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Pneumomediastinum and pneumoretroperitoneum after COVID-19: concealed intestinal perforation

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Abstract

Background With the prevalence of coronavirus disease 2019 (COVID-19), many severe cases have been discovered worldwide. Here, a case of concurrent pneumomediastinum, pneumoretroperitoneum, and intestinal perforation was reported. This case was the first report on COVID-19-induced related complications.

Case presentation A 74-year-old female patient was hospitalized for COVID-19. Air leakage was unexpectedly found during imaging reexamination. Considering the unobvious subjective feeling of the patient, a conservative treatment was given at the early stage, and finally, sigmoid colon perforation was surgically confirmed. The family gave up the treatment at last, because the patient could not be taken off the ventilator. Coincidentally, the patient also had abnormal renal anatomical position. This situation led to an abnormal air leakage direction and the atypical manifestations of peritonitis. It was also one of the important reasons for the delayed diagnosis and treatment of the disease.

Conclusions Clinicians should be vigilant for spontaneous gastrointestinal perforation in patients with COVID-19, particularly those undergoing treatment with glucocorticoids and tocilizumab. The case is shared to highlight this rare and fatal extrapulmonary manifestation of COVID-19 and further assist clinicians to raise their awareness and timely implement imaging investigation and multidisciplinary intervention so as to facilitate early discovery, diagnosis and treatment and reduce the mortality.

Keywords COVID-19, Pneumomediastinum, Pneumoretroperitoneum, Intestinal perforation, Air leakage

Background

In the recent century, coronavirus disease 2019 (COVID-19) is the most serious infectious disease in the world. The disease mainly involves the respiratory tract, but the manifestations beyond the respiratory system are not uncommon [1].The viruses can invade many systems and organs, such as heart, kidneys, digestive tract, nerves, blood, skin, eyes, endocrine secretion, sex hormones, muscles and bones. Gastrointestinal involvement is the most common, which can lead to bellyache, diarrhea, gastrointestinal hemorrhage, and even gastrointestinal perforation and peritonitis [2].Gastrointestinal manifestations may be the only symptom of mild patients or the complication of severe patients. With the virus variation, extrapulmonary involvement is a field worthy of active research. Post-COVID-19 air leakage is uncommon, whereas COVID-19-associated pneumothorax, pneumomediastinum, subcutaneous emphysema,

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pericardial emphysema, and pneumoperitoneum have been relatively reported [3, 4]. To the authors' knowledge, multisite-combined air leakage is very rare, with high mortality. In the present case, a patient with spontaneous pneumomediastinum combined with pneumoretroperitoneum was admitted in our hospital during the ongoing pandemic of COVID-19 in early 2023. No clear perforation of abdominal organs was found in the early examination. After conservative treatment was administered, the disease progressed and was finally confirmed as sigmoid perforation through surgery. Concealed intestinal perforation was caused by COVID-19, and pneumomediastinum and pneumoretroperitoneum were the first manifestations in the early stage. The best opportunity to perform the operation was delayed due to the misjudgment of the cause. This case was reported to warn clinicians, so that similar cases could be found, diagnosed, and treated early in the future.

Case presentation

A 74-year-old female patient with a history of rheumatic polymyalgia and aortic valve surgery had been receiving glucocorticoid, immunomodulator, and warfarin therapy for an extended period. The patient presented to the hospital with chest distress and shortness of breath after exercise for 2 weeks, but without any obvious symptoms such as cough, expectoration, fever, abdominal pain, or diarrhea. A severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antigen was found to be positive in a nasal swab at the early stage of the disease. During physical examination, lip cyanosis was observed, no rales were detected in both lungs, mechanical valve sounds were audible in the auscultation area of aortic valves, and no positive signs were noted in the abdomen. Upon hospitalization, the patient's laboratory results showed a white blood cell (WBC) count of 5.6×10^9/L, a C-reactive protein (CRP) of 78.9 mg/L, an arterial oxygen partial pressure (PaO_2) of 40.7 mmHg, a carbon dioxide partial pressure ($PaCO_2$) of 31.8 mmHg, a lactic acid of 1.9 mmol/L, a D-dimer level of 0.51 mg/L, and a lactic dehydrogenase (LDH) level of 752.9 U/L. Chest computerized tomography (CT) revealed diffuse and patchy high-density image in both lungs, with slight pleural effusion (Fig. 1-A). The drug treatment administered was comprehensive, encompassing oxygen inhalation, moxifloxacin hydrochloride, ambroxol hydrochloride, and additional supportive management measures. Notably, the patient did not report feelings of chest tightness after the oxygen flow rate was escalated to 4 L/min. At this point, the P/F ratio was recorded as 110 mmHg. Given the critical nature of the patient's condition, Methylprednisolone was introduced, initially at a dosage of 80 mg/day for the first week, which was subsequently tapered down to 20 mg/day. Additionally, Tocilizumab was administered in a single dose of 400 mg. Importantly, the patient did not require the use of inotropes during this

