Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab

The case reported by Guilpain *et al* attracted our attention. This case of granulomatosis with polyangiitis on immunosuppressants, including recent maintenance therapy with rituximab (RTX), developed a severe and life-threatening coronavirus-2 (SARS-CoV-2) disease 2019 (COVID-19). The particularity of this observation was the occurrence of a more progressive worsening than observed in most series.[1] Herein, we report the observation of three patients with systemic sclerosis (SSc) routinely treated with RTX who were affected by COVID-19 and who also experienced a late clinical worsening to severe pneumonia. RTX is often used off-label in patients with SSc mainly for refractory skin, musculoskeletal or interstitial lung disease. Observational studies reported a safety profile similar to that reported in rheumatoid arthritis.[2]

Their main disease characteristics are presented in table 1. Patient 1 had early diffuse cutaneous SSc, with positive RNA polymerase-3 antibodies, and severe cutaneous involvement (peak modified Rodnan Skin Score at 32/51) as the main clinical involvement. Patient 2 had long-lasting limited cutaneous SSc with recurrent digital ulcers and inflammatory arthritis as the main disease manifestations. Patient 3 had a limited cutaneous subset evolving from 2 years, with positive RNA polymerase-3 antibodies and persisting arthritis. None of these patients had interstitial lung disease and primary or secondary heart involvement. Regarding the main comorbidities, patient 1 was treated for high blood pressure by perindopril, furosemide and lercanidipine, and patient 2 had chronic renal insufficiency and history of pulmonary embolism (2002 and 2008).

All patients presented typical COVID-19 first symptoms (table 1). Patients 2 and 3 had confirmation of COVID-19 diagnosis by reverse transcription (RT)-PCR from nasopharyngeal swab specimens. Chest high-resolution CT was performed for all three patients and demonstrated typical bilateral interstitial pneumonia (figure 1). All patients experienced secondary clinical worsening and sudden respiratory failure requesting emergency hospitalisation. Due to acute respiratory distress syndrome, patients 1 and 3 were transferred to ICU and recovered after 7 and 15 days of non-invasive ventilation without other specific therapy, respectively, with withdrawal of oxygen support. Patient 2 also requested ventilatory support by high-flow nasal cannula. She received four subcutaneous daily injections of anakinra in association with lopinavir. Despite this treatment, rapid respiratory deterioration led to the use of intravenous corticosteroid pulses (120 mg) for 3 days and tocilizumab (1 infusion of 8 mg/kg). These treatments were associated with improved clinical outcome, characterised by decreased oxygen support requirement. No thromboembolism and bacterial secondary infection were observed in these three patients on heparin (prophylactic dosing: patients 1 and 3, therapeutic dosing: patient 2) and antibiotic therapies. Moreover, despite several recent descriptions of peripheral vascular manifestations in COVID+ patients, microangiopathy was not progressive in the three cases.

Some points regarding these observations are important to be considered and discussed. No specific disease subset specifically at risk of COVID-19 was identified. Indeed, the three patients had heterogeneous disease profiles in term of age, disease duration, cutaneous subset and disease manifestations. The World Scleroderma Foundation has recently proposed preliminary advices for the management of patients with SSc during the COVID-19 pandemic.[3] Given the frequent presence of interstitial lung disease (ILD) and concurrent immunosuppressive treatment, patients with SSc may be considered at risk for a more severe disease course and higher mortality when they develop SARS-CoV-2 virus infection. Importantly, these three patients had no pre-existing ILD that may have favoured the severity of the infection. On the other hand, the potential implication of age and comorbidities for patients 1 and 2 (table 1), as well as immunosuppressors including long-lasting RTX therapy, need to be taken in consideration.

As described by Guilpain *et al*, the COVID-19 course of these three patients was characterised by a late clinical worsening compared with what is classically described (days 19, 15 and 23, respectively).[1 4] RTX, but also methotrexate (patients 1 and 3) and/or long-term corticosteroid use (all three patients), may have initially but insufficiently limited the cytokine storm, leading to a delayed worsening. The impairment of antiviral humoral response, more specifically observed with RTX, might

Table 1 Clinical characteristics of the three patients with systemic sclerosis and COVID-19

