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Duodenal perforation in a SARS-CoV-2-positive patient with negative PCR results for SARS-CoV-2 in the peritoneal fluid

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Abstract. – OBJECTIVE: The coronavirus disease 2019 (COVID-19) pandemic has significantly affected health care organizations globally. Many aspects of this disease, as well as the risks for patients treated with multiple drug regimens to control severe COVID-19, are unclear. During emergency surgery for SARS-CoV-2-positive patients, the risk of SARS-CoV-2 exposure and transmission to the surgical staff has yet to be determined.

PATIENTS AND METHODS: In this report, we describe a SARS-CoV-2-positive patient with severe respiratory syndrome treated with multiple doses of IL-6 inhibitors who presented with a perforated duodenal ulcer and underwent emergency surgery. During and after surgery, we tested for SARS-CoV-2 at the ulcer site and in the peritoneal fluid.

RESULTS: The history of the patient allows for two possible interpretations of the pathogenesis of the duodenal ulcer, which could have been a stress ulcer, or a gastrointestinal ulcer associated to the use of IL-6 inhibitors. We also noticed that the ulcer site and peritoneal fluid repeatedly tested negative for SARS-CoV-2. Therefore, we reviewed the pertinent literature on gastrointestinal bleeding in patients with COVID-19 and on SARS-CoV-2 detection in the peritoneal fluid of surgical patients and discussed possible prevention strategies for bleeding and the actual risk of infection for the surgical staff.

CONCLUSIONS: The first implication of this case is that the relation between repeated administration of IL-6 inhibitors and upper gastrointestinal bleeding and perforation must be investigated, and that the threshold for administering prophylactic proton pump inhibitors therapy should be carefully considered for patients with severe COVID-19. The second implication is that further testing should be performed on the peritoneal fluid of COVID-19 patients undergoing emergency surgical procedures to clarify the discordant results for the presence of SARS-CoV-2 in the peritoneal cavity and the possible risk of transmission to the surgical staff.

Key Words:
COVID, Emergency surgery, Gastrointestinal perforation.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has significantly affected health care organizations globally, with a considerable impact on hospital organization and personnel management. Many aspects of this disease are unclear, and treatment is still nonstandardized and experimental. According to recommendations, patients are usually given dedicated antiviral and anti-inflammatory pharmacological treatments, which carry the risk of treatment-related complications. COVID-19 patients are usually managed in separate wards and ICU units due to the need to minimize contamination of hospital common spaces and interhuman transmission. Apart from internist or intensivist management, some COVID-19 patients also require surgical attention. In these cases, adjunctive measures are required for their management to protect the surgical staff from exposure as the risk for exposure to SARS-CoV-2 during surgery is unclear.

We recently treated a COVID-19 patient presenting with a perforated duodenal ulcer after repeated IL-6 antagonist treatment. During and after surgery, we tested for SARS-CoV-2 intraperitoneally. In this report, we present the patient's case and our considerations regarding several aspects of his management.

Case

A 72-year-old male with obesity, ischemic cardiopathy, type-2 diabetes, hypertension, previous brain ischemia and psoriasis undergoing domiciliary therapy with atenolol, valsartan, hy-

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drochlorothiazide, pravastatin, dutasteride, alfuzosin, glyceryl trinitrate and clopidogrel presented to the ER with worsening dyspnoea. He had been previously admitted to another hospital for respiratory symptoms, being diagnosed with COVID-19 by SARS-CoV-2 nasopharyngeal swab testing. He underwent therapy with hydroxychloroquine, lopinavir, ritonavir and subcutaneous administration of one dose of the IL-6 inhibitor tocilizumab (162 mg). After 3 days, he was discharged in stable clinical condition and instructed to continue isolation. However, in 7 days, his respiratory syndrome aggravated. At ER admission in our hospital, he was conscious but in poor general condition. His temperature was 37.4°C, he was hemodynamically stable (BPM 76, BP 100/60) but had tachypnoea and 70% SO_2. Arterial gas analysis (ABG) showed the following results: pH 7.1, pO_2 35.8 mmHg, pCO_2 27.1 mmHg and lactic acid 2.8 mmol/L. Laboratory tests were significant for leukocytosis (13.200/mmc), creatinine (1.34 mg/dl), Na (126 mEq/L), LDH (922 UI/L), D-dimer (2390 mg/dl), fibrinogen (593 mg/dl) and CRP (140 mg/dl). He immediately received positive-pressure ventilation, with improvement of his clinical condition and ABG assessment. A chest CT scan revealed severe interstitial pneumonia (Figure 1). He started therapy with hydroxychloroquine (200 mg b.d.), darunavir (800 mg q.d.), ritonavir (100 mg q.d.), piperacillin/tazobactam (4.5 g t.d.s.), azithromycin (500 mg q.d.) and linezolid (600 b.d.). The administration of alfuzosin was interrupted due to incompatibility with darunavir/ritonavir. A repeat SARS-CoV-2 nasopharyngeal swab tested positive. He was admitted to the clinical ward where he continued receiving positive-pressure ventilation. After 24 hours, due to worsening respiratory insufficiency, therapy with sarilumab (400 mg intravenously) was initiated. His condition remained severe but stable. After 48 hours, he was given

