High-titre convalescent plasma therapy for an immunocompromised patient with systemic lupus erythematosus with protracted SARS-CoV-2 infection

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SUMMARY

A 39-year-old woman with systemic lupus erythematosus treated with anti-CD20 monoclonal antibody rituximab was admitted to our hospital with COVID-19 pneumonia. Despite receiving dexamethasone, she developed hypoxaemia and persistent lung opacities. As bronchoalveolar lavage was suggestive of cryptogenic organising pneumonia, high-dose corticosteroid was administered, and she received antimicrobial therapy for opportunistic infections without improvement. Reverse transcription PCR was repeatedly positive for SARS-CoV-2, and virus replication was confirmed in cell cultures. As no anti-SARS-CoV-2 antibodies were detected more than 100 days after symptom onset, she was treated with convalescent plasma with fast clinical improvement, returning home days later. Our case shows that persistent SARS-CoV-2 infection in an immunocompromised patient may be overturned with the appropriate treatment.

BACKGROUND

Anti-CD20 monoclonal antibodies represent the cornerstone treatment of both B-cell malignancies and some autoimmune diseases.[1] However, in the current COVID-19 pandemic, patients treated with rituximab are at increased risk of developing severe COVID-19,[2] and a significant proportion of these patients will require hospitalisation when infected with SARS-CoV-2.[3] Several reports describe protracted SARS-CoV-2 pneumonia in this group of patients.[4–11] Although remdesivir might have a suppressive antiviral effect against SARS-CoV-2, it did not show a curative effect.[4] Choi *et al* described the case of a patient with antiphospholipid syndrome treated with rituximab who, despite having completed three courses of remdesivir, intravenous immunoglobulin and later a SARS-CoV-2 antibody cocktail, still developed prolonged SARS-CoV-2 infection, with a fatal outcome.[5] Phylogenetic analysis showed accelerated viral evolution with a high number of mutations, as in other immunocompromised patients with protracted COVID-19 treated with remdesivir.[6 11] A growing number of case reports of patients with profound B-cell lymphopenia and protracted COVID-19 showed a clear benefit of convalescent plasma therapy for this specific group of immunocompromised patients.[6–10 12]

CASE PRESENTATION

A 39-year-old woman presented with myalgia, sore throat, anosmia and on the following weeks she developed fever, headache, diarrhoea, and ultimately, cough and dyspnoea. She had a personal history of systemic lupus erythematosus (SLE) with articular and haematological manifestations, well controlled with hydroxychloroquine and leflunomide daily in combination with rituximab every 6 months, which had been administered 1 month before symptom onset.

As symptoms worsened, 19 days after symptom onset, she was admitted to the hospital. On examination, she was pale and normotensive with a blood pressure of 95/65 mm Hg and a heart rate of 105 beats/min, and she had tachypnoea with a respiratory rate of 20 breaths/min. She had frequent dry cough, and peripheric oxygen saturation of 96% at room air. On pulmonary auscultation, vesicular murmur was diminished in the left lower two-thirds, with the presence of crackles.

INVESTIGATIONS

Our patient was diagnosed with SARS-CoV-2 pneumonia, which rapidly progressed to acute respiratory failure with PaO_2:FiO_2 ratio <300 (figure 1A). Blood testing showed raised levels of C reactive protein, lactate dehydrogenase, ferritin and d-dimer, as well as anaemia and a low lymphocyte count (figure 1B,C). Chest CT scan revealed bilateral lung ground-glass opacities, initially with 25% of lung involvement (figure 2) but no evidence of pulmonary embolism on CT angiography. She started on dexamethasone 6 mg (figure 1D) and supplemental oxygen but was not a candidate for remdesivir because symptoms had started 19 days before. She also started prophylaxis for *Pneumocystis jirovecii* pneumonia with co-trimoxazole. However, as fever persisted and serial CT imaging showed persistent ground-glass opacities and infiltrates (figure 2), empiric piperacillin/tazobactam was started to treat a presumed nosocomial pneumonia. On day 36, bronchial fibroscopy was performed and bronchoalveolar lavage (BAL) revealed CD8 + lymphocytosis and foamy macrophages, suggesting cryptogenic organising pneumonia. Additionally, herpes simplex virus was detected on a second BAL, so our patient was treated with acyclovir (figure 1D). Corticosteroid was initially tapered, but fever recurred and new interstitial infiltrates and consolidating areas appeared (figure 2). *Pseudomonas aeruginosa* was

