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KEY WORDS: Rifampicin; Rifampin; Immediate Drug Hypersensitivity; Anaphylaxis; Drug Provocation Test; Urticaria; Peritoneal Tuberculosis; Antitubercular Hepatotoxicity.

IMMEDIATE RIFAMPICIN HYPERSENSITIVITY WITH ANAPHYLAXIS-COMPATIBLE MANIFESTATIONS FOLLOWING A POSITIVE LOW-DOSE ORAL DRUG PROVOCATION TEST IN A PATIENT WITH PERITONEAL TUBERCULOSIS: A CASE REPORT

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ABSTRACT

Background: Rifampicin is an essential component of first-line antitubercular therapy. Immediate hypersensitivity to rifampicin is uncommon but can produce potentially life-threatening systemic reactions and complicate tuberculosis treatment. Drug provocation testing (DPT) may clarify suspected drug hypersensitivity; however, culprit-drug testing in patients with previous systemic reactions requires careful risk assessment. **Case Presentation:** A 35-year-old woman receiving treatment for presumed peritoneal tuberculosis developed significant hepatotoxicity following initiation of a fixed-dose first-line antitubercular regimen. After treatment modification, rifampicin 450 mg was introduced on 10 October 2026. The patient subsequently reported urticaria, generalized pruritus and vomiting, although she could not reliably recall the interval between drug administration and symptom onset. Following normalization of liver function tests, a supervised oral rifampicin DPT was performed on 23 October 2026. Rifampicin 45 mg was administered as an oral liquid preparation at 12:35 PM. Approximately 45 minutes later, the patient developed objective urticaria, generalized pruritus and severe abdominal pain. Intramuscular adrenaline 0.5 mg was administered immediately, followed by intravenous hydrocortisone 100 mg. Intravenous pheniramine was subsequently administered for cutaneous symptoms. The patient remained clinically stable during approximately five hours of observation. **Discussion:** Reproduction of objective symptoms following rifampicin exposure strongly supported immediate rifampicin hypersensitivity. The acute cutaneous and severe gastrointestinal manifestations were compatible with anaphylaxis under World Allergy Organization criteria. However, a specific IgE-mediated mechanism was not established. The case highlights the diagnostic value of objectively documented reactions, the risks of culprit-drug provocation and the complexities of managing tuberculosis in patients with multiple antitubercular drug-related adverse events. **Conclusion:** A single oral rifampicin dose of 45 mg elicited immediate systemic hypersensitivity manifestations requiring intramuscular adrenaline. The case emphasizes accurate clinical phenotyping, individualized risk assessment, appropriate emergency management and careful documentation to prevent inadvertent rifampicin re-exposure.

INTRODUCTION

Rifampicin is a cornerstone of first-line treatment for drug-susceptible tuberculosis. Its potent bactericidal and sterilizing activity contributes substantially to treatment effectiveness. However, rifampicin can cause adverse drug reactions ranging from gastrointestinal intolerance and hepatotoxicity to immunologically mediated hypersensitivity reactions.

Immediate hypersensitivity to rifampicin is relatively uncommon but may present with urticaria, angioedema, respiratory manifestations, gastrointestinal symptoms or anaphylaxis. The mechanisms underlying rifampicin-associated hypersensitivity are heterogeneous and are not fully understood [1].

Published reports have described immediate reactions following rifampicin administration, including reactions reproduced during diagnostic testing and cases requiring drug discontinuation [2–4].

Diagnosis can be particularly challenging in patients receiving multidrug antitubercular regimens, as several medications are commonly introduced simultaneously. The clinical history, chronology of exposure and objective findings are therefore central to identifying the suspected culprit.

The European Academy of Allergy and Clinical Immunology/ European Network for Drug Allergy (EAACI/ENDA) position paper identifies drug provocation testing as the reference standard for investigating drug hypersensitivity. Nevertheless, the decision to perform DPT must account for the severity of the historical reaction, the likelihood of hypersensitivity, available diagnostic alternatives and the potential risks of re-exposure [5].

We report a patient with presumed peritoneal tuberculosis and previous antitubercular therapy-associated hepatotoxicity who developed an immediate systemic hypersensitivity reaction following administration of 45 mg of rifampicin during supervised oral provocation.

The case is discussed in the context of previously published

rifampicin hypersensitivity reports, EAACI/ENDA diagnostic principles and international anaphylaxis guidance.

