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Case Report

Invasive pneumococcal disease affected the fatal outcome in a COVID-19 patient

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ABSTRACT

A 68-year-old man experienced fever and cough and was referred to a hospital for day 4. He had a positive reverse transcription-polymerase chain reaction result for severe acute respiratory syndrome coronavirus-2. On day 12, his PaO_2/FiO_2 ratio worsened to 120 and he was transferred to Sapporo Medical University Hospital for treatment using extracorporeal membrane oxygenation. Venous blood cultures were positive for *Streptococcus pneumoniae*, which were serotype 3, mucoid-type, and penicillin susceptible. Coinfections with coronavirus disease-2019 and invasive pneumococcal disease are rare; however, they are associated with a higher case fatality than either of the conditions manifesting alone.

1. Introduction

The current coronavirus disease-2019 (COVID-19) pandemic is overwhelming the healthcare systems worldwide [1]. In-hospital mortality rate is higher in patients with COVID-19 than in those with seasonal influenza [1]. *Streptococcus pneumoniae (S. pneumoniae)* often causes invasive pneumococcal disease (IPD), which is a life-threatening condition. The incidence of adult IPD is predominantly high among the elderly and immunocompromised patients and in those with chronic diseases [2]. Even though the incidence of IPD during the pandemic is declining in Taiwan [3], we encountered a case of IPD associated with COVID-19.

2. Case report

A 68-year-old man experienced fever and cough. He was subsequently referred to a hospital for COVID-19 patients on day 4. He had a positive result of reverse transcription-polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and his oxygen saturation was 96% (room-air) at that time. He was hospitalized on day 7 and required canula oxygen (Fig. 1). On day 8, he was shifted to another hospital because his respiratory condition worsened. Chest computed tomography indicated bilateral upper and lower areas of ground glass opacities and consolidations at the subpleural and peribronchial legions (Fig. 2A and B). He was intubated and treated using a ventilator. On day 12, his PaO_2/FiO_2 ratio worsened to 120, and he was transferred to Sapporo Medical University Hospital to be treated using extracorporeal membrane oxygenation (ECMO). On examination, his body temperature was 37.5 °C, heart rate was 95 beats/min, and respirator setting was FiO_2 0.6, positive end-expiratory pressure 12 mmHg, and pressure support 10 mmHg. Favipiravir 3600 mg/day and nafamostat 14 mg/day were started on day 8, and prednisolone 70 mg/day was started on day 11. Prior to

Abbreviations: COVID-19, coronavirus disease 2019; *S. pneumoniae*, *Streptococcus pneumoniae*; IPD, invasive pneumococcal disease; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ECMO, extracorporeal membrane oxygenation; MOF, multiple organ failure; ARDS, acute respiratory distress syndrome.