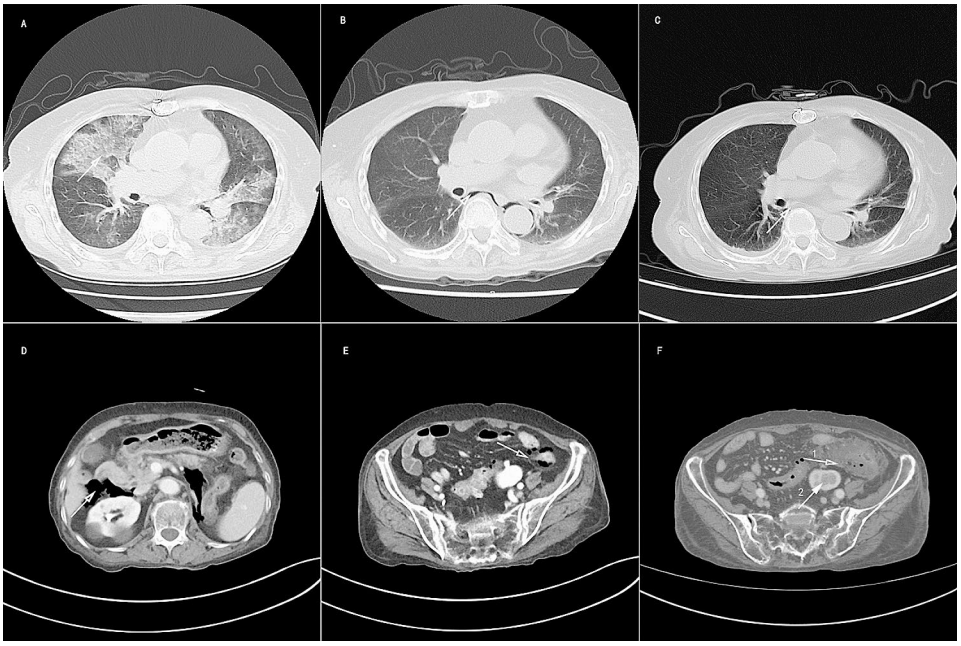

Fig. 1 CT scans of thorax and abdomen. **A**: Diffuse and patchy high-density image in both lungs, with slight pleural effusion at the beginning of admission (white arrow). **B**: Pneumomediastinum in the second week (white arrow). **C**: Pneumomediastinum had been absorbed in the third week (white arrow). **D**: Pneumoretroperitoneum in the second week (white arrow). **E**: Multiple free gases in the abdominal and pelvic cavity, but no ascites were detected. Free air around the sigmoid colon(white arrow). **F-1**: Exudate, effusion, and free gas near the descending colon and sigmoid colon (arrow 1). **F-2**: Congenital left kidney displacement (arrow 2)

