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CASE REPORT
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Spontaneous intestinal perforation in critical COVID: A case report

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ABSTRACT:

Spontaneous intestinal perforation is a rare extrapulmonary manifestations of critical COVID-19 case. The pathogenesis of viral etiology is still unclear and association to some essential therapeutic treatment such as steroid or interleukin-9 antagonist is also inconclusive. Surgery is not mandatory If source control and sepsis can be accomplished with available interventions reported in current literatures. This uncommon complication develops either at time of presentation or after hospital admission, both upper and lower gastrointestinal tract1 We reported an ARDS patient experienced cardiac thrombus without valvular defect or arrhythmia who was diagnosed of spontaneous intestinal perforation from acute necrotizing ileitis necessitated damage control surgery.

Keywords: COVID-19 peritonitis, Spontaneous small bowel perforation, Acute abdomen, Left atrial thrombosis

INTRODUCTION

SARS-CoV-2 is an RNA virus with an envelope that attaches to the angiotensin-converting enzyme 2 (ACE2) receptor and enters host cells via spike proteins 1 and 2. According to the literature prior to vaccination era, severe disease (defined as > 50% lung involvement or hypoxia) affects over 10% of patients, whereas critical disease (defined as respiratory failure, multiorgan injury, or shock) affects up to 5% of patients [1]. At the time of this report, the Delta (B.1.617.2 lineage) and Omicron (B.1.1.529 lineage) variants are the most recent concerning in Thailand. Extrapulmonary manifestations including cardiac, neurologic, gastrointestinal, and hematologic are common and attribute to clinical severity and poor prognosis in severe cases [2]. Notwithstanding, intestinal perforations have only been reported in a small number of COVID patients, implying that this is an uncommon consequence given the global prevalence of COVID. Given that this case report of a fatal intestinal complication will contribute to the body of knowledge about critical patients' gastrointestinal symptoms and outcomes. In order to better understand the treatment's effectiveness and precaution, it is useful to document relevant detrimental consequences experienced during ICU admission.

CASE REPORT

A 52-year-old female patient with previous history of SLE and type 2 diabetes mellitus (T2DM) had been hospitalized for low-graded fever productive cough and lethargy for a week. Relevant past history includes long-termed prednisolone treatment for SLE and CoronaVac vaccine immunization without specific details. By the time initial therapy for community acquired pneumonia had begun, the symptoms had not improved. The patient was then transferred to another hospital a few days later, where she was diagnosed with severe pneumonia and given meropenem combined with vancomycin to treat. Methylprednisolone 40 mg was started to control the active SLE disease, which lupus pneumonitis was also a differential diagnosis . A CT scan of the chest revealed a probable left ventricular thrombus, diffuse alveolar infiltration in both lower lung field, and pericardial effusion with suspected pericarditis. Electrocardiogram revealed sinus tachycardia without atrial fibrillation despite a transthoracic echocardiogram demonstrated the presence of a thrombus in left ventricle with unremarkable mitral valve and 70% ejection fraction . Enoxaparin therapy was required due to a high level of D-dimer. Due to cardiorespiratory failure, the patient was intubated at intensive care unit and mechanically ventilated. At this time, a nasopharyngeal swab tested negative for SARSCoV-2 polymerase chain reaction and also Mycobacterium profiles.

The patient was referred to our hospital two weeks later from first hospital admission. On ICU arrival, the SAR-CoV 2 pneumonia was diagnosed with Orf1ab (Ct) of 37.59 and N gene (Ct) of 34.62 in positive RT-PCR test. The inflammatory marker liked ferritin was high (level of 3210 ng/mL; normal range 15.0-150), otherwise such as hs-C reactive protein, complement-3 (beta-1 C) and complement-4 were within normal limit Except for the fact that the COVID-19 PCR test at admission turned out to be positive, the majority of management remained the same. Favipiravir was started, but not tocilizumab, as pulmonary profiles appeared to be improving. . Because the patient's condition remained stable in the first week, mechanical breathing support was gradually reduced to synchonized intermittent mandatory ventilation mode, positive end-expiratory pressure of 5 cmH_2O and fraction of inspired oxygen of 0.3 with recent chest X-ray (figure 1). On the eighth day in the ICU, the patient exhibited tachypnea as well as abdominal pain and distention requiring an abdominal CT scan, which revealed free air in peritoneal cavity and a perforation in distal ileum area (figure 2A) necessitated an emergency celiotomy. Norepinephrine was administrated because blood pressure continued to low despite adequate volume replenishment.

