CASE REPORT

Unpredictability of SARS-CoV-2: Pneumoperitoneum a rare complication

Hassan Ur Rehman, Ayesha Javed, Hawwa Ahmad Akhunzada, Nabeel Tariq, Nida Abbassi

Abstract

COVID-19 is a viral disease caused by a novel coronavirus that ignited the ongoing pandemic in December 2019. The infected patients may be asymptomatic, have fever and myalgias, develop mild pulmonary symptoms or go into overt respiratory failure. There is also a significant number of patients with gastrointestinal and thromboembolic disease presentation and complications. Since respiratory features predominate, physicians might miss other systemic manifestations. Here, we present the case of a 62-year-old male who was admitted with COVID-19 pneumonia and later went into septic shock and then developed acute abdomen caused by small gut perforation.

Keywords: COVID-19, Tocilizumab, Gastrointestinal perforation (GI perforation), Deep vein thrombosis.

DOI: https://doi.org/10.47391/JPMA.4000

Introduction

Corona Virus Disease 2019 (COVID-19) is caused by the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Infected people can either be symptomless carriers or may have multi-organ dysfunction encompassing pulmonary, cardiac, renal, and haematological systems, and sepsis.[1] Fever is the most common symptom at the start of the illness followed by cough, myalgias, expectoration, haemoptysis, and diarrhoea. Patients then may develop dyspnoea, acute respiratory distress syndrome (ARDS), and multi-organ involvement.[2]

COVID-19 increases the risk of thromboembolic events.[3] There is aberration of coagulation functions with D-dimers, Fibrin Degradation Products and fibrinogen being raised.[4] These may manifest as venous and arterial thrombosis with arterial thrombosis encompassing stroke, acute limb ischaemia, myocardial infarction, and acute mesenteric ischaemia (AMI).[1]

Since the focus of COVID-19 literature has been on respiratory symptoms, gastrointestinal manifestations may be missed. AMI may be the presenting feature in patients of COVID-19,[5] concurrently with other ischaemic events[6-7 or develop as a later complication.[2] Clinically patients having AMI may exhibit abdominal pain, nausea, vomiting, abdominal distention, and sepsis.[8] Imaging including CT of the abdomen with angiography is the main modality for establishing the diagnosis.[8] However, since COVID-19 affects both macro and microvasculature, imaging may not always establish thrombosis in cases of bowel ischaemia.[9]

In a letter to the author, Jhens Vikse suggested that the feared complication of intestinal perforation by Tocilizumab should be borne in mind while treating cytokine release syndrome caused by COVID-19.[10]

Our report discusses the case of a 62-year-old male who was treated for COVID-19 pneumonia, his oxygen demand improved and then he went into septic shock and developed abdominal pain that was discovered to have been caused by small gut perforation.

Case Report

A 62-year-old known type 2 diabetic, resident of Islamabad presented in the A&E Department of Pakistan Institute of Medical Sciences, Islamabad on April 8, 2021, with complaints of fever and generalised body aches for 10 days and shortness of breath for three days. Upon examination, he was hypoxic with saturation of 88% at room air, tachypnoeic with respiratory rate of 30 breaths/minute. The rest of the systemic examination was

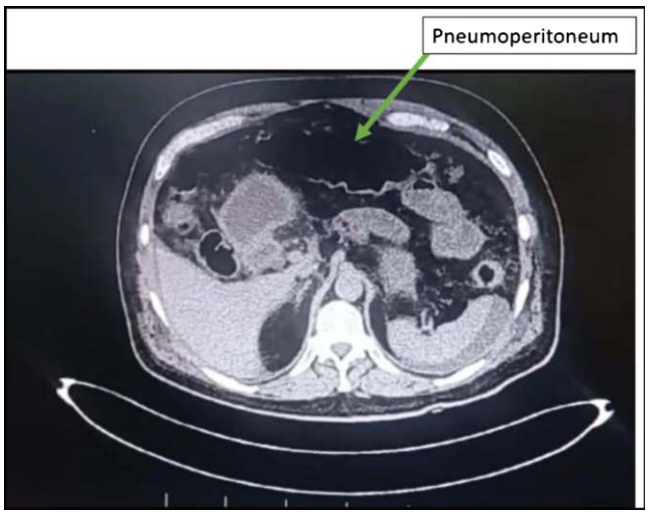

Figure: CT Scan Abdomen with Contrast showing pneumoperitoneum.

Department of Internal Medicine, Pakistan Institute of Medical University, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, Pakistan.
Correspondence: Hassan Ur Rehman. Email: drrehman.hassan@gmail.com

Table-1: Baseline and follow-up blood panel of the patient.

