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Autoimmune liver disease triggered by SARS-CoV-2: a case report and review of the literature

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Abstract. – BACKGROUND: An increasing number of coronavirus disease 2019 (COVID-19) related autoimmune hepatitis (AIH) and autoimmune liver disease (AILD) has been already described so far in the last three years. This rise has set up some diagnostic and therapeutic concerns, although steroid therapy has mostly been efficient, avoiding main significant side effects.

CASE PRESENTATION: We report the case of a 52-year-old subject displaying liver function impairment at the laboratory tests while positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) swab. Needle liver biopsy showed severe portal inflammation, interface hepatitis, lobular inflammation, abundant plasma cells, bridging necrosis, endothelialitis, bile duct vanishing disease, and ductular reaction. The diagnosis of autoimmune liver disease (AILD) was performed. After a month of steroid and ursodeoxycholic acid medications, liver function fully recovered. Azathioprine was introduced, and steroids were gradually reduced.

CONCLUSIONS: Probably triggered by the SARS-CoV-2-induced cytokine storm, the association between COVID-19 and autoimmune-related inflammatory injury may display a particular paradigm of AILD pathogenesis.

Key Words:
COVID-19, SARS-CoV-2, AILD, AIH, Autoimmune hepatitis, Overlap syndrome.

Background

Claimed to be merely responsible for a stern respiratory disease, the coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been recently associated with a more complex pathogenesis. Examples are multiple organ dysfunction, and immune pathologies[1,2]. Hepatic involvement has been widely reported in the COVID-19 setting. Many possible explanatory etiologies have been proposed for liver injury in such cases. For instance, drug-induced liver disease[3], thrombotic sinusoiditis[4], bile duct cell damage[5], and cholestatic liver pathology[6] have been declared as the main pathological issues related to COVID-19.

Nonetheless, few cases of autoimmune hepatitis settled close to the SARS-CoV-2 infection have also been reported. This fact has particularly pointed out some diagnostic and therapeutic concerns[7]. It ought to be admitted that steroid therapy has accomplished chiefly the task of recovering the patients and avoiding significant side effects. In 2020, Marabotto et al[8] described a 37-year-old woman hospitalized for COVID-19 showing elevated aminotransferases. A few months later, the patient beca-

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me positive for anti-nuclear antibodies (ANA) and anti-soluble liver antigen (SLA). The liver biopsy was suggestive of autoimmune liver disease (AILD)[8]. Similarly, a 54-year-old man developed autoimmune hepatitis (AIH) just a month after his diagnosis of COVID-19 in 2021[9]. Two other additional patients, a 49-year-old male and a 73-year-old female, were eventually diagnosed with AIH after having displayed abnormal serum levels of aminotransferases during COVID-19[10]. The first case of overlap syndrome – AIH plus primary biliary cholangitis (PBC) – triggered by COVID-19 was described in a 57-year-old man[11]. In 2022, three other case reports were labeled as AIH caused by COVID-19 in a 60-year-old female[12], a 40-year-old lady[13] and a 3-year-old child. The last patient also developed acute liver failure[14].

Nine case reports, all sharing the common ground of the AILD spectrum, have been described so far in the scientific literature. Now we introduce a new case and a detailed revision of the literature to outline the similarities with the previously mentioned ones and particularly analyze the single peculiarities.

Case Report

In April 2022, a 52-year-old woman was admitted to the emergency room of our university hospital because of severe asthenia and nausea for nearly a week. The laboratory tests pointed out liver function impairment. In this occurrence, the SARS-CoV-2 nasopharyngeal swab RT-PCR has revealed the infection. She was discharged for self-isolation at home because COVID-19 symptoms were mild, the thorax computed tomography (CT) was remarkable and the patient was not in any need of urgent hospitalization.

The patient had received the third dose of COVID-19 vaccination five months earlier. She was already treated for bipolar disorder and Hashimoto thyroiditis. She underwent cholecystectomy for gallbladder acute inflammation seven years before the current illness. No previous history of hepatitis or family history was recorded.