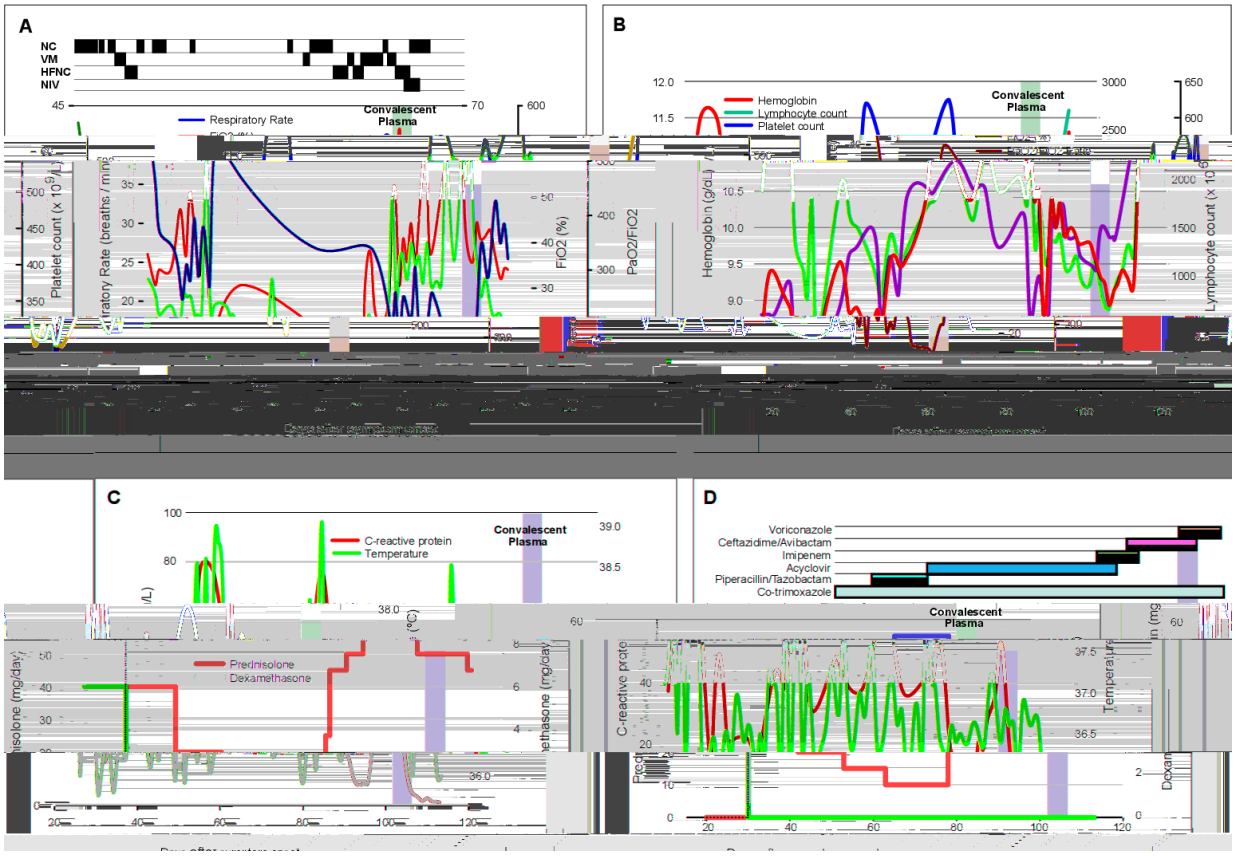

Figure 1 Timeline evolution during hospital admission and administered treatments. (A) Evolution of respiratory rate, percentage of FiO_2 administered and PaO_2:$FiO_{2:F,2}$