Haematology	08-04-21	11-04-21	14-4-21	15-4-21	19-4-21	23-4-21	26-04-21	28-04-21	29-04-21	Reference Range
WBC	5900/uL	8141/uL	20920/uL	17180/uL	23110/uL	15550/uL	19180/uL	10430/uL	14610/uL	4000 - 10500 /uL
Neutrophil %	76%	82%	93.8%	89%	89%	84.5%	89.0%	91%	89%	54 - 62 %
Lymphocyte %	17%	11%	3.9%	6.5%	5.2%	7.9%	4.5%	5%	3%	25 - 33 %
Haemoglobin	14.1 g/dL	14 g/dL	15.5 g/dL	14.3 g/dL	13.8 g/dL	14.4 g/dL	14.7 g/dL	12.8 g/dL	13.6 g/dL	13.5-18 g/dL
Platelets	145000 /uL	198000/uL	266000 /uL	242000 /uL	204000/uL	161000/uL	132000/uL	50000/uL	58000/uL	150k - 400k /uL
Serum Profile Liver Functions Tests, Renal Function Tests, Electrolytes, Cardiac Enzymes & Pancreatic Enzymes										
Urea	34 mg/dl	48.3 mg/dl	61 mg/dl	53 mg/dl		51 mg/dl	45 mg/dl	74.9 mg/dl	58.92 mg/dl	16.6 - 48.5 mg/dl
Creatinine	1.14 mg/dl	1.27 mg/dl	1.44 mg/dl	1.07 mg/dl		1.03 mg/dl	0.95 mg/dl	2.0 mg/dl	1.24 mg/dl	0.72-1.25 m mg/dl
Total Bilirubin	0.6 mg/dL	0.4 mg/dL	0.8 mg/dL	0.5 mg/dL		0.5 mg/dL	0.6 mg/dL			0.3-1.2 mg/dL
Alanine transaminase	22 U/L	28 U/L	24 U/L	19 U/L		38 U/L	33 U/L			4-42 U/L
Alkaline phosphatase	84 U/L	78 U/L	104 U/L	95 U/L		94 U/L	81 U/L			40-130 U/L
Sodium	142 mEq/L	139 mEq/L	136 mEq/L	135 mEq/L	137mEq/L	135 mEq/L	133 mEq/L	134 mEq/L	136 mEq/L	136-146 mEq/L
Potassium	4 mEq/L	4.4 mEq/L	4.1 mEq/L	4.1 mEq/L	4.2 mEq/L	4.4 mEq/L	4.2 mEq/L	5.23 mEq/L	4.2 mEq/L	3.5-5.1 mEq/L
Lipase					23 U/L			20 U/L		13-60 U/L
Amylase					27 U/L			440 U/L		25-125 U/L
Lactate								4.0 mmol/L	4.9 mmol/L	0.5-2.2 mmol/L
Troponin-I						8.1 pg/ml		24.1		
pg/ml	586.6 pg/ml	Upto 34.2 pg/ml								
CKMB						0.713 ng/ml		1.1 ng/ml	2.9 ng/ml	Upto 7.2 ng/ml
Inflammatory Markers										
CRP	152.68 mg/L	14.97 mg/L		3815 mg/L				277.64 mg/L	236.34 mg/L	<5.0 mg/L
Ferritin	1176 ng/ml	1296 ng/ml		722 ng/ml						30-400 ng/ml
D-Dimer	250 ng/ml	5573 ng/ml		3026ng/ml				1100 ng/ml		<500 ng/ml
Pro-Calcitonin	0.06 ng/ml	0.02 ng/ml		0.03 ng/ml					53.32 ng/ml	<0.05 ng/ml
Interleuikin-6	27 pg/ml	281.3 pg/ml		3815pg/ml						<7 pg/ml
LDH	390 U/L	446 U/L		533 U/L	403 U/L		247 U/L			135-225 U/L
Arterial Blood Gases										
pH								7.31 mmHg	7.208 mmHg	7.35-7.45
pCO_2								34.9 mmHg	45.6 mmHg	32-48 mmHg
pO_2								126.7 mmHg	49.6 mmHg	83-108mmHg
HCO_{3-}								17.2 mmol/L	17.7 mmol/L	22-29mmol/L
Oxygen saturation								98.4%	74.4%	94 - 98 %
Coagulation Profile										
APTT					45.28 seconds	22 seconds	28.98 seconds	75.70 seconds	53.10	28-42 seconds
PT					23.93 seconds	11.5 seconds	20.88 seconds	16.70 seconds	17 seconds	10-14 seconds
INR					2.06	1.1	1.78	1.53	1.57	0-1

WBC: White blood cell, CKMB: Creatinine kinase, CRP: Creactive protein, APTT: Activated partial thromboplastin time, PT: Prothrombin time, INR: International normalized ratio, HCO_{3-}: Bicarbonate, LDH: Lactate dehydrogenase.

unremarkable. HRCT of the chest was done on an urgent basis which had classical signs of Covid-19 Pneumonia with CT Severity Index 21/40. On the basis of HRCT and positive Covid-19 PCR, the patient was shifted to the isolation ward.

