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COVID-19 PANDEMIC: A GASTROINTESTINAL PERSPECTIVE

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ABSTRACT
The pandemic of the coronavirus disease-19 (COVID-19), the causative agent of the severe acute respiratory syndrome-2 (SARS-CoV-2), has become a public health emergency of the international concern. Although COVID-19 has been reported principally to affect the respiratory system, other system's involvement has also been reported. Gastrointestinal (GI) involvement has also been underlined in the published literature. Gastrointestinal involvement in SARS-CoV-2 usually corresponds to four situations: (a) gastrointestinal manifestation of COVID-19, (b) hepatobiliary manifestations, (c) pancreatic manifestation, and (d) COVID-19 infection in patients with gastrointestinal comorbidities. General gastrointestinal manifestations of the viral infection include anorexia, nausea, vomiting, abdominal pain, and diarrhea. Hepatobiliary manifestations include asymptomatic abnormal elevation of enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and bilirubin), and acute hepatitis. Pancreatic symptomology involves asymptomatic abnormal pancreatic enzyme elevation (lipase, amylase), and acute pancreatitis. Viral infection with GI comorbidities includes any GI malignancy, peptic ulcer disease, hepatitis, chronic liver disease (CLD), and inflammatory bowel disease (IBD). The pandemic of SARS-CoV-2 has become a unique challenge for the gastroenterologist. Various GI manifestations have been observed and reported in many cases, and even GI features may precede the classical respiratory signs and symptoms. In this review, we have summarized the information from published literature including, case reports and open-source data sets, to describe the spectrum of GI manifestations observed in COVID-19 cases.

KEYWORDS: ALT, AST, GGT, IBD.

INTRODUCTION AND BACKGROUND
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2), the causative agent of COVID-19 (coronavirus disease-2019), first originated from Wuhan, China during late December of 2019. It started as an outbreak which led to an epidemic with 44,672 confirmed cases in China by February 14, 2020, with 2.3% reported mortality rate, which was comparatively lower than the previously known epidemics caused by human coronaviruses (Severe Acute Respiratory Syndrome Coronavirus [SARS-CoV] and the Middle East Respiratory Syndrome Coronavirus [MERS-CoV]) in 2003 and 2012 respectively.[1,2] The World Health Organization (WHO) declared COVID-19 as a global pandemic on March 11, 2020.[3] The infection presents most commonly as fever, dry cough, shortness of breath, sore throat, and diarrhea with severe respiratory involvement in patients with advanced age (over age 80). The overall case fatality rate in this age group is about 14.3%.[4] The severity of this disease is characterized by

severe pneumonia, respiratory failure requiring mechanical support, sepsis, myocardial injury, multi-organ failure and mortality increases in patients having underlying comorbidities such as cardiovascular disease, diabetes, and chronic respiratory disease.[5,6] However, some patients may have very mild symptoms or act as asymptomatic carriers suggesting that the true number of cases may be much higher than reported.[2] Given the rapid spread of the virus, researchers across multiple nations have dedicated themselves to better understand the virus, disease pathophysiology, and develop effective drugs and preventive vaccines.

Even though, Although COVID-19 has been reported principally to affect the respiratory system, gastrointestinal (GI) involvement has also been underlined in the published literature, raising the concerns about GI invasion by COVID-19. The amount of literature on GI involvement by COVID-19 is small. However, we believe that a structured summary of existing data at this point would be requisite for gastroenterologists. Being well informed about the GI clinical presentations would not only provide support to them have a high index of clinical doubts but also take obligatory precautions. In this paper, we have summarized the information from published literature, including case reports and open-source data sets, to describe the spectrum of GI manifestations observed in COVID-19 cases.

MATERIAL AND METHODS

We performed a comprehensive review of the EMBASE and PubMed databases from inception to 25-May-2020 to find articles providing information on the effect of COVID-19 on gastrointestinal system and its related complications. Language restrictions were not imposed (see detailed search strategy in supplement 1). We expanded the search using a snowballing method and applied it to the references of published papers. We also searched the Chinese Clinical Trial Registry, Clinicatrial.gov, and the International Clinical Trials Registry Platform (WHO, ICTRP) to find ongoing trials. Three authors independently screened the databases and the trial registries and extracted relevant information. Doubts and incongruities about the relevance of the sources were solved by consensus with three more authors. We registered a narrative review protocol because we expected the very limited available data and evidence on the topic and due to the urgency of the matter.

