Data on lymphatic drainage of hepatic excess fluid in patients with cirrhosis are scarce. As hydrostatic pressure is the most relevant factor impacting transfer from the sinusoid to the interstitial space, liver lymphatic flow through the TD increases as a result of portal hypertension. The diameter of the cisterna chyli is associated with portal venous pressure in patients with cirrhosis.[6]

Witte *et al.*[7] showed that TD pressure was increased in patients with cirrhosis with a mean end pressure of 20 mmHg compared to 8.5 mmHg in controls. LVJ narrowing has been reported on cadaveric series,[8] which may limit lymph flow and be responsible for enlarged TD diameter.

These 2 cases highlighted that patients with cirrhosis and portal hypertension had a significant pressure gradient between TD and LSV and that its correction after TD stenting may induce ascites resolution. Thoracic duct stenting seems an interesting approach in the treatment of refractory ascites. Further studies are needed to confirm these results.

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Authors' contributions
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New-onset autoimmune hepatitis following mRNA COVID-19 vaccination in a 36-year-old woman with primary sclerosing cholangitis – should we be more vigilant?

To the Editor:
Recently, colleagues from different institutions reported in this Journal on 5 cases of newly diagnosed autoimmune hepatitis (AIH) following COVID-19-vaccination with the Pfizer/BioNTech[1,2] or the Moderna mRNA-vaccine.[3–5] The patients were all female and between 35 and 80 years of age; liver-specific symptoms occurred between 4[3] and 35 days[4] after the 1st vaccination, or 7 days after the 2nd vaccination.[2,5]

Two patients had possibly confounding risk factors for AIH development, namely recent pregnancy[1] and autoimmune thyroiditis.[2] The 5 cases have stirred up discussion about

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whether mRNA vaccines could trigger hepatic autoimmune reactions through molecular mimicry or bystander activation of dormant autoreactive T-helper cells.[6] Herein, we add another case to this discussion: the first case of a patient with pre-existing primary sclerosing cholangitis (PSC) diagnosed with AIH after mRNA-COVID-vaccination.

PSC is a chronic progressive cholestatic liver disease characterized by multi-focal biliary strictures. A subgroup of patients with PSC have biochemical, serological, and/or histological features that overlap with those of AIH;[7] in the largest international PSC cohort study, 8.1% of the 2,454 female and 5.8% of the 4,661 male patients were diagnosed with the PSC/AIH variant.[8]

Our patient (female, 36 years-old) was diagnosed with ulcerative colitis and PSC at the age of 33. Diagnosis was made after exclusion of viral or metabolic hepatopathy due to a typical cholangiogram and highly elevated alkaline phosphatase (AP, 1,077 U/L) and gamma glutamyltransferase (GGT, 757 U/L), while aspartate aminotransferase (AST, 117 U/L), alanine aminotransferase (ALT, 193 U/L) and Immunoglobulin G (IgG, 16.9g/L) were only slightly elevated. Following treatment with ursodeoxycholic acid (1,000 mg/day) and endoscopic biliary intervention, AP and GGT initially decreased and ALT and AST normalized. However, after 1 year, the patient presented with cholangitis and pruritus and had multiple high-grade intra- and extrahepatic strictures on endoscopic retrograde cholangiography (Fig. S1). Due to recurrent episodes of purulent cholangitis and refractory strictures scheduled balloon dilatations had to be performed regularly every 3 months. During episodes of cholangitis, aminotransferases were also elevated but less than AP/GGT (Fig. 1).

The patient received her first dose of Moderna mRNA-1273 vaccine on May 20th. Except for minor muscle aches the patient was without further symptoms. On May 31st she was hospitalized for a scheduled endoscopic balloon dilatation of the strictures. On admission, highly elevated ALT (588 U/L) and AST (581 U/L) were noticed with a rise in serum bilirubin (1.4 mg/dl) and international normalized ratio (INR, 1.2), while AP and GGT were only slightly elevated (Fig. 1). Serology was negative for acute viral infections (hepatitis A, B, C, E, cytomegalovirus, Epstein-Barr-Virus, herpes virus). Total IgG was elevated up to 24.75 g/L (upper limit of normal: 16 g/L) and antinuclear antibody (ANA, 1:2,560; homogeneous pattern) and anti-double-stranded DNA antibodies (186.8 IU/L; ULN: 100 IU/L) were positive. Anti-mitochondrial-, anti-smooth-muscle- and antineutrophil cytoplasmic antibodies were negative. Liver histology showed a dense lymphoplasmacellular portal infiltrate with involvement of the adjacent lobular parenchyma (interface hepatitis) and discrete presence of rosette formation and apoptotic hepatocytes (Fig. 1). Besides lymphocytes and plasma cells, few eosinophils and small bile ducts with associated neutrophilic granulocytes (ductular reaction) were observed.

