



CASE BASED REVIEW

## Protracted severe COVID-19 pneumonia following rituximab treatment: caution needed

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### Abstract

The outcomes of COVID-19 in patients treated with biologic agents are a subject of intense investigation. Recent data indicated that patients under rituximab (RTX) may carry an increased risk of serious disease. We performed an electronic search in Medline and Scopus using the keywords rituximab and COVID-19. We present a rare case of severe, protracted COVID-19 pneumonia in a patient with mixed connective tissue disease (MCTD) who was infected a few days following RTX treatment. In a relevant literature search, we identified 18 cases of patients with rheumatic diseases (6 RA, 8 ANCA vasculitis, 3 systemic sclerosis and 1 polymyositis) treated with RTX who experienced an atypical and/or prolonged course of COVID-19 pneumonia with no evidence of cytokine storm. Our case indicates that RTX may unfavorably affect outcomes following SARS-CoV-2 infection. B cell depletion may dampen the humoral response against the virus; we may hypothesize that B cell-depleted patients may be protected from cytokine storm but on the other hand may have difficulties in virus clearance leading to a protracted course. Taking into account that COVID-19 vaccines are available we may consider delaying RTX infusions at least in patients without life threatening disease, until vaccination is completed.

**Keywords** Rituximab · COVID-19 · SARS-Cov-2

### Introduction

The recent SARS-CoV-2 pandemic has caused enormous difficulties in the routine care and management of patients with immune-mediated diseases. One of the main concerns from the beginning of the pandemic was whether immunosuppressed patients, such as patients with systemic rheumatic diseases, are more prone to develop severe disease

following exposure to SARS-CoV-2. The outcomes of COVID-19 in patients treated with biologic agents is a subject of intense investigation and evidence is accumulating rapidly. Data from the COVID-19 Global Rheumatology Alliance, among other, indicated that patients under RTX may carry an increased risk of serious disease [1, 2]; this was confirmed recently in several registries [3, 4] fueling concerns regarding the use of B cell depleting agents during the pandemic, especially in patients not yet vaccinated against COVID-19. Herein, we present a rare case of severe, protracted COVID-19 pneumonia in a patient with MCTD who was infected a few days following RTX treatment with a fatal outcome. Moreover, we performed a focused minireview in the literature to identify similar cases of prolonged COVID-19 in patients exposed to RTX.

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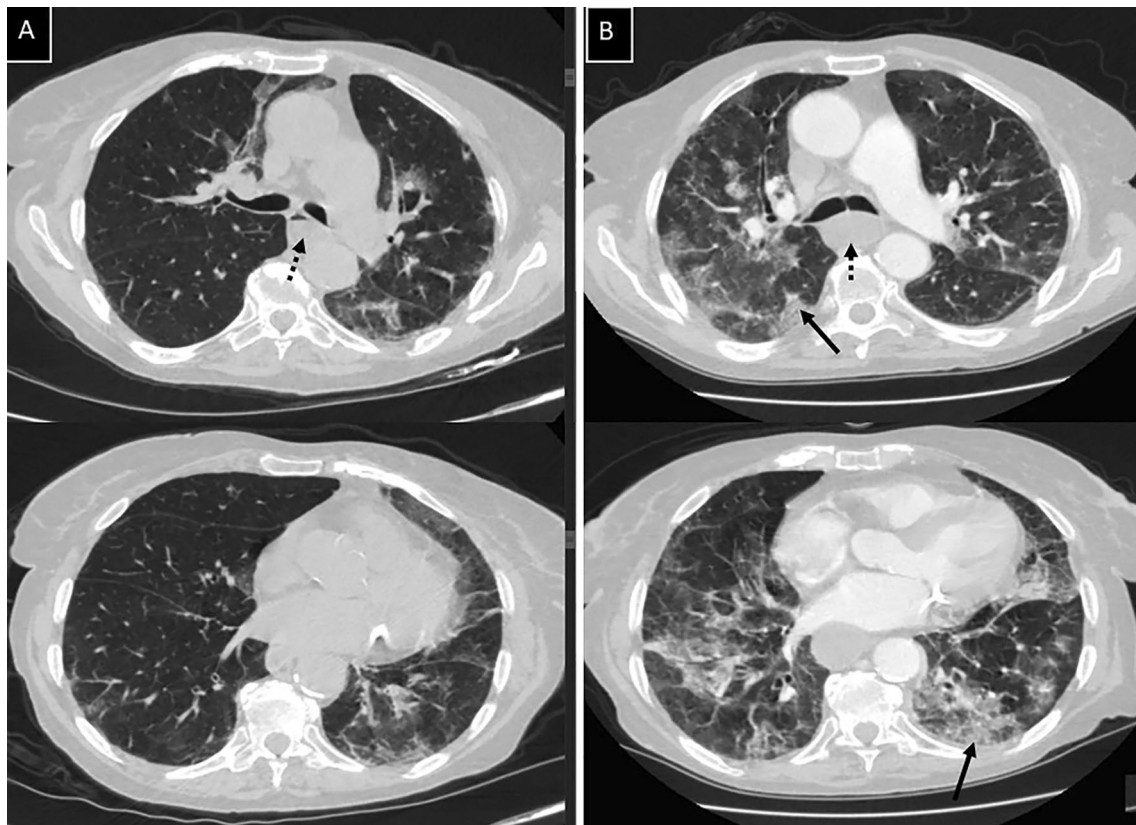
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## Results

