Report of 15 cases of Covid-19 including 3 cases requiring mechanical ventilation

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Background: Novel Coronavirus Infection (COVID-19)
Starting in Wuhan, China in December 2019, the number of infected people worldwide continues to increase after the World Health Organization (WHO) declared pandemic on March 11. As of March 15, 2020, there were a total of 762 cases of positive PCR in Japan (excluding the cruise ship and chartered flights) in Japan, and 141 cases in Hokkaido, where the number was higher than in other prefectures. In Hokkaido, the number of patients with symptom onset in mid-February increased (Fig. 1), and an emergency declaration was issued on February 28.
Our hospital is the only Category I Infectious Diseases Designated Medical Facility in Hokkaido. In addition to two private rooms where patients with Category I Infectious Disease can be hospitalized, there are three rooms for two patients, and up to a total of eight patients can be hospitalized. By March 11, our hospital has treated a total of 15 adult cases of COVID-19, including cases of discharge and transfer (Table 1). It is important to understand the background and clinical course of severe cases. Here, we report three cases requiring mechanical ventilation. Hereinafter, each date of symptom onset is defined as X.

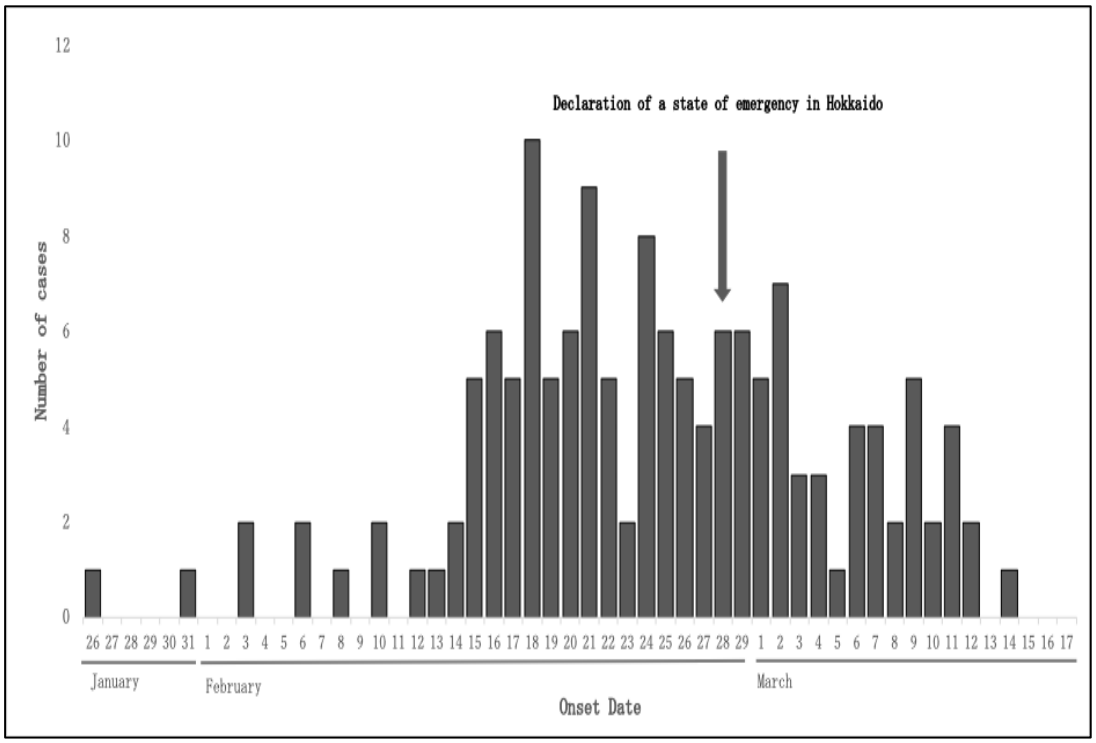


Fig. 1. COVID-19 epidemic curve in Hokkaido (based on information from the Hokkaido Government website as of 12:00 on March 17)

