Mesenteric ischemia in COVID-19 patients: A review of current literature

Asad Ali Kerawala, Bhagwan Das, Ahda Solangi

ORCID number: Asad Ali Kerawala 0000-0002-8732-5750; Bhagwan Das 0000-0003-1830-1613; Ahda Solangi 0000-0003-3292-2264.

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Abstract

BACKGROUND
Coronavirus disease 2019 (COVID-19) virus has affected all the systems of the body, defying all impressions of it being a respiratory virus only.

AIM
To see the association of mesenteric ischemia with COVID-19.

METHODS
After initial screening and filtering of the titles on PubMed and Google Scholar, 124 articles were selected. Articles were read in full, and the references were skimmed for relevance. Twenty-six articles (case reports and case series) were found to eligible for inclusion. References of these 26 articles were checked for any additional cases. Two more publications were found, and a total of 28 articles (22 case reports and 6 case series) have been included for review in this manuscript.

RESULTS
A total of 41 cases of acute mesenteric ischemia in COVID-19 patients have been reported in the literature since the outbreak of this pandemic. Most of them include patients with comorbidities.

CONCLUSION
In conclusion, based on this literature review and precise published knowledge regarding acute mesenteric ischemia in patients with COVID-19, it is essential to understand its relevance in all patients with gastrointestinal symptoms. The threshold for the diagnostic investigations should also be kept low for the timely diagnosis and management of this disorder.
Key Words: Mesenteric ischemia; COVID-19; SARS-CoV-2; Influenza; Severe acute respiratory syndrome; Acute abdomen

Core Tip: This review suggests that coronavirus disease 2019 (COVID-19) acute mesenteric ischemia in patients, especially those with preexisting comorbidities. Any patient suffering from COVID-19 and having gastrointestinal symptoms should be observed with a high index of suspicion for acute mesenteric ischemia. After diagnosis, surgical treatment should be offered, which is the only hope for survival for these patients.

INTRODUCTION

In December of 2019, the world witnessed the emergence of a novel virus that eventually gripped the whole world creating chaos and carnage. Wuhan, China was the first city to witness the fatal effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1], which causes coronavirus disease 2019 (COVID-19). By March 11, 2020, the World Health Organization had already declared it a pandemic[2].

As of December 15, 2020, over 70 million cases and 1.6 million deaths have been reported globally[3], and the numbers keep rising. The United States, being the most affected, has more than 15468098 cases reported[3] and more than 293000 deaths. Adding to the misery is the fact that no single treatment has shown clinical benefit, and the drugs that have shown any benefit are still a point of major debate. A vaccine has recently been developed and approved for use by the Food and Drug Administration. However, the long-term effects and efficacy are still unknown. All the evidence about this unprecedented disease and its treatment is based on anecdotal events and opinions as there are no any previous experiences.

COVID-19 was initially thought to affect only the respiratory system, but other systemic manifestations were reported. There is a plethora of evidence suggesting a hypercoagulable state and prothrombotic tendency in patients suffering from COVID-19[4,5]. Acute mesenteric ischemia (AMI) itself is a fatal disease. In combination with COVID-19, there is a high mortality. This manuscript is aimed at reviewing the medical literature for cases of AMI in COVID-19 patients.

MATERIALS AND METHODS

Methods
A rapid systemic review of the medical literature was done for the eligible cases.

Literature search strategy
An extensive search was carried out using PubMed and Google Scholar using the keywords “mesenteric ischemia,” “small bowel gangrene” and “COVID-19.” Only the cases reported after January 2020 were searched. No language restriction was applied. A manual search of the bibliographies of the included cases was done to detect additional eligible cases.

Eligibility criteria
The results from the mentioned search engines were filtered and screened by the title and the abstract. The articles of potential significance to our study were then assessed by full text. The inclusion criteria used were: (1) Case report/case series; (2) Patients
with clinical suspicion, radiological or biochemical diagnosis of COVID-19; (3) Reported after January 2020; and (4) Underwent laparotomy or abdominal computed tomography to confirm the diagnosis of mesenteric ischemia.

**Data retrieval**
The data extraction was performed by Kerawala AA and Das B. For all cases reported, the following parameters were recorded: country, date of publication, age and gender of the patient, comorbidities, clinical course, any complications, treatment given and eventual outcome.

**Findings**
The results of the extraction have been prepared and presented in a table form (Table 1) as well as narrated in text.

**RESULTS**
The initial search revealed 316 and 161 publications on PubMed and Google Scholar, respectively. After initial screening and filtering of the titles, 124 articles were selected. The full article was read, and the references were skimmed for relevance. Twenty-six articles (case reports and case series) were found to be eligible for inclusion. References of these 26 articles were checked for any additional cases. Two more publications were found. A total of 28 articles (22 case reports and 6 case series) have been included for review in this manuscript (Figure 1).

