

# Antituberculosis Drug-Induced Fixed Drug Eruption: A Case Report

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Published online: 21 May 2018  
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**Abstract** Fixed drug eruption (FDE) was caused by fixed-dose combination (FDC) of antituberculosis drugs in the form of tablet Forecox<sup>®</sup> (rifampicin [rifampin] 225 mg + isoniazid 150 mg + pyrazinamide 750 mg + ethambutol 400 mg) in a 40-year-old male patient with a history of drug allergy. The patient developed FDE after taking the third dose of tablet Forecox<sup>®</sup> for pulmonary tuberculosis. Tablet Forecox<sup>®</sup> was withdrawn and the patient recovered from the reaction after 15 days of treatment for FDE. As per World Health Organization–Uppsala Monitoring Centre (WHO-UMC) and Naranjo causality assessment criteria, the association between the reaction and tablet Forecox<sup>®</sup> was possible and probable, respectively. The reaction was moderately (Level 4b) severe according to the Modified Hartwig and Siegel scale. As there is an increased risk of allergic reaction in patients with a

history of drug allergy, FDCs should not be used in order to avoid complexity in identifying the culprit drug.

## Key Points

The fixed-dose combination (FDC) of antituberculosis drugs in tablet Forecox<sup>®</sup> can cause fixed drug eruption (FDE).

Of all the antituberculosis drugs, rifampicin (rifampin) is most commonly involved in causing FDE.

As there is an increased risk of allergic reactions in patients with a history of drug allergy, use of any FDC should be avoided.

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## Introduction

Fixed drug eruption (FDE) is characterized by a single or multiple oval erythematous patches due to systemic exposure to a drug, which mostly resolves with a residual hyper-pigmentation [1]. The overall incidence of FDE ranges from 3.77 to 15.34% [2]. Antimicrobials and non-steroidal anti-inflammatory drugs (NSAIDs) are the most common drug groups implicated in causing FDE [3, 4]. Among antimicrobials, co-trimoxazole, tetracycline, metronidazole, ciprofloxacin, amoxicillin, erythromycin, griseofulvin, clindamycin and albendazole commonly cause FDE [3, 4]. Antituberculosis drugs can also rarely cause FDE [5, 6]. Among antituberculosis drugs, rifampicin (rifampin) is the most often associated with FDE, followed by isoniazid, pyrazinamide and ethambutol [6]. In the present case, the FDE was caused by a fixed-dose combination (FDC) of antituberculosis drugs in the form

of tablet Forecox<sup>®</sup> (rifampicin 225 mg + isoniazid 150 mg + pyrazinamide 750 mg + ethambutol 400 mg) (Macleods Pharmaceuticals Limited, Mumbai, India), resulting in difficulty in identifying the culprit drug.

### Case Report

A 40-year-old male patient (weight 50 kg) was prescribed tablet Forecox<sup>®</sup> (rifampicin 225 mg + isoniazid 150 mg + pyrazinamide 750 mg + ethambutol 400 mg) every 12 h orally for pulmonary tuberculosis by a private physician. After taking the third dose, the patient noted multiple, discrete, hyper-pigmented patches on the nape of his neck, around the mouth, around both eyes, and on the lower abdomen, back and upper abdomen. He stopped taking the medication for the next 2 days but the lesions did not improve. The patient then visited the Sir Takhtsinhji General Hospital in Bhavnagar (Gujarat), India and was admitted to the dermatology ward. On taking a detailed history, it was noted that 6 months prior the

patient experienced similar skin lesions due to unknown drugs (probably an NSAID or antimicrobial drug) prescribed for fever and cough. At that time, the reaction started 2 days after taking the medicines and subsided within 7 days following withdrawal of the drugs. He had not taken antituberculosis drugs earlier. The patient did not take any over-the-counter or alternative medicines before development of the reaction.

The patient was advised not to take any more of the antituberculosis drugs and was treated with injection of intramuscular dexamethasone 4 mg immediately, then oral prednisolone 5 mg every 6 h; he was also administered intravenous ceftriaxone 1 g every 12 h, framycetin cream for local application, oral muccaine viscous gel every 12 h, and betadine gargles and tablet multivitamins for 15 days. The severity of the skin lesions was reduced and the patient recovered from the adverse event after 15 days. On discharge, the patient was prescribed antiretroviral therapy as he was found to be HIV reactive. Antituberculosis drugs were not prescribed as the physician wanted to ensure that the patient tolerated the antiretroviral therapy first.



Fixed drug eruption due to antituberculosis drug

Long-term follow-up of this patient was not possible in regards to the re-challenge status of antituberculosis drugs as the patient migrated to another state of India.

As per World Health Organization–Uppsala Monitoring Centre (WHO-UMC) causality assessment criteria, the association between the reaction and tablet Forecox<sup>®</sup> was possible [7] and the Naranjo score was 5 (probable) [8]. The Modified Hartwig and Siegel scale showed that the level of severity for the reaction was moderate (Level 4b) [9].

## Discussion

Multidrug antituberculosis regimens are associated with diverse clinical patterns of cutaneous adverse drug reactions such as pruritus, maculopapular exanthema, lichenoid eruptions, FDEs, urticaria, acute generalised exanthematous pustulosis, Stevens-Johnson syndrome and toxic epidermal necrolysis [10]. In the present case, the patient developed FDE after taking the third dose of tablet Forecox<sup>®</sup>. The positive de-challenge confirms tablet Forecox<sup>®</sup> as the culprit that caused the FDE. FDCs of antituberculosis drugs are preferred mainly due to improved patient compliance, even though there is no added advantage regarding clinical outcomes. In the present case, the patient had a history of skin rashes due to an unknown antimicrobial drug or NSAID. Use of any FDC should be avoided when the patient has a history of drug allergy as there is an increased risk of allergic reactions in such patients [11, 12]. When an adverse drug reaction occurs due to an FDC, identifying the causative drug becomes very difficult as the whole FDC has to be de-challenged and decisions relating to therapeutic adjustment are also delayed. We were not able to confirm the culprit drug via a patch test or skin prick test, which is a limitation of this case report. In vitro diagnostic testing should be performed to identify the culprit drug. Instead of an FDC, individual antituberculosis drugs should be started along with proper monitoring.

### Compliance with Ethical Standards

**Funding** No financial support was received for the conduct of this study or preparation of this case report.

**Conflict of interest** Jitendra Vaghela, Vivek Nimbark, Manish Barvaliya, Hita Mehta and Bhavesh Chavada declare no conflict of interest.

**Author contributions** Dr Jitendra H. Vaghela performed the literature review and wrote the case description, abstract, discussion and conclusion. Dr Vivek Nimbark contributed in understanding the case report event, identified the event and also helped to obtain clinically relevant information. Dr Manish Barvaliya helped in conducting the

search for the literature review, scrutiny of the case report, guided writing of the discussion and wrote the overall draft of the case report. Dr Hita Mehta helped in clinical diagnosis of the case report event, treatment of the adverse event, guidance regarding drafting of the case report and also in gathering clinically relevant data. Mr Bhavesh Chavada helped in informing the case report event, identified the event with the help of other team members of the Dermatology Department and also helped to obtain clinically relevant information.

**Informed consent** Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of the written consent may be requested for review from the corresponding author.

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