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BRIEF REPORT

Acute cellular rejection in liver transplantation recipients following vaccination against coronavirus disease 2019: A case series

To the editor,

Vaccination of liver transplantation (LT) recipients is vital to prevent transmissible infections and serious illness in a vulnerable population. The massive toll taken by the coronavirus disease 2019 (COVID-19) pandemic has resulted in the development of innovative, effective vaccines in record time. In December 2020, two messenger RNA (mRNA) vaccines (BNT162b2 vaccine from Pfizer–BioNTech and the mRNA-1273 vaccine from Moderna) were authorized by the US Food and Drug Administration under an Emergency Use Authorization.[1]

Most adverse events related to the COVID-19 vaccines are attributed to local adverse effects related to vaccine reactogenicity. However, there are reports of more serious reactions to COVID-19 vaccines possibly related to their immunogenicity, including one report describing several cases of new-onset autoimmune hepatitis.[2] In LT recipients, there has been one case report to date of biopsy-proven acute cellular rejection (ACR) after receiving a COVID-19 vaccine, albeit in the context of tapering off corticosteroids in the early posttransplant period.[3] We report a case series of 5 LT recipients who developed biopsy-proven ACR following vaccination against COVID-19.

Patient characteristics

Four of five patients were men. The median age was 54 years. The indications for LT were nonalcoholic steatohepatitis (NASH)–related cirrhosis in three patients and alcohol-related cirrhosis in two patients. The mean time from LT to the first dose of COVID-19 vaccination was 19 months (range, 7–26 months). Two patients had a history of ACR at 40 days and 418 days after LT (195 and 370 days prior to the first dose of COVID-19 vaccination, respectively). All patients had negative COVID-19 polymerase chain reaction tests prior to their liver biopsies (Table 1).

Immunosuppression

Two patients were on calcineurin-inhibitor monotherapy, whereas one patient was on calcineurin-inhibitor and antimetabolite therapy at the time of the first dose of COVID-19 vaccination. The remaining two patients were taking mycophenolate mofetil (MMF) 750 mg twice daily and prednisone (PRED) 5 mg daily. Where appropriate, prevaccination immunosuppression (IS) trough levels were in the target range for all patients.

COVID-19 vaccinations

Three patients received the Moderna COVID-19 vaccination, whereas two patients received the Pfizer–BioNtech COVID-19 vaccination. All patients completed their vaccination series. One patient had a delayed second dose of the vaccination (110 days after the first dose of the Pfizer–BioNtech COVID-19 vaccination) because of treatment for ACR.

Liver enzymes

Three patients developed elevations in their liver enzymes after the first dose of the COVID-19 vaccination. The median time from vaccination (three patients after the first dose and two patients after the second dose) to elevations in liver enzymes was 11 days (range, 7–19 days).

Abbreviations: A1AT, alpha-1-antitrypsin deficiency; ACR, acute cellular rejection; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, twice daily; C4d, complement component 4d; COVID-19, coronavirus disease 2019; CsA, cyclosporine A; FK-506, tacrolimus; IS, immunosuppression; IV, intravenously; LT, liver transplantation; METHYLPRED, methylprednisolone; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mRNA, messenger RNA; NASH, nonalcoholic steatohepatitis; PRED, prednisone; PV, portal vein; RAI, rejection activity index; SOT, solid organ transplantation; TB, total bilirubin.

Liver histopathology

All patients underwent liver biopsy following abnormal liver enzymes. Adequate samples were obtained from all five patients (Figure 1A–E), which demonstrated typical features of T cell–mediated ACR, including portal inflammation of predominantly mixed activated lymphocytes, portal vein (PV) phlebitis (Figure 1B–D, black arrows), and bile duct injuries (Figure 1D,E, red arrows). Complement component 4d (C4d) stain by immunohistochemistry was negative in all but one patient, who showed C4d in the PV, portal connective tissue, and small portal capillaries (Figure 1F). Three patients had rejection activity index (RAI) scores five of nine, whereas the other two had three of nine (Table 1).

Treatment

Two patients required hospital admission for the treatment of ACR. All patients were initially treated with high-dose intravenous methylprednisolone (METHYLPRED) for 3 days. Three patients were started on additional immunosuppressive medications. No patients required treatment with antithymocyte globulin.

Follow-up

Liver enzymes returned to normal (or baseline) in all patients following the treatment for ACR. Three patients had normalization of liver enzymes within 2 weeks of intravenous METHYLPRED. One patient had normalization of liver enzymes after 75 days following treatment of ACR. No patients required readmission to hospital, died, or developed graft failure. No patients had COVID-19 antibody titers checked during or after their vaccination series, and no patients developed symptomatic COVID-19 infection during the follow-up period after vaccination and treatment for ACR.

