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## Two Cases of Possible Exacerbation of Chronic Rejection After Anti-SARS-CoV-2 Messenger RNA Vaccination: A Case Report

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### ABSTRACT

In post–liver transplant recipients, SARS-CoV-2 infection is a health threat, and novel messenger RNA vaccines such as Pfizer BioNTech BNT162b2 and Moderna mRNA-1273 are aggressively recommended. However, there are few reports on their adverse effects, some of which may be potentially fatal. We have experienced 2 post–liver transplant recipients with exacerbated chronic rejection after vaccination, one of whom had to undergo retransplant and the other who is still in the process of liver function without improvement. These alarming cases will be presented as case reports.

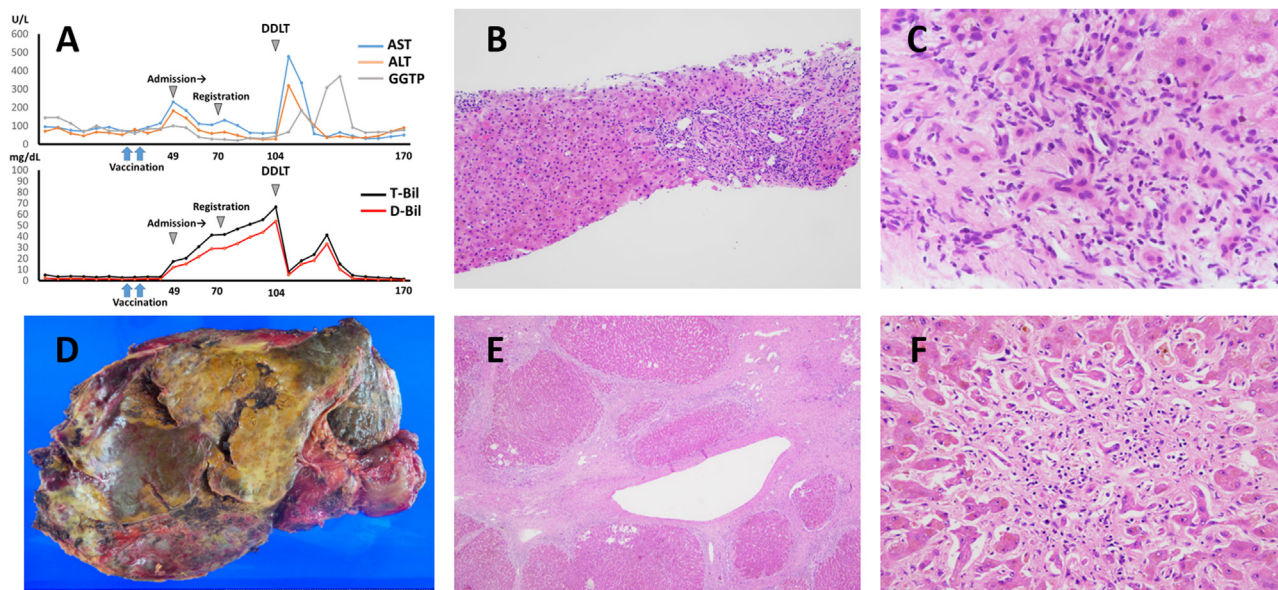
SARS-CoV-2 infection is a global public health threat that shows no signs of abating. With the rapid development and widespread use of novel messenger (mRNA) vaccines, such as the Pfizer-BioNTech (New York, NY, United States; and Mainz, Germany) BNT162b2 and Moderna (Cambridge, Mass, United States) mRNA-1273 vaccines, it has become possible to prevent infectious diseases and to control the severity of infection when it occurs. Patients using immunosuppressants after organ transplant are more prone than healthy individuals to exacerbation of clinical symptoms associated with SARS-CoV-2 infection, which is directly related to increased mortality, so it is recommended that these patients be proactively vaccinated against SARS-CoV-2 [1,2]. However, information on the safety and adverse effects of SARS-CoV-2 vaccination remains insufficient, such as the possibility that it may accelerate the immune response leading to rejection in these patients. We herein report 2 liver transplant (LT) recipients with exacerbation of chronic rejection (CR) after SARS-CoV-2 vaccination.

