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CASE REPORT | LIVER

Severe Hepatocellular Liver Injury After COVID-19 Vaccination Without Autoimmune Hepatitis Features: A Case Series

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ABSTRACT

Various vaccines were developed and administered to end the pandemic caused by the novel coronavirus diseases 2019 (COVID-19). These vaccines caused rare side effects not known during clinical trials. We report 2 cases of idiosyncratic drug-induced liver injury where the Pfizer BioNTech COVID-19 mRNA vaccine was administered. Both cases showed hepatocellular liver injury with negative autoimmune features on serology and histology and progressed to a protracted course of severe jaundice and pruritus before resolving without any immunosuppressants. We hope to raise awareness of possible rare side effects of the COVID-19 vaccine so that physicians can be vigilant.

INTRODUCTION

Effective vaccines are essential to stop the novel coronavirus diseases 2019 (COVID-19) pandemic, and administration of over 4 billion vaccine doses since December 2020 is an unprecedented effort.[1] Large-scale vaccination resulted in the discovery of rarer side effects that were previously not reported during clinical trials. We present 2 cases of drug-induced liver injury (DILI) without features of autoimmune hepatitis after administration of the Pfizer BioNTech COVID-19 mRNA vaccine.

CASE REPORT

Patient 1: A 38-year-old woman with asthma and no prior history of liver disease or allergies received her first dose of the Pfizer BioNTech COVID-19 mRNA vaccine on March 4, 2021. Six days after vaccination, she noted jaundice, tea-colored urine, and generalized itchiness. She denied consumption of alcohol, drugs, over-the-counter medications, or herbal supplements.

Clinical examination was unremarkable apart from yellow sclera. Her laboratory analyses showed hepatocellular injury with alanine transaminase (ALT) 366 U/L, aspartate transaminase (AST) 182 U/L, alkaline phosphatase 142 U/L, bilirubin 172 μmol/L, international normalized ratio (INR) 0.89, and absolute eosinophil count 0.2×10^9/L. Infective screens were negative for nasopharyngeal rapid test kit (RTK) COVID-19 swab, hepatitis A IgM, hepatitis B surface antigen, anti-HCV antibody, anti-HIV antibody, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus. Liver autoantibodies were negative for antinuclear antibody (ANA), anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), and normal gamma immunoglobulin (IgG). Paracetamol level and ceruloplasmin were normal.

Transabdominal ultrasound showed cholelithiasis, and endoscopic ultrasound confirmed no biliary tract obstruction. After 5 weeks, the transaminases improved spontaneously to nadir ALT 111 U/L and AST 68 U/L, before a second elevation, which peaked on day 63 with ALT 1280 U/L, AST 455 U/L, bilirubin 152 μmol/L, and INR 0.89. Repeat autoimmune screens were negative for ANA,

