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Successful treatment of prolonged COVID-19 with Bamlanivimab in a patient with severe B-Cell aplasia due to treatment with an anti-CD20 monoclonal antibody: A case report

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ABSTRACT

A 71-year-old female patient with B-cell depletion due to treatment with an anti-CD20 monoclonal antibody was admitted for worsening COVID-19. Overall, she had persistent viral shedding, worsening respiratory failure, and progressive pneumonia that did not improve despite dexamethasone and antibiotic therapy. After administration of bamlanivimab, a monoclonal antibody with high affinity for the receptor-binding domain of the SARS-CoV-2 spike protein, inflammatory markers rapidly decreased, SARS-CoV2 RT-PCR became negative, and the patient improved clinically and radiologically. In conclusion, we demonstrated successful treatment of prolonged COVID-19 in a patient with severe B-cell aplasia with a virus-neutralizing monoclonal antibody.

1. Introduction

The management of Coronavirus Disease 2019 (COVID-19) in immunocompromised patients can be very challenging due to prolonged infection and severe complications [1]. However, this group of patients represents a heterogeneous spectrum of different cellular and humoral immune deficiency disorders, which necessitates an individualized treatment strategy for COVID-19. SARS-CoV-2 anti-spike neutralizing antibody therapy is a promising approach that has not been adequately studied in immunocompromised patients [2]. Here, we report a case of severe COVID-19 in a patient with secondary severe B-Cell aplasia.

2. Case presentation

Three weeks prior to hospital admission, a 71 year old female patient was diagnosed with mild COVID-19 confirmed by a positive nasopharyngeal swab reverse-transcriptase–polymerase-chain-reaction (RT-PCR) test. Initially, she complained of cough and fever without dyspnea and had been managed as an outpatient for three weeks without COVID-19 specific therapy. She was finally hospitalized due to worsening cough, persistent fever up to 39 °C, and multiple syncopal episodes. One syncope episode was accompanied by slight head injury.

Abbreviations: BMI, body-mass index; CRP, C-reactive protein; ICU, intensive care unit; IL-2, interleukin 2; CT, computed tomography; COVID-19, Coronavirus Disease 2019; NK, natural killer; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; TNF-alpha, Tumor necrosis factor.

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On the day of admission [21 days after the first confirmation of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection] she complained of severe fatigue and malaise, inability to walk or to perform activities of daily living. There were no other symptoms in the review of systems (ROS).

The patient's medical history was notable for arterial hypertension and non-Hodgkin lymphoma (follicular lymphoma, initially grade 1–2), which had been diagnosed nine years ago in 2012. Initial treatment consisted of involved field radiation with 38 Gy of the cervical/mediastinal region leading to a partial remission. A laparoscopic biopsy of abdominal lymph nodes in 2013 confirmed disease recurrence and progression/transformation (FL grade 3A with areas of 3B/diffuse large B-cell lymphoma). She received six cycles of R-CHOP-21 (cyclophosphamide, doxorubicin, vincristine, and prednisone plus the recombinant anti-CD20 antibody rituximab, given every 21 days) leading to complete remission (CR) followed by Rituximab-maintenance every 8 weeks for two years. In 2017 another disease recurrence in the right inguinal region was treated with four cycles of systemic chemotherapy with Bendamustine together with the humanized anti-CD20 monoclonal antibody Obinutuzumab every eight weeks followed by atypical maintenance therapy with Obinutuzumab, given every eight weeks until December 2020 by her local hematologist. In order to counteract her B-cell aplasia and concurrent lack of immunoglobulins she also received subcutaneous IgG in irregular intervals. Concurrent medications included also Bisoprolol for treatment of arterial hypertension.

Body temperature at admission was 38.8 °C, heart rate 96 beats per minute, blood pressure 150/70 mm Hg, and oxygen saturation 96% while she was breathing room air. Weight was 66 kg and body-mass index (BMI) 24 gm/m². Physical examination was normal apart from a decreased general condition and bronchophony over the right superior lobe in the lung auscultation.

