Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

that molecular mimicry might be the potential mechanism underlying these mRNA vaccine-induced autoimmune conditions.

In conclusion, we would like to emphasize that clinicians need to remain vigilant and should consider DI-AIH secondary to mRNA vaccines in patients with similar presentation. However, this rare complication of the Moderna-COVID-19 vaccine (mRNA-1273) should not deter people from getting vaccinated.

Financial support
All the authors have no financial support statement to make.

Conflict of interest
All authors do not have any potential conflict of interest to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
Concept: CKT, RK; Data Collection: CKT,LMW; Manuscript Writing: CKT, YJW; LWM; RK; Critical Reviewing: All. Guarantor of article and data interpretation: LWM, RK.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.06.009.

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Author names in bold designate shared co-first authorship

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The mRNA COVID-19 vaccine – A rare trigger of autoimmune hepatitis?

To the Editor:

We read with interest the letters "Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) Vaccine: Causality or casualty?" by Bril *et al.*[1] and "Autoimmune hepatitis following SARS-CoV-2 vaccine: May not be a casuality" by Rocco *et al.*[2] which highlight the hypothesis that COVID-19 mRNA-based vaccines might increase the risk of developing autoimmune diseases. There are growing reports of autoimmune diseases developing after SARS-CoV-2 infection, including Guillain-Barré syndrome and primary biliary cholangitis.[3] It is speculated that SARS-CoV-2 can disturb self-tolerance and trigger autoimmune responses through cross-reactivity with host cells and that the COVID-19 mRNA vaccines may trigger the same response.[4,5]

We report a further case of autoimmune hepatitis (AIH) following COVID-19 mRNA vaccination. Our patient is a 71-year-old Caucasian female. Background history was significant for cholecystectomy 20 years previously, left total hip replacement and osteoarthritis of the knees. There were no risk factors for

Keywords: Autoimmune Hepatitis; COVID-19 Vaccine; mRNA vaccines.
Received 10 June 2021; received in revised form 23 June 2021; accepted 29 June 2021; available online 8 July 2021
https://doi.org/10.1016/j.jhep.2021.06.044

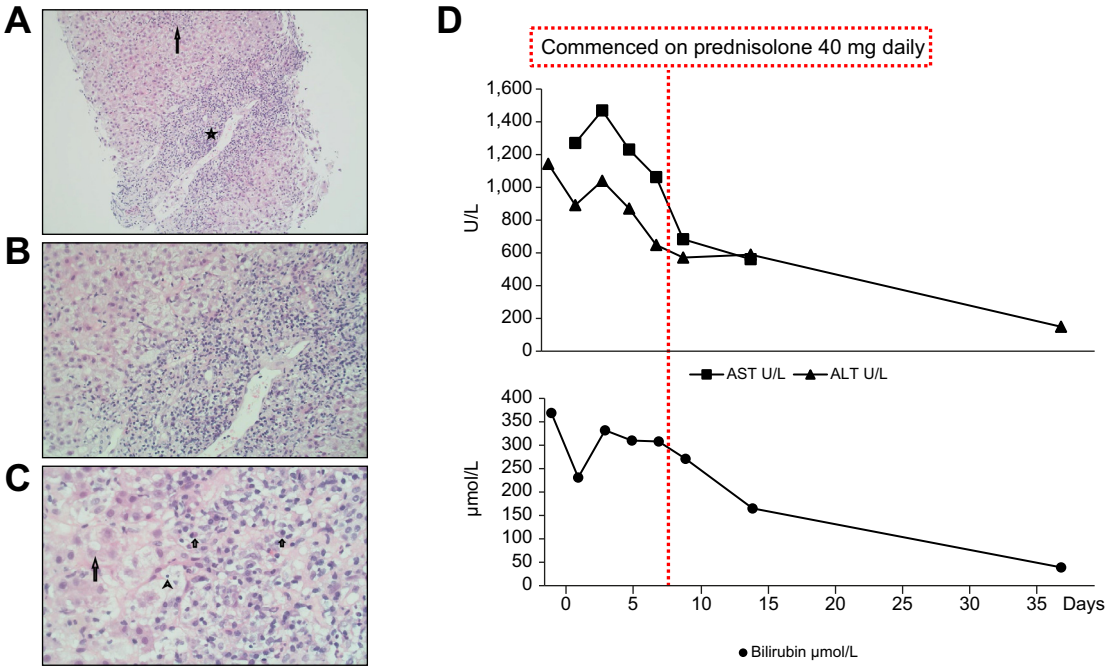

Fig. 1. Histological (H&E stain) and biochemical findings. (A) Marked portal tract (star) inflammation with enlargement and an irregular disrupted interface and a lobular hepatitis (long arrow)(100x). (B) At higher magnification the portal tract inflammation is mononuclear with spill over and damage to the periportal hepatocytes (200x). (C) At high magnification many of the mononuclear inflammatory cells are plasma cells (short arrows). This lymphoplasmacytic infiltrate damages periportal hepatocytes with some forming rosettes (long arrow) and with occasional emperipolesis of lymphocytes (arrowhead)(400x). (D) Trend of ALT, AST and bilirubin following introduction of steroids. ALT, alanine aminotransferase; AST, aspartate aminotransferase. (This figure appears in color on the web.)

autoimmune disease. She was on no regular medications or supplements.

