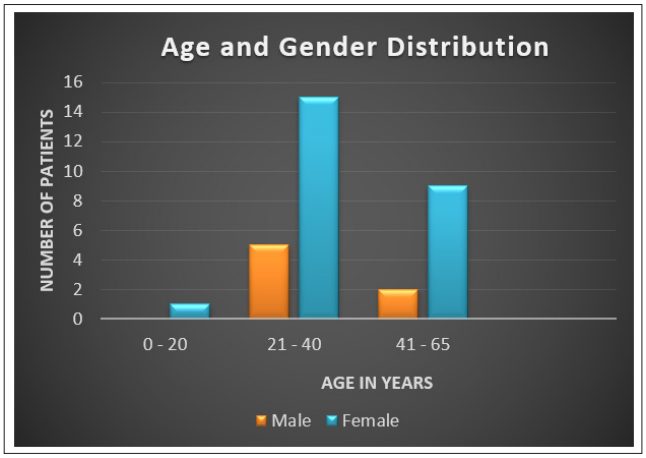

Figure 2: Demographic Profile of Patients with Age and Sex Distribution

Results

A total of 32 adult patients with CADR to ATT were included under the study over a period of 20 months. This study comprised of 7 males and 25 female patients, with male to female ratio of 1:3.5. All the patients were in the age group of 20 to 65years and the mean age was 45 years. Various haematological tests and histopathology helped in concluding the diagnosis of CADRs. All the patients, 32 (100%) were on category I, ATT regimen. The risk factors identified in the study participants were polypharmacy 12 (37.5%), smoking 8 (25%), alcohol intake 7 (21.9%), hypertension 6 (18.75%) and diabetes mellitus 5 (15.6%), %). Mean duration between drug intake and onset of rash was 41days (2 days to 150 days). The most common type of TB observed was Pulmonary TB, (n= 21, 65.6%) followed by extra-pulmonary in (n=11, 34.4%) patients. Among extra-pulmonary, 5 cases were cutaneous TB. Among 32 cases of CADRs, Maculopapular rash was the most common 15(46.87%) type followed by lichenoid drug rash 6(18.75%), urticarial5(15.63%) and generalised xerosis4(12.5%). Only 2(6.25%) had severe CADRs in the form of erythema multiforme1(3.1%) and DRESS syndrome1(3.1%). Systemic involvement was seen in 32 (80%) patients. Laboratory parameters were deranged in 28 (87.5) patients. Eosinophilia (eosinophil count more than 500/cu.mm) was seen in 24 (75%) patients. 8 (25%) patients had evidence of deranged liver function and 2 (6%) patients had deranged renal functions. Patients with milder forms of CADRs were continued ATT with concomitant topical treatment for cutaneous lesions. Re-challenging was performed as per the institutions protocol in 8 patient who gave consent. Ethambutol(E) was the most common 6(75%) offending drug followed by other first line anti-tubercular drugs in 2(25%) patients.

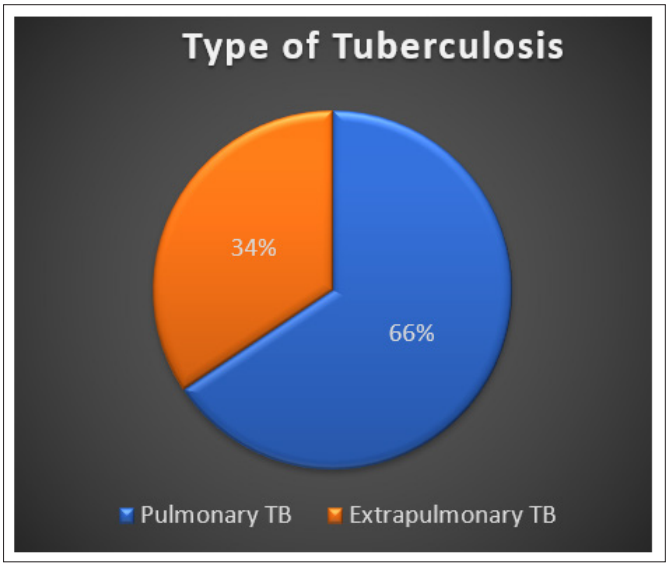

Figure 3: Type of Tuberculosis among Study Participants

Discussion

Adverse drug reaction as defined by the lancet "as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product [4]." The skin is one of the most common sites for adverse drug reactions. CADRs occur in up to 8% of hospitalized patients [5]. They account to 2% of all the dermatological outpatient consultations and ~5% of the admissions to an inpatient dermatology service [6]. CADRs are mediated by either an immunologic or a non-immunologic mechanism. Immunologic reactions result