### Case presentation

A 76-year-old Caucasian female was diagnosed with mixed connective tissue disease in early 2018 based on peripheral arthritis, Raynaud's, esophageal dysmotility, myositis and positive anti-RNP [5]. She was initially treated with steroids and methotrexate (MTX) with partial response and on July 2018 Rituximab (RTX) was added leading to disease remission. RTX infusions were repeated every 6 months in addition to MTX and 4 mg of methylprednisolone. MTX was discontinued in late 2019 due to hepatotoxicity and the patient remained on RTX monotherapy plus low dose steroids. On January 20, the patient was seen during an appointment in the Rheumatology Department of our institution. She was asymptomatic and received 1 gr of RTX, as scheduled. A few days later, her husband developed flu-like symptoms and was tested positive for SARS-CoV-2. On February 2, the patient with all her family members living in the same house were screened

for SARS-CoV-2 (RT-PCR, nasopharyngeal swab) and were all tested positive. The patient was initially asymptomatic but soon developed low-grade fever and fatigue. Gradually she got worse with high-grade fever and cough. On February 12 she was hospitalized in a regional hospital alongside her husband who subsequently died due to COVID-19 respiratory failure. On admission her oxygen saturation was 95% on ambient air, yet, a chest CT revealed ground-glass lesions. She was treated with remdesivir, dexamethasone and low molecular weight heparin according to standard protocol; she gradually improved and was discharged to domestic quarantine on February 22. A few days following her discharge the patient started feeling unwell and reported low-grade fever. Within the following days, the patient deteriorated with high-grade fever and dry cough and was referred for admission to our hospital on March 10. On admission, she had a positive RT-PCR SARS-CoV-2 test. Her oxygen saturation was 94% and her blood tests revealed a mild leukopenia (4500), lymphopenia (630), a twofold elevation of CRP, a ferritin level of 117 ng/ml whereas antibodies against SARS-CoV-2 were undetectable. Her chest CT showed



**Fig. 1** CT scans at the levels of the pulmonary artery and lower pulmonary vein. Extensive ground glass and crazy paving pattern with areas of consolidations [black arrows], more prominent at the right upper and both lower lobes in (B), indicating a prolonged evolution of

Covid 19 pneumonia. Disease progression of a mild category [severity index 6] at the initial scan (A), to a moderate category [severity index 12]. There is also marked esophageal dilatation [dotted arrow] due to the underlying rheumatic disease

typical features of COVID-19 pneumonia (Fig. 1A). The case of SARS-CoV-2 reactivation was considered taking into account that blood cultures and an extensive workout for bacterial, fungal, parasitic and mycobacterial infections was negative. The patient was treated with broad spectrum antibiotics plus remdesivir/dexamethasone. She became afebrile and steadily improved; she was discharged on March 22 following 2 negative RT-PCR tests for SARS-CoV-2. A few days following her discharge she reported malaise and low-grade fever. The patient progressively deteriorated with high-grade fever and dyspnea and was readmitted on April 7. On admission, she was again tested positive for SARS-CoV-2 by RT-PCR whereas antibodies were once more undetectable. She presented with respiratory failure (pO<sub>2</sub>/FiO<sub>2</sub> = 223), leukopenia (3500) with striking lymphopenia (200), a fivefold elevation of CRP, a threefold elevation of D-Dimers, a ferritin level of 924 mg/dl whereas immunoglobulin levels were low (IgG 323, IgM 7 and IgA 59, mg/dl). Her chest CT was markedly worse (Fig. 1B). She was treated with intravenous immunoglobulin (2 mg/kg in total divided into 5 consecutive days), dexamethasone, broad-spectrum antibiotics and nasal high flow oxygen therapy. Extensive workup for superimposed infections was negative. The patient gradually got worse and subsequently underwent mechanical ventilation on April 29. On that day, RT-PCR for SARS-CoV2 from both nasopharyngeal swabs and bronchial secretions were positive indicating a high viral load. The patient finally died on May 6 due to multi-organ failure. A timeline of the disease course is presented in Fig. 2.

