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# Acute Kidney Allograft Rejection Following Coronavirus mRNA Vaccination: A Case Report

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## INTRODUCTION

Since the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, worldwide efforts to develop and institute mass vaccination campaigns have proven efficacious in stemming coronavirus disease 2019 (COVID-19)-associated morbidity and mortality. Recipients of solid organ transplants (SOTs) represent a vulnerable population for infection with SARS-CoV-2 and subsequent morbidity and mortality from COVID-19.<sup>1</sup> Various studies have estimated mortality rates between 18% and 43% in kidney transplant recipients and higher rates of acute kidney injury and graft failure have been reported.<sup>1,2</sup>

Development of vaccines against SARS-CoV-2, including multiple mRNA-based vaccines, has largely resulted in preventing and reducing severe COVID-19 disease.<sup>3,4</sup> The immunogenicity of these vaccines has been demonstrated in healthy patients. However, the majority of these trials have excluded recipients receiving long-term immunosuppressive therapy

including SOT recipients. Two of the leading available vaccines use mRNA-based technology, with variable immunological responses in SOT recipients. Subsequent analyses of the efficacy of COVID-19 vaccination in this population confirmed their safe use, although patients exhibited diminished immunogenic responses, likely owing to baseline immunosuppression. Furthermore, vaccination side effects remain very uncommon, although complications such as myocarditis and Bell's palsy have been reported to the Centers of Disease Control Vaccine Adverse Events Reporting database.<sup>5</sup> Herein, we review a case of severe acute allograft rejection in a kidney transplant recipient temporally related to immunization with the mRNA-1273 SARS-CoV-2 (Moderna) vaccine.

## CASE DESCRIPTION

A 53-y-old Caucasian male presented to hospital following an asymptomatic nonoliguric rise in his serum creatinine after receiving his second immunization with the mRNA-1273 SARS-CoV-2 vaccine. His medical history was significant for hypertension, obstructive sleep apnea, and obesity (body mass index 33.5 kg/m<sup>2</sup>). The cause of his end-stage kidney disease was biopsy-proven secondary focal and segmental sclerosing glomerulosclerosis, for which he received a preemptive living-related kidney transplant (cytomegalovirus-mismatch) approximately 23 mo earlier. At that time, he received basiliximab for induction and was maintained on prednisone (5 mg), mycophenolate (Myfortic, 720 mg twice daily), and tacrolimus (trough target 4–6 µg/L). His posttransplant course was uncomplicated, with a baseline estimated glomerular filtration rate of 50 mL/min/1.73 m<sup>2</sup> (130 µmol/L) and no issues with medication adherence. There was no history of prior COVID-19 infection.

Following his first dose of the COVID-19 vaccine, the patient developed a self-limiting episode of Bell's palsy with right-sided facial involvement. This was treated with valacyclovir and prednisone with complete symptom resolution. In accordance with public health recommendations, he received the second dose of the vaccine 10 wk later. Incidentally, as part of routine allograft monitoring, the patient had investigations 24 h following his second vaccine dose. They demonstrated an elevated creatinine of 282 µmol/L (Figure 1; Table S1, SDC, <http://links.lww.com/TXD/A401>). He presented to a local secondary hospital for assessment, whereby a repeat measurement showed further decline in renal function with a creatinine of 349 µmol/L. He endorsed typical postvaccine symptoms including fatigue and muscle aches, as well

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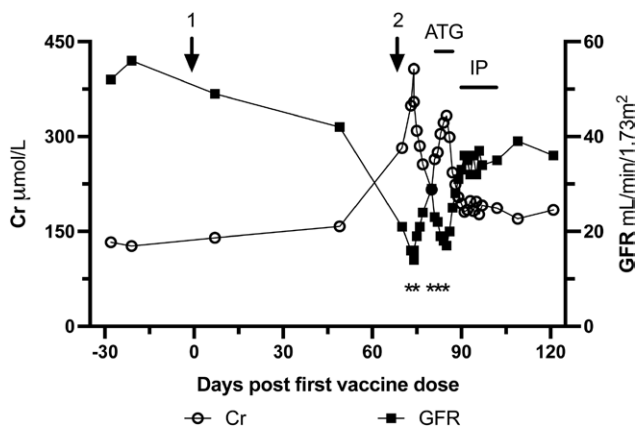
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**FIGURE 1.** Timeline of kidney function (Cr and GFR) in relation to first and second doses of COVID-19 vaccination (black arrows, denoted). Methylprednisolone (\*), ATG, and IP given as denoted. ATG, antithymocyte globulin; COVID-19, coronavirus disease 2019; Cr, creatinine; GFR, glomerular filtration rate; IP, IVIG with plasmapheresis.

