Liver histopathology in COVID-19 patients: A mono-Institutional series of liver biopsies and autopsy specimens

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ABSTRACT

Few studies have focused on COVID-19 patients' hepatic histopathological features. Many of the described morphological landscapes are non-specific and possibly due to other comorbidities or to Sars-CoV-2-related therapies. We describe the hepatic histopathological findings of 3 liver biopsies obtained from living COVID-19 patients in which active SARS-CoV-2 infection was molecularly confirmed and biopsied because of significant alterations of liver function tests and 25 livers analyzed during COVID-19-related autopsies. Main histopathological findings were (i) the absence of significant biliary tree or vascular damages, (ii) mild/absent lymphocytic hepatitis; (iii) activation of (pigmented) Kupffer cells, (iv) hepatocellular regenerative changes, (v) the presence of steatosis, (vi) sinusoidal ectasia, micro-thrombosis and acinar atrophy in autopsy specimens No viral particle actively infecting the hepatic or endothelial cells was detected at *in situ* hybridization. The morphological features observed within the hepatic parenchyma are not specific and should be considered as the result of an indirect insult resulting from the viral infection or the adopted therapeutic protocols.

1. Introduction

The definition and the pathophysiological understanding of SARS-CoV-2-related histopathological features are rapidly evolving [2]. Worldwide, many COVID-19 related autopsy series have been studied trying to define any possible specific histopathological pattern related to the viral infection [3,4,9,14,15,25,27].

Multiple gastrointestinal and hepatic manifestations of the disease have been described, including the dysregulation of circulating liver-associated enzymes, which are found to be mildly or moderately altered in a significant portion of COVID-19 patients [10,20,21,31]. However, limited information is available on hepatic histopathological features during SARS-CoV-2 infection.

The morphological features observed within the hepatic parenchyma were not unequivocal nor specific. Lymphocytic portal infiltrate of mild entity has been detected [9,12,14], as well as aggregates of acinar lymphocytes [31]. Moreover, focal spots of centroacinar necrosis and sinusoidal expansion and microthrombosis have been identified [12,13, 17,22,26,30,33,34]. Another rather frequently reported histopathological feature is the presence of steatosis, both micro and macrovesicular [6,12,14,15,18,35]; however, several authors have attributed this finding to pre-existing conditions or, partly, to secondary drug toxicity [14,31]. Hepatic hemophagocytosis was observed in rare cases [1].

2. Materials and methods

Three liver biopsies were obtained from living COVID-19 patients in which active SARS-CoV-2 infection was molecularly confirmed and biopsied because of significant alterations of liver function tests. One of these biopsies was previously described in the report about the series of COVID-19 patients (February-June 2020) hospitalized in the Infectious Diseases Unit of the University Hospital of Padua [31].

A consecutive series of 26 livers from COVID-19-related autopsies (age 82.4 ± 9.0 year-old; median age 83.0; range 61–97; M/F = 14/11) performed in the first semester of 2020 [4] was analyzed. The cardiovascular and pulmonary findings of these patients were previously published [5,7,11,24]. Multiple sampling of the organ was always performed with at least two tissue blocks available for each case. One case was discarded due to poor preservation of the hepatic structure at post-mortem histology.

All cases were jointly assessed by four experienced pathologists. Biopsies were stained with hematoxylin and eosin, the Perl's iron stain (Prussian blue reaction) and van Gieson's trichrome stain. Immunohistochemical stainings for CD8, CD68, cytokeratin 7 (CK7) and Ki67 (antibodies from Leica Biosystems, Newcastle Upon Tyne, UK) were automatically performed using the Bond Polymer Refine Detection kit (Leica Biosystems) in the BOND-MAX system (Leica Biosystems) on 4 µm-thick sections. Autopsy samples were stained with hematoxylin and eosin, the Perl's iron stain (Prussian blue reaction) and van Gieson's trichrome stain.

