

CASE REPORTS

A unique COVID-19 case

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ABSTRACT

We present the case of a patient with granulomatosis with polyangiitis (GPA) treated with rituximab, who was diagnosed with coronavirus disease 2019 (COVID-19). Following an index hospitalization with apparent resolution of the infection, the patient was readmitted with clinical deterioration. While repeat serial real-time polymerase chain reaction (rt-PCR) from nasopharyngeal swabs were negative, a bronchoalveolar lavage (BAL) sample demonstrated persistent COVID-19 to be the etiologic factor. Administration of convalescent plasma led to remarkable recovery.

Key Words: COVID-19, SARS-CoV-2, GPA, Rituximab, Convalescent plasma

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) poses great diagnostic and therapeutic challenges. The presence of viral ribonucleic acid (RNA) in nasopharyngeal swabs is the standard of diagnosis, although it has limitations in regards to sensitivity. The disease course in immunocompromised patients and the contribution of immunosuppressive therapy, in terms of disease severity, duration and recovery, remain to be elucidated.

We herein present a case of COVID-19 in an immunocompromised patient with granulomatosis with polyangiitis (GPA), receiving maintenance therapy with rituximab. The patient presented a prolonged disease course, complicated by several diagnostic difficulties, which may have been influenced by

the underlying disease and immunocompromised state. We describe the clinical course, laboratory findings, diagnostic dilemmas, and treatment.

2. CASE PRESENTATION

The patient is a 43-year-old male with GPA, diagnosed 2 years prior to the current admission. The disease presented with otolaryngologic, pulmonary, and renal manifestations, combined with high p-anti-neutrophil cytoplasmic antibody (pANCA) titers. He was initially treated with corticosteroids, and later sequentially with oral and intravenous cyclophosphamide. While disease remission was achieved, renal damage was partially irreversible, with stable chronic renal failure, and an estimated effective glomerular filtration rate

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(eGFR) of 30 mL/min. Following these events, the patient was started on a maintenance regimen of rituximab, receiving two doses of 500 mg. He was followed according to

the MAINRITSAN-2^[1] protocol. His disease was quiescent thereafter, and he was weaned off steroids.

Table 1. Main lab values, upon first and second admissions

	Value (First admission)	Value (Second admission)
WBC count, / μ l (4050-11,840)	4,000	2,300
Lymphocyte count, / μ l (1,170-3,450)	200	200
Hemoglobin, g/dl (12.4-16.1)	10.5 (baseline)	9.4
Creatinine, mg/dl (0.56-1.02)	3.9 (baseline)	3.4
CRP, mg/dl (0-0.50)	1.4	4
Ferritin, ng/L (10-291)	-	677
IgA, mg/dl (70-400)	163 (25 days after Rituximab)	58.6 (31 days after Rituximab)
IgM, mg/dl (40-230)	148	20.4
IgG, mg/dl (700-1,700)	824	520

Note. Normal range values appear in brackets in the first column. CRP: C-reactive protein, WBC: White blood cell