Routine laboratory tests at admission revealed mainly elevated inflammatory markers. Laboratory tests at admission and during hospital stay are listed in Table 1.

At admission, RT-PCR tests on nasopharyngeal swab were positive for SARS-CoV-2 and negative for influenza. Contrast enhanced computed tomography (CT) of the thorax (Fig. 1A) revealed mainly ground-glass opacities predominantly in the sub-pleural space in the right upper lung lobe. There were no signs of pulmonary embolism.

The patient was admitted to the isolation ward to initiate supportive therapy.

She had fever during the first night with temperature going up to 38.9 °C. The next day oxygen saturation went down to 90%, so supplemental oxygen therapy via nasal cannula at a rate of 2 L per minute was initiated and the patient was put on systemic corticosteroids (dexamethasone 6mg q.d.) for a total of ten days.

Table 1
Laboratory data and RT-PCR tests.

Variable	Reference Range, Adults	Laboratory tests on the respective days of hospitalization							
		Day 1 (Admission)	Day 9	Day 18	Day 21	Day 28 (Bamlanivimab Administration)	Day 31	Day 36 (discharge)	At follow-up in the outpatient clinic (14 days after discharge)
RT-PCR		+	+		+	+	–	–	–
Laboratory tests									
Hemoglobin (g/dl)	11.2–15.7	14	13	11	11	11	11	12	14
Hematocrit (%)	34.1–44.9	41	38	32	32	31	34	37	43
White-cell count (per μ l)	4000–10000	3800	3900	3000	3000	2800	3800	4000	6900
Differential count (per μl)									
- Neutrophils	1.6–7.1	1.97	2.82	2.15	2.15	1.97	–	–	3.87
- Lymphocytes	1.0–2.9	0.98	0.53	0.47	0.46	0.36	–	–	1.9
- Monocytes	0.2–0.6	0.63	0.30	0.15	0.15	0.17	–	–	1.0
- Eosinophils	1.0–6.0	0.03	0.00	0.04	0.04	0.07	–	–	0.07
- Immature granulocytes (%)	0–0.74	4.4	6.2	6.8	6.9	8.0	–	–	2.8
Platelet count (per μ l)	150000–400000	158000	175000	165000	181000	201000	337000	398000	250000
Creatinine (mg/dl)	0.50–0.90	0.49	0.46	0.37	0.42	0.37	0.54	0.50	0.7
CRP (mg/l)	\leq 5.0	70	68	159	101	126	28	13	1.7
Procalcitonin (ng/ml)	\leq 0.5	0.09	0.07	0.11	0.08	0.10	0.07	0.04	<0.02
D-dimer (ng/ml)	< 500	1418	1130	–	–	–	–	–	<150
Ferritin (ng/ml)	15–150	485	–	738	–	–	–	–	193
s-IL2-R (U/ml)	158–623	1335	–	1141	–	–	–	–	1077
IL-6 (pg/ml)	<7	68	–	61	–	–	–	–	5
B cells	/ μ l	absent	–	–	absent	absent	–	absent	absent
IgA (mg/dl)	70–400	58	–	–	40	43	47	53	55
IgG (mg/dl)	70–1600	392	–	–	282	296	323	355	370
IgM (mg/dl)	40–230	\leq 25	–	–	\leq 25	\leq 25	\leq 25	\leq 25	25

