Case Report

Progression of COVID-19 in a Patient on Anti-CD20 Antibody Treatment: Case Report and Literature Review

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Accumulating evidence suggests that anti-CD20 treatments are associated with a more severe course of COVID-19. We present the case of a 72-year-old woman treated with the B-cell-depleting anti-CD20 antibody rituximab for seropositive rheumatoid arthritis with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causing a clinical relapse more than 4 weeks after the first manifestation. Persistently positive reverse transcription polymerase chain reaction (RT-PCR) results along with a drop in cycling threshold (Ct) values, in addition to recovery of identical viral genotype by whole genome sequencing (WGS) during the disease course, argued against reinfection. No seroconversion was noted, as expected on anti-CD20 treatment. Several other case reports have highlighted potentially fatal courses of COVID-19 associated with B-cell-depleting treatments.

1. Introduction

Immunocompromised patients are at risk for severe disease courses of COVID-19 and prolonged viral shedding [1]. At the beginning of the pandemic, little was known about COVID-19 patients on anti-CD20 antibody treatment like rituximab, causing prolonged B-cell depletion. However, there is now growing evidence that rituximab is associated with adverse outcomes of COVID-19 infection [2]. Here, we report the intriguing case of a 72-year-old woman receiving rituximab for seropositive rheumatoid arthritis, who experienced a relapsing course of COVID-19. We performed a literature search for case descriptions, including patients with COVID-19 on anti-CD20 antibody treatment.

2. Case Presentation

A 72-year-old woman was tested positive for SARS-CoV-2 by RT-PCR in a nasopharyngeal swab on the 4th of February 2021. Her past medical history was remarkable for seropositive rheumatoid arthritis and connective tissue disease-associated interstitial lung disease, for which she received rituximab treatment biannually. Five months before COVID-19 onset, she had received her last dose. Other comorbidities included pulmonary arterial hypertension, coronary artery disease, and atrial fibrillation. At the early stage of the national vaccination campaign, our patient had not been vaccinated. Twelve days later, she was hospitalized in another hospital due to respiratory failure. In addition to the known interstitial lung disease, chest computed tomography revealed new bilateral ground glass opacities consistent with COVID-19 infiltrates. The patient received supplemental oxygen, dexamethasone, and a 10-day course of remdesivir. Following her gradual improvement, a nasopharyngeal SARS-CoV-2 antigen test turned out negative on day 22 and follow-up Ct values of RT-PCR were increasing; thus, isolation precautions were stopped. On day 27, the patient was discharged to inpatient pulmonary
rehabilitation. Thirty-three days after diagnosis, she was admitted to our hospital because of relapsing dyspnea, productive cough, and fever, along with respiratory failure requiring nasal high-flow oxygen therapy and intensive care monitoring. Differential diagnoses included bacterial pneumonia, reinfection with a SARS-CoV-2 mutant, or a relapse of preexisting COVID-19. Inflammatory markers were again elevated, and a computed tomography scan was unchanged (Table 1).

We started treatment with broad-spectrum antibiotics, but sputum analysis and Legionella antigen in the urine were negative. Further invasive measures like mechanical ventilation were not pursued, according to the patient’s wishes. 35 days after the first positive RT-PCR test, the patient died from worsening respiratory failure. Autopsy revealed acute diffuse alveolar damage with hyaline membranes due to COVID-19 in addition to underlying interstitial lung fibrosis.

Follow-up of Ct values of RT-PCR during the second course of disease showed a clear drop, which was indicative of a recurrence of previous COVID-19 (Figure 1).

To rule out reinfection by a mutant, we performed whole genome sequencing of SARS-CoV-2 of the first and last nasopharyngeal swab isolates (days 0 and 35, respectively). Viral genotypes showed identical sequence patterns, and mutational analysis for N501Y and E484K was negative. Furthermore, SARS-CoV-2 serology was not able to detect IgG or IgM antibodies. These findings led to the conclusion that our patient’s clinical deterioration was due to a prolonged and relapsing course of COVID-19.

### Table 1: Timeline of clinical and laboratory data during hospitalisation.

| Days after symptom onset | Day of admission to the other hospital, day 12 | Day of discharge from the other hospital, day 25 | Day of admission to our hospital, day 33 | Day of death, day 35 |
|--------------------------|-----------------------------------------------|-----------------------------------------------|------------------------------------------|---------------------|
| SARS-CoV-2 PCR (nasopharyngeal swab) | Positive | Positive | Positive | Positive |
| Ct value 23.0 | 31.4 | 18.2 | 15.2 |
| Heart rate (beats/min) 95 | 65 | 126 | 135 |
| Blood pressure (mmHg) 137/87 | 183/89 | 124/80 | 179/83 |
| Fever (°C) 36.6 | 36.4 | 38.1 | 38.2 |
| Breathing rate (breaths/min) 20 | 23 | 25 | 32 |
| SpO2 (%) 99 | 94 | 100 | 89 |
| FiO2 (%) 25 | 21 | 80 | 80 |
| White blood cell count (x10^9/l) 5.5 | 19.2 | 17.2 | 14.4 |
| C-reactive protein (mg/l) 152 | 5 | 220 | 224 |
| Ferritin (mcg/l) | | | 3446 |
| D-dimer (mg/l) | | | 3.22 |
| Lactate dehydrogenase (U/l) 550 | | | 793 |

