Case Report: Severe COVID-19 in a Kidney Transplant Recipient Without Humoral Response to SARS-CoV-2 mRNA Vaccine Series

Masaaki Yamada, MD,1,2 Eiyu Matsumoto, MB,1,3 Christie P. Thomas, MBBS,1,2 Jennifer R. Carlson, PA-C,3 J. Stacey Klutts, MD, PhD,4,5 Bharat Kumar, MD,1,2 Judy A. Streit, MD,1,2 and Melissa L. Swee, MD1,2

The ongoing global pandemic of coronavirus disease 2019 (COVID-19), due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has prompted the rapid development of several safe and effective vaccines.1 The earliest to receive emergency use authorization by the US Food and Drug Administration were 2 novel mRNA vaccines. The short-term efficacy of these mRNA vaccines from their phase 3 trials has been comparable with that of highly effective conventional vaccines. In healthy trial participants, these mRNA vaccines reduced symptomatic SARS-CoV-2 infection by over 90%.2-4 However, the efficacy and long-term immunogenicity of SARS-CoV-2 mRNA vaccines have not yet been thoroughly studied in immunocompromised populations. One of the earliest studies reported reduced humoral response to mRNA vaccine in solid organ transplant (SOT) recipients.5

We report a case of a long-term kidney transplant recipient on stable maintenance immunosuppression who acquired COVID-19 with onset of symptoms about 11 d after his second dose of SARS-CoV-2 mRNA vaccine.

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1 Department of Internal Medicine, University of Iowa, Iowa City, IA.
2 Department of Medicine, Iowa City VA Medical Center, Iowa City, IA.
3 Department of Emergency Medicine, Iowa City VA Medical Center, Iowa City, IA.
4 Department of Pathology, University of Iowa, Iowa City, IA.
5 Department of Pathology, Iowa City VA Medical Center, Iowa City, IA.
M.Y. and E.M. contributed equally to this article.
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CASE REPORT

A 76-y-old male individual with end-stage kidney disease secondary to IgA nephropathy who underwent kidney transplantation with antithymocyte globulin induction 6 y prior presented with exertional dyspnea. His post-transplant course has been uncomplicated without kidney allograft rejection, chronic infection, or hospitalization. His maintenance immunosuppression has been stable with tacrolimus (target drug trough level 5–8 ng/mL) and mycophenolate mofetil 1000 mg twice daily. He had a baseline serum creatinine ranging from 0.9 to 1.0 mg/dL without proteinuria. He completed a 2-dose series of COVID-19 vaccine (mRNA-1273, Moderna; Cambridge, MA) at the recommended 4-wk interval and received the second dose in mid-February (shown in Figure 1).

Approximately 26 d before admission, he started to develop a nonproductive cough and intermittent low-grade fevers. His symptoms gradually worsened, and 5 d before admission, he was evaluated in the emergency department. Vital signs were notable for tachypnea: body temperature 36.7 °C, blood pressure 127/83 mm Hg, heart rate 83 bpm, respiratory rate 24 bpm, and SatO2 96% on ambient air. His physical examination was otherwise unremarkable. Chest X-ray did not demonstrate any acute findings (shown in Figure 1, CXR #1). He was discharged with a 6-d course of glucocorticoid therapy. He was not tested for SARS-CoV-2 at that time because he had been fully vaccinated. However, his respiratory symptoms appeared around 11 d after the second vaccination.

He presented again to the hospital, where he was found to be tachypneic and severely hypoxic. His respiratory rate was 30 bpm, and pulse oximeter reading was 66% on ambient air. Arterial blood gas (FiO2 0.44) confirmed acute hypoxic respiratory failure: pH 7.49, Paco2 30.3 mm Hg, PacO2 55.5 mm Hg, HCO3 24.5 mmol/L, and SatO2 at 89.7% despite supplemental oxygen. Chest X-ray now showed an interstitial opacity in the left lower lung (shown in Figure 1, CXR #2). COVID-19 was confirmed with a positive nasopharyngeal swab sample by SARS-CoV-2 real-time reverse transcription-polymerase chain reaction with a cycle threshold value for target N2 of 19.5 (Xpert Xpress SARS-CoV-2, Cepheid; Sunnyvale, CA). He was admitted to the intensive care unit for further treatment.