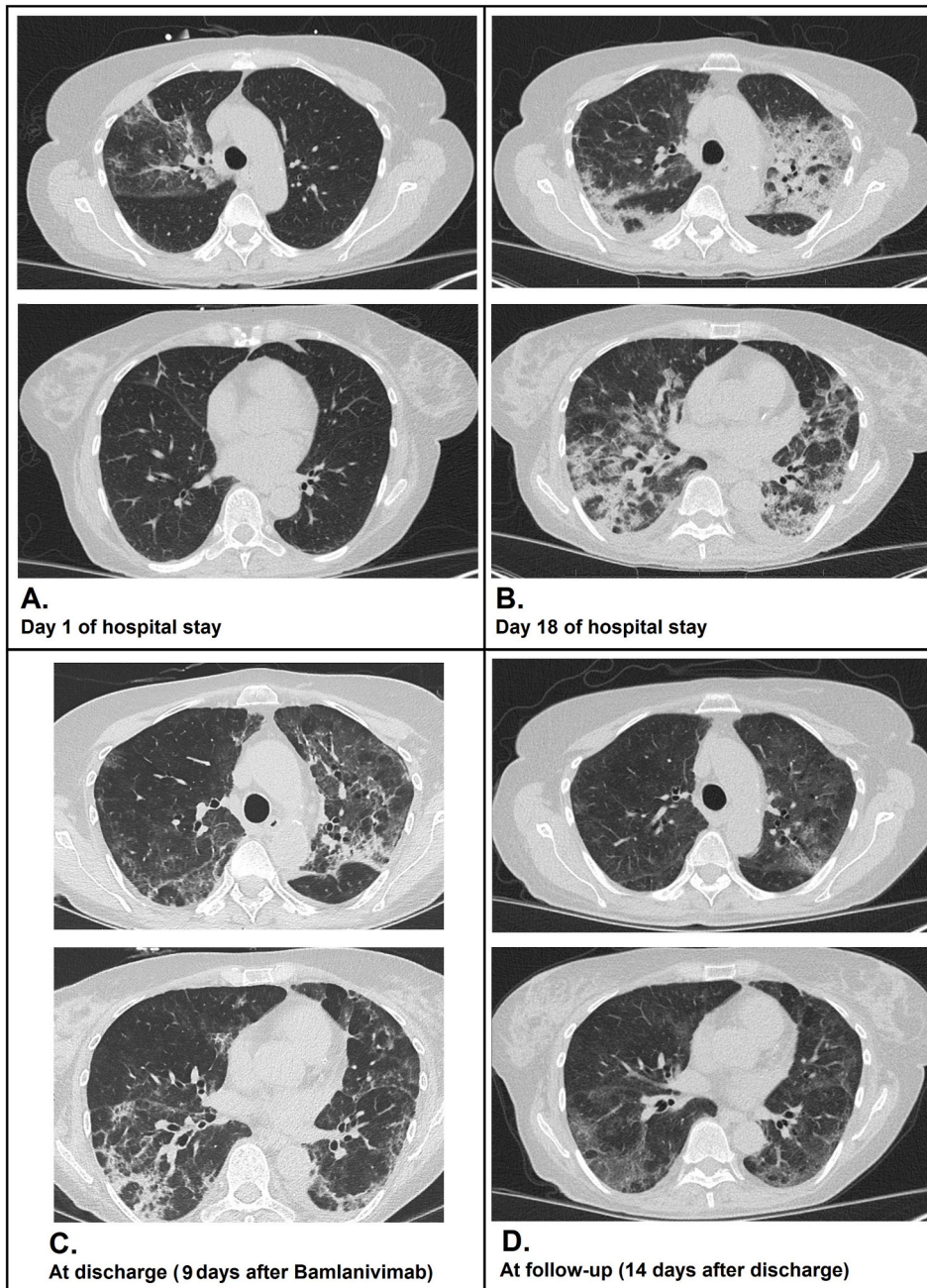


Fig. 1. Imaging studies of the chest.

In consideration of the patient's medical history, immunophenotyping of peripheral blood cells revealed mild leucopenia and a marked decrease across all lymphocyte subpopulations. Strikingly, B cells were completely absent ($0/\mu\text{L}$) due to subsequent treatment with two anti-CD20 monoclonal antibodies (Rituximab and Obinutuzumab) over the course of several years. B-cell quantification was repeated after one, four and five weeks with ongoing B-cell aplasia within peripheral blood. Accordingly, serum IgA (58 mg/dl [reference range: 70–400]), IgG (392 mg/dl [700–1600]) and IgM levels (<25 mg/dl [40–230]) were also markedly reduced without any improvement during her hospital stay.

The clinical situation was thereafter fluctuating, but malaise and respiratory failure persisted with worsening tendency and SARS-CoV-2 RT-PCR tests were still highly positive on days 6, 11, 18, 23 and 28 of hospital stay.

