Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Intestinal ischemia in the COVID-19 era

To the editor

From the end of December, the world is facing the threat of a new zoonosis caused by Severe Acute Respiratory Syndrome - Coronavirus – 2 (SARS CoV-2) which gave rise to a pandemic which is currently ongoing. The Bergamo province has been one of the most affected regions worldwide with an increase in the mortality rate in the first trimester of 2020 of + 568% [1] if compared with the first trimester of the previous four years (2015-2019). Papa Giovanni XXIII Hospital was the most affected structure with over 2000 admission for COVID-19 to date [2].

We describe a case of fatal intestinal infarction whit a difficult diagnosis, which was made possible throughout by using innovative technique.

A 62-year-old unconscious man was admitted to the Emergency Department of Papa Giovanni XXIII Hospital (Bergamo, Italy) with severe hypotension during the month of April 2020. The recent medical history reported by phone from his wife included three days of abdominal pain and bilious vomiting. The patient's main comorbidities were obesity, arterial hypertension, diabetes mellitus type 2 and hepatic cirrhosis (non-alcoholic steatohepatitis + hepatitis B). Blood tests revealed an increase in the blood levels of leukocytes (primarily neutrophils) and C-reactive protein blood levels, altered renal and liver function tests, and D-dimer levels increased of > 75-fold above the upper limit of normal. Owing to the rampage of the pandemic in our area, the patient was tested for SARS CoV-2and found negative in nasopharyngeal swab and bronco-alveolar lavage.

Chest CT was unremarkable while abdominal CT findings were highly suggestive for small bowel ischemia; moreover, thromboembolic filling defects in inferior vena cava and superior mesenteric vein were found (Fig. 1). The patient underwent small intestine resection, but eventually died for refractory septic shock 12 hours after surgery. The histological examination on the resected small bowel showed complete ischemic necrosis of the mucosal layer and acute perivisceral inflammation; the mesenteric vessel was characterized by complete recent thrombosis and inflammatory infiltration of the endothelium (Fig. 2). These histological findings, in particular the severe endothelial inflammation, were not what one might expect to find in a true intestinal infarction and, combined with the time period, the pandemic situation in our area and the recent experience in our center caused strong suspicion of COVID 19 infection. For this reason we decided to perform on resected small bowel an ISH (in situ hybridization) on the resected small bowel specimen, using the RNAscope technology(ACD, Advanced Cell Diagnostics), an RNA in situ hybridization technique described

