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Pyrazinamide Induced Maculopapular Rash: A Rare Case Report.

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ABSTRACT

Non immediate allergic reactions (NIRs) to drugs, due to specific immunologic mechanisms, can be induced by many commercially available drugs Maculopapular exanthema (MPE) is the one among the commonest manifestation following NIRs. Cytokines are known to play a dominant role in causing MPE. T helper 1 (Th1) cytokines and CD4 (+) T cells play a very pivotal role in the pathogenesis of this condition. As a part of pharmaovigilance program we hereby report a case of Maculopapular rash induced by pyrazinamide in a patient treated for pulmonary tuberculosis. The causality, severity, and preventability assessment of the adverse drug reaction was done to establish a causal relationship

Keywords: Pyrazinamide, maculopapular exanthema, allergic reactions.

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INTRODUCTION

Non immediate allergic reactions (NIRs) to drugs, due to specific immunologic mechanisms, can be induced by many commercially available drugs Maculopapular exanthema (MPE) is the one among the commonest manifestation following NIRs. NIRs elicits a Spectrum of manifestations, with trajectory of skin lesions ranging from Maculopapular exanthema and urticaria to more severe entities such as acute generalized exanthematic pustulosis(AGEP), drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome(DRESS/DIHS), Stevens-Johnson syndrome(SJS), and toxic epidermal necrolysis(TEN). Cytokines are known to play a dominant role in causing MPE. T helper 1 (Th1) cytokines and CD4 (+) T cells play a very pivotal role in the pathogenesis of this condition [1]. Many medications are found to be known culprits in causing this skin condition [2]. Pyrazinamide is used as a first line drug in treating pulmonary tuberculosis in combination with isoniazid, rifampicin and ethambutol. Side effect profile of pyrazinamide includes, nausea, vomiting, dysuria, flushing, hyperurecemia, hepatotoxicity, arthralgia, and sideroblastic anemia. Cutaneous skin manifestations are very rare and it includes skin rashes and photosensitivity during the course of treatment [3]. As a part of pharmaovigilance program we hereby report a case of Maculopapular rash induced by pyrazinamide in a patient treated for pulmonary tuberculosis. The causality, severity, and preventability assessment of the adverse drug reaction was done to establish a causal relationship.

CASE REPORT

A 55-year-old patient, belonging to a lower middle class family, with past history of diabetes mellitus, visited KMC, Manipal with complaints of severe cough with expectoration, fever, loss of appetite, and loss of weight since 1 month. He was suspected for pulmonary tuberculosis and sputum testing was done by Zeihl–Neelson (ZN) staining for acid-fast bacillus (AFB) as per Revised National Tuberculosis Control Programme (RNTCP) and sputum positive pulmonary tuberculosis was confirmed on 27/2/2016. Bilateral upper zone infiltrations were noted in chest x ray. On the basis of the above clinical examination and observation, diagnosis of sputum positive pulmonary tuberculosis was made and category 1 directly Observed Treatment (DOT) was initiated on 9/03/2016 as per national RNTCP guidelines according to his weight (59Kg). Category 1 anti-tuberculosis therapy includes isoniazid 600 mg (2 tablets), rifampicin 450 mg (1 capsule), pyrazinamide 1500mg (2 tablets), and ethambutol 1200 mg (2 tablets)[4].He tolerated the first dose of anti-tuberculosis therapy. On 10/03/2016 patient complaint of itchy, red Maculopapular rashes predominantly over abdomen and scattered over back [Fig 1]. So all ATT drugs were discontinued as per RNTCP guidelines and patient was put on oral anti-histamine. The condition improved and rashes slowly subsided and disappeared completely in two days. So decision was made to start the DOT therapy again and first ethambutol was introduced again followed by isoniazid. Patient tolerated well and there was no rash observed. Then pyrazinamide was introduced again on 15/03/2016 and the next day the rash reappeared again over his trunk and abdomen with pruritus. Pyrazinamide was stopped on 16/03/2016. Rifampicin was started on 18/03/2016 and there is no appearance of rashes and patient is discharged with review after one month and instructions to look for pruritus and appearance of rash.

