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CASE REPORT | LIVER

A Rare Case of COVID-19 Vaccination-Induced Cholangiopathic Liver Injury

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ABSTRACT

Drug-induced liver injury is a serious adverse drug reaction that can result in acute liver injury or cholestatic injury affecting the bile ducts, known as cholangiopathic liver injury (CLI). Although CLI is not as familiar as the hepatocellular pattern, emerging evidence suggests that it may occur after coronavirus disease 2019 (COVID-19) vaccination. This case report focuses on an 89-year-old woman who developed CLI after receiving the tozinameran COVID-19 vaccine. The main aim of this report was to raise awareness of the possibility of developing CLI after COVID-19 vaccination and to underscore the critical significance of promptly identifying and managing this infrequent but severe side effect.

KEYWORDS: COVID 19; DILI; cholangiopathic injury; vaccination

INTRODUCTION

Drug-induced liver injury (DILI) refers to the acute or chronic response of the liver to a specific agent that has been ingested, leading to cholestatic, hepatocellular, or mixed disease, and can result in acute liver failure.[1,2] The coronavirus disease 2019 (COVID-19) vaccine has been predominantly linked to hepatocellular liver injury with characteristics of immune-mediated hepatitis.[3] Although cholangiocytes are particularly susceptible to the SARS-CoV-2 virus because of a high concentration of angiotensin-converting enzyme 2 (ACE2) receptors, cholangiopathic liver injury patterns have rarely been reported.[4,5] In this report, we present a case of biopsy-proven cholangiopathic DILI, potentially caused by the COVID-19 vaccine.

CASE REPORT

An 89-year-old woman with a medical history of anxiety and atrial fibrillation, currently receiving apixaban, presented to the emergency department with yellowing of the skin for the past week. In addition, the patient reported a reduction in oral intake, weight loss, and constipation. There was no recent history of rash, fever, travel, alcohol overuse, antibiotics use, over-the-counter medications including herbal supplements, or illicit or recreational drug use. The patient had not undergone any medication changes, except for receiving the first shot of the tozinameran COVID-19 vaccine 2 weeks before presentation. She had never tested positive for COVID-19. Her only home medications were alprazolam and apixaban, which she had been taking for years without any adverse effects.

The patient was hemodynamically stable, at rest, without any acute distress, and showed no indications of chronic liver disease such as hepatosplenomegaly, ascites, or encephalopathy on physical examination. Comprehensive metabolic panel revealed elevated liver enzymes, including a total bilirubin level of 23.4 mg/dL (reference range: 0.2–1.3 mg/dL), direct bilirubin level of 10 mg/dL, aspartate aminotransferase of 46, alanine aminotransferase of 59, and gamma-glutamyl transpeptidase of 113 U/L. The R factor was 0.7, indicative of cholestatic injury. Despite undergoing an extensive workup (Table 1), all potential causes of elevated liver enzymes were negative.

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Table 1. Day of presentation vs 12-week follow-up results

Laboratory test result	Day 1	Day 3	Day 6	12-week follow-up
White blood cell (4,000–11,000 cells/mm^3)	6,400 cells/mm3			
Hemoglobin (11–15.1 g/dL)	14.1 g/dL			
Hematocrit (33.1%–44.5%)	45%			
Platelet (150,000–400,000 cells/mm^3)	226,000 cells/mm3			
Blood urea nitrogen (6–20 mg/dL)	13 mg/dL			
Creatinine (0.44–1.03 mg/dL)	0.58 mg/dL			
Alkaline phosphatase (32–91 U/L)	246 U/L	191 U/L	123 U/L	
Aspartate aminotransferase (15–41 U/L)	46 U/L	40 U/L	36 U/L	19 U/L
Alanine aminotransferase (7–52 U/L)	59 U/L	51 U/L	44 U/L	19 U/L
Total bilirubin (0.3–1 mg/dL)	23.4 mg/dL	18 U/L	13 U/L	0.7 mg/dL
Direct bilirubin (0.0–0.3 mg/dL)	10 mg/dL	4 U/L	2 U/L	0.02 mg/dL
GGT (5–45 U/L)	113 U/L	74 U/L	52 U/L	41 U/L
International normalized ratio (0.9–1.1)	1			
Lactate dehydrogenase (140-170 U/L)	162			
Haptoglobin (55–220 mg/dL)	50			
Serum Albumin (3.5–5.1 g/dL)	4.8 g/dL			
Hepatitis A, B, C, E	Negative			
Cytomegalovirus	Negative			
Parvovirus	Negative			
Herpes simplex virus 1 and 2	Negative			
HIV 1 and 2	Negative			
Human papilloma virus	Negative			
Influenza virus	Negative			
Epstein-Barr virus	Negative			
Urine drug screen	Negative			
A1 antitrypsin	Normal			
Ceruloplasmin levels	Normal			
Blood alcohol (<10 mg/dL)	<10 mg/dL			
Acetaminophen level (0–30 μg/mL)	<10 μg/mL			
Salicylate level (0–19.9 mg/dL)	<2.5 mg/dL			
Serum immunoglobulin G (610–1,616 mg/dL)	900 mg/dL			
Anti-smooth muscle antibody titers	Negative			
Anti-liver-kidney-microsomal antibodies	Negative			
Anti-mitochondrial antibodies	Negative			
Liver kidney microsome type 1 (anti-LKM-1) antibodies	Negative			
Liver kidney microsome type 2 (anti-LKM-1) antibodies	Negative			