She received the Moderna mRNA vaccine on the 16th of April 2021. During the 24-hour period around vaccination she took 2 g of paracetamol. Four days post vaccination she noticed jaundice. She attended her primary carer on the 26th of April (+10 days post vaccination). Laboratory results were markedly abnormal (bilirubin 270 µmol/L, alkaline phosphatase 217 U/L, alanine aminotransferase 1,067 U/L). She was promptly referred to our hepatology services.

On physical examination she was jaundiced. Laboratory results were negative for hepatitis B, C, and E, Epstein-Barr virus, cytomegalovirus and HIV. Hepatitis A IgG was positive with a negative IgM. Smooth muscle antibody was strongly positive with a titre of 2,560 and an anti-actin pattern. Total IgG was markedly raised at 21.77 g/L. Liver ultrasound, magnetic resonance cholangiopancreatography and computer tomography pancreas protocol showed distal common bile duct dilation of 1.4 cm consistent with prior cholecystectomy.

On receipt of positive autoantibodies and a rising liver profile (bilirubin 332 µmol/L, alanine aminotransferase 1,143 U/L, aspartate aminotransferase 1,469 U/L, alkaline phosphatase 237 U/L and international normalized ratio 1.4), steroids were commenced on the 4th of May and liver biopsy was performed the following day. Up to 20 portal tracts were present, each expanded with a marked polymorphous inflammatory cell infiltrate of plasma cells, lymphocytes, eosinophils, neutrophils and PASD-positive ceroid laden macrophages; interface hepatitis was present and continuous in most tracts, with portal-portal and portal-central bridging necrosis (Fig. 1A–C). The findings were compatible with AIH, however drugs, toxins or infections could not be ruled out as aetiological agents.

Since discharge from hospital our patient remains well and liver biochemistry has continued to improve on a tapering course of prednisolone (Fig. 1D).

There are a number of similarities between the previously described cases and our own. Firstly, there was a short interval between vaccination and symptom onset in all cases. In response to the first case, Capecchi *et al.*[6] questioned whether this was too short an interval to develop the necessary immune activation. It is indeed short when compared to established causatives agents of drug-induced autoimmune liver disease such as immune checkpoint inhibitors where a latency period of 2 to 24 weeks has been described.[7] However, a much shorter latency period is described for other vaccine-induced autoimmune conditions such as Guillain-Barré syndrome (median onset 13 days).[8]

Secondly, histological appearances are similar between our case and that described by Bril *et al.* Both cases had an eosinophil infiltration which is more typical of a drug-induced liver injury. This raises the possibility that this is a vaccine-related drug-induced liver injury with features of AIH rather than the vaccine causing immune dysregulation.

Unlike the other cases, our patient had no confounding risk factors for developing autoimmune liver disease such as other autoimmune conditions or recent pregnancy and she received a different mRNA vaccine, Moderna rather than Pfizer-BioNTech.

These findings raise the question as to whether COVID-19 mRNA vaccination can, through activation of the innate immune system and subsequent non-specific activation of autoreactive lymphocytes, lead to the development of autoimmune diseases including AIH or trigger a drug-induced liver injury with features of AIH. The trigger, if any, may become more apparent over time, especially following withdrawal of immunosuppression. As with other autoimmune diseases associated with vaccines the causality or casualty factor will prove difficult to tease apart and should not distract from the overwhelming benefits of mass COVID-19 vaccination. But it does beg the question of whether or not these individuals should receive the second dose of an mRNA COVID-19 vaccine.

Financial support
The authors received no financial support to produce this manuscript.

Conflicts of interest
The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
Dr Cathy McShane, Dr Clifford Kiat & Dr Órla Crosbie - involved in clinical care of patient and writing of manuscript. Dr Jonathan Rigby – interpreted histology and involved with writing of manuscript.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.06.044.

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An unusual case of acute cholestatic hepatitis after m-RNABNT162b2 (Comirnaty) SARS-CoV-2 vaccine: Coincidence, autoimmunity or drug-related liver injury

To the Editor:
We read with interest the article "Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: Causality or casualty?" by Bril *et al.* recently published in *Journal of Hepatology*.[1] In this case, autoimmune hepatitis had some atypical features such as the absence of immunoglobulin G elevation and the presence of eosinophils on liver histology.

We recently observed a case of severe cholestatic hepatitis occurring after the administration of m-RNA-BNT162b1 (Comirnaty©, Pfeizer Biontech), with no development of autoantibodies and with the presence of eosinophil infiltrate at liver histology. The patient responded well to steroid treatment, similarly to autoimmune hepatitis.

The patient, a 43-year-old woman, presented to the hospital on February the 4th with jaundice and itching. At admission, total bilirubin was 17.54 mg/dl (direct bilirubin 12.94), alanine aminotransferase (ALT) 52 U/L, aspartate aminotransferase (AST) 51 U/L. Personal history was negative, except a mild dyslipidaemia with intermittent ALT increase, treated with diet (ALT and cholesterol maximum level 50 U/L and 285 mg/dl, respectively). Because of venous insufficiency, she took ginkgo-biloba in August 2020, withdrawn next October, more than 100 days before admission. She was a sanitary assistant so she received the Comirnaty vaccine (first dose January the 12th, second February the 2nd). Itching started on January 27th and by

Received 21 June 2021; accepted 2 July 2021; available online 10 July 2021
https://doi.org/10.1016/j.jhep.2021.07.005