



Small Bowel Ischemia due to COVID-19

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Abstract

Background: The present study was planned to describe the characteristics, hospital course and outcome of COVID-19 positive patients who presented with features of mesenteric ischemia and subsequent bowel gangrene.

Material and Methods: The data of all COVID positive patients admitted to emergency surgery department from March 2021 to June 2021 was analyzed.

Results: The total of 99 patients, majority (32.3%) had skin and soft tissue infection followed by secondary peritonitis due to perforation of hollow viscus (17.1%). Five patients were identified to have gangrene of small bowel. On exploration, 4 patients had 'patchy gangrene' of small bowel where in 1 patient had gangrene of complete segment of small bowel been gangrenous.

Conclusion: Hyper coagulation state due to SARS-CoV-2 infection can lead to small bowel ischemia and, 'patchy gangrene' is characteristic of COVID-19 ischemia of small bowel.

Keywords: Small bowel ischemia; Coagulopathy; Reverse transcriptase polymerase chain reaction

Introduction

Ever since the outbreak of Coronavirus disease -19 (COVID-19) in Wuhan, China in December 2019, it has rapidly spread across the entire world and has become one of the most common cause of respiratory illness [1]. World Health Organization (WHO) declared it as a global pandemic on March 11th, 2020 and so far, more than 152 million people are affected by this novel virus worldwide, with mortality of over 3.19 million [2]. India alone reports 3,48,89,132 cases, second only to United States. Severe Acute Respiratory Syndrome Coronavirus- 2 (SARS-CoV-2) responsible for COVID-19, primarily affect respiratory system. But studies have found that it can also lead to coagulopathy as well as gastrointestinal complications, liver dysfunction, cardiac and neurological abnormalities [3,4].

Coagulopathy occurs secondary to hypoxia, immobilization, severe inflammation, and endothelial dysfunction and is seen in approximately 20% to 50% patients with COVID-19 [5,6]. This coagulopathy leads to more of thrombotic rather than hemorrhagic events and both and arterial and venous thromboembolism events have been reported in the literature. Thrombotic events associated with COVID-19 include deep vein thrombosis, pulmonary embolism, ischemic stroke, myocardial infarction, and peripheral arterial thrombosis. However, data is lacking regarding gastrointestinal manifestation of COVID-19 associated thrombotic phenomenon [6].

During second wave of COVID-19 pandemic in India (March to June 2021) we observed several COVID-19 positive patients with abdominal symptoms, who on exploration had gangrenous small bowel. Such phenomenon was rarely seen before. The present study was therefore, planned to describe the characteristics, hospital course and outcome of COVID-19 positive patients who presented with features of mesenteric ischemia and subsequent bowel gangrene.

Material and Methods

The data of all COVID-19 positive patients who were admitted to emergency surgery department in our hospital from March 2021 to June 2021 was analyzed. Only patient's with small bowel gangrene were further evaluated for demographics, presenting complaints, laboratory and radiological investigations, surgical and postoperative course, and outcome. The patients who were Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) negative but were suspicious of COVID-19 infection in view of Chest X-ray (CXR) changes and raised COVID-19 markers were subjected to Computed Tomography (CT) of chest. COVID-19 Reporting and Data system

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(CO-RADS) score of equal to or more than 4 in such patients was considered as positive for COVID-19.

Results

A total of 97 RT-PCR positive patients and 2 patients with CORADS=5 (RTPCR Negative) were recognized on initial search. Majority of these patients (32.3%) had skin and soft tissue infection followed by secondary peritonitis due to perforation of hollow viscous (17.1%). Overall mortality among these patients was 34.3% (Table 1).

On further evaluation of operative notes of patients who underwent exploratory laparotomy for abdominal complaints, 5 patients were identified to have gangrene of small bowel. Table 2 and 3 summarizes demographic, clinical and laboratory characteristics, imaging findings, operative procedure, and outcome of these patients.

All patients were elderly males (Age \geq 60 years) and presented after 3 to 12 days after onset of abdominal symptoms. At time of admission, biochemical parameters were suggestive of Multi Organ Dysfunction Syndrome (MODS). Apart from respiratory compromise and coagulopathy, all had deranged liver and renal function tests. After initial resuscitation, RTPCR for COVID-19 was done and 4 patients were found to be RT-PCR positive. Diagnosis of COVID-19 in 1 patient, who was RT-PCR negative, was established on basis of CT chest. X-ray abdomen in all the patients had features suggestive of small bowel obstruction, with pneumoperitoneum in 1 patient. CT abdomen was done in only 1 patient who showed pneumoperitoneum along with pneumatosis intestinalis.

