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Abstract

This is an article about how the use of medications such as nirmatrelvir/ritonavir can cause rebound COVID-19 and how the use of Rituximab, a biologic agent, can prolong the duration and increase severity of symptoms of COVID-19 in patients with pre-disposed autoimmune diseases that are on chronic pharmacotherapy.

Keywords

COVID-19, Rituximab, Paxlovid, Nirmatrelvir, ritonavir

Conflict of Interest Statement

No conflict of insterests.

CASE REPORT

Severe COVID-19 Following Rituximab and Nirmatrelvir/Ritonavir Treatment in a Patient with MCTD: Case Report

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Abstract

This is an article about how the use of medications such as nirmatrelvir/ritonavir can cause rebound COVID-19 and how the use of Rituximab, a biologic agent, can prolong the duration and increase severity of symptoms of COVID-19 in patients with pre-disposed autoimmune diseases that are on chronic pharmacotherapy.

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1. Introduction

A recent study indicated rates of COVID-19 rebound increase with time after treatment with Nirmatrelvir/ritonavir, especially in patients with immunosuppressant usage.[1] Immunosuppressant medications such as Rituximab have shown to lead to prolonged COVID-19 due to B-cell depletion, which dampens the humoral response against the virus.[2] The combination of patients taking both Rituximab and Nirmatrelvir/ritonavir places them at risk for prolonged severe COVID-19.

2. Case presentation

We present the case of a 65-year-old Caucasian female with a past medical history of Rheumatoid Arthritis on Methotrexate and Rituximab, Sjogren's disease, Asthma, and recent COVID-19 infection treated with Nirmatrelvir/ritonavir 1 month prior. Her last dose of Rituximab was 2 months prior, which she received every 6 months, and the last dose of Methotrexate was 2 weeks prior. Of note, she has a 12-pack year smoking history, quit 15 years ago, and may have been exposed to fumes when she used to work at a research lab years ago. She presented to the Emergency Department with a nonproductive cough, fever, chills, fatigue, body aches, and diarrhea for the past two weeks prior to admission. She endorsed taking Azithromycin with minimal improvement of symptoms. Physical exam showed blood pressure of 181/89 mm Hg with bilateral diffuse crackles on the chest exam. The workup included Complete blood count (CBC) with elevated platelets of 712,000/uL (150,000−450,000) and white blood cell count (WBC) of 11,000/uL (4000−11,000),a negative COVID-19 PCR, Chest X-Ray with bilateral infiltrates possibly attributed to pneumonia, and normal D-dimer of 284 ng/mL (220−500) with a follow-up CT angiogram of the chest that was negative for pulmonary embolism, positive for bilateral multilobe pneumonia, small bilateral pleural effusions, and small anterior pericardial effusion. Given her symptoms and radiology findings, infectious disease was consulted, and she was started on Ampicillin-Sulbactam, Levofloxacin, and IV methylprednisolone, followed by admission to the inpatient medicine unit for continued observation.

During the first week of her hospital admission, she had spiking fevers ranging from 110.4 to 103.7F,

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developed a productive cough with clear sputum, shortness of breath, labile blood pressures, and increased oxygen demand starting at 2 L/minutes via nasal cannula (NC). Her remaining symptoms were unresolved despite antibiotic treatment. Additionally, her pan culture, hypersensitivity panel, and bacterial cultures were all negative, suggesting an alternative diagnosis; bacterial pneumonia was lower on the differential. Upon further testing, inflammatory markers were elevated, including procalcitonin levels 0.55 (<0.07), ESR-125 mm/hour (0−30), and CRP-18.1 mg/dL (0.0−0.9). During a subsequent physical exam, she exhibited a malar rash. The patient was then tested for ANA-1.3 (<0.7), Anti-RNP-1.3 (0.0−0.9), and Anti-Sm/RNP-6.6 (0.0−0.9) all elevated, supporting the diagnosis of mixed connective tissue disease (MCTD). A repeat CXR showed worsening diffuse bilateral pneumonia and newly developed small bilateral pleural effusions, bronchodilators and prednisone were added to her treatment regimen in efforts to treat what was thought to be multi-lobular pneumonia vs rheumatoid lung disease. Pulmonary was consulted and a bronchoscopy with bronchoalveolar lavage was performed and ruled out pneumocystis jirovecii pneumonia (PCP), fungal, and acid-fast bacteria (AFB). Based on these findings, the antibiotics were discontinued, the patient was switched from PO prednisone to IV methylprednisolone and continued on 4 L/minutes via NC.

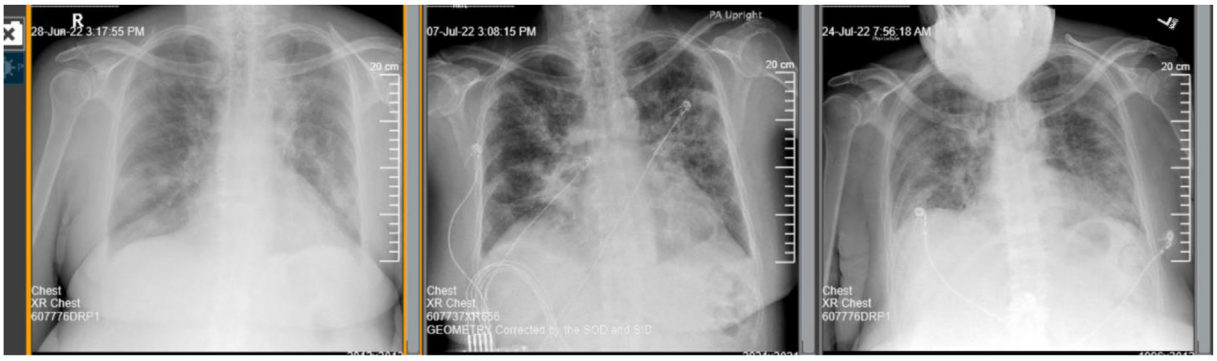
Despite these changes, her oxygen demand continued to trend upward to 10 L/minutes NC. Thus, a repeat COVID-19 PCR was done and tested positive. Rheumatology was consulted, subsequently, the patient was given a remdesivir course, followed by a single IV tocilizumab infusion of 600 mg in the setting of Interstitial Lung Disease (ILD) due to COVID-19. She was transitioned from IV methylprednisolone back to prednisone and placed on Trimethoprim/Sulfamethoxazole prophylaxis while on steroids. With this treatment, her oxygen demand trended downward to 2 L/minutes via NC and proceeded to have no acute events while ambulating. Her final CXR confirmed improved persistent moderate peripheral patchy infiltrates. Patient was discharged on prednisone taper for one week and 2 L of oxygen, and was advised to follow up with pulmonology, rheumatology and primary care physician.