### CASE PRESENTATION

Case 1: A 16-year-old girl had undergone living donor LT at 9 months old because of biliary atresia from an ABO blood type –identical donor. She had a history of acute cellular rejection (ACR) at 9 years old, and CR and liver fibrosis were revealed with a biopsy specimen at 12 years old; she was therefore administered tacrolimus, everolimus, and prednisolone as immunosuppressants. Her liver function at the time of the first

vaccination was a Child-Pugh score of 8 points (aspartate aminotransferase [AST] 92 U/L, alanine aminotransferase [ALT] 60 U/L, gamma-glutamyltranspeptidase [GGTP] 83 U/L, total bilirubin (T-Bil) 3.4 mg/dL, albumin [Alb] 2.8 g/dL, international normalized ratio of prothrombin time [PT-INR] 1.12). Three weeks after receiving the first dose of the SARS-CoV-2 vaccine, the second dose was given (BNT162b2 for both vaccinations). Subsequently, a blood test 49 days after the second vaccination revealed a Child-Pugh score of 10 points (AST 230 U/L, ALT 182 U/L, GGTP 100 U/L, T-Bil 17.4 dL, Alb 2.5 g/dL, PT-INR 1.29) (Fig 1A). A liver biopsy was performed on the same day, with results showing suppurative cholangitis and chronic cholestasis with bile duct loss, which was consistent with CR (Fig 1B, C). On the 70th day after the second vaccination, the patient was registered for deceased donor liver transplant (DDLT), which was performed 34 days after the registration. The pathologic findings of the explanted liver were bile duct paucity corresponding to CR and severe hepatic fibrosis (Fig 1D-F). Postoperatively, although there were complications with small intestinal perforation that required surgical repair, her condition improved, and she was discharged on post-operative day 188. She has been doing well since re-LT, with no abnormalities in her liver function.

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**Fig 1.** (A) The time course of hepatobiliary enzymes and bilirubin levels in the first case. (B) Liver biopsy findings on day 49 after the second vaccination. Suppurative cholangitis and suspicion of early chronic rejection were diagnosed. RAI = 2 (P2 B0 V0), METAVIR = A1 F2. (C) Gross findings of the explanted liver graft at the time of re-LT (DDLT). (D) Bridging fibrosis and cirrhosis were revealed, METAVA = A1F4. (E) The bile duct structures in the portal area disappeared, which is consistent with chronic rejection.

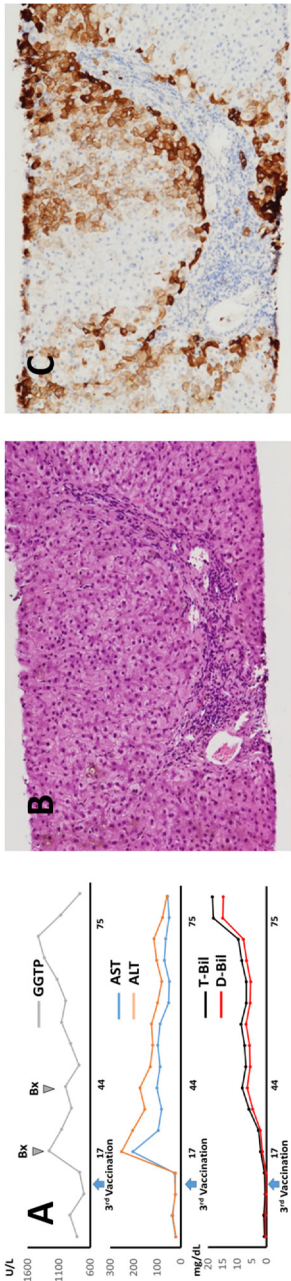
DDLT, deceased donor liver transplant; LT, liver transplant; RAI, rejection activity index.

