CORRESPONDENCE

Mild clinical course of SARS-coronavirus-2 infection early posttransplant in patients with adoptively transferred antibody response

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To the Editor:

Coronavirus disease 2019 (Covid-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), is associated with high morbidity and mortality in HCT recipients. The disease severity and mortality are particularly high in the first several months after HCT [1–4]. This is likely due to profound T and B lymphopenia, which is associated with poor antibody responses in the first several months after transplantation [5].

The studies showing the high morbidity and mortality of Covid-19 early posttransplant have generally reported on patients who underwent HCT before most donors became immune due to vaccination or infection. Antibody responses to tetanus toxoid or Haemophilus influenzae vaccines after HCT are known to be improved by immunizing the patient and/or the donor before HCT [5–7]. If this applies to SARS-CoV-2, the morbidity and mortality of SARS-CoV-2 infection contracted early posttransplant in patients who or whose donors were immunized by vaccination or infection pretransplant may not be as high as early in the pandemic.

Here we report on two patients who developed SARS-CoV-2 infection in the first 3 weeks after HCT, during a Covid-19 outbreak on our hematology/oncology/HCT ward. Both received HCT from donors immunized by vaccination or infection. Despite severe T and B lymphopenia, the patients' clinical course was mild, and they cleared the virus while specific antibodies rose.

Patient 1 was a 66-year-old male with a history of myocardial infarction. His donor received one dose of ChAdOx1 nCoV-19/AZD1222 vaccine (Astra-Zeneca) 7 weeks pretransplant. Consistent with that, the donor at 3 weeks pretransplant had detectable IgG for the spike protein receptor binding domain (RBD, coded for by the vaccine nucleic acid) and not for nucleocapsid protein (Table 1). The patient had no history of SARS-Cov-2 vaccination or infection and no evidence of immunity (Table 1). On day 17 he developed cough and fever. Chest x-ray and computer tomogram showed a mild left lower lobe opacification. Nasopharyngeal swab (NPS) was positive for SARS-CoV-2. He became asymptomatic by day 22, when chest X-ray showed near resolution of the left lower lobe opacification (Supplementary Fig. 1). Serial NPSs were negative from day 61 onward.

Patient 2 was a 59-year-old male with type 2 diabetes mellitus, chronic heart failure, and history of myocardial infarction. His donor was immune to SARS-CoV-2 (Table 1), presumably due to a mild or asymptomatic infection. The patient had no history of SARS-CoV-2 vaccination or infection and no evidence of immunity (Table 1). On day 5, a surveillance NPS was positive for SARS-CoV-2. The only potential Covid-19 symptoms were diarrhea, which resolved within several days, and sore throat until day 19. No pneumonia developed clinically or per serial chest X rays. Serial NPSs were negative from day 39 onward. Patient 2 died suddenly on day 52 due to myocardial infarction in the setting of grade 4 acute GVHD. On autopsy, there was no evidence of viral infection of the lungs or another organ.

Detailed case reports and other methodological information are provided in Supplementary Methods.

Lymphocyte subset counts are shown in Supplementary Fig. 2. Both patients had profound T and B lymphopenia in the first 2 months posttransplant, except for B-cell counts in Patient 1 normalizing by day 56.

Antibody levels are shown in Table 1. In Patient 1, RBD IgG was first detected on day 14 (3 days before onset of symptoms) and rose thereafter to high levels. The high level on day 27 could be due in part to bamlanivimab (monoclonal RBD IgG) given on day 18. However, the fact that the RBD IgG was detected already on day 14 and rose from day 27 to day 56 is consistent with in vivo production of RBD IgG. This was due to the transferred vaccine-induced humoral immunity as no IgM and no nucleocapsid IgG were detected. In Patient 2, SARS-Cov-2 antibodies were undetectable on day 14. Thereafter IgM and IgG for both nucleocapsid and RBD were detected, and the IgG rose to high levels. This was probably due to adoptively transferred humoral response from the donor immunized by a SARS-Cov-2 infection, as primary immune response is not expected to occur in the first 2 months after HCT [5], particularly in patients as lymphopenic and pharmacologically immunosuppressed as Patient 2.

We hypothesize that in both patients the mild clinical course and the virus clearance resulted from the adoptive transfer of humoral immunity. However, there are limitations: 1. We cannot rule out that the mild course and the clearance were due to the cells of innate immunity like respiratory epithelial cells or NK cells. Quantitative NK cell reconstitution was fast in both patients. We have not measured the function of NK cells or respiratory epithelial cells (e.g., production of antiviral cytokines such as interferon alpha/beta/lambda by the respiratory cells). Nevertheless, it is generally believed that adaptive immunity is needed for the viral clearance [8]. 2. Both patients were treated with remdesivir and Patient 1 also with bamlanivimab, so we cannot rule out that the mild course and the viral clearance were due to these medications. However, the efficacy of these medications is only modest, if any [9]. 3. We measured total CD4 and CD8 T cells and B cells but not those specific for SARS-CoV-2, which would provide a more complete information on the antiviral adaptive immunity. However, given the extremely low numbers of total T and B cells at most time points, it would

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Table 1. SARS-Cov-2-specific serum antibody levels.