RESULTS

We perceived that SARS-CoV-2 may have various gastrointestinal manifestations, and in many cases, the gastrointestinal signs and symptoms may precede typical respiratory symptoms. Holistic knowledge of the spectrum of the GI consequences of COVID-19 is crucial to get a hold on the spread of the virus. The most vital clinical information which we meet is that diarrhea and abdominal pain may be a presenting feature of COVID-19. Therefore, a high catalog of suspicion for such patients will be crucial to prevent or, at least, minimum exposure to health care providers and other patients. With the gradual settling of the outbreak, it can be predicted that several post-infectious gastrointestinal complications will surface up. The proper caution has to be practiced while treating and managing patients with gastrointestinal co-morbidities, particularly those needing immune-modulator therapy since framed guidelines are lacking at this point.

DISCUSSION

Mechanism of GI invasion

The current studies report that respiratory symptoms of COVID-19 represent the most common manifestation, which is highly suggestive of the droplet and contact transmission. However, the incidence of GI manifestations differs significantly among different populations including typical respiratory symptoms of COVID-19.[7] The increasing rationale from the previous studies of SARS reported that the detection confirmed GI tropism of SARS-CoV, in biopsy samples, and even in the stool of discharge patients, which can be the reason for possible explanations for GI manifestations, probable recurrence, and spreading of COVID-19 from the obstinately shedding human as well.[8] Particularly, the first case of COVID-19 infection in the United States reported having positive for viral nucleic acids of COVID-19 in his loose stool and both respiratory specimens.[9] Furthermore, most of the infected patients also had COVID-19 sequences in their saliva. Even serial saliva specimens of these patients also showed a decrease in viral load with improvement in hospitalization.[10] This positive viral culture underlines the possible transmission of the virus and infection of the salivary gland. Given the extra-pulmonary detection of viral ribonucleic acid (RNA) does not mean the presence of infectious virus.[10]

Generally, as the number of cases is rapidly growing, we should keep in mind that the digestive system apart from the respiratory system may also serve as an alternative route of infection. There is likely spread of the disease when people are in contact with the diseased person, asymptomatic carriers, or the patients with mild GI symptoms at an early stage. Clinicians should be careful to promptly identify the patients with initial gastrointestinal symptoms and explore the duration of infectivity with the delayed viral conversion.

The genome of the SARS-CoV-2 consists of single-stranded positive-sense RNA encapsulated within a membrane envelope, which has glycoprotein spikes giving coronaviruses their crown-like appearance.[11] Of the four classes of coronaviruses (alpha, beta, gamma, and delta), SARS-CoV, MERS-CoV, and COVID-19 causative SARS-CoV-2, are included in the class beta. While SARS-CoV, MERS-CoV, and SARS-CoV-2, all attack the lower respiratory tract, SARS-CoV-2 additionally also affects the heart, gastrointestinal

system, liver, kidney, and the central nervous system eventually leading to multi-organ failure.[12,13] Glycosylated spike (S) protein, which is one of the structural proteins encoded by the coronavirus genome, is a major inducer of host immune response. This protein binds to angiotensin-converting enzyme 2 (ACE2) receptor protein located on the host cell surface membrane and mediates the host cell invasion.[10-12] ACE2 (entry receptor for SARS-CoV) was particularly confirmed in COVID-19 infection regardless of mutations at key receptor-binding domains. Inhuman transmission and pathogenesis of COVID-19 are based on the interactions, involving virus binding, receptor recognition, cleavage of protease, and membrane fusion.

A recent analysis was conducted on the availability of single-cell transcriptomes data of healthy human lung and GI system, which revealed that ACE2 does not only express in the lung AT-2 cells but also express in the esophagus, small intestine, and large intestine. Upper and stratified epithelial cells of the esophagus and absorptive enterocytes from ileum and colon express ACE2.[14] The infection causes an increase in gastrointestinal wall permeability to foreign pathogens which resulting in GI symptoms like diarrhea because of invaded enterocytes malabsorption. Host cell produced serine protease TMPRSS211 facilitates the priming of S protein required for this invasion process. ACE2 and serine protease (TMPRSS2) exert hydrolytic effects responsible for S-protein priming and invasion. Because of the high co-expression of ACE2 and TMPRSS2 in the GI system, it renders additional evidence for enteric infectivity of COIVD-19. However, the exact mechanism of COVID-19-induced GI manifestations largely remains indefinable.