**Data synthesis**
A total of 41 cases of AMI in COVID-19 patients have been reported in the literature since the outbreak of this pandemic. The first case reported was on April 30 from Cremona, Italy by Beccara *et al.* [6]. The rapid review and fast track publication by journals in the COVID-19 era led to overlap of many cases published online at the same time in the preproof version and the final manuscript published later. After thorough research, this was the first reported case in our opinion.

**Age and gender of patients:**
Out of these 41 cases, 27 (67%) were males, 10 (24%) were females, and demographics were not available for 4 (9%) patients. The median age of presentation was 59 years. The median age for males was 58.0 and for females was 61.5. The youngest case presented was of a 9-year-old girl from Algeria by Khesrani *et al.* [7]. The oldest patients were 82-years-old and were from India and the United States.

**Country of origin**
France reported the most cases (n = 10) followed by Italy (n = 6), Turkey (n = 6), the United States (n = 5) and Spain (n = 4). Two cases were reported from Mexico. One case was reported from Iran, the United Kingdom, India, Algeria, Kuwait, Singapore, Brazil and the Netherlands each. The biggest case series was reported from Turkey (n = 5) [8]. Interestingly, no case has been reported from China, the country where the virus first emerged.

**Mode of diagnosis**
Reverse transcriptase polymerase chain reaction from the nasopharyngeal swab was the most frequently used test (n = 31) to confirm the diagnosis of COVID-19. Nine patients were diagnosed with COVID-19 on the presence of classical clinical symptoms and bilateral ground glass appearance on computed tomography chest, despite having a negative PCR from the nasal swab. One patient was diagnosed with COVID-19 after RNA detection by in situ hybridization from the necrotic bowel found on laparotomy.

**Comorbidities**
Thirteen patients had no comorbidities or past medical history. Hypertension was the most common comorbidity present in 10 patients followed by obesity (n = 7) and diabetes mellitus (n = 6). The details have been presented in Table 1.

**Treatment modality**
Thirty-three patients underwent an exploratory laparotomy and resection of the gangrenous bowel segment after confirming the diagnosis of AMI. Four patients were
Table 1 Reported cases of mesenteric ischemia in coronavirus 2019 patients

