Case Report
Two Cases of COVID-19 Pneumonia Including Use of Favipiravir

Akinari Noda [1)], Tatsuya Shirai [1)], Hiromi Nakajima [1)], Miku Oda [1)], Takeshi Saraya [1)], Haruyuki Ishii [1)], Hajime Takizawa [1)], Teppei Shimasaki [2)], Akihiko Sano [2)], Daisuke Kurai [2)], Eisuke Ito [3)], Yukiyoshi Tashima [4)], Yu Hada [5)], Tomoyuki Goto [5)], Shintaro Masuko [6)], Akihiko Katsumata [7)], Masanori Nakajima [8)], Shoichi Ichimura [9)]

1) Department of Respiratory Medicine, Kyorin University Hospital
2) Department of Infectious Diseases, Kyorin University Hospital
3) Department of Elderly Clinic, Kyorin University Hospital
4) Department of Cardiovascular Medicine, Kyorin University Hospital
5) Department of Gastroenterology, Kyorin University Hospital
6) Department of Kidney and Rheumatic Collagen Disease, Kyorin University Hospital
7) Department of Diabetes, endocrinology and metabolism, Kyorin University Hospital
8) Department of Neurology, Kyorin University Hospital
9) Department of Orthopedics, Kyorin University Hospital

Introduction

At the end of 2019, COVID-19 was confirmed to have developed a cluster of pneumonia patients in Wuhan, Hubei Province, China, and has since spread throughout China and has spread worldwide. In Japan, reports have emerged January 15, 2020, of Chinese males in their 30s who have traveled to Wuhan City, and many cases have been brought in mainly by travelers. After that, on January 28, a bus driver who had been carrying a group of travelers from Wuhan City, and a bus guide on January 29, etc., reported domestic cases without a history of traveling. Patient clusters have since been observed in various parts of the country. We report two cases of COVID-19 pneumonia considered to be domestic of origin in our hospital. One of these cases with hypoxemia made off-label use of favipiravir.

Case Report

[Case I] 38-year-old man
[Chief complaint] fever
[Present illness]
He felt pharyngeal discomfort on X Y-7, 2020. Minor fever, malaise, headache, nasal discharge, and wet cough were added on Day Y-5. He had diarrhea about four times a day, chills on Day Y-3, dizziness, and high fever of the order of 38°C from Day Y-2. On the same day, a colleague in the workplace was reported to have confirmed SARS-CoV-2 infection, and was contacted by a public health center. He was referred to our outpatient services on Y-1. The patient was hospitalized on Day Y with a diagnosis of COVID-19 pneumonia because the nasopharyngeal swab specimen became PCR-positive.
[Overseas travel history] None
[Past history] Hyperlipidemia (indicated in health examination but untreated)
[Commonly used drugs] None
[At the time of admission]
Body temperature 35.1°C, respiratory rate 16 breaths/min, SpO_2 97% (room air)
Blood pressure 144/100mmHg, heart rate 84 beats/min
Height 193.7cm, weight 110kg, BMI 29.3

General condition is rather poor and sweaty
No peripheral cold feeling, pale complexion
Head and neck: Conjunctival congestion and small amount of eye discharge (left> right)
Serous nasal discharge from both nostrils, no sinus tenderness
Slightly injected throat, no posterior pharyngeal lymph follicles
No tonsillar swelling
No cervical lymphadenopathy, no jugular vein distention
Chest: normal heart and lung sounds
Abdomen: flat, no tenderness
Nerve: Jolt accentuation of headache negative
Neck flexion test negative, no stiffness
Kernig sign negative, Brudzinski sign negative
[Inspection]
Table 1 Blood tests

Hematology			Biochemistry					
WBC	3,700	/μL	Na	140	mEq/L	CK	146	IU/L
Band	6.0	%	K	3.9	mEq/L	Amylase	51	IU/L
Seg	50.0	%	Cl	103	mEq/L	Lipase	16.3	IU/L
Eosino	0.5	%	BUN	11.9	mg/dL	HDL-Chol	40	mg/dL
Baso	0.0	%	Cre	0.85	mg/dL	LDL-Chol	100	mg/dL
Mono	14.0	%	UA	4.9	mg/dL	TG	436	mg/dL
Lympho	29.5	%	TP	7.3	g/dL	CRP	0.4	mg/dL
Atyp-Lympho	+		Alb	4.6	g/dL	Ferritin	230	ng/mL
Hb	15.6	g/dL	T.Bil	0.5	mg/dL	HbA1c	5.9	%
Plt	15.3	$\times 10^4/\mu L$	AST	29	IU/L	HIV-1/2 antibody	negative	
coagulation			ALT	42	IU/L			
PT-INR	0.88		LDH	204	IU/L			
APTT	34.5	sec	ALP	300	IU/L			
D-dimer	<0.50	μg/mL	γ-GTP	55	IU/L			

