Case Discussion in Medicine

COVID-19 : A Gastroenterologist's Perspective

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The ongoing novel coronavirus pandemic poses significant challenge to mankind in terms of healthcare resources and economic slowdown. Though mainly manifested as pneumonia, the virus can affect the digestive system producing a gamut of symptoms. The main clinical issues related to gastroenterology include possibility of faeco-oral route of transmission, occurrence of isolated digestive symptoms, abnormalities in liver function tests that correlate with disease severity, and effective infection control measures for endoscopy procedures.

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Key words **: Covid-19, SARS-CoV2, Angiotensin converting Enzyme 2, Liver Injury, Diarrhoea, Gastrointestinal Symptoms.**

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first reported in China, in December, 2019, has posed a critical threat to global public health. The World Health Organization (WHO) has declared the outbreak of COVID-19 a pendemic and the global fatality rate is estimated to be 5.7%[1]. Most common symptoms are fever (98%), cough (76%), myalgia or fatigue (44%)[2]. Approximately 80% of patients demonstrate mild symptoms; 20% have severe disease; about 5% exhibit critical disease symptoms such as respiratory arrest, septic shock, or multiple organ failure[3]. As time passes different case series have demonstrated systemic involvement other than Lung – ie gastrointestinal manifestations, anosmia, hepatic and neurological manifestations.

Case Study

A 45-year-old man, without any history of diabetes and hypertension, presented to us with a 5-day history of colicky abdominal pain associated with watery diarrhoea of four to five times per day. He did not give history of any fever, sore throat or shortness of breath. He only had mild dry cough for 3 days apart from diarrhoea. There was no recent history of sick contacts or travel. On initial presentation, he was afebrile,no evidence of tachycardia or tachypnea was found.There was mild generalised abdominal tenderness, but no, rigidity,guarding or rebound tenderness. Patient was diagnosed as having Tropical Diarrhoea and Intravenous Fluid, Doxycycline, ciprofloxacin, pre and Probiotics given.Patient partially improved but on 5th day of admission patient develop mild Shortness of Breath with saturation 90% in room air.The chest examination showed a few bi-basal crackles near lung bases. The rest of the physical examination was unremarkable. Initial work-up revealed mild anaemia, thrombocytopaenia and non-elevated inflammatory markers. Two repeated samples revealed asymptomatic hyponatraemia (Sodium values of 124 & 128 meq/L on Day 1 & Day 3). Liver enzymes, renal function and the endocrine panel were unremarkable. Chest Xray revealed a few patchy opacities near lung bases. Observing lung opacities Oropharyngeal & nasopharyngeal swab for COVID-19 was sent which came as positive. Patient was started therapy and Diarrhoea& pain abdomen subsided within 3 days. Patient was discharged after 10 days of admission in a clinically stable condition.

In world literature respiratory symptoms are

Editor's Comment :

- Compared with adult patients, paediatric Covid-19 patients seem to have clinically milder GI symptoms, although vomiting may be more prominent.
- Compared with Covid-19 patients without GI symptoms, those presenting with digestive symptoms have a longer time from onset to admission, more severe / critical disease, higher rates of liver injury, and a worse prognosis.
- Potential mechanisms of Liver Injury in Covid-19 include binding of viral particles to the *Angiotensin converting Enzyme 2* enzyme expressed on cholangiocytes, interaction of virus with mitochondrial proteins in liver and cytokine mediated hepatitis.
- On entry of SARS-CoV2 into the intestinal mucosal cells through the*Angiotensin converting Enzyme 2*, the virus alters the permeability of these cells, leading to diarrhoea.

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considered as principal pathognomic of COVID-19 patients. Gastrointestinal symptoms are not given due attention. Under recognition of symptoms or knowledge gap can lead to delay in diagnosis or missing of cases in community and can lead to viral transmission in community. Understanding of pathophysiology of COVID19 infection justify gastrointestinal manifestation can be a presenting feature.

Pathophysiology of liver involvement in COVID (Fig 1) :

The exact pathophysiology of hepatic injury in Covid-19 is not known. Potential mechanisms include binding of Covid-19 viral particles to the ACE2 enzyme expressed on cholangiocytes, interaction of virus with mitochondrial proteins in liver and cytokine mediated hepatitis. Other external causes of liver injury are drug induced, hypoxia induced and venous congestion induced (secondary to myocarditis). The immune response in Covid-19 involves a rise in IL-6, which has hepatotoxic potential. Sepsis induced liver damage is also a possible pathology.

