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Another case of autoimmune hepatitis after SARS-CoV-2 vaccination – still casualty?

To the Editor:

We read with interest the letter entitled "Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: Causality or casualty?" by Bril *et al.*[1] recently published in *Journal of Hepatology*. We had a similar case which strengthens the message of SARS-CoV-2 vaccines as a potential trigger for autoimmune hepatitis (AIH).

The patient is a 41-year-old female with a past medical history of premature ovarian failure undergoing substitutive hormonal therapy with no side effects. After receiving the first dose of SARS-CoV-2 Moderna vaccine (mRNA-1273) the patient presented epigastric pain, nausea and vomiting. These symptoms lasted for 3 weeks and then decreased in intensity. Seven days after the second dose, symptoms reappeared with higher intensity and were associated with choluria and jaundice. Liver tests showed aspartate aminotransferase 993 IU/L, alanine aminotransferase 1,312 IU/L, total bilirubin 2.3 mg/dl (peak of 8.5 mg/dl), gamma-glutamyltransferase 209 IU/L, alkaline phosphatase 190 IU/L. Laboratory results were negative for hepatitis A, B, C, E, cytomegalovirus, Epstein-Bar virus, herpes simplex virus type 1 and 2, and herpes 6 virus. Antinuclear antibody (1:80), anti-smooth muscle antibody (1:40), anti-soluble liver antigen (anti-SLA), anti-liver cytosol were positive. IgG levels were elevated (20.8 g/L). Liver ultrasound was normal. The liver biopsy (2.5 cm, 19 portal tracts) showed a marked expansion of the portal tracts with a dense inflammatory infiltrate composed of lymphocytes and plasma cells, severe interface hepatitis and lobular inflammation with disperse necroinflammatory foci, apoptotic bodies and hepatocyte ballooning. Masson's trichrome staining showed no signs of parenchymal or perisinusoidal fibrosis. The score of simplified diagnostic criteria of the International Autoimmune Hepatitis Group was 8 (definite diagnosis of AIH) and the patient was diagnosed with SARS-CoV-2 vaccine induced-AIH. Corticosteroid treatment with high-dose prednisone (1 mg/kg) was started with rapid normalization of liver enzymes. The patient was followed by the Liver Unit in collaboration with the active surveillance program established by the Technical Pharmacovigilance Committee of the Hospital.

Specific environmental factors, including viruses, drugs and herbal products can trigger the loss of self-tolerance to liver autoantigens. Several reports have shown that vaccination against influenza and hepatitis A viruses can trigger AIH.[2,3] The mechanism behind the development of vaccine-induced AIH is unknown but it is probably similar to that described for other autoimmune phenomena: genetic susceptibility, exposure to foreign peptides homologous to human peptides (molecular mimicry), and immune system stimulation by vaccine adjuvant.[4] The Moderna vaccine lacks immune adjuvants but the presence of anti-SLA in our patient prompted us to investigate whether there was homology between the SARS-CoV-2 spike protein and soluble liver antigen. Using protein BLAST to align the sequence of these 2 proteins, we found no significant similarity. However, linear sequence matches in amino acid motifs are not the only criteria for molecular mimicry[5] and we cannot completely rule-out that other factors could have been involved in this case, such as: i) similar native or glycosylated amino acid epitopes shared between the protein expressed in the host after vaccination and soluble liver antigen, and ii) structural similarities between the proteins.[6] It is also possible that other liver autoantigens (different from SLA) share sequence homology with the protein expressed by the host after SARS-CoV-2 vaccination with mRNA vaccines.[7]

Finally, we have to consider the specific features of mRNA vaccines. This approach is based on the synthesis of RNA coding for the desired antigenic protein, but in order to avoid degradation, RNA is encapsulated in nanoparticles or liposomes that deliver their content inside the target cells by endocytosis. Prior to translation, RNA binds to pattern recognition receptors (especially Toll-like receptors) resulting in the activation of several proinflammatory signals including type I interferon response.[8] The upregulation of these pathways is similar to what has been described in AIH (and other autoimmune diseases) and therefore we believe that more than casualty, the association between SARS-CoV-2 vaccines and AIH is causality.

