A Case Series of Patients With Acute Liver Allograft Rejection After Anti–SARS-CoV-2 mRNA Vaccination

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Transplant recipients are known to be at an elevated risk of mortality in the event of SARS-CoV-2 infection, and vaccination has been shown to improve survival.[1] No studies have specifically assessed the immunogenic risk of SARS-CoV-2 vaccination for solid organ transplant recipients. To date, there has only been 1 case report of liver allograft rejection associated with a SARS-CoV-2 vaccine, although this was confounded by simultaneous withdrawal of low dose prednisolone.[2]

Three liver transplant recipients from a single quaternary center developed deranged liver function within 2 wks of receiving SARS-CoV-2 vaccination without any alternate identifiable precipitant for rejection (see Table 1). They were all diagnosed with moderate or severe liver allograft rejection, which was confirmed on histopathological examination of liver allograft biopsies following identification of abnormal liver function tests (see Figure 1). All 3 cases were treated with intravenous methylprednisolone (dose of 1 g daily initially) followed by a wean of oral prednisolone starting at 40 mg.

Case 1 experienced a later relapse of rejection requiring retreatment with 2 courses of intravenous methylprednisolone. She remains on triple immunosuppression. Case 2 developed evolving liver allograft failure despite receiving empiric treatment for antibody-mediated rejection including plasma exchange, intravenous immunoglobulin, and rituximab. During workup for retransplantation, she contracted COVID-19 and ultimately died from its complications. Case 3 took a longer time to respond than is usually observed with typical rejection (post treatment peak gamma-glutamyl transferase at day 34, see Table 1). She was commenced on ursodeoxycholic acid (500 mg twice daily), which appeared to hasten the recovery of the gamma-glutamyl transferase. She remains on triple immunosuppression.

This case series suggests that there may be a causal link between the Pfizer-BioNTech vaccine and allograft rejection in susceptible liver transplant recipients. The temporal relationship between receipt of the vaccine, onset of symptoms, and subsequent liver biochemistry derangement is highly suggestive that the vaccine was at least partially responsible for the onset of rejection. These cases also had particularly dramatic cholestasis with jaundice, poor initial treatment response, and slower recovery than what would usually be seen in a rejection episode, which may suggest a unique pathophysiological mechanism underlying the rejection.

It is biologically plausible that an mRNA vaccination could precipitate acute cellular rejection of the liver in a predisposed individual. The mRNA vaccination induces the host to create the spike protein from the SARS-CoV-2, and it has been shown that recombinant antibodies to this spike protein can cross react with human tissue.[3] There have also been case reports of de novo autoimmune hepatitis following the SARS-CoV-2 vaccine among individuals without preexisting liver disease.[4,5]

Among liver transplant recipients at our center, a total of 2332 SARS-CoV-2 vaccines (Pfizer, n = 1189; AstraZeneca, n = 1048; Moderna, n = 95) have been administered. Therefore, it is clear that, if this association is real, clinically significant rejection triggered by vaccination appears to be rare. Nevertheless, we suggest biochemical monitoring of liver function in the weeks following vaccination. Further observation and experience with these vaccines are needed to establish if a true causal link exists.

REFERENCES

1. Ravanan R, Mumford L, Ushiro-Lumb I, et al; OTDT Clinical Team. Two doses of SARS-CoV-2 vaccines reduce risk of death due to COVID-19 in solid organ transplant recipients: preliminary outcomes from a UK Registry linkage analysis. *Transplantation*. 2021;105:e263–e264.
2. Vyhmeister R, Enestvedt CK, VanSandt M, et al. Steroid-resistant acute cellular rejection of the liver after severe acute respiratory syndrome coronavirus 2 mRNA vaccination. *Liver Transpl*. 2021;27:1339–1342.
3. Vojdani A, Vojdani E, Kharrazian D. Reaction of human monoclonal antibodies to SARS-CoV-2 proteins with tissue antigens: implications for autoimmune diseases. *Front Immunol*. 2020;11:617089.
4. Bril F. Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: one or even several swallows do not make a summer. *J Hepatol*. 2021;75:1256–1257.
5. Rela M, Jothimani D, Vij M, et al. Auto-immune hepatitis following COVID vaccination. *J Autoimmun*. 2021;123:102688.

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TABLE 1.