Pathophysiology of Intestinal injury in Covid-19 (Fig 2) :

A significant proportion of patients of Covid-19 have diarrhoea. In some cases, as the case study below will demonstrates, diarrhoea can even be the presenting symptom of Covid-19 infection. Again, the exact pathophysiology of diarrhoea is not known. Angiotensin converting enzyme 2 is the receptor for SARS-CoV2 in Human body. The intestinal mucosal cells express this protein in large quantities. This may help in entry of the virus into intestinal cells. Once the virus enters, there is altered permeability of these cells, leading to diarrhoea. Also, amino acid transport in intestinal mucosa is hampered. This alters the metabolism of gut microbiota and leads to intestinal inflammation. This can also cause diarrhoea.

Discussion

In one series in Singapore Diarrhoea accounted for 17% cases. In another study in Hubei, China, among 204 patients 20% presented with either gastrointestinal symptoms like diarrhoea, vomiting, nausea or abdominal pain. But most of them also had respiratory problems. Only 6 out of 204 patients had diarrhoea and fever without respiratory symptoms. Only one patient had diarrhoea but no respiratory problems or

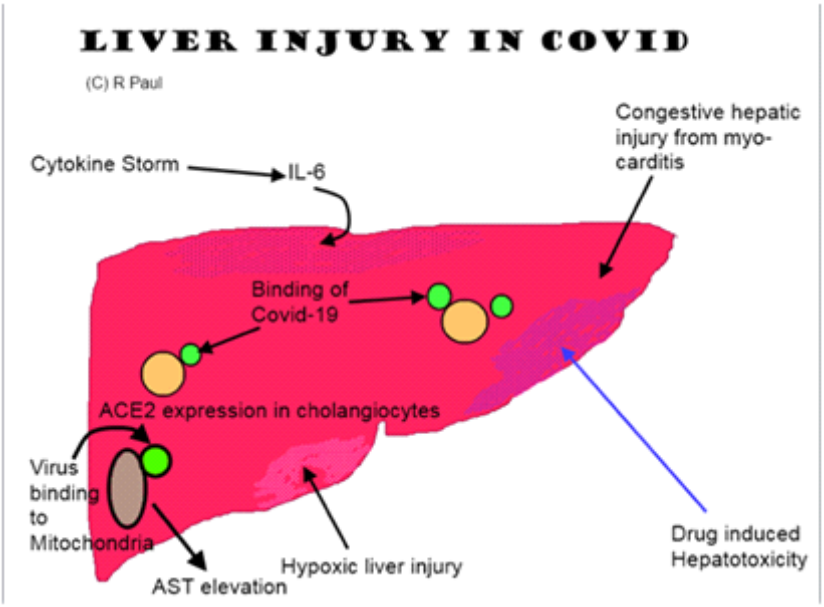

Fig 1 — Schematic representation of pathophysiology of hepatic injury in Covid-19

