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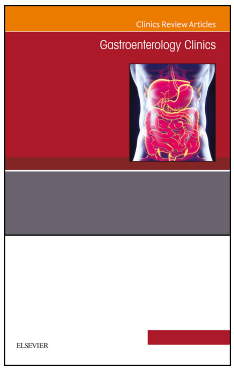

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Pathological characteristics of digestive tract and liver in patients with COVID-19

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Key points

- The common digestive manifestations associated with COVID-19 include anorexia, nausea, vomiting and diarrhea; the clearance of the viruses in COVID-19 patients with digestive symptoms is usually delayed.
- COVID-19-associated gastrointestinal histopathology is characterized by mucosal damage and lymphocytic infiltration.
- The most common hepatic changes are steatosis, mild lobular and portal inflammation, congestion/sinusoidal dilatation, lobular necrosis and cholestasis.

Keywords: COVID-19, pathological characteristics, SARS-CoV-2, lymphocytic infiltration

Introduction

With the high prevalence of coronavirus disease 2019 (COVID-19), there has been increasing understanding of the pathological changes associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus can infect multiple organs and cause multiorgan symptoms, causing a wide range of clinical manifestations[1], including respiratory, cardiovascular, gastrointestinal, and neurological symptoms **(**including loss of smell and taste**)**[2,3], as well as skin manifestations[4] (erythema, papules). A meta-analysis has shown that 17.6% of COVID-19 patients have gastrointestinal symptoms, and that viral RNA is detected in stool samples in 48.1% of patients[5]. Neglecting gastrointestinal symptoms may sometimes delay a timely diagnosis and may permit unchecked fecal-oral transmission of the virus. Ulcerative lesions occur in the gastrointestinal tract in some patients, but only a few studies have described the histopathology of these lesions[6]. In addition, hepatic injury is a frequent complication of COVID-19 and is associated with the severity of the disease. Studies in COVID-19 patients have shown the incidence of liver injury ranges from 14.8% to 62%, usually indicated by abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels accompanied by slightly elevated bilirubin levels[7-10]. In fatal cases, the incidence of liver injury may reach up to 58% to 78%[7]. Pathological findings in the gastrointestinal tract and liver come mostly from autopsies or postmortem biopsies but may include pathologic examination of GI biopsies obtained premortem by GI endoscopy. This review summarizes the pathological changes in the digestive system and liver associated with COVID-19, including the injuries induced by SARS-CoV2 infection of gastrointestinal epithelial cells and the systemic immune responses.

1. Esophageal pathology

Although the clinical manifestations of COVID-19 are usually dominated by respiratory symptoms, some patients may lack symptoms and imaging features of COVID-19 pneumonia but only show gastrointestinal (GI) symptoms[11]. SARS-CoV-2 infection may lead to esophageal mucosal injury, with acute esophagus necrosis (AEN) occurring in critically ill patients[12]. Two case reports have shown esophageal bleeding and multiple round herpetic-like erosions and ulcers by endoscopy in patients with GI symptoms, and SARS-CoV-2 RNA was detected in these esophageal lesions[12,13]. At autopsy, two necrotic ulcers were detected at the hypopharynx (Figure 1A-B). Histopathology showed full-thickness inflammatory cell infiltration with thinning of the pharyngeal wall at the level of the ulcer center (Figure 1C-D)[6]. Meanwhile, in the presence of cells positive for SARS-CoV-2 spike protein subunit 1, histological examination showed moderate lymphocytic infiltration in the esophageal mucosa (Figure 1E-H)[6], consistent with the histopathological features of viral esophagitis.

2. Gastric and intestinal pathology

The incidence of GI symptoms in COVID-19 patients is shown in Table 1.