Case		Initial symptoms	Before hospitalization Number of consultations	Before hospitalization Number of consultations	First hospitalization (X: Date of onset)	To our hospital Transfer	Blood collection at first hospitalization				CT glass shadow on both sides (date)		Oxygen start	Intubation	Ciclesonide (start date)	Antiviral drugs (start date)	37.5 ℃ or more duration	Outcome
							WBC	Positive	lymphocytes	CRP								
1	60's male	Diabetes mellitus, hypertension, atrial fibrillation	Fever, malaise	4	X+8	－	2,900	2,001	609	11.6	＋	(X+6)	X+9	X+12	＋ (X+11)	＋ (X+11)	14+ days	Transfer (X + 13)
2	70's male	Hypertension, emphysema, benign prostatic hypertrophy	Fever	3	X+8	X+10	4,700	3,826	517	11.58	＋	(X+8)	X+8	X+8	＋ (X+8)	＋ (X+10)	16 days	Discharge (X + 15)
3	50's male	Diabetes mellitus, Dyslipidemia, Hyperuricemia, Sleep Anpnea Syndrome	Fever, cough	4	X+11	X+15	11,510	10,612	541	31.59	＋	(X+11)	X+11	X+12	－	＋ (X+18)	25 days	Transfer (X + 27)
4	40's female	Hypothyroidism	Fever, cough	1	X+1	－	2,400	NA	NA	＞0.74	＋	(X+1)	X+1	－	－	－	6 days	Discharge (X + 19)
5	40's male	Nephrolithiasis	Fever, cough, nasal discharge, sore throat	1	X+5	－	4,000	2,236	1,320	0.35	＋	(X+5)	－	－	－	－	10 days	Discharge (X + 20)
6	50's male	Diabetes mellitus, hypertension, atiral fibrillation, CML, CKD, asthma	Fever, cough, nasal discharge, sore throat	3	X+4	－	9,800	7,742	1,274	7.33	－	(X+2)	－	－	－	－	7 days	Transfer (X + 10)
7	40's male	gout	Malaise, joint pain, muscle pain	3	X+11	－	3,100	1,457	341	1.5	＋	(X+9)	－	－	－	－	13 days	Discharge (X + 25)
8	40's male	Tonsillectomy	Fever	2	X+7	－	4,400	2,803	1,131	1.51	＋	(X+6)	－	－	－	＋ (X+7)	12 days	During treatment
9	40's male	None	Fever	3	X+10	－	4,730	3,358	1,178	10.7	＋	(X+7)	X+12	－	－	＋ (X+12)	21 days	During treatment
10	60's female	Diabetes mellitus, ashtma	Fever, diarrhea	3	X+4	X+7	2,300	1,451	651	3.14	＋	(X+4)	－	－	＋ (X+6)	－	8 days	During treatment
11	50's male	Diabetes mellitus, Hypertension, Dyslipidemia	Fever	5	X+13	X+14	NA	NA	NA	NA	＋	(X+13)	X+13	－	＋ (X+14)	＋ (X+14)	20 days	During treatment
12	80's male	Atrial fibrillation, liver cancer, emphysema	Chills, cough, nasal discharge	1	X+7	－	4,300	2,640	1,118	5.77	＋	(X+7)	X+8	－	＋ (X+8)	＋ (X+10)	13 days	During treatment
13	20's female	Epilepsy	cough	1	X+5	－	4,100	2,054	1,640	0.9	＋	(X+5)	－	－	－	－	6 days	During treatment
14	50's male	Diverticulitis	Pain in the body, dizziness	1	X+10	－	4,900	3,283	1,421	0.25	－※	(X+10) unilateral+	－	－	－	－	5 days	During treatment
15	50's female	Meniere's disease, sinusitis	Fever	5	X+8	X+9	3,100	1,922	899	1.16	＋	(X+8)	－	－	－	－	9 days	During treatment

NA＝not available

Table 1. case summary (as of March 11, 2020)

Case 1: Man in his 60's

Chief complaint: general fatigue, fever

Past medical history: diabetes mellitus, hypertension, atrial fibrillation

History of present illness:

Day X: Patient presented to medical institution A (1st visit) with fever of 37.5℃. First influenza antigen test was negative. He was sent home with symptomatic treatment.

