




Robust Antibody and T Cell Responses to SARS-CoV-2 in Patients with Antibody Deficiency

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Abstract

Immunocompromised patients, including those with inborn errors of immunity (IEI), may be at increased risk for severe or prolonged infections with SARS-CoV-2 (Zhu et al. *N Engl J Med.* 382:727–33, 2020; Guan et al. 2020; Minotti et al. *J Infect.* 81:e61–6, 2020). While antibody and T cell responses to SARS-CoV-2 structural proteins are well described in healthy convalescent donors, adaptive humoral and cellular immunity has not yet been characterized in patients with antibody deficiency (Grifoni et al. *Cell.* 181:1489–1501 e1415, 2020; Burbelo et al. 2020; Long et al. *Nat Med.* 26:845–8, 2020; Braun et al. 2020). Herein, we describe the clinical course, antibody, and T cell responses to SARS-CoV-2 structural proteins in a cohort of adult and pediatric patients with antibody deficiencies ($n=5$) and controls (related and unrelated) infected with SARS-CoV-2. Five patients within the same family (3 with antibody deficiency, 2 immunocompetent controls) showed antibody responses to nucleocapsid and spike proteins, as well as SARS-CoV-2 specific T cell immunity at days 65–84 from onset of symptoms. No significant difference was identified between immunocompromised patients and controls. Two additional unrelated, adult patients with common variable immune deficiency were assessed. One did not show antibody response, but both demonstrated SARS-CoV-2-specific T cell immunity when evaluated 33 and 76 days, respectively, following SARS-CoV-2 diagnosis. This report is the first to show robust T cell activity and humoral immunity against SARS-CoV-2 structural proteins in some patients with antibody deficiency. Given the reliance on spike protein in most candidate vaccines (Folegatti et al. *Lancet.* 396:467–78, 2020; Jackson et al. *N Engl J Med.* 383:1920–31, 2020), the responses are encouraging. Additional studies will be needed to further define the timing of onset of immunity, longevity of the immune response, and variability of response in immunocompromised patients.

Keywords Antibody deficiency · adaptive immune response · COVID-19 · common variable immunodeficiency · SARS-CoV-2 · T cell response

Introduction

Since the start of the COVID-19 pandemic there has been expanding evidence that immunocompromised patients may be at increased risk for severe or prolonged infections with SARS-CoV-2 [1–3]. Clinical descriptions of COVID-19 in patients with T cell and antibody-specific inborn errors of

immunity (IEI) are expanding, including reports of worsened disease course in patients with common variable immunodeficiency (CVID) as compared with pure agammaglobulinemia [4–7]. In the largest cohort described to date of patients with IEI and COVID-19, 20% of the cohort required intensive care, with an overall mortality rate of 10%; 6 of 9 deceased patients suffered from an antibody defect [6]. Their findings represent increased morbidity and mortality, especially at younger ages, as compared with the general population. While antibody and T cell responses to SARS-CoV-2 structural proteins are well described in healthy convalescent donors, adaptive humoral and cellular immunity have not yet been characterized in patients with antibody

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deficiencies [8–11]. Here, we describe five patients affected with antibody deficiencies who developed mild symptoms of COVID-19 and provide comprehensive analysis of their adaptive immune responses.

Methods

All patients provided written informed consent for clinical data and blood sample collection on protocols approved by the National Institutes of Health Institutional Review Board, in concordance with ethical standards as put forth by the Declaration of Helsinki.

Serology Assays

SARS-CoV-2 antibody testing was performed via luciferase immunoprecipitation assay on all subjects as previously described [9]. Briefly, plasma samples were incubated with spike and nucleocapsid proteins fused to *Gaussia* and *Renilla* luciferase, respectively. Protein A/G beads were added, and samples were washed prior to addition of coelenterazine substrate (Promega). A Berthold 165 LB 960 Centro Microplate Luminometer was used to measure luciferase activity in light units. Antibody levels were reported as the geometric mean level with 95% confidence interval. As described previously, cutoff limits for determining positive antibodies in the SARS-CoV-2-infected samples were based on the mean plus 3–4 standard deviations of the serum values derived from uninfected blood donor controls for nucleocapsid (125,000 LUs) and spike (45,000 LUs) [9]. Percentages for categorical variables, median, mean, standard deviation and range, and geometric mean were used to describe the data. Unpaired *t* tests were used for statistical analysis.

