LETTER TO EDITOR

Resolution of Persistent COVID-19 After Convalescent Plasma in a Patient with B Cell Aplasia

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To the Editor,

We read with interest the report from London et al. regarding the efficacy of convalescent plasma in the treatment of severe COVID-19 in two patients with primary immunodeficiencies [1]. Herein, we highlight our experience of using remdesivir and convalescent plasma to treat persistent symptomatic COVID-19 in a patient with secondary immunodeficiency following long-term rituximab treatment.

Case Report

A 57-year-old lady presented to the emergency department on 16/4/2020 with shortness of breath, a 2-week history of dry cough, pyrexia (38.4 °C), and raised inflammatory markers. Chest radiography demonstrated bilateral and lower-zone peripheral air space opacities; however, she was not hypoxic. She had a 13-year history of anti-CCP seropositive rheumatoid arthritis, previously treated with glucocorticoids, disease-modifying anti-rheumatic drugs, etanercept, and, most recently, 6-monthly rituximab infusions commenced in 2014. Her last dose of rituximab was on 13/3/2020, approximately 3 weeks prior to the onset of symptoms. Serial immunoglobulin measurements are shown in Fig. 1a. The patient had

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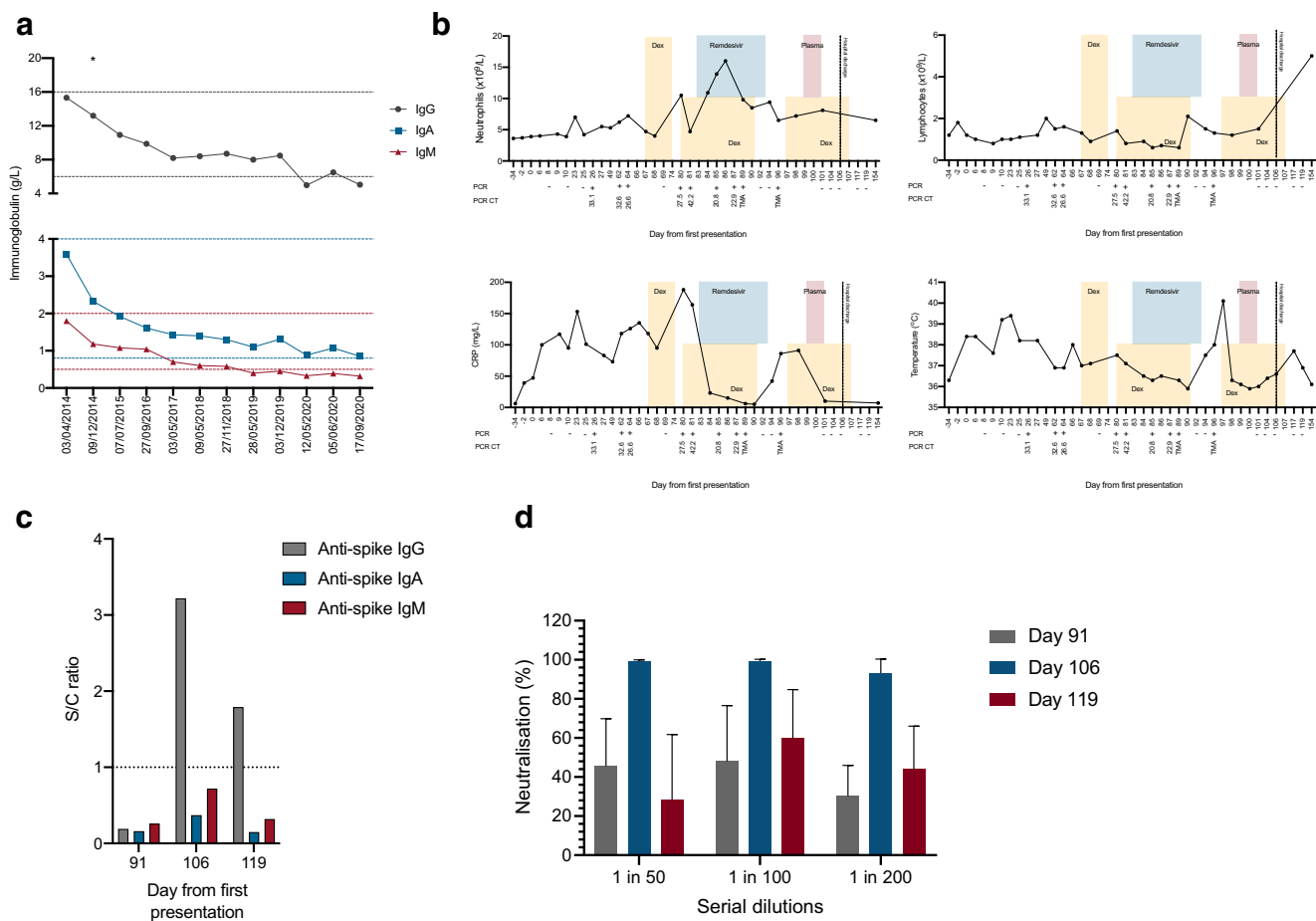
previously suffered from intermittent lower respiratory tract infections with fully sensitive *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae* previously grown in the sputum, despite protective IgG antibody concentrations in 8 out of 12 measured pneumococcal serotypes (Supplementary Table 1).