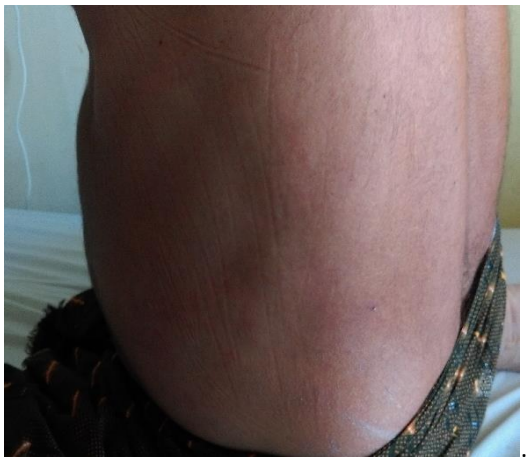

Figure 1: Maculopapular rashes over abdomen and back after pyrazinamide drug administration. Red itchy lesions are noted.

DISCUSSION

Maculopapular eruption is a very commonly seen cutaneous adverse drug reaction (CADR). A typical Maculopapular rash has two component. A macule which is a flat topped lesion and a papule which are usually raised lesions. Color of the rash is usually bright red associated with hot burning sensation along with pruritus. It extensively involves whole of the skin surface with facial sparing [5]. According to literature search about 5 percent of the patients put on treatment with sulfonamides, penicillin antibiotics phenytoin, or gold develop Maculopapular eruptions [6]. Nearly 5.3% of patients admitted to hospitals developed ADR's. Elderly patients receiving multiple medications for chronic illness usually have higher incidence of this side effect. Skin reactions are noted due to pyrazinamide with incidence of about 2.38 % worldwide. Literature evidence show case reports of erythema multiforme, exfoliative dermatitis and Maculopapular lesions following pyrazinamide treatment for tuberculosis but notably very fewer in number [7].Biopsy usually confirms the diagnosis. The cutaneous skin manifestations disappears usually with discontinuation of the drug but reappears after being rechallenged . In our case Maculopapular rash appeared in one day after initiation of category 1 ATT with no signs of fever, lymphadenopathy and angioedema of lips ruling out the possibility of drug induced hypersensitivity syndrome (DIHS) which is well known with ATT. All drugs were withheld. The rash subsided and condition improved with oral anti-histamines. HIV screening was done and it was found to be negative and other conditions causing skin rashes like auto immune disorders, environmental toxins, infections and insect bites were ruled out. Decision was made to start the treatment with Category 1 again. Ethambutol was introduced first and followed by isoniazid. Patient tolerated well ad there was no skin rashes and patient condition was fine. Pyrazinamide was rechallenged and Maculopapular rashes appeared again over his trunk and abdomen with itching. Pyrazinamide was stopped and rifampicin was started and patient tolerated well.

As a part of pharmaovigilance program, CDSCO guidelines was followed and adverse drug reactions were carefully noted and causality assessment was done as per Naranjo's scale [8]. Severity and preventability assessment was done suing hart wig's scale [9] and Thornton's scale [9] respectively [Table 1]. The causality assessment revealed a definite association (Naranjo score 9) between the ADR and pyrazinamide. The severity was found to be moderate (Level 4). The ADR is not preventable because there was no previous reports of Maculopapular rashes with pyrazinamide in this patient.

Table 1: Adverse Drug Reaction

Naranjo's Scale	Hartwig's Scale	Thorntons's Scale
Definite Causality	Moderate Severity	Not Preventable

CONCLUSION

Pyrazinamide is a common first line drug used in management of tuberculosis, and Tuberculosis being a very common problem in developing countries like India, the cutaneous adverse drug reactions due to pyrazinamide gains a greater deal of attention. The patients usually becomes Noncompliant due to cutaneous reactions , which accounts as one of the commonest cause for treatment failure in tuberculosis management .Since skin reactions caused by pyrazinamide are under reported , clinician should be aware of Maculopapular rashes due to pyrazinamide . When the above mentioned CADR is noted, the suspected drug should be withheld and symptomatic treatment should be given to patients. The patients treated on outpatient basis should be taken care and is prudent enough to counsel these patients for early recognition of the above mentioned ADR. As a probable causal relationship is established in our patient between the drug and ADR, this case becomes highly important. Further prospective studies are warranted on CADR's and HLA typing and genetic testing can be made to find the susceptibility of patients for developing cutaneous reactions and so that impact of TB in the country can be modified.

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