isolated in sputum on day 84, so imipenem plus ceftazidime/avibactam was administered, and prednisolone was adjusted to 1 mg/kg/day. In the following weeks, tachypnoea and hypoxaemia worsened, and there was an increasing intolerance after minimal physical exertion accompanied by oxygen desaturation to <90% with PaO_2:FiO_2 ratios reaching the minimum value of 143, high-flow nasal cannula and nocturnal non-invasive ventilation were required (figure 1A), justifying admission to our intermediate care unit.

TREATMENT

SARS-CoV-2 RT-PCR was persistently positive on repeated nasopharyngeal swabs, and on day 94, we confirmed virus replication in cell culture assay. The patient had low plasma gamma-globulin levels and peripheral blood analysis showed absence of B cells, more than 90 days after receiving the last dose of rituximab. Furthermore, no anti-SARS-CoV-2 antibodies were detected 100 days after symptom onset.

On day 102, she started a 4-day course of 200 mL/day intravenous high-titre convalescent plasma treatment with significant clinical improvement in the next days, with an increase of PaO_2:FiO2 ratio to 425, sustained apyrexy, normalisation of C reactive protein levels, and decrease of supplemental oxygen and ventilatory support in the following week. On day 114, arterial blood gas test at room air showed PaO_2 = 67 mm Hg at rest, and she was discharged from the hospital with home oxygen therapy on need and a prednisolone slow-tapering plan.

OUTCOME AND FOLLOW-UP

After hospital discharge, the patient engaged in a physical therapy plan with good results, being able to gain muscle strength, initially with the need of supplemental oxygen. At 2 months posthospital discharge, the patient was able to walk without home oxygen, being able to perform daily life activities. She recovered the sense of smell 2 months after discharge (and 5 months after COVID-19 diagnosis) but had parosmia since then. She started a 'smell training' plan, with some improvement.

DISCUSSION

Despite the rapidly growing information related to COVID-19 and the possibility of modification of guidance, European League Against Rheumatism and, more recently, the American College of Rheumatology (ACR) published a series of recommendations regarding patients with rheumatological disease in the context of the COVID-19 pandemic.[13 14] Both societies agree that glucocorticoids should be used at the lowest dose possible to control rheumatic disease, and these drugs should not be abruptly stopped, regardless of exposure or infection status.[14] Also, according to the ACR COVID-19 Clinical Guidance Task Force, in patients with