Management was started on the lines of severe Covid pneumonia including 12 litres oxygen via non-rebreather mask. He was prescribed Dexamethasone Intravenous 6 mg once daily for 14 days, enoxaparin subcutaneous 40mg once daily, Injection Remdesevir 200mg loading dose followed by 100mg daily dose for six days (total seven doses), Injection Ceftriaxone 1gm twice a day for 10 days, daily supplementation of vitamin C and Zinc along with Vitamin D 200,000 IU once weekly, oral lansoprazole 30mg once daily, anti-pyretic six hourly, and anti-emetics on as needed basis. Inflammatory markers were significantly raised with serum ferritin of 1176ug/L (Adult female (premenopausal): 20-220 µg/L. Adult female (postmenopausal): 30-370 µg/L. Adult male: 30-620 µg/L), CRP of 152.68 (Normal Range 0-10mg/dl), Interleukin-6 27 (Normal Range <7 pg·ml-1), D-dimers 250 (Normal Range220 to 500 ng/ml) (Table-1).

On the third day of admission, the patient's oxygen demand increased to 15 litres and inflammatory markers showed rising trend, especially IL-6, based on which he was advised two doses of Tocilizumab but only a single dose of 8mg/kg could be administered due to scarcity of the drug across the country.

The patient's increasing oxygen demand and rising D-dimers pointed towards pulmonary embolism for which CT-Pulmonary Angiogram was done on April 15, 2021 which showed filling defect in the 2nd and 3rd segmental branches on the left side but was inconclusive for an embolus which, the report stated, could be due to adjacent consolidations. However, since the patient's WELLS score was 7 and D-dimers significantly raised he was started on therapeutic doses (1mg/kg twice a day) of sub-cutaneous Enoxaparin. Subsequently, his condition started improving and oxygen demand decreased to two litres via nasal cannula over a span of 10 days.

On the 27th day of illness, he started complaining of sharp, sudden, moderate, left hypochondrium (LHC) pain (pain score 7/10), not associated with food or bowel movements. Abdominal examination was insignificant at this point. Ultrasound of the abdomen showed no evident pathology, so he was managed for dyspepsia along with analgesia. Serum amylase/lipase levels ruled out acute pancreatitis. Electrocardiogram (ECG) and cardiac markers were also within acceptable range. Despite analgesia, pain persisted and additionally the patient started complaining of burning micturition with pus at penile tip. Urinalysis showed multiple leukocytes with positive nitrites and leucocyte esterase. Urine cultures were sent and stat dose of 3gm Fosfomycin was given. The patient remained afebrile during this period.

On the 29th day of the illness, his condition worsened and the intensity of LHC pain increased (pain score 10/10). There was abdominal distension and guarding on examination. Chest X-ray was done, there was no air under the diaphragm. The patient went into septic shock with blood pressure of 80/40 mmHg and pulse 140 beats per minute. He was aggressively managed with IV antibiotics - Injection Piperacillin-Tazobactam 4.5gm IV every six hours, IV fluids and ionotropic support. Due to his critical status, the patient was shifted to the ICU where a CT of the abdomen with contrast and CT angiography abdominal vasculature was ordered for the unexplained abdominal symptoms. CT of the abdomen showed pneumoperitoneum (Figure) and no signs of mesenteric/gut ischaemia although there was defect in ileo-femoral vein pointing towards DVT despite being on therapeutic dose of Enoxaparin for more than 10 days. Surgical team was consulted, and exploratory laparotomy was performed on the 30th day of the illness. Per-operative findings were of proximal jejunal perforation, which was contained locally in a pocket having a small amount of reactionary fluid in the left subphrenic space. It was drained, the peritoneal cavity was washed, and jejunum was exteriorised keeping in view his hypotensive state. There was no sign of acute peritonitis or infection/inflammation depicting septic shock.

Post-op he was shifted to the surgical ICU where he remained on ventilator and triple ionotropic support. There, he had multiple episodes of supraventricular tachycardia for which he was DC cardioverted twice. Cardiac rhythm successfully reverted and remained stable until the morning of the 31st day of illness when he suddenly collapsed. ECG showed straight-line despite resuscitation attempts and this led to his sad demise.

Informed consent has been taken from the attendants for using the patient's details for reporting purposes.

