ORIGINAL ARTICLE e-ISSN: 2349-0659 p-ISSN; 2350-0964

# A Case of Atypical Delayed Anaphylaxis to Rifampin

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## Abstract

Rifampin is a mainstay in anti-tuberculosis therapy and is generally well tolerated and safe to take at therapeutic dosing. While anaphylactic reactions to rifampin are exceedingly rare, prompt recognition and awareness is vital to patient safety, and alternative medications should be considered desensitization has been associated with significant morbidity. Here we report a case of a severe anaphylactic reaction to rifampin. A 65-year-old Asian woman was diagnosed with active tuberculosis and initiated on rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE). A couple of weeks after initiating RIPE therapy, she developed urticaria and angioedema and therapy was held. Upon resumption of RIPE, she developed emesis, fever, chills, perioral cyanosis, and hypotension within a few hours of the first dose. She was admitted to the intensive care unit for a rifampin graded dose challenge and subsequently developed a severe anaphylactic reaction to rifampin four hours after the final dose of the challenge. She tolerated desensitization to isoniazid and ethambutol well and was prescribed an alternative anti-tuberculosis regimen of isoniazid, ethambutol, levofloxacin, and pyridoxine for a total of 18 months to complete her treatment.

**Keywords:** Anaphylaxis, Drug allergy, Graded challenge, Rifampin, Tuberculosis

*Asian Pac. J. Health Sci*., (2023); DOI: 10.21276/apjhs.2023.10.2.02

## Background

Tuberculosis is a curable infectious disease caused by *Mycobacterium tuberculosis*. Worldwide, a total of 1.6 million people died from tuberculosis in 2021 making it the 13th leading cause of mortality overall and the second leading cause of mortality from an infectious cause after COVID-19.[1] Tuberculosis treatment requires a combination of multiple agents, including rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE therapy). This first-line regimen is highly efficacious with a treatment success rate between 90% and 95%.

Hypersensitivity reactions to anti-tuberculosis drugs are generally benign and usually occur after a few weeks of initiating therapy. However, many of these agents have side effects including anaphylaxis, which is a potentially life-threatening emergency. Anaphylactic reactions to medications usually occur within minutes to a few hours of administration, and symptoms may include generalized hives, pruritis or flushing, swollen lips-tongue-uvula, respiratory compromise, and hypotension. While generally well tolerated, rifampin may cause delayed reactions which may not be readily recognized, potentially leading to delays in care and adverse outcomes. Here, we demonstrate an unusual case of delayed anaphylaxis induced by rifampin during a graded challenge conducted at a large academic community-based health center.

## Case Presentation

A previously healthy 65-year-old Asian woman presented to her primary care physician with several months of cough. Her QuantiFERON Gold was positive, and her chest radiograph revealed a left upper lobe opacity that was confirmed on further chest imaging. She underwent a biopsy and culture of the lesion which grew *Mycobacterium tuberculosis* complex, sensitive to rifampin, isoniazid, and ethambutol. She was diagnosed with active pulmonary tuberculosis and started on standard RIPE therapy with rifampin (600 mg/day), isoniazid (300 mg/day), pyrazinamide (1000 mg/day), and ethambutol (800 mg/day).

Ten days later, she developed lip swelling and rash on the arms, legs, and abdomen. RIPE therapy was held, and her symptoms resolved within three days with diphenhydramine use alone. Nine days later, she was started on low-dose rifampin (150 mg/day). Within a few hours of ingestion, she developed emesis, subjective fever, chills, perioral cyanosis, and hypotension as measured by a home blood pressure monitor (60s mmHg/40s mmHg). Her family opted to not seek emergent care and she recovered at home overnight with oral hydration.