X + 1 day: He visited the same medical institution A (2nd visit) for persisting fever of 37 to 38℃. The second influenza antigen test was negative. He was sent home with symptomatic treatment.

X + 5 days: He visited the same medical institution A (3rd visit) for persisting fever of 38℃ and higher. The third influenza antigen test was negative. He denied shortness of breathless and SpO_2 was 95% in the room air. He was sent home with cefcapene. He started to have a fever of 40℃, cough, and rhinorrhea after returning home.

X + 6 days: He visited the same medical institution A (4th visit), then he was referred to our hospital by the Sapporo City Public Health Center for suspected COVID-19. Nasopharyngeal specimen was obtained for SARS-CoV-2 PCR. Vital signs at initial consultation was temperature 37.7℃, heart rate 70 beats per minute, respiratory rate 14 breaths per minute, and SpO_2 97% (room air). The patient was in good physical condition without any respiratory distress. Chest CT ishowed ground glass opacity bilaterally. Clinical course and imaging study were considered to be consistent with COVID-19 (Fig. 2-1). He was sent home until the PCR result.

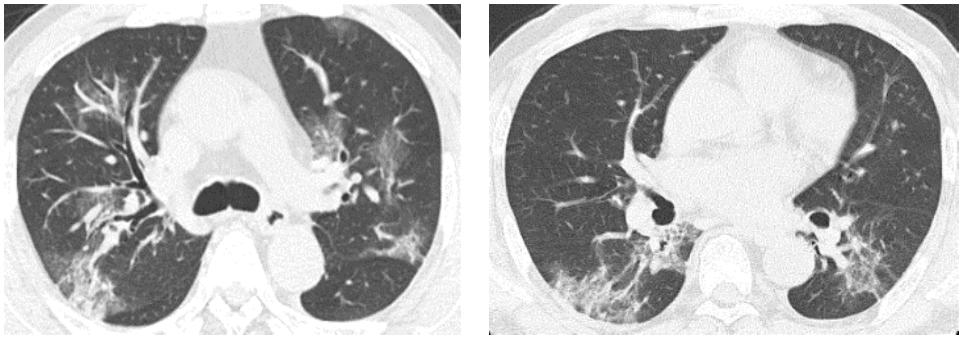


Fig. 2-1. Case 1: X + 6 days

Day X + 8 days: Nasopharyngeal SARS-CoV-2 PCR was confirmed positive, and he was admitted to our hospital.

Review of systems:

Positive: fever, general fatigue, cough, rhinorrhea

Negative: headache, nausea, sore throat, shortness of breath, abdominal pain, diarrhea, arthralgia, rash Physical examination on admission: Alert and oriented. Temperature 39.3℃, heart rate 82 beats per minute, blood pressure 141/62 mmHg, respiratory rate 12 breaths per min, SpO_2 97% (room air). A fine crackle was heard on bilateral lower lobe. Abdomen soft and flat, non-tender.

Blood test on admission: WBC 2,900 / μL (Seg 72%, Lym 21%), CRP 11.6mg/dL, PCT 0.08ng / mL, AST 44 U/L, ALT 25U/L

Culture test: Blood culture (collected on X + 8 days) 2 sets negative, sputum culture (collected on X + 8 days) negative

Hospital course:

On admission (X + 8 days), fever around 39℃ and cough were noted. However, there was no hypoxia and he denied shortness of breath. Due to drug interactions with rivaroxaban and other medication, lopinavir / ritonavir was not initiated. On X + 9 days, although he remained relatively mild symptom, his oxygenation level decreased, and 3 L/min of oxygen was started. Chest X-ray on the same day showed bilateral upper lobe infiltration (Fig.2-2). Ampicillin sulbactam 3g every 8 hours was added for possible concomitant bacterial pneumonia.