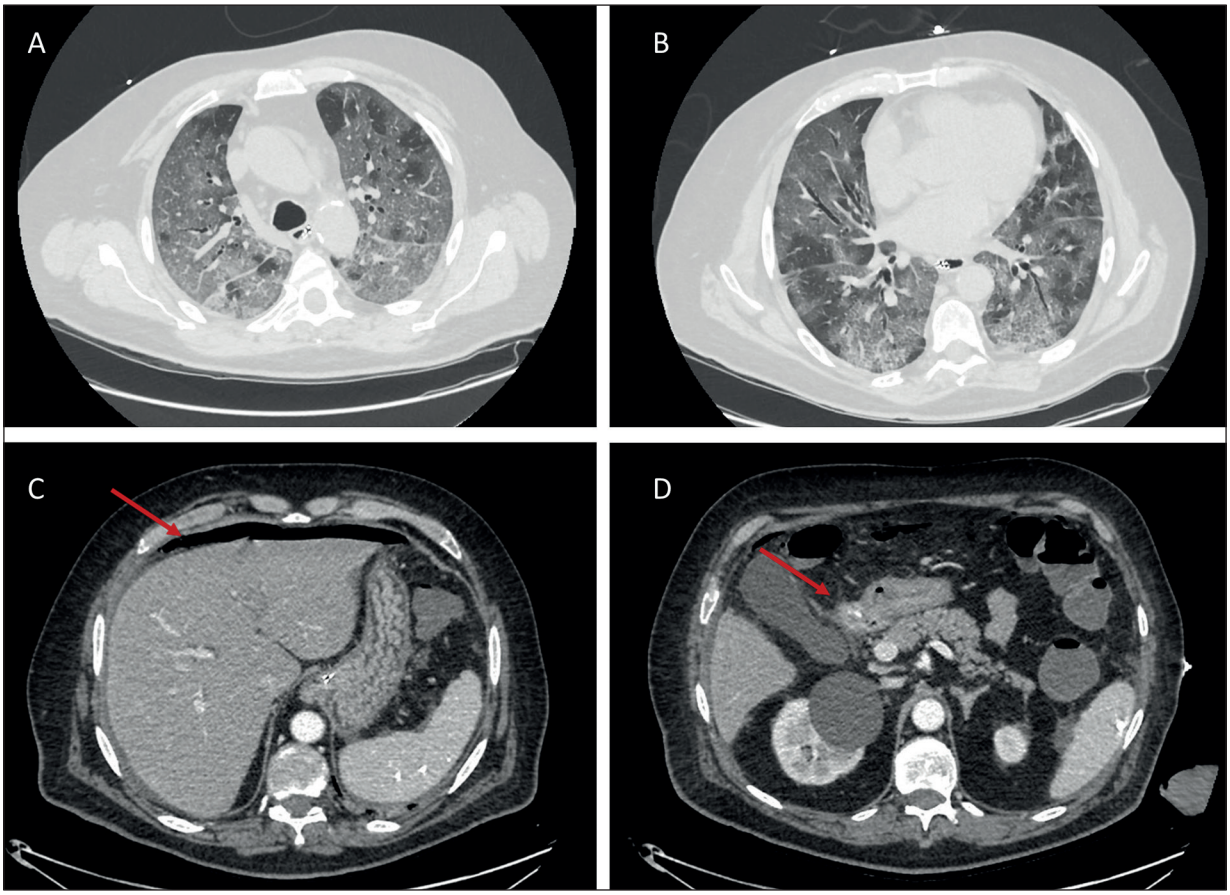

Figure 1. A-B, Chest CT at admission showing severe interstitial SARS-CoV-2 pneumonia in all segments. **C-D,** Abdominal CT during admission showing the presence of a pneumoperitoneum (Panel C, red arrow) and active arterial blush in the duodenal bulb (Panel D, red arrow).