T Cell Assays

Testing of T cell responses was performed via stimulation of peripheral blood mononuclear cells with peptide libraries encompassing SARS-CoV-2 structural proteins as previously described [12]. Cells were then cultured for 10 days in 96-well plates with IL-4 (400 IU/mL) and IL-7 (10 ng/mL). On day 10, expanded viral specific T cells (VSTs) were harvested. 2×10^5 VSTs were plated in a 96-well plate and re-stimulated with SARS-CoV-2 structural proteins pooled pepmixes or actin (negative control) with CD28/CD49d (BD Biosciences) and anti-CD107a- Pe-Cy7 antibody. After 1 h of stimulation, brefeldin A (Golgiplug; BD Biosciences, San Jose, CA, USA) and monensin (GolgiStop; BD Biosciences, San Jose, CA, USA) were added. Cells were then incubated for an additional 4 h. Cell viability was assessed using Live-Dead Aqua. Cells were surface stained with

fluorophore-conjugated antibodies against CD3-BV785, CD4-BV605, CD8- BV421, TCR $\alpha\beta$ -PerCP Cy5.5, TCR $\gamma\delta$ -APC-Fire750, CCR7-FITC, CD45-RO-PE Dazzle, HLA-DR-Alexafluor700, and CD56-BV650 (Miltenyi Biotec; BioLegend). Cells were fixed, permeabilized with Cytofix/Cytoperm solution (BD Biosciences), and subsequently stained with IFN- γ -APC and TNF- α -PE (Miltenyi Biotec). All samples were acquired on a CytoFLEX cytometer (Beckman Coulter, Brea, CA, USA). The gating strategy for analysis is presented in Supplemental Fig. 2.

Results

Clinical History

Immunodeficiency History

The proband of the kindred (P1) is an 11-year-old boy with CVID, atopy, celiac disease, and recurrent infections beginning in the first year of life. He is currently treated with immunoglobulin replacement therapy with improvement in infections (Supplemental Table 1). His twin brother (P2) had a history of periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA), recurrent sinusitis, eosinophilic esophagitis, and environmental allergies, as well as hypogammaglobulinemia (Supplemental Fig. 1) [13]. Their younger sister (P3) has history of recurrent sinopulmonary infections, otitis media requiring myringotomy tubes, pharyngitis with subsequent tonsillectomy, as well as atopy with a normal immunologic evaluation [14]. Their mother (P4) also has specific antibody deficiency with recurrent sinopulmonary infection and atopy. She is currently managed with early antibiotic therapy for infections and frequent booster vaccinations. P2, P3, and P4 have never received immunoglobulin therapy. Whole-exome sequencing performed on the proband did not identify any a causative variant (for additional clinical information, see Supplemental data S1).

Patient 6 (P6) is an unrelated 48-year-old male who was diagnosed with CVID at the age of 34 years in the setting of recurrent sinusitis, thrombocytopenia, leukopenia, and splenomegaly (Supplemental Table 2). He is currently treated with immunoglobulin replacement therapy and amantadine prophylaxis, but with ongoing infectious and non-infectious complications. Whole-exome sequencing did not reveal a causal genetic variant.

Patient 7 (P7) is an unrelated 21-year-old female with CVID diagnosed at the age of 14 years in the setting of alopecia areata and idiopathic thrombocytopenic purpura. Her course was complicated by anti-phospholipid syndrome and respiratory infections. She is currently treated with subcutaneous immunoglobulin and hydroxychloroquine. Whole-exome sequencing revealed 2 previously

reported compound heterozygous variants in TNFRSF13B (c.310 T > C, p.Cys104Arg and c.260 T > A, p.Ile87Asn) which are believed to be contributory to her CVID [15–17].