GGT, gamma-glutamyl transpeptidase.

Abdominal ultrasound and computed topography scan were unremarkable. Magnetic resonance cholangiopancreatography demonstrated diffuse hypointensities of the liver and spleen on T2-weighted sequences, with concern for hemochromatosis (Figure 1). A panel for hereditary hemochromatosis was performed, revealing only 1 copy of the H63D pathogenic variant of the HFE gene, along with a serum ferritin level of 200.7 and a transferrin saturation of 40%. Moreover, the negative Prussian blue stain on the liver tissue biopsy ruled out the presence of tissue deposition of iron, thereby eliminating the possibility of hemochromatosis.

The liver biopsy findings of the patient revealed severe cholestasis and bile duct damage, indicating liver injury attributed to COVID-19 vaccine-induced cholangiopathy (Figure 2). Based on the clinical history, biopsy results, and a Roussel Uclaf

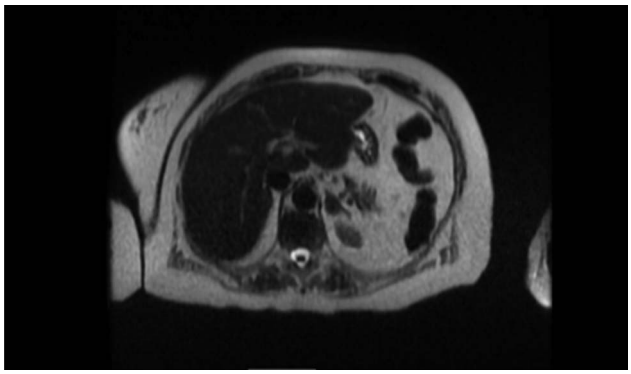

Figure 1. MRCP showed diffuse hypointensities of the liver on the T2-weighted sequences. MRCP, magnetic resonance cholangiopancreatography.

Causality Assessment Method score of 6, the patient was diagnosed with DILI caused by the COVID-19 vaccine. During hospitalization, the patient's laboratory values showed gradual improvement with supportive management, and she was discharged in a stable condition with a resumption of her pre-hospitalization medications, except for the COVID-19 vaccine. A follow-up appointment was scheduled 12 weeks (84 days) after the initial presentation, and the patient's results demonstrated complete resolution of jaundice and liver chemistries (Figure 3).

DISCUSSION

DILI is the leading cause of acute liver failure in the United States and worldwide, with intrinsic and idiosyncratic types and a multifactorial etiology involving drugs, genetics, and environmental factors.[6] The study by Efe et al[3] across 18 countries found that COVID-19 vaccines commonly cause a hepatocellular pattern of injury, with 84% of patients displaying this injury pattern after vaccination. Our case is notable for highlighting the occurrence of a cholangiopathic pattern of DILI after COVID-19 vaccination, which has rarely been reported.[5]

The cholestatic-type drug-induced liver injury observed in our case was not unexpected because cholangiocytes have a high concentration of ACE2 receptors.[4] SARS-CoV-2 specifically targets ACE2-expressing tissues and binds to receptors through its spike protein.[4] COVID-19 vaccines like tozinameran use mRNA technology to produce a spike protein that is specific to SARS-CoV-2.[7] This spike protein is recognized by the immune system, triggering an immune response to prevent or mitigate COVID-19 infection.[7] There is a strong possibility of an idiosyncratic reaction between the COVID-19 vaccine and cholangiocytes rich in ACE2 expression, possibly because of cross-reactivity between the ACE2 expression by cholangiocytes and the spike protein produced by the mRNA vaccines.[8,9]

