American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e927586
DOI: 10.12659/AJCR.927586

Received: 2020.07.22
Accepted: 2020.08.14
Available online: 2020.08.19
Published: 2020.08.25

Rifampicin-Induced Pneumonitis Mimicking Severe COVID-19 Pneumonia Infection

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ADEFG 1 Fateen Ata
DEF 2 Mousa Shaher Mousa Hussein
EF 3 Ahmad Y. Mismar
EF 1 Rohit Sharma
EF 4 Issam A. M. Bozom
EF 1 Zeinab Alsiddig Ali Ibrahim
EF 1,2,5 Wanis H. Ibrahim

1 Department of Internal Medicine, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar
2 Department of Pulmonology, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar
3 Department of Internal Medicine, Detroit Medical Center, Detroit, MI, U.S.A.
4 Department of Pathology, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar
5 Clinical Medicine, Weill-Cornell Medical College, Doha, Qatar

Corresponding Author: Fateen Ata, e-mail: docfateenata@gmail.com
Conflict of interest: None declared

Patient: Male, 43-year-old
Final Diagnosis: Rifampicin-induced pneumonitis
Symptoms: Dyspnea • fatigue • fever
Medication: —
Clinical Procedure: Bronchoalveolar lavage • bronchoscopy • CT scan • lung biopsy
Specialty: Pulmonology

Objective: Rare disease

Background: Rifampicin-induced pneumonitis is an infrequent occurrence, with only a few cases reported in the literature. Furthermore, this condition constitutes a diagnostic challenge, particularly in the era of COVID-19 infection. Here, we report a case of rifampicin-induced pneumonitis with clinical, imaging, and histological features of acute respiratory distress syndrome (ARDS), which required severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing to exclude a diagnosis of coronavirus disease 2019 (COVID-19) pneumonia.

Case Report: A 43-year-old man on anti-TB treatment for TB meningitis developed new-onset fever, fatigue, hypoxemic respiratory failure, and bilateral pulmonary opacities. His clinical, chest X-ray, and CT thorax findings of ARDS were similar to both rifampicin-induced pneumonitis and severe COVID-19 pneumonia. However, reverse transcription polymerase chain reaction (RT-PCR) testing from a nasopharyngeal swab and bronchoalveolar lavage (BAL) via the GeneXpert system was negative for SARS-CoV-2. A detailed workup, including lung biopsy, revealed drug-induced pneumonitis as the cause of his presentation. His pneumonitis improved after discontinuation of rifampicin and recurred following the rifampicin challenge.

Conclusions: This case highlights the importance of early, rapid, and accurate testing for SARS-CoV-2 during the COVID-19 pandemic for patients presenting with acute respiratory symptoms, so that accurate diagnosis and early patient management are not delayed for patients with treatable causes of acute and severe lung diseases. Timely identification of rifampicin-induced pneumonitis via a high clinical suspicion, detailed workup, and histopathological analysis is required to avoid permanent damage to the lungs.

MeSH Keywords: Antitubercular Agents • Coronavirus Infections • Lung Diseases, Interstitial • *Mycobacterium tuberculosis* • Rifampin

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/927586

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Background

Rifampicin is one of the cornerstone drugs in the treatment of TB and is associated with many adverse effects, especially gastrointestinal ones, including hepatotoxicity. These effects have been thoroughly studied in the setting of combination therapy with isoniazid in the treatment of TB [1]. Drug-induced pneumonitis is mainly linked to use of cytotoxic medications [2]. The prevalence of drug-induced pneumonitis varies depending upon the causative agent. Generally, for non-cytotoxic drugs, it ranges from 5% to 10%; however, it has been reported to be up to 50% with methotrexate [3,4]. The prevalence of antibiotic-induced pneumonitis is not well studied. The diagnosis usually requires extensive workup, including radiological imaging, bronchoscopy with lavage analysis, and biopsy to rule out other possibilities. Rifampicin, very rarely, can cause pneumonitis. To the best of our knowledge, it has been reported only a few times in the literature [2,5–9]. The clinical, radiological, and histological findings of drug-induced pneumonitis are comparable to those of ARDS (i.e., ground-glass opacities with air bronchograms) [2]. The early histological features of ARDS are diffuse alveolar damage (DAD), with an initial exudative phase, followed by hyaline membrane formation [10].

