



Case series

COVID-19 infection and large intestinal perforation: A case series

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ABSTRACT

Introduction: COVID-19 is a viral illness characterized primarily by respiratory symptoms. However, patients with COVID-19 infection may also present with gastrointestinal symptoms. Subsequent complications can be associated with high morbidity and mortality.

Methods: This is a retrospective observational study of three COVID-19 positive patients who developed large intestinal perforations and an analysis of their clinical characteristics, diagnosis, surgical treatment and outcomes. Three patients aged 45, 51 and 82 years old presented to our institution between November 2021 and March 2022 and were diagnosed with COVID-19 pneumonia requiring admission to the intensive care unit (ICU). All three patients received steroids and underwent surgery during their admission. None of our patients had prior history of bowel perforation or risks factors justifying their presentation.

Presentation of cases: Our first patient was found to have an ascending colon perforation and underwent right colon resection and end ileostomy. Our second patient was found to have a cecal perforation and underwent ileocecectomy with end ileostomy and mucus fistula creation. Our third patient was found to have a large cecal perforation and underwent right hemicolectomy and was left in discontinuity during the index operation.

Discussion: GI perforation is a less common but serious extra-pulmonary complication of COVID-19. The cases in the present study involve ascending colon perforations in the setting of active COVID-19 infection that occurred within two to five weeks after initial COVID-19 diagnosis. Given viral replication in GI cells, the local inflammatory effect of viral infection in the GI may play a role in bowel perforation. Providers should additionally be aware of the risk of perforation with steroids and immunomodulators. Immunosuppressive effects of these therapies may mask the classical signs of abdominal sepsis and lead to possible missed diagnoses.

Conclusion: Gastrointestinal perforation is a rare but serious complication of COVID-19 infection. A high degree of clinical suspicion is necessary for timely diagnosis and management.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic is an unprecedented global health crisis. To date, there have been over 305 million confirmed cases and more than 5.4 million deaths worldwide [1]. In 2020, COVID-19 was the third leading cause of death in the US [2]. While COVID-19 infection is primarily a respiratory illness, patients often experience extrapulmonary symptoms. Gastrointestinal (GI) symptoms including diarrhea, nausea, vomiting, and abdominal pain are frequently reported [3–6]. Additionally, bowel wall abnormalities were observed in 31 % of computed tomography (CT) scans performed in COVID-19 patients [7]. Spontaneous bowel perforation is a less common but potentially fatal GI manifestation that has been reported in the

literature [7–10]. We report a retrospective single-institution study of three non-consecutive cases of right colon perforation in the setting of active COVID-19 pneumonia and surgical management. This research has been reported in line with the PROCESS 2020 Guidelines criteria [11].

2. Methods

In this retrospective case series, we report three cases of large intestinal perforation in patients with COVID-19 pneumonia who presented to our urban academic institution in Washington, DC from November 6th, 2021 to March 26th, 2022. The patients were confirmed COVID-19 positive via polymerase chain reaction (PCR). All three

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patients were admitted to the ICU, received steroids during admission, and underwent surgical management of their bowel perforations.

We included patients who had no history of bowel perforation or significant risk factors justifying such presentations prior to their COVID-19 diagnoses. The patients were aged 45, 51 and 82 years old on presentation. Characteristics of our patients such as comorbidities and inpatient interventions including pharmacological and surgical therapy are reported in Table 1. All surgeries were performed open under general anesthesia by general surgeons with greater than 10 years of experience in the field. Any patient with a prior history of gastrointestinal disease or high risk of intestinal perforation was not included in this study. Research registry number was obtained for this series [UIN: researchregistry8202].

3. Results

3.1. Case 1

An 82-year-old female with past medical history of obesity, hypertension, heart failure, chronic kidney disease and recent transient ischemic attack (TIA) presented with altered mental status and lethargy. Labs were significant for a leukocytosis to 20.4 k/μL and acute kidney injury (AKI). She tested positive for SARS-CoV-2. Computed tomography (CT) scan of the head showed no acute intracranial abnormalities. However, CT chest was significant for multifocal pneumonia with bilateral pleural effusions.