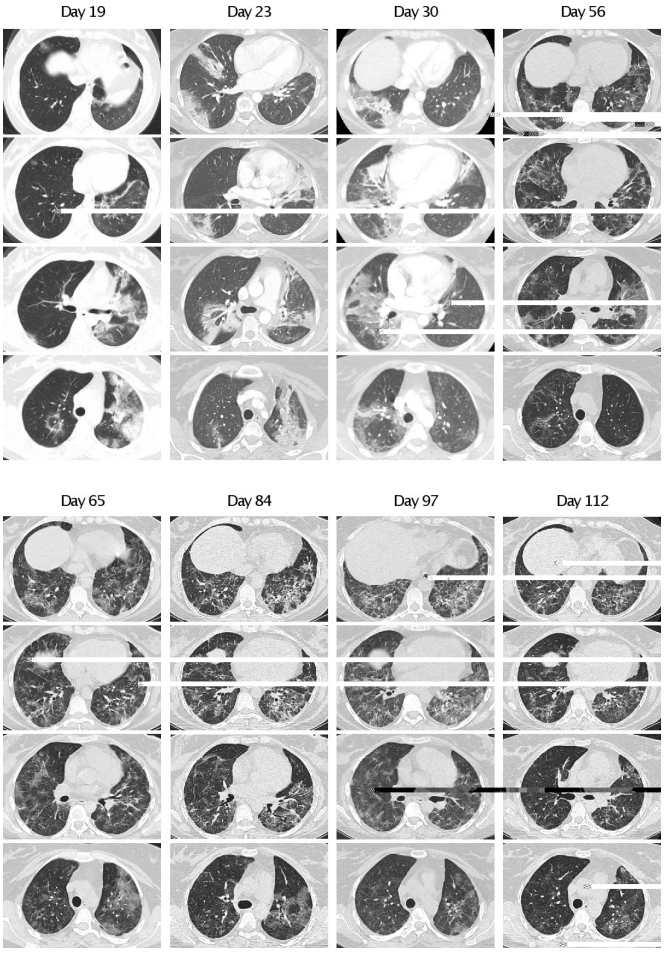

Figure 2 Chest CT images showing the evolution of COVID-19 pneumonia in our patient. Note the migrating bilateral ground-glass opacities and infiltrates at different time points. On day 102, our patient was treated with high-titre convalescent plasma for 4 days and repeated CT imaging 10 days after with visible improvement of infiltrates.

rheumatic disease with documented or presumptive COVID-19 infection, regardless of COVID-19 severity, antimalarial therapies (hydroxychloroquine/chloroquine), sulfasalazine, metothrexate, leflunomide, immunosuppressants, non-interleukin-6 biologics and Janus kinase inhibitors should be stopped or held.[14] In our patient, hydroxychloroquine, leflunomide and rituximab were stopped following SARS-CoV-2 infection diagnosis.

Rituximab induces a deep depletion of both humoral and B-cell response to several micro-organisms,[15] and it may even induce life-threatening infections.[16] Not only the antibody production is impaired (including postvaccination antibody production) but also the antigen presentation and cellular interactions with T cells may be altered, following rituximab administration.[17 18] Consequently, this may delay the inflammatory response to SARS-CoV-2, often resulting in fatal outcomes if not treated.[5 19] Results from the COVID-19 Global Rheumatology Alliance physician-reported registry found that in patients with rheumatic diseases, rituximab was associated with COVID-19-related death.[20] Our patient never developed spontaneous seroconversion against SARS-CoV-2, possibly due to the absence of B lymphocytes.

A Cochrane review found limited evidence of the effectiveness and safety of convalescent plasma therapy for people hospitalised with COVID-19.[21] Similar results were observed in patients with severe SARS-CoV-2 pneumonia treated with convalescent plasma, but only a minority of these patients (9 out of 333) were taking immunosuppressant drugs.[22] Another randomised trial suggested that, in order to be effective, high-titre convalescent plasma against SARS-CoV-2 should be administered early in the course of illness, thus reducing the progression to severe COVID-19 infection in mildly ill infected adults.[23] Importantly, immunocompromised patients seem to be good candidates for convalescent plasma therapy. Promising results have been reported using hyperimmune plasma from convalescent donors, which has been proven to be successful in multiple patients with different pathologies requiring immunosuppression with rituximab.[6–10 12]

Our patient was initially treated with corticosteroids, according to the Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial protocol, and because of recurrent fever, persistent lung infiltrates and moderate hypoxaemia, alternative causes were investigated. Microbial agents were identified and treated, as well as presumed opportunistic infections, without signs of clinical improvement. Because BAL was compatible with cryptogenic organising pneumonia, corticosteroid dose was increased, but hypoxaemia worsened. This highlights the fact that cryptogenic organising pneumonia may be mistaken for protracted SARS-CoV-2 pneumonia, which has important implications since each of these conditions require a different treatment. In fact, high-dose corticosteroid therapy can exacerbate viral replication, potentially increasing the mortality of patients with severe COVID-19.[24] Our patient had persistently positive SARS-CoV-2 RT-PCR on repeated nasopharyngeal swabs over the course of 3 months, but persistent infection was only proven after virus infectivity was confirmed in cell culture assays. Despite a prolonged hospital stay, the patient experienced a quick recovery following convalescent plasma treatment.

