Mini-Review

Gastrointestinal and hepatic involvement in patients with SARS-CoV-2 infection

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Abstract

The coronavirus disease-2019 (COVID-19) is primarily a disease of the respiratory system and is manifested by an infectious pneumonia, with fever, cough and breathlessness as the most common presenting symptoms. However quite a few number of the patients may suffer involvement of gastrointestinal system and liver. There is mild to moderate abnormality in the levels of liver enzyme observed in the patients with hepatic involvement, whereas gastrointestinal symptoms include nausea, vomiting and diarrhea. Nonetheless, gastrointestinal disease in COVID-19 patients may present with severe life threatening conditions, like gastrointestinal bleed, intestinal ischemia, acute liver failure and necrosis. The virus bind and invade the cells through Angiotensin Converting Enzyme 2(ACE2) receptors, which are expressed not only on endothelial cells of lung alveoli but also markedly expressed on epithelial lining of the oral mucosa, intestinal mucosa and cholangiocytes. Viral RNA has also been detected from stool specimens of COVID-19 patients, even during the convalescent phase, which is a matter of concern for the transmission of the disease via feco-oral route and needs to be elucidated.

Introduction

The severe acute respiratory syndrome–coronavirus–2 (SARS-CoV–2), a novel coronavirus is responsible for an ongoing pandemic and the disease has been named as coronavirus disease-2019 (COVID-19) by the World Health Organization [1,2]. At the time of submission of this article, the number of confirmed cases of COVID-19 has crossed fifty seven million and wiped away 1 population of more than 1.3 million with a mortality of approximately 3% and involving almost the entire world. The disease is primarily a respiratory disease with fever, cough, malaise and breathlessness being the outstanding features and resembles diseases caused by other coronaviruses viz. Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [3–5]. A small but significant numbers of patients infected with COVID–19 may present with gastrointestinal symptoms like diarrhea, vomiting and nausea initially, with [6] or without [7] respiratory symptoms. Additionally increasing number the patients are presenting with hepatic manifestations. Another important observation reported in patient with GI symptoms is the shedding of the virus in their stool samples for an additional period of 2–14 days, after pulmonary symptoms have resolved [8–10].

Although the primary route of transmission of COVID-19 remains the respiratory, via aerosolized droplet, yet there is a possibility of feco–oral transmission of the virus keeping in mind the fact that an asymptomatic individual or individuals before the manifestations of the symptoms can transmit the infection and also the virus has been detected in the stool specimens of the convalescent individuals even after negative viral RNA from nasopharyngeal swab [8,11–13]. This article will emphasize upon gastrointestinal and hepatic manifestations in patients with COVID-19 infection and their proposed mechanisms.

Gastrointestinal manifestations

The various studies published on epidemiological and clinical presentations of COVID–19 have shown that approximately 3–40% patients may present with one or the other gastrointestinal symptoms like diarrhea, nausea,
vomiting and abdominal pain [14–18]. A study from Wuhan, China have documented that 39.6% of COVID-19 patients complained about gastrointestinal symptoms, including nausea, diarrhea, poor appetite, abdominal pain, belching, and emesis. However the most common GI presentation in these patients was nausea (17.3%) followed by diarrhea (12.9%), abdominal pain (5.8%), belching (5%) and vomiting (5%) [18]. Another study has reported an incidence of diarrhea in 8% of the patients with COVID-19 disease [19]. A study from Singapore have shown that among the 18 hospitalized patients with PCR-confirmed SARS-CoV-2 infection, four of the patients developed nausea, vomiting, and/or diarrhea, and 3 of the patients developed abnormal liver function. The authors have stated that these patients probably had developed the gastrointestinal symptoms subsequent to treatment with lopinavir–ritonavir [3].