The patient was admitted to the intensive care unit (ICU) and was initiated on treatment for COVID-19 pneumonia with IV Cefepime, Decadron and Remdesivir. The patient exhibited a markedly elevated leukocytosis reaching a peak white blood cell count of 52.2 k/μL on hospital day 6. CT showed improved multifocal opacities in the lung, increased bilateral pleural effusions, and scattered free fluid in the abdomen and pelvis.

On hospital day 10, the patient had an acute drop in hemoglobin concerning for bleeding. She subsequently developed large volume diarrhea. CT was significant for air and fluid-filled colon with wall thickening concerning for colitis. Testing for *Clostridium difficile* was negative. A routine chest x-ray on hospital day 14 revealed new large volume pneumoperitoneum under her right hemidiaphragm. Repeat CT showed large pneumoperitoneum with a tract of air in the right upper quadrant and abdominal free fluid (Fig. 1).

The patient was taken emergently to the operating room and underwent exploratory laparotomy, right hemicolectomy and end ileostomy formation. She was noted to have a perforation in the ascending colon approximately 10 cm from the junction of the terminal ileum and



Fig. 1. CT shows large pneumoperitoneum with a tract of air in right upper quadrant and small amounts of free fluid.

the cecum with feculent spillage. She was extubated on post-operative day (POD) 3, started on tube feeds and eventually stepped down to the floors. Surgical pathology showed colon with mucosal erosion, underlying transmural acute inflammation, serositis and fat necrosis compatible with perforation.

3.2. Case 2

A 45-year-old male with history of obesity, hypertension, renal cell carcinoma, and end-stage renal disease status post kidney transplant who presented to the emergency department with one week history of fevers, chills, fatigue, and diarrhea. On presentation, the patient was febrile, tachycardic and hypotensive. His presentation was concerning for septic shock and he was resuscitated and started on vasopressors. He tested positive for SARS-CoV-2. Initial chest radiograph showed bilateral patchy opacities consistent with COVID-19 pneumonia. Additionally, stool antigen test was positive for *C. difficile*.

He was admitted to the ICU for septic shock and hypoxemic respiratory failure where he received stress dose steroids as well as oral vancomycin and IV metronidazole for *C. difficile* colitis. His hypoxemia worsened and he received convalescent plasma for COVID-19 infection. On hospital day 12, the patient was weaned off pressors and high flow nasal cannula (HFNC), tapered to home dose steroids, and stepped down from the ICU to a floor unit. At this time, his diarrhea and oxygen requirements were improving. However, the patient was noted to have a rising leukocytosis.

Table 1

Summarizing patient history, steroid administration, laboratory values prior to diagnosis of intestinal perforation, surgical management, surgical pathology, outcomes and follow-up.

Variables	Patient 1	Patient 2	Patient 3
Age	82	45	51
Gender	Female	Male	Male
Co-morbidities	Obesity, HTN, CHF, CKD, TIA	Obesity, HTN, RCC, ESRD	Obesity, HTN
Vaccination status	Unvaccinated	Vaccinated	Unvaccinated
Steroids	Yes	Yes	Yes
WBC count (k/μL)	52.2	23.7	32.3
Lactate (mmol/L)	1.5	0.9	3.2
Index surgery	Exploratory laparotomy, right colon resection and end ileostomy	Exploratory laparotomy, ileocecectomy, end ileostomy and mucus fistula creation	Exploratory laparotomy, right hemicolectomy and ABThera wound vac placement
Location of GI perforation	Right colon	Right colon	Cecum
Surgical pathology	Mucosal erosion, transmural acute inflammation, serositis and necrosis	Mucosal ulceration, transmural acute inflammation and serositis	Mucosal hemorrhagic necrosis, transmural acute inflammation and serositis
Outcome	Death	Discharged	Death
Follow-up	Not applicable	28 months	Not applicable

CHF = Congestive Heart Failure, CKD = Chronic Kidney Disease, ESRD = End-Stage Renal Disease, HTN = Hypertension, RCC = Renal Cell Carcinoma, TIA = Transient Ischemic Attack, WBC = White Blood Cell.

