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Delayed-Onset Rituximab Lung Injury in Neuromyelitis Optica Spectrum Disorder: A Case Report

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Case Report

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Abstract

Background: Rituximab (RTX) is a monoclonal antibody targeting CD20 on B cells. It has been used for many years as an effective off-label treatment for patients with neuromyelitis optica spectrum disorder (NMOSD). A serious, rare adverse effect of rituximab is interstitial lung disease (ILD), mainly reported in patients with lymphoma receiving combination therapy. Here, we report a progressive and fatal case of rituximab-induced interstitial lung disease (RTX-ILD) in a patient with NMOSD.

Case presentation: A 34-year-old man with a history of aquaporin-4 (AQP4)-positive NMOSD was hospitalized for severe dyspnea and a nonproductive cough. He has been receiving RTX, 1000 mg intravenously every six months, for the past three years with no previous complications. Pulmonary symptoms progressed despite outpatient care, and imaging revealed ground-glass opacities and pleural effusion. After excluding infectious causes, drug-induced pneumonitis was suspected, and corticosteroid therapy was initiated. However, the patient died of progressive respiratory failure.

Conclusion: RTX-ILD is a rare, potentially fatal adverse effect that should be considered in patients with NMOSD receiving RTX who develop respiratory symptoms. This complication may occur even after RTX therapy that was previously well tolerated.

Background

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory demyelinating disorder most commonly associated with aquaporin-4 immunoglobulin G (AQP4-IgG) antibodies. It typically presents with severe optic neuritis and transverse myelitis, which often lead to visual loss and paralysis, and immunosuppressive drugs are essential to prevent relapse (1). Due to the high cost of FDA-approved monoclonal antibodies for NMOSD, lower-cost agents such as rituximab (RTX) are widely used off-label (2).

RTX is a monoclonal antibody that targets CD20-positive B cells. It is used to treat hematologic malignancies, particularly B-cell lymphomas, and is increasingly used for immune-mediated diseases, including NMOSD (3). The most common adverse events of RTX are infusion-related reactions, such as chills, fever, flushing, angioedema, and bronchospasm, that often are mild and self-limited (4). Delayed adverse reactions are uncommon and include hypersensitivity reactions, hematologic, cardiovascular, and respiratory complications, and secondary infections. Severe respiratory complications like interstitial lung disease are rare and mostly known from case reports. Rituximab-induced ILD (RTX-ILD) is a potentially life-threatening delayed complication needing early diagnosis and treatment. The time from RTX exposure to symptom onset is clinically important, with reported cases occurring from one week after initial exposure to nine months after the last dose (5).

We report a fatal case of RTX-ILD in a patient with NMOSD, emphasizing the need to consider this complication in all patients treated with RTX, even those who previously tolerated it, as the indication for its use increases over time.

Case presentation

A 34-year-old man was admitted to the hospital with dyspnea and a nonproductive cough. His respiratory symptoms began three weeks ago and gradually worsened despite outpatient treatment, leading to his hospitalization.

His medical history is notable for seropositive aquaporin-4 (AQP4) NMOSD, diagnosed eight years ago based on the 2015 international consensus criteria, with the initial presentation of left optic neuritis. Brain magnetic resonance imaging (MRI) at that time showed lesions in the area postrema, and cervical MRI revealed extended transverse myelitis from C3 to C6 on T2-weighted images.

Following diagnosis, preventive immunotherapy with azathioprine and prednisolone was started. Despite this, he had a severe relapse of optic neuritis three years prior to the current admission, resulting in a switch to RTX at 1,000 mg IV every six months. He has remained relapse-free since that time. During RTX therapy, he received three doses of the COVID-19 vaccine. He received his most recent RTX infusion three months before the onset of his respiratory symptoms.

On admission, his vital signs were: blood pressure 125/70 mmHg, pulse 88 beats/min, respiratory rate 14 breaths/min, oral temperature 37.4°C, and peripheral oxygen saturation 90% on room air. His Expanded Disability Status Scale (EDSS) score was 2.0. Pulmonary examination revealed fine inspiratory crackles in the right lung and decreased breath sounds over the right lower lung field.

Laboratory investigations showed a white blood cell count of 8.6 × 10^9/L with lymphocyte predominance, an erythrocyte sedimentation rate (ESR) of 28 mm/h, and a C-reactive protein (CRP) level of 2 plus. COVID-19 polymerase chain reaction (PCR) testing was negative, and serum immunoglobulin G (IgG) and immunoglobulin M (IgM) levels were within the normal range. All other laboratory parameters were normal.