Decompressive celiotomy, ileal resection, and temporary abdominal closure was required due to persistent hypotension resulting to increased intra-abdominal. Multiple perforations of the ileum confined at length of 10 cm warranted the removal of the diseased segment followed by primary anastomosis and the second look procedure was scheduled over the next two days. On the first post-operative day, the patient's hemodynamics were stable, but developed left hemiparesis. A subsequent CT brain (figure 2B) identified a large infarction supplied by the right middle cerebral artery as well as the LV thrombus having vanished. The hemodynamic status appeared stable and norepinephrine could be tapered until clinical circumstances worsened 2 days later due to surgical wound hemorrhage and developing cerebral edema. The anastomosis was converted to an end ileostomy to prevent anastomotic leakage from hemodynamic instability and continuous bleeding points at surgical wounds were successfully controlled in an instant second look operation. Nevertheless, ongoing refractory intracranial hypertension worsened over time, and the patient passed away three days later.

KEY MESSAGES:

- Sponatneous intestinal perforation in severe COVID patient is uncommon gastrointestinal complication but potentially fatal. A high index of suspicion, early diagnosis and prompt treatment are crucial.
- Intestinal vulnerability to SAR-COV 2 and possible treatment side effects make the etiology multifactorial and unclear.

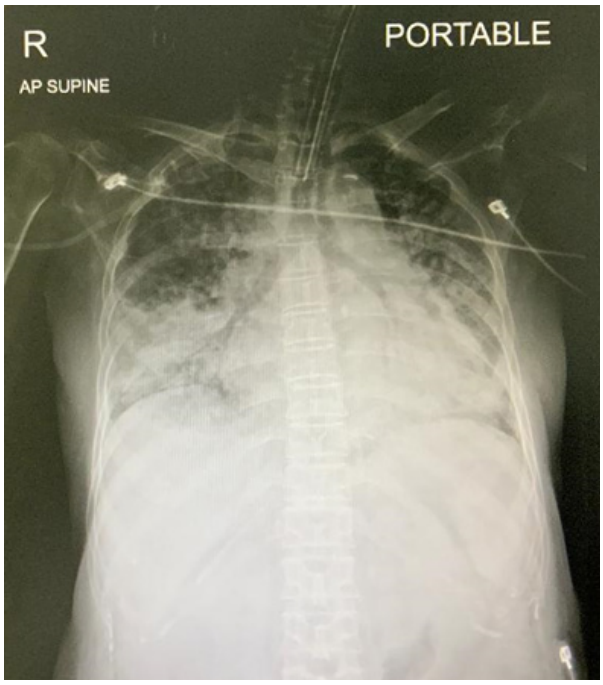
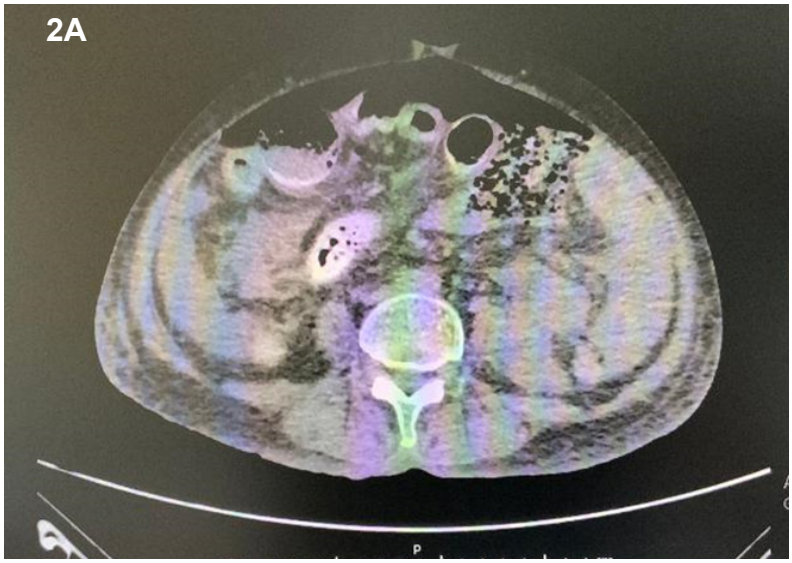