Case Presentation

Initial Clinical Presentation

A 35-year-old woman presented with persistent diffuse abdominal pain, abdominal tightness following meals, bloating, reduced appetite and significant unintentional weight loss of approximately 7–8 kg over three months. Abdominal ultrasonography performed on 12 August 2026 demonstrated mild ascites and cholelithiasis.

Contrast-enhanced computed tomography of the abdomen on 3 September 2026 demonstrated suspicious short-segment irregular circumferential thickening of the distal jejunum with luminal narrowing, diffuse omental thickening with associated fat stranding and moderate ascites.

Ascitic fluid examination performed on 4 September 2026 revealed a total leukocyte count of 640 cells/μL, with 90% lymphocytes, and an adenosine deaminase level of 79 U/L. Cartridge-based nucleic acid amplification testing for *Mycobacterium tuberculosis* was negative.

An omental biopsy performed at an outside institution on 4 September 2026 revealed granulomatous inflammation suggestive of tuberculosis.Based on the combined clinical, imaging, ascitic fluid and histopathological findings, the patient was treated for presumed peritoneal tuberculosis.

Antitubercular Treatment-associated Hepatotoxicity

On 6 September 2026, the patient was initiated on a fixed-dose first-line antitubercular regimen consisting of Akurit-4, four tablets daily.Following treatment initiation, she developed vomiting and pruritus, accompanied by marked hepatic transaminase elevation.

The recorded alanine aminotransferase level was 637 U/L, while aspartate aminotransferase was 1728 U/L. Anti-tubercular therapy-associated hepatotoxicity was suspected, and the initial regimen was discontinued.The patient was subsequently managed with a modified antitubercular regimen comprising streptomycin, levofloxacin and ethambutol.

Because the hepatic injury occurred during treatment with a multidrug preparation, the specific medication responsible for hepatotoxicity could not be identified with certainty.

Historical Reaction Following Rifampicin Exposure

On 10 October 2026, levofloxacin was discontinued, and rifampicin 450 mg was introduced.

Following rifampicin administration, the patient reported urticarial skin lesions, generalized pruritus and vomiting. Although an interval of approximately four hours was initially mentioned, the patient was unable to reliably recall the exact interval between rifampicin administration and symptom onset.

Consequently, the historical episode was considered suggestive of rifampicin-associated hypersensitivity, but its precise temporal classification remained uncertain.No objective respiratory compromise or cardiovascular instability was documented in the information available regarding this episode.

Subsequent Clinical Assessment

The patient was referred for specialist evaluation of suspected rifampicin hypersensitivity. At the time of assessment, she was receiving isoniazid 300 mg, levofloxacin 750 mg and ethambutol 1 g orally once daily. Isoniazid was reportedly tolerated.

Whole-body PET-CT performed on 12 October 2026 demonstrated metabolically active diffuse peritoneal and omental thickening, metabolically active lytic lesions with soft tissue components and metabolically quiescent abdominal ascites. The overall findings favored an infective or granulomatous process.

Relevant investigations included hemoglobin 8.2 g/dL, total leukocyte count 4,670 cells/μL, platelet count 219,000/μL, prothrombin time 18.4 seconds and INR 1.39.

Following discontinuation of the initial antitubercular regimen, liver function tests were monitored and had returned to normal before the rifampicin challenge performed on 23 October 2026.

Diagnostic Assessment

Clinical Suspicion of Rifampicin Hypersensitivity

The historical occurrence of urticaria, generalized pruritus and vomiting after rifampicin administration raised suspicion of a drug hypersensitivity reaction.

However, uncertainty regarding the timing of symptom onset limited the ability to classify the historical reaction definitively as immediate hypersensitivity.

The earlier hepatotoxicity was considered a separate adverse drug reaction phenotype because it occurred during administration of a multidrug first-line regimen and could not be specifically attributed to rifampicin.

Oral rifampicin Drug Provocation Test

A supervised oral rifampicin DPT was performed on 23 October 2026. Before the procedure, the patient was clinically stable, and her liver function tests had normalized.Rifampicin was administered as an oral liquid preparation.

A single dose of 45 mg was administered orally at 12:35 PM. Approximately 45 minutes after administration, the patient developed objective urticarial wheals associated with generalized pruritus and severe abdominal pain.The challenge was immediately discontinued and considered positive.

Management of the Challenge-induced Reaction

In view of the acute cutaneous and severe gastrointestinal manifestations concerning for anaphylaxis, intramuscular adrenaline 0.5 mg was administered immediately. Intravenous hydrocortisone 100 mg was subsequently administered.Intravenous pheniramine was administered thereafter specifically for the cutaneous manifestations, including urticaria and pruritus.