Chest computed tomography (CT) demonstrated right lower lobe consolidation with surrounding ground-glass opacities (GGOs) and a right-sided pleural effusion (Fig. 1). Empirical antibiotic therapy was initiated for presumed bacterial pneumonia.

[Figure 1]

His condition subsequently deteriorated, with worsening cough, progressive dyspnea, and declining oxygen saturation, leading to transfer to the intensive care unit (ICU). Pulmonary thromboembolism was excluded by CT pulmonary angiography, and repeated chest CT revealed marked progression of bilateral GGO. Despite supportive care, his oxygen saturation decreased to 80%, and worsening respiratory failure necessitated endotracheal intubation and mechanical ventilation. Flexible bronchoscopy with bronchoalveolar lavage (BAL) was performed to evaluate possible infectious etiologies, and microbiological analyses were negative. Empiric intravenous dexamethasone (8 mg every 12 hours) was initiated. Despite corticosteroid treatment and intensive supportive care, his respiratory status continued

to deteriorate, and he developed altered mental status. He ultimately died of progressive respiratory failure. Although a definitive causal relationship between RTX and ILD cannot be established, the clinical presentation, temporal association, exclusion of infectious causes, and radiologic findings supported RTX-associated ILD as the most likely diagnosis.

Discussion

This case report highlights a rare case of RTX-ILD in a middle-aged patient with NMOSD. The patient presented with progressive respiratory symptoms, and chest CT showed GGOs with pleural effusion 3 months after the last RTX administration. This complication occurred despite prolonged, previously well-tolerated RTX therapy. Despite intensive care and corticosteroid therapy, he developed fatal respiratory failure.

RTX-ILD is an uncommon adverse effect, with reported incidence rates ranging from 3.7% to 10% (6). Its exact mechanism remains unclear but may involve tumor necrosis factor α (TNF-α) release, rapid B-cell lysis, complement activation, and the release of other proinflammatory cytokines following rituximab infusion (7).

Clinical manifestations are nonspecific, and the most common symptoms are dyspnea, dry cough, and fever. (8, 9). Respiratory symptoms can occur acutely (within hours), delayed (1-3 weeks), or late (1-3 months) after a rituximab infusion (10).

Diagnosis of RTX-ILD requires a multidisciplinary approach because it can mimic infection, malignancy, and other pulmonary diseases. High-resolution chest CT (HRCT) is the imaging modality of choice and typically shows diffuse interstitial abnormalities, most commonly GGOs, diffuse pulmonary infiltrates, and features of alveolitis (8). Up to one-third of patients are asymptomatic and may be diagnosed incidentally based on radiologic findings. Pulmonary function tests usually show a restrictive pattern and decreased diffusing capacity for carbon monoxide (DLCO) (11) Bronchoscopy with BAL helps rule out infections and other differential diagnoses (12). Because rituximab-treated patients are at increased risk of bacterial, viral, atypical, and opportunistic infections, a complete infectious workup is essential (10). RTX-induced hypogammaglobulinemia, which increases susceptibility to infection, should also be considered in patients presenting with fever and respiratory symptoms (13).

The treatment of choice includes RTX discontinuation and steroid initiation (7). The prognosis of RTX-ILD ranges from mild disease to rapidly progressive respiratory failure. Continuing RTX treatment after symptom onset, often due to delayed diagnosis, is associated with worse outcomes. While many patients respond to high-dose corticosteroids, progression to mechanical ventilation or death may still occur, with reported mortality rates of approximately 18%–24% (10, 11)

To the best of our knowledge, most reports have been in patients with lymphoma (10, 11) and a smaller subset reported immune-mediated diseases like NMOSD-AQP4 (14, 15). A similar case reported a 48-year-old woman with NMOSD who presented with dyspnea and a nonproductive cough two months after

initiating RTX. After RTX discontinuation, her respiratory symptoms gradually resolved, and follow-up pulmonary function tests showed normal FVC and DLCO within eight months (14).

Our case differs from previously reported RTX-ILD cases, as it occurred in a patient with NMOSD receiving rituximab as maintenance immunotherapy rather than chemotherapy for malignancy. Furthermore, he had three years of well-tolerated RTX therapy. The patient developed RTX-ILD three months after the last infusion, with rapid progression to fatal respiratory failure despite corticosteroid therapy and intensive supportive care. However, the causes of ILD in an immunosuppressed patient are broad and cannot be completely ruled out. Therefore, RTX-ILD should be regarded as the most plausible clinical explanation in this case rather than a definitively confirmed diagnosis.