To diagnose DILI, it is crucial to establish a correlation between drug exposure and the onset of liver disease, while eliminating any other potential causes.[10] In this particular case, patients did not take any new medications or over-the-counter supplements

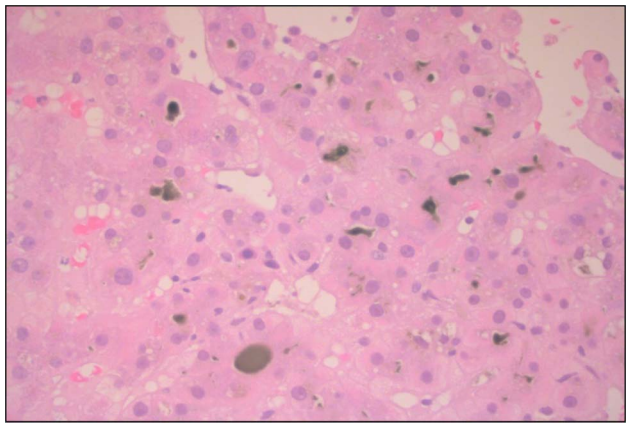

Figure 2. The histological slide stained with PAS-D shows severe hepatocellular and canalicular cholestasis characterized by the accumulation of glycogen in the hepatocytes, along with feathery degeneration. In addition, there is a ductular reaction and severe epithelial damage involving all bile ducts. However, no interface hepatitis is observed. The trichrome stain showed no fibrosis, and the Prussian blue stain was negative for iron deposition in the liver. PAS-D, periodic acid-Schiff with diastase.

and potential causes related to hepatitis were also ruled out. Given the temporal relationship between vaccine administration and symptom onset, there is a suspicion that the patients may have developed DILI because of the vaccine. In addition, although the usefulness of liver biopsy as a diagnostic tool is uncertain, it aided in both diagnosing DILI and eliminating other causes of liver damage in our patient.

At present, the prompt identification and discontinuation of the causative agent stand as the primary therapeutic approach for the management of DILI because no pharmacological interventions have been authorized for this condition.[11] Although the evidence is insufficient, steroids are recommended for the management of DILI and acute liver failure. Corticosteroids are frequently used and backed by the observations of the Drug-Induced Liver Injury Network. The findings demonstrate that corticosteroids were administered to 82% of patients who died or underwent liver transplants, as well as 36.6% of patients who were alive with the native liver at 6 months.[12] The management of DILI requires

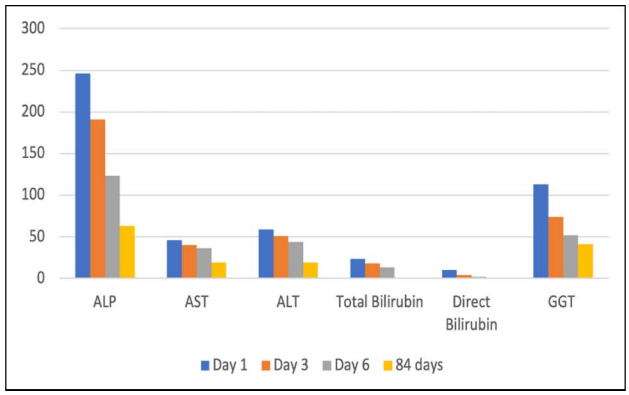

Figure 3. Trends of liver function tests.

precise diagnosis, identification, and cessation of the causative agent.[10] Although drug withdrawal is the primary strategy, outcomes can range from complete resolution to acute liver failure, and severe cases may necessitate liver transplantation.[10]

This report stresses the significance of monitoring for DILI as a COVID-19 vaccine complication in high-risk patients. Further research is needed to understand the mRNA vaccine's spike protein impact on ACE2 expression in cholangiocytes. Timely detection and management of DILI is critical, and drug cessation is the primary treatment. Ongoing research is required to develop effective therapeutic interventions and comprehend the complex etiology of DILI.

DISCLOSURES

Author contributions: S. Taj predominantly lead the writing. H. Sanekommu edited the paper and worked on introduction. A. Johal, J. Ravilla, S. Imburgio, S. Dandu, and A. Vedire all worked on editing the paper and collaborating on discussion. B. Miller obtained the biopsy images and described it. M. Hossain reviewed the paper and guided the direction of the paper. S. Taj is the article guarantor.

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