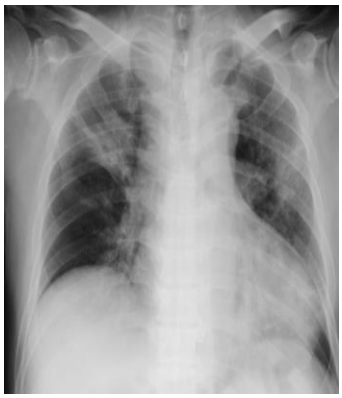


Fig. 2-2. Case 1: X + 9 days

On X + 10 days, Chest X-ray and chest CT showed worsening of bilateral pneumonia (Fig. 2-3). Blood pressure dropped at the same night, antibiotics was changed to meropenem 1g every 8 hours for possibel septic shock. On X + 11 days, oxygenation status became worse and nasal high flow therapy was initiated, however, his SpO_2 remained around 90% with FiO_2 of 1.0. Because of the rapid deterioration of oxygenation, favipiravir was stared after accelerated approval by hospital ethics committee regarding its off-label and compassionate use. Favipiravir was given 1,800 mg twice every 12 hours on day 1, then 800 mg once every 12 hours from day 2. In addition, ciclesonide 200μg inhalation four times a day also started on the same day. On X + 12 days, respiratory condition became worse, and he was intubated and mechanical ventilation was started. were managed. On X + 13 days, due to lack of improvement, he was transferred to another hospital for introduction of ECMO.

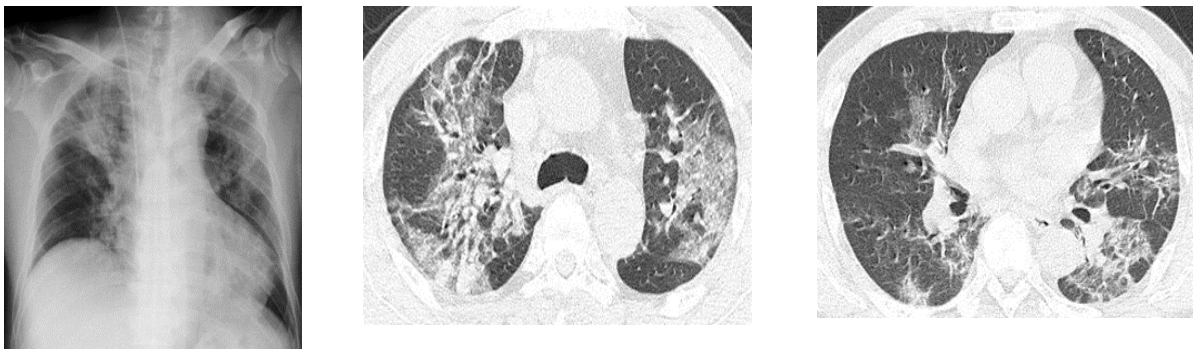


Fig. 2-3. Case 1: X + 10 days

Case 2: Man in his 70's

Chief complaint: fever

Past medical history: hypertension, emphysema, benign prostatic hyperplasia

History of present illness:

Day X: Patient started to have fever of 37.6℃, then fever of 37 to 38℃ persisted thereafter.

X + 2 days: He visited medical institution B (1st visit). He was sent home with garenoxacin.

X + 5 days: He visited the same medical institution B due to persistent fever (2nd visit) and chest pulmonary image Follow-up.

X + 8 days: He visited the same medical institution B (third visit). Chest X-ray showed pneumonia, and he was referred to medical institution C. Vital sign at that time showed temperature 38.8℃, SpO_2 87% (room air). He was admitted with 2 L/min oxygen. Chest CT showed diffuse ground-glass opacities bilaterally (Fig. 3-1). For possible COVID-19, sputum and throat swab specimen were obtained for SARS-CoV-2 PCR testing. Respiratory

condition worsened, endotracheal intubation was performed and mechanical ventilation was started. Levofloxacin and ciclesonide were started.