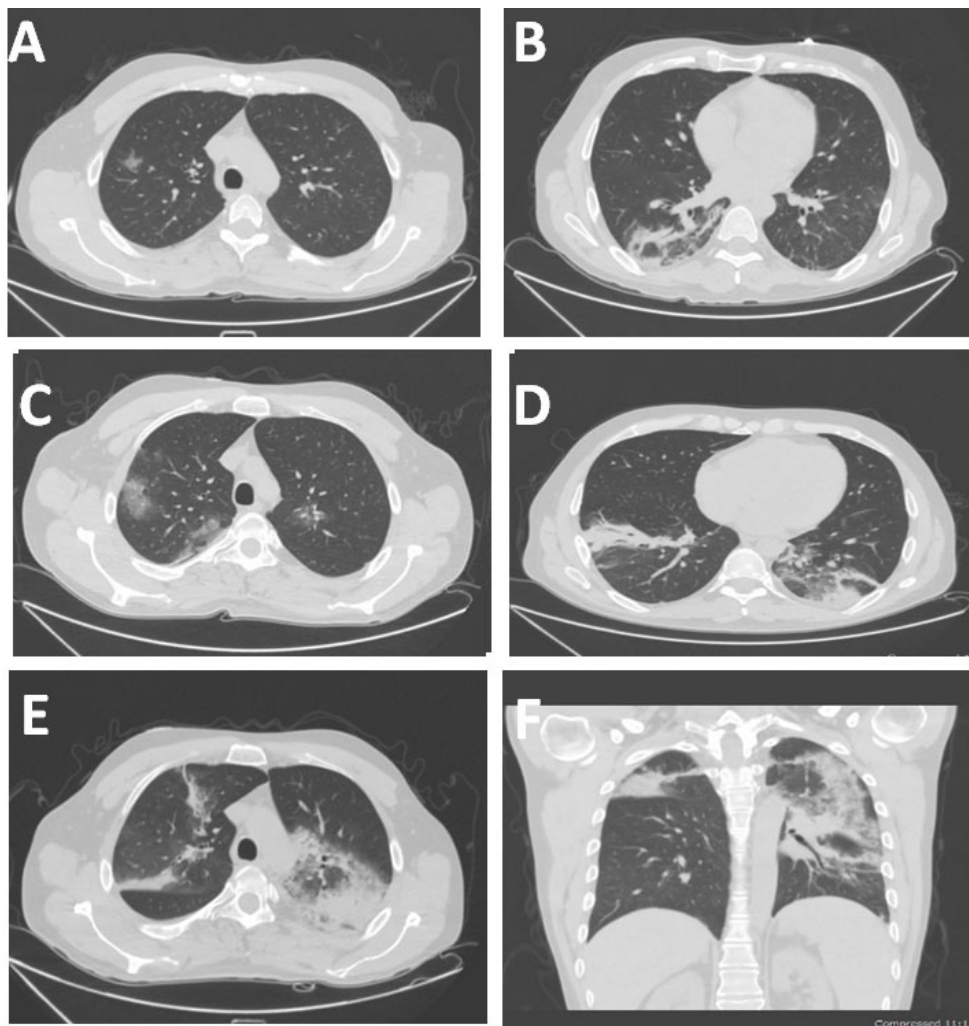


Figure 1. Unenhanced axial (A-E) and coronal (F) computed tomography (CT) images of our patient, showing: (A, B) A single small peripheral rounded GGOs (A), and right lower lobe consolidation (B) on admission. (C, D) Bilateral multifocal upper lobes GGOs (C), with bibasilar consolidations (D), on day 12. (E, F) Segmental consolidations without significant GGOs, on day 19 (Image F being coronal). (CT- computed tomography, GGOs- ground glass opacities)

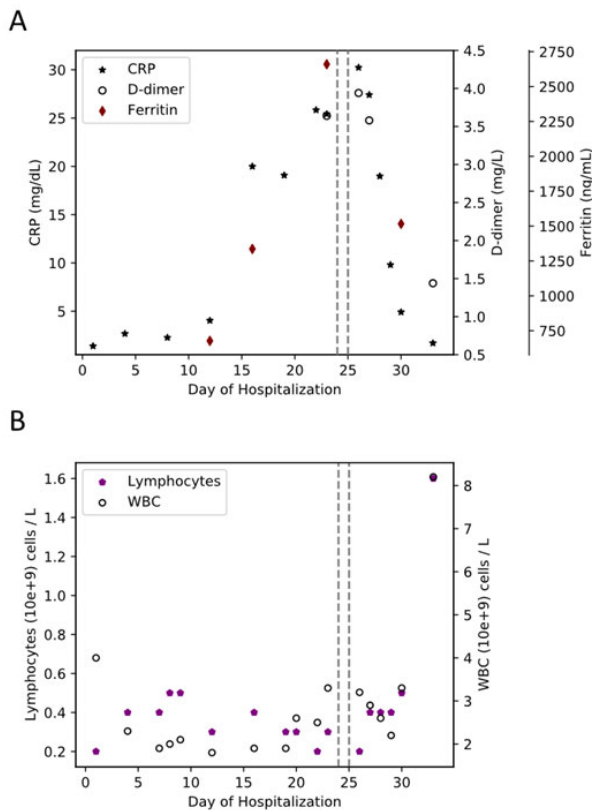


Figure 2. Temporal dynamics of acute phase reactants and cell counts

3 weeks prior to his admission, the patient started to suffer from myalgias, low-grade fever, and cough. Several nasopharyngeal PCR swabs for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during that time were all negative. After resolution of his complaints, which were attributed to a mild viral infection, the patient received a third, previously scheduled, 500 mg rituximab dose. A few days thereafter, the symptoms reappeared. His general physician, considering bacterial pneumonia as the likely etiology, started antibiotic therapy. In light of clinical worsening, the patient presented to the emergency department, suffering from fever and malaise. On admission, he was pale and mildly tachypneic, but with otherwise normal vital signs, including preserved oxygen saturation on room air. Physical examination revealed bronchial breath sounds over the right lung fields. Laboratory findings showed lymphopenia, anemia (stable compared to previous tests and attributed to chronic renal failure), and a mildly elevated C-reactive protein (CRP), as shown in Table 1. While chest x-ray displayed no gross findings, high-resolution computed tomography (HRCT) revealed peripheral oval ground glass opacities (GGOs), predominantly in the right upper lobe, and alveolar consolidation in the right lung base (see Figure 1 A, B). At

this point, a nasopharyngeal PCR swab for SARS-CoV-2 returned positive, and the patient was admitted to the designated COVID-19 ward. National early warning score 2 (NEWS2) 2^[2] score on admission was 2.

