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Case Report
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COVID-19 in a Post-transplant Heart Recipient Who Developed Aggressive Lymphoma: A Biphasic Course During Rituximab Treatment

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As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to spread with more than 131 million cases confirmed worldwide (as of April 6, 2021), patients treated for hematological disorders with concurrent SARS-CoV-2 infection have been reported.[1] Managing patients on active chemo-immunotherapy remains critical: severity of coronavirus disease 2019 (COVID-19) signs and symptoms, disease histotype and expected prognosis, together with individual patient characteristics, play a pivotal role.[2] Here we describe the case of a patient with diffuse large B-cell lymphoma (DLBCL) presenting as a post-transplant lymphoproliferative disorder (PTLD)[3] after heart transplantation.

In August 2019, a 22-year-old man underwent heart transplant for congenital hypertrophic cardiomyopathy. Six months later, hepatic lesions were noted on abdominal ultrasound, while the cardiac allograft function was normal (cardiac index 3.5 L/min/m^2 by right heart catheterization, no signs of cellular or humoral rejection on myocardial biopsy). A fluorodeoxyglucose positron emission tomography (PET) scan showed high uptake in the whole liver and detected an additional vertebral focal uptake that was later confirmed on computed tomography (CT) scan. Epstein-Barr virus (EBV)-DNA was positive in the serum (EBV-DNA 953,000 viral genomes/mL) and Epstein-Barr encoding region in situ hybridization conducted on tru-cut liver biopsy confirmed the diagnosis of EBV-positive monomorphic DLBCL-type PTLD. After multidisciplinary discussion, the initial treatment plan consisted of 4 weekly rituximab infusions and dose reductions of anti-rejection immunosuppressants, namely cyclosporine and everolimus.[4] Due to the widespread COVID-19 pandemic in Northern Italy, the patient underwent real-time polymerase chain reaction (PCR) nasopharyngeal testing for SARS-CoV-2 (extraction with QIAsymphony DSP Virus/Pathogen Midi Kit, amplification with Seegene Allplex apex 2019-nCoV Assay, target genes E, N, RNA-dependent RNA polymerase), influenza type A and type B. He tested negative for all 3 viruses prior to the start of treatment. After 2 rituximab infusions, in March 2020, the patient complained of flu-like symptoms with cough, fever (> 38°C) and nasal obstruction. Treatment was cautiously held. However, 1 week later, given the persistence of symptoms and the onset of dysgeusia, a newly performed nasopharyngeal swab (NPS) was positive for SARS-CoV-2 infection (Figure 1A). Hospitalization was not required as the patient remained stable without severe respiratory symptoms, and a home isolation protocol was implemented. At the time, preemptive treatment with hydroxychloroquine and azithromycin was administered as per local standard of care. Immunosuppressants were at the lowest therapeutic levels (everolimus and cyclosporine blood concentrations were 5.3 and 74 ng/mL, respectively; therapeutic ranges are 3–8 and 70–90 ng/mL, respectively). Clinical improvement was observed during the following 10 days.

Due to rapid enlargement of the patient's latero-cervical lymph nodes, there was high suspicion for progression of PTLD. As a result, rituximab treatment was resumed under watchful clinical monitoring despite the persistence of a positive SARS-CoV-2 NPS. Of note, concomitant flow cytometry analysis on peripheral blood showed total absence of CD19 and CD20-positive B-lymphocytes (0/uL, normal range: 72–520), a reduction in natural killer cells (16/uL, normal range: 73–654) and a decreased CD4+/CD8+ T-lymphocyte ratio (0.5, normal range: 0.9–2.5). While plasma concentrations of total IgG, IgM, and IgA were within normal range, anti-SARS-CoV-2 IgG antibodies were borderline (13 U/mL, lower limit of normal [LLN] = 12, tested with LIAISON SARS-CoV-2 S1/S2 IgG method; DiaSorin S.p.A., Saluggia, Italy). Interestingly, a repeat NPS, concomitant with rituximab therapy resume, resulted negative.

At the end of May 2020, after completing a 4-week rituximab course, restaging with PET/CT demonstrated complete

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HemaSphere (2021) 5:7(e592). http://dx.doi.org/10.1097/HS9.0000000000000592.
Received: 27 January 2021 / Accepted: 26 April 2021