from IgE-dependent, immune complex-initiated, cytotoxic, neutrophil and T cell-based or delayed-type/cell-mediated immune mechanisms [6]. Nonimmunologic reactions may result from nonimmunologic activation of effector pathways, overdosage, cumulative toxicity, delayed toxicity, pharmacological side effects, drug interactions, metabolic alterations, photosensitivity or exacerbation of preexisting dermatologic conditions [6]. Rarely, Idiosyncratic with a possible immunologic mechanism may result from drug reaction with eosinophilia and systemic symptoms (DRESS)/ drug-induced hypersensitivity syndrome (DIHS), Stevens–Johnson syndrome (SJS)/ Toxic epidermal necrolysis (TEN), drug reactions in the setting of HIV infection and drug-induced lupus erythematosus [6]. The incidence of CADRs reported in patients on ATT is 5.7%. Many TB patients are at increased risk of developing adverse drug reactions. Risk factors include genetic susceptibility, poly-pharmacy, infections such as HIV, elderly age group, diabetes, organ failure, autoimmune diseases, hematological malignancy and fixed dose combinations of ATT [5].

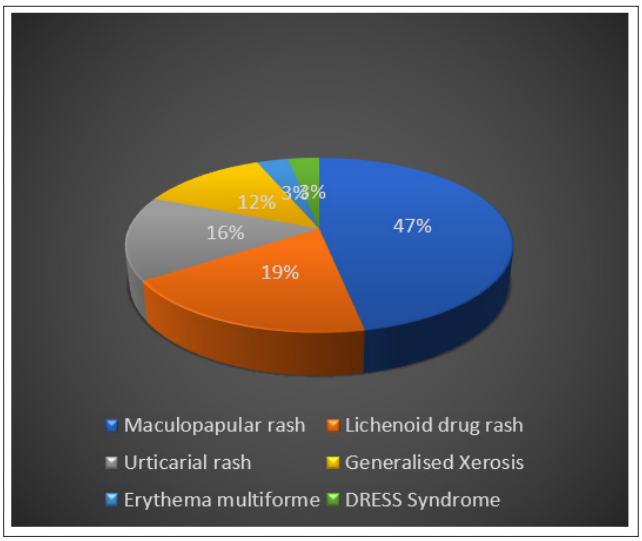

Figure 4: Pattern of Cutaneous Adverse Drug Reaction Seen with Anti-Tubercular Drugs

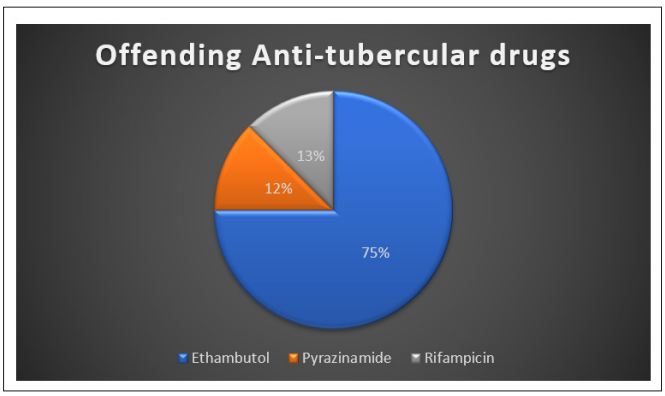

Figure 5: Commonly Implicated Drugs after Re-Challenge

Differences in body weight, body composition, gastrointestinal tract factors, liver metabolism, and renal function between males and females, alter the pharmacokinetic and pharmacodynamics of drugs explains the fact that CADRs are common in females [7]. In our study, females outnumbered males with male to female ratio of 1:3.5. This finding was in concordance with Sharma and David. Whereas Sinha and Suthar reported CADRs to be common in males [5,8-10].

All drugs can produce CADRs, but not all patients develop adverse reactions. Age affects the occurrence of CADRs. Elderly patients with multiple comorbidities, polypharmacy, variable drug absorption, metabolism and renal excretion puts them at risk of CADRs. In the present study mean age of occurrence of CADRs was 45years. Which was comparable to the study by Sharma and Sood A [5,11].