One of the challenges diagnosing drug-induced pneumonitis is its clinical and radiological manifestations, similar to those of SARS-CoV-2 pneumonia. It is vital to continue appropriate isolation precautions until COVID-19 is confidently ruled out to mitigate the spread of SARS-CoV-2. Here, we report a case of rifampicin-induced pneumonitis with clinical, imaging, and histological features of acute respiratory distress syndrome (ARDS), which required severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing to exclude a diagnosis of coronavirus disease 2019 (COVID-19) pneumonia.

Case Report

A 43-year-old Indian man presented to the Emergency Department with fever, headache, lethargy, and shortness of breath that began 1 week before. He did not experience a cough or flu-like symptoms. The patient was known to have TB meningitis, diagnosed 2 months before his admission. He was switched from the first-line to second-line anti-TB medication (Moxifloxacin 400 mg oral once daily, Cycloserine 500 mg oral twice daily, Rifampicin 600 mg oral once daily, Ethionamide 500 mg oral once daily, and Pyridoxine 50 mg oral once daily) 16 days before admission due to drug-induced hepatitis on first-line therapy. Due to the COVID-19 pandemic protocols and his symptoms suspicious of SARS-CoV-2 infection, he was kept on droplet isolation, and because of the possibility of pulmonary TB, airborne isolation was also added.

The patient was febrile (39°C), with bilateral basal crackles in the lungs. His oxygen saturation at room air was 91%, with the rest of the physical examination unremarkable. Initial lab work showed normal white blood cell counts, normal eosinophil count, high C reactive protein (109.2, normal range: 0–5 mg/L), normal procalcitonin, kidney, and liver function tests, and normal electrolytes.

A chest X-ray (CXR) showed bilateral pulmonary infiltrates and patchy bilateral consolidation (Figure 1A), which were not present in his previous CXR at the time of his diagnosis with tuberculous meningitis. The patient was not in overload clinically; hence, heart failure was unlikely. The initial sepsis workup was negative for any bacterial growth (including *Mycoplasma pneumonia*, *Legionella pneumophila*, and *Chlamydia pneumonia*). Nasopharyngeal PCR tests for common respiratory viruses (including Influenza, Parainfluenza, Respiratory syncytial virus, and Middle East respiratory syndrome coronavirus) were negative. Another diagnostic possibility was COVID-19 infection due to the ongoing pandemic and similarity of symptoms. SARS-CoV-2 nasopharyngeal reverse transcription polymerase chain reaction (RT-PCR) via the GeneXpert system was done twice, 24 h apart, and both PCR results were negative. Due to his known diagnosis of TB, reinfection/drug resistance was considered as a differential diagnosis. Acid-fast bacilli (AFB) smear, polymerase chain reaction (PCR) via Xpert nucleic acid amplification, and culture were sent from sputum, which were negative. Acute eosinophilic pneumonitis was also considered a diagnostic possibility, but was unlikely given a negative smoking history and a normal white cell differential count, including eosinophils. Hypersensitivity pneumonitis was unexpected because there was no history of exposure to animals or birds. A combined HIV antibody/p24 antigen test was non-reactive.

The patient was started empirically on antibiotics in consideration of atypical community-acquired pneumonia, and was kept on 2 L supplemental oxygen through a nasal cannula.

In the subsequent days, the patient remained febrile. As a part of the workup for fever of unknown origin, abdominal and thoracic CT scans were performed. His CT thorax showed perihilar and peri-broncho vascular ill-defined opacities with a patchy area of alveolar consolidation. There were ground-glass opacities seen at the base of the lungs, with small basal pleural thickening, and a few sub-centimetric lymph nodes in the mediastinum. It also showed patchy consolidation and air bronchograms, consistent with ARDS (Figure 2).

At this point (i.e., day 5) a bronchoscopy was performed. Bronchoalveolar lavage (BAL) and tissue samples were sent for a detailed analysis.