The patient was monitored for approximately five hours following the reaction and treatment.During the documented observation period, her vital parameters remained stable, and no further acute complaints were reported.

Table 1. Supervised Oral Rifampicin Drug Provocation Test

Parameter	Finding
Date	23 October 2026
Suspected culprit	Rifampicin
Formulation	Oral liquid preparation
Administered dose	45 mg
Time	12:35 PM
Baseline clinical status	Stable
Liver function before DPT	Normalized
Reaction onset	Approximately 45 minutes
Cutaneous manifestations	Objective urticaria and generalized pruritus
Gastrointestinal manifestations	Severe abdominal pain
Initial emergency treatment	Adrenaline 0.5 mg IM
Subsequent adjunctive treatment	Hydrocortisone 100 mg IV
Treatment for skin symptoms	Pheniramine IV
Post-reaction observation	Approximately 5 hours
Result	**Positive DPT**
Interpretation	**Immediate rifampicin hypersensitivity with systemic manifestations**

Diagnostic Interpretation

The reproduction of objective urticaria and generalized pruritus, accompanied by severe abdominal pain, following rifampicin administration strongly supported clinically relevant immediate hypersensitivity.The simultaneous involvement of the skin and gastrointestinal system was clinically compatible with anaphylaxis under World Allergy Organization diagnostic criteria [6].

However, the immunological mechanism was not established. The available records did not include validated rifampicin-specific IgE testing, mechanistic skin testing or paired acute and baseline serum tryptase measurements.

The most appropriate diagnosis was therefore: Immediate rifampicin hypersensitivity with systemic manifestations, clinically compatible with anaphylaxis, following a positive oral drug provocation test.

Clinical Timeline

Table 2. Chronological Clinical Course

Date	Event
04 September 2026	Omental biopsy showing granulomatous inflammation suggestive of tuberculosis
06 September 2026	First-line fixed-dose ATT initiated
September 2026	Vomiting, pruritus and significant transaminase elevation
Subsequently	Initial ATT discontinued; modified regimen introduced
10 October 2026	Rifampicin 450 mg introduced
After 10 October dose	Patient-reported urticaria, pruritus and vomiting; exact onset interval uncertain
12 October 2026	PET-CT showing findings favoring infective/granulomatous disease
Before 23 October 2026	Liver function tests normalized
23 October, 12:35 PM	Rifampicin 45 mg administered orally as liquid preparation
Approximately 1:20 PM	Objective urticaria, generalized pruritus and severe abdominal pain
Immediately after recognition	Adrenaline 0.5 mg IM
Subsequently	Hydrocortisone 100 mg IV
Thereafter	Intravenous pheniramine for cutaneous symptoms
Following reaction	Approximately five hours of observation; clinically stable

DISCUSSION

Rifampicin Hypersensitivity: Clinical Relevance

Rifampicin-associated hypersensitivity has been described in several clinical patterns, including cutaneous reactions, flu-like syndromes, hematological complications and anaphylaxis. Martínez and colleagues reviewed the clinical manifestations and possible mechanisms of rifampicin hypersensitivity, highlighting the heterogeneous nature of these reactions [1].Buergin and colleagues described three patients with immediate rifampicin hypersensitivity and discussed diagnostic procedures and induction of clinical tolerance [2].Farah and colleagues reported a patient with tuberculosis who experienced immediate hypersensitivity to rifampicin. Diagnostic testing was discontinued after the development of significant symptoms, including respiratory and gastrointestinal manifestations [3].Kim and colleagues described a patient with rifampicin-associated serum sickness-like manifestations and anaphylaxis, demonstrating the potential complexity of rifampicin-related immune reactions [4].These reports establish that rifampicin can produce clinically significant systemic hypersensitivity and that diagnostic re-exposure may itself provoke severe symptoms.

Diagnostic Significance of the Positive Low-dose Challenge

The principal finding in the present case was the reproduction of objective hypersensitivity manifestations following administration of a single oral rifampicin dose of 45 mg. The historical reaction followed administration of rifampicin 450 mg but had an uncertain onset interval.In contrast, the supervised challenge provided a clearly documented exposure time, administered dose, onset interval and clinical manifestations. The development of objective urticaria and generalized pruritus, accompanied by severe abdominal pain, approximately 45 minutes after administration strongly supported immediate rifampicin hypersensitivity.