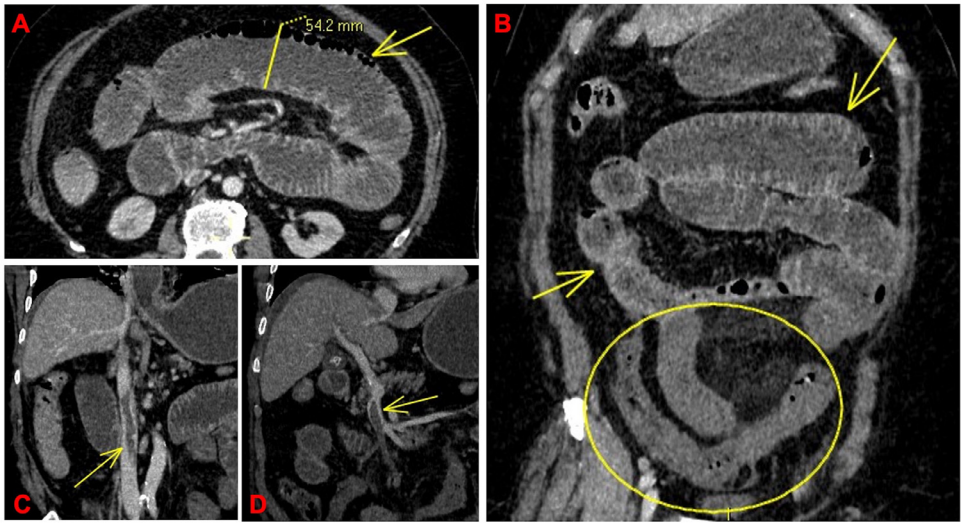

Fig. 1. Images from portal venous phase CT scan of the abdomen. **A:** Axial CT image highlighting the jejunal overdistension (caliber of ~ 54 mm; normal range < 30 mm), with associated signs of intramural bowel gas (arrow) as per pneumatosis intestinalis. Non signs of pneumoperitoneum identified. **B:** Paracoronal CT image nicely demonstrating the differences between the hypoenhanced/unenhanced (circle) and the regularly enhanced (arrows) small bowel loops: these findings are clearly suggestive of small bowel ischemia. **C:** Paracoronal CT image showing the longitudinal extension of a thromboembolic defect into the lumen of the inferior vena cava (arrow). **D:** Paracoronal CT reconstruction along the vascular axis of the superior mesenteric vein which is largely occupied by an extensive thromboembolic defect (arrow); the superior mesenteric artery and its main branches were patent (not shown).

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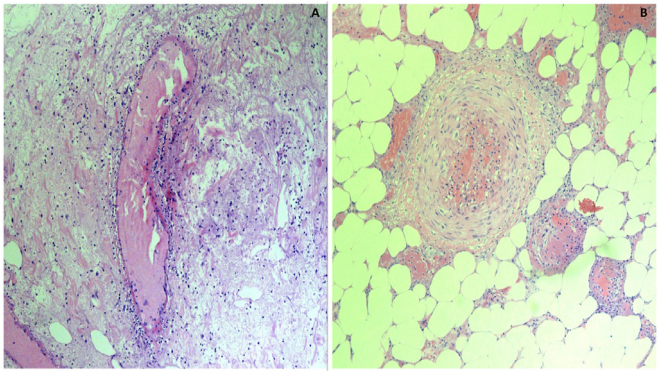

Fig. 2. Histological section of mesentery showing recent occlusive thrombosis of a medium size vein (left) and of a muscular artery (right); mixed inflammatory infiltrate is attacking the endothelium of both vessels (Hematoxylin and eosin, 400X).

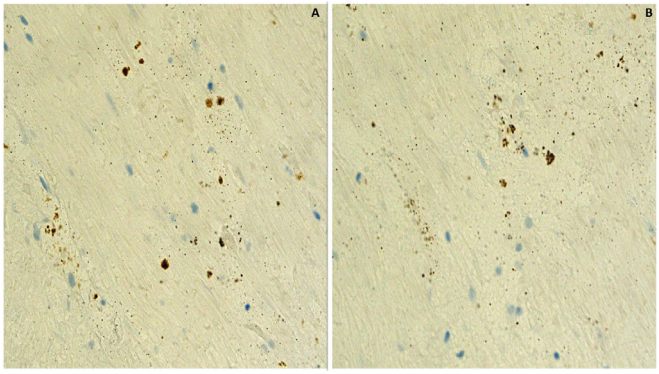

Fig. 3. The RNAscope probe detected positive staining for COVID-19 viral RNA (brown dots) in the intestinal mucosa, giving rise the chance to estimate the viral load in cells within the morphological context.

previously [3]. This method that enables the detection of the SARS-CoV-2 spike protein mRNA by means of the VnCov2019- S probe (Fig. 3).

Paired double Z oligonucleotide probes were designed against target RNA using custom software. The following probe was used : V-nCoV2019-S, 848568, NC_045512.2, 20 pairs, nt 21631-23303. The RNAscope 2.5 LSX Reagent Kit-Brown IVD Automation (Leica BOND III) was used according to the manufacturer's instructions. FFPE tissue section samples were prepared according to manufacturer's recommendations.

The RNA ISH assay confirmed SARS CoV-2 presence in the intestinal mucosa giving us the possibility of a direct visualization of the virus while retaining tissue morphology, a feature that is lost in other methods such as PCR.

Facing a pandemic emergency is a very hard challenge, beginning with the difficulties of employing accurate diagnostic tools [4]. Gastrointestinal symptoms have been described shortly after the SARS CoV-2 outbreak [5] and reported to be self-limiting in the vast majority of patients, but with the possibility of being linked to a high risk of complications. Furthermore, there is growing evidence of a link of COVID-19 to coagulopathy [6] and a state of hypercoagulability has been demonstrated by thromboelastography [7]. This state could also be the explanation of the diffuse thrombosis found in peripheral pulmonary vessels post-mortem by our pathology department [8] Thus, a link between the intestinal ischemia in our patient and COVID-19 infection is highly probable.

Declaration of Computing Interest

Authors declares no conflict of interest and no financial support for this study.

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