As the patient's reaction history at the time was unclear, the patient was admitted to the intensive care unit a month later for a planned rifampin graded dose challenge. The patient completed the graded dose challenge, a cumulative dose of 600 mg of rifampin over 3 h [Figure 1], without issues. However, four hours after the final dose, she developed a fever, urticaria, emesis, and severe hypotension with the lowest recorded blood pressure being in the 60 s mmHg/30 s mmHg and a mean arterial pressure of 46 mmHg. She required aggressive resuscitation as shown in Figure 2. She initially was treated with multiple liters of Lactated Ringer's solution and a norepinephrine infusion but continued to have recurrent hypotension. Her blood pressure eventually stabilized after she was started on an epinephrine infusion and given diphenhydramine and methylprednisolone. After recovery, she was kept off all anti-tuberculosis medications out of an abundance of caution. A baseline tryptase level obtained was normal at 2.1 mcg/L. Given the severity of her reaction, she was readmitted to the intensive care unit a month later for planned desensitization to isoniazid and ethambutol. She was able to tolerate desensitization to both medications

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**How to cite this article:** Nguyen CM, Sworzyn J, Mohyi P, Li M, Kwong K. A Case of Atypical Delayed Anaphylaxis to Rifampin. Asian Pac. J. Health Sci., 2023;10(2):2023;10(2):7-8.

**Source of support:** Nil.

**Conflicts of interest:** None.

**Received:** 01/03/2023 **Revised:** 09/04/2023 **Accepted:** 01/05/2023

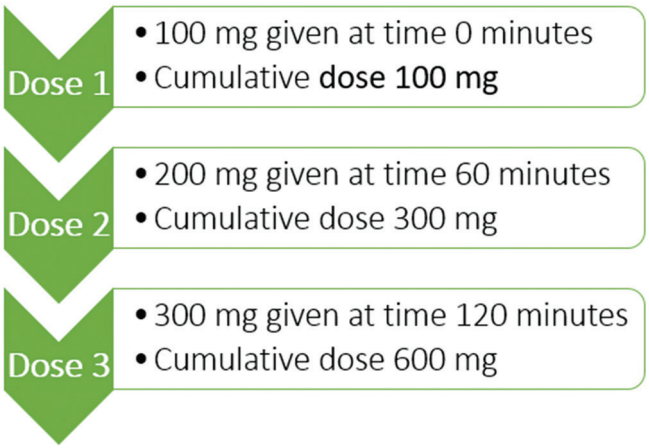


**Figure 1:** Oral rifampin graded dose challenge

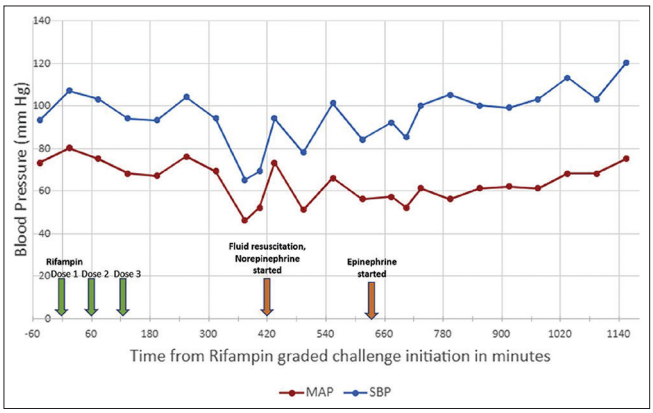


**Figure 2:** Changes in blood pressure after oral rifampin graded challenge

without any adverse events and was prescribed an alternative regimen of isoniazid, ethambutol, levofloxacin, and pyridoxine for a total of 18 months to complete her tuberculosis treatment, to which she tolerated well.

## Discussion

Rifampin is a mainstay of anti-tuberculosis therapy and is considered a relatively safe drug when administered at therapeutic dosing. A rifampin allergy is rare and may typically present as a mild cutaneous reaction but may include fever, acute kidney injury, flu-like syndrome, and/or hemolytic anemia.[2,3] Although exceedingly rare, anaphylactic reactions to rifampin can and do occur,[4] and providers must remain vigilant of this possibility. In addition, the constellation of delayed-onset fever, urticaria, emesis, and shock in this case is similar to other case reports[2,3] of rifampin drug reaction, suggesting this presentation may be unique to rifampin. It has been suggested that the underlying mechanism of such reactions consist of combined hypersensitivity pathways. For example, rifampin has been found to simultaneously induce a serum-sickness like reaction as well as anaphylaxis through a combined type III and type I hypersensitivity response.[2] Severe delayed reaction to anti-tuberculosis medications including rifampin has been reported with up to 18.97 days between ingestion and reaction. If unrecognized, this atypical reaction may lead clinicians to initiate graded challenge of rifampin leading to severe reactions. Alternative medications should be considered desensitization to rifampin has been associated with significant morbidity in the literature.[5]

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