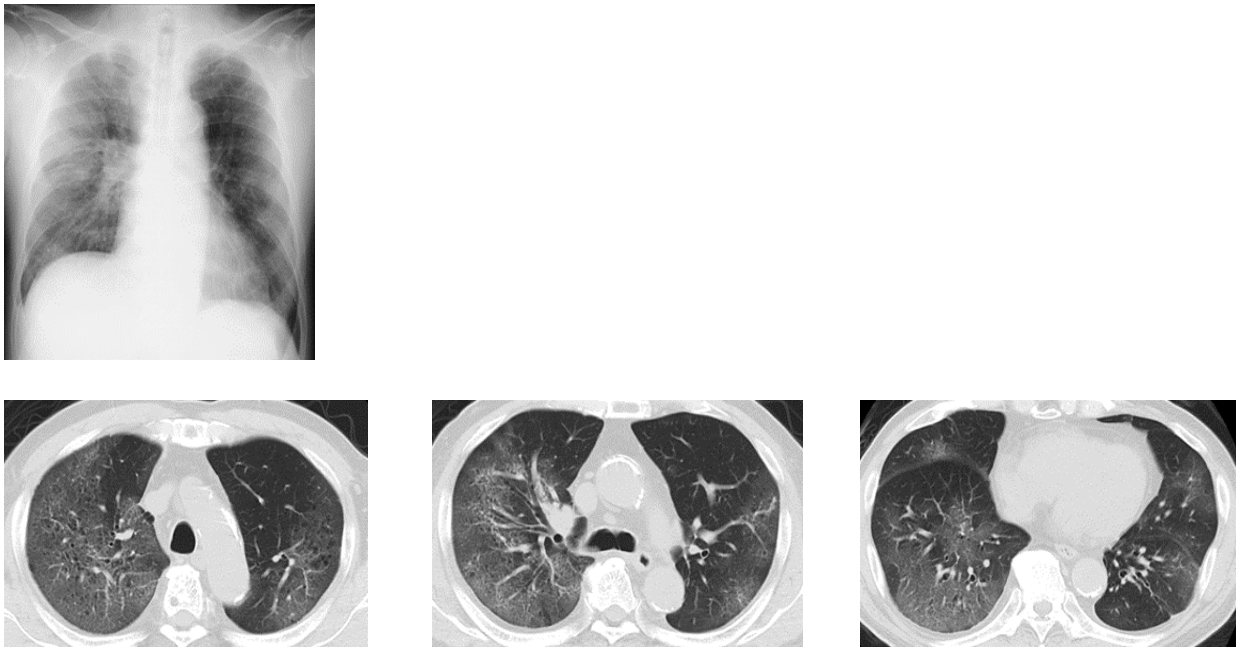
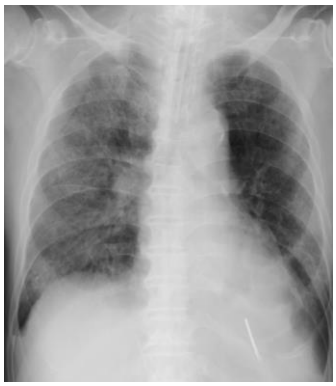
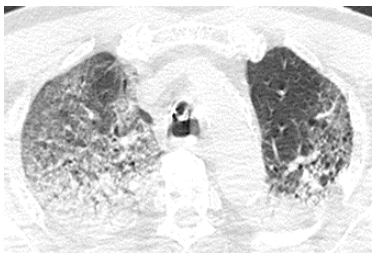
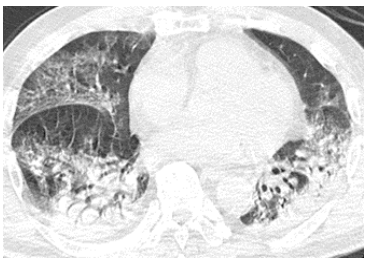


Fig. 3-1. Case 2: X + 8 days

X + 9 days: SARS-CoV-2 PCR was found to be positive.
X + 10 days: Patient was transferred to our hospital.
Vital signs on admission: temperature 37.7℃, heart rate 71 beats per minutes, blood pressure 83/54 mmHg, respiratory rate 20 breaths per minute, SpO_2 90%.
Ventilator settings on admission: SIMV + PS, FiO_2 1.0, PEEP12, PC15, PS8
Blood test on admission: WBC 8,600/μL (Seg 87%, Lym 5%), CRP 10.68 mg /dL, PCT 0.08 ng / mL, AST 53 U/L, ALT 25U/L
Culture test: Blood culture 1 set negative on X + 10 days,
urine culture negative on X + 10 days, endotracheal aspiration sputum culture with normal flora on X + 10 days
Hospital course:
Patient was in severe respiratory failure on admission to our hospital transfer (X + 10 days) and he was transferred to the ICU. Chest X-ray and chest CT on the same day showed rapid progression of bilateral ground-glass opacities (Fig. 3-2).
Ciclesonide was increased to 400 μg three times a day for severe COVID-19, and lopinavir / ritonavir 5mL (400mg /100mg) twice daily was started. Since no improvement of pneumonia was confirmed, ceftriaxone 2g daily was added for possible complication with bacterial pneumonia, On the same day, right chest tube was inserted for pneumothorax. Medical condition did not improve, and he died on day X + 15 days due to COVID-19 associated respiratory failure.