The appearance of gastrointestinal symptoms in COVID-19 patients seems to indicate disease progression, as GI symptoms are more common in severe and critically ill patients, and are associated with an increased risk of adverse outcomes[14-16]. Interestingly, other case-control studies had previously shown that the presence of GI symptoms was associated with longer illness duration, a trend toward lower ICU admissions, and lower mortality[17], and the presence of GI symptoms could predict reduced disease severity and mortality[18]. The presence of SARS-CoV-2 RNA in feces is related to GI symptoms. Fecal shedding of viral RNA suggests prolonged GI

infection[19]. Additionally, the virus may persist in the gastrointestinal tract after it was cleared from the respiratory tract. [19]

A multicenter study showed that ulcers were the most common lesions observed in upper gastrointestinal endoscopy in COVID-19 patients, with the lesions sometimes accompanied by active bleeding[20]. Bhayana et al.[21] retrospectively analyzed the abdominal imaging findings of 412 patients with COVID-19, and a variety of abnormalities were observed. Bowel-wall abnormalities were found on 13 CT images (31%), which were associated with ICU admission. Pneumatosis or portal venous gas were observed in 4 abdominal CT images obtained in patients in the ICU. Unusual yellow discoloration of the bowel was observed in 3 cases and bowel infraction in 2 cases. Pathologic examinations revealed ischemic enteritis, with patchy necrosis and fibrin thrombi in arterioles. Amarapurkar et al.[22] also reported a case of hemorrhagic enteritis associated with COVID-19. Histopathology revealed extensive transmural hemorrhages with many congested and dilated blood vessels, and fibrin thrombi were occasionally observed in capillaries.

The gastrointestinal (GI) pathology of SARS-CoV-2 infection had been verified in autopsy and biopsy studies. Liu et al[23] observed alternating segmental dilatations and stenoses of the small bowel at autopsy of a COVID-19 patient, associated with SARS-CoV-2 replication in gastrointestinal mucosa[19,20]. Another report described gastrointestinal alterations in COVID-19 patients as characterized by lymphoplasmacytic infiltration in the lamina propria of the GI tract[19]. Coagulative necrosis, micro-hemorrhages, microthrombi, and vascular congestion had been found in colonic mucosa, suggesting ischemia is one mechanism of injury. Such lesions have been found to be positive for COVID-19 by immunohistochemistry[20] . Duodenitis may also occur in critically ill COVID-19 patients, with endoscopic manifestations of diffuse

bleeding, mucosal edema, and severe inflammation with erosions. Intracytoplasmic and intranuclear inclusions consistent with a viral infection were identified in duodenal crypts[24].

Angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine type 2 (TMPRSS2) receptors for SARS-CoV-2, are expressed in gastrointestinal mucosa[25,26]. Experimental studies have shown human gastric organoids are susceptible to SARS-CoV-2 infection[27]. In addition, as both ACE2 and TMPRSS2 are expressed in the enteric nerve system, gut sensory-motor functions may be affected in susceptible COVID-19 patients[28].

3. Pancreatic pathology

SARS-CoV-2 receptors, including ACE2, TMPRSS2, NRP1[29,30], and TFRC[29], are expressed at very low levels in pancreatic β-cells; studies showed SARS-CoV-2 tropism for β cells in vitro[31]. SARS-CoV-2 infection has been shown to suppress insulin secretion and injure β cells ex vivo, eventually causing pancreatic dysfunction[31], which leads to infection-related diabetes[32]. Among patients hospitalized with COVID-19, the prevalence of acute pancreatitis is 0.27%. COVID-19-associated acute pancreatitis is more frequently associated with severe systemic disease and multi-organ complications[33].

4. Liver pathology

SARS-CoV-2 can cause hepatic injury via direct binding to ACE2 receptors in cholangiocytes and hepatocytes, antibody dependent enhancement of infection, systemic inflammatory response syndrome, inflammatory cytokine storms, ischemia/reperfusion injury, and adverse events due to drug therapy[9,34-37].

4.1 Findings in autopsies or postmortem biopsies of patients with COVID-19

The main liver findings in patients with COVID-19 are shown in Table 2 and are illustrated in Figure 2A-E. The most common histopathological changes associated with SARS-CoV-2 are hepatic steatosis, mild lobular and portal inflammation, congestion/sinusoidal dilatation, lobular necrosis, and cholestasis.[38,39]

In several autopsy studies, hepatic steatosis of variable severity were the main findings[40-42], which may be related to high BMI, as well as hypoxia and shock induced by COVID-19-related complications. It is well documented that shock and hypoxia can lead to lipid accumulation in hepatocytes and cause liver injury[43]. Postmortem liver biopsy examination carried out by Xu et al.[44] showed moderate microvesicular steatosis and mild lobular and portal activity, indicating the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury. In another study of 48 postmortem liver biopsies performed on COVID-19 patients, histological assessment also revealed microvesicular and macrovesicular steatosis (54%), mild portal inflammation (66%), and lobular inflammation (50%)[45]. The same histological findings were described in another study of 17 patients[43]. In a study of 40 autopsies, Lagana et al.[46] described gross findings of hepatic fibrosis in two patients. Histologically, macrovesicular steatosis was the most common finding, involving 30 patients (75%). Mild lobular necroinflammation and portal inflammation were present in 20 cases (50%) each.

