COVID-19-related organising pneumonia in patients with secondary antibody deficiency responds to immunoglobulin

Received: 2 July 2024
Accepted: 12 Oct 2024

To the Editor:

Organising pneumonia (OP) is a well-recognised complication of COVID-19 infection and typically responds well to systemic corticosteroids [1]. Individuals with antibody deficiencies, a group of B-cell disorders characterised by hypogammaglobulinemia and impaired antigen-specific antibody production [2], are at increased risk of COVID-19-related OP [3]. This subpopulation may be corticosteroid-refractory and the optimal treatment strategy is unclear. Here, we describe four patients with secondary antibody deficiency (SAbD) who developed refractory COVID-19-related OP (table 1). Treatment with corticosteroids and antiviral treatment failed but they responded well to immunoglobulin replacement therapy (IRT).

Patient 1 was a 77-year-old male with a history of follicular lymphoma treated 8 months prior (bendamustine and rituximab). He presented to the emergency department (ED) with 2 weeks of fever, night sweats and weight loss. COVID-19 was diagnosed by nucleic acid test (NAT), and he was discharged home with oral antibiotics. He returned to the ED 12 days later with worsening symptoms, although he was not hypoxemic. Chest computed tomography (CT) showed bilateral ground glass opacities and a small left pleural effusion. He was hospitalised and treated with remdesivir, tocilizumab, 10 days of dexamethasone, ceftriaxone and azithromycin. He developed hypoxemia and a repeat CT chest on post-admission day (PAD) 27 showed progression of the bilateral opacities to crazy paving. A clinicoradiologic diagnosis of OP was made and a tapering course of prednisone starting at 50 mg daily was initiated. By PAD 49, he required 14 $L \cdot min^{-1}$ supplemental oxygen to maintain oxygen saturations ⩾90% despite prednisone 30 mg daily. His COVID-19 NAT was persistently positive. Intravenous immunoglobulin (IVIG) 1 $g \cdot kg^{-1}$ was started on PAD 51 resulting in rapid improvement, and he was weaned off supplemental oxygen in 48 h and discharged home.

Patient 2 was a 61-year-old male with a history of thymoma treated with surgery and radiation 6 years prior. COVID-19 was diagnosed by NAT when he presented with headache, fevers and chills. 3 weeks later, he presented to the ED with dyspnoea and 13 kg of weight loss. He was not hypoxemic. A chest CT demonstrated bilateral, patchy ground glass opacities and a subpleural consolidation in the right lower lobe. He was admitted and treated with ceftriaxone, doxycycline, tocilizumab and methylprednisolone. He required a bronchoscopy on PAD 12 for mucus plugging and the bronchoalveolar lavage fluid was positive for COVID-19 RNA. He was discharged home on PAD 18 on supplemental oxygen and a prednisone taper. He underwent bronchoscopy 1 month later for worsening dyspnoea and hypoxemia, and transbronchial biopsies showed reactive, nonspecific inflammatory changes. His NAT remained positive 6 weeks after discharge. He was seen by a clinical immunologist and diagnosed with thymoma-associated immunodeficiency (Good syndrome) based on absent circulating B-cells and undetectable serum immunoglobulins. Subcutaneous immunoglobulin (SCIG) 0.5 $g \cdot kg^{-1}$ every 2 weeks was started 4 months following discharge. He was weaned off supplemental oxygen in 1 month and has remained well for 23 months.

Patient 3 was a 74-year-old male undergoing treatment for follicular lymphoma (bendamustine and rituximab). He was diagnosed with COVID-19 by NAT 4 weeks after cycle 2 of chemotherapy. He received doxycycline, sotrovimab and a 6-day course of prednisone as an outpatient. He presented 2 weeks later with productive cough, fever and hypoxemia, and a positive COVID-19 NAT; chest CT demonstrated bilateral ground glass opacities. He was discharged on PAD 2 with a 21-day course of dexamethasone but

Shareable abstract (@ERSpublications)
COVID-19-related organising pneumonia may not respond to antivirals and corticosteroids in patients with secondary antibody deficiency. Immunoglobulin replacement resulted in rapid clinical improvement in this case series of four such patients. https://bit.ly/3Yy2wlE

Cite this article as: Moolji J, Leung WM, Richman-Eisenstat J, *et al*. COVID-19-related organising pneumonia in patients with secondary antibody deficiency responds to immunoglobulin. *ERJ Open Res* 2025; 11: 00660-2024 [DOI: 10.1183/23120541.00660-2024].