This is particularly relevant because it shows that persistent severe hypoxaemia and pulmonary infiltrates for more than 100 days after initial SARS-CoV-2 infection might be caused by sustained viral infection, and it suggests that convalescent plasma could be considered as a valid therapy in this specific group of immunosuppressed patients. To our knowledge, this is the first case report of a patient with SLE treated with rituximab who received convalescent plasma, late in the course of a prolonged SARS-CoV-2 infection with success. A recent retrospective study reported a lower risk of death in hospitalised patients who received convalescent plasma within 3 days (early) after the diagnosis of COVID-19, compared with those who received a transfusion later in the disease course.[25] More studies are needed to determine the optimal timing for starting plasma therapy in immunosuppressed patients with COVID-19 pneumonia. We could speculate that, in severely immunocompromised patients who are hospitalised, early transfusion with high-titre plasma

Patient's perspective

The 93 days I spent in the hospital were hard, complicated, sometimes without hope of getting better but always with great professionals around, giving me hope and courage. I spent Christmas day and New Year's Eve in the hospital. The absence of my family was the hardest thing. I felt sad, abandoned, desolated, without distraction but always with a smile, so that things weren't even worse. Those were sad days. At the time of hospital discharge, I was very happy but then I was hit by the reality of living with the sequelae of COVID-19 … the extreme tiredness, not having the strength for the basic activities of daily life. To live one day at a time. That is my motto.

Learning points

- Rituximab induces a deep depletion of both humoral and B-cell response to several micro-organisms, increasing the risk of severe illness from COVID-19.
- Our patient was severely immunocompromised after receiving rituximab for her systemic lupus erythematosus and developed prolonged SARS-CoV-2 pneumonia with hypoxaemia that lasted more than 3 months.
- Cryptogenic organising pneumonia may be mistaken for protracted SARS-CoV-2 pneumonia, and each of these require different treatments.
- She was successfully treated after receiving a 4-day course of high-titre convalescent plasma.

could result in better outcomes. However, we recognise the limitations of our findings since they rely on a single case report and acknowledge that there is insufficient evidence and even conflicting data to recommend the generalised use of convalescent plasma in patients with SARS-CoV-2 infection.[22 26 27] More robust research is needed to evaluate the benefit of using convalescent plasma in immunosuppressed patients, in particular regarding patients with rheumatological disease in the context of COVID-19, and to determine the optimal timing for initiating plasma therapy in these patients.