as lower than normal home blood pressure readings (90–110 mmHg systolic compared with 130–140 mmHg). His clinical history was otherwise noncontributory. Remaining investigations (including hematological, chemistries, and microbiological including COVID-19 polymerase chain reaction) were unremarkable, with the exception of new mild proteinuria (protein:creatinine 30 mg/mmol). Ultrasound assessment of the allograft was also unremarkable, with no evidence of obstruction and patent renal artery and vein. Serum tacrolimus trough levels in the months preceding were within therapeutic range (5.5–8.3 µg/L), and he denied any medication noncompliance. He was fluid resuscitated and given empiric methylprednisolone (100 mg for 2 doses) with initial evidence of renal recovery. Given the rapidity of renal decline, we opted to transfer him to our tertiary transplant center for expedited biopsy.

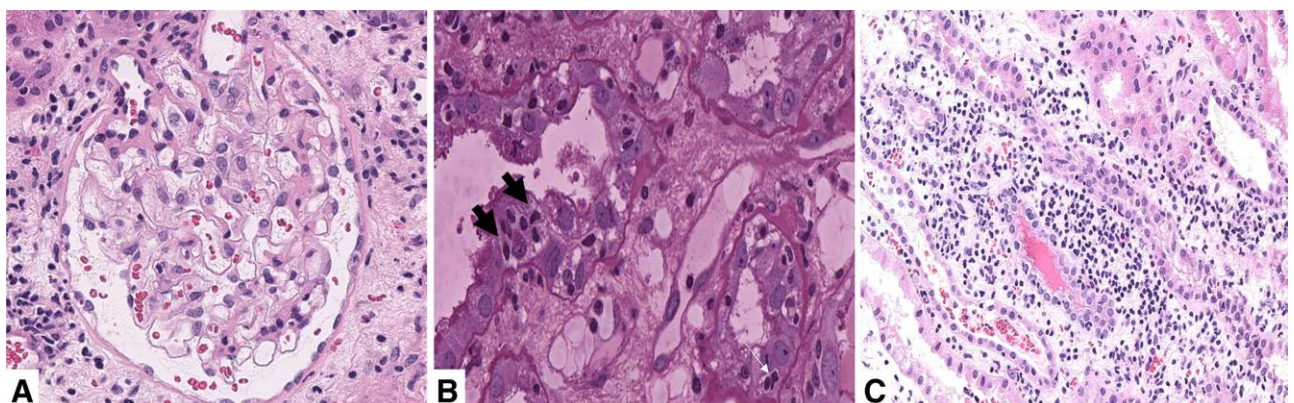
Following transfer, HLA antibody testing did not identify any new donor-specific antibodies (DSAs). We conducted serological testing for antibodies against the SARS-CoV-2 spike protein (DiaSorin, Saluggia, Italy), which was returned strongly positive, whereas antibodies against the nucleocapsid protein were not isolated. This suggested a strong immunogenic response to vaccination versus immunity through

natural infection. An allograft biopsy revealed interstitial edema and lymphocytic inflammation with severe lymphocytic tubulitis, consistent with severe T cell-mediated rejection (TCMR; Figure 2). There was marked acute tubular injury (tubular dilation, epithelial flattening), with minimal tubular atrophy (5%). There was no tubular necrosis or granular casts present. No evidence of vasculitis or arterial inflammation was seen. On light microscopy, 20 glomeruli were visualized with no histological abnormalities. The peritubular capillaries showed mild lymphocytic inflammation and weak positive immunoperoxidase staining for C4d (Figure 3). Immunofluorescence was negative for immunoglobulin (Ig)A, IgG, IgM, kappa, lambda, C1q, C3c, and fibrinogen. Electron microscopy showed mild focal podocyte effacement with no electron dense deposits visualized. The final Banff classification for this biopsy was denoted as g0, t3, i3, v0, cg0, ct1, cv0, ah0, ahp0, ptc1, ti0, i-IFTA0, C4d1, and SV40 negative.