Eighteen days after hospital admission there was an accelerated deterioration, the patient's body temperature rose to $39,3^{\circ}\text{C}$ accompanied by an increase in CRP levels (up to 159 mg per liter, reference range $<0,5$ mg per liter), without an increase in serum procalcitonin (0.11 ng per milliliter, reference range $<0,5$ ng per milliliter). Malaise progressed and an increasing demand in supple-

mental oxygen was observed and the patient had to be monitored in the intensive care unit (ICU) for 24 hours. Empiric antibiotic therapy with Piperacillin/Tazobactam was initiated after obtaining blood and urine cultures. Low-dose chest CT scan revealed progression of lung opacities now involving all lobes of the lung and increasing consolidations of the lung parenchyma in the affected areas (Fig. 1B). All cultures of blood and urine were negative in hindsight. In the following 72 hours, C-reactive protein (CRP) levels and the patient's temperature were fluctuating.

The clinical picture and radiographic findings without improvement under antibiotic therapy, aroused concerns about the long persisting SARS-CoV2 infection, given the prolonged B-Cell depletion and disordered adaptive humoral immunity. After intensive discussion, the decision to initiate neutralizing antibody therapy against SARS-CoV-2 was made.

A single dose Bamlanivimab (700 mg) (LY-CoV555), a monoclonal antibody with high affinity to the receptor-binding domain of SARS-CoV-2 spike protein, was administered 4 days after the patient was back from ICU while she showed no clinical improvement and was still needing supplemental oxygen therapy with 3 l/min. On the day of Bamlanivimab application (28 days after admission, 49 days after the first positive SARS-CoV-2 test overall), SARS-CoV-2 RT-PCR test was still highly positive, and inflammatory markers were still high (Table 1). After administration of Bamlanivimab, the inflammatory markers began to decrease rapidly (CRP going down from 120 mg/liter to 28 mg/liter on the 3rd day, and 13 mg/liter on the 5th day following administration of Bamlanivimab) and RT-PCR test converted to be negative (on the 3rd and 4th days after administration of Bamlanivimab, hence on the 31st and 32nd days of hospital stay). Concurrently the patient showed a marked improvement in clinical status; subsequently supplemental oxygen therapy could be discontinued on day 4 after Bamlanivimab. Further supporting the notion of rapid overall improvement following administration of Bamlanivimab, CT imaging at discharge (Day 9 after Bamlanivimab administration) showed clear improvement of the consolidating lung opacities (Fig. 1C). Importantly peripheral blood still showed persistent B-cell aplasia and reduced immunoglobulin levels (Table 1), suggesting that clinical and laboratory improvements were mostly due to the boost of humoral immunity via administration of a monoclonal antibody against SARS-CoV-2.

The patient presented to our pulmonology outpatient clinic 14 days after discharge. She reported a clear improvement of symptoms and a restored mobility, however with remaining moderate fatigue symptoms. SARS-CoV-2 RT-PCR was negative. Peripheral blood showed ongoing absence of B-cells and specific antibodies to SARS-CoV-2 (SARS-CoV-2 IgG antibodies against the nucleoprotein) were also negative. Pulmonary function tests showed normal lung volumes, however with a slightly reduced diffusion capacity. A low dose CT showed regressive opacities of the lungs, without any consolidation (Fig. 1D).

3. Discussion and conclusions

Over the course of roughly 5 weeks (35 days), a patient with B-cell aplasia showed prolonged respiratory failure type I (hypoxic), weaning and waxing inflammation and a lack of improvement despite dexamethasone and broad-spectrum antibiotic therapy.

Defining the leading problem in such a worsening patient with COVID-19 can be very challenging and requires a good understanding of the immune response in each phase.

First of all, the patient showed a prolonged SARS-CoV2 infection confirmed by persistently highly positive RT-PCR tests over a period of more than five weeks, which represents a well-known problem in severely immunocompromised patients, as they can keep shedding virus for more than 2 months [1].