https://doi.org/10.1183/23120541.00660-2024

TABLE 1 Patient clinical and immunologic profiles

Patient	Age (years)/ Sex	Diagnosis	Cause of SAbD	Serum immunoglobulins ($g \cdot L^{-1}$)	Lymphocyte counts ($10^9 \cdot L^{-1}$)	COVID-19 therapies	Days of corticosteroids before IRT	Cumulative days of hospitalisation before IRT	Days of hospitalisation after IRT	Months of follow up after IRT
1	77M	Follicular lymphoma	Bend Ritux	IgG 1.68 IgA 0.61 IgM 0.09	Total: 0.1 CD19+ 0.001 CD4+ 0.053 CD8+ 0.034	Dex Pred Rem Toc	25	43	9	1
2	61M	Thymoma	Good syndrome	IgG<0.70 IgA<0.15 IgM<0.08	Total: 0.9 CD19+ 0 CD4+ 0.183 CD8+ 0.572	Met Pred Toc	102	#	N/A	23
3	74M	Follicular lymphoma	Bend Ritux	IgG 1.73 IgA<0.15 IgM<0.08	Total: 0.1 CD19+ 0 CD4+ 0.040 CD8+ 0.050	Pred Dex Sot Rem Toc	43	24	7	22
4	64F	Follicular lymphoma	Bend Ritux	IgG 2.97 IgA 0.75 IgM 0.28	Total: 0.3 CD19+ 0 CD4+ 0.082 CD8+ 0.076	Dex Pred Rem	66	32	2	5

Bend: bendamustine; CD: cluster of differentiation; Dex: dexamethasone; F: female; IRT: immunoglobulin replacement therapy; M: male; Met: methylprednisolone; N/A: not applicable; Pred: prednisone; Rem: remdesivir; Ritux: rituximab; SAbD: secondary antibody deficiency; Sot: sotrovimab; Toc: tocilizumab. #: This patient was discharged from hospital on supplemental oxygen, which he required for about 5 months. He was liberated from supplemental oxygen approximately 1 month after IRT was initiated, on an outpatient basis.

was re-hospitalised three times over the following 4 months with relapsing hypoxemia, 10 kg weight loss and a positive COVID-19 nasopharyngeal swab NAT. Each time he was treated with piperacillin-tazobactam, remdesivir and dexamethasone, and on one occasion received tocilizumab, without sustained clinical effect. Clinical immunology was consulted, he was diagnosed with SAbD, and he received IVIG 0.5 $g \cdot kg^{-1}$ every 4 weeks. He was discharged 7 days later without supplemental oxygen. He had no further relapses of hypoxemia over 22 months of follow up.

Patient 4 was a 64-year-old female who completed treatment for follicular lymphoma (bendamustine and rituximab) 3 months prior to presentation. She presented to the ED with 6 weeks of respiratory symptoms and chest CT demonstrated a bilateral crazy paving pattern. She was hospitalised and underwent bronchoscopy. Her bronchoalveolar lavage fluid NAT was positive for COVID-19 and transbronchial biopsies demonstrated acute fibrinous and organising pneumonia. She received remdesivir and dexamethasone and discharged on PAD 27 with ongoing prednisone for OP treatment but readmitted 2 months later with worsening respiratory symptoms, new hypoxemia and a positive COVID-19 NAT. A chest CT showed interval worsening of the crazy paving pattern. Remdesivir and dexamethasone were re-initiated, followed by a 4-month tapering course of prednisone. IVIG 0.5 $g \cdot kg^{-1}$ every 4 weeks was started on PAD 5 and she was discharged on PAD 7 on 3 $L \cdot min^{-1}$ supplemental oxygen. The hypoxemia and imaging findings resolved 2 months later.

Presumably, COVID-19-related OP is triggered by an excessive immune response to viral antigens and host damage-associated molecular patterns and, therefore, typically resolves with corticosteroids. In contrast, our patients with SAbD had a highly prolonged course and were refractory to antiviral and corticosteroid treatment. We attribute this to persistent immune stimulation by viral antigens due compromised humoral immunity and impaired viral clearance. Anti-SARS-CoV-2 antibodies were readily detectable in IVIG/SCIG by 2021 [4] and the first dose of immunoglobulin in the patients reported here was given in August, 2022. We thus hypothesise that the anti-SARS-CoV-2 IgG present in the pooled immunoglobulin neutralised viral antigens in the lungs [5]. This eliminated the survival stimuli for antigen-activated effector T-cells, thereby facilitating the homeostatic contraction of the immune response and the resolution of pneumonitis. Antiviral therapy, which suppresses COVID-19 replication but does not completely eliminate viral particles from the lung, may thus be less effective in this patient population. An alternative hypothesis is that immunoglobulin can act as an immunomodulatory agent, particularly in cases like Patient 1 who received IVIG at the higher dose of 1 $g \cdot kg^{-1}$. This phenomenon has been described in a small number of cases of cryptogenic organising pneumonia [6], though it is not considered part of the standard treatment of this disease.

Three of the four patients in our case series were diagnosed with OP on clinical and radiologic grounds, and one had biopsy confirmation. Biopsies are often not pursued in COVID-19-related OP, as this sequela is routinely seen in respiratory practice. Patients may be too unwell to undergo bronchoscopy, and even when it is performed, the diagnostic yield of transbronchial biopsies is often insufficient to change to a clinicoradiologic impression due to the small size of the biopsies and sampling error. The diagnosis of OP in this series, therefore, reflects current practice.