Figure 1. Chest X-Ray revealed bilateral, peripheral, lower lungs predominated consolidation.

DISCUSSION

The early symptoms of this confirmed COVID-19 case were acute bilateral pneumonia accompanied by cardiac thrombosis. Elevated D-dimer levels and other factors increased the risk of thromboembolism, necessitating the administration of thromboprophylaxis drugs. The



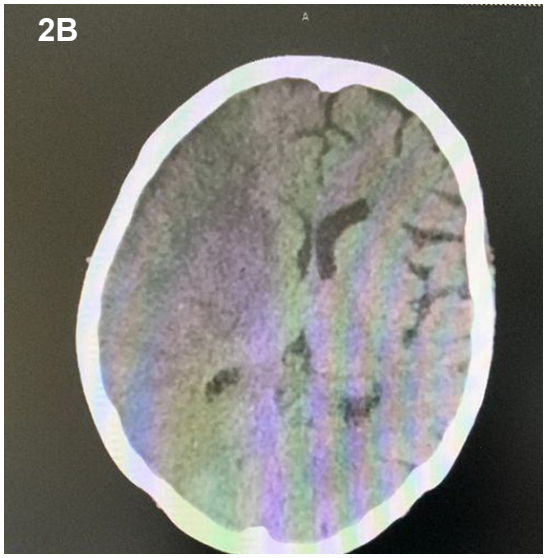
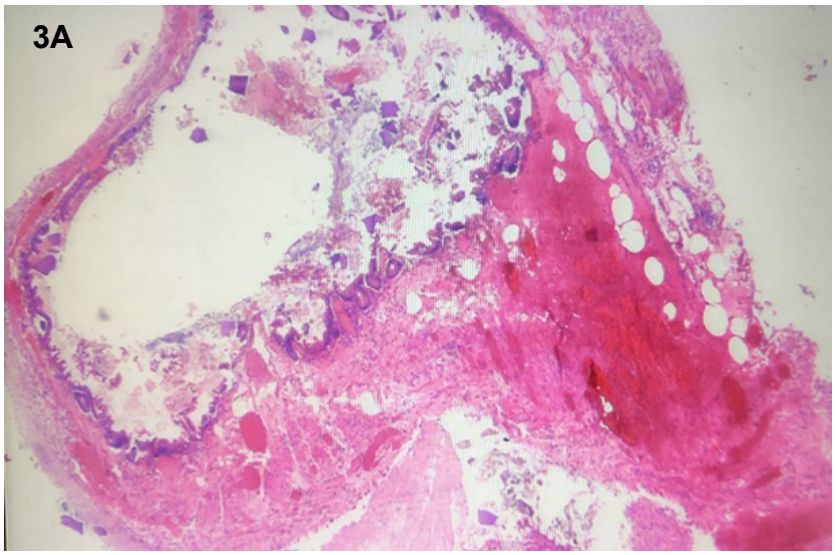


Figure 2A. Contrast enhanced CT of the abdomen showing free air representing pneumoperitoneum and disrupted wall of ileum.

Figure 2B. Non-contrast CT brain radiograph demonstrated large hypodense lesion involving right fronto-parieto-temporal region, suggestive of acute brain infarction along right middle cerebral artery territory.



