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PERSPECTIVES

Severe Acute Respiratory Syndrome Coronavirus 2 and the Digestive System

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1 Introduction

The coronaviruses belong to a family of related RNA viruses that notoriously spread through airborne transmission and were first identified in 1965 by Tyrrel and Bynoe[1]. The viruses of this family had contributed to two large epidemics, namely, the Severe Acute Respiratory Syndrome (SARS) in 2003 with a lethality rate of approximately 10% and Middle East Respiratory Syndrome in 2013 with a lethality rate of approximately 35%[1,2].

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), another member of the coronavirus family, is currently behind the coronavirus disease 2019 (COVID-19) pandemic which is thought to have originated in Wuhan city, China. SARS-CoV-2 is a beta-coronavirus of approximately 120 nm. The genomic assessment of SARS-CoV-2 in early patients highlighted a similarity of approximately 80% to the SARS-CoV genome[3]. The data reveals that SARS-CoV-2 is highly contagious with that varying case fatality rates among nations. According to the John Hopkins University Database, it has been reported that the COVID-19-attributed case fatality rate is about 2% worldwide while the rate in Italy stood at about 3.5% on December 25, 2020.

From the viral isolates of 11 Chinese patients with COVID-19, Yao *et al.* identified 33 mutations and reported up to 270-fold difference of cytopathic effect in the viral loads[4]. These observations may provide an explanation for the diverse lethality caused by SARS-CoV-2. Given that the most severe manifestations of these coronavirus variants are of respiratory nature, we wanted to further analyze if the other systems, more specifically the gastrointestinal system, could be affected by the virus.

2 SARS-CoV-2 and digestive system

Our hypothesis about the potential impact of coronavirus on other organ systems was conceived from an article by Shi *et al.* which reported the presence of SARS-associated coronavirus (SARS-CoV) in the intestinal epithelial cells and mucosal lymphoid tissue of the patients who died of SARS[5]. Similar to SARS, in the specific case of COVID-19, the virus needs to attach to angiotensin-converting enzyme 2 (ACE2) receptors found on the alveolar type II (AT2) cells of the lungs to infect the human cells, but the expression of this type of receptor has also been recently confirmed in the intestinal enterocytes[6].

The affinity between the virus and ACE2 receptors is determined by S1 and S2 subunits of the spike glycoprotein of the coronavirus. The mutations identified by Yao *et al.*[4] are related to the coding for the glycoprotein subunits. The work of Li *et al.* highlighted that the tissues of small intestine, kidneys, heart, and adipose tissues have the highest ACE2 receptor expression. The lungs, colon, liver, and bladder have an intermediate expression, while the bone marrow, brain, and muscles have a low expression[7].

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Minodier *et al.* highlighted that gastrointestinal symptoms were frequently present with coronavirus infections[8]. According to the preliminary experiences in Wuhan, Huang *et al*. and Wang *et al.* reported that nausea and diarrhea made up of about 10% of the symptoms[9,10]. Based on another report, 26% of the 254 patients with pneumonia caused by COVID-19 presented with unspecified gastrointestinal disturbances[11]. The difference in these observations is probably attributed to cognitive distortions concerning the gastrointestinal issues that happened among the authors. Considering these findings, we also diverted our attention to the first identified COVID-19 case in the U.S., a 35-year-old man who returned to Washington State after visiting his family in Wuhan, China[12]. Together with fever and cough, the patient also presented with abdominal discomfort and passed a loose bowel movement. Both the nasopharyngeal-oropharyngeal specimens and the stool specimens were positive for SARS-CoV-2 based on the real-time reverse-transcriptase–polymerase-chain-reaction (rRT-PCR) test.

After performing a meta-analysis of 69 studies, Cheung *et al.* reported that 17.6% of the COVID-19 patients had gastrointestinal symptoms, such as loss of appetite, nausea, vomiting, diarrhea, and abdominal pain[13]. Notably, it is important to discern that these papers do not explain the definitions of the gastrointestinal symptoms (e.g., how diarrhea is defined). In this analysis, 4243 patients were analyzed and 53 studies were carried out in China. Based on 11 studies that cover 2182 patients, the severity of the disease was correlated to gastrointestinal symptoms; the gastrointestinal symptoms were present in 17.1% of patients with severe form of COVID-19, and in 11.8% of patients with non-severe form. Interestingly, 70.3% of the patients who had negative results from the nasopharyngeal swabs were reported to have a persistence presence of SARS-CoV-2 viral RNA in their stool specimens. Thus, it is feasible to hypothesize that fecal-oral transmission is a possible route of transmission that occurs through the swallowing of the upper respiratory tract secretions.