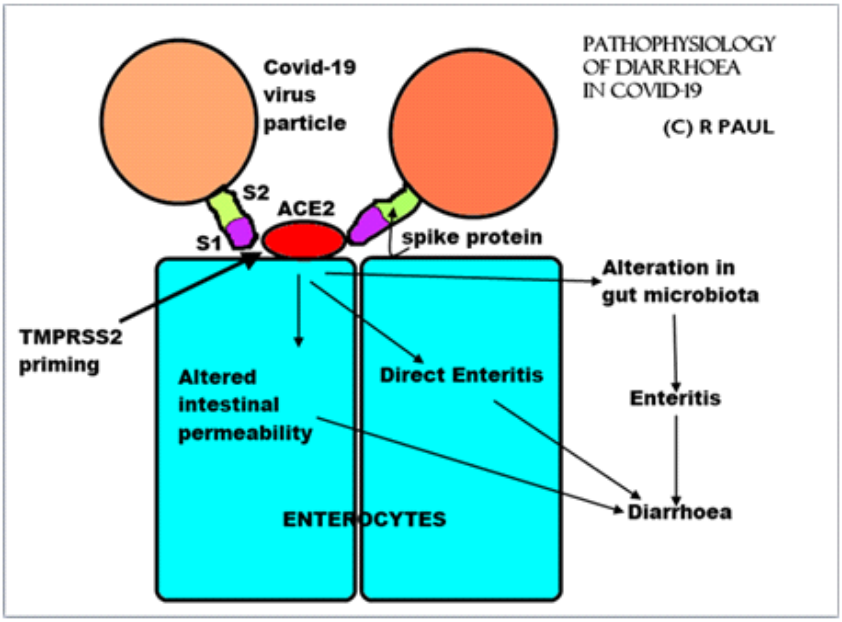

Fig 2 — Pathophysiology of Diarrhoea in Covid-19 infection

fever. S Sultan *et al* reported nausea and/ or vomiting (5.2-14.9%), abdominal pain (2.7- 5.3%), and diarrhoea (5.8-18.3%) cases[4]. Other symptoms include anorexia, anosmia, and dysgeusia. The mutual interaction between SARS-CoV-2 and angiotensin converting enzyme 2 (ACE2) receptors, highly expressed on proximal and distal enterocytes, might disrupt the function of absorptive mucosa and results in diarrhoea[5]. In addition, SARS-CoV-2–induced diarrhoea (mostly low volume and non-dehydrating) could be the onset symptom in patient with COVID-19[6]. Compared with patients without gastrointestinal symptoms, those presenting with digestive symptoms have a longer time from onset to admission, more severe / critical disease, higher rates of liver injury, and a worse prognosis. Notably, in 3.4% cases, digestive symptoms may be the only presenting symptom of COVID-19 with potential for delay in diagnosis[6]. However, no significant difference is seen when considering pooled rates of discharge, length of hospital stay, and rates of death between patients with and without gastrointestinal symptoms[6]. Compared with adult patients, paediatric patients seem to have clinically milder symptoms, with less severe alterations in laboratory parameters, although vomiting may be more prominent[7]. In MERS though respiratory symptoms was presentation at initial period, diarrhoea subsequently established as additional presenting feature

Isolation of viral ribonucleic acid (RNA) from intestinal epithelium and positive intracellular staining for viral nucleocapsid protein lend support for gastrointestinal involvement[8]. The RNA could be detected in the stool of patients with COVID-19 (up to 53%), implying that SARS-CoV-2 may be transmitted by the fecal–oral route[8]. The duration of positive stool ranges from 1 to 12 days, and 23% patients remain positive after showing negative in respiratory samples[8]. However, the clinical implications of prolonged viral excretion in faeces, including the association with disease course, severity, and disease recurrence remains unclear. Interestingly, this may provide an opportunity to develop stool-based less invasive diagnostic tests in those with digestive symptoms. The possibility of fecal–oral transmission emphasizes the importance of proper hygienic precautions, especially for healthcare workers and close household contacts. Strict precautions must be observed when handling the stools of patients and sewage from hospitals should also be properly disinfected. Similarly, the fecal microbiota transplant procedure in current circumstances may face various challenges in ensuring that stool samples from donors are not infected with SARS-CoV-2 virus.

Between 2% to 11% of patients with COVID-19 have liver co-morbidities and 16% to 53% cases report abnormal levels of alanine aminotransferase (ALT) (19.8% in non-severe disease *versus* 28.1% in severe disease) and aspartate aminotransferase (AST) (18.2% in non-severe disease *versus* 39.4% in severe disease)[4,9,10]. Elevation of AST is even higher (62%) in patients in the intensive care unit (ICU) suggesting that the liver injury is more prevalent in severe cases[11]. However, most patients only have mild elevation, which resolves with clinical improvement. Putative mechanisms for liver affection are: direct viral cytopathic effect (which is unlikely as hepatocytes do not express ACE2), drug-induced hepatotoxicity, systemic inflammation induced by cytokine storm or pneumonia-associated hypoxia[10].

Nearly 17% of patients experience pancreatic injury defined by any abnormality in amylase or lipase with majority developing acute hyperglycemia, though none exhibit clinical symptoms of severe pancreatitis[12].

The risk of severe disease is not increased among patients with COVID-19 with existing gastrointestinal or liver-related co-morbidities compared with patients without such co-morbidities. SECURE-Cirrhosis and COVIDHEP registries have been initiated internationally to collect data on SERS COV-2 infected patients with

COVID-19 current update
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Total cases (World)	**8.59 million**
Total Death (World)	**4,56,650**
Total cases (India)	**3,81,093**
Total Death (India)	**12,605**

cirrhosis, and liver transplantation candidates, respectively. Similarly open access SECURE-IBD database is accumulating data on inflammatory bowel disease (IBD) from 32 countries.

The gastrointestinal endoscopy departments face significant risk for transmissions of SARS-CoV-2 during endoscopy[13]. Possible routes of transmission include respiratory droplets, aerosols generated during endoscopy, and contact with contaminated surroundings, body fluids, and fecal material. It has been strongly advised to reschedule nonurgent endoscopic procedures and perform only in emergency cases[14]. All personnel involved with endoscopy should wear appropriate personal protective equipment (PPE) (gloves, mask, eye shield/goggles, face shields and gown).

There are currently no approved treatment recommendations for COVID-19 or its gastrointestinal manifestations except for symptomatic and supportive care. Patients of IBD receiving immunosuppressive therapy or autoimmune liver disease pose special challenges. Patients on >20 mg prednisolone, Infliximab, adalimumab, or ustekinumab should discontinue/ delay therapy or consider alternatives if positive for SARS-CoV-2[15].

Conclusion

Overall, gastrointestinal symptoms are reported in 15% of patients with COVID-19 and liver injury in 19% (ref 4). With increased recognition of gastrointestinal symptoms in SARS-CoV-2 infection, it is important to keep its risks in perspective and stay up to date on current research and recommendations in order to provide our patients with the most accurate advice.

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