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SHORT COMMUNICATION

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Long-term coexistence of SARS-CoV-2 with antibody response in COVID-19 patients

Bin Wang[1] | Li Wang[1] | Xianggen Kong[1] | Jin Geng[1] | Di Xiao[1] | Chunhong Ma[2] | Xue-Mei Jiang[1] | Pei-Hui Wang[2]

[1]Jinan Infectious Diseases Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China

[2]Advanced Medical Research Institute, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China

Correspondence
Xue-Mei Jiang, Jinan Infectious Diseases Hospital, Cheeloo College of Medicine, Shandong University, Jinan, 250021 Shandong, China.
Email: shdjxm@163.com

Pei-Hui Wang, Advanced Medical Research Institute, Cheeloo College of Medicine, Shandong University, Jinan, 250012 Shandong, China.
Email: pei-hui.wang@sdu.edu.cn and pei-hui.wang@connect.hku.hk

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causing coronavirus disease 2019 (COVID-19) has spread worldwide. Whether antibodies are important for the adaptive immune responses against SARS-CoV-2 infection needs to be determined. Here, 26 cases of COVID-19 in Jinan, China, were examined and shown to be mild or with common clinical symptoms, and no case of severe symptoms was found among these patients. Strikingly, a subset of these patients had SARS-CoV-2 and virus-specific IgG coexist for an unexpectedly long time, with two cases for up to 50 days. One COVID-19 patient who did not produce any SARS-CoV-2–bound IgG successfully cleared SARS-CoV-2 after 46 days of illness, revealing that without antibody-mediated adaptive immunity, innate immunity alone may still be powerful enough to eliminate SARS-CoV-2. This report may provide a basis for further analysis of both innate and adaptive immunity in SARS-CoV-2 clearance, especially in nonsevere cases.

KEYWORDS

antibody, COVID-19, IgG, immunity, SARS-CoV-2

1 | INTRODUCTION

The first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak was reported in December 2019, and the virus has rapidly spread worldwide within 3 months.[1] Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has become pandemic. Most COVID-19 patients show mild or moderate symptoms. Severe cases of COVID-19 might eventually develop acute respiratory distress syndrome, septic shock, multiple organ failure, bleeding, and coagulation dysfunction[2,3]; and is featured by pneumonia, lymphopenia, exhausted lymphocytes, and elevated serum levels of proinflammatory cytokines characterized as a cytokine storm.[3,4] Therefore, the host immune system is thought to have participated in the pathogenesis of COVID-19. The importance of innate and adaptive immunity in the defense against SARS-CoV-2 needs to be urgently determined.[5] To fulfill the pressing need, we examined antibody generation and virus clearance in 26 patients with SARS-CoV-2–induced COVID-19.

2 | MATERIALS AND METHODS

Specimens from sputum, stool, and nasopharyngeal swabs were collected throughout the illness from 30 January 2020 to 5 April 2020. Viral RNA was extracted from clinical specimens, and real-time reverse-transcription polymerase chain reaction was performed to test the presence of SARS-CoV-2 using "Novel Coronavirus 2019-nCoV Nucleic Acid Detection Kit" (Shanghai BioGerm Medical Biotechnology Co, Ltd, China). The serum was collected at distinctive time points, and SARS-CoV-2–specific antibodies were detected using "New Coronavirus (2019-nCoV) Antibody Detection Kit" (Innovita, China). This study was

Bin Wang and Li Wang contributed equally to this study.

TABLE 1 Clinical characteristics of the 26 hospitalized SARS-CoV-2 patients and corresponding timelines of IgG production

Patients/type	Gender/age (y)	Other diseases	AbT (d/IgG/IgM)	NAT (d/NP/Sp/St)	At least coexistence days
1/C	F/58	Congenital heart disease	22/+/+	22/+/NC/NC 25/−/NC/NC 27/−/NC/NC	0
2/C	M/49	No	7/+/+ 10/+/− 14/+/− 20/+/−	18/−/+/− 20/+/+/− 24/−/+/− 26/−/+/− 42/NC/+/NC 57/NC/NC/+	50
3/C	F/34	No	23/+/−	19/−/NC/NC 23/−/NC/NC	NA
4/C	F/55	No	16/+/− 20/+/− 26/+/− 34/+/−	16/NC/−/NC 20/NC/−/NC 26/+/−/+ 32/−/−/+ 34/NC/NC/−	16
5/C	F/22	No	23/+/+ 27/+/+	23/−/NC/NC 29/+/−/− 32/−/−/− 38/−/−/−	6
6/C	F/30	Valvular heart disease	17/−/+ 21/+/+ 27/+/+	17/−/NC/NC 21/−/−/+ 27/−/−/−	4
7/M	F/39	No	9/+/− 16/+/−	9/−/NC/NC 16/−/NC/NC	NA
8/C	M/40	No	23/+/+ 29/+/+ 35/+/+	8/+/NC/NC 16/+/NC/NC 23/+/NC/NC 29/−/+/NC 35/+/+/− 40/−/+/− 42/+/+/NC 43/+/−/NC 44/−/−/NC 56/+/NC/NC 73/+/NC/NC	50
9/C	M/38	Diabetes, 2-3 y	10/+/+ 13/+/+ 17/+/− 20/+/−	17/−/NC/NC 23/+/−/− 24/−/−/− 26/−/−/−	13
10/C	M/72	Ischemic heart disease; hypertension	9/+/+ 12/+/+ 19/+/+	19/+/+/− 24/−/−/− 28/−/−/−	10
11/C	M/38	No	17/+/+ 20/+/+ 24/+/+	24/−/NC/NC	NA