a second dose of sarilumab. A few hours later, he presented with epigastric pain, and laboratory examinations showed acute anaemia (Hb 6.9 g/dl). Meanwhile, his respiratory condition worsened. The patient received a transfusion and an intensivist evaluation. An abdominal contrast CT scan was also performed due to persistent abdominal pain, which showed active arterial blush at the duodenal bulb, pneumoperitoneum, and a moderate quantity of fluid in the upper abdominal quadrants and pelvic area (Figure 1). At the surgical assessment, the patient had a mildly tender abdomen in the upper quadrants and no peritonism. Due to the active blush, he was referred for emergency embolization and subsequent revaluation for surgery. Informed consent was verbally acquired. Due to worsening respiratory insufficiency, the intensivist determined that intubation and transfer to the ICU ward were indicated. The patient was transferred to the ICU and then to the radiology department to undergo arteriography. Arteriography did not show active bleeding; however, preventive embolization of the gastroduodenal artery was performed. The patient was transferred to the ICU in severe condition, and surgical evaluation yielded an indication for emergency surgery. Laparotomy was the preferred approach due to profound septic shock, respiratory insufficiency and the recommendation for caution regarding laparoscopy in COVID-19 patients in recent guidelines[1]. Xifoumbilical laparotomy was performed. Exploration of the abdomen revealed the presence of clear peritoneal fluid with fibrin in the upper quadrants and the Douglas cavity. A subcentimetric ulcer was located on the anterior wall of the duodenal bulb, and a mild output of clotted blood was noted (non-active bleeding). Samples at the ulcer site and of the peritoneal fluid nearby were collected and sent for microbiological and PCR assessments (negative for microbes and SARS-CoV-2). Thorough abdominal toilette was performed with 12-litre lavage. Then, primary suturing of the ulcer with a Graham omental patch was performed[2]. A nasogastric tube was placed near the ulcer. Two drains were placed proximal to the omental patch and in the lesser sac. Then, the patient returned to the ICU in a state of severe shock. He underwent empirical antibiotic and antimycotic therapy and PPI infusion. His general condition improved, and inotropic support was reduced. On the sixth postoperative day, a new sample of peritoneal fluid was sent for PCR analysis, which tested negative for SARS-CoV-2. However, faecal samples collected on the same day tested positive for SARS-CoV-2. The patient underwent a CT scan with diatrizoic acid administered through the nasogastric tube, which did not show signs of leak. Then, the drains were removed. On the 10th postoperative day, he started enteral nutrition through the nasogastric tube. His general condition initially improved, but on the 17th postoperative day, his respiratory insufficiency and general conditions worsened, and the patient died of cardiorespiratory insufficiency.

Discussion

This report has many implications. First, whether COVID-19 is associated with an increased risk for gastrointestinal (GI) bleeding is still unclear[3]. On one hand, some reports have indicated an important decline in acute upper GI bleeding during the COVID-19 pandemic in some countries[4]. This change has been attributed to lifestyle modification and reduced access to emergency departments for less severe bleeding events[4]. On the other hand, GI bleeding has been reported in 4-13.7% of COVID-19 patients with GI symptoms[5,6] in association with epithelial damage in the oesophagus, the presence of peptic ulcers[7,8] and SARS-CoV-2 detection in the cytoplasm of gastric, duodenal and rectal epithelial cells[6,7]. Of note, the first case of emergency surgery performed in a SARS-CoV-2-positive patient was performed in a patient with a perforated duodenal bulb ulcer[9]. The physiopathology of GI bleeding in COVID-19 patients may be due to different causes:

1. direct damage to the GI epithelium by SARS-CoV-2. Indeed, GI cells express angiotensin-converting enzyme 2 (ACE2), which is a receptor for viral entry[6,10]. Accordingly, GI symptoms are frequent and have been directly related to the severity of disease in COVID-19 patients[3];
2. the systemic inflammation, "cytokine storm" and coagulopathy associated with COVID-19 that may promote GI bleeding events[4];
3. administration of a pharmacological treatment including IL-6 inhibitors[11-13]. Indeed, in previous reports[14,15], the administration of IL-6 inhibitors has been associated with the occurrence of GI perforation (mostly lower), and the use of corticosteroids or nonsteroidal an-

ti-inflammatory agents has been reported to consistently increase this risk[14-16].