SARS-CoV-2 History

With regard to the kindred, the healthy father (P5) had onset of fever progressing to fatigue, anosmia, and cough in August of 2020. Symptoms persisted for 14 days, with a normal chest X-ray during his disease course. SARS-CoV-2 PCR was positive on the second day of illness. A day later, two of the children (P2 with hypogammaglobulinemia and P3) developed 2 days of fever without respiratory symptoms. P3 had persistent anosmia lasting weeks. Twenty days after the first family member became ill, the mother with SAD (P4) developed fever, fatigue, severe headache, and anosmia, with persistent symptoms over several weeks. SARS-CoV-2 testing was not performed on the other family members at the time of illness. Patient 1 with CVID remained asymptomatic when his family was ill. All family members recovered without need for hospitalization or treatment.

In November 2020, P6 with CVID (unrelated) was incidentally found to be SARS-CoV-2 positive on admission for post-operative bleeding after surgery for benign prostatic hypertrophy. His only symptoms of SARS-CoV-2 infection were dry mouth and cough 3 days after diagnosis. His course was otherwise uncomplicated.

P7 with CVID (unrelated) developed nasal and sinus congestion, mild anosmia, and fatigue in November of 2020. SARS-CoV-2 PCR was positive on day 4 of illness, with return to baseline 10 days after testing.

Five additional pediatric and adult immunocompetent controls with mild ($n=4$) to severe ($n=1$) symptoms of SARS-CoV-2 infection were included in the analysis for comparison.

Serologic Responses

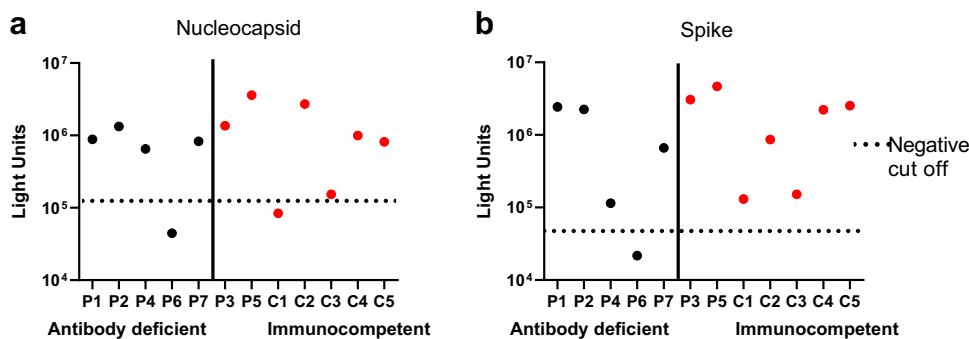
SARS-CoV-2 antibody testing was performed via luciferase immunoprecipitation assay on the kindred 84 days after the first family member developed symptoms (P5). At that

time, P2, P3 and P4 were 79 days, 80 days, and 65 days, respectively, from the onset of their own symptoms. Patient 6 was evaluated 33 days following detection of SARS-CoV-2 infection by PCR testing. Patient 7 was evaluated 80 days after first developing symptoms. All five subjects in our kindred (P1–P5) had detectable antibodies targeting both spike (median LU = 2.43×10^6) and nucleocapsid (median LU = 1.33×10^6 , Fig. 1) proteins of SARS-CoV-2. In contrast, P6 is seronegative for spike (LU = 2.16×10^4) and nucleocapsid (LU = 4.45×10^4), while P7 is seropositive for spike (LU = 6.61×10^5) and nucleocapsid (LU = 8.29×10^5) (Fig. 1). Antibody levels of additional pediatric and adult immunocompetent controls evaluated after SARS-CoV-2 infection are included for comparison (Fig. 1).