Clinical parameters

	Age	Gender	Allograft (etiology of liver disease)	Years posttransplant	Immunosuppression at presentation (tacrolimus trough level)	Pfizer-BioNTech dose	Detection postvaccination (d)	Peak LFT derangement (d postvaccination)					RAI
								ALT (U/L)	AST (U/L)	GGT (U/L)	ALP (U/L)	Bilirubin (mmol/L)	
Case 1	48	Female	Liver (cryptogenic cirrhosis)	3	Tacrolimus 1 mg BD (6 µg/L)	First	14	1235 (14)	820 (14)	1468 (43)	419 (43)	409 (42)	6–7
Case 2	24	Female	Liver-kidney[a] (Caroli's disease, autosomal recessive polycystic kidney disease)	7	Tacrolimus extended release (6.5 µg/L) Mycophenolate mofetil 1 g BD Prednisolone 5 mg daily	First	12	187 (12)	254 (12)	465 (36)	241 (36)	372 (27)	8
Case 3	20	Female	Liver (biliary atresia)	17	Tacrolimus extended release 3 mg daily (5.4 µg/L)	First	8	1674 (17)	530 (17)	992 (34)	200 (14)	91 (21)	5–6[b]

Case 3 had previously received the standard 2-dose regimen of the AstraZeneca vaccine 6 mo earlier.
[a]No renal allograft dysfunction was observed.
[b]Modified by pretreatment effect (4 d of oral prednisolone 40 mg daily).
ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BD, twice daily; GGT, gamma-glutamyl transferase; LFT, liver function test; RAI, rejection avidity index.

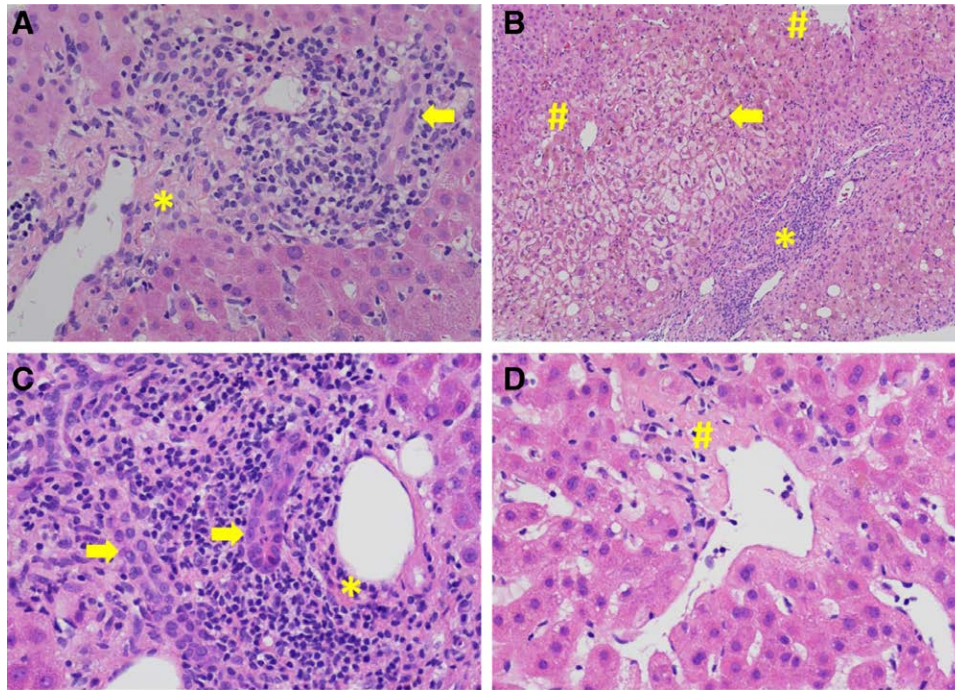

FIGURE 1. Histopathological findings of liver allograft biopsies after SARS-CoV-2 mRNA vaccination (Pfizer-BioNTech) for case 1 (A, H&E ×400), case 2 (B, H&E ×100), and case 3 (C, H&E ×400; D, H&E ×400). A, Post vaccination biopsy for Case 1 showed moderate to severe T cell mediated rejection with all portal tracts infiltrated and expanded by activated lymphocytes, neutrophils and eosinophils. Endotheliitis (*) and lymphocytic bile duct injury (arrow) were present in most portal tracts. B, Post vaccination biopsy for Case 2 showed severe T cell mediated rejection with expansile portal infiltrates (*), marked cholestatic lobular injury (arrow) and central venule perivenulitis with hepatocyte drop-out (#).C and D, Case 3 showed typical rejection infiltrate with endotheliitis (arrows), lymphocytic cholangitis (*) and limited lymphocytic central perivenulitis with perivenular hepatocyte damage (#).