3. Discussion

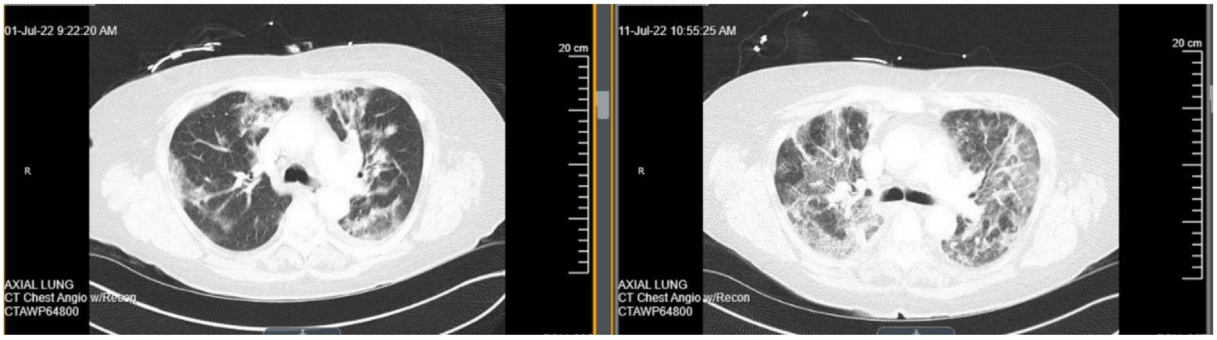
This case illustrates the development of interstitial lung disease (ILD) due to prolonged COVID-19 infection in the setting of Rituximab and Nirmatrelvir/ritonavir use. Rituximab is notably used in rheumatic diseases including Rheumatoid Arthritis, Sjorgen's disease, and MCTD. It is important to note, patients receiving this immunosuppressant treatment, have a high prevalence of comorbidities increasing the risk of poor health outcomes such as exhibiting severe COVID-19. In many cases, anti-SARS Cov2 antibodies were negative due to Rituximab, a B-cell depleting agent, which impedes the production of SARS-COVID antibodies possibly leading to a prolonged duration of infection.2 One study compared the severity of COVID-19 in patients treated or not treated with rituximab; of the patients treated with rituximab 35% had severe COVID-19 and 21% died.[3] In comparison, patients with no rituximab only 11% developed severe COVID and 7% died. Another study identified 18 cases of patients treated with Rituximab who experienced prolonged COVID courses.[4] Ultimately, these studies explain the possible false negative on admission, delayed diagnosis of COVID-19 as well as the progression of the ILD in our patient. Protective measures have been proposed such as testing the patient for COVID-19 prior to the treatment, lowering the dose of glucocorticoids during application, and advising the patient to strictly avoid contact after the treatment.[5]

Nirmatrelvir/ritonavir is an oral antiviral containing nirmatrevir and ritonavir used to treat COVID-19. Many studies have shown it to be effective in reducing the risk of severe COVID-19 in high risk patients including older and immunosuppressed patients.[5,6] The CDC released a health advisory on May 24, 2022, stating COVID-19 rebound symptoms may recur two to eight days after the treatment with Nirmatrelvir/ritonavir.[7] A study was done to examine the relative risk of COVID -19 in patients with Nirmatrelvir/ritonavir and attributes of patients who exhibited COVID-19 rebound.[8] It was found that patients with COVID-19 rebound had significant comorbidities including organ transplant and immunosuppressive usage. Furthermore, after treatment, the rate of COVID-19 infection rebound increased from 3.53% for 7 days to 5.40% for 30 days, a 53% increase. This study can be applied to our patient because their last dose of Rituximab was given in April 2022, they contracted COVID-19 and were treated with Nirmatrelvir/ritonavir in May 2022. In the beginning of June 2022, within 30 days after receiving the Nirmatrelvir/ritonavir treatment, she exhibited the same symptoms as her initial COVID-19 but tested negative via the PCR test. Thus, we concluded our patient possibly experienced COVID-19 rebound.

This case brings into question the necessary surveillance of immunosuppressed patients who



CXR Day 1 CXR Day 9 CXR Day 26



CT Angio w/ Recon Day 3 CT Angio w/ Recon Day 13

contract COVID-19 and are treated with Nirmatrelvir/ritonavir. In the instance of rituximab, it should be prescribed with caution as it leaves patients vulnerable to COVID-19. In regard to the use of Nirmatrelvir/ritonavir, further studies may need to be done to examine the rate of COVID-19 rebound in immunosuppressed patients and the effectiveness of the treatment within this population

Conflict of Interest

There is no conflict of interest.

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