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COVID 19 and the risk of gastro-intestinal perforation: A case series and literature review

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ABSTRACT

Background: COVID19 is a viral disease with pneumonia as its most common presentation. Many presentations and complications have been reported, but gastro-intestinal perforation has not received much attention.

Methods: three cases from our hospital are presented, and the current literature was reviewed.

Results, cases: All three patients were admitted to the ICU with respiratory failure due to COVID19 pneumonia and intubated. Our first patient was treated with steroids, and subsequently diagnosed with rectal perforation on day 34 of his hospital admission. The second patient was treated with steroids and tocilizumab, and diagnosed with colonic perforation 1 day after neostigmine administration, on day 14 of his hospital admission. Our third patient was treated with steroids and tocilizumab, and diagnosed colonic perforation 4 days after neostigmine administration, on day 14 of his hospital admission.

Results, literature: 25 more cases were found in current literature, both upper GI and lower GI perforations, either as a presenting symptom or during the course of hospitalization. These were often associated with treatment with steroids, interleukin 6 inhibitors, or both.

Conclusions: Gastro-intestinal perforation is a rare but dangerous complication of COVID19. Treatment with tocilizumab and steroids may both increase the risk of this complication, and hamper diagnosis.

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1. Cases

We present three cases of colorectal perforation in patients with COVID 19, two of which previously treated with steroids and tocilizumab.

A 65 year old male with a history of percutaneous coronary revascularization was admitted to our ICU with COVID 19 pneumonia, and intubated on day 5, for respiratory failure. From day 16 on he had recurring fevers despite multiple antibiotics. Prednisolone was started on day 22: 120 mg daily for five days, then tapered over 19 days. On day 28 rectal bleeding was noticed, a lower rectum perforation with perirectal abscess was diagnosed on day 34. A diverting colostomy was performed. He was discharged from the ICU on day 49. His ICU treatment was complicated by an ischemic stroke, hampering his recovery. He was discharged to a rehabilitation facility on day 90. Last follow-up was on

day 370, patient has returned home but has not yet fully recovered. Imaging and endoscopy suggest the defect has fully healed, restoration of intestinal continuity is under consideration.

A 58 year old male with a history of mild obesity was transferred to our ICU with COVID 19 pneumonia. He was intubated and received dexamethasone 6 mg/day continued for 19 days, starting one day previous to intubation. He also received tocilizumab (8 mg/kg, on day of intubation). On day 13, neostigmine was administered (2 mg/h for 24 h) because of increasing abdominal distension and failure to pass stool, with rapid result. On day 14 a CT scan of the chest and abdomen (performed to rule out pulmonary embolus) showed a distended caecum and marked intraperitoneal air, without free fluid or signs of focal inflammation. Because of a lack of sepsis, and a high risk of worsening his pulmonary status with surgery, we initially opted for a diagnostic peritoneal lavage, which was negative. 36 h later he developed signs of sepsis, and a repeat CT showed increased free air, and focal inflammation of the caecal region. Exploratory laparotomy showed perforation of focal necrosis/ischemia of the caecum. Iliocaecectomy was performed, and an end-ileostomy created. He was extubated 10 days

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Table 1
literature review of cases.