In this case, whether the duodenal perforation was caused by stress, a direct effect of SARS-CoV-2 or repeated treatment with IL-6 inhibitors is unclear. Due to the acute presentation while the patient was still in a subintensive ward, we believe that the second hypothesis should at least be considered. A possible implication is that patients with severe COVID-19 undergoing anti-IL-6 therapy can be considered for administration of prophylactic PPIs. The use of PPIs for the prevention of stress ulcers in non-critically ill patients admitted to general medicine units is currently not recommended or supported in the literature[17]general medicine population. Summary. The use of proton pump inhibitors and histamine H2-receptor antagonists for the prevention of stress ulcers has been well-defined in critical care patients. In 1999, the American Society of Health-System Pharmacists (ASHP, and in critically-ill patients, such therapy is recommended only for high-risk patients after risk stratification[18]. Therefore, COVID-19 and anti-IL-6 therapy could be regarded as adjunctive risk factors influencing risk stratification.

The second implication is that the exposure risk for surgical staff involved in procedures on COVID-19 patients urgently needs to be clarified. Knowledge of the exposure risk associated with laparoscopy remains insufficient. SARS-CoV-2 spreads mostly via respiratory droplets and direct contact and can be transmitted even with a low viral dose[12,19]. However, the presence of SARS-CoV-2 has been detected in faecal specimens, and an adjunctive risk for faecal-oral transmission has been theorized[20]. Moreover, human immunodeficiency virus, papillomavirus and *Corynebacterium* have been detected in surgical smoke[21-23]. Therefore, a cautious approach has been recommended for the treatment of COVID-19 patients during GI and abdominal surgery. Recommendations include the use of nonoperative treatments whenever possible (i.e., appendicitis, diverticulitis). With regard to laparoscopic surgery, the use of filtration systems and smoke evacuation systems for pneumoperitoneum induction have been strongly recommended. Moreover, the need for an accurate balance between operating room time and safety for both patients and healthcare staff has been suggested, especially when deciding whether a laparotomic or laparoscopic approach is more suitable[24,25]. In patients with perforated duodenal ulcers, the use of a laparoscopic Graham patch is a validated technique that is equivalent to open surgery in terms of efficacy and safety and is possibly superior to open surgery in terms of postoperative pain, wound infections and septic abdominal complications[26,27]. After reports of dismal outcomes and a high rate of severe pneumonia in COVID-19 patients undergoing laparotomic surgeries[28], some authors have underlined the benefits associated with a laparoscopic approach, including a minor risk of respiratory insufficiency and the possibility to apply prone ventilation as necessary without complications due to a laparotomic incision. In our patient, consideration of his clinical condition, the surgical timing and the exposure risk prompted the use of a laparotomic approach[29]. The risk of exposure for the surgical staff if the patient had undergone a laparoscopic procedure is unclear. Indeed, all abdominal samples collected at the time of the surgical procedure and postoperatively were negative for SARS-CoV-2, which is in line with another report describing a patient undergoing emergency surgery for acute appendicitis whose peritoneal samples tested negative for SARS-CoV-2[30]. Moreover, another paper initially reporting detection of SARS-CoV-2 in the peritoneal fluid of a patient undergoing peritoneal dialysis was subsequently retracted as this result was determined to be a false positive because the patient was negative for SARS-CoV-2 in the following 7 PCR tests and on serological testing[31]. Conversely, two reports of SARS-CoV-2 positivity in peritoneal fluid have been published, including one report of a patient undergoing emergency surgery for a volvulus of the small bowel[32] and one report of a patient undergoing peritoneal dialysis[33]. As a consequence of these discordant reports, the risk of exposure to SARS-CoV-2 for surgical staff is not clear. All reports involved conditions in which the lower GI tract was not opened, which is of particular importance as the risk of exposure may vary when faecal content is exposed since SARS-CoV-2 is frequently detected in faeces[5,20]. To clarify this issue, further testing should be performed on the peritoneal fluid of COVID-19 patients undergoing emergency surgical procedures.

Conclusions

Briefly, the relation between repeated administration of IL-6 inhibitors and upper GI bleeding and perforation must be investigated, and

the threshold for administering prophylactic PPI therapy should be carefully considered for patients with severe COVID-19. Further testing should be performed on the peritoneal fluid of COVID-19 patients undergoing emergency surgical procedures to clarify the discordant results for the presence of SARS-CoV-2 in the peritoneal cavity.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethical Approval

All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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