A diagnosis of likely COVID-19 was made, but not proven by polymerase chain reaction (PCR) studies; the patient was discharged with broad-spectrum, oral antibiotics but re-represented 8 days later with persistent pyrexia (39.2 °C), cough, dyspnoea, and new diarrhea and vomiting. Inflammatory markers remained elevated and she was admitted for treatment with intravenous antibiotics and fluids. Three nasopharyngeal swabs taken within the first 3 days of admission returned negative results; however, radiological progression suggested ongoing viral pneumonia; SARS-CoV-2 RNA was first detected in a sputum sample on day 25 and subsequently found on multiple nasopharyngeal swabs between May and July 2020.

Between May and July 2020, she was re-admitted to the hospital on four occasions with similar symptoms, increasing oxygen requirements (peak oxygen requirements 4 L via nasal cannula to achieve peripheral oxygen saturation of 96%; desaturation to 82% on room air on exertion) and progressive radiological changes (Supplementary Figure 1). Blood cultures, urine cultures, sputum cultures, sputum mycobacterial PCR, and virology for cytomegalovirus and Epstein-Barr virus undertaken during these admissions did not identify another concurrent infection. During these admissions, she received three separate courses dexamethasone (6 mg once daily, orally; one 7-day course; two 10-day courses) and one course of remdesivir (200-mg loading dose followed by 100 mg once daily, 10 days, intravenously). Monotherapy with dexamethasone achieved little objective change in physiological and biochemical parameters of infection but treatment with intravenous remdesivir was associated with a dramatic reduction in C-reactive protein (Fig. 1b). Twenty-four

Fig. 1 a Serial serum IgG (gray), IgA (blue), and IgM (red) measurements over time. Normal ranges are shown by dotted lines. Asterisk "*" represents date rituximab was initiated. b Changes in peripheral blood neutrophil count, lymphocyte count, C-reactive protein, and temperature over the time course of disease relative to pharmacological treatments received. Time course is relative to the first presentation on 16/4/2020. c Level of serum IgG, IgA, and IgM anti-SARS-CoV-2 trimeric spike glycoprotein antibodies were measured before and after treatment with convalescent plasma. Results are expressed as a signal to the cutoff calibrator ratio with the dotted line representing the cutoff for positivity. d In vitro SARS-CoV-2 neutralizing activity of serum from the patient before (day 91) and after (day 106 and day 119) the administration of convalescent plasma. Dex, dexamethasone; PCR, polymerase chain reaction; CT, cycle threshold; TMA, transcription-mediated amplification