	Author /Case	Period ^a / Age	Time of perforation	IL antagonist	Steroids	Location	Specifics	Treatment	outcome
Lower GI perforation	Nahas (6)	1 / 92	Before COVID diagnosis	none	None	Transverse colon	5 days postoperative after colostomy for obstructive rectal cancer	Resection	Deceased
	Giuffre / A (4)	1 / 87	Before hospital admission	none	None	Lower rectum		conservative	Deceased
	Santana (7)	2 / 43	Before hospital admission	none	none	Terminal ileum	Medical history of crohn's disease	Resection	Recovered
	Costanzi (3)	2 / 64	Before hospital admission	none	none	Sigmoid	Diverticulitis	Resection	Recovered
	Verma / B (8)	2 / 24	After hospital admission	none	none	Coecum	5 days post caesarean section	Primary closure and defunctioning ileostomy	Recovered
	Neto (2)	1 / 80	Before hospital admission	none	none	Sigmoid		Resection	Deceased
	Bulte / A	1 / 65	after ICU admission	none	Prednisolone tapering dose	Mid rectum		Defunctioning colostomy	Recovered
	Baiu (1)	2 / 66	Before hospital admission	none	Dexamethasone	Coecum	After clostridium difficile infection	Resection	Recovered
	Verma / A (8)	2 / 60	Before hospital admission	none	'steroids'	Upper rectum		Primary closure and defunctioning colostomy	Recovered
	Bulte / B	3 / 58	after ICU admission	Tocilizumab	Dexamethasone 6 mg/kg daily	Coecum	Neostigmine use, very distended ascending colon	Resection	Discharged to rehabilitation facility
	Bulte / C	3 / 57	after ICU admission	Tocilizumab	Dexamethasone 6 mg/kg daily	Transverse colon	Neostigmine use	Resection	Recovered
	Rojo (18)	1 / 54	After ICU admission	Tocilizumab	Methylprednisolone	Ascending colon		Resection	Deceased
	Bruce-Hickman (20)	1 / 43	After ICU admission	Tocilizumab	Hydrocortson (3 days, shock protocol)	Coecum	After embolization of bleeding ulcer	Resection	NR ^b
	Guardiola (16)	2 / 66	After ICU admission	Tocilizumab	Methylprednisolone 100 mg (previously)	Ascending colon		Resection	NR ^b
	Montorfano (17)	1 / 54	After ICU admission	Tocilizumab	Dexamethasone, 2 mg (single dosage)	Coecum		Resection	Discharge to long-term care facility
	De Nardi (10)	1 / 53	After ICU discharge	Anakinra	None	Coecum	Very distended ascending colon	Resection and anastomosis	Discharged from hospital
	Schwab (19)	2 / 34	After ICU admission	IL-6 receptor agonist	none	Coecum		Resection	NR ^b
	Giuffre / B (5)	1 / 68	After hospital admission	NR ^b	NR ^b	Rectosigmoid		Conservative	NR ^b
Giuffre / C (5)	1 / 84	After hospital admission	NR ^b	NR ^b	Rectum		Conservative	Deceased	
Bhayana (9)	1 / NR ^b	Not reported	NR ^b	NR ^b	Ileum		NR ^b	NR ^b	
Upper GI perforation	Verma / C (8)	2 / 21	Before hospital admission	none	none	Stomach		Primary closure and grahams patch	Recovered
	Kangas (13)	1 / 74	After ICU admission	none	none	Presumed upper GI	Refused sugery	Conservative	Deceased
	Lee (15)	1 / 73	After hospital admission	none	none	Duodenum	After embolization of a bleeding ulcer	Primary closure, pyloric exclusion and gastrojejunostomy	Deceased
	He (12)	1 / 71	After hospital admission	none	none	Duodenum		Primary closure	Recovered
	Marcucci (14)	1 / 71	After ICU admission	none	none	Stomach	After bag-mask ventilation, large defect	Surgically, not specified	Deceased
	Galvez (11)	1 / 59	After hospital admission	none	Methylprednisolone 1 mg/kg/day	Gastrojejunostal anastomosis	8 years After RYGB	Graham patch repair	Recovered

(continued on next page)

Table 1 (continued)

	Author /Case	Period ^a / Age	Time of perforation	IL antagonist	Steroids	Location	Specifics	Treatment	outcome
	Agnes (21)	2 / 72	After hospital admission	Tocilizumab, Sarilumab	None	Duodenum	After embolization of a bleeding ulcer	Primary closure	Deceased
NR ^b	Toniati (22)	1 / NR ^b	After hospital admission	Tocilizumab	NR ^b	NR ^b		Not reported	Alive at ten days

^a Period 1: first half of 2020. Period 2: second half of 2020. Period 3: 2021.

^b NR: not reported.

postoperatively. A perisplenic abscess was drained percutaneously on day 14, he was discharged from the ICU 19 days postoperatively. Histology showed circumscribed ulceration with transmural abscess formation and necrosis.

A 57 year old male with a history of mild obesity was admitted with a COVID 19 pneumonia, and started on dexamethasone, 6 mg/day, continued for 17 days. On day 2 he was admitted to our ICU with impending respiratory failure, and intubated on day 3. He received tocilizumab (8 mg/kg, on day 3). Because of increasing abdominal distension and failure to pass stool on day 10, a CT scan was performed to rule out mechanical obstruction. This showed a distended colon and distal small intestine, a small amount of ascites, no free air. Neostigmine was started (2.5 mg/h for 24 h) with rapid result. On day 14 an abdominal CT was performed because of progressive abdominal distension without signs of sepsis, and found a moderately distended caecum, massive intraperitoneal air. Exploratory laparotomy showed a distended proximal colon, fixed to the ventral abdominal wall, with perforation of the distal transverse colon. An extended right hemicolectomy was performed, and an end-ileostomy created. He was extubated two days postoperatively and discharged from the ICU on postoperative day 4. He was discharged to a rehabilitation facility on postoperative day 19. Histology of the colon showed abrupt transitions from normal tissue to non-specific ischemic necrotic changes with a regenerative response. Elective stoma reversal was performed 189 days post initial admission.