Gastrointestinal symptomology

Fever, cough, fatigue, dyspnea, sore throat, headache, and myalgia are the characteristic symptoms of COVID-19.[15] Almost 80% of the patients present with mild symptoms, 20% demonstrate severe disease, and 5% of the patients present severe signs and symptoms of COVID-19 like respiratory arrest, septic shock, cardiac arrest, or multi-organ failure.[15] As COVID-19 has widely been studied, as a lung pathogen, the GI involvement has also been reported in recent studies. Studies have underlined that approximately 50% of COVID-19 patients develop gastrointestinal (GI) symptoms of nausea, vomiting, diarrhea, and abdominal pain. Time for hospital presentation from the onset of GI symptoms compared to respiratory symptoms was found to be higher (9.0 vs 7.3 days).[16,17] A similar study reported the involvement of GI in COVID-19 patients. 11.4% of the patients exhibited at least one of the GI symptoms involving nausea, vomiting, or diarrhea, and 10.8% of having pre-existing liver disease. It was also reported having higher rates of fever, fatigue, shortness of breath in COVID-19 patients with GI symptoms.[16] The first patient diagnosed with COVID-19 in the USA, presented with cough, nausea, vomiting, abdominal pain, and diarrhea.[9] The first case of bleeding per rectum as an initial presenting symptom of COVID-19 has also been reported.[18] GI manifestations of COVID-19 have been reported in both children and adults. Tian et al. reported that diarrhea was the most common symptoms among other GI symptoms: anorexia (39.9%-50.2%), vomiting (3.6%-66.7%), nausea (1%-29.4%), abdominal pain (2.2%-6.0%), and gastrointestinal bleeding (4%-13.7%).[19]

The possible mechanisms for GI manifestations secondary to SARS-CoV-2 infection include:

1. Both the respiratory tract and GI tract epithelium have ACE2 receptors used by the virus to gain cellular entry. Hence, the virus can replicate in the GI tract.
2. Inflammatory response induced by the infection can directly injure the GI system.
3. SARS-CoV-2 can destroy absorptive enterocytes, leading to malabsorption, dysregulated intestinal secretion, and activated enteric nervous system leading to diarrhea.[14]

A recent analysis reported on COVID-19 patients who developed GI symptoms, it was found that 391/1194 (32.7%) patients developed GI symptoms, while 903/1194 (67.3%) didn't develop any GI symptoms. GI symptoms in the absence of respiratory symptoms may often be the only presenting problems in adults and children with COVID-19.[18]

Hepatobiliary symptomology

Hepatobiliary injury ranging from mild to severe damage has also been reported in Covid-19 patients. Hepatobiliary injury has been manifested in the laboratory setting in the form of elevated ALT, ALP, GGT, total bilirubin. The disease process may be suggested as the pathophysiology of liver injury.[20] 20-30% of the patients with COVID-19 have been reported to have abnormal hepatic enzymes.[21] Fan Z et al. reported that 50.7% of the patients had abnormal liver function tests at admission.[20] Furthermore, a study also reported similar results with abnormal hepatic enzymes and total bilirubin levels. Patients with abnormal liver enzymes reported having moderate-high grade fever. These liver abnormalities were found to be transient. Patients with already suffering from liver disease are an important group of individuals that require additional attention in the COVID-19 pandemic. Mao A et al. reported that out of 1099 COVID-19 patients, 23 patients had hepatitis B infection - critical cases of COVID-19 were more likely to have hepatitis B infection than non-severe cases (2.4% vs. 0.6%).[22] Moreover, in patients with COVID-19 with autoimmune hepatitis, the use of glucocorticoids in disease management is currently unclear.[23] In the setting of primary biliary cholangitis (PBC), COVID-19 may exacerbate cholestasis. Therefore, alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) serum levels should carefully be monitored. Given their immunocompromised state, patients with hepatic

cirrhosis or cancer may be more susceptible to COVID-19.[23]