The 45 mg administered dose represented one-tenth of the previously administered 450 mg dose.This finding is clinically important because a relatively small exposure was sufficient to reproduce the patient's symptoms.

However, 45 mg cannot be interpreted as the minimum eliciting dose because lower doses were not evaluated. Furthermore, reaction severity during subsequent exposures cannot be predicted reliably from the dose associated with a previous reaction.

EAACI/ENDA Recommendations and Drug Provocation Testing

The 2024 EAACI/ENDA position paper emphasizes that DPT should be performed only after appropriate clinical risk stratification [5]. The guidance recommends consideration of the historical reaction, severity, available diagnostic investigations, comorbidities and the expected therapeutic benefit of confirming or excluding hypersensitivity.

Patients with a history of anaphylaxis or other high-risk immediate reactions require particularly cautious evaluation. The position paper recommends preliminary testing where appropriate and restricts high-risk culprit-drug provocation to circumstances in which the anticipated benefit justifies the risk and appropriate specialist facilities are available.

It also identifies previous drug-induced organ dysfunction as an important contraindication to provocation with the implicated drug.In this patient, the historical rifampicin reaction was suggestive of hypersensitivity but had uncertain timing. The previous hepatic injury had occurred during treatment with a multidrug preparation, and the specific causative medication had not been established.

Liver function tests had normalized before the challenge, indicating recovery from the earlier hepatic injury. Nevertheless, normalization of liver function did not eliminate the potential risk of recurrent hepatotoxicity or immediate hypersensitivity during re-exposure.

The present case therefore illustrates the importance of documenting the individual risk–benefit assessment, informed consent and emergency preparedness whenever high-risk drug provocation is considered.It should not be interpreted as recommending routine rifampicin challenge in patients with suspected systemic hypersensitivity.

Immediate Hypersensitivity Versus Proven IgE-mediated Allergy

Immediate drug hypersensitivity is a clinical phenotype characterized by the development of compatible manifestations shortly after drug exposure.Such reactions may involve IgE-dependent or non-IgE-dependent pathways.

Urticaria, pruritus and systemic symptoms are compatible with mast-cell mediator release but do not independently establish an IgE-mediated mechanism. In the present case, the positive rifampicin challenge provided objective evidence of immediate clinical reactivity.

However, no validated mechanistic investigations were available to establish rifampicin-specific IgE involvement. The diagnosis should therefore remain clinically confirmed immediate rifampicin hypersensitivity, rather than definitively proven IgE-mediated rifampicin allergy.

This distinction is particularly important in case-report literature because a positive DPT establishes clinical hypersensitivity under the test conditions but does not necessarily identify the underlying immunological pathway.

Anaphylaxis-compatible Clinical Manifestations

The World Allergy Organization anaphylaxis guidance recognizes acute skin involvement accompanied by severe

gastrointestinal symptoms as a presentation consistent with anaphylaxis, particularly following exposure to a non-food allergen [6].

The patient developed objective urticaria, generalized pruritus and severe abdominal pain within approximately 45 minutes of rifampicin administration.



The simultaneous cutaneous and severe gastrointestinal manifestations were therefore compatible with anaphylaxis. The absence of documented respiratory compromise or hypotension does not necessarily exclude anaphylaxis.

However, complete serial vital signs and detailed respiratory and cardiovascular assessments were not available for independent severity grading. The reaction was treated promptly with intramuscular adrenaline.

Emergency Management and Treatment Sequence

Intramuscular adrenaline is the first-line treatment for anaphylaxis [6,7]. In this patient, adrenaline 0.5 mg IM was administered immediately following recognition of the systemic reaction. Intravenous hydrocortisone 200 mg was administered subsequently. Intravenous pheniramine was then administered for the cutaneous symptoms.

This sequence is clinically relevant because antihistamines may relieve urticaria and pruritus but do not treat the potentially life-threatening physiological manifestations of anaphylaxis.Corticosteroids should not replace or delay adrenaline and have not been shown reliably to prevent biphasic reactions.

The patient remained clinically stable during approximately five hours of documented observation. Observation duration and discharge planning after anaphylaxis should be individualized according to reaction severity, treatment response, recurrence risk and access to emergency medical care [7].

Comparison with Previously Published Rifampicin Reactions

Published rifampicin hypersensitivity cases provide important context for the present report. Buergin and colleagues described immediate hypersensitivity in three patients and reported diagnostic approaches and induction of tolerance in selected circumstances [2].