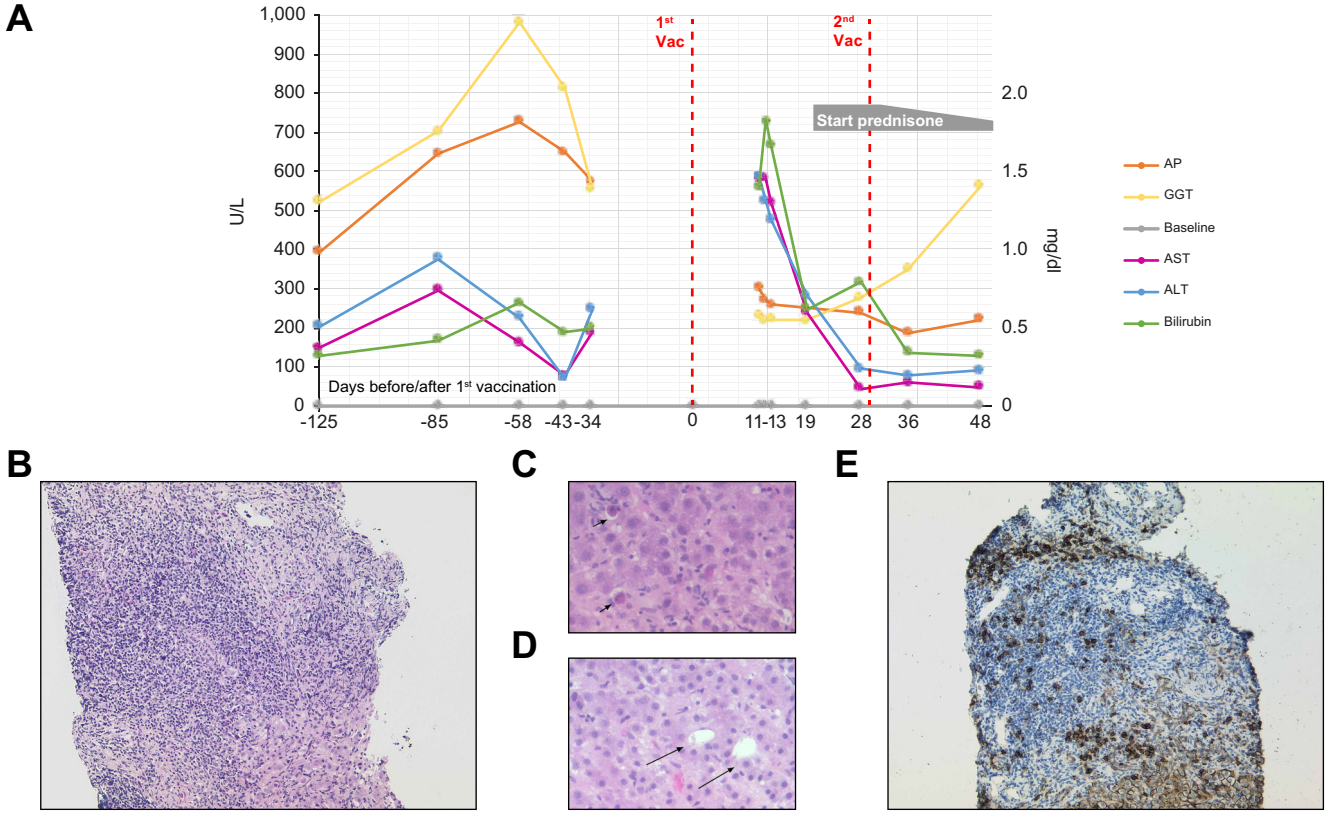

Fig. 1. Biochemical and histological findings. (A) Shows AP, GGT, AST, ALT (all in U/l) and serum bilirubin (in mg/dl) at certain time points in days before and after the 1st COVID-19-vaccination (Day 0). Histology (B) shows a dense lymphoplasmacellular portal infiltrate with involvement of the adjacent lobular parenchyma (interface hepatitis), which consists of lymphocytes, plasma cells and few eosinophils. Additionally, small bile ducts with associated neutrophilic granulocytes (ductular reaction) are visible. Higher magnification shows apoptotic hepatocytes (C) and discrete rosette formation (D). Immunostaining with CD138 confirms positive stained plasma cells (E). ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase. (This figure appears in color on the web.)

Hence, we diagnosed AIH and started treatment with prednisone (50 mg) on June 10th with rapidly decreasing liver enzymes. Since the SARS-CoV2-antibody-titer 2 weeks after the 1st vaccination was only weak, we decided to vaccinate a 2nd time on June 19th while the patient was still treated with 50 mg prednisone. Nonetheless, we recorded a further decline of liver enzymes and normalization of INR, bilirubin and of total IgG (14.6 g/L), while prednisone was slowly tapered down and azathioprine (75 mg) was added July 1st. The SARS-CoV2-IgG-antibody-response 2 weeks after the 2nd vaccination was sufficient with >384 BAU/ml.

Our case has some unique features when compared to the previous cases. Due to PSC, liver enzymes were well documented before vaccination, leaving no doubt about the temporal coincidence between vaccination and increase of aminotransferases. Although we interpreted the elevated aminotransferases prior to vaccination as a concomitant periductular hepatitis during severe cholangitis, we cannot exclude that a latent AIH may already have existed, which was accelerated by the vaccination. Of note, our patient was without liver-specific symptoms when we diagnosed AIH during routine liver enzyme tests. Since classical AIH takes an asymptomatic subclinical course in about half of cases,[9] this raises the question of whether the 5 symptomatic cases[1–5] documented so far represent just the tip of the iceberg of mRNA-vaccine triggered AIH. One can speculate whether in the 2 cases that were diagnosed after the 2nd vaccination,[2,5] a subclinical AIH was already induced after the 1st vaccination and – without treatment - exacerbated after the 2nd vaccination. In our patient, the 2nd vaccination was well tolerated under concomitant therapy with prednisone and induced a sufficient antibody response. In summary, the question arises whether we should be more vigilant, at least in female patients with pre-existing predisposition to autoimmune diseases, and routinely check aminotransferases 2-4 weeks after COVID-19-vaccination.

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Authors' contributions
TZ and TJW wrote the letter to the editor. TZ, LD, CPS and TJW were involved in the patient's clinical care. FF performed the pathology examination and interpreted the histology. All authors reviewed the final version of the manuscript.

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The search for optimum thiopurine metabolite levels in autoimmune hepatitis continues…

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To the Editor:
We read with great interest the article by Candels *et al.* who concluded that measuring thiopurine metabolites (TMs) in