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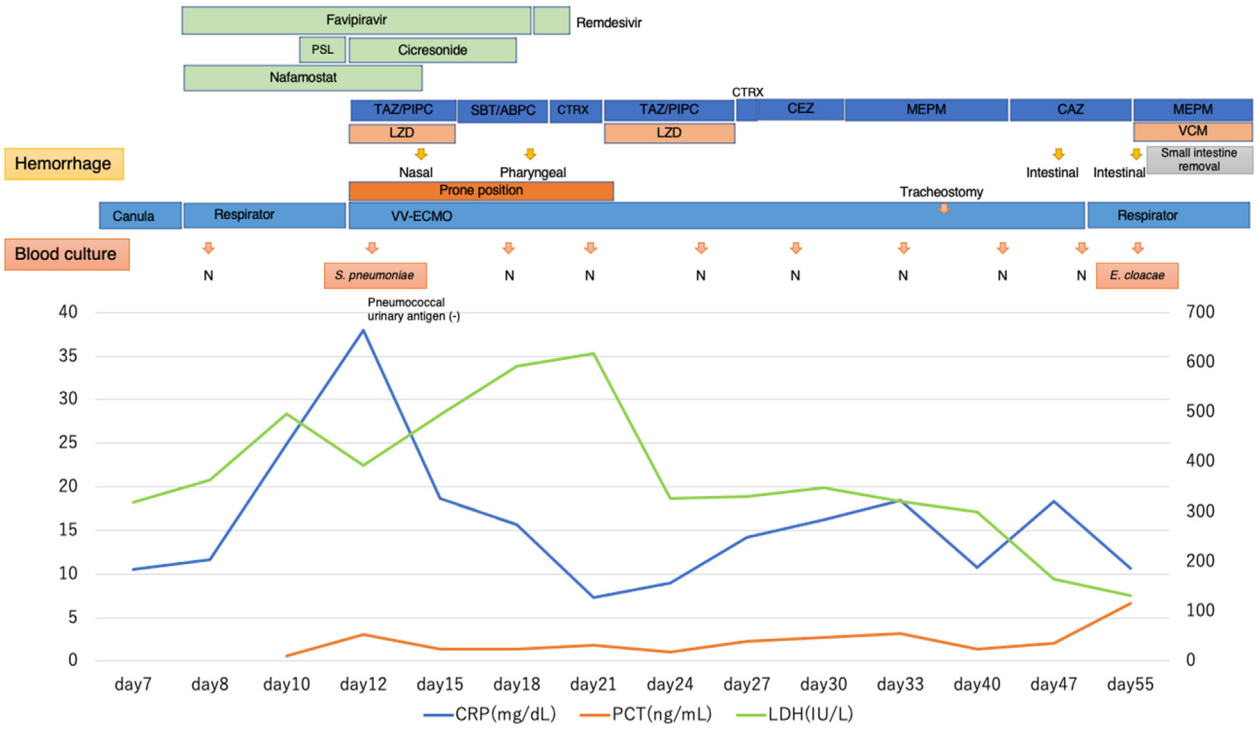

Fig. 1. Clinical course of the patient. Left axis represents CRP (mg/dL) and PCT (ng/mL). Right axis represents LDH (IU/L).
PSL; prednisolone, TAZ/PIPC; tazobactam/piperacillin, SBT/ABPC; sulbactam/ampicillin, CTRX; ceftriaxone, CEZ; cefazoline, MEPM; meropenem, CAZ; ceftazidime, LZD; linezolid, VCM; vancomycin, VV-ECMO; veno-venous extracorporeal membrane oxygenation, N; negative for blood culture, *S. pneumoniae*; *Streptococcus pneumoniae*, *E. cloacae*; *Enterobacter cloacae*, CRP; C-reactive protein, PCT; procalcitonin, LDH; lactate dehydrogenase.