Farah and colleagues reported severe rifampicin hypersensitivity in a patient receiving tuberculosis treatment, with reactions during diagnostic testing necessitating discontinuation [3]. Kim and colleagues described simultaneous serum sickness-like manifestations and anaphylaxis associated with rifampicin [4].

Harland and colleagues also reported rifampin-associated anaphylaxis, demonstrating that severe immediate systemic reactions have long been recognized in the literature [8].The present case differs in several clinically relevant respects.The patient had a history of significant antitubercular therapy-associated hepatotoxicity, uncertainty regarding the timing of her initial rifampicin reaction, and an objectively documented positive oral challenge following a 45 mg dose.

The challenge-associated reaction was predominantly characterized by cutaneous and severe gastrointestinal manifestations, without documented respiratory or cardiovascular compromise.These features contribute to the clinical literature on the heterogeneous presentation of rifampicin hypersensitivity.However, the available evidence is insufficient to establish that the 45 mg dose represents a uniquely low threshold compared with all previously published cases.

Implications for Tuberculosis Treatment

Rifampicin plays an important role in the treatment of drug-susceptible tuberculosis, and its exclusion may necessitate substantial modification of the treatment regimen.The World Health Organization's consolidated tuberculosis treatment guidance emphasizes individualized treatment decisions based on disease characteristics, drug susceptibility and treatment-related risks [9].

In this patient, the selection of an alternative regimen was complicated by both previous antitubercular therapy-associated hepatotoxicity and clinically significant rifampicin hypersensitivity.

Following the positive challenge, further routine rifampicin exposure was contraindicated.The patient was receiving a modified regimen containing isoniazid, levofloxacin and ethambutol under specialist supervision.The appropriateness, duration and monitoring of the rifampicin-sparing regimen require individualized assessment by tuberculosis and Infectious Disease specialists.

The positive challenge also underscores the importance of providing written drug allergy documentation and ensuring that the rifampicin reaction is recorded prominently in future medical records.

Clinical Lessons

This case demonstrates that historical drug-reaction timing may be uncertain and should not be presented as objectively established.It also demonstrates that clinically significant immediate hypersensitivity manifestations may occur following exposure to a relatively small oral rifampicin dose.A positive DPT can establish clinical reactivity but does not independently prove an IgE-mediated mechanism.

Most importantly, culprit-drug provocation in patients with possible systemic hypersensitivity requires careful risk assessment, specialist supervision and immediate availability of emergency treatment.

Strengths and Limitations

The principal strength of this case is the objectively documented reproduction of immediate hypersensitivity manifestations following rifampicin administration, including a recorded dose, administration time, reaction onset and treatment sequence. The case also provides a clinically relevant example of drug hypersensitivity evaluation in a patient with previous multidrug-associated hepatotoxicity.

Several limitations should be acknowledged.The exact timing of the historical reaction was uncertain because the patient could not reliably recall the interval between rifampicin administration and symptom onset.

The manufacturer, concentration, excipient composition and preparation method of the oral rifampicin liquid were not available. The administered dose was documented as 45 mg, but the corresponding volume was not provided.

The available information did not establish whether skin testing or in vitro investigations had been performed before DPT. The original documented indication, risk–benefit assessment, written informed consent and procedural emergency preparedness arrangements require verification.

Although liver function tests had normalized before challenge, the exact numerical pre-challenge results were not available.Acute and baseline serum tryptase values were unavailable, limiting mechanistic assessment of mast-cell activation.Complete serial vital signs and detailed respiratory and cardiovascular observations during the reaction were not available for independent severity grading.

The long-term outcome of the rifampicin-sparing antitubercular regimen was not available.

CONCLUSION

We report immediate rifampicin hypersensitivity with systemic manifestations in a 35-year-old woman receiving treatment for presumed peritoneal tuberculosis.The patient had previously experienced urticaria, pruritus and vomiting following rifampicin exposure, although the exact onset interval was uncertain.

Following biochemical recovery from earlier antitubercular therapy-associated hepatotoxicity, a supervised oral rifampicin challenge was performed.Administration of rifampicin 45 mg as an oral liquid preparation elicited objective urticaria, generalized pruritus and severe abdominal pain within approximately 45 minutes, requiring immediate intramuscular adrenaline followed by adjunctive treatment.

The findings strongly supported immediate rifampicin hypersensitivity with an anaphylaxis-compatible presentation, although the underlying IgE-mediated mechanism was not established.This case emphasizes accurate clinical documentation, careful application of EAACI/ENDA risk-based diagnostic principles, prompt anaphylaxis management and specialist-guided tuberculosis treatment planning.

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