

Rifampicin-Induced Fever

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Abstract: Rifampicin is a commonly used first-line antitubercular drug well known for its safety and efficacy and is generally well tolerated. Flu-like syndrome is the main cause of fever in rifampicin treated patients. High grade fever without accompanying features of hypersensitivity or flu is an extremely rare occurrence. Our patient presented with pyrexia of unknown origin and diagnostic work-up revealed sufficient evidence of tuberculosis. Consequently, she was started on first-line antituberculous treatment (ATT) following which fever aggravated. Repeat diagnostic work-up did not reveal any other clue to the cause of fever. To our surprise, the fever subsided promptly on stopping ATT, suggesting it to be drug-induced. Sequential reintroduction of the drugs revealed rifampicin to be the culprit. Thereafter, rifampicin was withdrawn permanently from the therapy and patient was put on modified ATT, following which, patient became afebrile and significant clinical improvement was noticed.

I. Introduction

In usual doses, adverse effects with rifampicin therapy are seen only in less than 4% of the patients. They are commonly seen with intermittent therapy (frequency lower than twice a week) or daily doses of 1.5 gm or greater. 20% of the treated patients develop flu-like syndrome comprising of fever with chills and myalgia along with other systemic manifestations, which could be easily managed on shifting to a daily regimen. We present a patient who developed rifampicin-induced fever without any other evidence of flu-like illness. This is very rarely, if encountered in clinical practice and contradicts our diagnosis. Therefore, in such clinical scenario, there is a need to revise the treatment and not the diagnosis and urgent withdrawal of the offending drug is required.

II. Case Report

A 35 years old housewife presented in our out-patient department with fever along with progressive loss of weight and appetite for the past 4 months. Fever was continuous, ranging between 101-102 degrees Fahrenheit and relieved by over-the-counter antipyretics. Before presenting to us, she received treatment with antimalarials and repeated courses of antibiotics without any relief, when she was referred to us. There was no history of cough with expectoration, chest pain, hemoptysis, headache, vomiting, burning micturition, yellowish discoloration of eyes or urine or pain abdomen. No history of tubercular contact was present. General and systemic examination was normal except mild pallor. Complete and differential blood count and general blood picture was normal. Liver function tests revealed raised globulin (5.9 gm/dl), alkaline phosphatase (512 IU/L) and gamma-glucuronyl transferase (103 IU/L). Renal function tests and chest skiagram were normal. Mantoux skin testing was positive with 22 mm induration. Erythrocyte sedimentation rate was 50 mm at the end of first hour. Ultrasonography abdomen revealed 29 X 22 mm solitary periportal lymph node. A presumptive diagnosis of abdominal tuberculosis was made and patient was started on antituberculous treatment (ATT) comprising of Isoniazid (I), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E) in the conventional daily dosages along with pyridoxine.

Histopathology of the lymph node revealed chronic granulomatous lymph node with minimal caseous necrosis compatible with mycobacterial etiology. Within two weeks of starting ATT, patient became afebrile and her appetite began to improve. However, on 20th day of treatment, fever again shot up and this time it ranged from 102-104 degrees Fahrenheit, however. At this time, liver function tests were normal and the periportal lymph node also regressed in size (5 X 12.5 mm). ATT was continued for the next 2 months but the fever did not subside. Excision biopsy of the lymph node was performed and histopathology report revealed chronic granulomatous picture with minimal caseous necrosis compatible with mycobacterial etiology. Following this, Streptomycin (S) and Levofloxacin were added to the current ATT and continued for one month without any response. Subsequently, all drugs were stopped in order to re-evaluate the patient. To our surprise, patient became afebrile the very next day of stopping of drugs. Considering it to be a drug fever, each drug was added sequentially. On second day of reintroduction of rifampicin, she again started having high grade fever that improved on stopping the drug. Patient was continued on other four drugs which she tolerated well and remained afebrile. Streptomycin and pyrazinamide were stopped after one month and patient continued on HE and levofloxacin. After two months of remaining asymptomatic, the patient was rechallenged with rifampicin. The patient again developed fever which subsided promptly on discontinuation of the drug.

III. Discussion

Commonly seen side effects with rifampicin therapy include fever, rash, nausea and vomiting. Fever, seen in only 0.5% of the cases, is a part of flu-like syndrome or a hypersensitivity reaction¹. Possible mechanism is the development of rifampicin-induced antibodies a few months after the treatment has started². It occurs mostly within months of beginning of intermittent therapy or a high dose daily therapy. Symptoms usually last for few hours and resolve spontaneously or switch to daily dosing is required. Other antituberculous drugs known to cause fever include streptomycin, para-amino salicylic acid and very rarely, isoniazid and ethambutol^{1,3,4}.

Flu-like syndrome was unlikely in our case because of conventional daily dosing of rifampicin, early occurrence of fever and absence of other associated features. Rifampicin-induced fever is, moreover, a diagnosis of exclusion as fever subsided on its withdrawal and recurred on re-administration of the drug. Re-challenge of the drug did not have any adverse effects which also weakens the hypothesis of “hypersensitivity reaction” for the drug. Such a presentation is extremely rare and not many reports are available despite extensive search of literature⁵. However, due to lack of facilities, anti-rifampicin antibodies could not be tested and purported mechanism could not be established conclusively.

References

- [1]. Grosset J. And Leventis S. Adverse effects of Rifampin. *Rev. Infect. Dis.*; 1983,5,Supp 3, S 440.
- [2]. Poole G, Stradling P, Worledge S. Potentially serious side-effects of high-dose twice weekly rifampicin. *Br Med J* 1971; 3: 343.
- [3]. Girling D.J. Adverse effects of antituberculosis drugs. *Bull. Int. Union. Tub.*; 1984, 59, 152.
- [4]. Jain N.K., Madan A., Gupta K.K. et al. Ethambutol induced fever. *Ind. J. Tub.*; 1989, 36, 239.
- [5]. Bedi R. S. Rifampicin induced fever: a case report. *Ind. J. Tub.*, 1991, 38, 233.