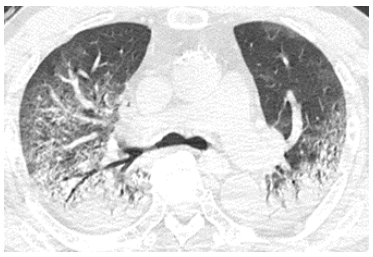


Fig. 3-2. Case 2: X + 10 days

Case 3: Man in his 50's

Chief complaint: fever, general fatigue, cough

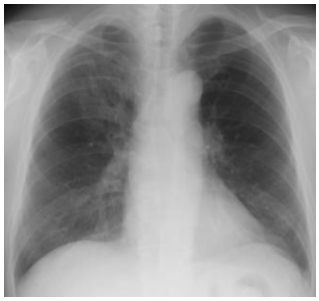
Past medical history: diabetes mellitus, hypertension, dyslipidemia, hyperuricemia, sleep apnea syndrome

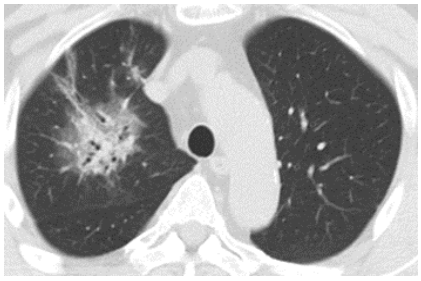
History of present illness:

Day X: Patient started to have fever, malaise, and cough.

X + 3 days: He visit medical institution D (1st visit), and first influenza antigen test for influenza was negative.

Day X + 4 days: He visited the same medical institution D (2nd visit), and the 2nd influenza antigen test was negative. Chest X-ray showed pneumonia in upper right lung field. He was referred to medical institution E where chest CT was obtained (Fig. 4-1). He was sent home for pneumonia after ceftriaxone administration and azithromycin prescription.





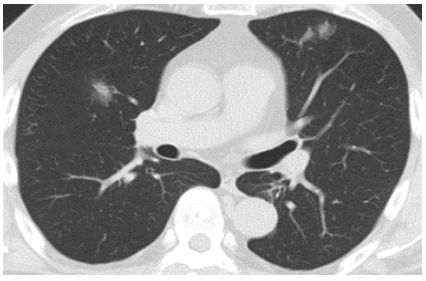


Fig. 4-1. Case 3: X + 4 days

X + 7 days: He visited the same medical institution E (3rd visit). Ceftriaxone was given and he was sent home with garenoxacin prescription.
X + 11 days: He visited medical institution F due to persistent fever and shortness of breath. At consultation, temperature 38.7℃, SpO_2 around 80% (room air), and chest CT showed worsening of pneumonia bilaterally (Fig. 4-2). After admission, nasal high flow therapy, steroid pulse therapy for ARDS, and meropenem and minocycline for possible complication of bacterial pneumonia were started.