Further, a meta-analysis of 60 studies involving a total of approximately 4000 patients, the pooled prevalence of all gastrointestinal symptoms was 17.6% with statistically significant variations noted among studies. The pooled prevalence of loss of appetite was (26.8%), nausea/vomiting was 10.2% of diarrhea was 12.5%, and of abdominal pain/discomfort was 9.2%. However not all the studies included in the meta-analysis have reported individual GI symptoms [20]. In contrast, another meta-analysis including approximately 6000 patients reported the presentation of GI symptoms in only 9% of the patients [15].

Another common GI symptoms reported in patients with COVID-19 are, loss of smell, and dysgeusia/ageusia. Of the total 59 hospitalized patients in a study reported that 33.9% of the patients had either anosmia or dysgeusia, whereas 18.6% of the patients reported with both taste and olfactory disorders. Twelve patients (20.3%) presented the symptoms before the hospital admission, whereas 8 (13.5%) experienced the symptoms during the hospital stay [21, 22]. Therefore loss of smell and taste during the early phase of the disease can be used as a marker for the diagnosis of the disease, at least during the pandemic as these features are non specific and could be present in other viral infections as well [23].

A case of mesenteric ischemia with severe hypotension, a rare gastrointestinal manifestation of COVID-19 has also been reported in a 62-year-old man. The clinical history of the patient included three days of abdominal pain and bilious vomiting prior to hospital admission in an unconscious state. The patient had comorbidities like obesity, arterial hypertension, diabetes mellitus type 2 and hepatic cirrhosis (non-alcoholic steatohepatitis + hepatitis B). The patient's nasopharyngeal swab and bronco-alveolar lavage was tested negative for SARS-CoV-2 and CT chest was unremarkable. However, abdominal CT findings were highly suggestive for small bowel ischemia. Histological examination of the resected bowel showed complete ischemic necrosis, recent thrombosis and severe endothelial inflammatory infiltration in inferior vena cava and superior mesenteric vein. In view of the ongoing pandemic ISH (in situ hybridization) on the resected small bowel specimen was performed to detect the SARS-CoV-2 spike protein mRNA using VnCov2019- S probe and the test confirmed SARS-CoV-2 presence in the intestinal mucosa [24]. Interestingly, quite a few studies have reported gastrointestinal symptoms without any respiratory symptoms [25, 26]. One of the unusual presentations in this context was hemorrhagic colitis reported in a 71-year-old female and was tested positive on nasopharyngeal swab SARS-CoV-2 RT-PCR. The lower GI bleed in this patient was attributed to SARS-CoV-2 after ruling out other etiologies [27]. Another rare gastrointestinal manifestation of the COVID-19 is the gastrointestinal bleed during the initial phase of the disease, reported from a 53-year-old male patient presented to the emergency department with epigastric pain, diarrhea, and respiratory symptoms. The patient had comorbid conditions like hypertension, diabetes mellitus, and chronic renal failure [28]. On the contrary, most of the other COVID-19 gastrointestinal bleeding cases are the critical or terminally sick patients [29, 30].

Hepatic manifestations

Recent epidemiological and clinical data on COVID-19 have elucidated that a moderate to severe liver function abnormality may be detected in these patients, with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above the normal range [31]. A study from China including 7736 hospitalized patients with Covid-19, published during the early phase of pandemic, have reported that total bilirubin, ALT and AST were elevated in 10.5%, 21.3% and 22.2% of patients respectively [14]. There are several large-scale case studies published on the clinical presentation and laboratory finding in the patients with COVID-19. These studies indicate that 14-53% of the cases had liver dysfunction during the progression of the disease. Severity of the liver dysfunction has been correlated with adversity of the COVID-19 disease progression as abnormally high AST levels were observed in 62% of the patients in need of intensive care, whereas only 25% of the patient who did not require ICU care had elevated AST levels [9, 14, 16, 18]. There is not much data available on liver pathology in COVID-19 except a report of one patient who underwent a autopsy. The liver autopsy specimens of the patient with COVID-19 showed microvascular steatosis with mild lobular and portal inflammation. However the etiology behind the liver damage could not be ascertained as the injury could have been caused by either directly by invasion of the liver by SARS-CoV-2 infection or drug-induced [32]. In addition to the above discussed liver dysfunctions an isolated case report has associated acute hepatitis with COVID-19 Infection, presenting much before the appearance of respiratory symptoms [33].