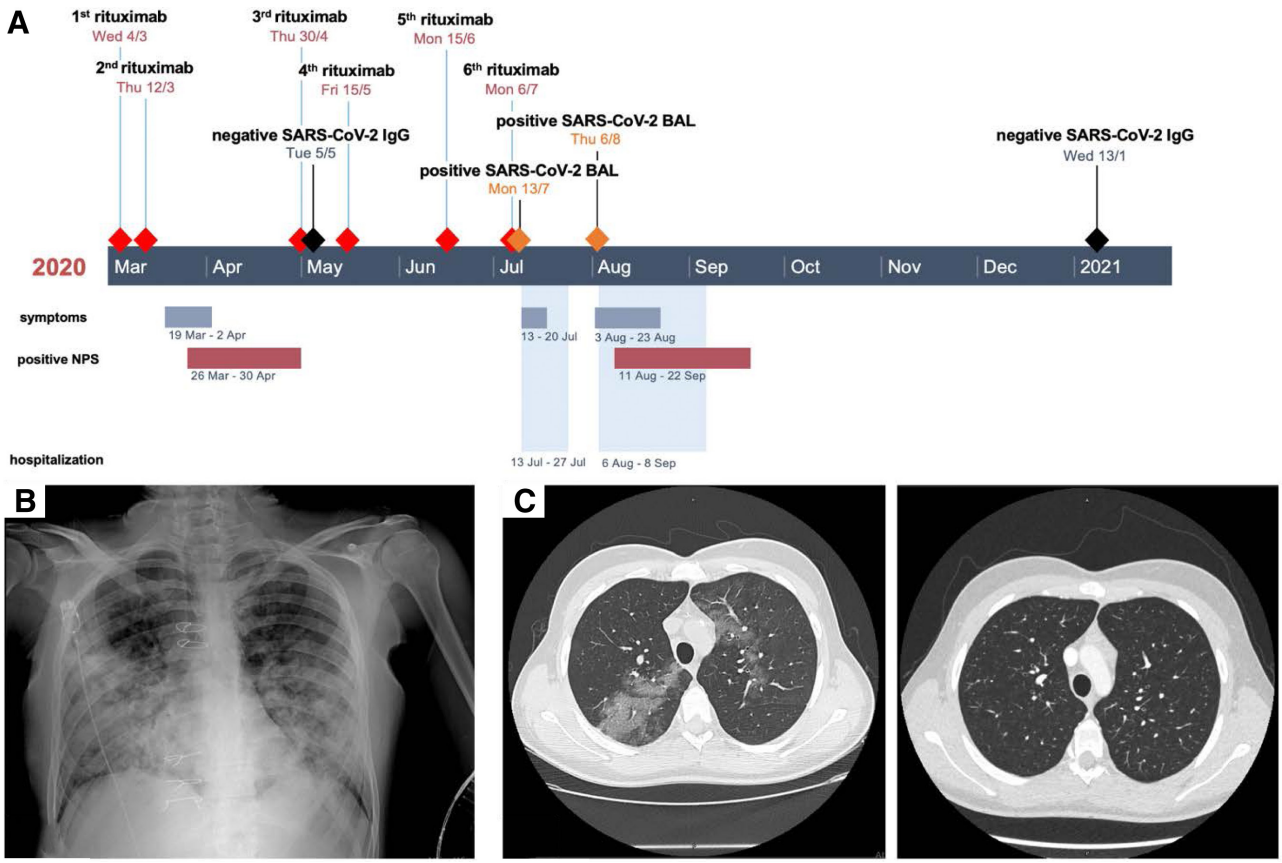

Figure 1. COVID-19 course. (A), Timeline of rituximab infusions, tests for SARS-CoV-2, symptoms and hospital admissions. (B), Ground glass opacities on chest radiograph. (C), CT scan showing bilateral ground glass infiltrations and their resolution at restaging. BAL = bronchoalveolar lavage; COVID-19 = coronavirus disease 2019; CT = computed tomography; NPS = nasopharyngeal swab; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

metabolic response of DLBCL. A mild abnormal bilateral lung uptake, suggestive of post-infectious changes, was also observed. Of note, anti-SARS-CoV-2 IgG antibodies were negative at the time (8.34 U/mL, LLN = 12). Consolidation treatment with 4 additional rituximab administrations was planned, however the patient presented with recurrence of fever and dysgeusia in July 2020 after only 2 infusions. NPS was persistently negative, but a CT scan revealed bilateral lung ground glass infiltrations (Figure 1, B and C). A bronchoalveolar lavage (BAL) was positive for SARS-CoV-2 and low positive for galactomannan antigen. Right after the procedure, the patient developed respiratory distress and hypotension, requiring oxygen therapy with a reservoir mask and fluid resuscitation. During the first 2 weeks of hospital stay, he received low flow oxygen support and 5 days of remdesivir through the Expanded Access Protocol. Antibiotic therapy with ceftobiprole and azithromycin and antifungal therapy with isavuconazole was also started. He was discharged after testing negative for SARS-CoV-2 on follow up NPSs.