SARS-CoV-2 in nasopharyngeal swabs along with either a benign or adverse outcome is a notable feature, independent of the underlying disease. To our knowledge, only one case report has provided whole genome sequencing to rule out reinfection during a prolonged clinical course [2]. This was an important differential diagnosis in our case, since our patient’s clinical worsening occurred during the epidemiological situation of a nationwide third wave of COVID-19 with upcoming variants of concern. The substantial drop in Ct values during the second course of disease could not be explained by preanalytical sampling differences [18], and reinfection was ruled out by genetically identical viral variants of the first and last isolate. A possible hypothesis explaining the initial decrease in viral load, based on in vitro data but not confirmed by clinical studies [19, 20], could be that remdesivir reduced viral replication, but after stopping antiviral treatment, viral clearing was not possible due to an insufficient antibody response and re-emerging viral replication led to a clinical relapse. The potentially severe COVID-19 course under rituximab suggests that, in addition to cellular immunity, humoral immunity plays an important role. Therefore, monitoring of immunocompromised patients with B-cell depletion after stopping antiviral treatment is crucial, and repeat quantitative RT-PCR, in addition to clinical assessment, might be useful to detect re-emerging viral replication and infectivity.

Our single case description may not be generalizable to other immunocompromised populations. However, cases with relapsing and prolonged courses have been attributed to reduced viral clearance due to the lack of anti-SARS-CoV-2 antibody production by prolonged B-cell depletion after anti-CD20 therapy, as was the case in our patient [3, 5, 7, 10, 17].

This case also highlights the infection control challenges in the handling of this special population with persistent shedding of potentially viable virus.

In conclusion, caution should be taken in patients with anti-CD20 antibody treatment, as they can acquire SARS-
Table 2: Literature search of patients with COVID-19 and receiving immunosuppressive treatment including rituximab.

| Study                  | Number of patients | Age (years) | Gender | Underlying disease                                      | Repetitive positive respiratory sample by RT-PCR<sup>a</sup> | Duration of symptoms (days) | Cumulative hospital-days (days) | Outcome |
|------------------------|--------------------|-------------|--------|--------------------------------------------------------|-------------------------------------------------------------|-----------------------------|---------------------------------|---------|
| Avouac et al. [2]      | 63                 | 59<sup>d</sup> | 25 males 38 females | Inflammatory rheumatic and musculoskeletal diseases | NA                                                          | NA                           | 13<sup>d</sup>                    | 13/63 died |
| Baang et al. [3]       | 1                  | 60          | Male   | Mantle cell lymphoma                                     | Yes                                                         | NA                           | 6                               | Survived |
| Sepulcri et al. [4]    | 1                  | 60–70       | Male   | Mantle cell lymphoma                                     | Yes                                                         | 271                          | 268                             | Died    |
| Lancman et al. [5]     | 1                  | 55          | Female | B-cell lymphoma                                           | Yes                                                         | 55<sup>c</sup>              | 40<sup>c</sup>                   | Survived |
| Choi et al. [6]        | 1                  | 45          | Male   | Antiphospholipid antibody syndrome                        | Yes                                                         | NA                           | 5                               | Died    |
| Friedman and Winthrop [7]| 1          | 30          | Female | Granulomatosis with polyangiitis                         | Yes                                                         | Several weeks                | NA                              | Survived |
| Leipe et al. [8]       | 1                  | 63          | Male   | Granulomatosis with polyangiitis                         | NA<sup>b</sup>                                              | 32                           | 30                              | Survived |
| Tepasse et al. [9]     | 2                  | 65          | Male   | Cerebral diffuse large B-cell lymphoma                   | NA<sup>b</sup>                                              | 23                           | 22                              | Died    |
|                        | 66                 | Male        | Mantle cell lymphoma                                     | NA<sup>b</sup>                                              | 30                           | 26                              | Died    |
| Benucci et al. [10]    | 1                  | 60          | Female | Polymyositis and Sjögren syndrome                        | Yes                                                         | 63                           | 63                              | Survived |
| Yasuda et al. [11]     | 1                  | 61          | Female | Follicular lymphoma                                       | Yes                                                         | 59<sup>e</sup>              | 59                              | Survived |
| Guilpain et al. [12]   | 1                  | 52          | Female | Granulomatosis with polyangiitis                         | Yes                                                         | 29                           | 25                              | Survived |
| Schulze-Koops et al. [13]| 2            | 71          | Male   | Rheumatoid arthritis                                     | No                                                          | 14                           | 12                              | Died    |
|                        | 80                 | Female      |        | Rheumatoid arthritis                                     | No                                                          | 17                           | 17                              | Died    |
| Kos et al. [14]        | 1                  | 72          | Male   | Nodal marginal zone lymphoma                              | Yes                                                         | 31<sup>c</sup>              | 24                              | Survived |

<sup>a</sup> RT-PCR: Reverse Transcription Polymerase Chain Reaction

<sup>b</sup> NA: Not Available

<sup>c</sup> Died

<sup>d</sup> Survival

Figure 1: Timeline of cycling threshold (Ct) values during disease course.
CoV-2 infection despite vaccination because of the lack of antibody emergence and prolonged or relapsing disease courses have to be expected.

**Data Availability**

The data supporting the results are available, on request, from the authors.

**Consent**

Consent was obtained from the patient’s husband.

**Conflicts of Interest**

The authors declare that there are no conflicts of interest.

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