She was admitted at the hepatology outpatient clinic as soon as the swab became negative 20 days later. After she was admitted, her general conditions were heavily worsened. Jaundice was observed. The details of the laboratory data, including those at the outset, at the time of liver biopsy, at the discharge, and after the discharge are listed in Table I. Ultrasound examination revealed pericardial effusion and slight hepatomegaly with heterogeneous texture. Abdominal CT evidenced hilar lymphadenopathy (17 mm).

Needle liver biopsy showed severe portal inflammation, interface hepatitis, and lobular inflammation, including abundant plasma cells (Figures 1, 2), bridging necrosis, endothelialitis (Figure 3), bile duct vanishing disease in about half of the portal spaces and ductular reaction (Figure 4). Also matching the clinical picture, the pathological findings suggested the diagnosis of AILD. According to the simplified diagnostic criteria for AIH the score was 8, leading to the final diagnosis of definite AIH.

After induction with intravenous methylprednisolone (60 mg/day) and ursodeoxycholic acid (900 mg/day) for 8 days, prednisone (50 mg/die) and ursodeoxycholic acid (900 mg/die) were prescribed. After 35 days of her first admission, once improvement of the clinical picture occurred, the patient was discharged with prednisone (50 mg/day) and ursodeoxycholic acid (900 mg/day) treatment. After a month, when the liver function appeared fully recovered (Table I), she underwent maintenance therapy with prednisone (25 mg/day), azathioprine (50 mg/day), and ursodeoxycholic acid (900 mg/day).

Discussion

AILD is a spectrum of immune-mediated, chronic, inflammatory liver diseases characterized by distinctive histological features and standardized criteria[15-19]. Though the precise physio-pathological mechanisms leading to AILD are not fully understood yet, both genetic and environmental causes have been claimed to play a role[11]. Among all the possible suspected triggers, different viruses, such as hepatotropic B virus (HBV)[20], hepatotropic C virus (HCV)[21], and Epstein-Barr virus (EBV)[22], have already been described. Those viruses can break immunological tolerance and increase the cytokines that allow the inflammatory process of AILD. In this scenario, by inducing the cytokine storm, SARS-CoV-2 certainly is to be considered the best-fitting paradigm in this pathogenesis[1,2].

COVID-19 vaccine-induced AIH has been also documented in 32 cases. However, in those cases

Table I. The laboratory data. Details of our patient from the outset, at the time of liver biopsy, at the discharged, and at the first checkup.

	Onset	Liver biopsy: after 20 days	Discharged after 35 days	Two months after the discharge
AST	580 U/L	628 U/L	321 U/L	14 U/L
ALT	681 U/L	697 U/L	298 U/L	13 U/L
GGT	709 U/L	645 U/L	459 U/L	36 U/L
LDH	358 U/L	276 U/L		177 U/L
Cholinesterase	4,245 U/L	2,386 U/L		3,500 U/L
ALP	170 U/L	208	168 U/L	73 U/L
Total Bilirubin	2.16 mg/dL	20.2 mg/dL	10.45 mg/dL	0.3 mg/dL
Direct Bilirubin	1.54 mg/dL	15.5 mg/dL	8.68 mg/dL	0.2 mg/dL
PCR	20.3 mg/dL	32.2 mg/dL		
ANA		1:160		
ASMA		Negative		
LKM		Negative		
SLA		Negative		
IgG		3,317 mg/dL		
IgA		490 mg/dL		
IgM		263 mg/dL		
HBV-DNA quantitative		Negative		
HCV-RNA quantitative		Negative		
HBsAg		Negative		
antiHBsAg		Negative		
HBeAg		Negative		
antiHBeAg		Negative		
antiHBcAg		Negative		
antiHCV		Negative		
ENA screening		Negative		
AMA		Negative		
pANCA		Negative		
cANCA		Negative		

