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JOURNAL OF HEPATOLOGY

Primary biliary cholangitis associated with SARS-CoV-2 infection

To the Editor:

We would like to present the case of a female patient who developed primary biliary cholangitis (PBC) concomitant with Guillain-Barré syndrome (GBS) during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1]

A 44-year-old obese and hypertensive woman already suffering from Hashimoto's thyroiditis, was admitted to hospital with fever, cough and dyspnoea on March 18, 2020. Chest X-rays showed bilateral interstitial pneumonia and she had a positive SARS-CoV-2 nasopharyngeal swab. Because of clinical deterioration, the patient was intubated and treated in the intensive care unit with mechanical ventilation and the following drugs in chronological order: tocilizumab, ceftriaxone, azithromycin, darunavir/cobicistat, anakinra, remdesivir and fluconazole. After 2 weeks of mechanical ventilation, the patient's condition began to improve. She was extubated but, because of respiratory worsening, non-invasive ventilation was initiated. Then, she experienced a rapid cognitive deterioration (Glasgow coma scale 3) with good oxygen saturation and was re-intubated. In the following days the state of consciousness improved with complete recovery, but she displayed a proximal hyposthenia at the 4 limbs without altered sensitivity; osteo-tendon reflexes were absent at the upper limbs, weakly evocable the patellars, present at the heels. The electromyography showed signs of radiculo-neuropathy with prevalent interesting of the proximal section of the four limbs and diffuse signs of active neurogenic sufferance with modest re-innervating activity. An acute motor axonal neuropathy (AMAN) subtype of GBS was diagnosed and the patient was treated with intravenous immunoglobulins with a progressive clinical improvement enabling transfer to a rehabilitation ward.

During the hospitalization in intensive care, an important rise in serum gamma-glutamyltransferase (GGT) was observed with initially normal levels of alkaline phosphatase (AP) that progressively increased later (Fig. 1A). Serum bilirubin was normal or slightly augmented while alanine aminotransferase (ALT) tended to fluctuate between normal and slightly increased levels (28–120 IU/L, normal range 1–31). The patient had no history of previous increases in cholestastic indexes (last blood exams in 2015, including GGT and AP, were normal) or symptoms before COVID-19 infection. Family history was negative for autoimmune and hepato-biliary diseases; clinical examination was unremarkable. An abdominal ultrasound showed a slightly enlarged liver with moderate steatosis and a mildly enlarged spleen. Liver stiffness measured with Fibroscan was 9.1 kPa. Serology for hepatotropic viruses was negative, immunoglobulins were normal, while total cholesterol was slightly augmented (251 mg/dl, normally <200) as was low-density lipoprotein (LDL) cholesterol (174 mg/dl, normal <110). The patient tested positive for anti-nuclear (titre 1:160, cytoplasmic pattern) and anti-mitochondrial (titre 1:640) autoantibodies, but negative for anti-smooth muscle, anti-liver kidney microsome and anti-neutrophil cytoplasmic antibodies, as well as extractable nuclear antigens. From the liverblot panel of autoantibodies, anti-mitochondrial M2/BCOADC (branched chain 2-oxo acid-dehydrogenase) were positive while anti liver-kidney microsome type 1, glycoprotein 210, substance P (sp) 100, liver cytosol type 1 and soluble liver antigen were negative. Given the AP increase associated with anti-mitochondrial antibody positivity, PBC was suspected; however, a liver biopsy was performed to exclude possible concomitant non-alcoholic steatohepatitis. The histological examination (Fig. 1B and 1C) showed a preserved architecture and a moderate peri-portal fibrosis. Micro and macro-vesicular steatosis were present in 15% of hepatocytes. In the portal spaces a moderate-marked chronic inflammatory infiltrate, sometimes dense in similar-follicular aggregation, a focal piecemeal necrosis and damaged bile ducts surrounded by lymphocytes and scanty plasma-cells were observed. Focal ductular metaplasia of periportal hepatocytes was also noted while parenchymal confluent necrosis was excluded. The histological findings, consistent with florid ductal lesions, combined with clinical history were compatible with an early stage of PBC (stage I in both Scheuer and Ludwig classifications)[2] while the micro and macrovesicular steatosis are possible evidence of drug-induced liver injury and non-alcoholic fatty liver disease, respectively.[3]

On May 27, the patient was discharged from hospital. Her vital parameters were normal, she could breathe autonomously in ambient air. Her motor function was slowly improving. Following an observation period in which both GGT and AP got lower, but still