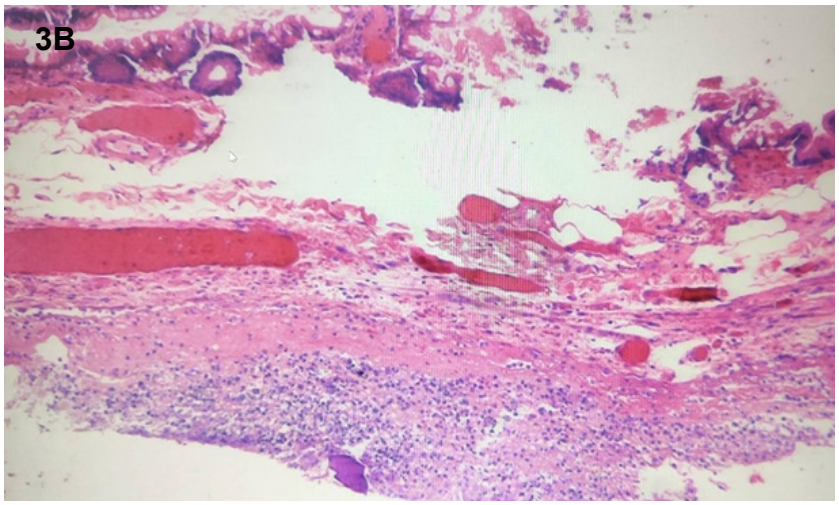


Figure 3A-B. Histology of acute necrotizing ileitis showing transmural ischemic changes exhibiting loss of villi, glandular drop-out, diffused vascular congestion and neutrophil infiltration. No vasculitis, atherosclerosis nor vascular thrombosis were seen. Both surgical margins revealed focal necrotizing inflammation.

mechanism of coagulation activation following SARS-CoV-2 infection is currently unclear[2], however it could be attributed to an enhanced inflammatory response rather than the virus directly. The involvement of the intestine was another extrapulmonary issue. According to a comprehensive review, the severity of gastrointestinal problems is proportionate to the severity of COVID-19 disease[3], although the surgical implications of gastrointestinal diseases during the COVID-19 pandemic are currently unclear.

At three weeks following the onset of critical illness, this case developed generalized peritonitis and CT scans demonstrated perforated ileum resulting in pneumoperitoneum without suggestive findings of inflammatory bowel disease, diverticular condition, or malignancy. The distal ileum had multiple areas of necrotic perforation without primary pathology, according to the operative findings . Several explanations have been proposed to elucidate GI involvement in COVID-19 patients. According to research [4], viral entrance mechanism is mediated by the ACE-2 receptor which the receptor overexpression can be found in gastrointestinal epithelial cells and pneumocytes, as well as the hepatic, renal, and cardiovascular systems. The presence of protein S in the gastrointestinal system also encourages virus fusion with host cells. This mechanism makes the gastrointestinal system vulnerable to SARS-CoV-2 infection [5], as evidenced by the presence of SARS-CoV-2 in stool. Furthermore, a recent study [6] found that ACE2 and transmembrane serine protease 2 (TMPRSS2) co-expression is significantly enriched on nasal goblet secretory cells, type II pneumocytes in the lung, and absorptive enterocytes in the terminal ileum, but not colonic enterocytes, suggesting that the small and large intestines are vulnerable in distinct ways.

In a post mortem analysis [7] demonstrated significant atrophy of Peyer's Patch (PP) which are concentrations of gut-associated lymphoid tissue (GALT) located in the terminal ileum, are affected by the disease regardless of virus concentration in the area. As a result, it appears that a significant reduction in numbers of T and B lymphocytes in PP is due to inflammation process rather than virus alone and may attributed to an increased apoptosis rate.