Presence and distribution of the virus was checked by *in situ* hybridization using RNAscope probes (V-nCoV2019-S, v-nCoV2019-orf1ab-sense, dapB, Hs-UBC; Advanced Cell Diagnostics, Inc.; Minneapolis, MN) on a BOND-III autostainer (Leica Biosystems, Wetzlar, Germany).

3. Series description

3.1. Liver biopsies obtained from living COVID-19 patients

The three biopsies showed some common histopathological features: (i) the absence of significant biliary tree or vascular damages; (ii) mild lymphocytic hepatitis; (iii) multiple aggregates of (pigmented) Kupffer cells; (iv) hepatocellular regenerative changes with occasional mitotic figures and Ki67 positive nuclei; (v) the presence of steatosis or cytoplasmic microvacuolar degeneration; (vi) no viral particle actively
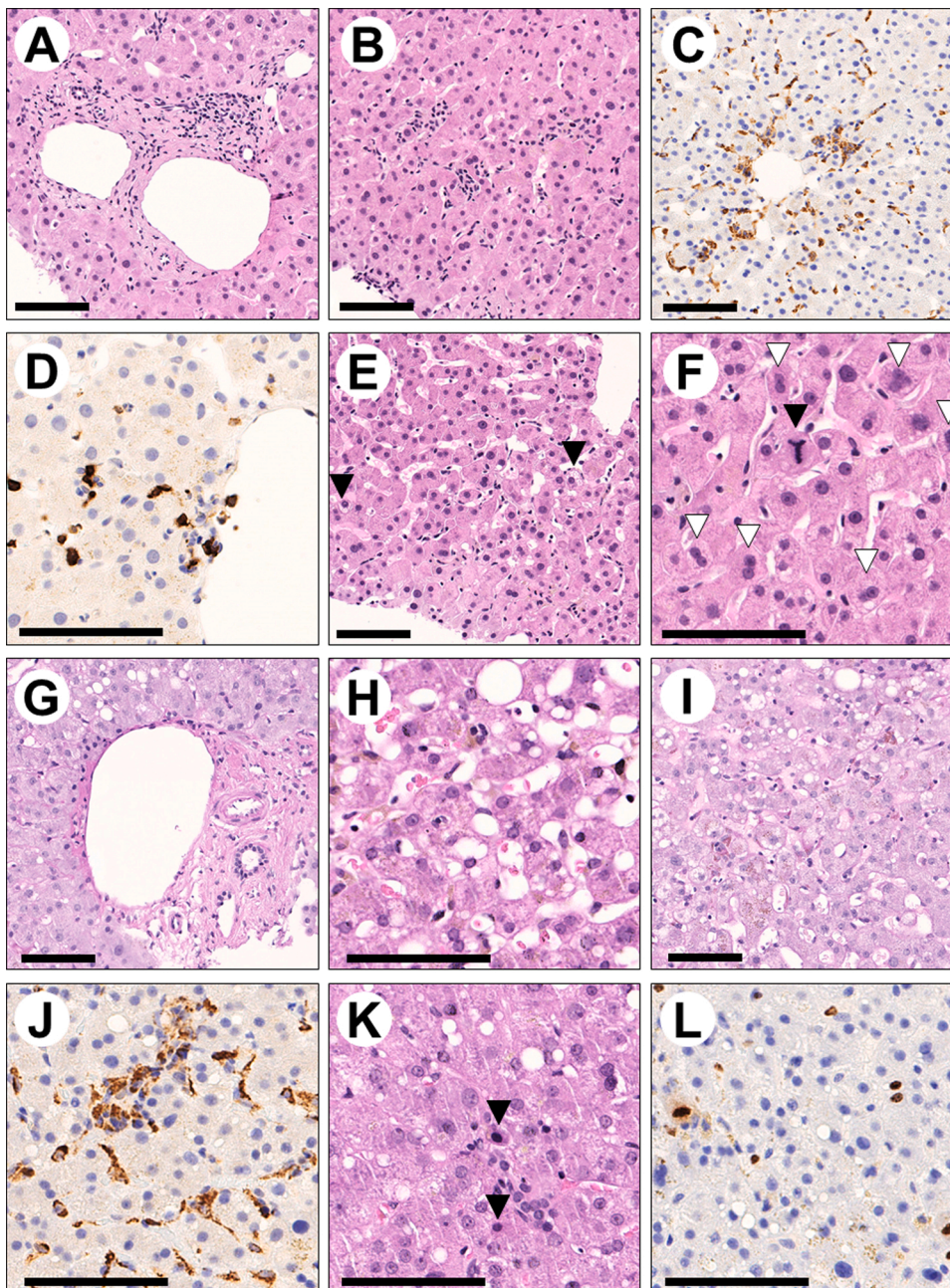

