Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Two Cases of Possible Exacerbation of Chronic Rejection After Anti-SARS-CoV-2 mRNA Vaccination: Case Report.

Tatsuya Okamoto , Hideaki Okajima , Eri Ogawa , Elena Yukie Uebayashi , Miki Yamamoto , Masashi Kadohisa , Yosuke Yamada , Sachiko Minamiguchi , Hironori Haga , Etsurou Hatano

PII: S0041-1345(22)00831-4
DOI: https://doi.org/10.1016/j.transproceed.2022.11.009
Reference: TPS 31264

To appear in: *Transplantation Proceedings*

Please cite this article as: Tatsuya Okamoto , Hideaki Okajima , Eri Ogawa , Elena Yukie Uebayashi , Miki Yamamoto , Masashi Kadohisa , Yosuke Yamada , Sachiko Minamiguchi , Hironori Haga , Etsurou Hatano , Two Cases of Possible Exacerbation of Chronic Rejection After Anti-SARS-CoV-2 mRNA Vaccination: Case Report., *Transplantation Proceedings* (2022), doi: https://doi.org/10.1016/j.transproceed.2022.11.009

Original works

***Title: Two Cases of Possible Exacerbation of Chronic Rejection After Anti-SARS-CoV-2 mRNA Vaccination: Case Report.**

***Authors:** Tatsuya Okamoto, M.D.[1*], Hideaki Okajima, M.D.[1,2], Eri Ogawa, M.D.[1], Elena Yukie Uebayashi, M.D.[1], Miki Yamamoto, M.D.[1], Masashi Kadohisa, M.D.[1], Yosuke Yamada, M.D.[3], Sachiko Minamiguchi, M.D.[3], Hironori Haga, M.D.[3], and Etsurou Hatano, M.D.[1]

[1] Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan.

[2] Department of Pediatric Surgery, Kanazawa Medical University, Kanazawa 920-0265, Japan.

[3] Department of Diagnostic Pathology, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan.

***E-Mail address:** Tatsuya Okamoto, M.D.;okamotot@kuhp.kyoto-u.ac.jp, Hideaki Okajima, M.D.; ho62@kuhp.kyoto-u.ac.jp, Eri Ogawa, M.D.;erio24@kuhp.kyoto-u.ac.jp, Elena Yukie Uebayashi, M.D.; elenayy@kuhp.kyoto-u.ac.jp, Miki Yamamoto, M.D.; mimi.mimi.music@gmail.com, Masashi Kadohisa, M.D.; kadohisa@kuhp.kyoto-u.ac.jp, Yosuke Yamada, M.D.; yyamada@kuhp.kyoto-u.ac.jp, Sachiko Minamiguchi, M.D.; minami@kuhp.kyoto-u.ac.jp, Hironori Haga, M.D.; haga@kuhp.kyoto-u.ac.jp, and Etsurou Hatano, M.D.; etsu@kuhp.kyoto-u.ac.jp.

***Address all correspondence to:** Tatsuya Okamoto, M.D.

Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan

***Corresponding author e-mail:** okamotot@kuhp.kyoto-u.ac.jp

***Grant information:** No funding.

***Key words:** Liver transplantation (LT), SARS-CoV-2 mRNA vaccination, Acute cellular rejection (ACR). Chronic rejection (CR).

***Abbreviations:** ACR: Acute cellular rejection, CR: Chronic rejection, DDLT: Deceased donor liver transplantation, LDLT: living donor liver transplantation, LT: liver transplantation, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

***Tables:** None

***Figures:** 2 (Color-Yes)

Abstracts

In post-liver transplant patients, SARS-CoV-2 infection is a health threat and novel mRNA vaccines such as Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273 are aggressively recommended. However, there are few reports on its side effects, and some of them may have potentially fatal side effects. We have experienced two post-liver transplant patients with exacerbated chronic rejection after vaccination, one of

whom had to be re-transplanted, and the other who is still in the process of liver function without improvement. These alarming cases will be presented as case reports.

Introduction

Severe acute respiratory syndrome coronavirus 2 (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 mRNA vaccines, such as the Pfizer-BioNTech (New York, NY, USA; and Mainz, Germany) BNT162b2 and Moderna (Cambridge, MA, USA) 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 transplantation 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 side 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 two liver transplantation (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 liver transplantation (LDLT) at 9 months old due to biliary atresia from an ABO blood type identical donor. She had a history of acute cellular rejection (ACR) at 9 years old, and chronic rejection (CR) and liver fibrosis were revealed with a biopsy at 12 years old; she was therefore followed up with Tacrolimus, Everolimus, and Prednisolone as immunosuppressants. Her liver function at the time of the first vaccination was a Child-Pugh score of 8 points (AST 92 U/L, ALT 60 U/L, GGTP83 U/L, T-Bil 3.4 mg/dL, Alb 2.8 g/dL, 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/d L, PT-INR 1.29) (Figure 1A). A liver biopsy was performed on the same day, showing suppurative cholangitis and chronic cholestasis with bile duct loss, which was consistent with CR (Figure 1B, C). On the 70th day after the second vaccination, the patient was registered for deceased donor liver transplantation (DDLT), which was performed 34 days after the registration. The pathological findings of the explanted liver were bile duct paucity corresponding to CR and severe hepatic fibrosis (Figure 1D-F). Postoperatively, although she was complicated 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.