**Case 2:** A 19-year-old woman had undergone living donor LT for end-stage liver disease from biliary atresia with the left lateral segment of the liver from her ABO blood type-identical father as a graft at 1 year and 4 months old, and at 17 years old, she had undergone DDLT because of progressive graft liver dysfunction caused by CR. After DDLT, mild to moderate ACR and CR relapsed but were controlled with 4 immunosuppressive agents (tacrolimus, mycophenolate mofetil, prednisolone, and everolimus). There were no liver functional abnormalities according to a blood sample obtained at the first SARS-CoV-2 vaccination, showing a Child-Pugh score of 6 points (AST 20 U/L, ALT 29 U/L, GGTP1088 U/L, T-Bil 1.7 mg/dL, Alb 3.4 g/dL, PT-INR 0.87). After the first and second vaccinations (both mRNA-1273), no liver functional abnormalities were observed. However, 14 days after the third vaccination (using BNT162b2), hepatobiliary enzymes were elevated (AST 204 U/L, ALT 252 U/L, GGTP 1257 U/L, T-Bil 2.0 mg/dL, Alb 3.8 g/dL, PT-INR 0.94) (Fig 2A), and 17 days after the third vaccination, liver biopsy specimen showed moderate ACR relapse and CR. The patient was treated with steroid bolus therapy and increased doses of everolimus. However, ACR was uncontrolled, and liver biopsy specimen taken 44 days after the third vaccination indicated CR with 60% bile duct loss and moderate ACR (Fig 2B, C). Her hepatobiliary enzymes and jaundice worsened to a Child-Pugh score of 10 points (AST 54 U/L, ALT 60 U/L, GGTP 989 U/L, T-Bil 16.9 mg/dL, Alb 3.1 g/dL, PT-INR 1.47).

## DISCUSSION

BNT162b2 and mRNA-1273 are novel mRNA-based vaccines, and information on their safety and adverse effects in solid-organ transplant recipients is still limited. Recent reports have shown that vaccination in healthy individuals cause liver function abnormalities and autoimmune hepatitis-like changes after vaccination, events attributed to the activation of CD8+ T cells by the mRNA vaccine [3]. A case series of post-LT recipients who developed ACR after vaccination has also been reported [4,5], suggesting that the immunogenic potential of these mRNA vaccines may be higher than that of conventional inactivated vaccines or recombinant vaccines.

In the authors' group, transient elevation of hepatobiliary enzymes and ACR have been observed in post-LT recipients vaccinated with the SARS-CoV-2 mRNA vaccine, and they generally responded to treatment without any problems. However, in the 2 cases reported here, CR, such as bile duct epithelial metaplasia and ductopenia, worsened after vaccination, leading to DDLT in the first case. Before vaccination, both patients required immunosuppressants with multiple regimens, but their graft liver function was preserved, and vaccination was recommended as usual. Whether or not vaccination was the direct cause of the hepatic dysfunction is unclear, but no other events inducing hepatic injury were specifically noted in either case. Regarding the cause of the CR, we speculate that the ACR triggered after vaccination may have been the cause of the CR in the second case, but in the first case, there was a time lag



**Fig 2.** (A) The time course of hepatobiliary enzymes and bilirubin levels in the second case. (B) Liver biopsy findings 44 days after the third vaccination. Moderate ACR (RAI=P2 B2 V1) and fibrosis (METAVIA=A1F2) were prolonged. (C) Immunohistochemical staining of CK7 revealed extensive bile duct paucity in the portal region, which is consistent with chronic rejection in the late phase.  
ACR, acute cellular rejection; RAI, rejection activity index.

between the appearance of liver injury and the liver biopsy, so the image of ACR was not captured.

CONCLUSIONS

In conclusion, we encountered 2 cases of exacerbation of CR after SARS-CoV-2 mRNA vaccination in LT recipients. The causal relationship between vaccination and CR and underlying mechanism in these 2 recipients are unclear at present, so we cannot recommend avoiding SARS-CoV-2 mRNA vaccination in LT recipients. However, we should closely monitor LT recipients who have undergone vaccination. We also believe that an evaluation protocol for prevaccination and a postvaccination monitoring protocol for post-LT recipients may need to be promptly developed.

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