3 SARS-CoV-2 and liver

The liver could be affected by COVID-19 with alteration of transaminases in approximately 20% of patients[14]. The possible ways that the liver could be affected by COVID-19 include direct or indirect damage caused by virus-linked inflammatory processes or the use of antiviral drugs. Therefore, liver transplant donors and potential recipients must be screened for SARS-CoV-2 with PCR or antigen tests in addition to noting any relevant symptoms such as fever[15]. It is advisable not to reduce immunosuppression for asymptomatic post-transplantation patients without COVID-19, but for patients with liver transplant and COVID19, it is important fine to minimize but not to discontinue the immunosuppressive therapy completely. Furthermore, the transplant surgeons and staff should be screened for SARS-CoV-2.

4 SARS-CoV-2 and inflammatory bowel diseases (IBD)

IBDs represent a serious clinical problem in the context of COVID-19. Before commencing the treatment with immunosuppressants or biologic agents, the patients with IBD should be arranged for SARS-CoV-2 screening in addition to a string of tests (e.g., hepatitis B, hepatitis C, human immunodeficiency viruses, and tuberculosis). If they are found positive for SARS-CoV-2 but remains asymptomatic, treatment can only be prescribed after 14 days of observation. In cases of patients with IBD who test positive for COVID-19, the American Gastroenterological Association suggested a suspension of the use of immunosuppressant medications until the symptoms subside[16]. When the recurrence of IBD is suspected, fecal tests should be indicated not only for cytomegalovirus but also SARS-CoV-2. If the tests are positive for SARS-CoV-2, it is useful to suspend treatment involving the immunosuppressive drugs and restarts the therapy 2 weeks after the patients cease to develop any symptoms of COVID-19. On the other hand, in the absence of SARS-CoV-2 and COVID-19, continued treatment is recommended to control the inflammation caused by IBD, which is a predisposing factor for COVID-19[16].

5 SARS-CoV-2 and digestive endoscopy

The arrival of COVID19 has put how we administer endoscopic examination in a tough spot[17]. Nevertheless, as a rule of thumb, the endoscopic examination should be deferred for non-urgent cases and prescribed for urgent cases, such as the patients who have tested positive for or are suspected to have COVID-19 and present significant gastrointestinal bleeding, cholangitis, and biliary pancreatitis.

In China, computed tomography (CT) scanning of the chest is indicated routinely before endoscopy in urgent conditions, in accordance with the recommendation by the Chinese Society of Digestive Endoscopy in consideration of a higher sensitivity of chest CT for detecting COVID-19 in the early stage[18,19]. In addition, it is crucial to establish procedures that minimize the risk of transmitting SARS-CoV-2 to endoscopy operators and other patients. The procedure should include screening with viral detection on nasopharyngeal swabs and/or in stools, either antigenic or RNA detection. Importantly, the health-care personnel should be periodically checked for SARS-CoV-2.

6 Conclusion

COVID-19 should not only be the subject of research in the respiratory field but also in the field of gastroenterology,

as evidenced by the presence of SARS-CoV-2 in fecal specimens which represent a hidden danger in some developing countries with poor public sanitation[20]. Undoubtedly, practicing thorough hand and toilet hygiene remains the key measure for deterring the widespread transmission of COVID-19, especially for the people living in closed communities[21]. Since the information regarding the treatment is scanty, the COVID-19 patients with gastrointestinal disturbances should be monitored closely. Nevertheless, we believe that the treatment for this subset of patients might involve the modulation of microbiota.

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Conflicts of interest

The authors report no conflicts of interest.

Author contributions

P.S. and F.A. conceived the concept of the paper. P.S. wrote the paper. P.S., S.U. and F.A. reviewed drafts of the paper.

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