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Case Report

A fatal case of COVID-19 pneumonia due to possible pulmonary thrombosis

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The relationship between the severity of COVID-19, hyperinflammation, and intravascular coagulopathy is of critical importance. We report on a case of severe COVID-19 pneumonia treated with favipiravir during the earliest phase of the pandemic. The present case showed improvement in SARS-CoV-2 viral load and the presence of SARS-CoV-2 IgG with decreased radiological evidence of pulmonary infiltration. Moreover, the levels of serum IL-6 and TNF-*α* did not increase markedly. However, the hypoxia failed to recover, leading to the patient's death due to possible pulmonary thrombosis, because D-dimer was markedly elevated, and an electrocardiogram showed typical changes. At present, the fact that some COVID-19 patients with mild to moderate symptoms suddenly die at home has become a major issue in Japan. These findings suggest that additional treatment with anti-coagulants should be considered in some COVID-19 patients at risk of hypercoagulation to prevent sudden death from pulmonary thrombosis.

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Key words: COVID-19, coagulopathy, possible pulmonary thrombosis, hyperinflammation

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Introduction

Coronavirus disease 2019 (COVID-19) pneumonia results from direct viral injury to alveolar epithelial cells and excessive cytokine release from immune or non-immune cells. The association between the severity of COVID-19 and intravascular coagulopathy has been a serious concern[1,2], but the details of this interaction of hyperinflammation and coagulopathy remain unknown in clinical practice. At present, the fact that some COVID-19 patients suddenly die at home has become a critical issue both in Japan and in the rest of the world[3,4]. The case of a patient with severe COVID-19 pneumonia during the earliest phase of the pandemic, in whom treatment with favipiravir decreased the viral load of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and improved the radiological pulmonary infiltration is presented. However, hypoxemia was exacerbated due to possible pulmonary thrombosis, and the patient died.

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Case report

An otherwise healthy, 79-year-old Japanese man, ex-smoker, presented to another facility due to 6 days of high fever and fatigue. High-resolution computed tomography (HRCT) of his chest showed multiple bilateral ground-glass opacities predominantly in the subpleural areas with emphysematous lesions. The patient was diagnosed with COVID-19 pneumonia based on a nasopharyngeal swab sample using real-time reverse-transcriptase-polymerase-chain-reaction (rRT-PCR) for SARS-CoV-2 and transferred to our hospital. On physical examination, his temperature was 37.7 °C, blood pressure was 170/102 mmHg, pulse was 93 beats/min, respiratory rate was 20 breaths/min, and oxygen saturation was 94% on supplemental oxygen (nasal cannula 2 liters/min). He complained of severe fatigue and moderate hemoptysis. On lung auscultation, fine crackles were heard in the left lower lung field, and a bedside chest X-ray showed patchy peripheral left lung opacities (Figure 1). Laboratory examinations showed thrombocytopenia (platelets: 86,000/μL) and a slight increase in C-reactive protein (CRP: 3.05 mg/dL). The semiquantitative SARS-CoV-2 load of the nasopharyngeal swab sample was assessed by a reverse-transcription loop-mediated-isothermal-amplification (RT-LAMP) assay, as previously reported[5]. The time to obtain a positive result was classified as ++ ($\leq$ 8 min) and + (> 8 min).

Treatment for COVID-19 pneumonia was initiated with favipiravir (3200 mg/day on day 1, 1600 mg on days 2-14), ciclesonide inhaler (600 μg/day on days 1-10), and azithromycin (2 g/day on day 1) (Figure 2). These drugs had been considered part of standard treatment during the earliest phase of the pandemic in Japan and were administered with the patient's consent. On day 3, the patient had a high fever, and his oxygen saturation dropped to 90% on supplemental oxygen (nasal cannula 2 liters/min). The patient was started on high-flow-nasal-cannula oxygen (PaO_2/FiO_2 ratio 215) and administered methylprednisolone (250 mg/day). On day 13, CRP, ferritin, and D-dimer levels were elevated without worsening oxygenation. On day 15, his respiratory condition deteriorated (PaO_2/FiO_2 ratio 102), and his SARS-CoV-2 viral load was increased. A portable chest X-ray and HRCT showed increased bilateral peripheral consolidation and diffuse ground-glass opacities. The treatment was switched to hydroxychloroquine (400 mg/day on days 15-23) and azithromycin (2 g/day on day 15). Hydroxychloroquine was considered one of the standard treatments at that time. Nevertheless, on day 20, his respiratory condition, inflammatory markers, and D-dimer had worsened. A portable chest X-ray showed increased diffuse bilateral consolidation. On day 22, however, the SARS-CoV-2 viral load of his nasopharyngeal swab samples became negative. Although a portable chest X-ray showed remarkable improvement

