

Rifampicin-Induced Fever in a Patient with Brucellosis: A Case Report

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Abstract We present a 35-year-old female patient who was started on rifampicin (900 mg orally once daily) and trimethoprim/sulfamethoxazole (TMP/SMX) (160/800 mg orally twice daily) after being diagnosed with brucellosis. Following defervescence and improvement in her general condition, fever recurred on the 12th day of treatment. A re-challenge drug test lead to causality assessment and treatment was switched to a combination of streptomycin (1 g intramuscularly) for 10 days and TMP/SMX (160/800 mg orally twice daily) for 4 weeks. Our patient is doing well after 12 months of follow-up.

Key Points

The most common mechanism for rifampicin-induced fever is hypersensitivity reactions.

Fever generally occurs 7–10 days after initiation of the drug, disappears rapidly with cessation of the drug, and recurs within hours of rechallenge with the drug.

Rechallenge provides definitive diagnosis, but should be performed carefully.

Introduction

Drug fever is a clinical syndrome defined by the temporal relationship between fever onset and administration of the drug involved [1]. It is a potentially important, though underdiagnosed and under-reported, adverse drug reaction (ADR) responsible for unnecessary diagnostic procedures, hospitalizations, prolongation of hospitalizations, and inappropriate antibiotic prescriptions [2].

Reliable data on the exact incidence of drug fever are not available; however, drug fever represents 3–5% of all ADRs occurring among inpatients in the US [3, 4]. Interestingly, the incidence may be higher in patients receiving antiviral agents and medications other than antimicrobials, particularly cardiovascular drugs [5]. It has been demonstrated that drug fever due to antibiotics is more likely to occur in younger patients [6].

Drug fever most commonly occurs after 7–10 days of drug administration and may persist as long as the drug is continued, disappearing soon after the drug is stopped [3]. Rechallenge with the offending drug will usually cause recurrence of fever within a few hours and provides a definitive diagnosis.

Rifampicin is a highly effective drug mainly used for treatment of tuberculosis (TB) and brucellosis; it is well known for its safety and efficacy and is generally well tolerated. Although the main cause of fever in rifampicin-treated patients is flu-like syndrome, it may also occur as part of a generalized hypersensitivity reaction [7].

Adverse effects with rifampicin therapy in standard doses (900 mg/day) are seen in <4% of patients [7]. Flu-like syndrome, comprising fever with chills and myalgia, may be seen in up to 20% of patients treated with intermittent therapy or with daily doses of ≥ 1.5 g [7]. We present here a patient who developed fever while receiving

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rifampicin without any other evidence of flu-like syndrome.

Case Report

A 35-year-old female patient was referred to our clinic with fever and back pain for the past 2 months. She denied use of alcohol, tobacco or any drugs. She had no history of any disease or hypersensitivity reactions. General and systemic examination was normal. Her vital signs were heart rate 110/min (sinus rhythm), blood pressure 110/70 mmHg, respiratory rate 12/min, body temperature 38.5 °C, and capillary refill <2 s. Complete blood count (CBC) was normal. Her C-reactive protein (CRP) was 43 mg/L and erythrocyte sedimentation rate was 40 mm/h. Magnetic resonance imaging of the spine revealed abnormal findings in first and second lumbar vertebrae consistent with spondylodiscitis. She had a history of a normal delivery 6 months earlier and was nursing her baby. Brucellosis was immediately suspected since she was living in an endemic area and had a history of consumption of unpasteurized dairy products. Her serum tested positive for the Rose Bengal test and had a *Brucella* antibody titer of 1/320 with the Coombs Wright test. Her blood cultures were taken, which grew *Brucella melitensis* in 4 days. Since she was nursing at the time of the diagnosis, she was treated with a combination of rifampicin (900 mg orally once daily) and trimethoprim/sulfamethoxazole (TMP/SMX) (160/800 mg orally twice daily).

She defervesced on the 7th day of treatment; however, she was readmitted to our clinic with fever on the 12th day of treatment. She reported taking her medications regularly and denied any other drug use. She was in good general condition and reported no symptoms including malaise, headache, or myalgia, but discomfort caused by fever. She had no history of earlier rifampicin use. Examination of other systems revealed no abnormality. CBC was normal. CRP was 60 mg/L and other biochemical tests were within normal limits. Transthoracic echocardiography remained negative. A presumptive diagnosis of drug-induced fever was made and rifampicin was stopped and TMP/SMX was continued. Streptomycin (1 g intramuscularly) was added to treatment. She defervesced in 24 h; however, to make sure of the offending drug, a re-challenge was made and rifampicin was restarted 900 mg orally once daily. Fever reoccurred with rifampicin therapy in 12 h. There were no cutaneous, gastrointestinal, or hematologic findings. Her treatment was continued with a combination of streptomycin (1 g intramuscularly) for 10 days and TMP/SMX (160/800 mg orally twice daily) for 4 weeks. She is doing well after 12 months of follow-up. Written informed

consent was obtained from the patient for publication of this case report.