T Cell Responses

Intracellular cytokine staining demonstrated specific CD4⁺ T cell responses in all affected patients ($n=5$) targeting spike (mean IFN- γ /TNF- α ⁺ 0.75%; standard deviation [SD] 0.62), membrane (mean IFN- γ /TNF- α ⁺ 1.94%; SD 1.9), and nucleocapsid (mean IFN- γ /TNF- α ⁺ 1.58%; SD 1.37) (Fig. 2a, Supplemental Fig. 3). All immunocompetent control patients ($n=7$) demonstrated specific CD4⁺ T cell responses to spike (mean IFN- γ /TNF- α ⁺ 0.33%; SD 0.20), membrane (mean IFN- γ /TNF- α ⁺ 1.12%; SD 0.80), and nucleocapsid (mean IFN- γ /TNF- α ⁺ 0.75%; SD 0.89) (Fig. 2b, Supplemental Fig. 3). Specificity was determined as a response > 2 \times the mean of the negative control, actin (mean IFN- γ /TNF- α ⁺ 0.025%; SD 0.05). There is no statistically significant difference between the affected patients and control groups with respect to CD4⁺ T cell responses to actin ($p=0.67$) or any of the SARS-CoV-2 proteins: membrane ($p=0.32$), envelope ($p=0.86$), nucleocapsid ($p=0.23$), or spike ($p=0.13$) (Fig. 2c). Single IFN- γ ⁺ and TNF- α ⁺ CD4⁺ populations are reported in Supplemental Table 3. Affected and control patients did not show appreciable CD8⁺ T cell responses (Supplemental Fig. 4). CD107a expression was minimal and did not differ between patients with antibody deficiency compared to immunocompetent controls (data not shown).

Fig. 1 Antibody responses as measured by LIPS assay for patients with antibody deficiencies (P1, P2, P4, P6, P7) in black compared to immunocompetent controls (P3, P5, C1–C5) in red for nucleocapsid (a) and spike (b). Negative cutoff values (denoted by the dotted line) are based on uninfected negative controls as previously described [9]