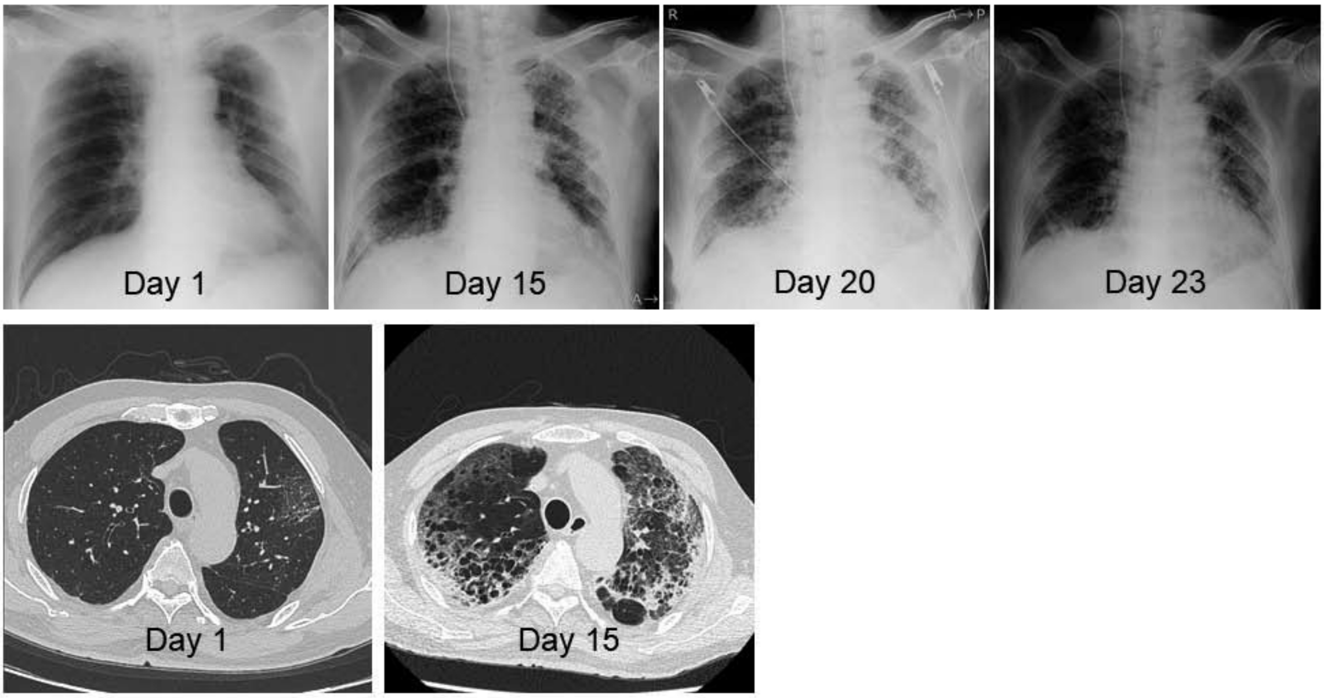

Figure 1. Serial chest X-ray and high-resolution computed tomography images of the patient.
The top row shows progression of prominent bilateral peripheral infiltration on chest X-ray, which resolves on day 23 of admission. The bottom row shows the HRCT on day 1 and day 15 with worsening of bilateral peripheral consolidation and diffuse ground-glass opacities on day 15.