Case 2: A 19-year-old girl had undergone LDLT 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 due to progressive graft liver dysfunction caused by CR. After DDLT, mild to moderate ACR and CR relapsed but were controlled with four 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) (Figure 2A), and 17 days after the third vaccination, a liver biopsy showed moderate ACR relapse and CR. The patient was treated with steroid bolus therapy and increased doses of Everolimus. However, ACR was uncontrolled, and a liver biopsy performed 44 days after the third vaccination indicated CR with 60% bile duct loss and moderate ACR (Figure 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 vaccine, and information on their safety and

side 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-liver transplant patients who developed acute cellular rejection following 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 author's group, transient elevation of hepatobiliary enzymes and ACR have been observed in post-liver transplant recipients vaccinated with the SARS-CoV-2 mRNA vaccine, and they generally responded to treatment without any problems. However, in the two 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 between the appearance of liver injury and the liver biopsy, so the image of ACR was not captured.

In conclusion, we encountered two 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 two 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 pre-vaccination and a post-vaccination monitoring protocol for post-LT recipients may need to be promptly developed.

References

[1] American Society of Transplantation. COVID-19 vaccine FAQ sheet. https://www.myast.org/sites/default/files/2022.05.04%20AST%20Vaccine%20FAQ-CLEAN.pdf. Accessed September 2022.

[2] American Association for the Study Liver Diseases. AASLD expert panel consensus statement: vaccines to prevent COVID-19 infection in patients with liver disease. https://www.aasld.org/sites/default/files/202207/AASLD%20COVID19%20Vaccine%20Document%20Update%203.28.2022%20FINAL.pdf. Accessed September 2022.

[3] Boettler T, Csernalabics B, Salié H, Luxenburger H, Wischer L, Salimi Alizei E, et al. SARS-CoV-2 vaccination can elicit a CD8 T-cell dominant hepatitis. J Hepatol. 2022; 77: 653-659.

[4] Vyhmeister R, Enestvedt CK, VanSandt M, Schlansky B. Steroid-Resistant Acute Cellular Rejection of the Liver After Severe Acute Respiratory Syndrome Coronavirus 2 mRNA Vaccination. Liver Transpl. 2021; 27:1339-1342.

[5] Hume SJ, Jackett LA, Testro AG, Gow PJ, Sinclair MJ. A Case Series of Patients With Acute Liver Allograft Rejection After Anti-SARS-CoV-2 mRNA Vaccination. Transplantation. 2022;106: e348-e349.

Figure regends

Figure 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. Rejection activity index: 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.

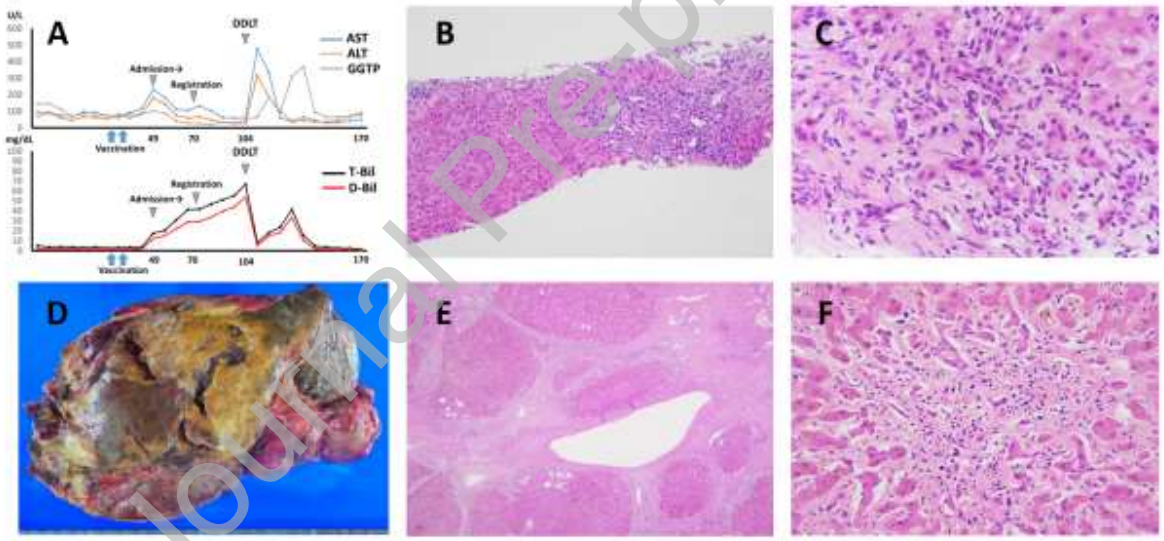
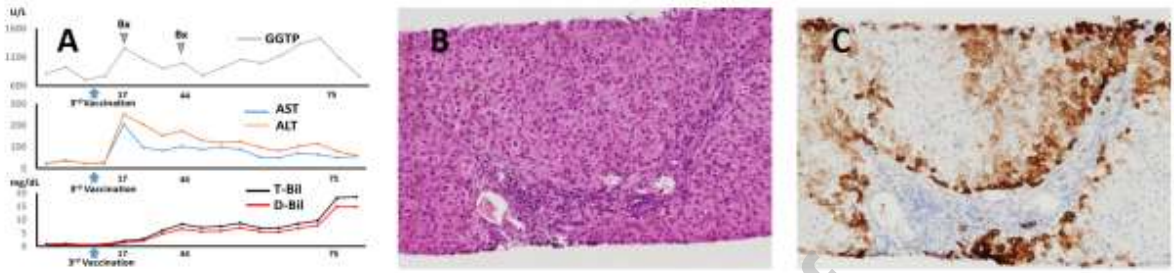


Figure 2. The time course of hepatobiliary enzymes and bilirubin levels in the second case. (B) Liver biopsy findings 44 days after the third vaccination. Moderate ACR (RAI=P2 B2 V1) and fibrosis

(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.



Conflict of Interest Disclosures (includes financial disclosures):

The authors declare no conflicts of interest in association with the present study. The authors have no financial relationships relevant to this article to disclose.