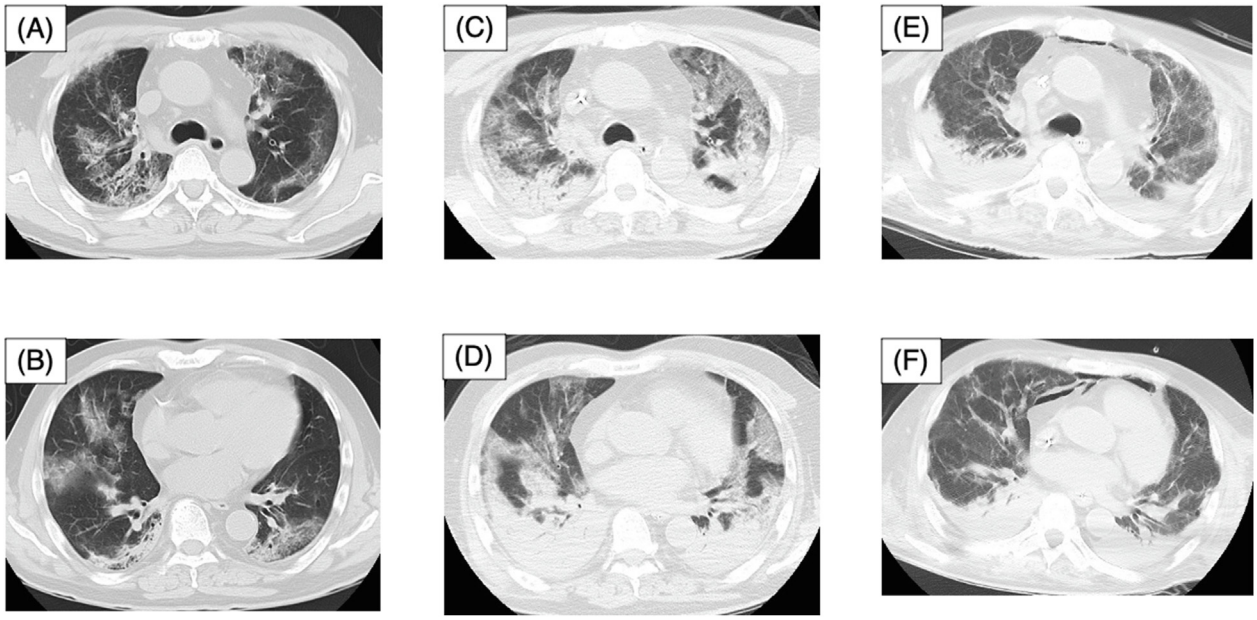

Fig. 2. Serial chest CT images of the patient. (A) Hospital day 8, Upper lobes (B) Hospital day 8, Lower lobes (C) Hospital day 12, Upper lobes (D) Hospital day 12, Lower lobes (E) Hospital day 56, Upper lobes and (F) Hospital day 56, Lower lobes. (A, B) Bilateral upper and lower areas of ground glass opacities and consolidations at the subpleural and peribronchial legions. (C, D) Increased bilateral ground glass opacities and dorsal consolidations with air bronchogram. (E, F) Improvement in the bilateral ground glass opacities. Slight mediastinal emphysema can be seen.

being diagnosed with COVID-19, he had been taking candesartan 4 mg/day and amlodipine 5 mg/day for hypertension, and his performance status was 0. He smoked 1 pack/year 20–40 y.o. and drank shochu, a Japanese liquor, 200–300 mL daily. He had no history of admission or operation. He had no history of pneumococcal vaccination either. He lived with 94 y.o. mother, wife and son. He had no contact with children. Blood examination showed the following results: WBC 10.0 $\times$ $10^3/\mu L$ (neutrophils 88.7%,

Table 1

Antibiotics	MIC
PCG	≤0.03
ABPC	≤0.06
AMPC/CVA	≤0.25
CTM	≤0.5
CDTR-PI	≤0.06
CTX	≤0.12
CTRX	≤0.12
CZOP	≤0.12
CFPM	≤0.5
MEPM	≤0.12
EM	≤0.12
AZM	≤0.25
CLDM	≤0.12
MINO	≤0.5
CP	≤4
VCM	0.25
LVFX	1
ST	≤0.5
RFP	≤1

