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A Spectrum of Rare Cutaneous Adverse Reactions to First Line Antituberculosis Drugs at a Tertiary Care Centre in South India

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Abstract
BACKGROUND AND OBJECTIVE: *Cutaneous adverse drug reactions are one of the commonest side effects of antituberculosis drug. Early recognition, prompt withdrawal of suspected ATT drug and administration of steroids in severe cases are the corner stone of its management*
MATERIALS AND METHODS: *Five patients admitted with cutaneous adverse reactions to anti tuberculosis therapy in various forms such as Toxic Epidermal Necrolysis, Severe Exfoliative Dermatitis,DRESS , pellagra, and Lichenoid eruptions during different time periods of December 2019 to December 2020 in Department of Thoracic medicine at Thanjavur Medical College and Hospital and Kilpauk Medical College and HospitalAmong five cases first three were drug sensitive pulmonary tuberculosis, next two cases were Extrapulmonary tuberculosis like pleural effusion, and spinal TB Offending drugs were stopped and treated with supportive measures, antihistaminics and steroids. ATT rechallenging done for all the patients as per National guidelines and the offending drugs identified as isoniazid, Rifampicin,Rifampicin,isoniazid,and Ethambutol respectively and the drug replaced with levofloxacin and streptomycin. During one week observation, Patients were stable and no cutaneous adverse reactions observed. Patients were advised to continue modified Antituberculous drugs as per guidelines.*
CONCLUSION: *Severe hypersensitivity reactions to anti tuberculosis drugs are rare but may be fatal and must be recognized early to reduce associated morbidity and mortality.*
Keywords: *Anti-tubercular therapy,cutaneous adverse drug reaction*

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I. Introduction

First line anti-tubercular (Anti-TB) therapy (ATT) with rifampicin (R), isoniazid (INH), pyrazinamide (Z), ethambutol (E), and streptomycin (S) remains the cornerstone of the Tuberculosis treatment. Owing to the increased prevalence of TB worldwide and increased availability of the facilities for diagnosis and treatment, the rate of adverse drug reactions (ADRs) to the first line therapy has also increased. Cutaneous adverse drug reactions (CADRs) are well known side effects of these drugs and can range from a mild pruritus to life threatening toxic epidermal necrolysis (TEN) which require discontinuation of the treatment and may complicate the tuberculosis management. Re-challenge- desensitization remains the only option for re-introducing ATT[1]. Among the ATT drugs, pyrazinamide reported as the commonest drug causing CADRs(38%) Tan *et al*.[5] .Incidence of adverse reaction to Isoniazid estimated to be 5.4%. Cutaneous side effects to Isoniazid is 2%.

II. Case Series:

CASE 1 -ISONIAZID INDUCED TOXIC EPIDERMAL NECROLYSIS:

• A 38 years old married female who was diagnosed as microbiologically confirmed drug sensitive Pulmonary Tuberculosis , on Anti Tuberculosis treatment for 1 month .She was admitted with complaints of Itchy Skin lesions and Fever . ATT was stopped .Skin rashes subsided after treating with steroids. ATT rechallenging was done.Subsequent to that, patient developed lip swelling, urticaria and vesicles all over the body after taking Isoniazid . On local examination multiple purpuric macules present over trunk and extremities. Multiple vesicles present over trunk with few hemorrhagic vesicles, diffuse erosions and crusted plaques present over face, trunk and extremities.

Dermatologist opinion obtained and clinically diagnosed as Isoniazid induced Toxic Epidermal Necrolysis. Patient was treated with Intravenous fluids ,IV antibiotics,IV steroids,Antihistaminics and other supportive measures.Offending drug Isoniazid was stopped and replaced with levofloxacin. During the course of treatment patient was stable , no skin rashes .She was observed for one week and advised to continue modified ATT for 6 months.