Upon admission, his exam was notable for bibasilar crackles in lower lung fields without peripheral edema. White blood cell count was 7500/µL; absolute lymphocyte count, 150/µL.
(baseline 5 mo prior: 550/µL); serum creatinine, 1.5 mg/dL; Troponin-I, 0.01 ng/mL; BNP, 175 pg/mL; and D-dimer, 557 ng/mL (shown in Table 1, SDC, http://links.lww.com/TXD/A349). Nonfasting glucose was 492 mg/dL, and hemoglobin A1c was 8.2%. A SARS-CoV-2 antispike antibody was undetectable (<0.8 units) by semiquantitative immunoassay (Elecsys Anti-SARS-CoV-2 S, Roche Diagnostics; Indianapolis, IN). A repeat nasopharyngeal sample obtained 2 d after admission confirmed persistent positivity of SARS-CoV-2 by reverse transcription-polymerase chain reaction with a cycle threshold value for target N2 gene of 15.2.

Shortly after admission, noninvasive positive pressure ventilation was initiated for increasing oxygen requirements. Dexamethasone 6 mg daily and remdesivir 100 mg daily were given intravenously. Monoclonal antibody and convalescent plasma therapy were considered but not pursued because of the delay in diagnosis of COVID-19 and the insufficient evidence of efficacy in hospitalized patients. His tacrolimus dose was reduced, and mycophenolate mofetil was discontinued. Despite these efforts, he continued to decompensate and died on the seventh day after admission.

**DISCUSSION**

This case of a kidney transplant recipient who developed a fatal COVID-19 infection about 11 d after completion of the SARS-CoV-2 mRNA vaccine series highlights the importance of stratifying the risk of COVID-19 in immunosuppressed patients, even after vaccination. Although the immunogenicity of the mRNA vaccines is robust enough to prevent severe COVID-19 in immunocompetent patients, this case suggests that the efficacy of mRNA vaccine could be less in SOT recipients who require ongoing immunosuppression. In transplant recipients, therefore, it is imperative to consider and test for SARS-CoV-2 in symptomatic patients even after vaccination.

The safety and efficacy of the SARS-CoV-2 mRNA vaccines (BNT162b2 and mRNA-1273) have been established in 2 large randomized placebo-controlled double-blind phase 3 trials that enrolled healthy adults. Antibodies against the SARS-CoV-2 spike protein were measurable by day 15–21 following the first dose and reached levels similar to patients recovering from COVID-19 by day 28. In those vaccine trials, protection from infection began around day 10, when antibody responses were still fairly weak, although it reached its maximum efficacy after the second dose, coinciding with the robust rise in antibody titers. Both SARS-CoV-2 mRNA vaccines lowered the rate of symptomatic COVID-19 by 90%–95% and prevented the development of severe COVID-19. Occasionally, postvaccination breakthrough infection has been reported in the general population. It is defined as the detection of SARS-CoV-2 in a person ≥14 d after the completion of all recommended doses. This also illustrates the importance of early detection of SARS-CoV-2 infection because diagnostic delays may lead to uncertainty in differentiating a breakthrough infection from the infection that began before day 14 of the second vaccination. The
emergence and evolution of novel variants of SARS-CoV-2 could play a major role in those postvaccination breakthrough infection or reinfection with SARS-CoV-2.\textsuperscript{11-13}

Once emergency use authorization was approved by the Food and Drug Administration, COVID-19 mRNA vaccinations were prioritized for healthcare workers, the elderly, and those with comorbidities that increase their risk of severe COVID-19 and mortality. After tens of millions of vaccinations having been administered, early observed protection appears similar to that seen in clinical trials.\textsuperscript{4,9,14,15} However, we have little data on the efficacy of these novel vaccines in immunocompromised individuals, and early data on the vaccine response are being collected in SOT recipients.\textsuperscript{5,16} Boyarsky et al\textsuperscript{16} reported that 357 of 658 SOT recipients (54\%) mounted appreciable anti-spike protein antibody at a median of 29 d after the second dose of COVID-19 vaccine; however, the remaining patients remain seronegative. Grupper et al\textsuperscript{5} reported that the incidence of seroconversion was only 38\% (51 of 136 patients with SOT) following the second dose of BNT162b2; 2 seronegative patients developed severe COVID-19 during the follow-up period and 1 patient died. Additionally, preprint data of total 104 vaccinated individuals (39 healthy controls, 39 age-matched kidney transplant recipients, and 26 hemodialysis patients) suggest that kidney transplant recipients demonstrate diminished humoral response (<20\%) to BNT162b2 despite a complete 2-dose series.\textsuperscript{17} In the same data, SARS-CoV-2 spike-specific T-cell response was seen in >90\% of transplant recipients, though, with the reduced magnitude of the T-cell response.\textsuperscript{17} These studies also shed light on uncertainties in identifying and documenting immune responses, including the degree to which humoral immunity is protective and the correlation between antibody levels and degree of protection.