In studies by Beigmohammadi et al.[47] and Bradley et al.[48], congestion, steatosis and minimal-to-mild portal inflammation were the most common findings, while lobular inflammation was not prominent. Conversely, Yurdaisik et al.[49] observed lobular inflammation in most cases. Tian et al.[50] reported mild sinusoidal dilatation and focal macrovesicular steatosis in post-mortem liver biopsies of 4 patients. There was

mild lobular lymphocytic infiltration, which was insignificant in portal areas; the same findings were reported in another pathological study[9,51].

In addition, patchy hepatic necrosis has been described in postmortem liver biopsies and autopsies[43,48-53], mainly in centrilobular areas (zone 3) and without evident inflammatory cellular infiltration. This pattern is consistent with acute ischemic injury. More severe changes such as confluent necrosis[45,47] and coagulative necrosis[51] were observed in rare cases.

Other histopathological changes frequently described in COVID-19 patients include proliferation of the intrahepatic bile ducts and the presence of intra-canalicular bile plugs, consistent with cholestasis[40,49,51-53]. In fact, 38% of patients were shown to have lobular cholestasis among 40 autopsied cases, which were generally mild and focal[46] . Four (10%) of these patients had ductular cholestasis[46]. However, bile duct injury has not been observed[43].

In postmortem wedge liver biopsies of 48 patients, Sonzogni et al.[45] noted alterations of vascular structures, both acute (thrombosis of portal and sinusoidal vessels, luminal ectasia) and chronic (fibrous thickening of vascular wall or phlebosclerosis, and abnormalities of the portal intrahepatic vasculature). Lagana et al.[46] reported similar changes, such as phlebosclerosis and sinusoidal microthrombi in six cases (15%)[43]. Portal arterioles were abnormal (Figure 2F) in nine cases (22.5%), including arteriolar muscular hyperplasia, hyalinosis of the vessel wall, and fibrinoid necrosis with endothelial apoptosis. These findings strongly suggest marked derangement of the intrahepatic blood vessel network secondary to systemic changes induced by the viral infection.

Other uncommon histological changes include histiocytic hyperplasia in the portal tract[43], platelet-fibrin microthrombi in the hepatic sinusoids, central vein, or portal vein,

and rare megakaryocytes in sinusoids[43]. Minor to massive hepatocytic apoptosis[8,51], and mild ballooning degeneration[9,40,46,47,54] have been described as well. Presence of SARS-CoV-2 in hepatocytes has been confirmed by in situ hybridization or RT-PCR[45,46,50,52,55-57].

4.2 Liver pathology of patients with COVID-19 in controlled studies

To further delineate the role of pre-existing conditions, Falasca et al.[58] showed in 22 COVID-19 autopsies (18 with comorbidities and 4 without comorbidities), that the incidence of macroscopic parenchyma congestion, histological sinusoidal congestion, steatosis, and inflammatory infiltrate were similar between the two groups[58].

In another postmortem study, patients with COVID-19 (n = 8) were compared to controls (n = 4). Minimal to focal mild portal tract chronic inflammation ($p < 0.05$) and mild focal lobular activity ($p = 0.06$) were more frequently observed in COVID patients[46].

McConnell et al.[54] compared postmortem liver biopsies between 43 patients with COVID-19 versus normal controls (n = 12). Dilated sinusoids with congestion ($p < 0.01$), lobular inflammation ($p < 0.01$), steatosis ($p = 0.02$), and sinusoidal erythrocyte aggregation ($p < 0.01$) were more frequently observed in patients with COVID-19.