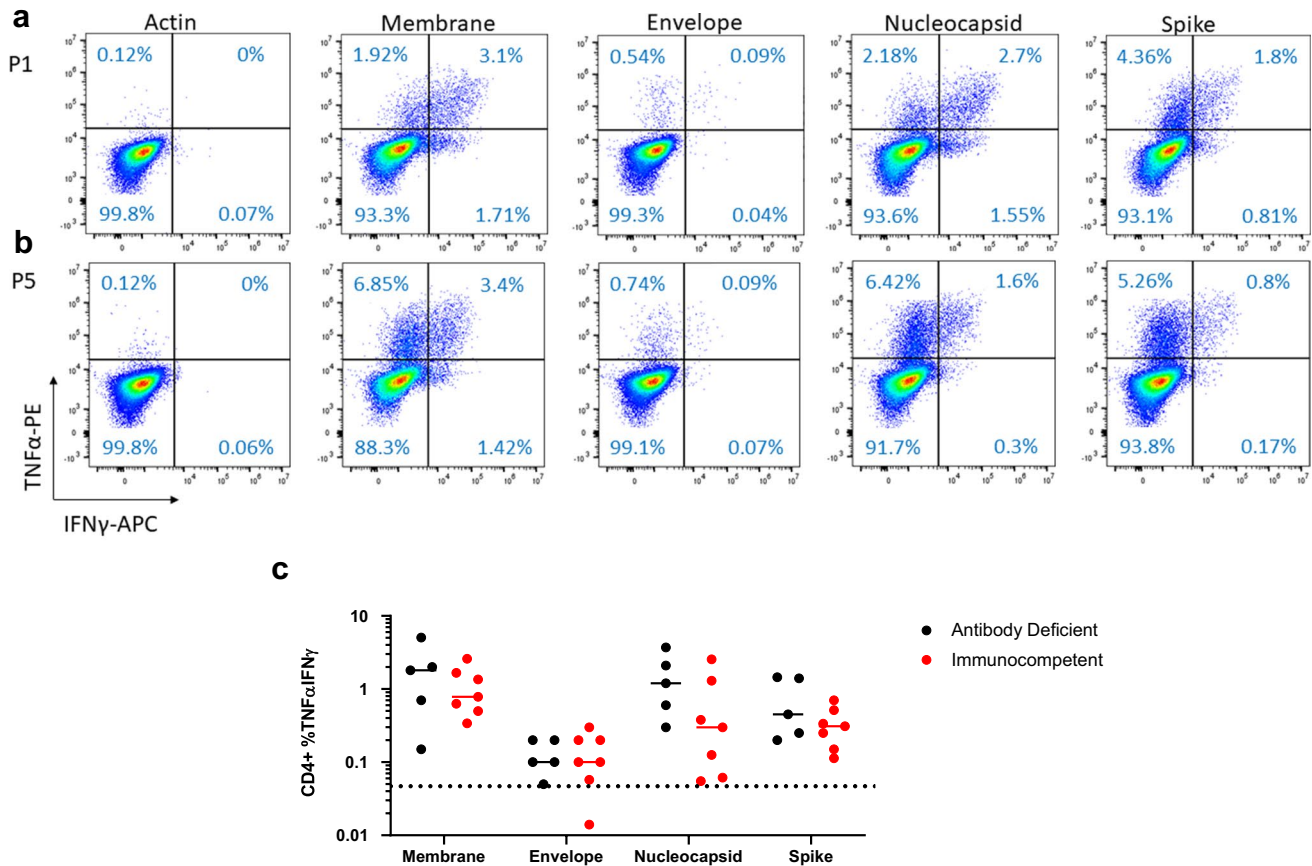


Fig. 2 Flow cytometry of CD4⁺ cells positive for IFN- γ and TNF- α for actin (negative control), and for SARS-CoV-2 membrane, envelope, nucleocapsid, and spike for (a) affected patient (P1) and (c) immunocompetent control patient (P5). Mean percent positive IFN- γ and TNF- α responses by intracellular flow cytometry for CD4⁺ cells for membrane, envelope, nucleocapsid, and spike are presented graphically (c) for antibody-deficient (in black) and

immunocompetent (in red) patients. Specificity was determined as a response $>2\times$ the mean of the negative control (actin) as denoted by the dotted line. No significant difference between affected and control CD4 T cell response for actin ($p=0.67$), membrane ($p=0.32$), envelope ($p=0.86$), nucleocapsid ($p=0.23$), and spike ($p=0.13$) was found by unpaired t test. Flow plots for other patients and controls are shown in supplemental Fig. 3

Memory T Cell Phenotype

Memory T cell phenotype of SARS-CoV-2-specific cells was evaluated after 10 days of VST microexpansion. In P1-P5, SARS-CoV-2-specific CD3⁺ cells were primarily effector (mean 78.59%; SD 10.7) and central memory (mean 20.83%; SD 10.5) T cells. Patient 6 (unrelated) also had detectable SARS-CoV-2-specific CD3⁺ cells comprising both effector (14.74%) and central memory T cell (55.21%) populations despite an undetectable humoral response. Patient 7 had detectable SARS-CoV-2-specific CD3⁺ cells comprising effector (51.92%), central memory (26.71%), naïve (16.92%), and terminal effector (4.45%) memory T cell populations. The specific CD4⁺ T cell memory response in the affected patients was predominantly effector memory for membrane (mean 70.89%; SD 39.72), nucleocapsid (mean 68.63%; SD 39.40), and spike (mean 76.86%; SD 20.75) (Fig. 3). The specific CD4⁺ T cell memory response

in the control patients is predominantly effector for membrane (mean 90.87%; SD 5.62), envelope (mean 73.32%; SD 1.80), nucleocapsid (mean 91.1%; SD 4.03), and spike (mean 85.32%; SD 11.56) (Fig. 3). There was no significant difference in CD4⁺ T cell memory response for spike between affected and control patients with respect to naïve ($p=1.0$), central memory ($p=0.63$), effector memory ($p=0.62$), and terminal effector ($p=0.57$) T cells. Overall, the T cell responses in all the CVID patients were not significantly different from healthy adult and pediatric convalescent subjects (additional data not shown).