### Literature review

We performed an electronic search in Medline by using the keywords rituximab and COVID-19. The search (last accessed July 29) revealed 203 results. An additional search was also performed in Scopus. Our aim was to identify cases with similar characteristics with our own case: (i) carrying a diagnosis of systemic rheumatic disease, (ii) having received RTX either as monotherapy or combined with disease-modifying antirheumatic drugs in the last year prior to SARS-CoV-2 exposure and (iii) exhibit an atypical and/or protracted course. Patients with non rheumatic, immune-based diseases such as multiple sclerosis were excluded. We focused on case reports and case series where full clinical data for each individual patient were presented. Studies reporting large datasets from registries where individual data were not shown, were excluded.

We identified 18 cases of patients with rheumatic diseases (6 RA, 8 ANCA vasculitis, 3 Systemic sclerosis and 1 polymyositis) treated with RTX who experienced an atypical, prolonged course [6–19]. By reviewing these cases we found that most had a similar protracted course with no evidence of cytokine storm (details for each case are presented in Table 1). In many cases anti-SARS-CoV2 antibodies were negative and immunoglobulin levels were low. From these limited data, it appears that IVIG and convalescent plasma on top of standard treatment may have a favorable effect on outcome. Our case is unique, however, in 2 features. The first one is the extended period of more than 3 months and the second one is that our patient was infected less than 2 weeks from RTX infusion something that might have contributed to the fatal outcome.

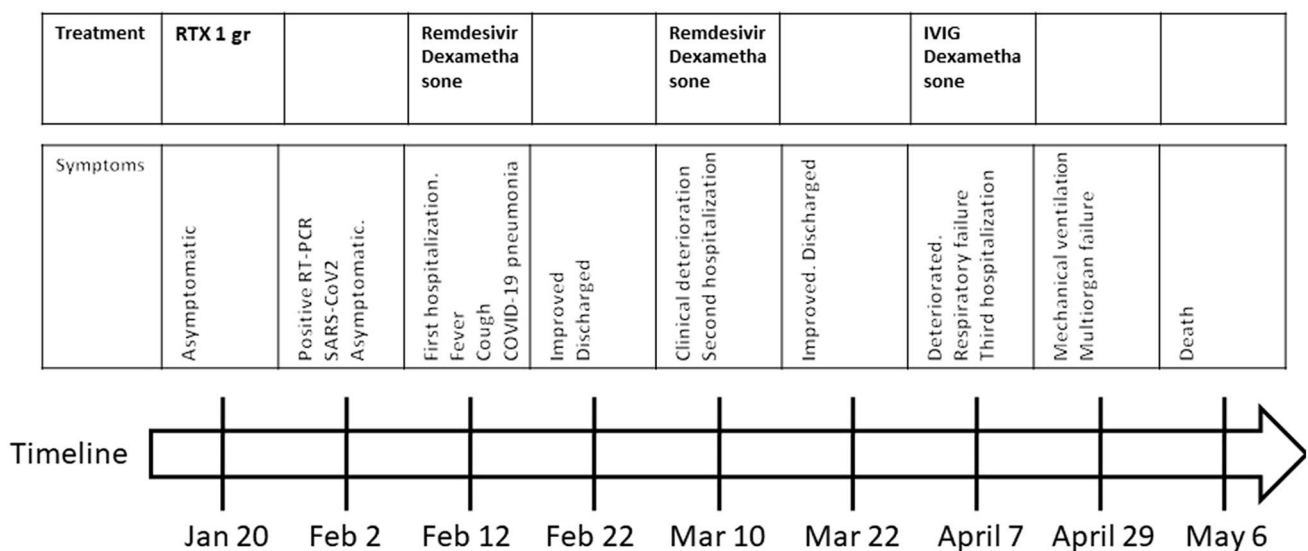


Fig. 2 Timeline of disease course

**Table 1** Studies reporting patients with systemic rheumatic diseases under RTX treatment who developed an atypical and/or protracted course of SARS-CoV-2 infection