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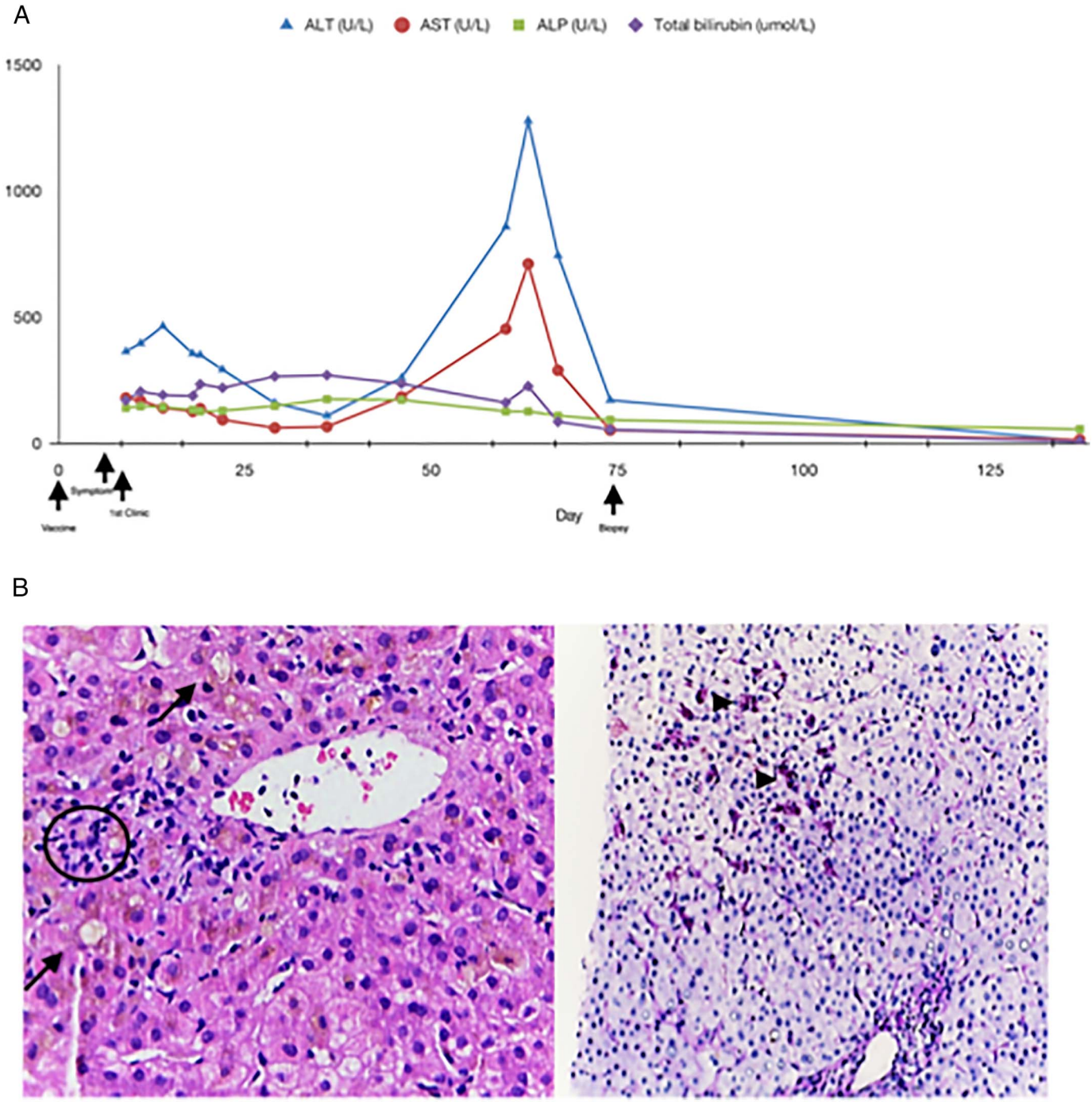

Figure 1. Histological and biochemical findings of patient 1: (A) trends of plasma alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and total bilirubin over time. (B) Cholestasis with rosettes formation (black arrows) and lobular inflammation (black circle) (hematoxylin and eosin stain, ×400 magnification) with ceroid pigment-laden Kupffer cells (black arrowheads) (periodic acid–Schiff with diastase, ×200).

AMA, ASMA, anti-liver-kidney microsomal, anti-neutrophil cytoplasmic antibody, sp100, gp210, anti-LC1, anti-SLA/LP, and normal IgG. She again denied taking any over-the-counter medications or herbal supplements. She had percutaneous liver biopsy, which showed intact native bile ducts. The lobules displayed marked hepatocellular cholestasis, distributed mainly at perivenular areas and ceroid-laden Kupffer cells as evidenced by positive periodic acid–Schiff with diastase stain. Subsequently, liver enzymes slowly normalized at week 20 after vaccination (Figure 1).

Patient 2: A 31-year-old woman without a history of concomitant illness or allergies received her first dose of the Pfizer BioNTech COVID-19 mRNA vaccine without any side effects.