DISCUSSION

Vaccination is a vital tool as the world works toward ending the COVID-19 pandemic. Although ACR is

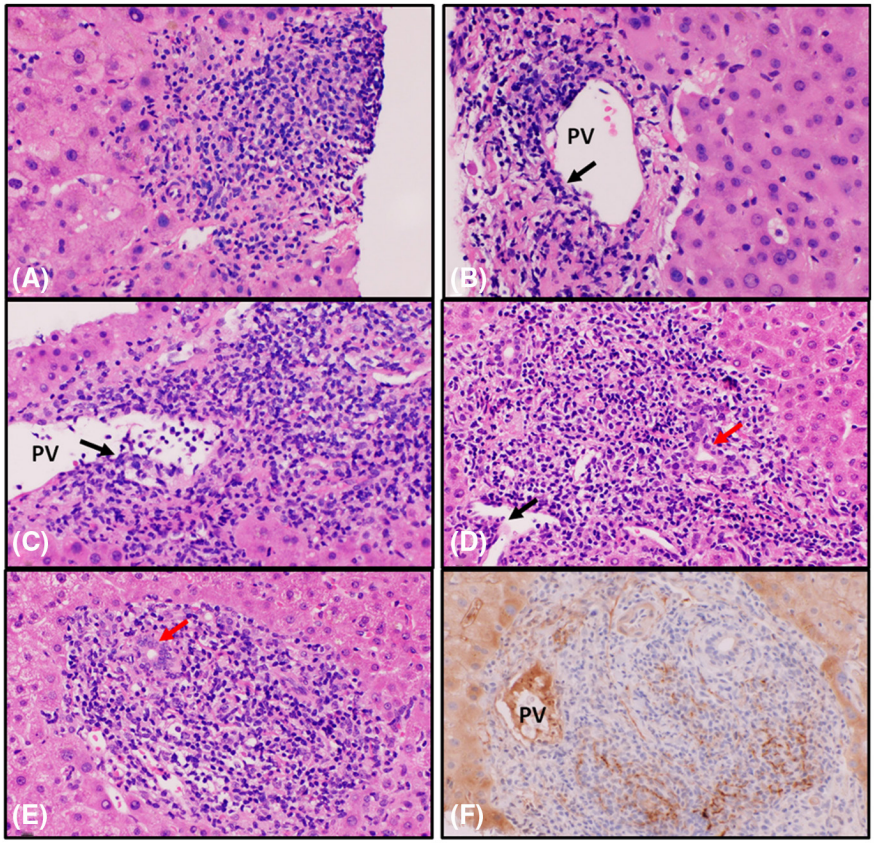

FIGURE 1 Liver histopathology in five patients showing ACR and C4d staining in one patient. (A–E) Representative sections from five patients who developed T cell–mediated rejection. The features include portal-based predominantly lymphocytic inflammation with activated phenotypes, causing PV wall injury, that is, phlebitis (black arrows); bile duct inflammation (red arrows) and absence of lobular or other pattern of injury. (F) PV staining for C4d by immunohistochemistry as well as portal connective tissue and tiny portal capillaries seen in only one of the five patients (A–E, hematoxylin and eosin stain; A–F, magnification 40×)

TABLE 1 Clinical characteristics of patients with COVID-19 vaccination and ACR

Patient	Age and sex	Race	Etiology of liver disease	Time since LT, days	History of ACR?	IS regimen	History of COVID-19 infection?	COVID-19 vaccine	Time from LT until vaccine dose 1, days	Time from LT until vaccine dose 2, days
1	52 years, male	White	Alcohol	827	No	MMF 750 mg bid + PRED 5 mg daily	No	Pfizer	620	731
2	71 years, male	White	Alcohol	1029	Yes	FK-506 (goal 7–10) + MPA 720 mg bid	No	Moderna	788	816
3	50 years, male	White	NASH	438	Yes	FK-506 (goal 6–8)	No	Moderna	235	263
4	61 years, female	White	NASH/ A1AT/ iron overload	778	No	CsA (goal 80–120)	No (previous test positive)	Moderna	578	606
5	54 years, male	White	NASH	906	No	MMF 750 mg bid + PRED 5 mg daily	No	Pfizer	699	720

Abbreviations: A1AT, alpha-1-antitrypsin deficiency; ACR, acute cellular rejection; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, twice daily; C4d, complement component 4d; COVID-19, coronavirus disease 2019; CsA, cyclosporine A; IS, immunosuppression; IV, intravenously; LT, liver transplantation; METHYLPRED, methylprednisolone; MMF, mycophenolate mofetil; MPA, mycophenolic acid; NASH, nonalcoholic steatohepatitis; PRED, prednisone; RAI, rejection activity index; FK-506, tacrolimus; TB, total bilirubin.

