COMMENTARY

Chronic active SARS-CoV-2 in B-cell immunodeficiency

Jiuyang Xu,[1] Hui Zhang,[1] Yeming Wang,[1] Shiyao Wang,[1] and Bin Cao[1,*]

[1]National Center for Respiratory Medicine; State Key Laboratory of Respiratory Health and Multimorbidity; National Clinical Research Center for Respiratory Diseases; Institute of Respiratory Medicine, Chinese Academy of Medical Sciences; Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing 100029, China

*Correspondence: caobin_ben@163.com

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The Coronavirus Disease 2019 (COVID-19) has gradually evolved from a global pandemic into seasonal epidemic disease, marked by the end of the public health emergency of international concern (PHEIC) in May, 2023. The viral pathogen, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has also been widely recognized as one of the common pathogens for community-acquired lower respiratory tract infections. With the introduction of effective COVID-19 vaccine, several small-molecule anti-viral medications against SARS-CoV-2, and the well-established steroid-based immunomodulatory therapy for severe patients, COVID-19 no longer seems to pose great threat to the general population. However, challenge still remains when it comes to COVID-19 in special populations, especially in the immunocompromised hosts in whom virus clearance can be substantially delayed. Further research is imperative to unravel the intricacies of COVID-19 in such immunocompromised cohorts.