Conclusion

RTX-induced ILD should be considered a rare differential diagnosis in RTX-treated patients with NMOSD presenting with respiratory symptoms. This complication may occur even after RTX therapy that was previously well tolerated. Because prompt steroid therapy can be effective for suspected RTX-ILD, an appropriate clinical and radiologic work-up is recommended to differentiate this condition from infectious causes.

Abbreviations

AQP4
Aquaporin-4
BAL
Bronchoalveolar lavage
CRP
C-reactive protein
CT
Computed tomography
EDSS
Expanded disability status scale
ESR
Erythrocyte sedimentation rate
GGOs
Ground-glass opacities
HRCT
High-resolution computed tomography
ICU
Intensive care unit
IgG
Immunoglobulin G

IgM
Immunoglobulin M
ILD
Interstitial Lung Disease
MRI
Magnetic Resonance Imaging
NMOSD
Neuromyelitis Optica Spectrum Disorder
PCR
Polymerase Chain Reaction RTX:Rituximab
TNF-α
Tumor necrosis factor alpha.

Declarations

Ethics approval and consent to participate: Isfahan University of Medical Sciences, Isfahan, Iran, approved this case report. The patient provided written informed consent to participate in the case report.

Consent for publication: The patient provided written informed consent to publish the case report and any accompanying images or clinical information.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

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Authors' contributions: FA collected the clinical data and revised the manuscript. SS drafted the manuscript and prepared the final version. FK and SHA contributed to clinical data collection and reviewed the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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References

1. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet. 2004;364(9451):2106-12.
2. Aungsumart S, Youngkong S, Dejthevaporn C, Chaikledkaew U, Thadanipon K, Tansawet A, et al. Efficacy and safety of monoclonal antibody therapy in patients with neuromyelitis optica spectrum disorder: A systematic review and network meta-analysis. Front Neurol. 2023;14:1166490.
3. Rastetter W, Molina A, White CA. Rituximab: expanding role in therapy for lymphomas and autoimmune diseases. Annu Rev Med. 2004;55:477-503.
4. Paul F, Cartron G. Infusion-related reactions to rituximab: frequency, mechanisms and predictors. Expert Rev Clin Immunol. 2019;15(4):383-9.
5. Zamfir AS, Marinca MV, Zamfir CL, Bordeianu G, Deac AL, Ciuntu BM, et al. Rituximab-Induced Interstitial Lung Disease: A Possible Underestimated Complication-A Systematic Review. Cancers (Basel). 2025;17(23).
6. Hadjinicolaou AV, Nisar MK, Parfrey H, Chilvers ER, Ostor AJ. Non-infectious pulmonary toxicity of rituximab: a systematic review. Rheumatology (Oxford). 2012;51(4):653-62.
7. Chari R, Abdelghany Y, Purcell M, Kenaa B. Rituximab induced lung injury. BMC Pulm Med. 2025;25(1):359.
8. Naqibullah M, Shaker SB, Bach KS, Bendstrup E. Rituximab-induced interstitial lung disease: five case reports. Eur Clin Respir J. 2015;2.
9. Tej S, Undrajavarapu A, Kadian K, Khurana A, Goyal A. Rituximab-Induced Interstitial Lung Disease: A Stitch in Time Saved Nine. Cureus. 2022;14(7):e27088.
10. Liote H, Liote F, Seroussi B, Mayaud C, Cadranel J. Rituximab-induced lung disease: A systematic literature review. Eur Respir J. 2010;35(3):681-7.
11. Zou W, Zhang J, Li Y, Zhang Z, Yang R, Yan Y, et al. Interstitial lung disease presents with varying characteristics in patients with non-Hodgkin lymphoma undergoing rituximab-containing therapies. Ann Hematol. 2025;104(1):527-44.
12. Fernandez Perez ER, Travis WD, Lynch DA, Brown KK, Johannson KA, Selman M, et al. Diagnosis and Evaluation of Hypersensitivity Pneumonitis: CHEST Guideline and Expert Panel Report. Chest. 2021;160(2):e97-e156.
13. Labrosse R, Barmettler S, Derfalvi B, Blincoe A, Cros G, Lacombe-Barrios J, et al. Rituximab-induced hypogammaglobulinemia and infection risk in pediatric patients. J Allergy Clin Immunol. 2021;148(2):523-32.e8.
14. Ahn SH, Kim SM, Sung JJ. Rituximab-induced interstitial lung disease in a patient with aquaporin-4 immunoglobulin G-positive neuromyelitis optica spectrum disorder. Mult Scler Relat Disord. 2018;20:192-3.
15. Cheema M, Mustafa S, Siddiqui S, Nawaz M, Iftikhar A. Rituximab Induced Organizing Pneumonia: A Case Report. A53 CASE REPORTS IN ILD: American Thoracic Society; 2024. p. A2051-A.