Mechanism for the gastrointestinal and hepatic damage

Different mechanisms and theories have been put forwarded for the gastrointestinal and hepatic damage caused by SARS-CoV-2.

**Viral invasion:** Binding and Invasion of the virus in the target cell is a phenomenon known as tissue tropism and it is a receptor –legend interaction between the host cell and the pathogen. In case of SARS-CoV-2 it has been found that receptors on the host cell are Angiotensin-Converting enzyme 2 (ACE 2) complementary to virus transmembrane spike
glycoprotein (S-protein). These receptors are present on the surface of different human cell types including alveolar cells (AT2 cells) of the lung tissue and also on certain intestinal epithelial cells in the ileum and colon [34–35]. The active multiplication of the virus in the gut epithelium has already been proved by virus culture as well as direct visualization by electron microscopy [10]. Histology of the autopsied specimen of a patient with COVID–19 had also shown degeneration and necrosis of the gastrointestinal mucosa [36]. Binding, invasion and multiplication of the virus to intestinal epithelial cells can very well explain the pathogenesis of gastrointestinal manifestations associated with COVID–19. In the context of binding of virus to intestinal epithelial cells and shedding of the virus in the stool sample [9,43] also fecal–oral transmission of the virus needs to be studied. Additionally, ACA 2 receptors are also widely expressed on the epithelial cells of the mucosa of the oral cavity [37]. These findings could explain the underlying pathogenetic mechanism of taste and olfactory disorders in SARS–CoV–2 infection.

A preliminary study has suggested that cholangiocytes are also enriched in expression of ACE2 receptors indicating that SARS–CoV–2 might directly bind to ACE2 positive cholangiocytes and indirectly dysregulate the liver function. Nonetheless, histology of liver tissue from a patient who died from COVID–19 did not showed any viral inclusion, an indirect evidence of absence of active multiplication of the virus in the hepatocytes and also the absence of ACE 2 receptors on the liver cells [38].

**Ischemic damage:** Ischemia/ hypoxia due to respiratory complications of COVID–19, leading to acute respiratory distress syndrome (ARDS) can also damage the liver [39-40]. A study using an in vitro mouse model of ischemia and hypoxia have demonstrated hepatocytes necrosis and inflammatory cell infiltration of the liver [41] because of continuous release of reactive oxygen species and its peroxidation products [42].

**Cytokine storm:** Various studies have reported that though there was a decrease in peripheral CD4 and CD8 T cell counts in the patients with COVID–19 severe disease, however these cells are in hyperactive state, leading to increase of Th17 and high cytokotoxicity of CD8 T cells, which is further responsible for severe immune injury in this patient due to cytokine storm [40,43,44]. Other studies have also observed that during the early stage of the disease there is mild elevation of the liver enzymes which is not dangerous; however, sudden deterioration of the liver during the late stage of the disease is related to Systemic Inflammatory Response Syndrome (SIRS) and activated immune system due to viral infections. SIRS and immune damage can cause multiple organ damage including the liver [39,44,45].

**Drug toxicity:** Another suggested mechanism which might be involved in liver damage during management of COVID–19 is the use of hepatotoxic drugs. Antipyreric (Acetaminophen), antivirals (oseltamivir, abidol, lopinavir, and ritonavir), antibiotics, steroids, certain herbal medications which are widely used for the treatment of COVID–19 have been reported with adverse reactions including liver damage [39,43,44].

**Conclusion**

Although COVID–19 primarily a respiratory disease and is responsible for pneumonia, gastrointestinal and manifestations are frequently associated with COVID–19. These manifestations are primarily associated with the presence of ACE2 receptors on the intestinal epithelial cells and cholangiocytes. The role of fecal viral shedding in the current pandemic and its role in the transmission of the disease needs to be evaluated further.

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