（1）報告タイトル：Two cases with Coronavirus Disease 2019 (COVID-19) Pneumonia Treated with Hydroxychloroquine

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（2）症例

（3）経過

CASE 1

A man of late-sixties, who was an ex-smoker, visited his local hospital because of general fatigue and a fever over

38 ℃ that lasted 2 days. He was prescribed antipyretics. Seven days later, he was admitted to our hospital following consultation from his local hospital by direction of the health center because he was diagnosed with pneumonia. Clinical course and chest high-resolution CT (HRCT) images were shown in figure 1. He had no respiratory symptoms, including cough or dyspnea, and no abnormality on chest radiograph. Chest HRCT images showed patchy ground-glass attenuation (GGA) predominantly in a subpleural lesion, a finding which is consistent with those previously reported for coronavirus disease 2019 (COVID-

19) pneumonia. In our hospital, the patient was diagnosed with COVID-19 pneumonia based on a positive test result from a polymerase chain reaction (PCR) test for severe acute respiratory syndrome CoV-2 (SARS-CoV-2) on an oropharyngeal swab sample. Test results of naso/oropharyngeal swab samples for antigens of influenza, respiratory syncytial virus (RSV), and adenovirus were negative. The patient had been treated for type 2 diabetes mellitus, hyperlipidemia, chronic kidney disease, hypertension, and benign prostatic hyperplasia in his local hospital. Vital signs on admission were as follows:

respiratory rate, 20 breaths/min; SpO_2, 95% (room air); heart rate, 90 beats/min; blood pressure, 149/82 mmHg; and body temperature, 38.5 °C. Auscultation revealed no abnormal respiratory or heart sounds. Hematology and other laboratory examinations showed a slight increase in the levels of C-reactive protein (CRP; 20.17 mg/dL), lactate dehydrogenase (LDH; 518 IU/ml), creatinine (Cr 1.24 mg/dL), and D-dimmer (1.2 μg/ml). Arterial blood gas analysis showed hypoxemia (PaO_2, 63.1 torr; PaO_2/FiO_2 ratio, 315.5 torr) and hypocapnia ($PaCO_2$, 32.4 torr). We started treatment with lopinavir and ritonavir (800 and 200

mg/day, respectively), peramivir (300 mg), and levofloxacin (500 mg/day) at admission. However, treatment with lopinavir and ritonavir was discontinued on day 7 because the patient had appetite loss, which was suspected to be a side effect of those drugs. On day 3 after admission, the patient's hypoxemia further deteriorated (PaO_2/FiO_2 ratio, 120 torr). HRCT images showed an expansion of GGA and a change from GGA to constructed consolidation. The patient was started on respiratory management by endotracheal intubation and mechanical ventilation, and he was relocated to another hospital capable of performing extracorporeal

membrane oxygenation as required for further disease deterioration. After changing hospitals (day 3), the patient began treatment with protective lung ventilation, which is standard treatment for acute respiratory distress syndrome, and hydroxychloroquine (400 mg/day). On day 4, he was started on continuous hemodiafiltration for deterioration of his CKD. His fever, respiratory condition, and elevated inflammatory parameters all improved (CRP, 5.64 mg/dL; LDH, 329 IU/L; PaO_2/FiO_2, 300 on day 12). The patient stopped treatment with hydroxychloroquine on day 9 and returned our hospital on day 15. On day 16, recurrence of

COVID-19 pneumonia was suspected because his HRCT images showed a change from GGA to contracted consolidation predominantly in the right upper lobe, and PaO_2/FiO_2 ratio had decreased to 159, so he re-started treatment with hydroxychloroquine. In addition, we also started treatment with linezolid (1,200 mg/day) because methicillin-resistant staphylococcus aureus (MRSA) was detected by culture of sputa obtained in the other hospital. After the treatment change, the patient's fever, elevated CRP and LDH levels, and PaO_2/FiO_2 ratio all improved. The endotracheal intubation and mechanical ventilation were

withdrawn on day 22. HRCT images taken on day 26 showed a reduction of consolidation and GGA. We confirmed his recovery with negative results from a PCR test for SARS-CoV2, then stopped treatment with hydroxychloroquine. The patient was discharged on day 38 and his condition was stable after discharge.