Figures

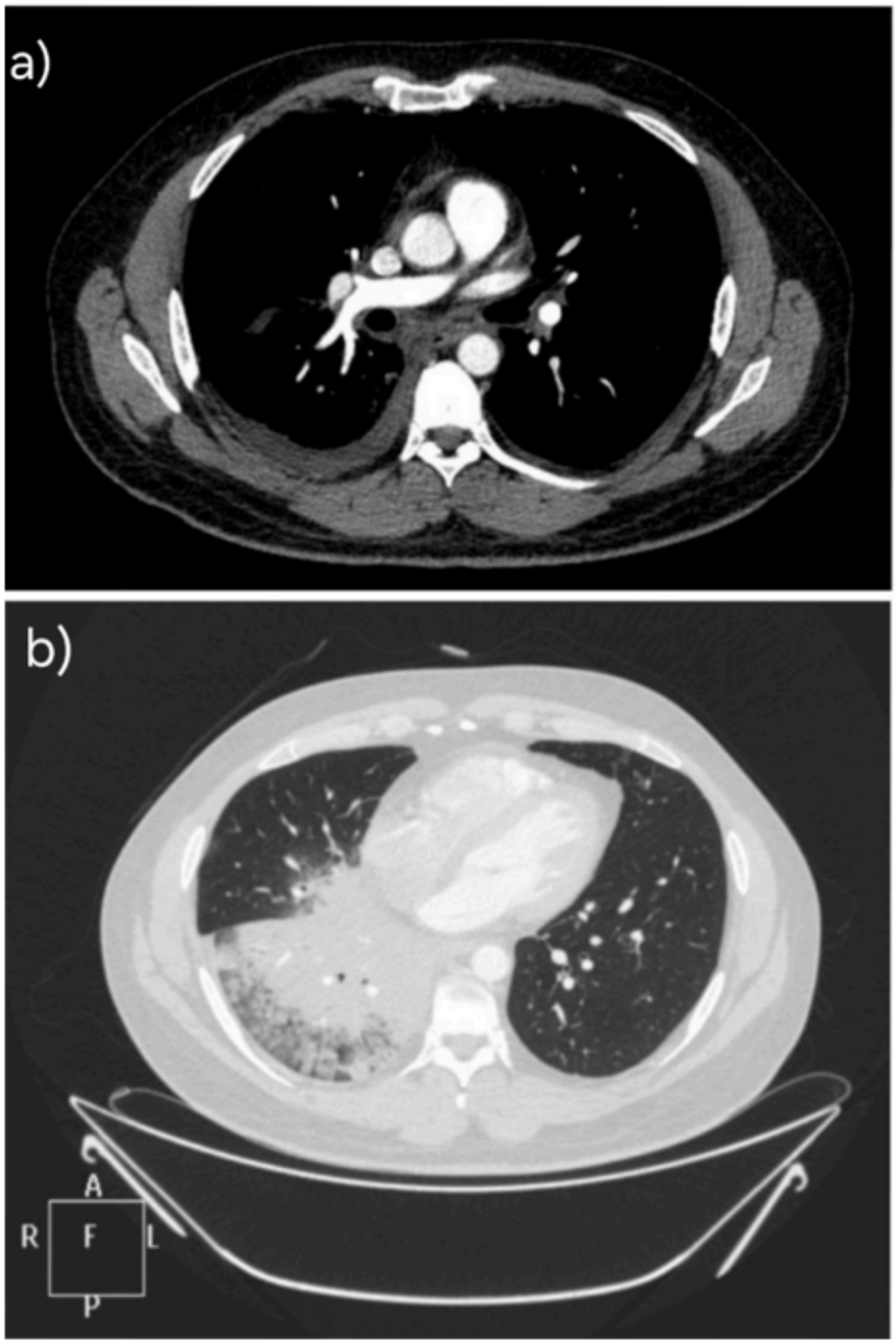


Figure 1

Chest computed tomography findings.
(a, b) Axial CT images showing dense parenchymal consolidation without air bronchograms, surrounded by ground-glass opacities in the right lower lobe.

Supplementary Files

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