Discussion

To date, there are very little data on adaptive immune responses to SARS-CoV-2 in patients with IEI. Though it may be expected that antibody responses could be impaired

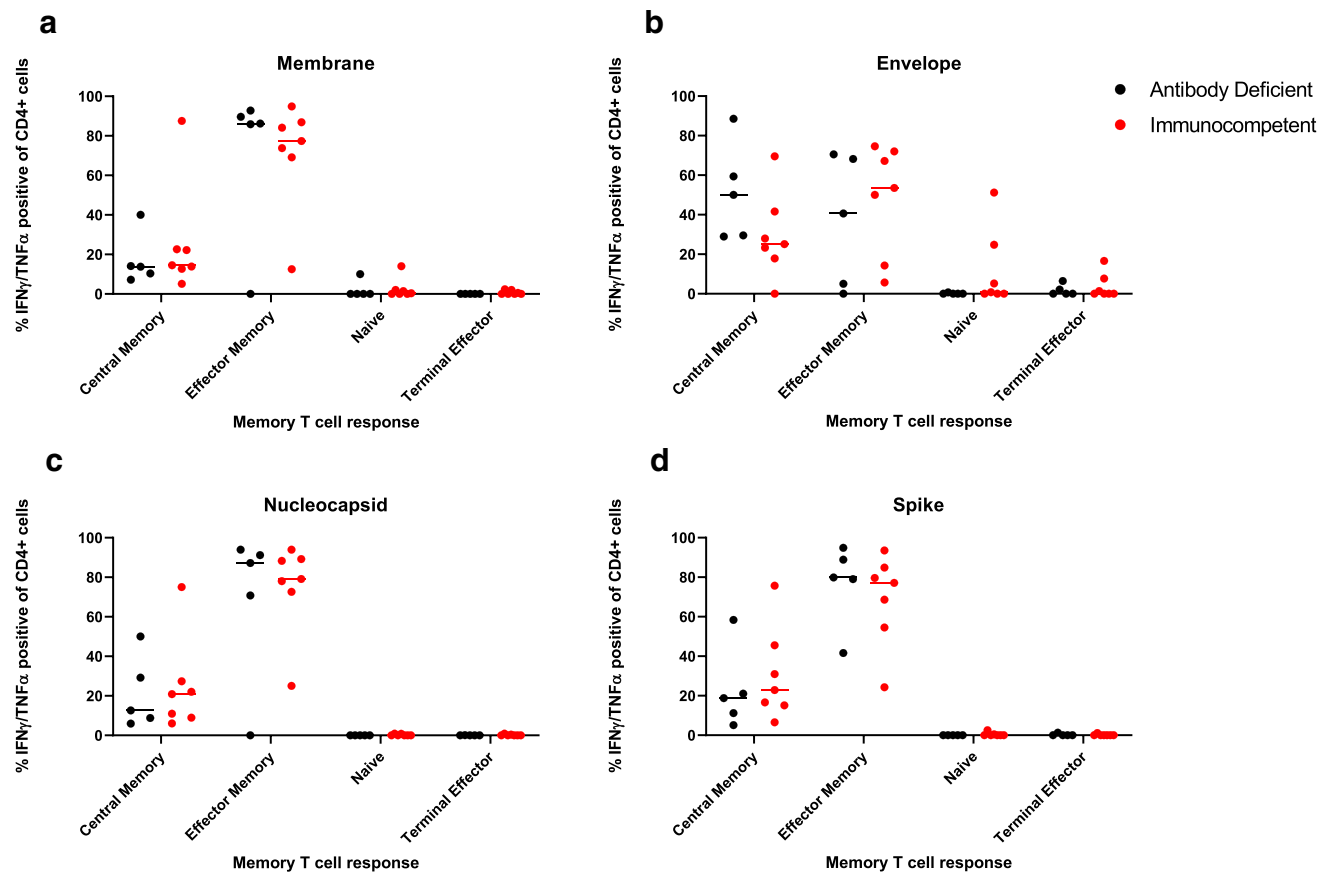


Fig. 3 Flow cytometry memory phenotype of CD4⁺ cells positive for IFN- γ and TNF- α in antibody-deficient (in black) and immunocompetent control (in red) patients. Percent distribution and mean (horizontal lines) are shown for each T cell phenotype (naïve, central memory,