hours after the cessation of remdesivir, a rebound increase in CRP and temperature was observed suggestive of a release of suppression of viral replication; SARS-CoV-2 RNA remained detectable following nasopharyngeal swabbing. Despite prolonged PCR positivity, anti-spike and anti-nucleocapsid SARS-CoV-2 antibodies were not detectable in the patient's serum by mid-July 2020 secondary to ongoing, complete, peripheral B cell aplasia. On day 99, the patient received two units of convalescent plasma (275 mL/unit, units were centrally pre-screened by the NHS Blood Transfusion Service for a SARS-CoV-2 neutralizing antibody titer greater than 1:100). Convalescent plasma was well tolerated with rapid symptomatic improvement, reduction in inflammatory markers, and defervescence.

Following the administration of convalescent plasma, SARS-CoV-2 PCR was not detected on seven consecutive swabs taken between day 101 and day 119. IgG but not IgA or IgM antibodies directed against the spike protein remained detectable in the patients' serum 3 weeks following administration of the plasma product (Fig. 1c). A serum sample taken 7 days after the administration of convalescent plasma showed > 95% neutralization of SARS-CoV-2 infectivity at a 1/200 dilution compared to pre-convalescent plasma serum (Fig. 1d). Neutralizing activity had been lost by day 119. A full description of the neutralizing assay is available in the supplementary methods. Resolution of plain-film radiological changes was observed by day 154 (Supplementary Figure 1).

Discussion

Adults with primary and secondary immunodeficiencies are at increased risk of morbidity and mortality from COVID-19 compared to the general population [2]. There are limited

treatments for severe COVID-19; of the empirical treatments used in this study (dexamethasone, remdesivir, convalescent plasma), the only dexamethasone is associated with reduced 28-day mortality in the general population [3–5]. Whether the results from these large trials can be rationally generalized to patients with immune deficiencies is unknown.

Remdesivir is a ribonucleotide analog that inhibits the SARS-CoV-2 RNA-dependent RNA polymerase and arrests viral RNA synthesis by acting as a delayed chain terminator [6]. Concordant with previous case reports (Supplementary Table 2), we found the administration of remdesivir was associated with significant improvements in immunological and physiological biomarkers of SARS-CoV-2 infection. However, the rapid recrudescence of symptomatic COVID-19 following the cessation of remdesivir supports the hypothesis that remdesivir monotherapy is insufficient to support virological clearance and resolution of COVID-19 in patients with humoral immunodeficiency.

In our patient, and others treated with both remdesivir and convalescent plasma (summarized in Supplementary Table 2), complete virological clearance and prolonged symptomatic resolution were only achieved following the administration of convalescent plasma. The efficacy of convalescent plasma in the treatment of COVID-19 in patients has been reported in small case series of individuals with both congenital and acquired B cell aplasia [7–9]. Of note, two reports demonstrate that viral persistence can occur despite the generation of CD4 and CD8 T cell responses to viral antigens and that magnitude of ex vivo antiviral T cell responses is augmented following the administration of convalescent plasma [10, 11]. These data point to a non-redundant role for humoral immunity in immunological control of SARS-CoV-2, potentially via mechanisms such as antibody-dependent cellular cytotoxicity or opsonization, and suggest convalescent plasma is a rational therapeutic choice for individuals with humoral immune deficiencies, particularly when current immunoglobulin replacement products lack SARS-CoV-2-specific antibodies [12].

However, the administration of convalescent plasma to immunodeficient patients has been associated with the emergence of novel genomic variants within SARS-CoV-2 encoding spike proteins that demonstrate reduced susceptibility to neutralization in vitro [13]. Thus, combination treatments that simultaneously suppress viral RNA synthesis and facilitate viral clearance may be appropriate in immunocompromised individuals, to prevent the emergence of novel viral variants. A more comprehensive understanding of mechanisms through which convalescent plasma mediates its therapeutic effect and how these mechanisms are defective in primary and secondary immune deficiency may allow the selection of individuals who would benefit from such interventions.

Declarations

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