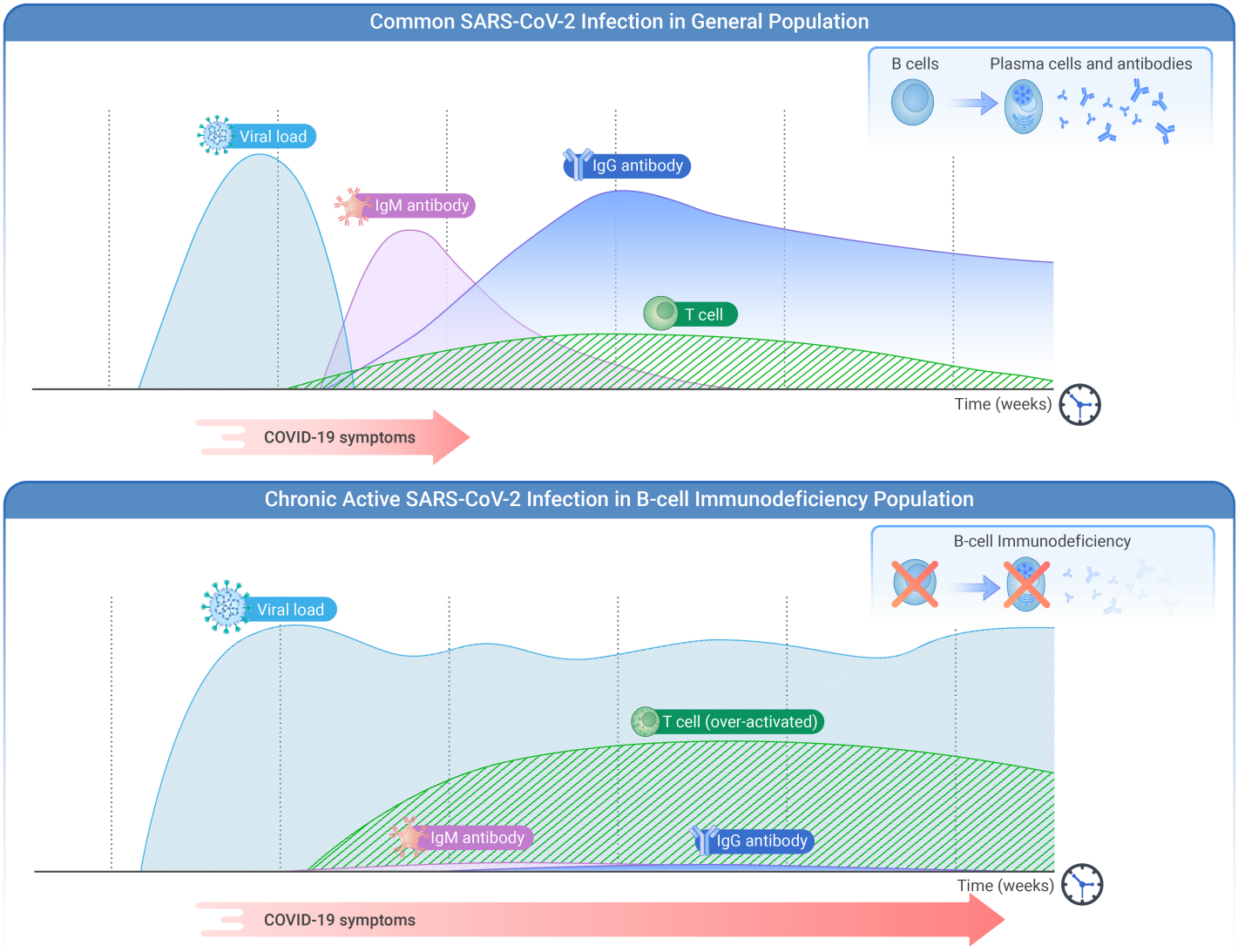

Figure 1. Schematic diagram for chronic active SARS-CoV-2 in B-cell immunodeficiency.

Conventionally, respiratory viruses such as influenza and respiratory syncytial virus cause acute infections typically resolved within 1-2 weeks. However, emerging data challenge this narrative, suggesting that SARS-CoV-2 infection may manifest as *persistent* or *prolonged* in certain circumstances. In a recent article published in *Nature*, Ghafari and colleagues elucidated the concept of "persistent SARS-CoV-2 infection" within a large community-based surveillance endeavor.[1] Within the frame of a national infection survey, the investigators identified individuals with high-titer SARS-CoV-2 RNA test results spanning for at least 30 days, some even longer than 60 days. Viral genome sequencing analysis confirmed persistent infection instead of rein-

fection with a different virus strain. The percentage of persistent infection can be as high as 0.4% in this cohort. Subsequent analyses revealed intra-host evolution and positive selection for the virus, potentially serving as the source for novel mutant strains.

Numerous investigations have shed light on the delayed viral clearance in immunocompromised individuals, particularly those with B-cell immunodeficiency.[2] Humoral immunity, complemented by robust $CD4^+$ T cell responses, plays a pivotal role in viral eradication.[3] This is exemplified by prolonged viral shedding in patients with B-cell lineage hematologic malignancies or those undergoing B-cell targeting therapies like anti-CD20 treatment. We and others have reported such clinical cases – patients who have previously received B-cell targeting therapies and were currently on extended cortical steroids treatment (affecting also the T cell activity) would experience prolonged respiratory symptoms following SARS-CoV-2 infection.[4] Clinical observations underscore the lingering respiratory symptoms following SARS-CoV-2 infection in patients subjected to such therapies, further emphasizing the urgent need for clinical research and therapeutic interventions tailored to this demographic.

A definitive nomenclature for this phenomenon remains elusive. Some studies describe them as *persistent infection*,[5] reflecting the persistence of positive RNA test results and/or prolonged shedding of viable virus in these patients. However, this definition is not perfect, because it also includes the asymptomatic infections, and it does not comprehend the host response and virus-host interplay in the process. In these patients, the limited inflammatory response against viral infection leads to persisting symptoms such as fever and shortness of breath; on the other hand, the immune response is not strong enough to clear the virus, leading to the lesions being migratory in radiological examinations.[4] We propose to describe this scenario as *chronic active SARS-CoV-2 infection*, particularly in *B-cell immunodeficiency* (CASBI) (Figure 1). The *chronic* here describes the persistent detection of SARS-CoV-2 in the respiratory tract samples and prolonged viral shedding, usually for more than 30-60 days. The *active* in the name depicts the effect of persistent viral replication and the host imbalanced response towards virus infection. Since the humoral response is diminished, the cellular response may be abnormally activated and lead to persisting symptoms. CAS is different from long COVID, defined as any persisting symptoms for more than 3 months after COVID-19 and cannot be explained by other reasons, in that persistent virus infection is required, apart from the lasting symptoms.