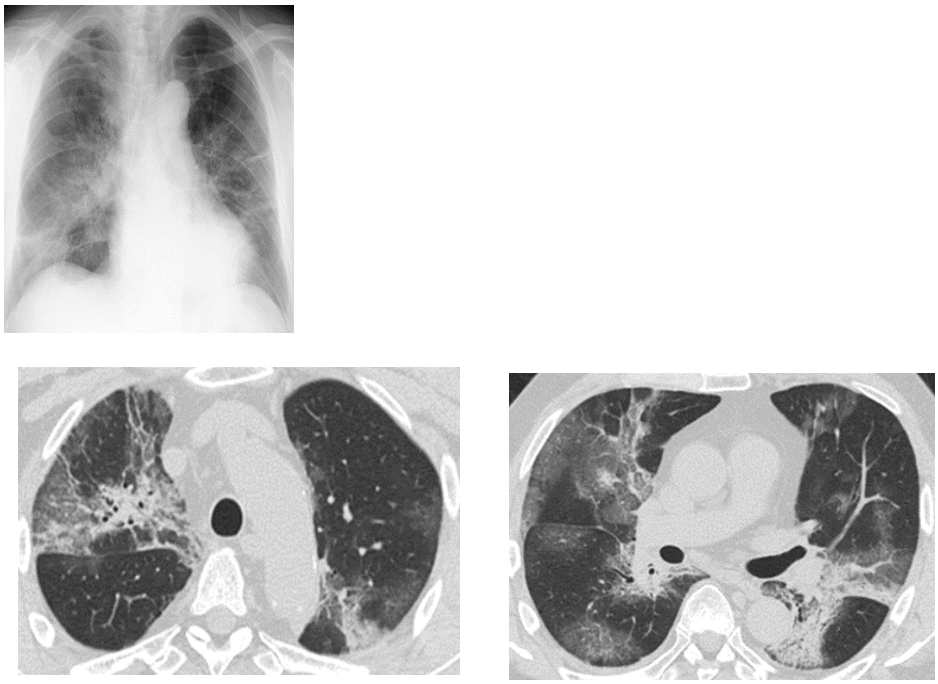


Fig. 4-2. Case 3: X + 11 days

X + 12 days: Since respiratory condition did not improve, he was intubated and mechanical ventilation was started in the ICU.
X + 14 days: Although respiratory status improved, cause of severe pneumonia was unknown, SARS CoV-2 PCR test was performed on with sputum and throat swab specimen, which came back positive.
X + 15 days: Transferred to our hospital. Vital signs and physical examination on admission: temperature 37.4℃, heart rate 60 beats per minute, blood pressure 170/80 mmHg, respiratory rate 15 per minute, SpO_2 98%. Fine crackle were noted on bilateral posterior lower lobe diffusely.
Ventilator settings on admission: SIMV + PS, FiO_2 0.6, PEEP10, PS10, RR15
Blood test at admission: WBC 8,600/μL (Seg 90%, Lym 3%), CRP 2.6mg /dL, PCT 0.11ng /mL, AST 185 U/L, ALT 442 U/L.
Culture test: sputum culture *Klebsiella oxytoca* on X + 11 days, endotracheal aspiration sputum with normal flora on X + 15 days. Blood culture 2 sets negative on X + 17 days.
Hospital course:
We did not give systemic steroid based on available recommendations for COVID-19 management. There were no established evidence in antiviral effectiveness at that time. Of clinical trials conducted in China on lopinavir / ritonavir, inclusion criteria were within 7 days of onset (NCT04261907), or within 72 hours after confirmation of abnormal chest X-Ray or symptom onset (NCT04251871). Since patient was transferred 15 days after symptom onset, we initially did not give lopinavir / ritonavir. We discontinued minocycline due to elevated liver function tests, and continued meropenem 1g every 8 hours for possible concomittant bacterial pneumonia. After admission to our hospital, fever above in 39℃ continued every day, and respiratory condition did not improve. Although there was no clear evidence of benefit at that time, we started lopinavir / ritonavir (400/100mg twice daily) from X

+ 18 days after accelerated approval by hospital ethics committee regarding its off-label and compassionate use. On X + 19 days, the intubation tube was blocked due to clogged sputum, he was re-intubated. After this event, respiratory status worsened and there was continuing high risk of re-occlusion of endotracheal tube due to viscous sputum, emergent tracheostomy was performed on the same day. Thereafter, his respiratory condition gradually improved to the point he could participate rehabilitation program in the ICU. His general condition improved to the extent possible. Meropenem was discontinued on X + 21 days. On X + 22 days, chest CT showed organizing process of ground-glass infiltration bilaterally (Fig. 4-3). On X + 23 days, chest X-ray showed bilateral consolidation process possibly due to effect of scarring (Fig. 4-4). After X + 25 days, fever resolved, and a total of two SARS-CoV-2 PCR were negative on X + 25 days and X + 26 days. On X + 27, he was transferred to the High Care Unit. Lopinavir / ritonavir was discontinued on X + 27 days.