effector memory and terminal effector) based on stimulation with each peptide library evaluated (membrane (a), envelope (b), nucleocapsid (c), spike (d))

in patients with various forms of antibody deficiency, it has been demonstrated that some patients with CVID do have detectable primary antibody responses to viral antigens (e.g., influenza) as well as memory B cell responses [18, 19]. Furthermore, patients with many forms of antibody deficiency can demonstrate cellular responses to antigens which impact clinical decision-making regarding inactivated vaccine administration to patients on immunoglobulin therapy [18–21]. Here, we demonstrate that 3 members of a family with varying degrees of antibody deficiency and 2 unrelated patients with CVID all had a robust adaptive immune response to SARS-CoV-2 following asymptomatic or mild disease. While supplemental immunoglobulin therapy has been shown to potentially contain some anti-SAR-CoV-2 antibodies, the high antibody titers in the proband (P1) and unrelated P7 suggest that this was in fact a primary immune response. Furthermore, the type and magnitude of B and T cell response was similar between this small group of antibody-deficient patients and healthy controls. Of note, the LIPS assay used for this study has been compared to the commercially available Roche assay for nucleocapsid [22],

with result concordance in 383 of 400 tested samples. Similar to the administration of influenza vaccination in patients with IEI, these findings provide some preliminary support for vaccination in the management of patients with antibody deficiencies.

In contrast, an unrelated adult (P6) with CVID receiving immunoglobulin supplementation who was positive for SARS-CoV-2 by PCR testing did not have a demonstrable antibody response at 33 days after diagnosis but did have a detectable SARS-CoV-2-specific T cell response. Lack of a humoral response following relatively asymptomatic infection (similar to this patient's course) has been described, which may have contributed to these findings [23]. However, given the spectrum of severity of patients with CVID and related antibody disorders, it also stands to reason that not all patients will have robust B cell and/or T cell responses to SARS-CoV-2 following infection or vaccination.

To our knowledge, this is the first report showing robust T cell activity and humoral responses against SARS-CoV-2 structural proteins in patients with antibody deficiency. Given the reliance on spike protein in most

candidate vaccines [24, 25], the responses demonstrated are encouraging, though additional studies will be needed to further define the quality of the antibody response and the longevity of immune responses against SARS-CoV-2 in immunocompromised patients compared with healthy donors.

Abbreviations CVID: Common variable immunodeficiency; IEI: Inborn errors of immunity; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; LU: Light units; PFAPA: Periodic fever, aphthous stomatitis, pharyngitis, adenitis; SAD: Specific antibody deficiency; VST: Viral specific T cell

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Authors' Contribution HK, JDS, CAL, JC, and CMB conceived and designed the experiments; HK, JDS, MJW, VK, KW, CAL, and PB conducted the research; HK, JDS, CAL, JIC, CMB, and MDK analyzed data; HK, JDS, CAL, JIC, CMB, and MDK wrote the manuscript; IF, AK, and KMR provided patient samples and history; LN and MW provided genetic sequencing support. All authors have read and approved the final manuscript.

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Data Availability This data or associated data is not in a data repository.

Code Availability Not applicable.

Declarations

Ethics Approval All patients provided written informed consent on protocols approved by the National Institutes of Health Institutional Review Board.

Consent to Participate See above.

Consent for Publication All authors concur with the submission of this manuscript, and the material submitted for publication is original research and has not been previously reported and is not under consideration for publication elsewhere.


Conflict of Interest CMB is co-founder and on the scientific advisory boards for Catamaran Bio and Mana Therapeutics with stock and/or ownership, is on the Board of Directors for Caballeta Bio with stock options and has stock in Neximmune and Repertoire Immune Medicine. MDK is on a scientific advisory panel for Enzyvant Therapeutics. The other authors declare that there are no conflicts of interests.

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