Several lines of evidence suggest that the novel mRNA vaccines stimulate both humoral and cellular immune systems, leading to a coordinated immune response to counter viral infection.\textsuperscript{18,19} Notably, SARS-CoV-2-specific T-cell response can be present even in seronegative individuals.\textsuperscript{20} These discordant responses are more often seen in those with mild or asymptomatic COVID-19 such as exposed family members.\textsuperscript{21} This suggests that T-cell immunity, even without detectable anti-spike antibody, could be the primary immune response in those with asymptomatic or milder form of COVID-19. Although there are scarce data about T-cell responses induced by SARS-CoV-2 mRNA vaccines in the immunocompromised population, our patient’s clinical presentation suggests that he was unable to mount both cellular and humoral responses to the virus. Lymphocyte transformation studies to mitogen and antigen were not performed. The undetectable level of anti-spike antibody confirms decreased humoral responses, while concomitant use of tacrolimus and mycophenolate mofetil at the therapeutic levels could impair cellular responses. This is analogous to decreased cellular and humoral immune responses after influenza vaccine in SOT recipients compared with ones in healthy controls.\textsuperscript{22-24}

The efficacy of most vaccines, including influenza vaccine, is generally lower in transplant recipients.\textsuperscript{24-27} Patients with inadequate immune response after vaccination, as in our case where antispikes antibodies to SARS-CoV-2 were undetected, would be more susceptible to SARS-CoV-2 infection.\textsuperscript{3} Postvaccination breakthrough infection with SARS-CoV-2 may occur more often in susceptible individuals due to inadequate immune response.\textsuperscript{28,29} Therefore, it is crucial for front-line healthcare providers to be aware of this fundamental limitation of the COVID-19 vaccine in immunocompromised individuals and to suspect SARS-CoV-2 infection in high-risk patients presenting with compatible symptoms. One strategy to protect this high-risk population is to achieve herd immunity by promoting vaccination (c.f., influenza vaccination in the community).\textsuperscript{30,31} Preprint data from Israel seem to indicate that mass vaccination could potentially reduce the risk of SARS-CoV-2 infection in the community\textsuperscript{32}; and data from Scotland suggest that vaccination was associated with the reduced risk of household transmissions.\textsuperscript{33} Another strategy is to improve efficacy of mRNA vaccination in SOT recipients by various approaches such as doubling dosage or administering an additional vaccine as a booster.\textsuperscript{34} While vaccines remain the cornerstone of COVID-19 prevention, passive immunotherapy using neutralizing monoclonal antibodies could potentially be used prophylactically or as therapeutic in certain vulnerable populations, including recipients who were recently transplanted within 3 mo.\textsuperscript{35,36} Compared with the mass vaccination strategy, justification of alternative vaccine dosage or schedule and the prophylactic use of passive immunotherapy are still lacking scientific evidence. Nevertheless, this case report and the review of the vaccine immunogenicity studies in transplant recipients reinforce the importance of continuing precautions to reduce exposure such as masking and physical distancing, mass vaccination, and vaccination of close household contacts, or until further studies are available on vaccine efficacy in these vulnerable patients.\textsuperscript{34,37}

CONCLUSION

The present case documents that fatal COVID-19 can occur in immunocompromised patients, even after vaccination. This has broad ramifications for immunocompromised patients and healthcare providers. First, physicians should have a high suspicion for COVID-19 regardless of vaccination history in this susceptible population to prevent diagnostic delays. Second, patients at risk for severe COVID-19 should be advised to continue protection against the disease because vaccination will not eliminate the likelihood of infection. Finally, policymakers and regulators should be aware that the only effective way to halt the spread of COVID-19 and protect vulnerable populations is achievement of herd immunity.

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