The most common risk factors identified was polypharmacy 12 (37.5%). It is defined as taking several drugs, whether prescription or over-the-counter at the same time for a particular patient [7]. The severity of ADRs increases disproportionately as the number of drugs taken increases [7]. Mechanism by which polypharmacy causes CADRs is possibly due to drug interaction, synergism, duplication, additive effect, discontinuation of therapy, changing the dose to save money, skipping some medications and physiological antagonism [7]. 8 (25%) patients in our study had history of smoking. It is one of the major risk factors for many dermatological and non-dermatological conditions. Smoking affects the drug metabolism by inducing hepatic cytochrome P-450 isoenzymes [7]. 7 (21.9%) patients were alcoholics. It increases the incidence of development of CADRs making it more toxic either in a pharmacokinetic or pharmacodynamic manner. It also increases the risk of drug-induced liver injury during ATT. Other risk factors associated with CADRs in our study was hypertension and diabetes mellitus in 6 (18.75%) and 5 (15.6%) respectively.

After the advent of weight band wise fixed dose combination for drug sensitive TB and increased rate of case detection in 2016 there by better implementation of revised national TB control program (RNTCP), rate of CADRs to ATT also significantly raised. In 2020 in order to achieve WHO's sustainable development goals of eliminating TB by 2030, RNTCP was renamed to national TB elimination program (NTEP). NTEP, 100-Day TB elimination campaign in 2024 and good adherence to treatment due to better tracking system has further increased the incidence of CADRs to ATT.

All the patients, 32 (100%) were on category I, ATT regimen. Mean duration between drug intake and onset of rash was 41days (2 days to 150 days). Which was in concordance with observation by [5]. Latent period for onset of urticarial and maculopapular rash, erythema multiforme and DRESS syndrome was short. Whereas lichenoid and xerosis was noticed at later stages. The most common type of TB observed was Pulmonary TB, (n= 21, 65.6%) followed by extra-pulmonary in (n=11, 34.4%) patients. Among extra-pulmonary, 5 cases were cutaneous TB.

Among 32 cases of CADRs, Maculopapular rash was the most common 15(46.87%) type. This finding is in concordance with similar findings by sharma and Tan WC [5,12]. Other CADRs observed were lichenoid drug rash 6(18.75%), urticarial 5(15.63%) and generalised xerosis4(12.5%). Only 2(6.25%) had severe CADRs in the form of erythema multiforme1(3.1%) and DRESS syndrome1(3.1%). Other forms of severe CADRs reported in literature by Tan WC and Lehloenya were acute generalized exanthematous pustulosis, exfoliative dermatitis and stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) [12,13]. Laboratory parameters were deranged in 28 (87.5) patients. Eosinophilia (eosinophil count more than 500/cu.mm) was seen in 24 (75%) patients. 8 (25%) patients had evidence of deranged liver function and 2 (6%) patients had deranged renal functions.

Patients with milder forms of CADRs were continued ATT with concomitant topical treatment for cutaneous lesions and symptomatic treatment for pruritus. Severe forms of CADRs were managed with systemic corticosteroid and ATT was still continued. As discontinuing ATT increases the risk of disseminated disease and drug-resistant tuberculosis. Therefore, re-challenge should be initiated as early as possible considering it is relatively safe. There are no specific re-challenge guidelines, re-challenge can be done with each ATT drug as per the institution's protocol till the culprit drug is found and a final regimen established [5].

Re-challenge is defined as a controlled administration of a drug in order to diagnose drug hypersensitivity reactions [5]. Re-challenging was performed as per the institutions protocol [modification of European Academy of Allergology and Clinical Immunology guidelines till the culprit drug is found and a final regimen is established [3]. 8(25%) patient gave consent for rechallenge. Ethambutol(E) was the most common 6(18.75%) offending drug followed by other first line anti-tubercular drugs [pyrazinamide(Z) and rifampicin(R) in one each] in 2(6.25%) patients. Multiple drug hypersensitivity was not observed in any patients. This finding is in contrast with findings by sharma et al, where they reported 10 cases with multiple drug hypersensitivity [5].

CADRs associated with ATT will have better disease outcome if re-challenge is performed, as offending drug can be omitted from the treatment regimen and safely alternative ATT can be initiated. India and other countries worldwide have highest TB burden, re-challenge helps in avoiding treatment interruption thereby decreasing morbidity, mortality and transmission rate [14].

Conclusion

CADRs to ATT is like a poisoned chalice. As stopping ATT and treating CADRs with systemic steroids can aggravate underlying TB. Re-challenge with ATT will help in sniffing out the culprit drug and reintroduction of safer alternative regimen.

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Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent.

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Nil

Conflicts of Interest

There are no conflicts of interest.

Use of Artificial Intelligence (AI)–Assisted Technology for Manuscript Preparation

The authors confirm that there was no use of artificial intelligence (AI)–assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

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