| Ref. | Date of publication | Country          | No. of patients | Gender | Age  | Comorbidities      | Modality used for diagnosis | Intervention | Outcome |
|------|---------------------|------------------|----------------|--------|------|--------------------|----------------------------|--------------|---------|
| A Beccara et al[6] | April 30, 2020     | Italy            | 1              | M      | 52   | None               | PCR                        | Surgery      | Alive   |
| Ignat et al[22]   | May 4, 2020        | France           | 3              | F      | 28   | None               | PCR                        | Surgery      | Alive   |
|                  |                     |                  |                | M      | 56   | DM, HTN            | PCR                        | Surgery      | Alive   |
|                  |                     |                  |                | M      | 67   | DM, cardiac transplant | PCR                        | Expired      |         |
| Helms et al[23]  | May 4, 2020        | France           | 1              | NA     | NA   | NA                 | PCR                        | NA           | NA      |
| Farina et al[24] | May, 2020          | Italy            | 1              | M      | 70   | None               | PCR                        | Surgery      | Alive   |
| Azouz et al[25]  | May, 2020          | France           | 1              | NA     | NA   | NA                 | PCR                        | NA           |         |
| Vuillaume et al[26] | May 12, 2020    | United Kingdom   | 1              | M      | 75   | None               | PCR                        | Surgery      | NA      |
| Fraissiet et al[27] | June 2, 2020    | France           | 3              | NA     | NA   | NA                 | CT chest                   | NA           |         |
| Bianco et al[28] | June 6, 2020       | Italy            | 1              | F      | 59   | None               | PCR, CT chest              | Surgery      | Expired |
| Do Carmo Filho et al[29] | June, 2020  | Brazil           | 1              | M      | 33   | Obesity            | PCR                        | Thrombolytics | Alive   |
| Mitchell et al[30] | June, 2020        | United States    | 1              | M      | 69   | HTN                | PCR                        | Surgery      | NA      |
| English et al[31] | July 12, 2020      | United Kingdom   | 1              | M      | 40   | Obesity            | CT chest, clinical         | Multiple surgeries | Alive   |
| Cheung et al[32] | July 29, 2020      | United States    | 1              | M      | 55   | None               | PCR                        | Surgery      | Alive   |
| de Barry et al[33] | July, 2020        | France           | 1              | F      | 79   | None               | CT chest                   | Surgery, embolectomy | Expired |
| Kraft et al[34]  | August, 2020       | Spain, Italy     | 4              | F      | 62   | Obesity            | PCR                        | Surgery      | Alive   |
|                  |                     |                  |                | F      | 57   | COPD               | PCR                        | Expired      |         |
|                  |                     |                  |                | M      | 62   | Obesity            | PCR                        | Expired      |         |
|                  |                     |                  |                | F      | 69   | None               | PCR                        | Surgery      | Alive   |
| Besutti et al[35] | August, 2020       | Italy            | 1              | M      | 72   | CKD, IHD, HTN      | PCR                        | Resection, splenectomy | NA      |
| Sehat et al[36]  | September, 2020    | Iran             | 1              | M      | 77   | HTN                | PCR                        | Surgery      | Expired |
| De Roquetaillade et al[37] | September, 2020 | France           | 1              | M      | 65   | HTN                | PCR                        | Surgery      | Expired |
| Singh et al[38]  | September, 2020    | United States    | 1              | F      | 82   | HTN, DM            | CT chest, clinical         | Surgery      | Alive   |
| Lari et al[39]   | September, 2020    | Kuwait           | 1              | M      | 38   | None               | PCR                        | Surgery, ECMO | NA      |
| Thulva SK et al[8] | September, 2020  | Singapore        | 1              | M      | 29   | None               | PCR                        | Enoxaparin   | Alive   |
| Levolger et al[40] | September, 2020   | Netherlands      | 1              | M      | 58   | Obesity, OSA       | PCR                        | Surgery      | NA      |
| Akkoomkanyan et al[41] | September, 2020 | Turkey           | 5              | M      | 62   | DM, HTN            | PCR                        | Surgery      | Alive   |
| Rodriguez-Nakamura et al | October, 2020 | Mexico           | 2              | M      | 45   | Vitiligo           | PCR                        | Surgery      | Alive   |
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| Study          | Month     | Country   | Gender | Age  | Risk Factors                      | Diagnostic Tests                          | Treatment | Outcome       |
|----------------|-----------|-----------|--------|------|-----------------------------------|-------------------------------------------|-----------|---------------|
| Bhayana et al. | October   | United States | M      | 47   | NA                                | PCR                                       | Surgery   | NA            |
| Norsa et al.   | October   | Italy     | M      | 62   | Obesity, HTN, cirrhosis, hepatitis B, DM | RNA ISH assay on necrotic bowel             | Surgery   | Expired       |
| Khesrani et al.| October   | Algeria   | F      | 09   | Idiopathic medullar aplasia        | PCR                                       | Surgery   | Expired       |
| Ucpinar et al. | October   | Turkey    | F      | 82   | Atrial fibrillation, HTN, CKD      | PCR                                       | Enoxaparin| Expired       |
| Karna et al.   | October   | India     | F      | 61   | DM, HTN                           | PCR                                       | Surgery   | Expired       |

M: Male; PCR: Polymerase chain reaction; F: Female; DM: Diabetes mellitus; NA: Not available; CT: Computed tomography; CKD: Chronic kidney disease; IHD: Ischemic heart disease; OSA: Obstructive sleep apnea; COPD: Chronic obstructive pulmonary disease; ISH: In situ hybridization; ECMO: Extra corporeal membrane oxygenation; HTN: Hypertension.

Figure 1 PRISMA flowsheet.

124 articles for full text reading → 98 articles excluded after full text reading as not relevant to our objectives → 26 articles (case reports and case series) → 2 articles from relevant references added → Total 477 articles on PubMed and Google scholar → 353 articles irrelevant on the basis of title.

Mortality

Fourteen (34%) patients were reported dead out of the published group. No information was available for 11 (27%) patients, and 16 (39%) patients were reported alive at the time of the publication of their case. However, most of the cases were published immediately after the presentation of the patient to the hospital and the cases reported a follow-up of 2-3 d only. Some cases reported the patient was still in the intensive care unit postoperatively. Hence, it is difficult to ascertain the true mortality rate of AMI in COVID-19 patients unless a complete follow-up of the patient is reported by the authors.

Of those expired, 12 (86%) had undergone laparotomy and resection of the necrotic bowel and still succumbed to the disease. Two (14%) were treated conservatively with low molecular weight heparin. Of those reported alive, 14 (87%) patients underwent a laparotomy and resection of bowel. Two (13%) patients were treated conservatively. However, this was not statistically significant (95% confidence interval (CI): 0.1043 to 7.0432, P = 0.88) treated conservatively with enoxaparin likely because the general condition of patient was not fit for anesthesia. One of these had a thrombus in the portal vein and superior mesenteric vein and was treated successfully without surgical intervention by thrombolytics[8]. No treatment details were available for 4 patients.
Out of the 14 expired, 10 (72%) had comorbid conditions and 4 (28%) did not have any. However statistical significance could not be ascertained without complete data on all the patients published. Again, no statistical significance was found (95%CI: 0.3633 to 5.9522, P = 0.58).