Clinically, the patient's fever persisted, up to 38°C. He had no signs of respiratory distress, and his blood pressure and oxygen saturation were normal. Lab tests were significant for leukopenia and lymphopenia. He was treated with intravenous fluids and antipyretics. Following defervescence, and in light of the benign course, the patient was discharged to a designated COVID-19 isolation hotel after an uneventful hospital stay. The next day, he was readmitted due to reappearance of fever, malaise and shortness of breath. Laboratory findings showed elevated inflammatory markers and leukopenia, as shown in Table 1. He was started on hydroxychloroquine (as per the accepted practice at the time) and another HRCT was preformed (on day 12 after index presentation), revealing worsening multifocal pneumonia (see Figure 1 C, D). By day 16, three nasopharyngeal swabs were performed – all negative for SARS-CoV-2 - and the patient was transferred to the general medical ward. In the ward, his fever persisted, and he developed worsening dyspnea, tachypnea, and desaturation (continuously requiring 4 L/min oxygen by nasal cannula). His CRP levels continued to rise, peaking at 20 mg/dl. Considering his repeatedly negative SARS-CoV-2 swabs, alternative infectious and non-infectious etiologies were entertained, and empiric antibiotic treatment with piperacillin-tazobactam was started for presumed hospital acquired pneumonia. Concurrently, a broad microbiologic investigation was carried out, consisting of serologic and PCR tests for a wide variety of infectious agents, including Epstein Barr virus (EBV), cytomegalovirus (CMV), mycoplasma pneumoniae, treponema pallidum, legionella pneumophila, and human immunodeficiency virus (HIV) – all returned negative. c-ANCA and p-ANCA titers were within normal levels. Meanwhile, a third HRCT was performed, showing segmental consolidations without significant GGOs (see Figure 1 E, F). Reported at this time, a SARS-CoV-2 IgG serological test was negative. Considering the fruitless work-up, and in light of the ongoing clinical deterioration, a bronchoscopy with bronchoalveolar lavage (BAL) was done. Gram stain and microbial cultures from the BAL were negative, as were acid fast and silver stains. To our surprise, SARS-CoV-2 PCR from the BAL was positive. The patient was transferred back to the COVID-19 ward. Notably, immunoglobulin levels at this time were low, in contrast to those reported during the first admission, as shown in Table 1.

In the COVID-19 ward, in an attempt to ameliorate this apparently prolonged infection, and in light of the hypogam-

maglobulinemia, the patient was treated with convalescent plasma. He received two doses (total 400 ml), on days 23 and 24 of his hospital stay. Soon thereafter, he showed remarkable improvement, with resolution of his respiratory symptoms, decline in inflammatory markers, and raise in lymphocyte counts (see Figure 2 for temporal dynamics of lab parameters). The patient was discharged in good condition, 32 days after his initial presentation.

3. DISCUSSION

In this paper we present a unique case, reflecting several aspects of the clinical and diagnostic challenges posed by the COVID-19 pandemic.

Several diagnostic conundrums faced by clinicians are illuminated. To date, the diagnosis of COVID-19 is based mainly on rt-PCR performed on nasopharyngeal swabs. This test, however, has several sensitivity limitations. Recent data suggest that sample test accuracy may be influenced by the time from exposure.^[3] Other data propose that samples obtained from lower respiratory secretions (i.e. BAL or sputum) have greater sensitivity for diagnosis.^[4] It remains possible that PCR positivity "migrating" to BAL positivity reflects progression to lower airway disease. Whether underlying immunosuppression may impact these methods of diagnosis is an unanswered question.

Previous publications have questioned the need for the discontinuation of immunomodulatory medications in patients diagnosed with, or exposed to, COVID-19.^[5,6] The decision is likely to be influenced by the activity of the underlying disease and the mechanism of action of the immunosuppressive therapy. In the case of rituximab, B cell death is induced via direct cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular cytotoxicity, leading to B-cell depletion. While this was initially estimated to last for 6 to 9 months, later studies showed a more prolonged

effect. The B cell depletion, with the resultant hypogammaglobulinemia, remain risk factors for infection.^[7] The COVID-19 duration in our patient was longer than in previously reported cases in large cohorts.^[8] This could be attributed to the immunosuppression induced by rituximab. Whether the ultimate improvement in the clinical and laboratory characteristics could be linked to the administration of convalescent plasma remains unclear. Although several studies have showed post-transfusion viral elimination, besides clinical and radiological improvement,^[9-13] a recent randomized controlled trial demonstrated no statistically significant benefit from adding convalescent plasma to standard care in severe or life-threatening COVID-19 cases.^[14]

In summary, our case emphasizes the complexity of diagnosing and treating immunocompromised patients suffering from COVID-19. Data regarding the disease course in such patients, and the effectiveness of available therapies, are lacking.

We believe that several aspects of our case, including the disease course in a GPA patient under rituximab therapy, the importance of BAL in diagnosing clinically active but swab-negative disease, and the satisfactory response to treatment with convalescent plasma, may help illuminate some outstanding questions for clinicians. Until large trials provide hard evidence, shared clinical experiences may help guide patient care. In particular, we hope our case will alert physicians to the possibility of prolonged and atypical disease manifestations in immunosuppressed patients.

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CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

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