period. In the first week of hospitalization, the dosage of methylprednisolone was reduced from 80 mg/day to 40 mg/day with the improvement of symptoms and the absorption of lung inflammation. In the second week, the patient complained of fatigue and accepted CT reexamination. Surprisingly, pneumomediastinum (Fig. 1-B) and pneumoretroperitoneum were observed (Fig. 1-D). Further refined abdominal enhanced CT found multiple free gases in the abdominal and pelvic cavity, including around the sigmoid colon, but no ascites were detected (Fig. 1-E).The possibility of digestive tract perforation was considered at first, but the patient did not exhibit any digestive tract symptoms or abdominal signs. As a precautionary measure, thoracic and gastrointestinal surgeons were invited to make joint diagnosis and treatment. Finally, air leakage was considered to have possibly originated from patient self-inflicted lung injury (P-SILI), so conservative treatment was adopted. Our treatment plans were to give cefoperazone sodium and sulbactam sodium for anti-infection (later changed to imipenem and cilastatin sodium), esomeprazole magnesium for preventing upper gastrointestinal bleeding, enoxaparin sodium for anticoagulation, methylprednisolone sodium for anti-inflammation, nutritional support with compound amino acid, and potassium chloride and sodium chloride for maintaining the electrolyte balance on the basis of fasting. The patient's condition improved in the third week. In the fourth week, the patient suddenly suffered from left lower abdominal pain, and CT reexamination showed that pneumomediastinum had been absorbed (Fig. 1-C), but exudate, effusion, and free gas were found near the descending colon and sigmoid colon (Fig. 1-F). Once again, a multi-disciplinary discussion was organized to evaluate the condition of the disease, followed by sufficient communication with her family members. Then, a surgical treatment was performed after obtaining consent from the patient. During the operation, sigmoid colon perforation concurrent with surrounding tissue infection was confirmed. A large amount of pus was found in abdominal cavity, pelvic cavity, and retroperitoneal cavity. The middle and lower segments of the descending colon turned black with pus attached. The surgeons conducted multiple surgeries, including a partial colectomy, intestinal adhesiolysis, the creation of a colostomy, and flushing of the abdominal cavity. The surgical pathology report indicated the presence of purulent inflammation on the serosal surface of the descending colon wall. However, the patient could not be taken off the ventilator after the operation, and finally, the family decided to discontinue treatment. The timeline of all events is shown in Fig. 2.

Discussion and conclusions

COVID-19 is a global epidemic disease, and the infected people have different manifestations [5]. As a rare complication, air leakage is common after positive pressure ventilation, but it can also occur spontaneously [6]. The patient in the present case did not accept any iatrogenic intervention that could lead to air leakage before pneumomediastinum and pneumoretroperitoneum were discovered. The direction of air leakage was initially considered as lung → mediastinum → retroperitoneum on a theoretical basis of the Macklin effect [7] and P-SILI [8]. The Macklin effect refers to the linear air collection