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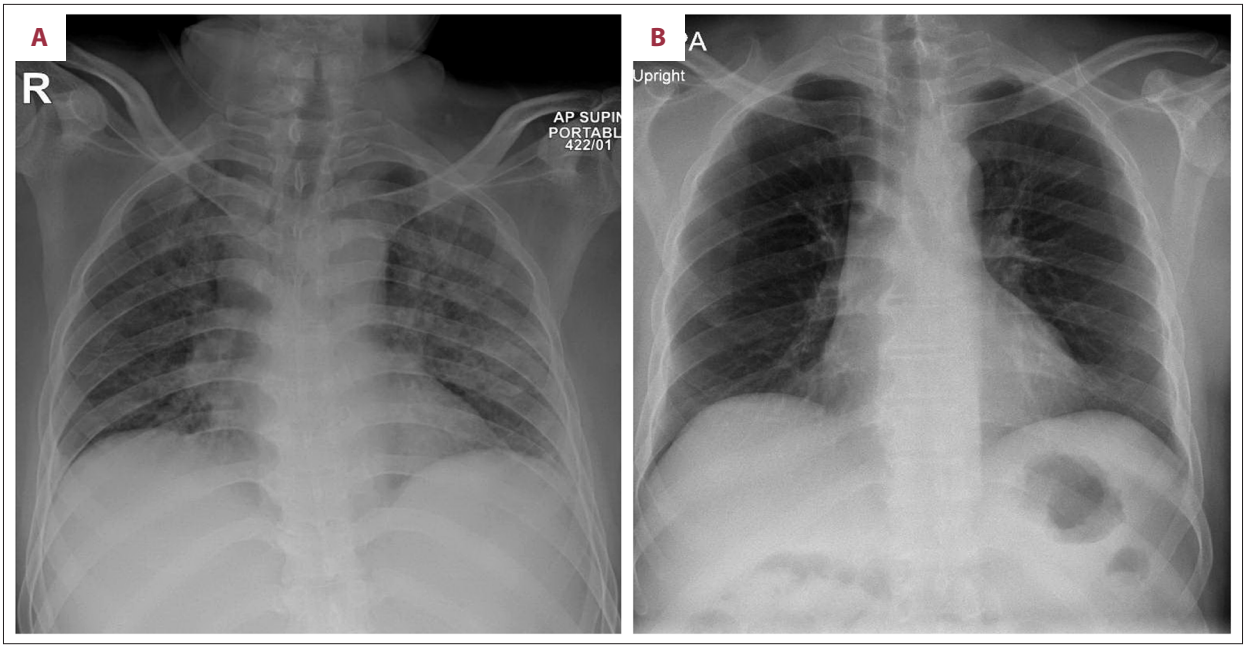

Figure 1. Chest X-ray (CXR) (**A.** Initial CXR showing bilateral pulmonary opacities, **B.** Follow-up CXR showing post-treatment resolution of opacities).

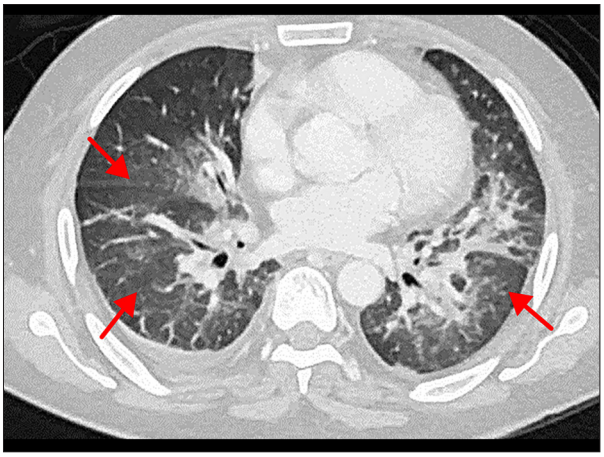

Figure 2. Computed tomography (CT) scan Thorax (Red arrows: Patchy consolidation and air bronchograms consistent with ARDS).

BAL fluid showed a predominance of lymphocytes (63% lymphocytes, 20% neutrophils, and 16% macrophages), with negative results for AFB, bacterial, viral, and fungal cultures. PCR for Pneumocystis jiroveci and SARS-CoV-2 were negative, and alveolar hemorrhage was also ruled out by the BAL analysis.

Histopathological examination revealed widened interstitial septae by loose connective tissue and few chronic inflammatory cells, including lymphocytes, histiocytes, and rare eosinophils (Figure 3A) but without dense fibrosis. In addition, the alveolar ducts and sacs were filled with organizing fibrinous material. Type II pneumocyte hyperplasia (Figure 3B) was evident, with no evidence of granulomas, vasculitis, viral inclusions, fungal elements, or malignancy. The collective picture was suggestive of a drug-induced pneumonitis.