"One swallow does not make summer" and the benefits of vaccination are far higher than the potential risks of the vaccines and therefore the report of these 2 cases should not be used as an argument against vaccination. It should be noted that these reports illustrate a rare adverse event that has only been detected after the administration of millions of doses of mRNA vaccines in a "real-world" setting. Indeed, the coverage of the active surveillance monitoring program established in the hospitals, together with a close collaboration within medical departments, supported the detection of this rare adverse event and its association with previous vaccination.

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Conflict of interests

The authors declare not conflict of interests related to this manuscript.

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Authors' contributions

MCL detected the case and wrote the letter, JGG and JSP actively participated in the management of the patient and critically reviewed the manuscript.

Supplementary data

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Autoimmune hepatitis developing after the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine

To the Editor:

We read with interest the recent letter published by Bril *et al.* recently published in *Journal of Hepatology*.[1] The authors describe a possible case of COVID-19 vaccine-associated autoimmune hepatitis (AIH) in a 35-year-old woman 3 months post-partum. The patient presented with pruritis and jaundice 13 days after receiving a BNT162b2 mRNA (Pfizer-BioNTech) COVID-19 vaccine, which may be the first report of COVID-19 vaccine-associated liver injury. As vaccination programs are being rolled out globally,[2] many clinically significant side effects are starting to be identified, such as vaccine-induced immune thrombotic thrombocytopenia.[3]

Herein, we report the case of a 36-year-old Iraqi-born male physician who developed likely vaccine-induced AIH following COVID-19 vaccination. He has a past medical history of hypertension treated with olmesartan and laser eye surgery 2 weeks prior that required topical fluoroquinolone eye drops, 1 g of acetaminophen TDS, and 400 mg of ibuprofen TDS for 1 week total. He had no previous history of liver disease. Of note, he had his first dose of ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca) 26 days prior to presentation with a subsequent mild febrile reaction requiring 1 g of acetaminophen TDS, and 400 mg of ibuprofen TDS for 3 days. He was referred to our emergency department after a finding of markedly abnormal liver function tests on routine blood tests and was asymptomatic at the time.

His physical examination was unremarkable. Blood tests were significant for the following: bilirubin 17 μmol/L, alanine aminotransferase (ALT) 1,774 U/L, aspartate aminotransferase (AST) 633 U/L, gamma glutamyltransferase 136 U/L, alkaline phosphatase 118 U/L, albumin 45 g/L, and international normalized ratio 1.1. Serology was negative for hepatitis A, B, C and E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and HIV. Antinuclear antibody was positive at a titre of 1:160 in a speckled pattern. Immunoglobulins were normal with an IgG of 12.8 g/L (ref 7.0–16.5 g/L). Anti-liver-kidney microsomal, anti-smooth muscle, anti-mitochondrial antibodies, and anti-soluble liver antigen were normal. His caeruloplasmin, transferrin saturation, alpha-1-antitrypsin level and creatine kinase levels were also normal. Abdominal ultrasound revealed a normal-sized

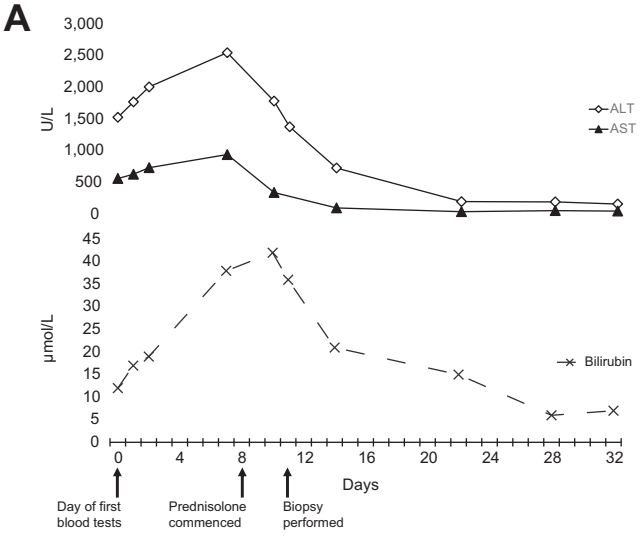

Fig. 1. Trends of plasma biochemistry over time.

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