2. Discussion

Table 1 shows a number of intestinal perforations in COVID patients have been reported, but considering the worldwide incidence of COVID, this appears to be a rare complication. A review of the literature to date (April 2021) showed a total of 25 gastro-intestinal perforations. We found 18 perforations in patients not treated with IL-6 inhibitors. Of these 18 cases, 12 were lower GI perforations (1–10), 6 were perforated gastroduodenal ulcers (8,11–14). One of these after embolization of a bleeding ulcer (15). Seven cases occurred after treatment with tocilizumab or sarilumab: an additional 5 cases of lower GI perforation (16–19), including one subclinical perforation after embolization of a bleeding ulcer (20). One additional upper GI perforation was found, also after embolization of a bleeding ulcer (21). One was only reported as 'gastro-intestinal perforation' (22). When looking at the use of steroids: treatment with steroids was reported in 10 cases. Of these 10 cases, six received concurrent treatment with tocilizumab. Including the present report, 13 patients recovered, 9 patients died, outcome was not reported for 6 patients. While the reporting might very well be biased, prognosis of gastro-intestinal perforation in COVID patients is not abysmal.

Intestinal perforation is a well-known complication of tocilizumab in rheumatoid arthritis, affecting approximately 3/1000 patient years (23,24). Risk is increased with concurrent steroid treatment (24). The pathophysiology of perforation is unknown.

Based on this data in rheumatoid arthritis, when tocilizumab was first used in COVID 19, it was hypothesized that perforation might complicate treatment (25). Our cases and the review of the literature

indicate a risk of perforation in COVID19 patients not treated with tocilizumab as well. Whether this association is enhanced by tocilizumab treatment remains unsure.

Perforation complicating neostigmine treatment for Ogilvie's syndrome has also been reported a few times (26–29). Though there was no evidence of mechanical obstruction in our patients, the use of neostigmine could also have been contributory.

Tocilizumab is increasingly used in the treatment of severe COVID 19, and this is likely to increase further since the publication of the results of the REMAP-CAP trial (401 patients on IL-6 inhibitors, 402 controls) and the RECOVERY trial (2022 patients on tocilizumab, 2094 controls) (30,31). Both studies report only low numbers of serious adverse events, neither study reports any perforations. It is generally combined with steroids, compounding perforation risk. Whenever possible, other risk factors (e.g. the use of neostigmine, colonic instrumentation) should be avoided. While the benefits of tocilizumab may well justify its use in severe COVID19 patients, health care providers should be mindful of potential intestinal perforation in patients with COVID, perhaps even more so when they are also treated with tocilizumab. Specifically: classic signs of abdominal sepsis might not be apparent due to the immunosuppressive nature of tocilizumab and concurrent steroid use. Tocilizumab is a powerful suppressor of CRP, but not leukocytosis (32). This can make it extra challenging to differentiate between gastro-intestinal perforation, and pneumoperitoneum from other causes, e.g. alveolar barotrauma (the Macklin effect) (33,34). Similar to perforation in non-COVID patients, rapid diagnosis and surgical treatment is of the utmost importance, and can lead to favorable outcomes.

Declarations

Ethics approval for case report is not required under Dutch law.

Consent for publication

All included patients consented to the use of their data.

Availability of data and materials

Not applicable.

Competing interests

None.

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None.

Authors' contributions

JPB: Conceptualization, data curation, formal analysis, writing - original draft and review & editing. NP, MB, BI and AGS data curation,

writing - review & editing. HvdH took Ceconceptualization, formal analysis, writing - review & editing.

Take home message

Gastro-intestinal perforation is a rare but dangerous complication of COVID19. Treatment with tocilizumab and steroids possibly increase the risk of this complication, and hamper its diagnosis.

Tweet

Gastro-intestinal perforation: a rare but dangerous complication of COVID19. Tocilizumab and steroids possibly increase risk, hamper diagnosis.

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