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ABOUT COVER

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SYSTEMATIC REVIEWS

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

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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.

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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.

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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	Surgery	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	CT chest	Conservative	Expired
Azouz *et al*[25]	May, 2020	France	1	M	56	None	PCR	Surgery	Alive
Vulliamy *et al* [26]	May 12, 2020	United Kingdom	1	M	75	None	CT chest/ clinical	Surgery	NA
Fraisséet *al*[27]	June 2, 2020	France	3	NA	NA	NA	CT chest	NA	NA
Bianco *et al*[28]	June 6, 2020	Italy	1	M	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	Surgery	Expired
				M	62	Obesity	PCR	Surgery	Expired
				F	69	None	PCR	Surgery	Alive
Besutti *et al*[35]	August, 2020	Italy	1	M	72	CKD, IHD, HTN	PCR	Resection, splenectomy	NA
Sehhat *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
Thuluva 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
Aktokmakyan *et al*[41]	September, 2020	Turkey	5	M	62	DM, HTN	PCR	Surgery	Alive
				M	NA	COPD	PCR	Surgery	Alive
				M	NA	COPD	PCR	Surgery	Alive
				M	NA	None	PCR	Surgery	Expired
				M	NA	None	PCR	Surgery	Alive
Rodriguez-Nakamura *et al*	October, 2020	Mexico	2	M	45	Vitiligo	PCR	Surgery	Alive

[42]									
				F	42	Obesity	CT Chest	Surgery	Expired
Bhayana *et al*[21]	October, 2020	United States	2	M	47	NA	PCR	Surgery	NA
				M	52	NA	PCR	Surgery	NA
Norsa *et al*[43]	October, 2020	Italy	1	M	62	Obesity, HTN, cirrhosis, hepatitis B, DM	RNA ISH assay on necrotic bowel	Surgery	Expired
Khesrani *et al*[7]	October, 2020	Algeria	1	F	09	Idiopathic medullar aplasia	PCR	Surgery	Expired
Ucpinar *et al*[44]	October, 2020	Turkey	1	F	82	Atrial fibrillation, HTN, CKD	PCR	Enoxaparin	Expired
Karna *et al*[45]	October, 2020	India	1	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.

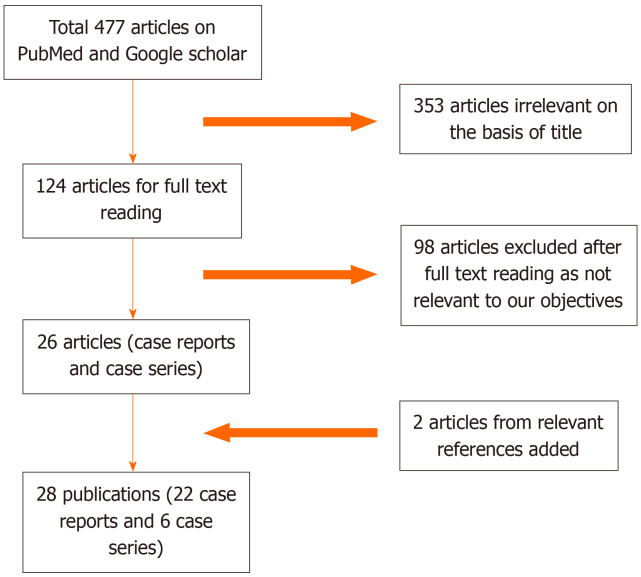

Figure 1 PRISMA flowsheet.

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.

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, $P = 0.88$)

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 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 fulfil 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.

Hypercoagulpopoathy, 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 thrombolytics, 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

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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