Fig. 1. Representative pictures obtained from two liver biopsies obtained from COVID-19 patients (**A-F** and **G-L**). (**A**) A representative portal tract showing mild lymphocytic and plasmacellular inflammation. (**B**) Aggregates of pigmented Kupffer cells. (**C**) CD68 immunostaining highlighting the aggregates of pigmented Kupffer cells surrounding a central vein. (**D**) Isolated focus of lymphocytic vasculitis (CD8 staining) associated to occasional lymphocytic infiltration of the hepatic parenchyma; the other vessels did not show any other significant area of inflammatory reaction. (**E**) Aspects of hepatocellular regeneration with altered thickening of the trabeculae and rare hepatocytes characterized by cytoplasmic microvacuolar degeneration (black arrows' heads). (**F**) Other aspects of hepatocytes' regeneration with binucleation (white arrows' heads) and a mitotic figure (black arrow's head). (**G**) A representative portal tract with no specific pathological alteration (PAS-D histochemical staining). (**H**) Aggregates of pigmented Kupffer cells (Hematoxylin and eosin staining). (**I**) Aggregates of pigmented Kupffer cells and hepatocytes showing focal lipofuscin-like cytoplasmic pigment (PAS-D histochemical staining). (**J**) Aggregates of pigmented Kupffer cells (CD68 immunostaining). (**K**) Focal acidophilic bodies. (**L**) Ki67-positive hepatocytes and Kupffer cells. (Hematoxylin and eosin staining; black arrows' heads). (scale bars =100 µm).

infecting the hepatic cells detected at *in situ* hybridization. In particular:

- Biopsy #1 (Male, 68yrs; therapy with lopinavir/ritonavir, chloroquine, methylprednisolone and enoxaparin; ALT = 995 UI/L, AST = 204 UI/L, gamma-glutamyl transferase = 78 UI/L; Fig. 1A-F). Portal tracts showed focal mild lymphocytic and plasmacellular inflammation. No significant bile duct alteration was observed, but focal ductular metaplasia of the peri-portal hepatocytes was present (CK7 staining). The lobular parenchyma showed multiple foci of pigmented Kupffer cells (isolated or in aggregates, mainly located in the perivenular zone), occasional lymphocytic infiltration and diffuse hepatocellular regenerative changes with binucleation, pseudorosettes formation and occasional mitotic figures and Ki67 positive nuclei. qRT-PCR of the tissue did not detect Sars-CoV-2 RNA.

- Biopsy #2 [31] (Male, 61yrs; inactive HCV-related hepatitis; therapy with lopinavir/ritonavir, chloroquine, methylprednisolone and enoxaparin; ALT = 1189 UI/L, AST = 347 UI/L, gamma-glutamyl transferase = 108 UI/L). Portal tracts showed focal mild lymphocytic inflammation. Focal ductular metaplasia of the peri-portal hepatocytes was observed (CK7 staining). The parenchyma showed moderate centrilobular macrovesicular steatosis, mild lymphocytic lobular hepatitis associated with isolated foci of hepatocellular necrosis, Kupffer cells' aggregates, centrilobular acidophilic bodies and occasional mitotic figures and Ki67 positive nuclei. Sars-CoV-2 RNA was detected at qRT-PCR on the tissue.