CASE 2

A woman of mid-sixties visited her local hospital with a temporal shivering fever over 38 ℃, but this fever improved without intervention. Three days later, she visited

our hospital in compliance with direction from the health center on suspicion of a secondary COVID-19 infection contracted from her husband, who had been diagnosed with COVID-19 pneumonia. Clinical course and chest HRCT images were shown in figure 2. This patient had no symptoms, and her chest radiograph was normal. However, patchy peripheral GGA involving subpleural area in the right lower lobe, that was consistent with previously reported findings of COVID-19 pneumonia. She was admitted to our hospital and diagnosed with COVID-19 pneumonia based on positive results from a PCR assay for

SARS-CoV-2 from an oropharyngeal swab sample. Tests results from similar samples for antigens of influenza, RSV, and adenovirus were negative. The patient's medical history included only a mackerel allergy, and she had no history of smoking. Her vital signs on admission were as follows: respiratory rate, 18 breaths/min; SpO_2, 96% (room air); heart rate, 96 beats/min; blood pressure, 151/70 mmHg; and body temperature, 36.7 °C. Auscultation revealed no abnormal respiratory or heart sounds. Hematology and other laboratory examinations showed slightly elevated levels of C-reactive protein (CRP; 0.62 mg/dL) and lactate

dehydrogenase (LDH; 245 IU/ml), along with lymphocytopenia (610 cells/μl). Clinical course and chest high-resolution CT (HRCT) images were shown in figure 2. At the time of hospital admission, the patient did not have any symptoms. However, on day 4 after admission, she had a fever (38.3 ℃), so she was started on treatment with levofloxacin (500 mg/day), lopinavir (800 mg/day), and ritonavir (200 mg/day). On day 6, the lopinavir and ritonavir were discontinued because the patient had diarrhea that was suspected to be a side effect of those drugs. On day 7, her condition had deteriorated; she had an elevated

body temperature (39.1 ℃), high CRP level (8.25 mg/dL), high LDH level (353 IU/L), and decreased SpO_2 (91% on room air), so we started treatment with hydroxychloroquine (400 mg/day). On day 7, HRCT showed newly appeared GGA in the right lobe. Interlobular septal thickening, perilobular opacities, and curvilinear lines were also observed in the peripheral zone of both lungs. After treatment with hydroxychloroquine, the patient's fever was improved on day 9, and all other symptoms improved on day 15 as follows: CRP, 0.19 mg/dL; LDH, 208 IU/L; and SpO_2, 98% on room air. We confirmed that results from a PCR assay for

SARS-CoV2 had changed to negative, then stopped treatment with hydroxychloroquine. The patient was discharged on day 16, and follow-up HRCT images taken on day 19 showed improvement. Her condition was stable after discharge.

（4）考察

The basic therapeutic strategy for COVID-19 is symptomatic and consists of therapies such as intravenous infusion and oxygen administration. Treatments with several drug candidates for reducing the risk of acute respiratory distress syndrome (ARDS) development have been attempted in COVID-19 patients, and clinical trials of some antiviral drugs, including remdesivir and favipiravir [1-2]. Anti-inflammatory drugs such as corticosteroid and monoclonal anti-interleukin (IL)-6 antibody have been also theorized to suppress the progression of COVID-19 to ARDS

[3-4].

Hydroxychloroquine and chloroquine phosphate, which are widely-used anti-malarial drugs that are also used to treat autoimmune diseases such as systemic lupus erythematosus, exert antiviral effects by increasing the endosomal pH to a level above that required for virus/cell fusion. They also can interfere with the glycosylation of cellular receptors for SARS-CoV [5-7]. The combination therapy with hydroxychloroquine and the 15-membered macrolide antibiotic azithromycin (AZM) has been attempted for treating COVID-19. The SARS-CoV-2 RT-PCR

negative conversion rate (i.e., rate of confirmed COVID-19 patients later obtaining negative SARS-CoV-2 RT-PCR results) after combined treatment with hydroxychloroquine and AZM was 83% and 93% on disease days 7 and 8, respectively [8]. Additionally, a retrospective study conducted in New York suggested that the incidence of cardiac arrest was significantly higher in patients receiving both hydroxychloroquine and AZM (15.5%) but not in those receiving hydroxychloroquine (13.7%) or AZM (6.2%) alone, compared with patients receiving neither drug (6.8%) [9]. Although that cohort study found no significant differences

in the relative likelihood of abnormal electrocardiogram findings among patient groups, it also revealed that therapy with hydroxychloroquine and/or AZM did not significantly improve in-hospital mortality [9]. However, the interpretation of these findings may be limited by the observational design of that study. In the present cases, COVID-19 pneumonia was improved after treatment with hydroxychloroquine and had no cardiac events such as arrhythmia. The therapeutic efficacy and tolerability of hydroxychloroquine as a treatment for COVID-19 should be established by further clinical studies.