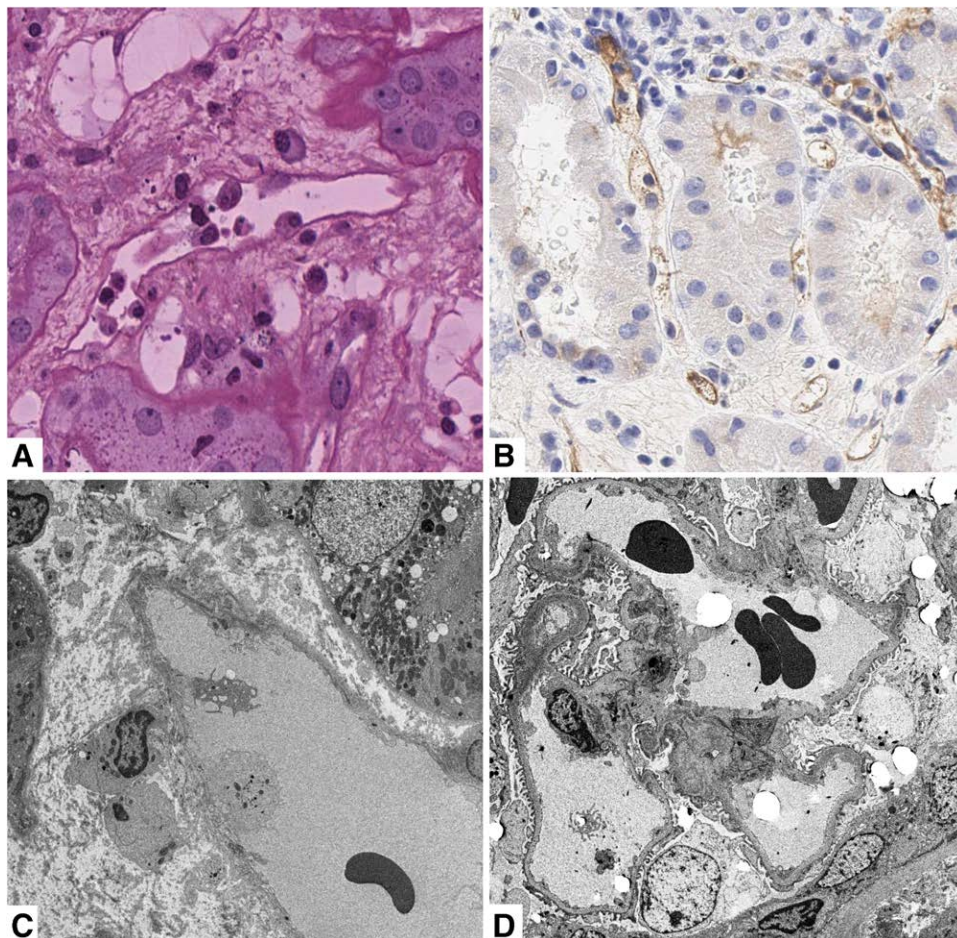
Given the severity of TCMR and worsening renal function, reinduction with methylprednisolone (500 mg for 3 doses) and antithymocyte globulin (total 5 mg/kg in divided doses) was administered with marginal effect. Despite the absence of a detectable DSA and available non-DSA (anti-MIC and antiendothelial), with the presence of C4d stain on histology, there was concern for antibody-mediated rejection contributing to allograft dysfunction. As such, a course of IVIG (0.4 g/kg × 5 d) interspersed with plasmapheresis (5 sessions) was initiated. A follow-up biopsy 9 wk following initial presentation demonstrated improved, albeit ongoing evidence of TCMR (Fig S1, SDC, <http://links.lww.com/TXD/A401>), and as such, his prednisone taper was extended, although no further improvement in renal function was observed (creatinine stabilized between 170 and 190 µmol/L).

## DISCUSSION

COVID-19 continues to pose a significant risk to SOT recipients, and with limited therapeutic options once infected, vaccination remains the mainstay for prevention. The mortality associated with COVID-19 infection has been widely reported to be significantly greater in patients receiving immunosuppressive agents following organ transplantation.<sup>1,2,6</sup> Historically, recipients of SOTs have shown a diminished immunogenic response to vaccination, which imparts the



**FIGURE 2.** Kidney biopsy, light microscopy. Severe acute T cell-mediated rejection. A, Photomicrograph showing an unremarkable glomerulus (H&E section, PAS). B, Photomicrograph showing severe lymphocytic tubulitis (black arrows) (plastic section, PAS). C, Photomicrograph showing marked interstitial lymphocytic inflammation (H&E section). Final Banff classification was denoted as g0, t3, i3, v0, cg0, ct1, cv0, ah0, ahp0, ptc1, ti0, i-IFTA0, C4d1, and SV40 negative. H&E, hematoxylin and eosin; PAS, periodic-acid Schiff.