On hospital day 13, the patient had a hypoxemic episode with ambulation. Chest radiograph showed worsened bilateral lung opacities and free air under the diaphragm. CT of the abdomen and pelvis confirmed moderate to large pneumoperitoneum with inflammatory changes to the cecum (Fig. 2). The patient was taken to the operating room for exploratory laparotomy. A right colon perforation was noted with feculent spillage and fibrinous exudate. An ileocecectomy was performed followed by creation of an end ileostomy and mucous fistula. On POD 1, the patient was extubated and stepped down from the ICU to a floor unit.

His post-operative course was significant for intra-abdominal abscesses requiring drainage. Surgical pathology was negative for *H. pylori*, metaplasia, dysplasia, or malignancy. The patient received his last day of antibiotic treatment on POD 22 and was discharged home on POD 25 in stable condition.

3.3. Case 3

A 51-year-old male with PMH of obesity and hypertension was diagnosed with COVID-19 pneumonia at an outside institution. He completed a course of steroids and was discharged on home oxygen. He was readmitted for shortness of breath, altered mental status, and increasing oxygen requirements. CTA chest demonstrated extensive bilateral multifocal atypical pneumonia. He was treated with a five-day course of ceftriaxone and azithromycin and restarted on IV dexamethasone. He was admitted to the ICU for worsening respiratory status requiring intubation, septic shock requiring pressors and an AKI.

The patient was transferred to our tertiary care center for continuous renal replacement therapy. He was treated for acute respiratory distress syndrome and IV steroids were continued. After three weeks at our center, he developed hemochezia and hemorrhagic shock requiring blood transfusions and multiple pressors. CTA of the chest, abdomen and pelvis demonstrated bilateral pulmonary emboli as well as cecal perforation with free air (Fig. 3). He was taken for emergent surgery. An approximately 10 cm perforation of the cecum with associated necrosis



Fig. 2. On CT, moderate to large pneumoperitoneum appears to originate from the cecum, which has significant inflammatory change, adjacent free fluid and adjacent foci of gas.



Fig. 3. CT reveals scattered foci of pneumoperitoneum and gas along the anterior wall of the cecum suspicious for cecal ischemia and perforation.

was noted (Fig. 4). A right hemicolectomy was performed and the abdomen was left open with bowel in discontinuity. Surgical pathology showed hemorrhagic necrosis of the colon segment and underlying transmural acute inflammation with no dysplasia or malignancy.

Post-operatively, there was an improvement in peak pressures and pressor requirements. The patient underwent re-exploration and washout after 48 h. He returned two days later for distal ileum resection with end ileostomy creation, gastrojejunostomy tube placement and abdominal closure. He tolerated enteral feeds with return of bowel function on POD 5. However, his hospital course was further complicated by multi-drug resistant bacteremia, and he ultimately succumbed to this infection after being placed on comfort care.

4. Discussion

GI symptoms are the most frequently reported extra-pulmonary

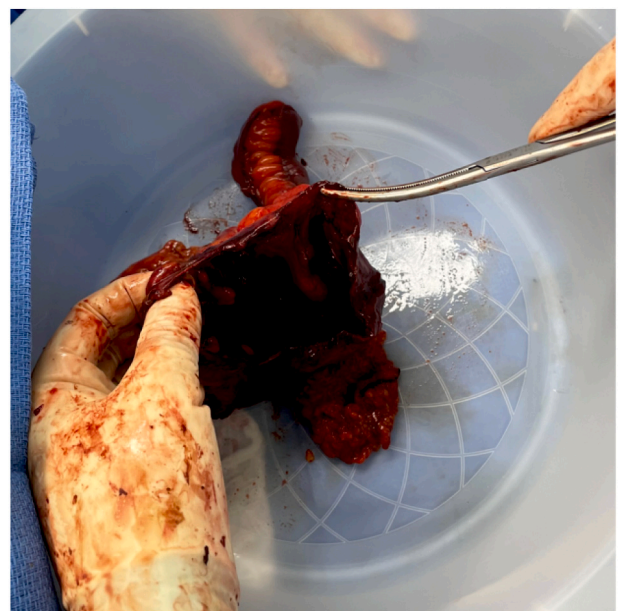


Fig. 4. Surgical specimen reveals an obliterated, necrotic cecum with large perforation.