- Biopsy #3 (Male, 66yrs; therapy with hydroxychloroquine, ceftriaxone and enoxaparin; ALT = 660 UI/L, AST = 582 UI/L, gamma-glutamyl transferase = 362 UI/L; Fig. 1G–L). Portal tracts showed no significant inflammatory reaction. Focal ductular metaplasia of the peri-portal hepatocytes was observed (CK7 staining) in the absence of significant bile duct alterations. The lobular parenchyma presented multiple pigmented and activated Kupffer cells, mild steatosis, sporadic acidophilic bodies and occasional mitotic figures and Ki67 positive nuclei.
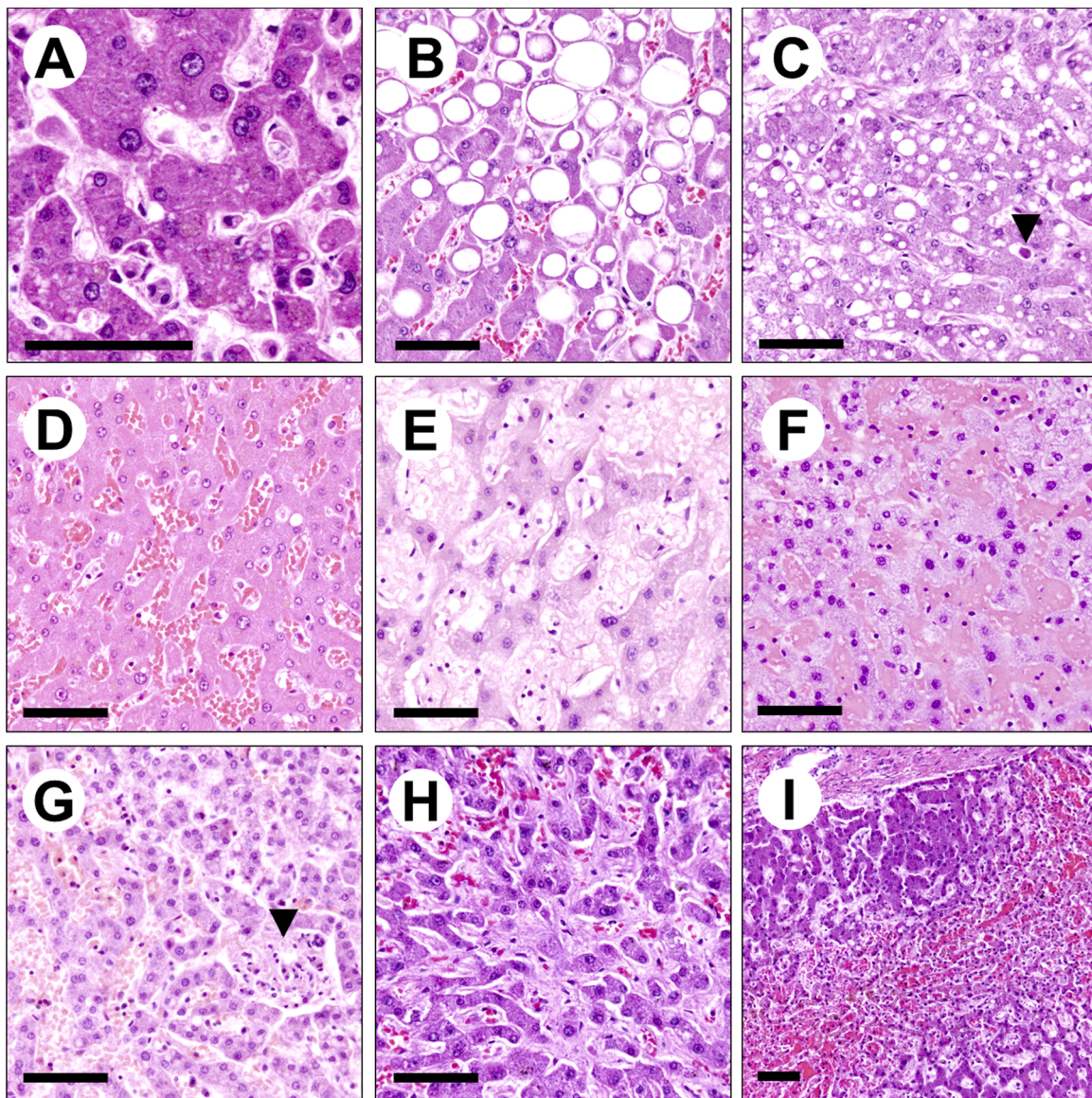

