The atypical presentation of COVID-19 as gastrointestinal disease:

key points for primary care

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INTRODUCTION

Since the SARS-CoV2 outbreak in Wuhan, China, in late 2019, the world has been ravaged by a roaring pandemic. Unlike coronavirus SARS-CoV that caused the severe acute respiratory syndrome (SARS) outbreak in 2002, SARS-CoV2 has proven to be more contagious and difficult to control. A key challenge is that the disease presentation can be very variable: patients in the early phase of infection may be asymptomatic, have subclinical symptoms, or atypical symptoms of COVID-19. This, compounded with the lack of easily accessible diagnostic tests, makes it challenging to diagnose COVID-19 in the community.

The most common symptoms of patients with COVID-19 are fever (72–88%) and cough (68–83%).[1,2] A sore throat may be present in 14–61% of patients, and dyspnoea is usually seen in severe cases and is less frequent (11–19%).[1,2] Other non-specific symptoms such as myalgia, headaches, rhinorrhoea, anosmia, ageusia, nasal congestion, conjunctivitis, and haemoptysis have been reported but are comparatively infrequent. However, of significant concern is the atypical presentation of gastrointestinal (GI) symptoms.

Early experience in Wuhan illustrated how a cluster outbreak occurred from a single index patient being mistakenly admitted to surgical services for abdominal pain. This resulted in nosocomial spread to 10 healthcare workers and four other patients, all presenting with abdominal symptoms of diarrhoea, nausea, and loss of appetite.[3]

COVID-19 AND LOWER GASTROINTESTINAL SYMPTOMS

Non-bloody diarrhoea as a main presenting complaint has been observed in approximately 20% of all patients with COVID-19.[4,5] In a study of 204 hospitalised patients with COVID-19 in China, 18.6% (38/204) had respiratory symptoms with a combination of abdominal pain, diarrhoea, and vomiting.[5] Importantly, these GI symptoms including loss of appetite were commonly observed to precede the onset of respiratory symptoms and often delayed presentation to hospitals.

It was observed that 2.9% (6/204) of patients had GI symptoms without any respiratory symptoms but most had a fever. COVID-19 may also cause bloody diarrhoea but such cases are rare. Therefore, COVID-19 may be mistaken as gastroenteritis with or without febrile illness, inflammatory bowel disease (IBD), treatment-related diarrhoea, irritable bowel syndrome, or malignancy, especially in the early phase of the infection.

The exact mechanism of how diarrhoea is caused in COVID-19 is unknown but it is likely multifactorial. SARS-CoV2 binds to the angiotensin-converting enzyme 2 receptor (ACE2) to invade target cells, but ACE2 is also an important regulator of intestinal inflammation. Therefore, some hypothesise that this is the mechanism of intestinal injury by which diarrhoea is caused; however, approximately 70–80% of all patients with COVID-19 have normal stool consistency.[2,5] Oro-faecal transmission of SARS-CoV2 remains debatable. Unfortunately, testing for the virus in stool samples of patients with diarrhoea is not a useful diagnostic solution. Only half of all patients with COVID-19 have viral ribonucleic acid (RNA) in their stool detectable by real-time polymerase chain reaction (RT-PCR), and, based on current understanding of the disease, faecal viral RNA positivity does not correlate with GI symptoms.[4]

A respiratory swab taken from the nasopharynx or throat is the most sensitive and accessible method of diagnosis at present, although rapid antigen detection kits are being developed. Routine diagnostic endoscopy for diarrhoea would be delayed at present because of the risk of aerosolisation and nosocomial transmission to uninfected patients or

hospital staff. However, in the case of bloody diarrhoea when malignancy or acute colitis is suspected, current guidance by the British Society of Gastroenterology (BSG) allows for referrals to be discussed on a case-by-case basis.

Nonetheless, in the event where an atypical presentation of COVID-19 is suspected, national guidance on testing and isolation practices should be followed.

COVID-19 AND THE LIVER

Data from China and Singapore suggest that abnormal liver function tests (LFTs) can be present in 43–51% of all patients with COVID-19. The most common pattern of derangement is a hepatic transaminitis.[4] Cholestatic LFTs are rare even though ACE2 is highly expressed in bile ducts. It is not known if LFT derangement secondary to SARS-CoV2 infection can exist in isolation without any COVID-19 symptoms or whether it exists as part of a yet undefined or complex syndrome.

Current studies are limited because they are cross-sectional and cannot control for pre-existing liver disease. Other confounding factors include the presence of myositis, concomitant use of antimicrobials, ischaemic hepatitis, and sepsis-related liver dysfunction. There is a paucity of data from liver biopsies; however, to date, acute liver failure from COVID-19 has not been reported. In mild COVID-19 infection, LFTs tend to resolve with time and the stoppage of antiviral therapy.[4]

However, in endemic areas, when faced with an acute presentation of non-specific or prodromal symptoms coupled with deranged LFTs, a mild rise in alanine aminotransferase or aspartate transaminase ($<2 \times$ ULN) with lymphopenia and leucopenia can be telling of COVID-19. However, other causes of acute LFT derangement such as viral hepatitis, autoimmune hepatitis, drug-induced liver injury, and metabolic liver disease should also be excluded. In any situation of uncertainty, hepatology advice should be sought.

Although the BSG and British Association for the Study of the Liver (BASL) have recommended social isolation measures for high-risk liver patients and the reduction of outpatient clinic activity, hospitals are exploring alternative means of maintaining patient care and providing advice such as virtual or telephone clinics. BSG and BASL guidance are also constantly updated, so it is important that all physicians looking after at-risk or complex GI patients review these guidelines regularly.

COVID-19 AND UPPER GASTROINTESTINAL SYMPTOMS

SARS-CoV2 has been found in gastric and duodenal biopsies, although no known associated pathology is known. Loss of appetite has been reported in as many as 39.7% of all patients with COVID-19; nausea, vomiting, and abdominal pain are less frequent (1.0–4.0%).[3,5] However, these symptoms are not specific to the upper GI tract and the cause may be multifactorial.

CONCLUSION

In summary, an awareness that COVID-19 can mimic GI disease will help in its early detection and the prevention of spread while better screening tools are being developed. More needs to be understood as to why GI manifestations occur in only some patients.

The emergence of SARS-CoV2 has significantly affected clinical practices within the field of gastroenterology, and physicians should regularly keep abreast with updates to current guidelines during this uncertain and dynamic phase of the outbreak.

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