	Patient 1	Patient 2	Patient 3
Age (years)	71	84	44
Gender	Male	Female	Female
Body mass index (kg/m^2)	24.5	20	29
Disease duration (years)	4	18	2
Cutaneous subset	Diffuse	Limited	Limited
Autoantibody profile	Anti-RNA polymerase 3	No specific autoantibody	Anti-RNA polymerase 3
Interstitial lung disease	No	No	No
Pulmonary hypertension	No	No	No
Other comorbidities	High blood pressure Dyslipidaemia	Chronic renal insufficiency Pulmonary embolism	Thyroidectomy for goitre
Rituximab			
Date of the first infusion	07/17	01/15	01/18
Dose	500 mg/6 months	500 mg/8 months	1 g/8 months
Last infusion	01/20	06/19	10/19
B-cell depletion	Complete (February 2020)	Complete (February 2020)	Complete (January 2020)
Gammaglobulin (g/L)	7.0 (February 2020)	12.9 (February 2020)	9.5 (January 2020)
Associated treatments			
csDMARDs	Methotrexate (20 mg/week)	None	Methotrexate (15 mg/week)
Prednisone (mg/day)	5	5	2.5
COVID-19			
Day 0	01/04/20	12/04/20	15/03/20
Confirmation by RT-PCR	Not done	Yes	Yes
Compatible chest CT scan	Yes	Yes	Yes
First symptoms	Fever, cough, dyspnoea	Fever, diarrhoea, cough	Fever, cough, sore throat, myalgia
Day of clinical worsening	Day 19	Day 15	Day 23
Hospitalisation	Yes	Yes	Yes
Hospitalisation in ICU	Yes	No	Yes
Duration in hospitalisation/ICU	7 days	Still in the general ward	Still in the general ward
Ventilatory support	NIV	HFNC	CPAP
Antibiotics	Yes	Yes	Yes
Other specific treatment	No	Yes (anakinra, corticosteroids, tocilizumab)	No
Outcome	Favourable	Favourable	Favourable

CPAP, continuous positive airway pressure; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HFNC, high-flow nasal cannula; ICU, intensive care unit; NIV, non-invasive ventilation; RT-PCR, reverse transcription PCR.

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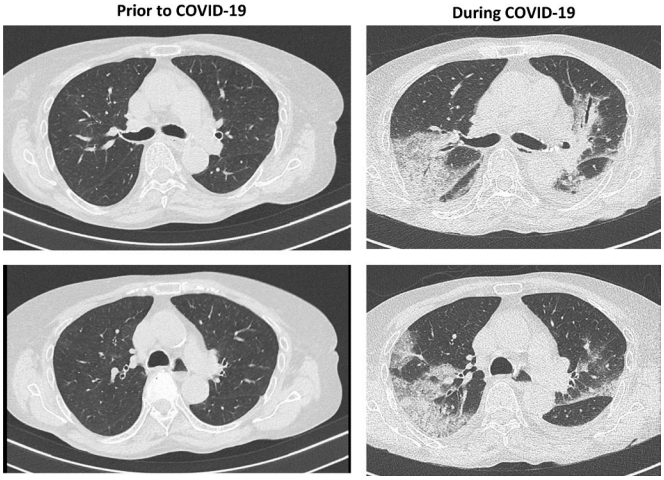

Figure 1 Representative images of chest high-resolution CT scan performed of patient 2, showing no pre-existing systemic sclerosis–associated interstitial lung disease and typical bilateral interstitial pneumonia related to COVID-19.

also have contributed to this secondary worsening. In these three patients, the routine RTX regimen with a complete B-cell depletion confirmed at least 2 months before COVID-19, but without severe hypogammaglobulinemia, might have been an additional risk of infection. Although the impact of RTX on infectious events remains to be clarified, two additional observations of COVID-19-related severe pneumonia on RTX maintenance therapy have been recently reported. The first case concerned a 32-year-old woman with SSc and pulmonary involvement treated with hydroxychloroquine and RTX. She developed a severe pattern of COVID-19 interstitial pneumonia requiring hospitalisation in intensive care, where, despite intubation and an attempt with tocilizumab, she died.[5] The second case, described by Guilpain *et al*, was a 52-year-old woman followed for granulomatosis with polyangiitis, who presented sudden COVID-19-related respiratory failure on day 18, requiring endotracheal intubation and mechanical ventilation, before its clinical condition secondarily improved. Therefore, altogether, these cases suggest that a careful follow-up is required for patients with autoimmune diseases treated by RTX. In particular, a specific attention should be given to the fact that these patients may experience a delayed progression, which need a careful monitoring.

Preliminary experience suggested that patients with chronic inflammatory rheumatic disorders receiving biologic or synthetic targeted disease-modifying anti-rheumatic drugs might not exhibit an increased risk of severe COVID-19.[6–8] However, these observations of severe and life-threatening form of COVID-19 support the continuous attention of patients with SSc under immunosuppressants. The launch of the EUSTAR COVID-19 registry (https://nettskjema.no/a/146481) will permit to obtain additional relevant information from a large number of patients and draw more robust conclusions.

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