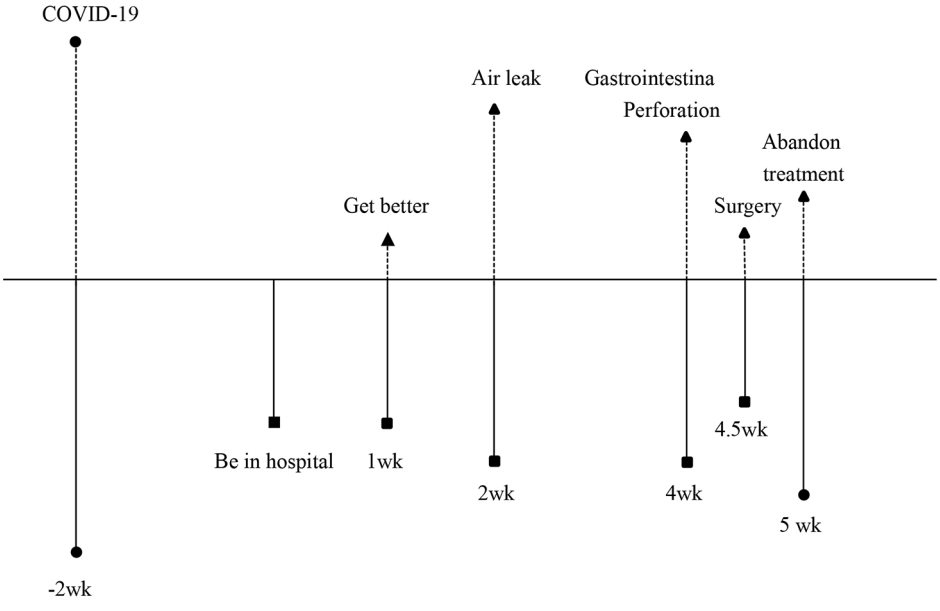

Fig. 2 Timeline of the clinical manifestations exhibited by the patient

near the bronchovascular sheath. Some scholars believe that the Macklin effect has high accuracy in predicting pneumomediastinum and pneumothorax in patients with COVID-19 [9], especially when the lungs are heavily involved, which may be an important potential factor for air leakage [10]. Meanwhile, COVID-19 leads to P-SILI, which is a phenomenon that refers to high respiratory motility, followed by increased lung stress and strain, uneven distribution of ventilation, and mismatch of ventilation and blood flow. Non-intubated patients with spontaneous respiration may have a predilection for P-SILI [11]. The cytokine storm triggered by P-SILI and COVID-19 leads to diffuse alveolar injury, so the alveoli rupture more easily [12].The lung image of the patient was reviewed again and no typical Macklin effect was found. Therefore, we were more inclined to P-SILI as the cause of air leakage in the early stage of the disease. And porous diaphragm syndrome can explain the passage of air from the thorax to the abdomen.This was also the reason for the pneumoperitoneum. Surgery was unnecessary in this situation [13]. The possibility of hollow organ perforation could not be completely ruled out. Pneumoperitoneum after perforation often occurs near the perforation site [14]. And the patient's abdominal CT also did indicate free air around the sigmoid colon.However, the patient did not show any active signs of peritonitis or intestinal perforation, and conservative treatment could be an acceptable treatment strategy.The willingness of the patient and her families was also crucial. They harbored significant concerns regarding surgical treatment. Conservative management was implemented on the basis of the above pathological mechanism and successful cases of non-surgical treatment. The later evolution of the disease serves as a reminder that the air leakage in this patient may have originated from intestinal perforation.The manifestations of intestinal perforation in this patient are significantly different from those reported by other scholars. This patient had no typical symptoms of pneumoperitoneum or peritoneal irritation. Air leakage was accidentally found in routine chest imaging, and mediastinal emphysema and retroperitoneal emphysema occurred simultaneously. The occurrence of which may be related to the following mechanisms. The virus can bind to the angiotensin converting enzyme 2 receptor in the gastrointestinal epithelium to invade the intestinal mucosa and affect the homeostasis of gastrointestinal microflora [15]. The bacterial diversity of patients with COVID-19 was significantly reduced compared to the healthy population. This reduction of beneficial symbiotes was accompanied by a significant increase in opportunistic pathogens [16]. Many studies have indicated the crucial immunological relationship between the intestinal microbiota and the lungs, which has been termed the "gut-lung axis". A compromised intestinal immune system can further influence the respiratory tract [17, 18]. The hypercoagulable state is also a reason worth mentioning. It is considered as one of the four vicious feedback cycles (the viral loop, the hyperinflammatory loop, the non-canonical renin-angiotensin system axis loop, and the hypercoagulation loop) in the pathogenesis of COVID-19 [19]. Some scholars have reported intestinal perforation associated with COVID-19 and found that histopathological examination of excised specimens revealed inflammatory cells accompanied by edema and vascular thrombosis [20]. In this study, a large number of inflammatory cells and severe congestion of the mucosa were also observed on the serosal surface of the descending colon. The virus may induce mass endothelial ischemia, extensive blood coagulation disorders, and complement-induced thrombosis, coupled with factors such as old age, bed rest, and basic diseases concurrent with autoimmune diseases, which may lead to systemic microangiopathy and thromboembolism [21]. Finally, the occurrence of intestinal perforation is jointly promoted by non-negligible drug factors. Monoclonal antibodies and steroid hormones are often used to alleviate the inflammatory storm of patients and reduce the risk of destructive multi-organ dysfunction [22]. However, such drugs conceal the symptoms of infection while exerting anti-inflammatory action. Many studies have shown that tocilizumab can increase the risk of gastrointestinal perforation, which can be especially higher when steroid hormones are used simultaneously [23]. Most of the perforation associated tocilizumab occurred in the lower digestive tract [24]. The specific mechanism remains not completely clear, but diverticulitis has been considered a risk factor [23]. The British Society for Rheumatology recommends that patients who take steroids with a history of diverticulum should be cautious in using tocilizumab. Coincidentally, these factors were manifested in our patient. The risk of gastrointestinal perforation was significantly aggravated by COVID-19 and the combined use of drugs. Another notable detail that this patient had congenital left kidney displacement (Fig. 1-F-2). The ectopic kidney led to local discontinuity of the retroperitoneum, and the gas after perforation entered the retroperitoneal space through the defect of the retroperitoneum, which also makes the symptoms and signs of perforation less obvious. This situation seriously interferes with the doctor's observation line of sight. Most importantly, gastrointestinal perforation needs to be solved through surgical intervention in most cases, but choosing whether to operate is difficult in patients with COVID-19. The risk of surgery and the other complications caused by it, especially the recurrence of lung diseases, are issues that surgeons have to consider .