the latency time between the first COVID-19 vaccine dose to the first symptoms' onset ranged from two days to two months[23]. Our patient received the third dose of COVID-19 vaccination five months before being diagnosed as AILD. In the scientific literature, a total number of nine cases of AILD have already been reported to be related to COVID-19 regardless of COVID-19 vaccination. The first association between SARS-CoV2 and AIH appeared in 2020[7,8]. Nonetheless, it was argued that COVID-19 could not be responsible for the development of AIH because of the advanced fibrosis detected by Marabotto et al[8]. Thus, they suggested that COVID-19 disclosed a still unnoticed underlying liver disease. The COVID-19 related cytokine storm may certainly deteriorate an underlying liver disease[24,25], though further case reports revealing clinical and histological findings consistent with AIH were then published in 2021 and 2022. Table II summarizes the data reported in the scientific literature. The disease occurred in a broad range of ages, from 3 to 73 years, with a slight female gender prevalence. The insurgence of the disease was reported to be concomitant in two cases[12] or after a variable timing range between two days[10] and 2-3 months[8]. Only one patient reported a previous history of autoimmune disease but not of hepatitis[9]. In almost all cases, laboratory tests

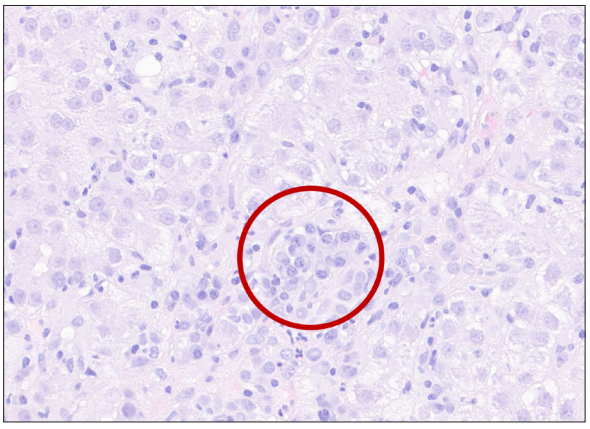

Figure 1. Liver biopsy findings. Severe inflammation, including abundant plasma cells easily recognizable inside the circle. Hematoxylin and eosin staining (x400).

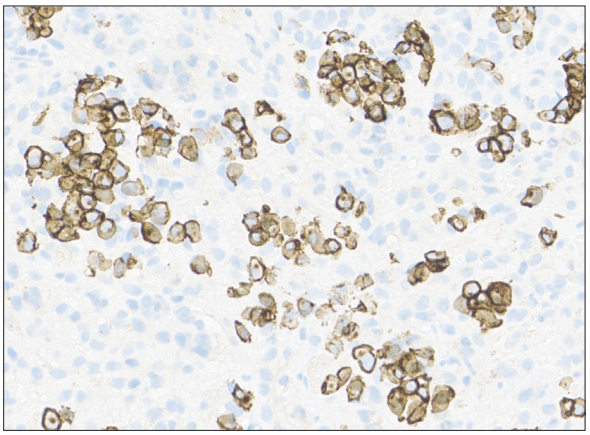

Figure 2. CD 38 immuno-stain (x400) underlines the huge amount of plasma cells.

detected enhanced impairment of autoimmunity assessment and a huge rise of liver enzymes (ALT and AST). In 7 cases an increase of bilirubin serum levels was observed. ALP and GGT were affected in 5 cases, including the one which was diagnosed as AIH-PBC overlap syndrome. Accordingly, our patient reported the rise in ALT, AST, total and direct bilirubin, ALP, GGT, and IgG. Moreover, the positivity for ANA was also found, whereas the main viral markers were negative. Thus, the score for AIH has led to the diagnosis of definite AIH.