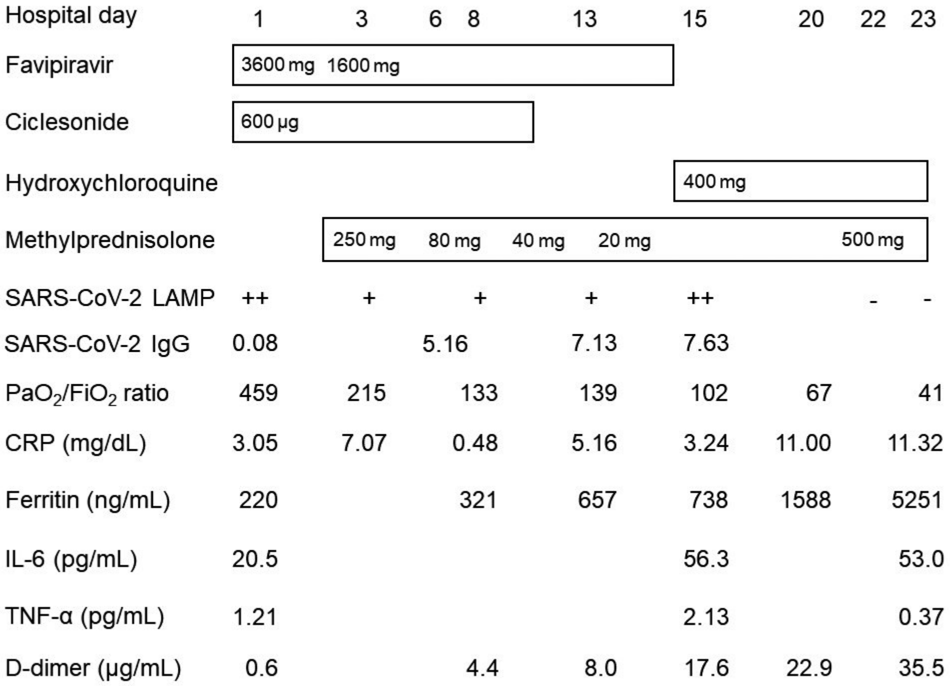

Figure 2. Treatment regime and laboratory data of the patient.
Of note, the SARS-CoV-2 viral load of the nasopharyngeal swab sample becomes negative on day 22. The patient dies possibly due to pulmonary thrombosis on day 23.
LAMP: loop-mediated-isothermal-amplification.

in the diffuse bilateral infiltration, the patient unfortunately died of possible pulmonary thrombosis on day 23. D-dimer was markedly elevated to 35.5 μg/mL (upper limit: 1 μg/mL), whereas serum IL-6 was 53.0 pg/mL (upper limit: 4.0 pg/mL) and TNF-α was 0.37 pg/mL (upper limit: 1.66 pg/mL). On day 23, the electrocardiogram showed sinus tachycardia (113 beats/min), and the presence of an S wave in lead I and a Q wave with T wave inversion in lead III, consistent with pulmonary thrombosis. There was no evidence of QT prolongation or serum creatine phosphokinase elevation. The Wells score of 7.0 points with the positive D-dimer resulted in the probability of pulmonary embolism of 79.6%[6]. No leg swelling suggesting deep vein thrombosis was observed. Due to the patient's family's request, post-mortem CT was not performed.

Discussion

A previous pathological study showed microthrombi in pulmonary arterioles in both damaged and normal lung parenchyma in a fatal COVID-19 case[7]. A high serum D-dimer level is associated with mortality in COVID-19[8]. The severe hypoxemia in the present case may, at least in part, have resulted from pulmonary intravascular microthromboses. Currently, administration of heparin is provisionally recommended for some patients with COVID-19[9], but heparin was not given to the present patient due to persistent hemoptysis and possible diffuse alveolar hemorrhage. Aggressive administration of heparin might have saved this patient.

The present case highlights the following important finding. The level of serum D-dimer had been increasing dramatically during treatment, but the elevations of serum IL-6 and TNF-α were mild compared with previous reports[10, 11]. Several studies have shown that serum IL-6 levels were associated with the severity of COVID-19 pneumonia[12]. Further, it is widely known that cytokine elevation, such as in hyperinflammation or cytokine storm, increases the D-dimer level and causes coagulopathy in COVID-19 patients[13]. However, inflammatory cytokine elevations in patients with severe and critical COVID-19 are profoundly lower than those reported in patients with acute respiratory distress syndrome (ARDS) unrelated to COVID-19 and sepsis[14]. The vital question in the progression of COVID-19 lies in determining the link between the immune response and coagulation[13]. To date, anti-cytokine monoclonal antibodies that block IL-6 have been the most intensively studied treatments[15]. Recently, in addition to treatment with immunosuppressive medicines and anticoagulants, host-directed therapeutic pathways such as anti-von Willebrand factor monoclonal antibodies, activated complement C5a inhibitors, and recombinant ADAMTS13 have emerged to treat COVID-19-associated coagulopathy[15].

In the current COVID-19 pandemic, patients with hyperinflammation are admitted to the hospital, but many patients with mild to moderate COVID-19 have to stay home in Japan[3]. Although oxygen and oral dexamethasone have been encouraged in these settings, anticoagulants are not considered[16]. Unexpectedly, some patients have been found dead throughout the world, possibly due to pulmonary thrombosis[4]. Although the COVID-19 treatment guidelines of the National Institutes of Health reject the administration of anticoagulants as prophylaxis for non-hospitalized patients with COVID-19[17], it could prevent sudden death at home of patients with a risk of hypercoagulation, such as those with obesity, hypertension, and type 2 diabetes mellitus[1]. Further research is necessary to evaluate the benefits of anticoagulation therapy in non-hospitalized patients.