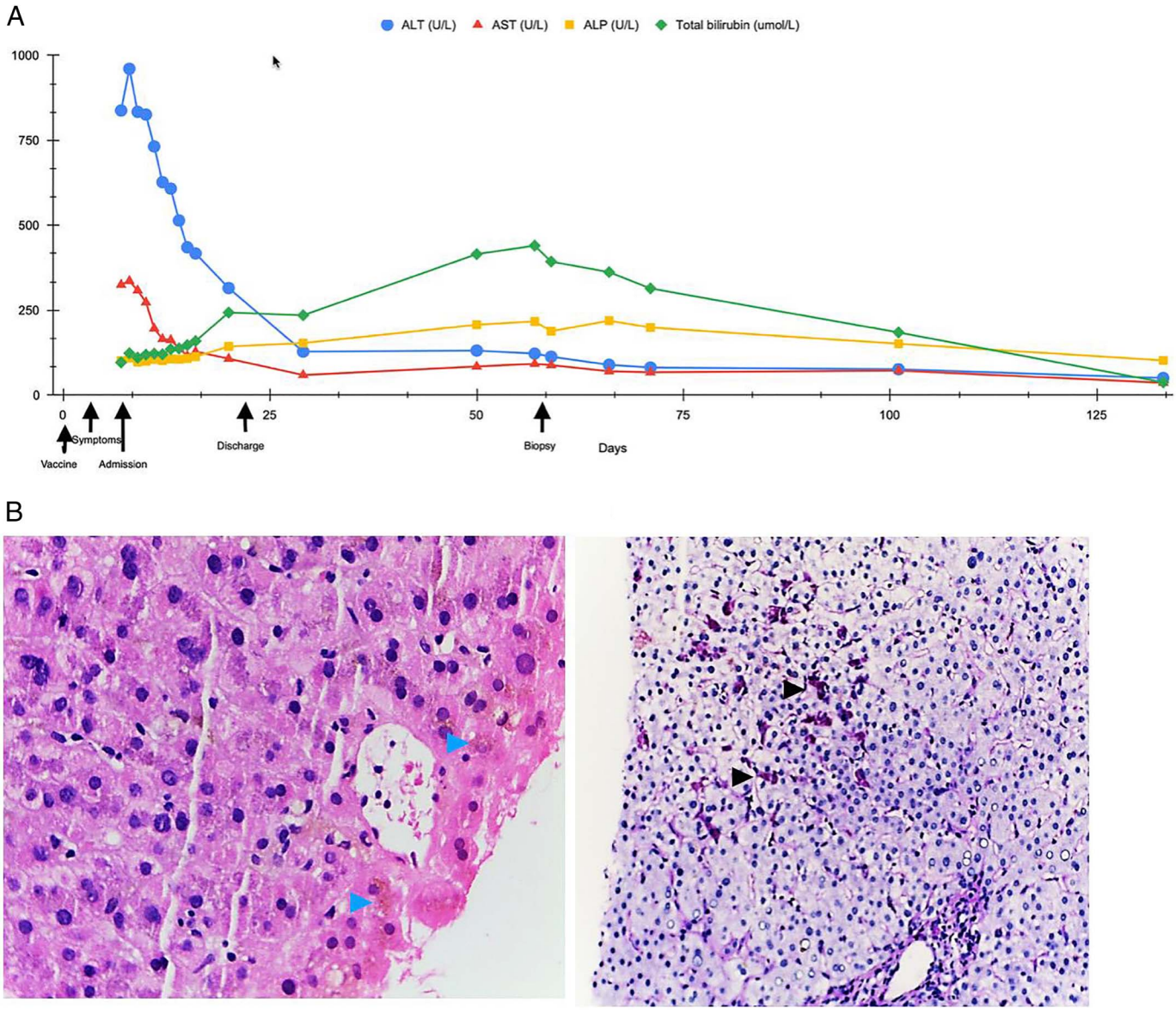

Figure 2. Histological and biochemical findings of patient 2: (A) trends of plasma alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and total bilirubin over time. (B) Cholestasis (blue arrowheads) (hematoxylin and eosin stain, ×400 magnification) with ceroid pigment-laden Kupffer cells (black arrowheads) (periodic Acid–Schiff with diastase, ×200).

After her second vaccine dose, she vomited 3 times within 30 minutes, which resolved spontaneously. On day 2 after vaccination, she noted generalized pruritus, jaundice, and tea-colored urine, which worsened. She denied consuming alcohol, drugs, over-the-counter medications, or herbal supplements.

Physical examination was normal except for jaundice and scratch marks on lower extremities. Laboratory analyses showed hepatocellular injury (ALT 838 U/L, AST 325 U/L, alkaline phosphatase 101 U/L, bilirubin 96 μmol/L, and INR 1.01) and absolute eosinophil 0.05×10^3 U/L. Infective screens were negative for nasopharyngeal RTK COVID-19 swab, hepatitis A IgM, hepatitis B surface antigen, anti-HCV, anti-HIV, and herpes simplex virus antibodies. Liver autoantibodies were negative for ANA, AMA, ASMA, anti-liver-kidney microsomal, anti-neutrophil cytoplasmic antibody, and normal IgG. Paracetamol level and ceruloplasmin were normal.

Transabdominal ultrasound revealed cholelithiasis. Endoscopic ultrasound showed no biliary obstruction and patent hepatic vessels. Although transaminases improved, she continued to have increasing bilirubin and intense protracted pruritus, which was not relieved with loratadine, chlorphenamine, and cholestyramine. Bilirubin peaked at 440 μmol/L with INR 1.02 at 8 weeks after vaccination (Figure 2). There was no clinical hepatic decompensation.