Reference	Type of systemic rheumatic disease (sex/age)	Severity of COVID-19	Treatment (apart from steroids)-Outcome	Comments
Aviv et al.	RA (F/50)	Initially mild symptoms that persisted. Later she developed relapsing COVID-19 pneumonia	IVIG, remdesivir and CP Fully recovered	Hypoglobulinemia Absence of anti-SARS-CoV-2 antibodies
Guilpain et al.	GPA (F/52)	Severe disease requiring mechanical ventilation	Lopinavir/ritonavir and HCQ Fully recovered on day #29	RTX was administered a day prior to COVID-19 diagnosis. The patient was also on 15 mg prednisone when infected
Friedman et al.	GPA (F/30)	Initial mild disease that resolved completely but a month later developed COVID-19 pneumonia	Banlavitimab Fully recovered within weeks	Absence of anti-SARS-CoV-2 antibodies
Benucci et al.	Polymyositis (F/60)	Severe pneumonia requiring mechanical ventilation	Remdesivir, CP, tocilizumab and IVIG Full recovery	Absence of anti-SARS-CoV-2 antibodies
Quartuccio et al.	GPA (F/73)	Severe pneumonia leading to respiratory failure	Died on day #25	Absence of anti-SARS-CoV-2 antibodies. Low total IgG levels
Leipe et al.	GPA (M/63)	Atypical symptoms with initial mild pneumonia that gradually deteriorated requiring oxygen supplementation	Recovered on day #32	RTX was administered 2 weeks before COVID-19
Gerber et al.	RA (M/46)	Pneumonia requiring oxygen supplementation	Remdesivir and CP Fully recovered on day #56	Absence of anti-SARS-CoV-2 antibodies
Kenig et al.	1. GPA (M/45) 2. RA (F/64)	1. Protracted pneumonia 2. Severe pneumonia requiring oxygen supplementation	1. Dramatic response to CP administered on day #50 2. Improved 10 days following CP	
Daniel et al.	GPA (M/55)	Protracted pneumonia	HCQ, lopinavir/ritonavir Full recovery but persistent viral shedding for 2 months	Absence of anti-SARS-CoV-2 antibodies
Koff et al.	GPA (F/71)	First symptoms on day #21 following positive PCR. Developed pneumonia on day #36	Full recovery	Hypoglobulinemia Absence of anti-SARS-CoV-2 antibodies
Schulze-Koops et al.	1. RA (M/71) 2. RA (F/80)	1. Severe pneumonia leading to multiorgan failure 2. Severe pneumonia leading to multiorgan failure	1. Died on day #12 2. Died on day #17	Both had normal IgG levels
Avouac et al.	1. SSc (M/71) 2. SSc (F/84) 3. SSc (F/44)	Initial mild symptoms. Deteriorated on days #19, #15 and #23 respectively	2. Anakinra, Tocilizumab All patients recovered	None had interstitial lung disease
Vasconcelos et al.	RA (F/43)	Protracted pneumonia	Dramatic response to IVIG Fully recovered on day #32	Hypoglobulinemia Absence of anti-SARS-CoV-2 antibodies
Rodriguez-Pla et al.	GPA (M/77)	Prolonged course	CP	Absence of anti-SARS-CoV-2 antibodies

CP convalescent plasma, GPA granulomatosis with polyangiitis, RA rheumatoid arthritis, IVIG intravenous immunoglobulin, HCQ hydroxychloroquine, SSc Systemic sclerosis

## Discussion

Our case indicates that RTX may unfavorably affect

outcomes following SARS-CoV-2 infection. B cell depletion may dampen the humoral response against the virus; we may hypothesize that B cell-depleted patients may be

protected from cytokine storm but on the other hand may have difficulties in virus clearance leading to a protracted course. Taking into account that COVID-19 vaccines are available we may consider delaying RTX infusions at least in patients without life-threatening disease, until vaccination is completed.

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