Fig. 2. Representative pictures obtained from COVID-19 autopsy specimens. (**A**) Aggregates of Kupffer cells within the sinusoidal spaces. (**B**) Macro-vesicular steatosis. (**C**) Diffuse steatosis; an apoptotic body is present (arrow's head). (**D**) Sinusoidal dilatation with red blood cells' congestion. (**E** and **F**) Late and early micro-thrombosis of the sinusoidal spaces. (**G**) Sinusoidal dilatation with a micro-thrombus (arrows' heads). (**H**) Sinusoidal and pericellular fibrosis. (**I**) Collapsing of the centrilobular area with concurrent sinusoidal dilatation and red blood cells' congestion. (scale bars =100 μm).

3.2. Livers of COVID-19-related autopsies (Fig. 2)

Most of the patients presented at least one comorbidity (24/25; 96 %). 5 patients had a body mass index ≥40 (20 %), 4 had active neoplastic disease (16 %; pharynx carcinoma, pulmonary solitary fibrous tumor, chronic lymphocytic leukemia, multiple myeloma), 8 were bedridden (32 %) and 21 (84 %) suffered from hypertension. One patient had HCV-related cirrhosis.

Lobular architecture was well preserved in all the samples, but the cirrhotic one. In most cases was evident a zone 3 sinusoidal ectasia with significant red cells congestion (84 %) and 5 cases (20 %) presented signs of centrilobular parenchymal atrophy. Two cases (8%) showed areas of sinusoidal and pericellular fibrosis. Sinusoidal diffuse platelet-fibrin microthrombi were observed in 5 cases (20 %), whereas portal vein thrombosis was detected in 3 cases (12 %). Two cases (8 %) presented substantial areas of centroacinar ischemic-type hepatic necrosis. In all cases an activation of Kupffer cells was observed.

No significant damages to the portal tract structures was observed, but mild portal inflammation was present in one case, which was the cirrhotic one. No significant interface activity was identified. Portal tract veins luminal dilatation was observed in 18 cases (72 %). Steatosis was present in 9 cases (36 %), 7 cases showed spots of macro-vesicular centroacinar steatosis and 2 cases showed diffuse and severe steatosis.

At ISH analysis, no viral particle actively infecting the hepatic or endothelial cells was detected. No significant correlation emerged between the histological alterations and clinical variables. In particular, all patients suffered from SARS-CoV-2 related pneumonia and no specific relationship between lung and liver histopathological characteristics were observed.

4. Discussion

The histopathological findings observed in this living and autopsy series of hepatic samples are consistent with what previously observed in literature [6,9,12–15,17,22,26,30,31,33–35]. No peculiar virus-related phenotype was observed.

In this case series we had the opportunity to analyze both liver biopsies obtained during COVID-19 infection and post-mortem autopsy samples. Some shared elementary lesions were observed, such as Kuppfer cells' activation and the presence of steatosis in one third of cases, with no association to the concurrent comorbidities. Kuppfer cells' activation could represent an initial attempt to eliminate circulating immune complexes [32] or a secondary effect of the so-called "cytokine storm" described in COVID-19 patients. On the other hand, steatosis may result from potential SARS-CoV-2 cytopathic effects, as well as drug side effects. In fact, most of the drugs used in the treatment of COVID-19 patients have been found to have a a hepatotoxic potential [21]. For instance, corticosteroid therapy is also clearly associated with steatosis or glycogenosis [21]. The heterogeneous prevalence and grading of these lesions may be due to inconsistencies in the therapeutic protocols adopted in the first pandemic phase. In fact, at the beginning of the COVID-19 outbreak, evidence-based drug therapy was not available and several drugs have been used in the clinical setting [21].