4.3 Pathology of liver biopsies in living patients with COVID-19

While findings at autopsy are often "contaminated" by terminal iatrogenic changes, liver biopsies performed in patients premortem likely present more specific pathological findings. Such findings include mild portal inflammation, scattered hepatocyte apoptosis, ground-glass hepatocytes consistent with cytoplasmic accumulation of fibrinogen[59], activation of Kupffer cells, and steatosis[56]. In another study of 2 patients without significant lung disease, acute hepatitis, prominent bile duct

damage, foci of centrilobular necrosis and endothelitis were identified, although some of these changes may be due to post-transplant changes in one of the patients.[57]

4.4 Liver pathology in patients with underlying chronic liver diseases

Overall, 2%-11% of patients with COVID-19 had underlying chronic liver disease[37]. Fatty liver disease or non-alcoholic steatohepatitis accounted for 42% of COVID-19 patients with preexisting liver diseases[60]. Hepatic dysfunction was significantly higher in patients with pre-existing liver disease, especially in patients with cirrhosis and this was associated with poor outcome[60].

In a study of 202 consecutive patients with COVID-19[61], patients with NAFLD had a higher risk of disease progression (p <0.0001) and longer viral shedding (p <0.0001) than those without NAFLD. Postmortem liver biopsies in one of these patients showed microvesicular steatosis with overactivation of T cells. However, other autopsy and biopsy studies only showed histological findings consistent with shock liver[62] or the pre-existing liver disease[50].

4.5 Liver pathology in patients after vaccination

Hepatitis has been observed in some individuals after vaccination, that share some histologic features with autoimmune liver disease[63,64]; some contain diffusely distributed highly activated T cells[65]. Moreover, among the infiltrating T cells, there is an enrichment of T cells that are reactive to SARS-CoV-2, suggesting that the vaccine-induced cells can contribute to hepatic inflammation. In a cohort of 16 patients who presented with hepatic dysfunction after vaccination, 10 underwent liver biopsy. All exhibited portal inflammation (60% of which graded as moderate or severe)[66].

In a case report of an 86-year-old man who died of acute renal and respiratory failure after receiving the first dose of the BNT162b2 mRNA COVID-19 vaccine, autopsy showed stenosis and sinus dilatation in the liver[67].

In summary, the most common histological changes associated with SARS-CoV-2 in the liver are steatosis, mild lobular and portal hepatitis, congestion with sinusoidal dilatation, lobular necrosis, and cholestasis. Hepatocyte apoptosis, vascular pathology with or without thrombosis, histiocytic hyperplasia, and Kupffer cells hyperplasia may also occur.

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FIGURE LEGENDS

Figure 1. Macroscopic examination of fresh (A) and fixed (B) hypopharynx; C. Histopathology of ulcer in hypopharynx; D. Inflammatory infiltration of the muscle layer with necrosis and degeneration of the skeletal muscle fibers. E-H. Moderate lympho-monocytic infiltration in esophageal mucosa (E. anti-CD68; F. anti-CD3; G. anti-CD20; H. positive for SARS-CoV-2 spike subunit 1). *(Adapted from Porzionato A, Stocco E, Emmi A, et al. Hypopharyngeal Ulcers in COVID-19: Histopathological and Virological Analyses - A Case Report. Frontiers in immunology. 2021;12:676828. doi:10.3389/fimmu.2021.676828; under CC BY 4.0)*

Figure 2. Histology of liver changes in patients with COVID-19

A. steatosis, B. mild portal activity, C. mild lobular activity, D. mild sinusoidal dilatation with increased lymphocytic infiltration, E. focal centrilobular hepatic necrosis, F. Portal arteriolar muscular hyperplasia (left arrow) and hyalinosis of a smaller branch of portal arteriole (right arrow). *(Adapted from Refs 43, 46, 50, 55; with permissions)*