manifestations of COVID-19 [12,13]. These symptoms are often associated with severe COVID-19 illness and may arise with or without concurrent respiratory symptoms. Recent studies estimate higher overall GI involvement in patients with COVID-19 than previously recognized [14]. Given the global burden of COVID-19, GI perforation is considered a rare but serious complication. On literature review, a total of 25 GI perforations were reported through April 2021 [15]. Timing of perforation in relation to hospitalization varied with some occurring before the onset of respiratory symptoms and others occurring during hospitalization for COVID pneumonia. Notably, 11 cases of GI perforation occurred after ICU admission, similar to the cases in this study. Of those reported, all but three patients were treated surgically. The cases in the present study involve ascending colon perforations in the setting of active COVID-19 infection.

GI manifestations of infection with SARS-CoV-2 may be a result of several mechanisms. The virus enters host cells via the angiotensin-converting enzyme 2 (ACE-2) receptor. This receptor is expressed on the surface of lung alveolar epithelium, enterocytes of the small bowel, and vascular endothelium suggesting that these areas are particularly susceptible to infection [16]. After replicating within GI cells, the virus is excreted into the lumen of the GI tract [17]. SARS-CoV-2 viral RNA has been detected in fecal samples with viral loads peaking 2–3 weeks after symptom onset [18]. In our series, large bowel perforations occurred within two to five weeks after initial COVID-19 diagnosis. Surgical pathology of the resected colon specimens revealed no cryptitis, dysplasia or malignancy to suggest pre-existing risk factors for perforation. The local inflammatory effect of viral infection in the GI tract may have several impacts. GI perforation in this setting may be a result of microvascular thrombosis and ischemia, pseudo-obstruction, non-occlusive mesenteric ischemia, or neuronal damage resulting in altered colonic motility [8,10].

A concern among the reported cases of bowel perforation is the impact of the use of tocilizumab and high dose steroids, which are therapies indicated in severely ill COVID-19 patients. Lower intestinal perforation is a well-known complication of tocilizumab in rheumatoid arthritis [19,20]. This risk has been shown to increase with concurrent steroid treatment but the pathophysiology is unknown [19,20]. Of the 25 previous GI perforations reported in COVID-19 patients, treatment with steroids was reported in 10 cases. Of these, 6 were treated with tocilizumab concurrently. In this case series, all three patients received steroid therapy during hospitalization. Providers should be aware of the risk of perforation with steroids and immunomodulators. Additionally, immunosuppressive effects of therapy may mask the classical signs of abdominal sepsis and lead to possible missed diagnoses.

5. Conclusion

In summary, we report three cases of colonic perforations in patients with COVID-19 pneumonia. Although intestinal perforation is a rare complication of COVID-19 infection, it should be included in the differential diagnosis in patients who develop gastrointestinal symptoms and/or sepsis. A high degree of clinical suspicion is necessary for timely diagnosis, management and prevention of further complications. Further retrospective studies are necessary to establish etiology and recommendations for prevention and treatment.

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Ethical approval

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013).

Consent

Written informed consent was obtained from the patients for publication of this case series. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Monika Masanam: Conceptualization, Methodology, Investigation, Data Curation, Writing, Review & Editing, Project Administration. Sarah Cheney: Investigation, Data Curation, Writing, Review & Editing. Whitney Sutton: Investigation, Data Curation, Writing. John Keyloun: Writing, Review & Editing. Shima Fitzgibbons: Conceptualization, Methodology, Supervision, Project Administration, Writing, Review & Editing

Registration of research studies

1. Name of the registry: Research Registry
2. Unique identifying number or registration ID: researchregistry8202
3. Hyperlink to registration: <https://www.researchregistry.com/browse-the-registry/#home/registrationdetails/62f98b7af115f8002172b437/>.

Guarantor

Shima Fitzgibbons, MD.

Declaration of competing interest

The authors report no declarations of interest.

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