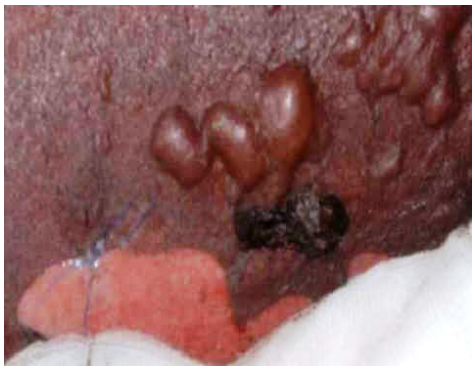


Fig : Toxic Epidermal Necrolysis

CASE 2 –RIFAMPICIN INDUCED EXFOLIATIVE DERMATITIS

60 years old female who was diagnosed as microbiologically confirmed drug sensitive Pulmonary Tuberculosis on Antituberculous drugs for 2 months… She was presented with complaints of itching and rashes all over the body.On local examination there was diffuse scaling and erythema of skin involving trunk, both upper limbs and lower limbs with hair loss.Dermatologist opinion obtained and they advised to stop ATT and skin biopsy.

Skin biopsy section studied showed mounts of parakeratosis with epidermal hyperplasia, mild spongiosis and few apoptotic keratinocytes. Papillary showed inflammatory infiltrate composed of lymphocytes and neutrophils. Upper dermis showed congested blood vessels with extravasation of RBCs .Features are consistent with drug induced Exfoliative Dermatitis.

Patient was treated with antihistamines and other supportive measures. ATT rechallenging done as per National guidelines and the offending drug identified as Rifampicin and the drug replaced with levofloxacin.During the course of the treatment Patient was stable and no cutaneous reactions developed. Patient was advised to continue modified ATT for nine months.

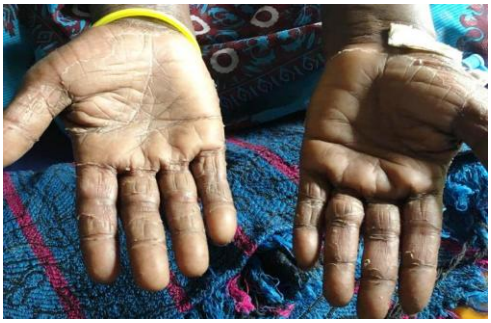
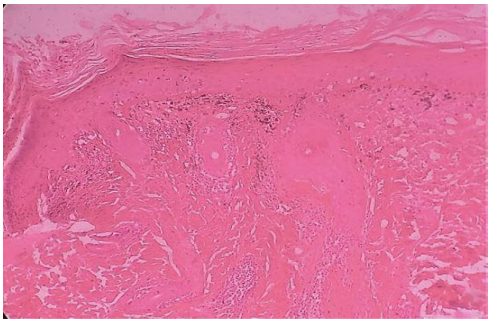


Fig :Exfoliative dermatitis



HPE Report

CASE 3-RIFAMPICIN INDUCED DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

30 years old male who was diagnosed as microbiologically confirmed Pulmonary Tuberculosis on Anti Tuberculosis treatment for three days presented with complaints of fever of new onset and skin lesions all over the body with elevated LFT. Complete blood count shows leukocytosis and eosiniphilia.Local examination showed maculopapular rash involving whole body, symmetrical in distribution with itching and excoriation.