Others have also reported favourable responses to IRT for COVID-19-related OP in patients with hypogammaglobulinemia from B-cell depleting therapy for hematologic malignancies [6–8]. Sansen *et al.* [8] recently published a series of six adults with hypogammaglobulinemia and COVID-19 OP, two of whom were treated successfully with IRT.

Our case series adds several important observations to this literature: a) We report the first case (to our knowledge) of the successful treatment of COVID-19-related OP with IRT in a patient with Good syndrome, suggesting that patients with antibody deficiency from any cause are at risk of COVID-19-related OP and may benefit from IRT; b) This is the first description of successful use of SCIG, which has significantly different pharmacokinetics and a more favourable adverse event profile compared to IVIG for the treatment of COVID-19-related OP in SAbD; c) We describe more rapid clinical improvement, resolution of hypoxemia and hospital discharge in patient 1 who received a higher IVIG dose of 1 $g \cdot kg^{-1}$, suggesting doses greater than typical for IRT (0.4–0.6 $g \cdot kg^{-1}$) may be more effective; and d) All of the patients received treatment for OP with corticosteroids and IRT alone and no other immunosuppressants (*e.g.*, mycophenolate mofetil or tofacitinib), and this highlights the importance of IRT as a component of treatment.

Immunocompromised patients may develop refractory COVID-19-related OP that does not respond to corticosteroids or antiviral therapy. Patients with a history of B-cell malignancies or thymoma should be

investigated for SAbD and, if present, treated with IRT. We posit that IRT facilitates the clearance of immune-stimulating viral antigens from the lungs, resulting in rapid clinical improvement.

This case series does provoke ideas that may stimulate future research. It may be useful to provide prophylactic IRT to patients with SAbD and COVID-19 to prevent OP. The duration of IRT following the resolution of COVID-19 and its complications remains unknown. Finally, sipavibart is an investigational monoclonal antibody being developed to prevent COVID-19 in immunocompromised patients, and it may also influence the clinical course of COVID-19, to reduce the risk or severity of OP.

Jalal Moolji[1,2], Winnie M. Leung[1,2], Janice Richman-Eisenstat[1,2] and Adil Adatia[1,2]

[1]Division of Pulmonary Medicine, Department of Medicine, University of Alberta, Edmonton, AB, Canada. [2]Alberta Respiratory Centre, Edmonton, AB, Canada.

Corresponding author: Adil Adatia (adatia@ualberta.ca)

Provenance: Submitted article, peer reviewed.

Author contributions: A. Adatia and J. Moolji conceptualised and designed the study. J. Moolji collected the data. A. Adatia and J. Moolji performed data analyses and interpretation. All authors had full access to all the data, and contributed to data analysis, and interpretation and writing of the manuscript.

Conflict of interest: A. Adatia reports grants from Octapharma AG; consulting fees from CSL Behring and Takeda; payment or honoraria for lectures, presentations, manuscript writing or educational events from CSL Behring and Takeda; and support for attending meetings from CSL Behring and Takeda, all disclosures made outside the submitted work. The remaining authors have nothing to disclose.

References

1 Kho SS, Lim KC, Muhammad NA, *et al.* Clinical and radiological outcomes of SARS-CoV-2 related organising pneumonia in COVID-19 survivors. *Med J Malaysia* 2023; 78: 131–138.
2 Petrov AA, Adatia A, Jolles S, *et al.* Antibody deficiency, chronic lung disease, and comorbid conditions: a case-based approach. *J Allergy Clin Immunol Pract* 2021; 9: 3899–3908.
3 Evans RA, Dube S, Lu Y, *et al.* Impact of COVID-19 on immunocompromised populations during the Omicron era: insights from the observational population-based INFORM study. *Lancet Reg Health Eur* 2023; 35: 100747.
4 Volk A, Covini-Souris C, Kuehnel D, *et al.* SARS-CoV-2 neutralization in convalescent plasma and commercial lots of plasma-derived immunoglobulin. *BioDrugs* 2022; 36: 41–53.
5 Upasani V, Townsend K, Wu MY, *et al.* Commercial immunoglobulin products contain neutralizing antibodies against severe acute respiratory syndrome coronavirus 2 spike protein. *Clin Infect Dis* 2023; 77: 950–960.
6 Dimala CA, Patel U, Lloyd B, *et al.* A case report of steroid-resistant cryptogenic organizing pneumonia managed with intravenous immunoglobulins. *Case Rep Pulmonol* 2021; 2021: 9343491.
7 Lyzwa E, Sobiecka M, Lewandowska K, *et al.* Prolonged SARS-CoV-2 infection and organizing pneumonia in a patient with follicular lymphoma, treated with obinutuzumab-challenging recognition and treatment. *Viruses* 2023; 15: 693.
8 Sansen PY, Coche E, Hainaut P, *et al.* Secondary organizing pneumonia associated with protracted COVID: A case series. *Infect Dis Now* 2024; 54: 104888.