This case was the first report on COVID-19-induced intestinal perforation, which further led to

pneumomediastinum and pneumoretroperitoneum. The risk of such complications is aggravated after COVID-19 for critically ill patients with basic diseases. Attention should always be paid to the complications related to air leakage because they can be easily concealed by the condition of COVID-19. Efforts should be given to dynamically observe the changes in physical signs and timely complete lung and abdominal imaging examinations. Especially for critically ill patients, an early-stage definite diagnosis is conducive to making timely and correct therapeutic decisions to improve their prognosis and increase the success rate of treatment.

Abbreviations

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WBC	White blood cell
CRP	C-reactive protein
PaO_2	Arterial oxygen partial pressure
$PaCO_2$	Carbon dioxide partial pressure
CT	Computerized tomography
P- SILI	Q- Self-inflicted lung injury
LDH	Lactic dehydrogenase

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Author contributions
JY S, FM Z and JP Y conceived and designed the project. JY S and XY S collected, analyzed and interpreted the data. JY S drafted the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was reviewed and approved by the Medical Ethics Committee of Huzhou Central Hospital (code: 202310011-01). Informed consent was obtained from the patient to publish this case report in an online open-access publication.

Consent for publication
Informed consent for publication was obtained from the patient for publication of this case report.

Competing interests
The authors declare no competing interests.