(Continues)

TABLE 1 (Continued)

Patients/type	Gender/age (y)	Other diseases	AbT (d/IgG/IgM)	NAT (d/NP/Sp/St)	At least coexistence days
12/M	F/9	No	14/+/− 18/+/− 24/+/− 15/+/−	5/+/NC/NC 14/−/NC/NC 18/−/−/+ 24/−/NC/− 25/−/−/NC 28/NC/NC/+ 29/NC/NC/− 30/NC/NC/−	14
13/C	M/36	No	15/+/− 21/+/− 29/+/−	15/−/NC/NC 21/+/NC/NC 25/−/+/− 29/+/−/− 32/+/+/NC 34/−/−/+ 36/−/NC/− 37/NC/−/− 51/−/+/NC	36
14/C	F/50	No	10/+/− 17/+/− 23/+/−	14/−/NC/NC 17/−/+/− 23/−/−/− 25/−/−/− 29/−/−/NC 34/NC/+/NC 35/NC/−/NC 36/NC/−/NC	24
15/C	M/37	No	24/+/+ 28/+/+ 34/+/+ 39/+/+	34/−/+/− 36/+/−/− 41/−/−/− 42/−/−/−	12
16/C	F/28	No	15/+/− 19/+/− 26/+/−	19/−/NC/NC 22/−/+/− 26/−/−/− 29/−/+/− 31/−/−/− 33/NC/−/NC 48/+/NC/NC 49/NC/+/NC 60/+/NC/NC	45
17/C	M/40	No	20/+/− 26/+/− 31/+/−	7/+/NC/NC 15/−/NC/NC 20/+/NC/NC 26/−/NC/NC 31/−/+/− 36/−/+/NC 38/NC/−/− 39/NC/−/−	16
18/M	M/32	No	17/+/− 24/+/−	20/−/NC/NC 24/+/NC/NC 30/−/NC/NC	7

TABLE 1 (Continued)

Patients/type	Gender/age (y)	Other diseases	AbT (d/IgG/IgM)	NAT (d/NP/Sp/St)	At least coexistence days
19/C	M/41	No	12/+/+ 15/+/+ 17/+/+ 21/+/+ 27/+/+ 31/+/+	17/−/NC/NC 21/−/+/NC 27/−/−/− 31/−/−/−	9
20/C	F/49	No	18/+/+ 25/+/+ 31/+/+	21/−/−/− 25/−/−/− 31/−/−/− 33/−/−/−	NA
21/C	F/66	Diabetes, 1 y	14/+/+ 21/+/+ 24/+/+	12/+/−/− 21/−/−/− 26/−/−/−	NA
22/M	M/23	No	10/+/−	8/−/NC/NC 10/−/NC/NC 12/−/NC/NC	NA
23/C	F/34	Breast cancer, more than 3 y	15/+/+ 22/+/+	19/−/NC/NC 22/−/NC/NC 26/−/−/−	NA
24/C	F/33	No	18/+/+ 22/+/+	19/−/NC/NC 22/−/NC/NC	NA
25/C	F/5	No	10/+/− 14/+/− 20/+/−	14/+/NC/NC 20/−/NC/NC 23/−/−/+ 29/NC/−/− 30/NC/−/−	13
26/M	F/5	No	30/−/− 40/−/− 66/−/−	20/+/NC/NC 27/−/NC/NC 34/−/NC/NC 40/−/−/NC 42/−/−/NC 46/NC/−/+ 47/−/−/− 48/−/NC/−	NA

Note: The severity of COVID-19 was judged according to the "Fifth Revised Trial Version of the Novel Coronavirus Pneumonia Diagnosis and Treatment Guidance" (http://www.nhc.gov.cn/yzygj/s7652m/202002/41c3142b38b84ec4a748e60773cf9d4f.shtml).
Abbreviations: AbT, antibody testing; C, common type, with fever, respiratory tract and other symptoms, the manifestations of pneumonia can be seen on imaging; d, day; M, mild type, the clinical symptoms were mild and no pneumonia was found in imaging; NA, not applicable; NAT, SARS-CoV-2 nucleic acid testing; NC, not collected due to physical condition or clinical state of the patients; NP, nasopharyngeal; Sp, sputum; St, stool; y, year; +, antibody or nucleic acid testing-positive; −, antibody or nucleic acid testing-negative.

approved by the ethics commissions of Jinan Infectious Disease Hospital, Shandong, China.