Seven out of the ten cases reported a histological pattern characterized by moderate to severe portal inflammation, mild to moderate interface hepatitis, moderate lobular inflammation, lymphocytes and plasma cells as the main common features[8,9,12,13]. Less common features were focal[12] or submassive[14] necrosis, endothelialitis[8], fibrosis[8,12], and ballooning degeneration[12]. Our case shared the presence of severe portal inflammation, interface hepatitis, lobular inflammation, abundant plasma cells, bridging necrosis, and endothelialitis. Despite the high ALP and GGT serum levels and the absence of septal bile ducts in the majority of portal tracts, we could not perform a diagnosis of overlap syndrome due to the absence of florid duct lesions and the absence of AMA[26,27]. In the case diagnosed as overlap syndrome, the liver biopsy was not performed as the diagnosis was mainly based on the finding of AMA positivity[11].

In contrast to the usual AIH clinical history, SARS-CoV2-induced cases appeared to resolve with temporary steroid treatment without the need for long-term therapy[13]. In all but one case, the main treatment was based on immunosuppression (prednisone, azathioprine[10,12,14] and tacrolimus[10]). This approach has constantly fast improved the clinical picture. The case diagnosed as overlap syndrome[11] was treated with ursodeoxycholic acid. In our case, which was likewise characterized by laboratory and pathological features suggestive of AILD with additional bile duct vanishing disease and ductular reaction, ursodeoxycholic acid was added to steroid therapy. Azathioprine was overlapped later after the full recovery of liver function tests to support the steroid's gradual reduction.

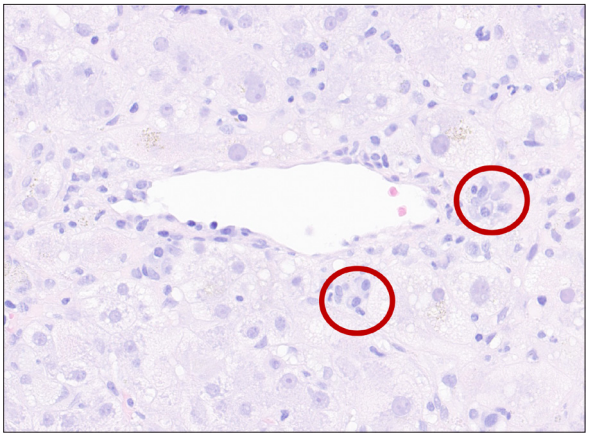

Figure 3. Endothelialitis surrounded by lobular lymphoplasmacellular inflammation and clusters of plasma cells (circle) in zone 3 (HE staining, x400).

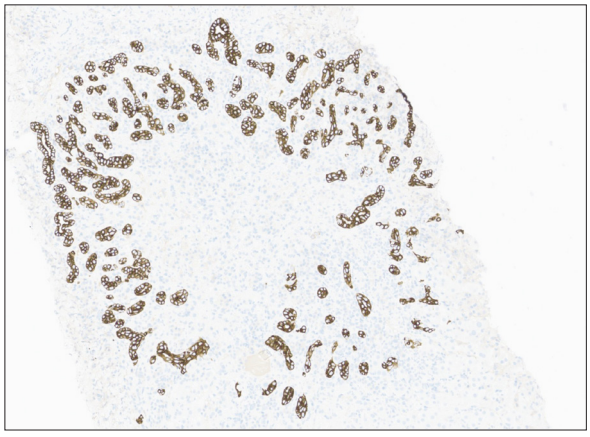

Figure 4. Keratin 7 immunostaining showing the absence of the septal portal duct, and budding ductular proliferation around a portal space (D: x100).

Table II. Sum up of the cases previously reported in the scientific literature.