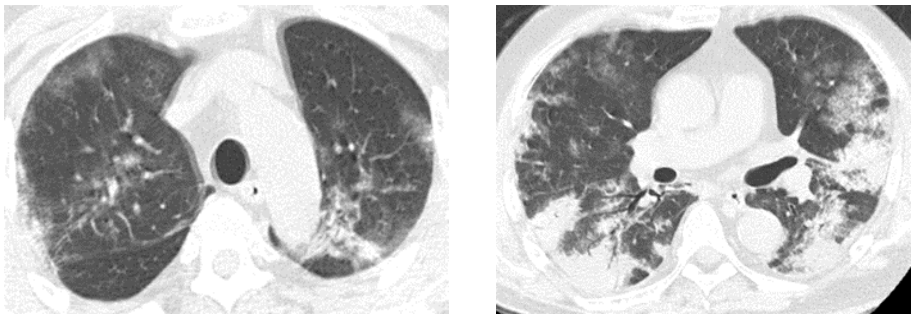


Fig. 4-3. Case 3: X + 22 days

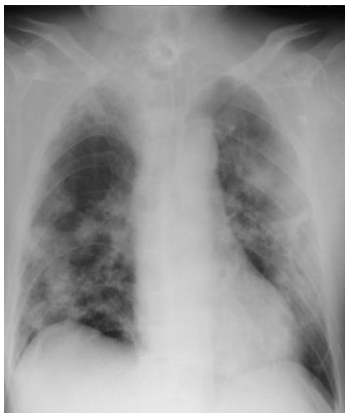


Fig. 4-4. Case 3: X + 23 days

Discussion

In our hospital, 3 cases of COVID-19 who required endotracheal intubation and mechanical ventilation intubation experienced relatively mild symptom until just before the admission. Eight to 11 days after the onset, oxygen was started, and endotracheal intubation were required 1-3 days afterwards. As previously reported[1)], our patients also rapidly deteriorated after oxygen administration became necessary. Risk factors for severe disease are elderly, underlying diseases (hypertension, diabetes mellitus, cerebrovascular diseases, etc.), lymphopenia, increased inflammatory markers [2) 3)]. In our hospital, all intubated patients are over 50 years of age, and had risk factors for severe disease such as hypertension or diabetes. In all three cases, lymphopenia and elevated inflammatory markers were seen. Based on clinical courses of 15 cases in our hospital, among patients over 50 years of age, those who required oxygen administration tended to deteriorate.

At the time of this writing, antiviral drugs and ciclesonide are treatment options. With the approval of the hospital ethics committee, and consent from patients or patients' family, antiviral drugs of lopinavir / ritonavir and favipiravir were given based on guideline from The Japanese Association for Infectious Diseases and reports from China [4) 5)]. According to the guideline, antiviral therapy is indicated for those who are older than 50 years of age

and who require oxygen. Since patients who require mechanical ventilation usually progress rapidly, timing to give antivirals for patients with risk factors for severe disease should be further discussed. In addition, it has been reported that ciclesonide is also effective [6]. We are considering using it in patients with risk factors such as diabetes mellitus. According to package insert, combination of ciclesonide and lopinavir / ritonavir is not recommended due to drug interactions. Care must be taken when choosing drug therapy. Further studies are needed in safety, efficacy, and timing of those treatment.

Lastly, we are facing various problems as there are more SARS-CoV-2 PCR positive patients in Hokkaido. One of those is deficiency of hospital beds espacially due to incresing number of mildly ill patients. At present, asymptomatic virus carriers and patients with mild symptoms are also hospitalized for isolation purpose. Coordination and cooperation work are required between Public Health Center and each hospital in PCR testing at Returnees and Potential Contacts Outpatient and at Public Health Center, triage and bed assignment of mild, moderate, severe patients.

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