lymphocytes 7.1%, eosinophils 0.0%), Hb 9.3 g/dL, platelets 25.1 × 10^4/μL, Na 136 mEq/L, K 5.3 mEq/L, Cl 103 mEq/L, CRP 37.92 mg/dL, PCT 3.08 mg/dL, BUN 50 mg/dL, Cre 1.45 mg/dL, AST 46 IU/L, ALT 22 IU/L, LDH 393 U/L, and d-dimer 16.6 μg/mL. He tested positive for SARS-CoV-2 by RT-PCR (E-gene 25.72, N-gene 32.01 Crossing point from Roche). Four bottles of venous blood cultures were positive for *S. pneumoniae* on day 12. The bacteria were serotype 3, mucoid-type, and penicillin susceptible (Table 1). Blood cultures on day 8 were negative. Chest computed tomography showed broad bilateral ground-glass opacities and consolidation, which was difficult to indicate if it was bacterial pneumonia (Fig. 2C and D). He was treated using veno-venous ECMO and was prescribed ciclesonide 800 μg/day, tazobactam/pireracillin 4.5g, q6h, and linezolid 600 mg, q12h. The antibiotics were de-escalated to sulbactam/ampicillin on day 14, and the patient was switched to ceftriaxone 1g, q12h on day18. On day 16, blood cultures were turned to negative. Tracheostomy was performed on day 35. On day 46, he experienced hematochezia. Gastrointestinal endoscopy revealed multiple ulcers in the intestine. Chest computed tomography showed improvement in the bilateral ground glass opacities on day 56 (Fig. 2E and F). However, he had diarrhea and intestinal hemorrhage from day 44. On day 55, small intestine was surgically resected because of repeated hemorrhage. Pathologically, small intestinal mucosal tissue had epithelial erosion and bleeding without blood clots. On day 57, cholecystectomy due to poor color tone of the swollen gallbladder wall, resulting in acute gangrenous cholangitis. His status was declared as multiple organ failure (MOF) on day 76. He died on day 85 owing to MOF, IPD, acute respiratory distress syndrome (ARDS), and COVID-19.

3. Discussion

Many COVID-related complications have been reported till date, and it has been suggested that systemic inflammation and pulmonary complications mainly lead to significant morbidity and mortality [4,5]. We have presented the case of a COVID-19 patient with IPD. He was generally healthy before being infected by SARS-CoV-2; however, the high severity of the infection led to the other comorbid disorders. Among patients with confirmed COVID-19, concurrent influenza and IPD have not been identified in UK in the 2019/2020 season [6]. Tooms et al. reported two cases of IPD in COVID-19 patients, and one of the patients died in UK [7]. COVID-19 and IPD coinfections are rare in England, representing only 0.025% of the confirmed SARS-CoV-2 infections (40/160,886) and 3.5% of the IPD cases (40/1137). However, such a combination is associated with a higher case fatality when compared with either of the conditions manifesting alone [8].

Bloodstream infections appear to be very rare in COVID-19 patients [9]. In New York City, 1.6% of COVID-19 inpatients had co-bacteremia including *Escherichia coli* (16.7%), *Staphylococcus aureus* (13.3%), *Klebsiella pneumoniae* (10.0%), and *Enterobacter cloacae* complex (8.3%) [9]. However, adults with severe influenza, particularly those who succumb to the illness, have been shown to have a high prevalence of bacteremia [10]. Low rates of bacteremia have also been found among patients with other respiratory viral infections, including SARS and respiratory syncytial virus. In our case, repeated blood cultures helped in the early detection of bacteremia and were able to accurately assess the severity even during COVID-19 infection. Since there was no specific clinical feature to IPD, it was important to confirm the deterioration of respiratory condition and parameter changes such as CRP and PCT.

Sputum culture was negative for *S. pneumoniae*. It is unknown whether the severe pneumonia was attributed to SARS-CoV-2 infection only or to a bacterial co-infection. Pathological anatomy did not show the presence of any bacterial focus in the lungs. Antibiotic therapy seemed to be effective; however, the pneumococcal infection could have possibly affected the clinical course of ARDS, intestinal hemorrhage, acute gangrenous cholangitis and MOF.

IPD associated with COVID-19 is rare but highly fatal. Hence, pneumococcal vaccination is needed for aged and higher risk subjects.

Authorship statement

All authors meet the ICMLE authorship criteria.

Authors' contributions

KK was responsible for the organization and coordination of the report, and drafted the manuscript. NB mainly treated the patient. YF, EN and ST made intellectual contributions and helped in patient management. CB and KO were responsible for the data analysis. All authors contributed to the writing of the final manuscript and contributed to the management or administration of the trial.

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Declaration of competing interest

None.

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