**DISCUSSION**

COVID-19 was initially thought to be a respiratory virus causing pneumonia and other respiratory complications only. However, throughout the pandemic the world has witnessed it affecting almost every single body organ along with coagulopathy and AMI[9-11].

AMI is a rare life-threatening abdominal emergency with a reported mortality around 60% to 80%[12]. It requires a prompt diagnosis and imaging in highly suspicious patients. Because of the evolving nature of SARS-CoV-2, the exact pathogenesis leading to thrombosis and AMI after this infection remains ambiguous. There are different hypotheses behind this deadly manifestation. Taking them all into account, it appears that patients with COVID-19 fulfill the classic Virchow’s triad required for thrombosis.

Endothelial injury is the first element of Virchow’s triad and has been reported to be caused by direct invasion by SARS-CoV-2 via its binding with angiotensin-converting enzyme 2 receptors expressed on vascular endothelium[13,14]. In addition to this, immune complex-mediated vasculitis has also been postulated as one of the mechanisms behind vascular damage in COVID-19[15]. Both of these in combination can cause endothelial dysfunction and predispose a patient to thrombus formation.

Hypercoagulopathy, the second element of Virchow’s triad, is also seen in this infection secondary to the number of pathological changes in the vascular prothrombotic factors, like elevated fibrinogen and factor VIII, hyperviscosity, neutrophil extracellular traps and circulating prothrombotic microparticles[16-18]. This hypercoagulability state has been documented via thromboelastography in COVID-19 patients admitted in intensive care units[17].

Stasis, the final element of Virchow’s triad, can be expected in all critically ill patients because of isolation in a confined area, prolonged bed rest, immobilization in the intensive care unit and possible limitations to physiotherapy.

In addition to the above mechanisms, it has also been postulated that COVID-19 can cause direct damage to the bowel via binding with angiotensin-converting enzyme 2 receptors expressed on enterocytes[19,20]. Lastly, hemodynamic instability in severe COVID-19 infection leading to hypotension and shock can be a possible mechanism of nonocclusive mesenteric ischemia seen in these patients.

Due to the poor prognosis of both severe COVID-19 infection and AMI, AMI should be suspected in all patients who present with nausea, vomiting, diarrhea, abdominal pain and abdominal distension or develop these symptoms during hospitalization. As inflammatory and coagulation profiles can be deranged in COVID-19 infection itself, blood tests will not aid in the diagnosis of AMI in these patients. Computed tomography angiography is the modality of choice for the diagnosis of AMI along with clinical correlation.

Preliminary data from a few reports have pointed towards in situ thrombosis of small vasculature as evidence for bowel necrosis with thrombosis in the submucosal arterioles[21], but new cases are being reported with involvement and complete occlusion of large vessels as well. Because of the paucity of data, exact incidence, pathogenesis and outcome of these patients is not known.

From available data, we have concluded that it is more commonly reported in males, and hypertension is found to be the most common comorbidity along with other metabolic syndromes entities, like obesity and dysglycemia. Most patients (80%) underwent laparotomy and bowel resection. A few patients were managed conservatively with anticoagulation and thrombolitics, mostly due to being unfit for surgery. True outcome data of AMI in COVID-19 patients is also difficult to report from this review as complete follow-up and the current status of many patients has not been reported. This is a limitation of our study.

**CONCLUSION**

In conclusion, based on this literature review of published reports regarding AMI in patients with COVID-19, it is essential to understand the relevance of AMI in all
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patients with gastrointestinal symptoms. The threshold for the diagnostic investigations should also be kept low for the timely diagnosis and management of this disorder.

ARTICLE HIGHLIGHTS

Research background
Presently, coronavirus disease 2019 (COVID-19) has been causing mortalities mainly due to respiratory complications. It is essential to ascertain whether other organs are affected as well.

Research motivation
To understand the effects of COVID-19 on multiple systems, it is essential to review the published literature and their outcomes.

Research objectives
We aim to ascertain whether mesenteric ischemia is also caused by COVID-19 and leads to added mortality.

Research methods
Detailed review of the published literature (case reports and series) was done. Data was analyzed and entered in table format. Frequencies were calculated.

Research results
Severe acute respiratory syndrome coronavirus 2 may cause acute mesenteric ischemia.

Research conclusions
Acute mesenteric ischemia should be considered in COVID-19 patients presenting with abdominal symptoms.

Research perspectives
Prospective trials are required.

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