3 | RESULTS AND DISCUSSION

A total of 26 patients from 5 to 72 years old were determined to be SARS-CoV-2 RNA-positive by sputum, stool, or nasopharyngeal swabs. The clinical characteristics of the patients and chest computed tomography (CT) scans were also examined. All of them are non-severe COVID-19 patients (Table 1).[2,3]

Specimens from patients 2, 8, 13, and 16 who had been confirmed to be immunoglobulin G (IgG)-positive still tested positive for SARS-CoV-2 nucleic acid after an additional 35 days (Table 1), indicating that SARS-CoV-2 can coexist with its specific antibodies in the human body for an unexpectedly long time (36-50 days).

According to the data collected from patient 2, IgG can be produced at least as early as the 7th day post illness. The average number of days for IgG to be first detected in the four patients was 15; thus, the early production of antibodies does not mean early elimination of this virus. Perhaps the specificity and titer of antibodies are more important. To our knowledge, to date, this is the longest period (36-50 days) to observe the coexistence of SARS-CoV-2 with its specific IgG antibodies in COVID-19 patients. How this virus can circulate in the presence of specific IgG antibodies for such a long time is an interesting question. Whether SARS-CoV-2 can act like hepatitis C virus that have developed strategies to subvert humoral immunity and persists in the body is worth further investigation.[6]

Patient 26, a 5-year-old female, was SARS-CoV-2 nucleic acid testing-positive in a stool sample after 46 days of illness but became nucleic acid testing-negative in specimens of sputum, stool, and nasopharyngeal swabs on day 47 post illness (Table 1). No SARS-CoV-2–specific IgG and IgM antibodies were detected in the patient's serum until the last sample collection day, which was the 66th day post illness. Although we did not collect data about virus-specific cellular immunity, it is known that cellular immunity is generated concomitantly with humoral immunity, so we could preliminarily exclude the potential role of cellular immunity in SARS-CoV-2 elimination in this case. Thus, this is the first report to state that innate immunity plays an essential role in SARS-CoV-2 clearance, which highlights the importance of innate immunity in SARS-CoV-2 clearance. Moreover, innate immunity alone might be enough to clear the virus. Further studies are required to determine which factors or signaling pathways of innate immunity contribute to this process. A broadly protective and universal vaccine for SARS-CoV-2 would take a long time to develop.[7,8] Boosting innate immunity by drugs that mimic viral RNA may contribute to SARS-CoV-2 clearance.[9] Therefore, vaccine combined with innate immune stimulators may be more effective for fast SARS-CoV-2 clearance. We propose that the importance of innate immunity should be investigated further and that the titer and specificity of SARS-CoV-2–specific antibodies are important and should be seriously considered in vaccine development. This case may also indicate that some individuals may not generate specific IgG or IgM antibodies after infection with SARS-CoV-2; thus, only testing SARS-CoV-2–specific antibodies is not a good standard to determine infection, but the combination with the nucleic acid testing method may improve the accuracy of SARS-CoV-2 detection.

Patient 25, another 5-year-old female, was found to be IgG-positive on the 10th day post illness, and the patients turned SARS-CoV-2 nucleic acid testing-negative on the 23rd day post illness. We also observed that a 9-year-old female patient (patient 12) produced IgG antibodies on the 14th day post illness, and this patient turned SARS-CoV-2 nucleic acid testing-negative on the 29th day post illness. These two cases may reveal that children may not show any defects in antibody production and SARS-CoV-2 elimination compared with adults.

The disease severity and fatality were increased with age in COVID-19 patients, which may be explained by the augmentation of proinflammatory responses and the reduction of antiviral cytokines in elder individuals.[10] In our study, the younger patients clear SARS-CoV-2 faster, thus, whether the antiviral immunity such as type I interferon responses were maximized and proinflammatory responses were minimized in these patients is of great interest; and the molecular mechanism involved in the process would be fundamental to our understanding of the immune system.

Taken together, we showed that SARS-CoV-2 could coexist with virus-specific IgG antibodies in COVID-19 patients for an unexpectedly long time and, without adaptive immunity, innate immunity may still be powerful enough to eliminate SARS-CoV-2. The long-term coexistence of IgG with SARS-CoV-2 in the human body raises the question of whether patients with antibodies are still at risk for reinfection, which may make COVID-19 "immunity passports" unfeasible. Our follow-up studies may answer this question and would, therefore, be beneficial to vaccine development.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

XMJ and P-HW conceptualized the study and analyzed the data. CM contributed to reagent and manuscript preparation. BW, LW, XK, JG, and DX performed the experiments. P-HW wrote the first draft of the manuscript. All the authors contributed to revision of the manuscript, and read and approved the final version for publication.

ORCID

Pei-Hui Wang http://orcid.org/0000-0001-6853-2423

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