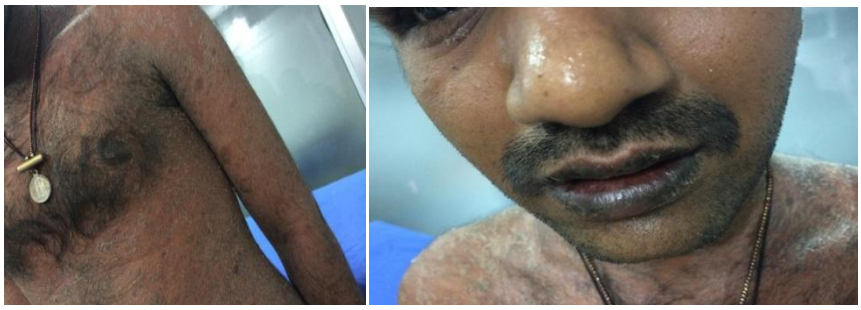


Fig : DRESS

Dermatologist opinion obtained and clinically diagnosed as Drug induced DRESS.Patient was treated with Steroids,Antihistamines and other supportive measures. ATT was stopped. ATT rechallenging done as per National guidelines and the offending drug identified as Rifampicin and the drug replaced with Streptomycin.Patient was adviced to continue HESZ for two months and HE for ten months.During the course of the treatment Patient was stable and no cutaneous reactions developed.

CASE 4 –ISONIAZID INDUCED PELLAGRA

60years old female who was a case of extrapulmonary tuberculosis, pleural effusion on Anti Tuberculosis treatment for one week presented with complaints of itching and hyperpigmented rashes all over the body. Local examination showed maculopapular rash with erythema, scaling present mainly over the maculopapular region involving both forearm .The lesions were well demarcated from normal skin with casal collar around the neck.ATT was stopped. She was treated with antihistamines, nicotinamide supplementation and dietary advices.ATT rechallenging done as per National guidelines and the offending drug identified as Isoniazid and the drug replaced with levofloxacin. She was advised to continue modified ATT for 6months.

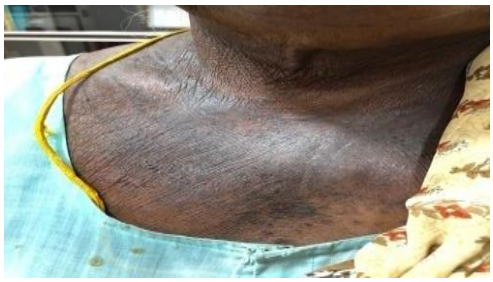
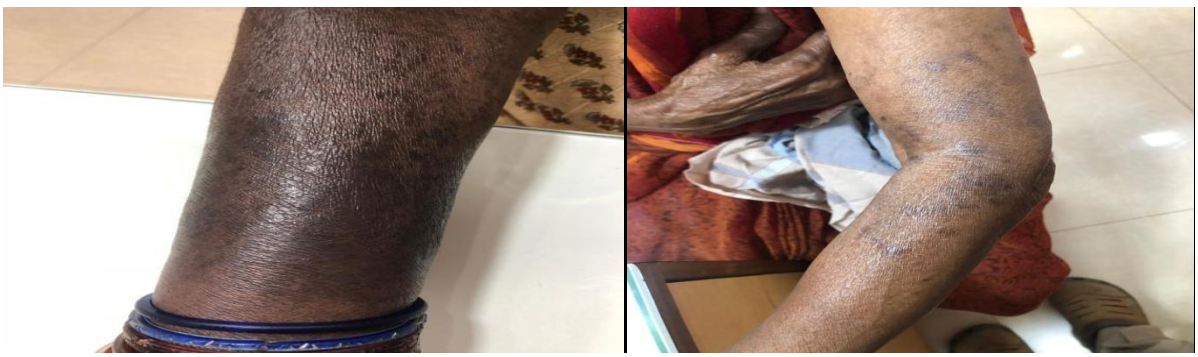


Fig: casal collar



Lesions recovered

CASE 5 –ETHAMBUTOL INDUCED LICHENOID REACTIONS

65years old male who was a case of extrapulmonary tuberculosis, SPINE TB on Anti Tuberculosis treatment for 4 months presented with complaints of itching and hyperpigmented rashes all over the body. On local examination multiple symmetrical hyperkeratotic papules and plaques present over flexors of both upper limbs and extensors of both lower limbs with itching and excoriation.Dermatologist opinion obtained .They advised to stop ATT and skin biopsy.Patient was treated with oral steroids,antihistamines and other supportive measures.