In autoptic specimens the presence of micro-thrombotic disease involving the parenchymal sinusoids was evident in a 20 % of cases, even mild and focal endothelial damages were observed. Acinar atrophy and perisinusoidal fibrosis could be considered late events of the same pathogenetic cascade, as zone 3 sinusoidal ectasia with significant red cells congestion could be considered as an early phase of these lesions. Overall, these findings could be related to the severe coagulopathy observed in late-stage COVID-19 patients [29]. In fact, several authors suggested that the prevalence of these alterations may be influenced by the adoption of anticoagulation treatments or can be directly related to the pre-agonic levels of D-dimer [30,34]. No specific association was observed between the hepatic and pulmonary histopathological findings in the autoptic series. However, several studies are postulating that the

hepatic commitment in COVID-19 patients is multifactorial and, thus, this association should be explored in a larger series of patients with a similar clinical and therapeutic background.

We further demonstrated that cholangiocytes are preserved even if several report demonstrated that they are characterized by the over-expression of ACE2, the cellular receptor for SARS-CoV-2, at high levels [12]. Focal and patchy periportal biliocytic metaplasia was observed, but this could be related to the activation/proliferation of the hepatic progenitor cells due to parenchymal damage [28]. Some authors reported the presence of biliary plugs in autoptic specimens [12], however, this finding appears to be related to the septic state that can complicate COVID-19 end-stage disease [16,21].

We failed to demonstrate the presence of the virus by ISH analysis but found viral RNA at qRT-PCR in one of the liver biopsies. Contrasting data have been published so far on this point. Some authors molecularly demonstrated the presence of the viral RNA in most liver samples [17, 23], whereas other were not able to detect the virus by qRT-PCR [8]. Wang and colleagues [33] recently observed the typical coronavirus particles in the cytoplasm of hepatocytes by TEM analysis, and most viral particles existed without membrane-bound vesicles. Sonzogni and colleagues [26] detected SARS-CoV-2 particles in 15/22 tested samples inside blood cloths or within endothelial cells cytoplasm by using an ISH approach similar to what we adopted. However, other authors did not detect the virus with either ISH or immunohistochemical approaches [9, 19]. In particular, Massoth and colleagues were not able to detect the virus by ISH, IHC, and qRT-PCR in the heart, liver, and kidney [19]. Of note, in some of the cases included in the present series we tested the lung specimens by ISH and we were able to detect the virus within pulmonary parenchyma, further supporting an important role of ISH analysis to detect the presence and cellular location of Sars-CoV-2 in FFPE specimens. Overall these data support an indirect role of Sars-CoV-2 in the onset of hepatic damage, with no or minimal hepatic tropism for the virus. Actually, in almost all the current histopathological reports a classic hepatitic picture has not been reported.

Few reports have tried to elucidate the histopathological landscape of Sars-CoV-2 hepatic injury. Most of the lesions were not specific and the great heterogeneity in disease management and therapeutic approaches significantly affected an overall definition of hepatic involvement in COVID-19 infection. International studies should be carried out in order to identify and describe the most common histopathological features, thereby eliminating any possible bias. In fact, no study has evaluated the histopathological consequences due to the hepatotoxic damage determined by most of the drugs used in Sars-CoV-2 infection treatment regimens. Moreover, since a significant portion of COVID-19 patients presented an alteration of liver function tests, prospective studies should investigate both clinically and histologically the follow-up of these patients to better elucidate the role of liver injury in Sars-CoV-2 infection.

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Availability of data and material

Upon request.

Authors' contributions

MF, CM, MS, VG, CB, APDT conceived and carried out the experiments. FPR, RF, MT, FP, AMC, PN, FF, RV contributed to sample preparation. MF, CL, MS, APDT contributed to the interpretation of the results. MF, CM, MS, APDT took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research,

analysis and manuscript.

Institutional review board statement

Investigations have been conducted in accordance with the ethical standards, the Declaration of Helsinki, and national and international guidelines.

Informed consent statement

Patient consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

Declaration of Competing Interest

The authors report no declarations of interest.

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