Table 1. Incidence of gastrointestinal symptoms in COVID-19 patients

studies	Number of patients, n	GI symptoms, n (%)	Anorexia, n (%)	Nausea, n (%)	Vomiting, n (%)	Diarrhea, n (%)	Abdominal Pain, n (%)	virus RNA in stool (+), n (%)
Xiao et al[19]	73	NA	NA	NA	NA	NA	NA	39(53.4)
Nobel et al[17]	278	97(34.9)	NA	63(64.9)		56(57.7)	NA	NA
Luo et al[68]	1141	183(16.0)	180(98.4)	134(73.2)	119(65.0)	68(37.2)	45(24.6)	NA
Hunt et al[33]	206	48(23.3)	NA	NA	NA	67(32.5)	NA	NA
Cheung et al[5]	59	15(25.4)	NA	NA	1(6.7)	13(86.7)	7(46.7)	9(60.0)
Pan et al[69]	204	103(50.5)	81(78.6)	NA	4(3.9)	35(34.0)	2(1.9)	NA
Jin et al[15]	651	74(11.4)	NA	17(23.0)	18(24.3)	56(75.7)	NA	NA
Wang et al[70]	138	NA	NA	14(10.1)	5(3.6)	14(10.1)	3(2.2)	NA
Ferm et al[71]	892	219(24.6)	105(11.8)	148(16.6)	91(10.2)	177(19.8)	70(7.8)	NA

NA, not available.

Table 2. Summary of main hepatic findings in patients with COVID-19

Ref.	No. Cases	Specimen type	Steatosis	Portal inflammation	Lobular inflammation	Congestion/ sinusoidal dilation	Lobular necrosis	Cholestasis	Hepatocyte apoptosis	Vascular pathology and/or thrombosis
Greuel et al[40]	6	Autopsies	2/6 (33.3%)	-	-	-	-	1/6 (16.7%)	-	-
Xu et al[44]	1	Postmortem biopsy	1/1 (100%)	1/1 (100%)	1/1 (100%)	-	-	-	-	-
Tian et al[50]	4	Postmortem biopsies	1/4 (25%)	-	1/4 (25%)	3/4 (75%)	1/4 (25%)	-	-	-
Wang et al[8]	2	Postmortem biopsies	2/2 (100%)	2/2 (100%)	1/2 (50%)	-	-	-	2/2 (100%)	-
Sonzogni et al[45]	48	Postmortem biopsies	26/48 (54.2%)	32/48 (66.7%)	24/48 (50%)	-	18/48 (37.5%)	-	-	48/48 (100%)
Cai et al[9]	1	Postmortem biopsy	1/1 (100%)	-	1/1 (100%)	-	-	-	-	-
McConnell et al[54]	43	Postmortem biopsies	20/43 (46.5%)	10/43 (23.3%)	-	42/43 (97.7%)	-	-	-	-
Beigmohammadi et al[47]	7	Postmortem biopsies	7/7 (100%)	7/7 (100%)	-	7/7 (100%)	1/7 (14.3%)	2/7 (28.6%)	-	-
Lagana et al[46]	40	Autopsies	30/40 (75%)	20/40 (50%)	-	-	20/40 (50%)	15/40 (37.5%)	10/40 (25%)	6/40 (15%)
Yurdaisik et al[49]	7	Postmortem biopsies	4/7 (57.1%)	2/7 (28.6%)	5/7 (71.4%)	1/7 (14.3%)	6/7 (85.7%)	2/7 (28.6%)	-	1/7 (14.3%)

Ramos-Rincon et al[52]	5	Postmortem biopsies	1/2 (50%)	-	-	-	1/5 (20%)	1/5 (20%)	-	-
Barton et al[41]	2	Autopsies	1/2 (50%)	-	-	-	-	-	-	-
Zhao et al[43]	17	Autopsies	12/17 (70.6%)	8/17 (47.1%)	5/17 (29.4%)	-	2/17 (11.8%)	-	-	-
Bradley et al[48]	14	Autopsies	9/14 (64.3%)	4/14 (28.6%)	1/14 (7.1%)	11/14 (78.6%)	4/14 (28.6%)	-	-	-
Wang XX et al[51]	1	Postmortem biopsy	1/1 (100%)	-	1/1 (100%)	-	1/1 (100%)	1/1 (100%)	1/1 (100%)	-
Chornenkyy et al[55]	8	Autopsies	4/8 (50%)	7/8 (87.5%)	6/8 (75%)	6/8 (75%)	4/8 (50%)	1/8 (12.5%)	-	-
Falasca et al[58]	22	Autopsies	12/22 (54.5%)	-	11/22 (50%)	10/22 (45.5%)	-	-	-	-
Fassan et al[56]	25	Autopsies	9/25 (36%)	-	-	21/24 (87.5%)	2/25 (8%)	-	-	3/25 (12%)
	3	Liver biopsies	2/3 (66.7%)	2/3 (66.7%)	1/3 (33.3%)	-	1/3 (33.3%)	-	-	-
Fraga et al[59]	1	Liver biopsy	-	1/1 (100%)	-	-	-	-	1/1 (100%)	-
Fiel et al[57]	2	Liver biopsies	-	2/2 (100%)	1/2 (50%)	-	2/2 (100%)	-	1/2 (50%)	-

−, finding was not described or found.