SARS-CoV-2 can use ACE2 receptors and infect cholangiocytes. ACE2 expression is upregulated in hepatocytes in patients with SARS-CoV-2 infection resulting in viral infection of hepatocytes and liver injury. The histological examination of a liver biopsy from COVID-19 patients showed microvascular steatosis and mild lobular activity but no viral inclusions. The hepatocellular injury in COVID-19 patients may be secondary to hypotension or immune-mediated inflammation or drug=induced hepatotoxicity due to drugs like remdesivir or hydroxychloroquine.[23]

Pancreatic symptomology

In a recent study by Wang et al. reported that the incidence of pancreatic injury was not much low in patients with COVID-19. Out of 52 patients with COVID-19, 17% of the patients experienced pancreatic injury (abnormal elevation in lipase or amylase). However, these patients did not experience the clinical symptoms of acute pancreatitis. Five patients also had underlying diseases. Patients with pancreatic injury had a higher incidence of diarrhea, anorexia, a higher level of ALT, GCT, and severe illness on admission.[24] Acute pancreatitis has also been reported as a presenting symptom in the literature.[25,26] The pancreatic islet cells have high expression of ACE2 receptors, therefore, COVID-19 can cause cell damage theoretically, resulting in acute diabetes mellitus. Among the nine patients with pancreatic injury, six patients had abnormal glucose findings. Direct cytopathic effects of COVID-19 or immune-mediated and indirect systemic inflammatory response could be the mechanism of pancreatic injury.[27] Antipyretics, which most of the patients take before admission, could also cause drug-induced pancreatitis. Further research is obligatory to determine the full effect of COVID-19 on pancreatic morphology.

Patients with gastrointestinal comorbidities

Patients have also been diagnosed with underlying GI disease like diabetes and chronic liver disease. However, data is not satisfactory to determine the COVID-19 impact on their health. A recent study by Mao R et al. reported a study on GI manifestation and prognosis of patients diagnosed with COVID-19. In this study, four percent of the patients have underlying GI and liver disease. This study reported that the risk of severe disease was not increased among the patients with underlying GI diseases as compared to the patients without these comorbidities (OR 0·57 [95% CI 0·15-2·18]; p=0·41; I2=44%.[22] It is also unclear for patients with underlying GI diseases like inflammatory bowel disease (IBD), to be affected by COVID-19. There is a likelihood of susceptibility to be infected with COVID-19 if the patient is taking specific medications such as immune-modulating drugs or steroids. Still, the answer is not known. The most expert consensus statements have reported that GI patients on immunosuppression, such as those with inflammatory bowel disease or autoimmune hepatitis, should be compliant with their medications to prevent a flare of their disease," Ungaro says. "Uncontrolled inflammation, in itself, may increase the risk of infections," he explains, "and we don't want patients to have a flare that requires going to the hospital, where the risk of getting COVID is higher".[28] "We do recommend that patients on immunosuppression consider themselves as an at-risk group since it is possible that COVID-19 could be more severe in patients on medications that lower the immune system,".[28]

CONCLUSION

The pandemic of COVID-19 presents for a gastroenterologist some exceptional challenges. We perceive that SARS-CoV-2 may have various gastrointestinal manifestations, and in many cases, the gastrointestinal signs and symptoms may precede typical respiratory symptoms. Holistic knowledge of the spectrum of the GI consequences of COVID-19 is crucial to get a hold on the spread of the virus. The most vital clinical information which we meet is that diarrhea and abdominal pain may be a presenting feature of COVID-19. Therefore, a high catalog of suspicion for such patients will be crucial to prevent or, at least, minimum exposure to health care providers and other patients. With the gradual settling of the outbreak, it can be predicted that several post-infectious gastrointestinal complications will surface up. The proper caution has to be practiced while treating and managing patients with gastrointestinal co-morbidities, particularly those needing immune-modulator therapy since framed guidelines are lacking at this point. The above review of the gastrointestinal manifestations of COVID-19 will help the gastroenterologist have a pivotal preparation, which is of extreme importance to prevent infections.

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