Discussion

Covid-19 has significant mortality and morbidity. COVID-19 diagnosis is established on the basis of reverse transcriptase Polymerase Chain Reaction (rt-PCR) detecting viral RNA. HRCT of the chest is also an important modality for diagnosing COVID-19 in hospitalised patients. Our patient's CT scan showed typical features of COVID-19 pneumonia with bilateral peripheral and central ground glass opacities and consolidations and septal thickenings.[11] His treatment centred on steroids, prophylactic anticoagulation (since his D-dimers were markedly raised),[12] Remdesevir, Tocilizumab, and vitamin supplements. He was switched to therapeutic anticoagulation later when pulmonary embolism was suspected. He responded to the treatment and his supplemental oxygen requirement decreased to two litres.

COVID-19 patients may deteriorate because of a wide array of complications, including ARDS, sepsis and shock, thromboembolism, cardiomyopathy and arrhythmia, acute kidney injury, secondary bacterial and fungal infections, and gastrointestinal perforation. Gut perforation secondary to ischaemia has been documented in COVID-19 patients.[1] Our patient developed jejunal perforation around the 17th day of admission. There are three rationales for the perforation. Firstly, vascular compromise to the gut due to the hypercoagulable state in Covid-19 or due to the endothelial damage.[8] Secondly, direct invasion of small intestinal cells by the virus through angiotensin converting enzyme 2 receptors.[8] Thirdly, Tocilizumab has been reported as a suspected cause of gastrointestinal perforation in COVID-19 patients.[13] Tocilizumab has already been reported in Rheumatoid Arthritis patients to cause gut perforation at 2/1,000 patients per year,[14] with greater risk with dose of 8mg/kg.[15] The risk increases with concurrent glucocorticoid therapy.[13] It was theorised that this serious side effect may be extended to its use in

COVID-19 patients, especially with the already compromised haemodynamic status as in the case of our patient who was already developing sepsis.[10]

Gastrointestinal manifestations of Covid-19 are overshadowed by respiratory features and, hence, might be missed. Presence of abdominal pain, guarding, persistent nausea and vomiting with or without deteriorating haemodynamics of a patient should alert for gastrointestinal perforation, especially if the patient has also been treated with Tocilizumab.

Conclusion

There should be low threshold for CAT scan abdomen with contrast in patients treated with tocilizumab, so as not to miss the potentially lethal complication. Despite normal sonogram of the abdomen reaching out for CT of the abdomen would have been beneficial for this patient and prompt intervention may have saved his life. Though the cause of shock was not intestinal leak, the delay should have been omitted.

Disclaimer: None to Declare.

Conflict of Interest: None to Declare.

Funding Sources: None to Declare.

References

1. Singh B, Kaur P. COVID-19 and acute mesenteric ischemia: A review of literature. Haematol Transfus Cell Ther. 2021; 43:112-6.
2. Yang X, Yu Y, Xu J, Shu H , Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8:475-81.
3. Kiwango F, Mremi A, Masenga A, Akrabi H. Intestinal ischemia in a COVID-19 patient: case report from Northern Tanzania. J Surg Case Rep. 2021; 2021:rjaa537.
4. Han H, Yang L, Liu R, Liu F, Wu KL, Li J, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020; 58:1116-20.
5. Vulliamy P, Jacob S, Davenport RA. Acute-aorto-iliac and mesenteric arterial thromboses as presenting features of COVID 19. Br J Haematol. 2020; 189:1053-4.
6. Cheung S, Quiwa JC, Pillai A, Onwu C , Tharayil ZJ, Gupta R, et al. Superior mesenteric artery thrombosis and acute intestinal ischemia as a consequence of COVID-19 infection. Am J Case Rep. 2020; 21:e925753.
7. Azouz E, Yang S, Cholley LM , Arrivé L, et al. Systemic arterial thrombosis and acute mesenteric ischemia in a patient with COVID-19. Intensive Care Med. 2020; 46:1464-5.
8. Parry AH, Wani AH, Yaseen M. Acute mesenteric ischemia in severe coronavirus-19 (COVID-19): possible mechanisms and diagnostic pathway. Acad Radiol. 2020; 27:1190.
9. Keshavarz P , Rafiee F , Kavandi H, Goudarzi S , Heidari F , Gholamrezanezhad A, et al. Ischemic gastrointestinal complications of COVID-19: a systematic review on imaging presentation. Clin Imaging. 2020; 73:86-95.
10. Vikse J, Henry BM. Tocilizumab in COVID-19: Beware the risk of intestinal perforation. Int J Antimicrob Agents. 2020; 56:106009.
11. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020; 20:425-34.
12. Tang N, Bai H, Chen X, Gong J , Li D , Sun Z, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020; 18:1094-9.
13. Guardiola PG, Ares JÁ, Tomás NP, Tomás JCS, Martínez SN. Intestinal perforation in patient with COVID-19 infection treated with Tocilizumab and corticosteroids. Cir Esp (Engl Ed). 2021; 99:156-7.
14. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF, et al. Integrated safety in Tocilizumab clinical trials. Arthritis Res Ther. 2011; 13:R141.
15. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with Tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008; 67:1516-23.