There are several challenges to recognize and diagnose *chronic active SARS-CoV-2*. Firstly, unlike acute infection, the upper respiratory tract sample may be negative for SARS-CoV-2 and the virus only remains in the lower respiratory tract; in this case, sputum sample or bronchoalveolar lavage fluid sample has to be used for initial diagnosis and sequential follow-up evaluations, especially when CASBI is suspected and upper respiratory tract sample is negative for microbiology tests. Secondly, the radiological presentation of CASBI is not specific to SARS-CoV-2 infection. For example, the migratory ground glass opacities can also be seen in organizing pneumonia, aspirated pneumonia, and drug-associated interstitial lung diseases. Thirdly, the concept of persistent infection for respiratory virus has not been widely accepted. Therefore, we suggest that comprehensive diagnostic evaluations should be taken when caring for special population. In particular, *chronic active SARS-CoV-2* should be added to the differential diagnosis list when encountering patients with sustained respiratory symptoms and pulmonary radiological presentations, especially in patients with B-cell immunodeficiency. Forming a comprehensive diagnostic framework for CASBI is necessary for future clinical practice. Larger case-series or cohort studies are needed to gather further information and portrait CASBI, and a detailed diagnostic criterion or algorithm for the accurate identification of CASBI should be established.

The clinical management of CASBI presents a formidable challenge. To date, there has been few clinical studies focusing on this special condition. While it is acknowledged that the standard 5-day antiviral regimen falls short of addressing the needs of B-cell immunocompromised patients, the ideal dosage and treatment duration remain enigmatic. Whether combination of anti-viral is better than monotherapy still awaits further research evidence. Given the inherent deficiency in humoral response characteristic of CASBI, the potential benefits of antibody-based therapies, including monoclonal antibodies targeting SARS-CoV-2, polyclonal intravenous immunoglobulins (IVIG), and convalescent plasma, warrant thorough examination. Additionally, the role of innate immune responses in CASBI pathogenesis necessitates scrutiny. Investigating the modulation of these pathways, including the interferon signaling, holds promise for enhancing clinical outcomes. Future research is necessary for further understanding of this disease and formulating optimal clinical management strategies.

REFERENCES

1. Ghafari, M., Hall, M., Golubchik, T., et al. (2024). Prevalence of persistent SARS-CoV-2 in a large community surveillance study. Nature **626**: 1094–1101. DOI: 10.1038/s41586-024-07029-4.
2. DeWolf, S., Laracy, J.C., Perales, M.A., et al. (2022). SARS-CoV-2 in immunocompromised individuals. Immunity **55**: 1779–1798. DOI: 10.1016/j.immuni.2022.09.006.
3. Lyudovyk, O., Kim, J.Y., Qualls, D., et al. (2022). Impaired humoral immunity is associated with prolonged COVID-19 despite robust CD8 T cell responses. Cancer Cell **40**: 738-753 e735. DOI: 10.1016/j.ccell.2022.05.013.
4. Wang, S.Y., Wang, Y.M., Liu, M., et al. (2023). Migratory pulmonary ground glass opacities caused by SARS-CoV-2 infection in a patient on B-cell depletion therapy. Zhonghua Jie He He Hu Xi Za Zhi **46**: 1233–1239. DOI: 10.3760/cma.j.cn112147-20230809-00061.
5. Machkovech, H.M., Hahn, A.M., Garonzik Wang, J., et al. (2024). Persistent SARS-CoV-2 infection: Significance and implications. Lancet Infect. Dis. **24**: e453–e462. DOI: 10.1016/S1473-3099(23)00815-0.

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DECLARATION OF INTERESTS

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