The present case report had some limitations. The lack of a contrast-CT scan on the day of the patient's death resulted in an inability to confirm the presence of pulmonary thrombosis because of his severe respiratory failure. Additionally, elimination of viral load may have resulted from the natural course. Last, it was not possible to analyze von Willebrand factor, complement, or ADAMST13 activity in the present case. However, the improvement of pulmonary infiltration on chest X-ray and the deterioration of hypoxemia with serum D-dimer elevation was attributed to possible pulmonary thrombosis.

In conclusion, COVID-19 continues to spread, and novel therapeutic strategies against the COVID-19 pandemic are required. The present case suggests that methods to identify the patients at risk of virus-induced hypercoagulation are needed, and that the administration of anticoagulants could potentially prevent sudden death from pulmonary thrombosis in some patients.

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Ethical approval

The antiviral agents were approved by the institutional committee for compassionate use. Written, informed consent was obtained from the patient's family for publication of this case.

Declaration of interests

The authors declare no conflicts of interest.

References

1. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol* 2: e437-e445, 2020. https://doi.org/10.1016/S2665-9913(20)30121-1
2. Varga Z, Flammer AJ, Steiger P et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 395: 1417-1418, 2020. https://doi.org/10.1016/S0140-6736(20)30937-5
3. Tasuku M, Yoshihiro Y, Bon O. Strategies for preventing sudden unexpected COVID-19 deaths at home. *Resuscitation* 157: 106-107, 2020. http://dx.doi.org/10.1016/j.resuscitation.2020.09.039
4. Benzakoun J, Hmeydia G, Delabarde T et al. Excess out-of-hospital deaths during the COVID-19 outbreak: evidence of pulmonary embolism as a main determinant. *Eur J Heart Fail* 22: 1046-1047, 2020. https://doi.org/10.1002/ejhf.1916
5. Kurosaki Y, Martins DBG, Kimura M et al. Development and evaluation of a rapid molecular diagnostic test for Zika virus infection by reverse transcription loop-mediated isothermal amplification. *Sci Rep* 7: 13503, 2017. https://doi.org/10.1038/S41598-017-13836-9
6. Wells PS, Anderson DR, Rodger M et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 83: 416-420, 2000.
7. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. *J Thromb Haemost* 18: 1517-1519, 2020. https://doi.org/10.1111/jth.14844
8. Zhang L, Yan X, Fan Q et al. D-dimer levels on admission to predict in-hospital mortality in patients with COVID-19. *J Thromb Haemost* 18: 1324-1329, 2020. https://doi.org/10.1111/jth.14859
9. Thachil J, Tang N, Gando S et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 18: 1023-1026, 2020. https://doi.org/10.1111/jth.14810
10. Yao Y, Cao J, Wang Q et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. *J Intensive*

Care 8: 49, 2020. https://doi.org/10.1186/s40560-020-00466-z

11. Del Valle DM, Kim-Schulze S, Huang HH et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 26: 1636-1643, 2020. https://doi.org/10.1038/s41591-020-1051-9
12. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis* 71(15): 769-777, 2020. https://doi.org/10.1093/cid/ciaa272
13. Shreya RS, Kedar SP, Lokesh KB. Cytokine storm associated coagulation complications in COVID-19 patients: pathogenesis and management. *Expert Rev Anti Infect Ther* 19: 1397-1413, 2021. https://doi.org/10.1080/14787210.2021.1915129
14. Leisman DE, Ronner L, Pinotti R et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med* 8: 1233-1244, 2020. https://doi.org/10.1016/s2213-2600(20)30404-5.
15. Plasek J, Gumulec J, Maca J et al. COVID-19 associated coagulopathy: mechanisms and host-directed treatment. *Am J Med Sci* S0002-9629(21)00403-1, 2021. https://doi.org/10.1016/j.amjms.2021.10.012
16. Japan COVID-19 Case Management Guide Review Committee. Clinical management of patients with COVID-19: a guide for front-line healthcare workers. Version 6.0. [Internet]. In Japanese. Available from: https://www.mhlw.go.jp/content/000851082.pdf. Accessed Nov 2, 2021.
17. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/. Accessed Nov 14, 2021.