	Donor preHCT[d]	Patient preHCT[e]	Patient day +14	Patient day +27 or +28	Patient day +51 or +56	Convalescent non-HCT persons
Patient 1 (infection first documented on day +17)						
Nucleocapsid IgM[a]	Neg	Neg	Neg	Neg	Neg	N/A
Spike RBD IgM[a]	Neg	Neg	Neg	Neg	Neg	N/A
Nucleocapsid IgG[b]	<1.4	<1.4	<1.4	<1.4	<1.4	<1.4–8.0
Spike RBD IgG[c]	189	<40	87	25,376	>80,000	<40–1250 or 22,535
Patient 2 (infection first documented on day +5)						
Nucleocapsid IgM[a]	Neg	Neg	Neg	Pos	Pos	N/A
Spike RBD IgM[a]	Neg	Neg	Neg	Neg	Pos	N/A
Nucleocapsid IgG[b]	<1.4[f]	<1.4	<1.4	1.6	6.5	<1.4–8.0
Spike RBD IgG[c]	405[f]	<40	<40	4 111	>80,000	<40–1250 or 22,535

HCT hematopoietic cell transplantation, *RBD* receptor binding domain, *Neg* negative, *Pos* positive, *N/A* not applicable.
[a]Negative IgM was defined as mean fluorescent intensity <250.
[b]Negative nucleocapsid IgG was defined as index value <1.4. The index values in convalescent non-HCT persons are from Bryan et al. Performance characteristics of the Abbott Architect SARS-CoV-2 IgG assay and seroprevalence in Boise, Idaho. J Clin Microbiol. 2020;58:e00941.
[c]Negative spike RBD IgG was defined as <40 arbitrary units (AU)/ml. The range of levels in convalescent non-HCT persons is from Eyre et al. Quantitative SARS-CoV-2 anti-spike responses to Pfizer-BioNTech and Oxford–Astra-Zeneca vaccines by previous infection status. Clin Microbiol Infect. 10.1016/j.cmi.2021.05.041. In press. (undetectable to 1250 AU/ml) and from Resman-Rus et al. Performance of the rapid high-throughput automated electrochemiluminescence immunoassay targeting total antibodies to the SARS-CoV-2 spike protein receptor binding domain in comparison to the neutralization assay. J Clin Virol. 2021:139:104820 (undetectable to 22,535 AU/ml). As in the Resman-Rus et al. study the results were expressed in World Health Organization binding antibody units (BAU)/ml, these were converted to AU/ml as AU/ml = BAU/ml/0.142, i.e., a formula recommended by the assay manufacturer (Abbott).
[d]Day −22 for the donor of Patient 1. Day 0 for the donor of Patient 2.
[e]Day −8 (pre-conditioning) in both Patient 1 and 2.
[f]The positive spike RBD IgG and negative nucleocapsid IgG in the unvaccinated donor is consistent with a known decline of nucleoprotein IgG but long-term persistence of RBD IgG after recovery from SARS-CoV-2 infection (Fenwick et al. Changes in SARS-CoV-2 spike versus nucleoprotein antibody responses impact the estimates of infections in population-based seroprevalence studies. J Virol. 2021;95:e01828, and Grandjean et al. Long-term persistence of spike antibody and predictive modeling of antibody dynamics following infection with SARS-CoV-2. Clin Infect Dis. 10.1093/cid/ciab607. In press).

be technically challenging to detect SARS-CoV-2-specific CD4 and CD8 T or B cells by flow cytometry or elispot. Apheresis instead of a simple blood draw would be needed to collect a sufficient number of T and B cells for analysis, which would be ethically questionable. Even if we detected SARS-CoV-2-specific T cells, interpretation would be difficult as these cells were detected in ~50% individuals unexposed to SARS-CoV-2 [10, 11], and SARS-Cov-2-specific CD8 T cells were not detected in 30% immunocompetent persons who had recovered from Covid-19 [11]. 4. We did not measure neutralizing antibodies. Nevertheless, the IgG measured by the Abbott assay we used correlates well with neutralizing IgG [12]. 5. We have not studied control patients, i.e., infected early posttransplant and whose donors had not been immunized (by vaccination or infection). Thus, we cannot rule out that Covid-19 would have a mild course even in these patients. The literature is remarkably silent about patients infected with SARS-CoV-2 in the first month posttransplant, possibly because infection prevention precautions instituted on HCT wards are usually effective. We found reports with patient-level information on four patients from the pre-vaccine era, when most donors were presumably nonimmune, who developed Covid-19 in the first 4 weeks after HCT (Supplementary Table 1). One had a mild course and three had pneumonia requiring ventilatory support. Importantly, reports on large numbers of HCT recipients infected with SARS-CoV-2 in the pre-vaccine era, that did not give patient-level information, identified the following risk factors for severe pneumonia or death: short time from HCT, older age, comorbidities, neutropenia, and immunosuppressive therapy [1–4]. Our two patients had all these risk factors. Thus, they would be expected to have a severe clinical course in the pre-vaccine era.

In summary, barring the above limitations, humoral immunity can be transferred from immune donors and may protect recipients infected early posttransplant from severe Covid-19.

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AUTHOR CONTRIBUTIONS

JS conceived the idea and wrote the paper. JNK and MC provided input into and supervised the determination of SARS-Cov-2 antibody levels. AK and PDK determined lymphocyte subset counts. AC, KJ and FMK provided critical comments.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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