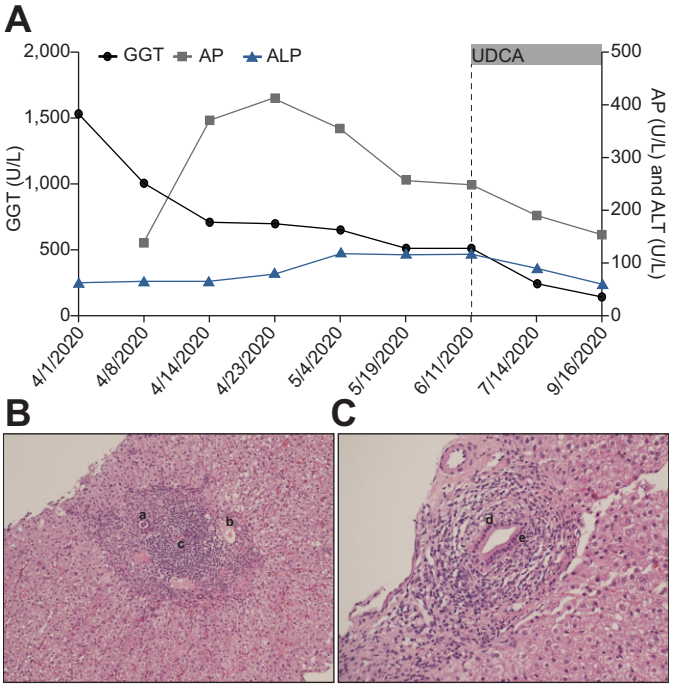

Fig. 1. Patient's biochemical course and liver histology. (A) The 3 lines represent the temporal trend in GGT, AP and ALT. (B) A widened portal tract, with its bile duct (a) and portal vein (b), containing a lymphoid follicle/aggregate with a germinal centre (c); (H&E stain, magnification 10x). (C) A damaged bile duct (d) surrounded by infiltrating lymphocytes and plasma-cells (e). This is a typical florid ductal lesion; (H&E stain, magnification 20x). (This figure appears in color on the web.)

Keywords: COVID-19; PBC; Guillain-Barré syndrome; auto-immune diseases; auto-immune disease triggers.
Received 11 January 2021; received in revised form 31 January 2021; accepted 3 February 2021; available online 19 February 2021
https://doi.org/10.1016/j.jhep.2021.02.006

remained increased (Fig. 1A), on June 11, 2020, the patient began therapy with ursodeoxycholic acid (UDCA; 10 mg/kg). At the last blood exams on September 16, 2020, after 3 months of treatment, GGT and AP were reduced to 144 U/L (normal 1–38) and 155 U/L (normal 38–126), respectively. Transaminases fluctuated during the follow-up period between normal and only slightly increased values.

The supposition of a possible overlap syndrome between PBC and autoimmune hepatitis, advanced during the acute phase, was thereafter excluded based on EASL's revised criteria.[4] On the basis of these results, we hypothesize that SARS-CoV-2 infection could have triggered the expression of PBC and GBS in a genetically predisposed individual already suffering from autoimmune thyroiditis. This hypothesis is further supported by the fact that SARS-CoV-2 is an RNA virus capable of inducing a profound activation of the immune system and also by the previous finding that infection by a human RNA beta-retrovirus, related to the mouse mammary tumor virus, was suggested as a possible trigger for PBC development.[5]

To the best of our knowledge this is the first reported case of PBC developing during or soon after COVID-19. We conclude that the search for anti-mitochondrial autoantibodies should be performed in individuals with elevated GGT and/or AP during SARS-CoV-2 infection, particularly in those with a pre-existing autoimmune disease.

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

Conflict 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 Bartoli and Dr Gitto share the co-authorship, they retrieved and analysed the literature and wrote the major part of the case report, Dr Cursaro revised the manuscript, Dr Sighinolfi provided histology data and microscope images and Prof Andreone revised the entire work, largely contributing with the conclusions.

Acknowledgments
We sincerely thank Dr Tatiana Alicandro and Dr Marco Rivi who contributed to the realization of this scientific report.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.11.006.

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Impact of the COVID-19 pandemic on HCV elimination in Spain

To the Editor:

We read with great interest the article by Sarah Blach and co-workers[1] investigating the impact of COVID-19 on global hepatitis C elimination efforts. The authors show that over the next 10 years a *1-year delay* scenario related to COVID-19 would result in 44,800 excess hepatocellular carcinoma (HCC) cases globally and 72,300 excess liver-related deaths, relative to a *no delay* scenario. The excess HCC cases and deaths would be among high-income countries.[1]

Spain is one of the 45 high-income countries on the right track to reach HCV elimination by 2030 if the current screening

Keywords: COVID-19; Elimination; HCV.
Received 14 December 2020; accepted 15 December 2020; available online 20 December 2020
https://doi.org/10.1016/j.jhep.2020.12.018