Skin biopsy showed lining by stratified squamous epithelium with parakeratosis ,mild acanthosis and vacuolar degeneration and apoptotic change in the basal keratinocytes.Dermoepidermal junction showed dense band like lymphocytic infiltrate admixed with eosinophils.upper dermis shows focal mild perivascular inflammatory infiltrate .Features are suggestive of lichenoid drug reactions.ATT was stopped . ATT rechallenging done as per National guidelines and the offending drug identified as ethambutol and the drug replaced with levofloxacin. Patient was advised to continue Modified ATT for 9 months.

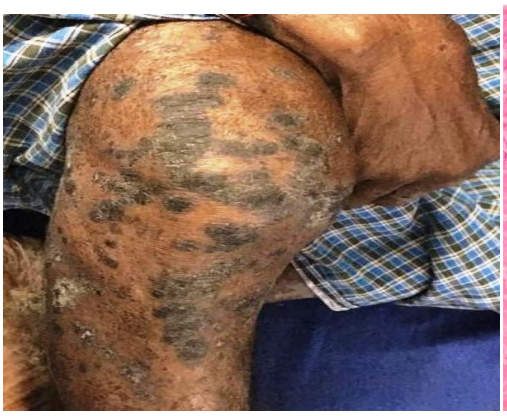
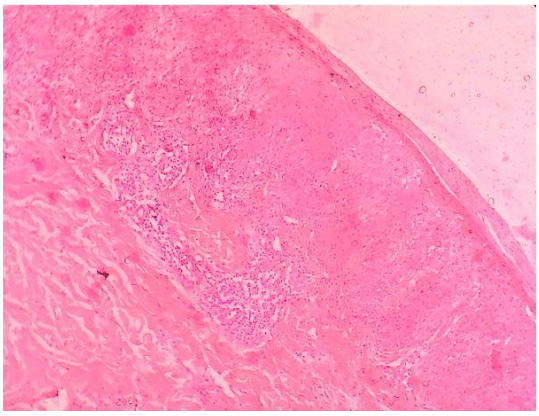


Fig: lichenoid reactions



HPE Report

III. Discussion

Adverse drug reaction as defined by WHO is "a response to a drug that is noxious and unintended and occurs at doses normally used in human for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function."[3].The majority (75–80%) of adverse drug reactions are caused by predictable, nonimmunologic effects of drugs. The remaining 20–25% events are caused by unpredictable effects that may or may not be immune-mediated. Immune-mediated reactions account for 5–10% of all drug reactions [.4] The incidence of cutaneous adverse drug reactions (CADRs) reported in patients on antitubercular therapy is 5.7%.[5] Various type of rash observed are urticarial drug rash, maculopapular rash, lichenoid drug rash, acute generalized exanthematous pustulosis (AGEP), exfoliative dermatitis, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

Re-challenge is defined as a controlled administration of a drug in order to diagnose drug hypersensitivity reactions [2]. Tuberculosis outcomes are better if re-challenge is undertaken and only the offending drug is removed from the treatment regimen[.6] Re-challenge is of utmost importance because of increased burden of TB in India/World, limited number of first line ATT drugs, increased toxicity of second line drugs and keeping second line drugs reserve for resistant cases. It helps in avoiding treatment interruption due to ADR thereby decreasing morbidity, mortality and transmission rate. Interruption of therapy during the intensive phase is associated with a three times higher risk of death [7]. The sequence of re-challenge is still a matter of debate whether most effective drugs, rifampicin, and isoniazid should be re-challenged first or the drugs least likely to cause a reaction.. More than 90% of re-challenge reactions occur within 72 hours. So, re-challenging with a new first line drug every 96 hours is recommended, while monitoring] closely for features of a re-challenge reaction [.6]

IV. Conclusion:

Any type of cutaneous drug reaction may develop from any of the first line drugs. Re-challenge is a ray of hope for adverse drug reaction to anti-tubercular drugs as it decreases the risk of ATT interruption/default. The offending drug can be found out by re-challenge and safer ATT regimen can be restarted.It should be recognized early to reduce associated morbidity and mortality and the patient should be counselled regarding adverse reactions.[1]

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