Secondly, secondary infection was considered as differential diagnosis in our patient though this does not appear to be a common complication of COVID-19 [3,4]. Nevertheless, as the clinical features of COVID-19 are sometimes difficult to distinguish from bacterial pneumonia, especially when there are areas with consolidation on chest CT scan, an empiric antibiotic therapy seems to be appropriate in such cases. However, the normal procalcitonin values, the negative microbiologic cultures, and the lack of improvement under empirical broad-spectrum antibiotic therapy were argumentative for the absence of bacterial superinfection.

Thirdly, this patient consistently presented with signs and markers of a hyperinflammatory status [persistent fluctuating fever, elevated D-dimer, CRP, ferritin, soluble interleukin 2 (IL-2) receptor, IL-6 and Tumor necrosis factor (TNF)-alpha] (Table 1). The immune response induced by SARS-CoV-2 seems to be complex and is probably multifactorial and synergetic. The innate immunity plays a crucial role, which includes natural killer (NK) cell functionality, complement activation, and interferon production [5]. But also, the adaptive immune response, in terms of humoral and cell-mediated immunity, contributes to the fight against the virus [5]. Frequently, patients with severe COVID-19 show an exuberant inflammatory response, with persistent fever, elevated inflammatory markers (e.g., D-dimer, ferritin), and elevated proinflammatory cytokines [6–8].

Besides that, cardiac and cardiovascular complications as well as venous thromboembolism and pulmonary embolism are common among patients with COVID-19 and should be considered in every patient with worsening respiratory status [9–13]. However, a detailed work-up did not reveal cardiac or thromboembolic complications. According to current guidelines, the patient was treated from the first day of her hospital stay with prophylactic-dose low molecular weight (LMW) heparin.

B-Cell depletion and severe hypo-gammaglobulinemia, due to the great capacity for B-cell depletion of Obinutuzumab and other monoclonal B-cell antibodies could compromise antiviral immunity [14,15]. The potential risks of hypo-gammaglobulinemia secondary to anti-CD20 therapy are very justified concerns in the time of the current pandemic [15]. Mehta et al. suggested that convalescent serum could be a potential therapeutic option for these patients who develop severe COVID-19 [15], though clinical trials are still lacking. Bamlanivimab binds to the receptor binding domain of spike protein of SARS-CoV-2, blocking the spike protein's attachment to human ACE2 receptor [16]. However, SARS-CoV-2 anti-spike monoclonal antibodies are not recommended for hospitalized patients with COVID-19 requiring high flow oxygen therapy or mechanical ventilation [16]. In contrast, in an unpublished report of an open-label randomized trial by the RECOVER Collaborative Group, administration of an anti-spike neutralizing SARS-CoV-2 monoclonal antibody cocktail in hospitalized patients resulted in a significant reduction in 28-day mortality among patients who

were seronegative at baseline [2]. Of note, about 20% of patients in the last-mentioned study were treated with non-invasive ventilation at baseline. Consecutively, this kind of therapy should be considered in the treatment of COVID-19 in immunocompromised patients with B-cell deficiency leading to uncontrolled viral replication, even if respiratory support is required. Nevertheless, the decision to administer SARS-CoV-2 anti-spike neutralizing antibody therapy to an immunocompromised patient should be made after a multidisciplinary discussion and a detailed informed consent by the patient.

In conclusion, we have shown that prolonged COVID-19 in severe B-cell aplasia can be successfully treated with a single dose of Bamlanivimab (LY-CoV555), which has the ability to terminate prolonged viral shedding in the upper airways, alleviate hyperinflammatory status, ameliorate lung inflammation, and likely improve prognosis in this patient population.

Ethics approval

The protocol for this study was approved by the local ethics committee (EK 080/20). All investigations were performed in accordance with the ethical standards of the latest revision of the Helsinki Declaration.

Consent for publication

Written informed consent was obtained from the patient.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

Acquisition, analysis, and interpretation of Data: A.D., T.M., J.S., M.D., J.P.. Drafting the work and revising it critically for important intellectual content: A.D., T.M., M.D., J.P.. Final approval: A.D., T.M., M.D., J.P.. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: A.D., T.M., M.D., J.P..

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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