Given the clinical presentation, tissue diagnosis, and available literature, this was attributed to rifampicin, which was consequently discontinued on the 6th post-admission day. The rest of his anti-TB medications were continued. The patient was started on steroids (prednisolone 40 mg orally once daily). He showed a rapid response to the management, and he was afebrile on the second day of steroids, with normal oxygen saturation on room air. He was discharged on steroids with a 3-week tapering dose regimen, in an asymptomatic condition with a follow-up appointment with medicine and infectious disease clinics.

At 2 weeks after discharge, the patient was seen in the TB clinic. He was asymptomatic. Reintroduction of rifampicin was tried in the TB clinic, which resulted in the reproduction of his symptoms. Rifampicin was subsequently removed, and the diagnosis of Rifampicin-induced pneumonitis was confirmed. The patient was seen in the medical clinic 1 month later. He was afebrile, maintaining saturation on room air, and asymptomatic. He had a complete resolution of the infiltrates on a repeated CXR (Figure 1B).

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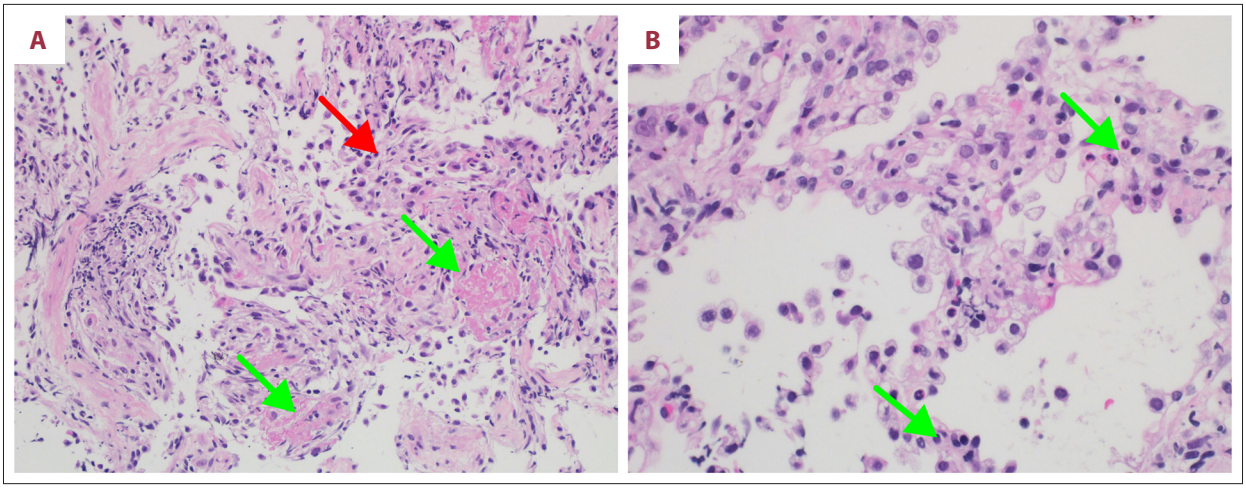

Figure 3. Photomicrographs of the histology of the lung biopsies (day 5 of admission) in a 43-year-old man with a history of tuberculous meningitis and rifampicin pneumonitis who presented with symptoms that mimicked severe COVID-19 pneumonia with negative test results for SARS-CoV-2 infection. (**A**) Histology of the lung shows thickening of the alveolar walls (Red arrow) with an increase in mononuclear cells and pink hyaline membranes (Green arrows), consistent with diffuse alveolar damage (DAD) and with acute respiratory distress syndrome (ARDS) and also with rifampicin-induced pneumonitis. Hematoxylin and eosin (H&E) ×200. (**B**) Histology of the lung shows some residual thickening of the alveolar walls and type II pneumocyte hyperplasia without hyaline membranes. H&E ×400.

Discussion

The use of rifampicin in eradicating pulmonary tuberculosis was first described in 1970 in a small study of 49 participants [11]. Since then, many large trials have shown the efficacy of rifampicin, and the drug has thus become part of the first-line treatment regimen.