**FIGURE 3.** Kidney biopsy, light microscopy. A, Photomicrograph showing peritubular capillary lymphocytic inflammation (plastic section, PAS). B, Photomicrograph showing weak positive staining of C4d in peritubular capillaries. Electron microscope images showing unremarkable peritubular capillary (C) and glomerular basement membranes (D) with mild focal podocyte effacement. PAS, periodic-acid Schiff.

risk of breakthrough infections.<sup>7</sup> This has been demonstrated with influenza and hepatitis B vaccinations, among others.<sup>8,9</sup> The immunogenicity toward COVID-19 vaccinations in this population has demonstrated wide variances from 0% to 59%, with one large study demonstrating that almost half of participants did not generate an immunological response.<sup>10-12</sup> In contrast, our patient developed a strong antispikes protein antibody titer, having received a full vaccine series, highlighting the unpredictability of immunological response.

Earlier literature postulated a mechanism by which vaccinations might trigger an episode of allograft rejection, although this association has never been substantiated. In the case of influenza vaccinations, no apparent risk of rejection has been attributed, although development of *de novo* antibodies postvaccination has been reported.<sup>13</sup> Studies examining the safety profile of COVID-19 vaccination in kidney transplant recipients did not identify allograft rejection as a consequence. Rather, typical side effects such as injection site pain and fatigue postvaccination were comparable between immunosuppressed and nonimmunosuppressed patients.<sup>14</sup> None of the patients in these studies developed *de novo* DSAs. Only 1 other case of acute cellular rejection has been associated with the BNT162b2 (Pfizer BioNTech) mRNA vaccine has been reported,<sup>15</sup> and in that instance, novel class II DSAs were detected. Despite a modest response to steroids, our patient's renal function was minimally affected by therapies directed

against antibody-mediated rejection (ie, plasmapheresis and IVIG). In conjunction with weak C4d stain and no detectable DSA, this suggests that the primary mechanism behind our patient's episode of acute allograft rejection is unlikely to be antibody mediated, consistent with his biopsy histology.

Emerging research suggests discordant humoral and T cell-mediated responses to mRNA vaccines in kidney transplant recipients.<sup>14,16</sup> In certain instances, T cell-mediated responses after vaccination, although both remain relatively lower compared with nonimmunosuppressed patients. In one series, 29.9% of patients developed detectable antibody responses 2 wk postvaccination, whereas 54.7% mounted a detectable T-cell response.<sup>14</sup> Factors that portended poor humoral or cellular responses to COVID-19 vaccination included diabetes, antithymoglobulin, or transplantation within 1 y and lymphopenia, all of which were not applicable to our patient. Robust T-cell responses following mRNA vaccination have been postulated to infer greater protection to COVID-19 disease through contribution to long-term immunological memory.<sup>17,18</sup> Clarifying the interactions between humoral and T-cell responses to COVID-19 vaccination in SOT recipients remains an area of great interest, particularly in development of strategies to mitigate disease severity in this vulnerable population.

With our patient, treatment of TCMR required aggressive therapy leading to incomplete allograft recovery and

highlights the limited utility of therapies directed at antibody-mediated rejection. By comparison, risk of COVID-19-related morbidity and mortality is much greater compared with the risk of vaccination-related allograft rejection. In our program, of 1178 active transplant recipients with functioning allografts, 71 (6.9%) contracted COVID-19, higher than both the provincial (5.3%) and Canadian (3.7%) incidence rates.<sup>19</sup> Of greater concern, 7 (9.9%) transplant recipients died from COVID-19, compared with rates of mortality in both Alberta (0.98%) and Canada (1.9%), a mortality rate 5- to 10-fold higher than the general populace. Thus, vaccination offers modest protection against severe disease and adverse outcomes and is recommended in this patient population.<sup>20</sup> Currently, there are no consensus recommendations for biological monitoring postvaccination, and evidence for booster vaccinations in transplant recipients has only recently been established.<sup>21</sup> Ultimately, this case highlights a possible, rare complication of mRNA-based COVID-19 vaccines and the need for further close monitoring in the transplant population.

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