Figure 1

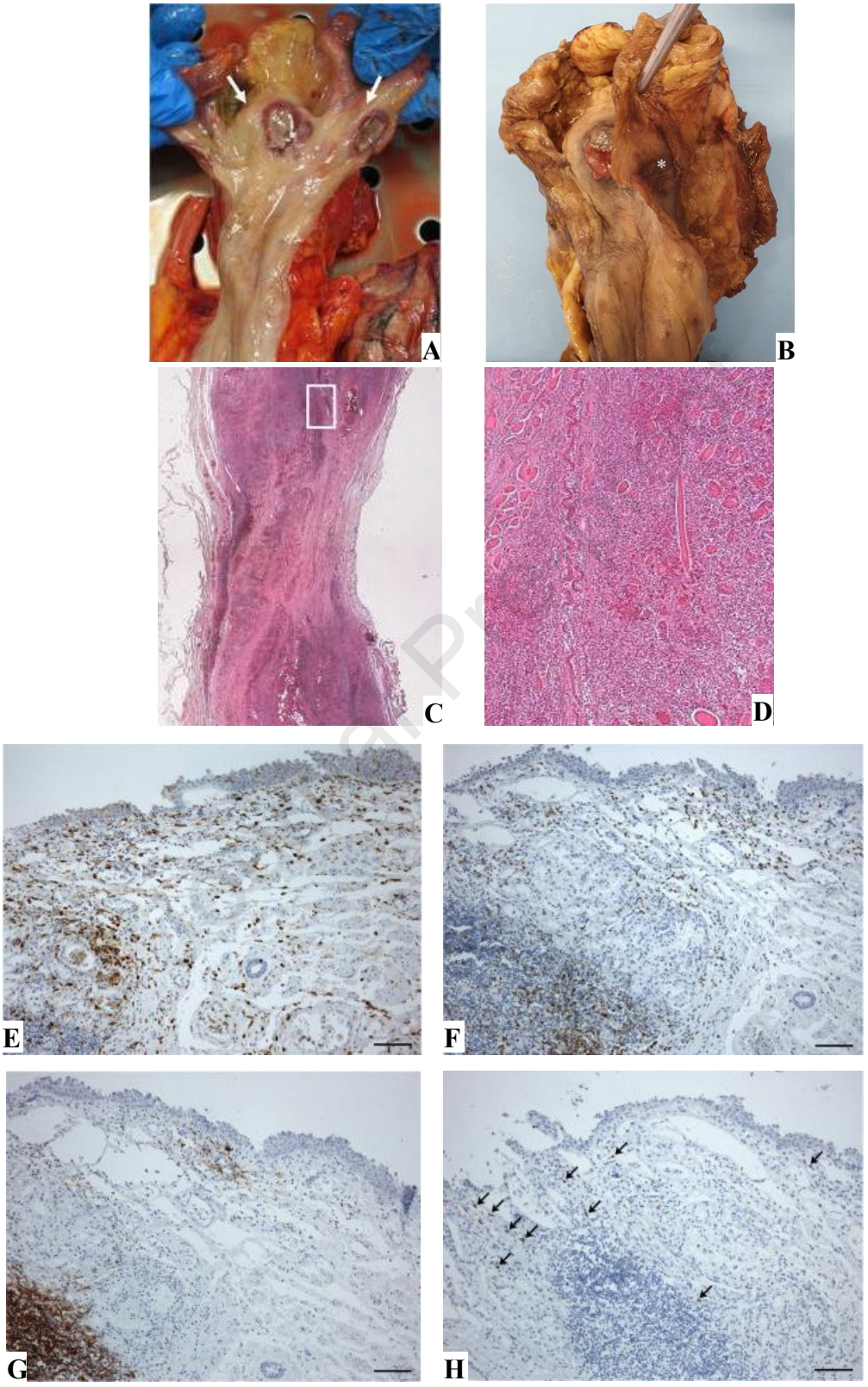

Figure 2