Rifampicin is a DNA-dependent RNA polymerase inhibitor [12]. It has broad bactericidal activity against mycobacteria and many gram-positive organisms [13].

One of the challenges in TB treatment is the adverse effects of first-line drugs, such as rifampicin. The common adverse effects of rifampicin can range from skin reactions to fulminant liver or kidney failure, and have been extensively studied [14]. However, pneumonitis secondary to rifampicin is rare, with only a handful of cases reported [2,5–9].

Patients with rifampicin-induced pneumonitis tend to present with persistent low-grade fever and shortness of breath with or without cough, as previously reported [5,6]. Our patient had a similar presentation. A CXR should be the initial radiological investigation, which may reveal interstitial infiltrates [5,6]. Negative cultures for viral, bacterial, and mycobacterial pathogens with persistent symptoms despite antibiotic and anti-TB coverage should prompt further investigation. In a study of 60 patients, CT thorax findings for antibiotic-induced pneumonitis included patchy ground-glass opacities with central opacities [2]. Specifically, in rifampicin-induced pneumonitis, the radiological findings were of "generalized smooth interlobular septal thickening" with ground-glass opacifications [2].

Clinical and radiological similarities between rifampicin-induced pneumonitis and COVID-19 infection pose a diagnostic challenge for physicians. Timely differentiation is especially important in a pandemic situation where all efforts should be made to mitigate the spread of the SARS-CoV-2. Both conditions can present with fever, cough, dyspnea, desaturation, and ground-glass opacities on CT scans of the thorax [15]. It is thus vital to confidently rule out SARS-Cov-2 infection in such individuals and to continue isolation precautions until an alternate diagnosis is made [16]. Other relevant differentials to consider in a patient with features of pneumonitis can include malignancies, allergic bronchopulmonary aspergillosis, autoimmune conditions (such as Churg-Strauss vasculitis and acute eosinophilic pneumonia and systemic lupus erythematosus), and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome [17].

Risk factors previously studied for non-cytotoxic drug-induced pneumonitis include diabetes mellitus, a low serum albumin level, involvement of lungs and pleura by rheumatoid arthritis, a history of disease-modifying agents use, female sex, and older age [17,18]. However, specific risk factors vary with the causative drug class.

Bronchoscopy can aid in diagnosing drug-induced pneumonitis and ruling out alternate possibilities. Previous case reports have shown a lymphocytic predominance in the BAL analysis,

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which was also evident in our case [5,6]. A SARS-CoV-2 RT-PCR should be sent from BAL to rule out COVID-19, as it is highly sensitive (sensitivity of 95%) [19].

A drug lymphocyte stimulation test (DLST) has been previously performed to determine the mechanism of pneumonitis by rifampicin. However, it is of little diagnostic value and is controversial with regards to its diagnostic capability. The sensitivity of this test has varied from 33% to 92% [20,21]. In a previous study, the sensitivity of DLST for rifampicin was as low as 11.6% [22]. A positive test suggests an immunological reaction [6, 9]. In contrast, a negative test may be due to a cytotoxic process or false-negative owing to a decreased immunity secondary to steroid therapy [5].

Histopathological examination of a tissue biopsy can aid in the diagnosis. Commonly seen findings in interstitial pneumonitis secondary to drug toxicity include a homogenous interstitial proliferation secondary to inflammatory cell infiltration, mild fibrosis, and type II pneumocyte hyperplasia [4].

Treatment of rifampicin-induced pneumonitis is like other well-studied drug-induced pulmonary toxicities. The first step is to discontinue the offending drug, which can be difficult in situations where options are limited or when the drug is a significant management cornerstone (as in our case). Glucocorticoids have been studied in observational studies as the treatment of choice, with excellent results. Hence, they should be added in the management if there are no contraindications [23].

Conclusions

This case highlights the importance of early, rapid, and accurate testing for SARS-CoV-2 during the COVID-19 pandemic for patients presenting with acute respiratory symptoms, so that accurate diagnosis and early patient management are not delayed for patients with treatable causes of acute and severe lung diseases. Timely identification of rifampicin-induced pneumonitis via a high clinical suspicion, detailed workup, and histopathological analysis is required to avoid permanent damage to the lungs.

Department and Institution where work was done

Department of Internal Medicine, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar.

Conflict of interest

None.

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