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TRANSPLANT INFECTIOUS DISEASE

EDITORIAL

Uncovering hidden sources of SARS-CoV-2 viral evolution: A call to action

The COVID-19 pandemic continues to wreak havoc worldwide with a substantial fraction of the population already been infected with SARS-CoV-2 despite the increasing availability of vaccines. This is largely due to the repeated waves of novel variants (e.g., alpha, beta, gamma, delta, and omicron), with increased transmissibility and more adept immune escape.[1,2] These novel variants appear suddenly with a large collection of mutations that arise unexpectedly without evolutionary intermediates or a documented step-wise accumulation of mutations. This paradox is further compounded by the fact that the coronavirus replication machinery encodes proofreading function that results in fewer errors than other RNA viruses.[3] Together, these findings suggest that a source of cryptic SARS-CoV-2 evolution in the community exists that is not yet readily identified by the current viral surveillance strategies.

In 2020, reports began to surface about the appearance of unusual patterns of SARS-CoV-2 infection and evolution within immunosuppressed patients. One of the first such reports was in a heavily immunosuppressed patient with an autoimmune disease who had 5 months of persistent infection and a prolonged period of SARS-CoV-2 viral evolution, especially within the receptor-binding domain (RBD) of the S gene.[4] A number of the SARS-CoV-2 mutations found in this individual were ultimately found to be signature mutations for subsequent variants of concern or interest (VOC/VOIs), raising the possibility that emergence of new viral variants may have arose in an immunocompromised individual before spilling over to the general population.

In the study by Simons et al. published in this issue of *Transplant Infectious Diseases*, the authors extend our knowledge of SARS-CoV-2 evolution by reporting two additional cases of immunosuppressed individuals with persistent SARS-CoV-2 infection in whom the viral populations acquired mutations associated with circulating VOCs. There were steady increases in intra-host viral population diversity over the course of infection in both patients. Over 131 days, patient A developed a Spike E484Q mutation (also observed in formerly monitored variant Kappa) and the deletion of residues 241–243 (VOC Beta), while Patient B developed a Spike E484K mutation (VOCs Beta and Gamma as well as formerly monitored variants Zeta, Eta, Theta, and Iota) over 106 days of infection. These mutations have been previously associated with humoral immune evasion and decreased neutralization by convalescent serum.[5] Both patients had a history of B-cell malignancies and were receiving rituximab; Patient A had also undergone a hematopoietic stem cell transplant. While Patient A had low levels of antibody targeting the N-terminal domain of Spike, neither patient had detectable levels of antibody targeting the RBD of Spike at the time of sampling. These findings are consistent with previously published reports that humoral immune deficiencies are a common theme in these cases and that those with persistent COVID-19 have evidence of accelerated viral evolution, especially in the S gene.[6] However, additional studies are needed to understand the underlying immune conditions that predispose to SARS-CoV-2 persistence as advanced HIV and other immunosuppressive conditions not primarily targeting the humoral immune response may also lead to prolonged infection.[7] Taken together, these results demonstrate the potential for concerning variants to evolve in immunosuppressed patients with persistent SARS-CoV-2 infection, support increased viral surveillance in immunosuppressed patients over prolonged disease courses, and emphasize the importance of ongoing efforts to develop effective antiviral drugs for the suppression of viral replication.

Another interesting aspect of this report is that both patients were treated early in their infections with the monoclonal antibody (mAb) bamlanivimab. Both patients developed mutations at the E484 amino acid position in the RBD that is known to confer resistance to bamlanivimab. In the bamlanivimab clinical trials, E484KQ mutations represented the most frequent treatment-emergent mutations to arise, and resistance emergence was linked to resurgence of high level viral shedding and worsening symptoms.[8,9] While bamlanivimab is no longer used clinically, especially as monotherapy, it is nevertheless instructive as proof-of-principle of the risk and clinical implications of treatment-emergent resistance within the mAb class of antiviral agents. Furthermore, resistance to single mAb treatment is not restricted to bamlanivimab as a recent report identified sotrovimab resistance emergence in several immunosuppressed patients treated with that single mAb,[10] and treatment-emergent resistance to bebtelovimab was been detected in 5% of mAb-treated participants in the BLAZE-4 study.[11] While combination mAb treatment results in lower rates of resistance emergence overall, immunosuppressed patients appear to remain at risk of resistance development even with dual mAb treatment.[12] The results highlight the potential for rapid emergence of resistance during mAb treatment and the need for close monitoring for signs of viral persistence and drug resistance.

While these case reports contribute to our understanding of viral evolution in immunosuppressed patients, it also highlights the need for systematic evaluations of SARS-CoV-2 persistence and optimal treatment strategies in this understudied patient population to answer pressing questions. These fundamental questions include what is the frequency of persistent COVID-19 in the immunosuppressed

population, which immunosuppressive conditions or medications confer the greatest risk of suboptimal viral clearance, and should combinations of antiviral treatments be used for the treatment of immunosuppressed patients with COVID-19? Given the broad spectrum of immunosuppressive conditions and the challenges of identifying sufficient numbers of patients at any one clinical center, filling these knowledge gaps will likely require a coordinated effort among a network of committed investigators and funders. The answers to these questions will not only allow us to better care for our immunosuppressed patients with COVID-19 but will provide crucial insights into the immune correlates of viral clearance and may uncover the keys to prevent the emergence of future SARS-CoV-2 variants that serve to fuel the ongoing pandemic.

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CONFLICT OF INTEREST

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