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REFERENCES

1 Teeling JL, Mackus WJM, Wiegman LJJM, *et al*. The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. *J Immunol* 2006;177:362–71.
2 Schulze-Koops H, Krueger K, Vallbracht I, *et al*. Increased risk for severe COVID-19 in patients with inflammatory rheumatic diseases treated with rituximab. *Ann Rheum Dis* 2020:annrheumdis-2020-218075.
3 Hasseli R, Mueller-Ladner U, Schmeiser T, *et al*. National Registry for patients with inflammatory rheumatic diseases (IRD) infected with SARS-CoV-2 in Germany (recovery): a valuable mean to gain rapid and reliable knowledge of the clinical course of SARS-CoV-2 infections in patients with IRD. *RMD Open* 2020;6:e001332.
4 Helleberg M, Niemann CU, Moestrup KS, *et al*. Persistent COVID-19 in an immunocompromised patient temporarily responsive to two courses of Remdesivir therapy. *J Infect Dis* 2020;222:1103–7.
5 Choi B, Choudhary MC, Regan J, *et al*. Persistence and evolution of SARS-CoV-2 in an immunocompromised host. *N Engl J Med* 2020;383:2291–3.
6 Martinot M, Jary A, Fafi-Kremer S. Remdesivir failure with SARS-CoV-2 RNA-dependent RNA-polymerase mutation in a B-cell immunodeficient patient with protracted Covid-19. *Clin Infect Dis* 2020;28:ciaa1474.
7 Clark E, Guilpain P, Filip IL, *et al*. Convalescent plasma for persisting COVID-19 following therapeutic lymphocyte depletion: a report of rapid recovery. *Br J Haematol* 2020;190:e154–6.
8 Lancman G, Mascarenhas J, Bar-Natan M. Severe COVID-19 virus reactivation following treatment for B cell acute lymphoblastic leukemia. *J Hematol Oncol* 2020;13:131.
9 Betrains A, Godinas L, Woei-A-Jin FJSH, *et al*. Convalescent plasma treatment of persistent severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in patients with lymphoma with impaired humoral immunity and lack of neutralising antibodies. *Br J Haematol* 2021;192:1100–5.
10 Hueso T, Pouderoux C, Péré H, *et al*. Convalescent plasma therapy for B-cell-depleted patients with protracted COVID-19. *Blood* 2020;136:2290–5.
11 Borges V, Isidro J, Cunha M, *et al*. Long-term evolution of SARS-CoV-2 in an immunocompromised patient with non-Hodgkin lymphoma. *mSphere* 2021:e0024421.
12 Moore JL, Ganapathiraju PV, Kurtz CP, *et al*. A 63-year-old woman with a history of non-Hodgkin lymphoma with persistent SARS-CoV-2 infection who was seronegative and treated with convalescent plasma. *Am J Case Rep* 2020;21:e927812.
13 Landewé RB, Machado PM, Kroon F, *et al*. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. *Ann Rheum Dis* 2020;79:851–8.
14 Mikuls TR, Johnson SR, Fraenkel L, *et al*. American College of rheumatology guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic: version 3. *Arthritis Rheumatol* 2021;73:e1–12.
15 Nazi I, Kelton JG, Larché M, *et al*. The effect of rituximab on vaccine responses in patients with immune thrombocytopenia. *Blood* 2013;122:1946–53.
16 Tudesq J-J, Cartron G, Rivière S, *et al*. Clinical and microbiological characteristics of the infections in patients treated with rituximab for autoimmune and/or malignant hematological disorders. *Autoimmun Rev* 2018;17:115–24.
17 Avouac J, Airó P, Carlier N, *et al*. Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. *Ann Rheum Dis* 2020:annrheumdis-2020-217864.
18 Guilpain P, Le Bihan C, Foulongne V, *et al*. Response to: 'Severe COVID-19 associated pneumonia in 3 patients with systemic sclerosis treated with rituximab' by Avouac *et al*. *Ann Rheum Dis* 2020. doi:10.1136/annrheumdis-2020-217955. [Epub ahead of print: 05 Jun 2020].
19 Tepasse P-R, Hafezi W, Lutz M, *et al*. Persisting SARS-CoV-2 viraemia after rituximab therapy: two cases with fatal outcome and a review of the literature. *Br J Haematol* 2020;190:185–8.
20 Strangfeld A, Schäfer M, Gianfrancesco MA, *et al*. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 global rheumatology alliance physician-reported registry. *Ann Rheum Dis* 2021;80:930–42.
21 Chai KL, Valk SJ, Piechotta V, *et al*. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database Syst Rev* 2020;10:CD013600.
22 Simonovich VA, Burgos Pratx LD, Scibona P, *et al*. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med* 2021;384:619–29.
23 Libster R, Pérez Marc G, Wappner D, *et al*. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med* 2021;384:610–8.
24 Li S, Hu Z, Song X. High-Dose but not low-dose corticosteroids potentially delay viral shedding of patients with COVID-19. *Clin Infect Dis* 2021;72:1297–8.
25 Joyner MJ, Carter RE, Senefeld JW, *et al*. Convalescent plasma antibody levels and the risk of death from Covid-19. *N Engl J Med* 2021;384:1015–27.
26 Li L, Zhang W, Hu Y, *et al*. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA* 2020;324:460.
27 Alunno A, Najm A, Machado PM, *et al*. EULAR points to consider on pathophysiology and use of immunomodulatory therapies in COVID-19. *Ann Rheum Dis* 2021;80:698–706.