Acute Cholestatic Hepatitis Following mRNABNT162b2 SARS-CoV-2 Vaccination: Could It Be Genetic?

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Introduction

Given the morbidity and mortality of COVID-19, development of vaccines targeting SARs-CoV-2 was essential. Despite their overall safety and efficacy, atypical complications have been reported. Here we report a case of post-vaccination acute cholestatic hepatitis, consistent with drug-induced liver injury (DILI).

Case Description

A 61-year-old man with no past medical history presented with 2 weeks of acute onset jaundice and pruritus, approximately 1 month after his second dose of the mRNABNT162b2 SARS-CoV-2 vaccine. He denied use of any medications or supplements. He had never undergone surgery and had no known allergies. There was no known family history of liver disease. He reported rare consumption of alcohol (approximately two beers once per year). He denied history of tobacco or substance use.

Vital signs and physical exam were unremarkable. Admission labs were notable for aspartate aminotransferase (AST) 50 U/L, alanine aminotransferase (ALT) 68 U/L, alkaline phosphatase (ALP) 265 U/L, total bilirubin 14.9 mg/dL, and direct bilirubin 12 mg/dL (Table 1). White blood cell count, hemoglobin, platelets, international normalized ratio (INR), creatinine, blood urea nitrogen (BUN), albumin, and gamma-glutamyl transpeptidase (GGT) were normal (Table 2).

Abdominal ultrasound revealed a smooth liver surface with normal echogenicity. There was no evidence of gallstones or biliary ductal dilatation. These findings were confirmed with magnetic resonance cholangiopancreatography (MRCP). Viral serologies (HIV, HAV IgM, HBV core IgM, HBV surface antigen, HCV antibody), autoimmune markers (immunoglobulin G, immunoglobulin M, ANA, anti-mitochondrial antibody, anti-actin antibody, anti-liver-kidney-microsomal antibody), and respiratory viral panel (SARS-CoV-2, influenza A/B, RSV) were negative (Table 2).

Case Description

Percutaneous liver biopsy revealed cholestasis with mild portal lymphocytic infiltrates, atypical bile ducts, and lobular necroinflammatory change (Figure 1), without portal fibrosis, alpha-1-antitrypsin inclusion, stainable iron, or tumor. Molecular genetic testing (Next Generation Sequencing, Prevention Genetics® 77 Gene Cholestasis Panel) was performed. No genetic variants were identified in 77 genes associated with cholestasis, though single copy variants of several autosomal recessive genes were detected.

Symptoms completely resolved with supportive care. Labs one month later were notable for unreportable AST (hemolyzed) , ALT 68 U/L, ALP 175 U/L, and total bilirubin 3.2 mg/dL (Table 1). The patient was subsequently lost to follow up.

Table 1. Relevant lab values from admission and follow up

Blood Test	Admission Value	Follow Up Value	Reference Range
AST	50 U/L	-- (hemolyzed)	10-40 U/L
ALT	68 U/L	68 U/L	20-35 U/L
ALP	265 U/L	175 U/L	43-115 U/L
GGT	45 U/L	35 U/L	8-61 U/L
Total Bilirubin	14.9 mg/dL	3.2 mg/dL	≤ 1.2 mg/dL
Direct Bilirubin	12 mg/dL	-- (not reported)	≤ 0.4 mg/dL
Albumin	4 mg/dL	4 mg/dL	3.5-5.0 mg/dL
INR	0.86	0.9	0.8-1.1

AST = Aspartate Aminotransferase
ALT = Alanine Aminotransferase
ALP = Alkaline Phosphatase
INR = International Normalized Ratio

Table 2. Additional laboratory values from initial evaluation

Lab Test	Admission Value	Reference Range
WBC	6.3 x 10^9/L	4.5-10 x 10^9/L
Hemoglobin	15 g/dL	12-16 g/dL
Platelets	265 x 10^9/L	150-450 x 10^9/L
Creatinine	1.01 mg/dL	0.7-1.2
BUN	10 mg/dL	7-20 mg/dL
IgG	1,145 mg/dL	600-1600 mg/dL
IgM	60 mg/dL	40-250 mg/dL
ANA	Negative	Negative
AMA	Negative	Negative
ASMA	Negative	Negative
Anti-LKM	Negative	Negative
HIV	Negative	Negative
Hepatitis serologies	Negative	Negative
Respiratory viral panel	Negative	Negative

WBC = White Blood Cell Count
BUN = Blood Urea Nitrogen
IgG = Immunoglobulin G
IgM = Immunoglobulin M
ANA = Antinuclear Antibodies
AMA = Antimitochondrial antibody
ASMA = Anti Smooth Muscle (actin) Antibody
Anti-LKM = Anti Liver-Kidney-Microsomal Antibody

Hepatitis serologies = Hepatitis A IgM, Hepatitis B surface antigen & antibody, Hepatitis B core antigen, Hepatitis C antibody

Respiratory viral panel = Sars-CoV2, influenza A/B, Respiratory Syncytial Virus

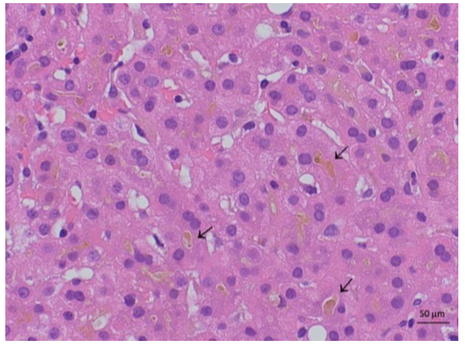

Figure 1. Liver biopsy showing cholestasis (arrows) in a patient who developed jaundice after COVID mRNA vaccination

Discussion

Prior reports have described cholestasis due to immune-mediated hepatitis after COVID mRNA vaccination[1], but these features were absent in this case. Given the patient's normal GGT, we hypothesized that increased cytokine release led to cholestatic injury in an individual genetically predisposed to cholestasis by genetic variation in ATP8B1 or ABCB11. Future studies comparing genetic variants in patients with liver injury may provide insight into mechanisms of idiosyncratic DILI following mRNA vaccination against SARS-CoV-2.

References & Acknowledgements

1. Bril F et al. Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: Casuality or casualty? J Hepatol. 2021 Jul; 75 (1): 222-224

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