Nine days after discharge, the patient sought care in the Emergency Department with remittent fever (up to 40°C) and dry cough. While admission NPS remained negative, a CT scan showed partial regression of the previous interstitial lesions with new bilateral ground glass areas suggesting persistence of the infection. SARS-CoV-2 positivity was confirmed by a repeat BAL. Noninvasive ventilation with continuous positive airway pressure was required and broad-spectrum antibiotics were started given high levels of procalcitonin and C-reactive protein. During hospitalization he was randomized to plasma treatment (either control or convalescent) through the PLACO-COVID trial (NCT04428021) and received IgM-enriched IVIGs and dexamethasone. An echocardiogram and right cardiac catheterization with pressure measurement to monitor heart function and rule out complications were also performed. Other than a small circumferential pericardial effusion, normal pressures and pulmonal resistances, as well as cardiac output and index, were observed. A concomitant myocardial biopsy ruled out COVID-19 involvement and graft rejection. The patient clinically improved over a 4-week hospital stay. Interestingly, NPS tested positive only 5 days after admission and remained positive until discharge. He is currently asymptomatic and clinically stable, while both EBV viral load and SARS-CoV-2 serology remain negative (IgG 5.60 U/mL, LLN = 12).

To our knowledge, we report the first case of a heart transplant recipient with COVID-19 while on active treatment for a life-threatening lymphoma. Observations and management of this patient may provide a framework for critically ill, immunocompromised COVID-19 patients.

Recipients of solid organ transplants are thought to be at higher risk of severe COVID-19 complications though data are scarce. Two Chinese heart transplant recipients developed COVID-19 disease at 1.5 and 17 years post-transplant.[5] Presentation was mild in 1 case and severe in the other though both eventually cleared SARS-CoV-2 with complete resolution of symptoms. By contrast, an observational study of 20 kidney transplant recipients with documented SARS-CoV-2 pneumonia reported severe clinical presentation and high mortality rate.[6] Interestingly, immunosuppression to prevent rejection was withdrawn and steroid therapy instituted in all of them. Another report by D'Antiga[7] on a cohort of pediatric liver transplant recipients treated in Bergamo (Italy) suggested that immunosuppressed patients should not be considered at increased risk of severe pulmonary disease

as compared with the general population. Thus, the authors concluded that there is no reason to postpone potentially life-saving treatments during coronavirus outbreaks. In general, observations on past (SARS and MERS-CoV) and present coronavirus outbreaks suggest that advanced age and comorbidities may be more relevant for patients' outcome rather than the iatrogenic inhibition of the T-cell compartment via immunosuppressive agents.[7,8]

EBV-positive PTLDs are life-threatening complications after solid organ transplantation and usually occur within the first year of transplant.[3] The initial management is commonly to reduce immunosuppression without compromising organ function. However, the anti-CD20 monoclonal antibody rituximab is the standard of care in patients who do not adequately respond or have rapidly progressive disease.[4] Rituximab is a potent anti-inflammatory and anti-neoplastic agent, potentially leading to long-lasting B-cell aplasia. In case of SARS-CoV-2 positivity, treatment with anti-CD20 antibodies should be withheld, especially when combined with chemotherapeutic agents.[9] Although a less dramatic inflammatory response may be hypothesized in patients on active immunosuppression, a higher frequency of secondary infections may be expected given a potentially long period of lymphopenia.[10] Even if it is still unclear if anti-SARS-CoV-2 IgG can confer a robust immune response against the virus, anti-CD20 antibodies could prevent the production of neutralizing antibodies leading to worse outcomes. Recently the effects of rituximab on the risk of developing infection with SARS-CoV-2 and severity of the COVID-19 disease were described.[11–13]

Finally, even though the case of a SARS-CoV-2 reinfection in a young patient has been recently reported,[14] our case study, like others,[11,12,15] suggests a prolonged period of viral shedding following anti-CD20 immunotherapy, in the absence of anti-SARS-CoV-2 antibodies. Moreover, the diagnostic yield of PCR on NPS in this subset of highly immunocompromised patients may be associated with a higher risk of false negative results and additional laboratory tests on BAL or imaging studies (ie, CT scan) may be highly recommended.

The SARS-CoV-2 outbreak and the associated COVID-19 disease have indeed led to a great deal of uncertainty among physicians about the safety of both immunosuppressive drugs and intense chemotherapy in the setting of organ transplantation and hematological malignancies. In our patient, as suggested by recently published guidelines,[9] the risk of rapidly progressive PTLD appeared to outweigh the risk of SARS-CoV-2 infection. He eventually achieved complete remission of his aggressive lymphoma. However, due to the impossibility of performing next-generation sequencing on SARS-CoV-2 positive specimens, we were unable to determine whether the second, more aggressive SARS-CoV-2 pneumonia was an evolution of the previous disease, a reinfection or a new primary infection with a different variant in the setting of rituximab related B-cell aplasia.

Author contributions

MC, ID, AC, DC, SF, CB, and FC were involved in data collection, analysis, and interpretation. MC, ID, BB, and FC wrote the article. All remaining authors critically revised the article.

Disclosures

The authors have no conflicts of interest to disclose.

Sources of funding

ID was supported by Società Italiana di Ematologia (SIE) and Associazione Italiana per la lotta contro le leucemie i linfomi e i mielomi (AIL).

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