（5） 結 論

Randomized controlled trial is required to clarify the efficacy and tolerability of hydroxychloroquine

We hope that we will overcome this phase of Corona trouble as soon as possible.

（6） 引 用 文 献

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（7） 図・写真の説明

（8） 表

（9） 図・写真

Figure 1. Clinical course of Case 1

Disease day	1	4	7	10	13	16	19	22	25	28	38
Lopinavir and ritonavir	800/200 mg/day										
Levofloxacin	500 mg/day										
Sulbactam/Ampicillin	500 mg/day										
Linezolid						1200 mg/day					
Hydroxyhloroguine			400 mg/day			400 mg/day					
↑ **Peramivir** 300 mg											
Mechanical ventilation											
	↑ **Change of hospital**					↑ **Return to hospital**					↑ **Discharge**

COVID-19-PCR	Positive									Negative	
Body temprature (℃)	38.5	39.8	38.0			37.1	36.8		36.9		
PaO_2/FiO_2 ratio	316	120			350		159		418		
CRP (mg/dL)	20.17	24.52	8.43		5.64	6.16	9.18		0.85		
LDH (IU/mL)	518	576	470		329	339	261		263		
KL-6 (IU/mL)	224					391			286		

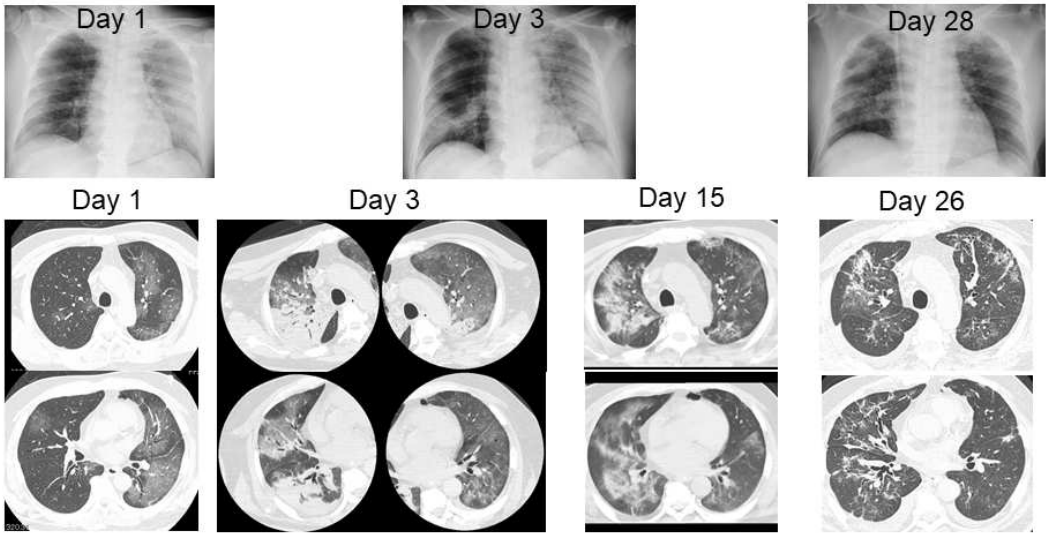

Figure 2. Clinical course of Case 2

Disease day	1	4	7	10	13	16
Lopinavir and ritonavir	800/200 mg/day					
Levofloxacin	500 mg/day					
Hydroxychloroguine	400 mg/day					
O_2 inhalation dose	2 L/minutes					
						↑ **Discharge**
COVID-19-PCR	Positive				Negative	
Body temprature (℃)	36.7	38.3	39.1	37.1	37.5	37.4
SpO_2 (%)	96 (room air)	96 (room air)	91 (room air)	96 (O_2 1 L/min)	96 (room air)	98 (room air)
CRP (mg/dL)	0.62	0.53	8.25	2.15	0.41	0.19
LDH (IU/mL)	245	229	353	267	224	208
KL-6 (IU/mL)	209		236		232	

Day 0 **Day 7**

Day 19