Discussion

Drugs may cause fever by a number of mechanisms that may sometimes coexist [8]. Drug-induced fever may be divided into five general categories: altered thermoregulatory mechanisms, administration-related reactions, fevers relating to the pharmacologic action of the drug, idiosyncratic reactions, and hypersensitivity reactions [9, 10]. The most common cause of drug-induced fever is a hypersensitivity reaction, which is most commonly caused by antibiotics. The reaction may be immune complex mediated (type 3), cell mediated (type 4) or IgE mediated (type 1). Immediate type hypersensitivity reactions have been documented by the presence of anti-rifampicin IgE antibodies and/or urticarial response to skin testing [11]. The drug itself or its metabolite may act as an antigen or a hapten in an immune complex mediated reaction. Circulating antibody-antigen complexes can stimulate the release of pyrogens from granulocytes, resulting in fever. Moreover, absence of anti-rifampicin antibodies may not rule out hypersensitivity-induced drug fever since the antibodies formed may not be directed against the drug itself [10]. Typically, fever appears 7–10 days after starting the drug with such a reaction, and disappears rapidly with withdrawal of the drug, then recurs within hours of rechallenge with the drug [1].

Rechallenge of the drug did not produce any adverse effects including maculopapular rash, urticaria, gastrointestinal effects, hepatitis, and thrombocytopenia in our patient. This may weaken the ‘hypersensitivity reaction’ hypothesis; however, the time period from administration of the drug to appearance of fever, rapid resolving of fever upon stopping the drug, and recurrence of fever within hours of readministration made us think ‘hypersensitivity reaction’ was the best elucidating mechanism of drug-induced fever in this case.

Severe immune allergic reactions due to rifampicin causing fever, hypotension, disseminated intravascular coagulation, fever, thrombocytopenia, clotting abnormalities, and renal impairment have been reported [12–14], and some of these cases had a fatal outcome [15, 16]. This condition was also generally associated with intermittent treatment. Immune allergic reaction was not considered in our patient due to absence of associated symptoms and laboratory findings and daily dosing in our patient.

The drugs that have been most commonly associated with drug fever are anticonvulsants, certain antihypertensive drugs, antiarrhythmic agents, and antibiotics.

Penicillins and cephalosporins are the most often implicated antibiotics that cause drug-induced fever.

Presence of relative bradycardia and appearance of wellbeing relative to the degree of fever are two common observations in patients with drug fever [17]. These two findings may help in differential diagnosis of drug-induced fever.

Rifampicin-induced fever occurs in about 0.5% cases, but mostly as a hypersensitivity reaction or flu-like syndrome. The symptoms last for a few hours and resolve spontaneously [18, 19]. The flu-like syndrome associated with rifampicin includes fever, shivering, faintness, headache, myalgia, and arthralgia [5]. Flu-like syndrome is almost exclusively associated with intermittent treatment. The reaction occurs more frequently when rifampicin is administered once a week than when it is given two or three times a week or when the daily dose is relatively high [18]. We believe that flu-like syndrome was unlikely to be responsible for the fever in our case because of the time of occurrence of fever, the absence of other associated features, and the daily dosing of rifampicin. Anti-rifampicin antibodies were not tested in our patient's serum.

A rechallenge often allows definitive diagnosis of drug-induced fever, as in our case; however, it is a controversial issue and should be performed with extreme caution, since there is potential for a more severe drug reaction.

In cases with rifampicin allergy where continuation of treatment with rifampicin is essential, as in isoniazid-resistant TB, various desensitization or graded challenge protocols have been published [20–23]. In case of serious adverse reactions such as thrombocytopenia, hemolytic anemia, or acute renal failure, desensitization is contraindicated [24].

In a descriptive cohort study from the French national pharmacovigilance database, where the authors have used quantitative analysis in order to describe proportional reporting ratios (PRR) for drug-induced fever for each drug in their database, rifampicin was reported to have a PRR of 4.0 (95% CI 1.8–9.2). This means fever was reported four times as frequently for rifampicin compared with other drugs in the database causing fever. For comparison, amikacin and oxacillin—the most frequently reported antibacterials causing fever—had PRRs of 39.6 and 9.1, respectively. Five of 167 drug fever cases were due to rifampicin in the database from 1986 to 2007 [25]. Rechallenge with rifampicin has not caused any worsening of the patients' clinical states in the French national database [25]. Numerous patients have been rechallenged with various drugs causing fever and relatively few serious sequelae have been reported; however, it should be kept in mind that there is always a potential for the occurrence of a more severe drug fever reaction after rechallenge [5].

Rifampicin-induced fever is a diagnosis of exclusion as fever subsided immediately on its withdrawal and recurred on re-administration of the drug. Moreover, the Naranjo ADR probability scale showed a definitive case-causality assessment with a score of 9 [26].

Conclusion

It is important for clinicians to be aware of the clinical presentation of patients with drug fever and of drugs including antimicrobials as a cause of fever. Since a common response among clinicians to a patient's fever is to suspect infection, drug fever can lead to overutilization of anti-infectives.

Diagnosis of drug-induced fever is only confirmed after elimination of other causes, the demonstration of the progressive association between initiation of the drug and the onset of fever and the resolution of fever within hours of discontinuing the contributing agent.

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Compliance with Ethical Standards

Conflict of interest Mesut Yilmaz, Canan Yasar, Selda Aydin, Okan Derin, Bahadir Ceylan, and Ali Mert have no conflicts of interest that are directly relevant to the content of this study.

Ethical approval Not applicable.

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

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