Authors and year	Age and sex	Clinical History	Laboratory	Diagnosis	Timing	Liver biopsy	Therapy
Rajendiran et al[7] 2020	No information available	No information available	No information available	AIH	No information available	No information available	No information available
Marabotto et al[8] 2020	37-year-old women		ALT 1,417 U/L; AST 1,135 U/L, normal bilirubin; IgG 22.7 gr/L ANA+ (1:80); SLA+	AIH	2-3 months	Moderate-marked chronic portal and moderate interface hepatitis, lymphocytes and plasmacells, endothelitis suggestive of AIH, with advanced fibrosis (Ishak score 3)	Prednisolone plus azathioprine
Hong et al[9] 2021	54-year-old man	Rheumatoid arthritis and scleritis, treated with infliximab	ALT 1,238 U/L, AST 1,084 U/L, total bilirubin to 25 mg/dL, ALP 251 IU/L, IgG 3,151 mg/dL AIH score 8	AIH	1 month	Moderate portal inflammation and mild interface hepatitis and moderate lobular inflammation consistent with AIH	Prednisone
Kabaçam et al[10] 2021	49-year-old male		ALT 264 U/L, bilirubin 1.5 mg/dL, ANA+, IgG 2,260	AIH	20 days	Not performed	Prednisolone (30 mg/die) plus azathioprine (50 mg/die)
Kabaçam et al[10] 2021	72-year-old female		ALT 640, bilirubin 11.2, IgG 4,250, SMA+ mg/die	AIH	2 days	Not performed	Prednisolone (40 plus Tacrolimus (4 mg/die)
Singh et al[11] 2021	57-year-old man		Elevated liver enzymes (AST/ALT/GGT), SMA+, AMA+, ANA+	AIH–PBC overlap	1 month	Not performed	Ursodeoxycholic acid
Montón Rodríguez et al[12] 2022	60-year-old female		ALT 1,422 U/L, AST 1,830 U/L, ALP 116 U/L, GGT 224 U/L, IgG 2,775, ANA+, SMA+, AIH score 19	AIH	0	Portal and lobular inflammation, lymphocytes and plasma cells, interface hepatitis, focal necrosis, ballooning, fibrosis, some fine bridges	Induction with steroid Maintenance with azathioprine
Folman et al[13] 2022	40-years old female		ALT 1,300 U/L, AST 1,000 U/L, ALP 170 U/L, GGT 140 U/L, direct bilirubin 16 mg/dL, total bilirubin 22 mg/ dL, ANA+, IgG 2,190 mg/mg/dL	AIH	1 month	Portal and lobular inflammation with abundance of plasma cells	Prednisone (1 mg/kg)
Osborn et al[14] 2022	3-years old female		ALT 939 U/L (normal 0-35 U/L), AST 1,321 U/L (normal 15-46 U/L), total bilirubin 5.5 mg/dL, conjugated bilirubin 0.9 mg/dL, and INR (2.0), LDH 1,292 U/L, IgG 1,070 mg/dL, LKM LKM) titer of 1: 1,280	Type 2 AIH	3 weeks	Acute submassive hepatic necrosis, lobular collapse, and an intense mixed inflammatory infiltrate, consisting primarily of $CD3^+$ T lymphocytes	Intravenous vitamin K intravenous methylprednisolone (2 mg/kg/day) followed by azathioprine (1 mg/kg/day)

Conclusions

In conclusion, COVID-19 has been lately linked with multiple organ dysfunction and autoimmune pathologies. Among them, an increasing, though still limited, number of AILDs have been related to SARS-CoV-2 in the last three years. Displaying a peculiar paradigm in the pathogenesis, this disease seems to be triggered by the cytokine storm due to SARS-CoV-2 infection. All patients described had the chance of a full recovery of liver function. Here we report a further case showing the previously unrevealed histological picture of bile duct vanishing disease with ductular reaction. We revised the scientific literature to sum up this emerging pathology's similarities and peculiarities.

Informed Consent
Written informed consent was provided by the patient for the procedures and to publish this case report.

Ethics Approval
Not applicable.

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Conflict of Interest
The authors declare that they have no conflict of interest.

Authors' Contributions
The concept of this study was developed by Daniela Fanni, Gavino Faa, Giorgio La Nasa, and Maria Guido; The literature review was done by Clara Gerosa and Peter Van Eyken, and Ferdinando Coghe; the data collection was made by Giancarlo Serra and Michela Miglianti; the writer of the article is Daniela Fanni; Critical Review was made by Gavino Faa, Giorgio La Nasa, and Maria Guido. The final version of the article was approved by all authors for publication.

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