rare following vaccination, no solid organ transplantation (SOT) recipients were included in the initial COVID-19 vaccine trials.[1] Case reports of patients developing autoimmune hepatitis linked to COVID-19 vaccination have postulated that molecular mimicry to the spike protein S1 may stimulate upregulation of proinflammatory pathways, which could also theoretically induce ACR in susceptible patients.[4]

Our cohort of patients did not all have typical risk factors associated with ACR: all patients were older than 50 years, and none underwent LT for autoimmune liver disease. One patient did have a history of late ACR at 14 months after LT but was taking both a calcineurin inhibitor and an antimetabolite at the time of vaccination. Two patients were maintained on less-intense IS regimens but had been stable for several months prior to receiving their first doses of the vaccine.

The median time from transplant to first dose of the vaccine in our cohort was 19 months in comparison with a recent survey of SOT recipients that reported no episodes of ACR; however, the median time from transplant to first dose of the vaccine was 6 years.[5] In a similar manner, one report of a kidney transplant recipient who developed acute rejection possibly related to the COVID-19 vaccine was 18 months after transplant.[6] Therefore, it is possible that more recent SOT recipients may be at higher risk for the development of ACR following COVID-19 vaccination.

Every patient in our cohort required treatment with intravenous corticosteroids and uptitration of their maintenance IS, which eventually resulted in the normalization of liver enzymes. In contrast, in a recent report, a patient who may have developed ACR following COVID-19 vaccination required rescue therapy with ATG for severe, persistent ACR.[3] Of note, three patients in our cohort developed ACR after their first dose of the COVID-19 vaccine. However, each individual eventually received their second dose of the COVID-19 vaccine without complication. Our limited experience can provide some reassurance to providers concerned about the development of ACR in LT recipients receiving booster vaccine doses. COVID-19 antibodies were not checked in our cohort during or after vaccination, so it is not clear how they may guide booster vaccinations or how treatment of ACR may affect serum levels. Although prophylactic monoclonal antibodies conferring passive immunity against COVID-19 are currently available, active vaccination

Time from vaccination to elevated liver enzymes, days	Last prevaccine TB/AST/ALT/ALP	Peak postvaccine TB/AST/ALT/ALP	Liver biopsy (RAI score = n/9)	Treatment	Most recent TB/AST/ALT/ALP	Outcomes
19	0.8/19/42/67	2.6/327/789/225	ACR (5/9)	METHYLPRED 1 g IV ×3 days, oral PRED taper, added EVE	1.0/25/26/106	Improved
12	1.4/50/72/136	2.4/61/128/128	ACR (3/9)	METHYLPRED 500 mg IV ×3 days, oral PRED taper	1.4/59/67/142	Improved; repeat biopsy on Day 890 because LT showed mild portal and lobular inflammation with pseudo ground-glass inclusions
7 (after second dose)	0.2/20/25/182	0.7/184/318/349	Immune-med (2–3/9)	METHLYPRED 1 g IV ×3 days, increased FK-506 goal	0.6/32/30/201	Improved
9	1.7/68/65/172	2.0/75/72/180	ACR (5/9), focal C4d +	METHYLPRED 1 g IV ×3 days, oral PRED tapered, increased CsA goal, added MMF	1.9/49/42/153	Improved
11 (after second dose)	2.8/22/25/82	2.2/235/354/119	ACR (5/9)	METHYLPRED 500 mg IV ×3 days, oral PRED tapered, added FK-506	2.6/36/51/86	Improved

should still be considered the primary defense against COVID-19 in SOT recipients given its proven track record. For now, we would simply recommend that liver enzymes are monitored in LT recipients soon after any COVID-19 vaccination to identify any potential development of ACR.

In summary, we report a series of LT recipients who developed ACR following their COVID-19 vaccinations. Our findings highlight the need for comprehensive post-vaccination surveillance programs in patients where the high immunogenicity of the vaccines could potentially provoke adverse events. It is important to note that all episodes of ACR in our series were easily treated without any serious complications, and our preliminary findings should not be used to discourage vaccination for COVID-19 in LT recipients. Further study is clearly required to better understand this association in a patient population that is at higher risk of both acquiring and developing serious complications of COVID-19 infection.

CONFLICT OF INTEREST

Nothing to report.

ETHICS STATEMENT

This study was approved with a waiver of consent by the Institutional Review Board at the University of Minnesota (STUDY00013579).

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