Percutaneous liver biopsy showed intact bile ducts. The lobules display hepatocellular cholestasis with many ceroid-laden macrophages. Pruritus improved after ursodeoxycholic acid

was added, and liver enzymes gradually normalized after week 19 postvaccination.

DISCUSSION

We presented 2 adults with hepatocellular liver injury and negative autoimmune markers but progressed to a protracted course of severe jaundice and pruritus after receiving the Pfizer BioNTech COVID-19 mRNA vaccine. Both patients were not on any medications or herbal or dietary supplements. Secondary causes related to hepatitis were excluded. Given the temporal relationship between vaccine administration and presentation of symptoms, we hypothesized that these patients might have vaccine-related DILI.

The first case had hepatitis with ALT at ×11 upper limit of normal (ULN) and AST at ×6 ULN. The hepatitis improved over 5 weeks after vaccination, before it relapsed and peaked at week 9, and subsequently spontaneously recovered. The second case had markedly raised transaminases during presentation (ALT at ×25 ULN and AST at ×10 ULN), which subsequently improved but protracted severe pruritus and hyperbilirubinemia continued, until ursodeoxycholic acid was initiated at week 8 after vaccination and resulted in a gradual decrease in hyperbilirubinemia and pruritus.

Recent case reports of liver injuries after COVID-19 mRNA vaccinations found a higher magnitude of elevations in transaminases compared with our patients and the presence of autoimmune serological markers, liver histology, and steroid responsiveness, which may suggest autoimmune hepatitis.[2–4] In our case, autoimmune serological markers were negative and IgG was normal even when these were repeated in the one who had relapse of hepatitis. The hepatitis eventually improved without any immunosuppressive treatment. The histological findings were significant infiltrations by inflammatory cells with predominant neutrophils, evidence of recent inflammatory process with ceroid-laden macrophages and Kupffer cells, and marked intrahepatic cholestasis. There was no bile duct loss or damage and absence of fibrosis or infiltrative liver disease changes. Because of the variable short latency period and clinical course after administration of the vaccine, without any systemic allergic features and eosinophilia, we propose the mechanism of idiosyncratic DILI.[5]

To date, the CDC WONDER database has reported 424,277 COVID-19 vaccine-related adverse events while the 2021 VAERS database has reported 79 cases with symptoms of jaundice without anemia after receiving the COVID-19 vaccine, plausibly suggesting vaccine-related DILI.[6,7] We hope to raise awareness of possible rare side effects of the COVID-19 vaccine and our report adds information on the spectrum of DILI from COVID-19 vaccines. The benefit of mass COVID-19 vaccination far outweighs the potential harm, and the current effort of global vaccination should be supported to stop this pandemic.

DISCLOSURES

Author contributions: CZ Hoo wrote the article and revised the article for intellectual content. KC Tan wrote the article. S. Abdullah, BLH Sim, and H. Omar revised the article for intellectual content. SS Tan wrote the article, revised the article for intellectual content, and is the article guarantor.

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REFERENCES

1. *Coronavirus Disease (COVID-19)–World Health Organization*. Who.int (https://www.who.int/emergencies/diseases/novel-coronavirus-2019) (2021). Accessed September 8, 2021.
2. Bril F, Al Diffalha S, Dean M, Fettig D. Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: Causality or casualty? *J Hepatol.* 2021;75(1):222–4.
3. Londoño M, Gratacós-Ginès J, Sáez-Peñataro J. Another case of autoimmune hepatitis after SARS-CoV-2 vaccination. Still casualty? *J Hepatol.* 2021;75(5):1248–49.
4. Rela M, Jothimani D, Vij M, Rajakumar A, Rammohan A. Auto-immune hepatitis following COVID vaccination. *J Autoimmun.* 2021;123:102688.
5. Andrade R, Aithal G, Björnsson E, et al. EASL clinical practice guidelines: Drug-induced liver injury. *J Hepatol.* 2019;70(6):1222–61.
6. The vaccine adverse event reporting system (VAERS) request. Wonder.cdc.gov (https://wonder.cdc.gov/vaers.html) (2021). Accessed September 8, 2021.
7. *VAERS–Download Data File*. Vaers.hhs.gov (https://vaers.hhs.gov/eSubDownload/index.jsp?fn=2021VAERSSYMPTOMS.csv) (2021). Accessed September 8, 2021.

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