Based on clinical features, two patients who had features of generalized peritonitis were operated within 24 h of admission whereas the other three, who were suspected to have small bowel obstruction, were operated after failure of initial conservative trial (nil per oral, nasogastric tube aspiration and intravenous fluids) for 48 h to 72 h. On exploration, four patients had patchy gangrene of small bowel where in one patient complete segment of small bowel was gangrenous (Figure 1). Resection of gangrenous segment with exteriorization of proximal and distal segment was done in all patients due to extensive dilation and edema of viable bowel. In view of progressive gangrene 2 patients required re-exploration.

Table 1: Spectrum of COVID positive patients and their management and outcome.

Etiology	Patients (n)	Management (n) (Surgical/Non-Surgical)	Mortality (n)
Small bowel gangrene	5	05/00	4
Skin and soft tissue infection*	32	29#/03	7
Hollow viscus perforation **	17	14/03	4
Trauma***	10	06/04	3
Intestinal obstruction	8	04/04	1
Post - operative with stoma	8	03/05	1
Malignancy	8	01/07	1
Gall stone disease	4	00/04	0
Acute Appendicitis	3	02/01	0
Peripheral Vascular disease	2	02/00	1
Liver abscess	1	00/01	0
Faecal fistula (referred from outside)	1	01/01	0

*Include diabetic foot infection; **Include gall bladder and appendicular perforation ***Include head injury and hollow viscous perforation secondary to trauma; # Include surgical debridement



Figure 1: Small bowel with 'patchy' gangrenous changes.

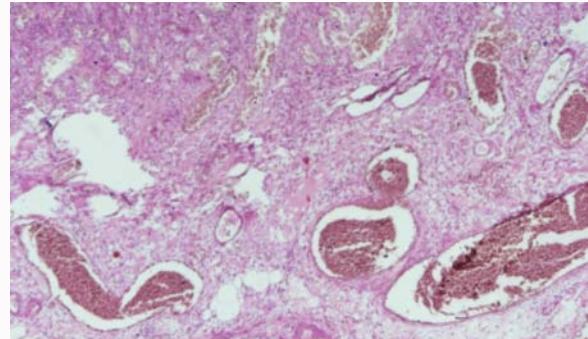


Figure 2: Histopathology of resected bowel showing thrombus in micro vessels.

Post-operatively, patients were managed in intensive care unit and were started broad spectrum antibiotics, vasopressor and intravenous steroids and low molecular weight heparin according to institute protocol for management of COVID-19 positive patients. Four patients required ventilatory support in postoperative period and all of them died due to MODS.

Discussion

The whole world is battling the impact of COVID-19 for the last more than 2 years. Originally considered to be a disease of the respiratory tract, COVID-19 is now recognized as a systemic disease. Direct cytotoxic effect or inflammatory response to SARS-CoV-2 infection can affect any organ of the body [4].

In initial studies it was reported that Angiotensin Converting Enzyme-2 (ACE2) receptors on the surface of epithelial cells of respiratory tract facilitates the entry of virus into the cells. The innate inflammatory response because of virus invasion and direct effect of virus on ACE2 receptors, leads to various changes in the body resulting in mild to severe illness. Patients with severe disease are found to have elevated levels of D-dimer, prolonged PT (prothrombin time), thrombocytopenia, and/or low fibrinogen levels, suggesting activation of coagulation system in response to viral invasion [7]. "Cytokine release syndrome" because of SARS-CoV-2 infection leads to increased levels of pro-coagulant markers like Interleukin -6 (IL-6), Tumor Necrosis Factor (TNF) and IL-1 which promotes coagulation, and this is further enhanced by increased availability of angiotensin II (Ang-II) due to direct binding of virus to ACE2 receptors. Ang-

Table 2: Characteristics (clinical and laboratory parameters) of patients with gangrenous bowel at the time of presentation.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	60	70	75	68	62
Gender (Male/Female)	Male	Male	Male	Male	Male
Duration of abdominal symptoms (Days)	4	6	12	3	5
Systolic blood pressure (mm of Hg)	90	60	120	110	80
Respiratory rate (per minute)	30	36	29	26	38
CXR severity score	5	6	5	7	8
CT Chest	Not done	Not done	CO-RAD 4	Not done	CO-RAD 5
Co-morbidity	DM	DM, HT	None	CAD, HT	COPD
RT-PCR	Positive	Positive	Positive	Positive	Negative
Hemoglobin (g/dl)	11.3	13.6	14.6	12.6	11.9
Total leukocyte count ($\times 10^9/L$)	1.6	2.1	3.4	2.2	1.4
Platelet Count ($\times 10^9/L$)	90	120	130	70	85
Prothrombin time	16	18	19	18	19
Neutrophil to Lymphocyte Ratio (NLR)	2.8	3.3	1.7	4	3.2
Blood Urea (mg/dl)	230	272	70	316	102
Serum Creatinine (mg/dl)	3.3	3.9	1	4.5	1.9
Total bilirubin (mg/dl)	3.5	3.1	1.2	5.5	2.8
D-dimer (mgFEU/ml)	6	9.4	4.5	11	14.3
Blood lactate	5.6	8.4	3.8	7.9	7.4
C reactive protein (CRP)(mg/L)	156	190	58	161	214
IL 6 (pg/ml)	215.4	114.9	21.1	528.5	2017.5
Procalcitonin (pg/ml)	29.2	31.2	18.4	28.7	65.5

Table 3: Operative details and outcome of patients with gangrenous bowel.