Long-term steroid use has also been linked to the development of intestinal perforation or other GI issues such as peritonitis and abdominal discomfort [13-14]. Patients with prolonged steroid treatment are at a higher risk of gastrointestinal perforation and the delayed clinical presentation also leads to increased morbidity. Existing case reports have suggested a possible relationship between bowel perforation and the use of high doses of steroids, notably in vasculitis-predominated conditions [8] like Henoch-Schönlein purpura, where fibroblast growth and collagen formation are inhibited. However, the recent publication of the RECOVERY trial [9], steroid has become more routinely utilized in the treatment of severe COVID-19. Intestinal problems were not reported in studies, and there were only a few other severe side effects such as gastrointestinal hemorrhage, hyperglycemia and psychosis. In spite of the lack of proven evidence that high-dose steroids indeed affects spontaneous bowel rupture in COVID-19, more case reports [10] published recently described the risk of GI perforation in individuals after using a combination of high-dose steroids and tocilizumab. Recent systemic review [11] found patients using tocilizumab for rheumatoid arthritis had a GI perforation risk of 1.55-1.9 per 1000 patient years.

Although IL-6 activity induces transmural intestinal inflammation, it also encourages the formation of adipose tissue in mesentery, which may alleviate minute perforation in some patients theoretically [12]. As a result, the inhibition of IL-6 by tocilizumab and the resulting breakdown of mesenteric fat could be another component in multifactor of perforated processes [13]. Nevertheless, critical COVID patient who developed cytokine storm appeared to release more cytokines enhancing mucosal degradation. While the benefits of tocilizumab might indeed warrant its administration in individuals with severe COVID-19, intensivist ought to be aware of the potential of intestinal perforation in critical COVID19 patients.

Therefore, while the exact pathophysiology of spontaneous ileal perforation is uncertain, the hypothesis is that the mechanism is orchestrated by either an underlying inflammatory dysregulation compounded by some degree of treatments effect. Even the literature cannot prove a causal association between steroid use and adverse events such intestinal perforation. However, significant advantages of cytokine storm therapy considerably exceed the risks associated with this potentially rare lethal intestinal complication.

Fortunately, recent studies [14] have found that in some stable patients with a confined and limited perforation, nonoperative therapy may be utilized successfully. Nonoperative approaches can be considered if GI perforation is confined and possibly treated successfully by combination of antibiotics intervention, and if surgical intervention is required, the appropriate method can be chosen on an individual basis.

CONCLUSION

When managing COVID-19 patients with predisposing risk factors for GI complications, such as present diarrhea, nausea, vomiting, proven GI bleeding, or a history of inflammatory bowel disease, diverticulitis, or diverticulosis, intensivists should take precautions. Patients with COVID-19 may develop spontaneous intestinal perforation even if they are not on tocilizumab, thus if the patient has other risk factors for this, steroids should be given with close monitoring. In this unpreventable condition, periodic monitoring and a high index of suspicion are required. While reporting overview for COVID patients with gastro-intestinal perforation may be skewed, treatment should be considered on a case-by-case basis, and the prognosis is not dismal.

CONFIDENTIALITY

Informed consent is obtained from the first degree relative. Instead of personal information, anonymous data is utilized in manucript only. The data for this study is only kept in medical data form and is pass-word secured on the computers of the researchers.

DISSEMINATION POLICY

The manuscript was approved by the Institution Review Board of the hospital that author working for. We plan to disseminate the case report in Clinical critical care journal, conferences nationally and internationally.

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AUTHORS' CONTRIBUTIONS
(I) Writing – original draft, Visualization, Conceptualization: Pusit Fuengfoo, Nichaphat Phancharoenkit; (II) Writing – review & editing: Amorn Jongstapongpan; (III) Writing – review & editing: Poonnapong Hansiriphan; (IV) Writing – review& editing, Conceptualization: Nattachai Srisawat; (V) Writing – review & editing: Pitaks Detporntewan; (VI) Writing – original draft: Ratchamon Pinyotepprataran; (VII) Conceptualization: Panu Boontoterm; (VIII) Supervision and Conceptualization: Apirak Palwatwichai.

SUPPLEMENTARY MATERIALS
None

ABBREVIATIONS
SLE, Systemic Lupus Erythematosus; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; SIMV, Synchronized intermittent mandatory ventilation; PP, Peyer's Patch; GALT, Gut-associated lymphoid tissue; ACE-2, Angiotensin-converting enzyme; TMPRSS-2, Transmembrane serine protease 2.

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