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References

1. Parotto M, Gyöngyösi M, Howe K, Myatra SN, Ranzani O, Shankar-Hari M, et al. Post-acute sequelae of COVID-19: understanding and addressing the burden of multisystem manifestations. Lancet Respir Med. 2023;11(8):739–54.
2. Abobaker A, Raba AA, Alzwi A. Extrapulmonary and atypical clinical presentations of COVID-19. J Med Virol. 2020;92(11):2458–64.
3. Khan HH, Witkowski A, Clark JA, Mata A. A 17-Year-old girl with a recent history of Marijuana Use presented with Pneumomediastinum and Pneumopericardium and tested positive for SARS-CoV-2 infection on Hospital Admission. Am J Case Rep. 2021;22:e931800.
4. Ahmed AOE, Mohamed MFH, Ahmed K, Severe. COVID-19 Pneumonia complicated by Pneumothorax, Pneumomediastinum, and Pneumoperitoneum. Am J Trop Med Hyg. 2021;104(6):1951–2.
5. Vetter P, Vu DL, L'Huillier AG, Schibler M, Kaiser L, Jacquerioz F. Clinical features of covid-19. BMJ. 2020;369:m1470.
6. Nasa P, Juneja D, Jain R. Air leak with COVID-19 - a meta-summary. Asian Cardiovasc Thorac Ann. 2022;30(2):237–44.
7. Belletti A, Pallanch O, Bonizzoni MA, Guidi L, De Cobelli F, Landoni G, et al. Clinical use of Macklin-like radiological sign (Macklin effect): a systematic review. Respir Med. 2023;210:107178.
8. Elabbadi A, Urbina T, Berti E, Contou D, Plantefève G, Soulier Q, et al. Spontaneous pneumomediastinum: a surrogate of P-SILI in critically ill COVID-19 patients. Crit Care. 2022;26(1):350.
9. Paternoster G, Belmonte G, Scarano E, Rotondo P, Palumbo D, Belletti A, et al. Macklin effect on baseline chest CT scan accurately predicts barotrauma in COVID-19 patients. Respir Med. 2022;197:106853.
10. Brito J, Gregório P, Mariani A, D'ambrosio P, Filho M, Ferreira L, et al. Pneumomediastinum in COVID-19 disease: outcomes and relation to the Macklin effect. Asian Cardiovasc Thorac Ann. 2021;29(6):541–8.
11. Battaglini D, Robba C, Ball L, Silva PL, Cruz FF, Pelosi P, et al. Noninvasive respiratory support and patient self-inflicted lung injury in COVID-19: a narrative review. Br J Anaesth. 2021;127:353–64.
12. Machiraju PK, Alex NM, Safinaaz, Baby NM. Pneumomediastinum in COVID-19: a series of three cases and review of literature. SAGE Open Med Case Rep. 2021;9:2050313X211011807.
13. Sharma M, Ojha P, ,Taweesedt PT, ,Ratnani I, ,Surani SA. Intriguing case of Pneumoperitoneum in a patient with COVID-19: do all Pneumoperitoneum cases need. Surgery? Cureus. 2020;12(12):e12279.
14. Kulinna-Cosentini C, Hodge JC, Ba-Ssalamah A. The role of radiology in diagnosing gastrointestinal tract perforation. Best Pract Res Clin Gastroenterol. 2024;70:101928.
15. Zuo T, Zhan H, Zhang F, Liu Q, Tso EYK, Lui GCY, et al. Alterations in fecal fungal microbiome of patients with COVID-19 during time of hospitalization until Discharge. Gastroenterology. 2020;159(4):1302–10.
16. Gu S, Chen Y, Wu Z, Chen Y, Gao H, Lv L, et al. Alterations of the gut microbiota in patients with coronavirus disease 2019 or H1N1 influenza. Clin Infect Dis. 2020;71(10):2669–78.
17. Banerjee S, Singh SK, Thakur SD, Pneumomediastinum. Tension Pneumoperitoneum secondary to Bowel Perforation in Post COVID-19 patient: a Case Report. Ann Clin Case Rep. 2021;6:1915.
18. Ancona G, Alagna L, Alteri C, Palomba E, Tonizzo A, Pastena A, et al. Gut and airway microbiota dysbiosis and their role in COVID-19 and long-COVID. Front Immunol. 2023;14:1080043.
19. Domingo P, Mur I, Pomar V, Corominas H, Casademont J, de Benito N. The four horsemen of a viral Apocalypse: the pathogenesis of SARS-CoV-2 infection (COVID-19). EBioMedicine. 2020;58:102887.
20. Hashim Z, Khan A, Areekkara P. Thrombosis leading to acute abdomen in corona virus disease- 19:a case series. Indian J Gastroenterol. 2022;41(3):313–8.
21. Iba T, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. Inflamm Res. 2020;69(12):1181–9.
22. Rojo M, Cano-Valderrama O, Picazo S, Saez C, Gómez L, Sánchez C, et al. Gastrointestinal perforation after treatment with tocilizumab: an unexpected consequence of COVID-19 pandemic. Am Surg. 2020;86(6):565–6.
23. Vikse J, Henry BM. Tocilizumab in COVID-19: beware the risk of intestinal perforation. Int J Antimicrob Agents. 2020;56(1):106009.

24. Xie F, Yun H, Bernatsky S, Curtis JR, Brief, Report. Risk of gastrointestinal perforation among rheumatoid arthritis patients receiving Tofacitinib, Tocilizumab, or other Biologic treatments. Arthritis Rheumatol. 2016;68(11):2612–7.

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