Operative details	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Intraoperative findings	Gangrenous small bowel (approximately 100 cm in length)	Gangrenous patches involving approximately 50 cm of small bowel	Gangrenous patches involving approximately 70 cm of small bowel with perforation	Gangrenous patches involving approximately 60 cm small bowel	Gangrenous patches involving approximately 150 cm of small bowel
Re-exploration	Yes	Yes	No	No	No
ICU Stay (Days)	5	6	14	3	6
Outcome	Died	Died	Discharged	Died	Died

II activates the Renin-Angiotensin System (RAS) which in turn is responsible for platelet adhesion and aggregation [7,8].

The evidence is now emerging that these ACE-2 receptors are expressed by the cells of other organs like heart, kidney and Gastrointestinal (GI) tract. Therefore, virus can directly invade into these cells also and can incite similar inflammatory response leading to varied symptoms related to these organs [9].

GI tract is involved in 2% to 20% of patients with COVID-19 and can present with symptoms, like abdominal pain, diarrhea, nausea, or vomiting and 3% to 10% of these patients may have isolated GI symptoms in the absence of respiratory symptoms [3,10]. Severe disease due to GI involvement is rarely seen and there is only few isolated case reports in the literature related to GI bleed or bowel ischemia [11]. Preliminary reports suggested that bowel ischemia with resultant gangrene occur due to small vessel thrombosis (arterioles and venules) subsequent to hypercoagulable state, which can be further aggravated by hypoperfusion [12,13]. But there are few other case reports also which found thrombus in major mesenteric vessels suggesting thromboembolism a cause of bowel ischemia [14].

However, histopathological examination of resected bowel in previous studies and in present study revealed bowel necrosis with submucosal small arteriole thrombosis, thus predicting role of thrombosis rather than emboli as an initiating event to bowel ischemia (Figure 2).

In this series of 99 COVID-19 patients, who presented to surgery emergency department, we came across 5 patients who had small bowel ischemia. On exploration except for 1 patient, all had gangrenous patches with areas of healthy tissue in between, involving significant portion of small bowel. As hypercoagulable state mainly affects micro-vessels of GI tract, we believe this 'patchy gangrene' is characteristic of COVID-19. This is in contrast to acute mesenteric ischemia due to thrombosis of major vessels, where large segment of bowel is usually gangrenous. It was also observed that presence of patchy necrosis may obscure signs of peritonitis that are evident in ischemia due to large vessel involvement, thus making it difficult to diagnose this condition clinically. In the present series though, Contrast Enhanced CT (CECT) of the abdomen was done in only one patient but available evidence suggests that it is quite useful in establishing the diagnosis. The presence of pneumatosis intestinalis, decreased enhancement of intestinal wall and gas in portal venous

system are found to be suggestive of bowel ischemia [12]. Surgical exploration and resection of gangrenous segment with exteriorization of proximal and distal segment or end to end anastomosis depending on the condition of bowel, is the only cure for this condition.

Small bowel gangrene due to COVID-19 is found to be associated with high mortality. In present series, only 1 patient out of 5 survived. Others died because of multi organ failure due of COVID-19 infection or due to sepsis associated with gangrenous bowel. Early intervention is, therefore, must to have a favorable outcome. On retrospective analysis, it was observed that apart from abdominal symptoms all patients had elevated levels of D-dimer, prolonged Prothrombin Time and thrombocytopenia, which are considered as markers of severe disease. Based on these findings, it is recommended that derangement of coagulation profile in presence of abdominal symptoms should raise the suspicion of underlying small bowel ischemia. Such patients should be subjected to early intervention, as clinical signs of ischemia can be non-reliable.

Conclusion

Hypercoagulation state due to SARS-CoV-2 infection not only involves respiratory tract but can also lead to other severe manifestations like small bowel ischemia. High index of suspicion is required to diagnose this condition. Deranged coagulation profile in presence of abdominal symptoms should prompt surgeon for an early intervention to have a better outcome.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dr. Keshav Jindal and Dr. Monika Gureh. The first draft of the manuscript was written by Dr. Sanjay Gupta and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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