[image]

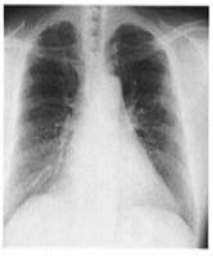


Fig.1-1 Chest X-ray

(a) Day before hospitalization (Day 6 on onset)　(b) Day 14 of hospitalization (Day 20 of onset)

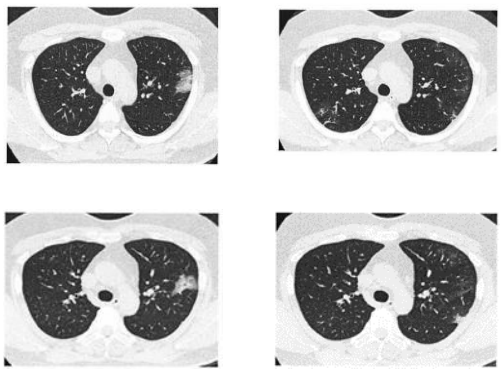
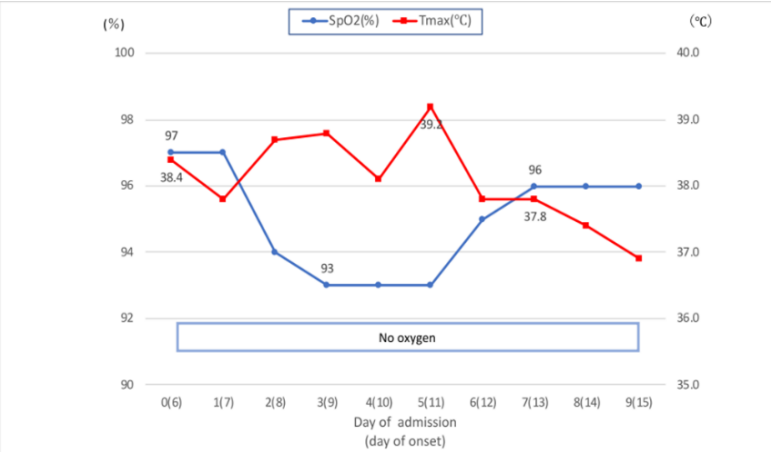


Fig. 1-2. Chest CT

[Progress after hospitalization]
This case was relatively young, in his 30s, had no major medical history except for hyperlipidemia, and showed that supportive care alone with a tendency to gradually improve fever reduction and oxygeneration after peaking on the 11th day of onset. During the hospitalization, there was no loss of appetite and dry cough was recognized, but there was no complaint of respiratory distress. He had consistently complained of a severe headache at the time of fever, but no meningeal irritation symptoms were observed, and no detailed examination of lumbar puncture was performed. Blood tests showed that the white blood cell count was consistently normal throughout the hospitalization period, and that the number of monocytes was increased from the time of the visit (day 6 of onset) in the differentiation. On the 19th and 20th days after the onset of the disease, a negative PCR was confirmed and the patient was discharged.



day of admission(onset)	0(6)	1(7)	2(8)	3(9)	4(10)	5(11)	6(12)	7(13)	8(14)	9(15)
dietary intake(out of 10)	10	10	10	10	10	10	10	10	10	10
WBC	3,700				2,500		4,000			
Lympho	29.5				36.5		28.5			
Mono	14.0				9.0		14.5			
Plt	15.3				12.7		14.7			
Hb	15.6				15.1		14.7			

[Case II] 64-year-old man
[Chief complaint] fever
[Present illness]
Diabetes, hypertension, visiting a nearby hospital. On X Y-4, 2020, the onset of general malaise and low-grade fever occurred. A chest CT scan performed by a family doctor revealed a ground-glass opacities with superior margins in both lung fields, and he was referred to our hospital for fever outpatients on Y-1. The patient was hospitalized on Day Y with a diagnosis of COVID-19 pneumonia because the nasopharyngeal swab specimen became PCR-positive.
[Overseas travel / contact history] Diving trip in the Philippines from Y-20th to Y-16th (12 days before onset)
[Past history] Diabetes, hypertension bilateral hip osteoarthritis left 54 years old, right 59 years old
[Commonly used drugs]
Amlodipine 5mg/day, losartan 100mg/hydrochlorothiazide 12.5mg/day, alogliptin 25mg/day, metformin 1,000mg/day
[Allergy] None
[At the time of admission]
Body temperature 38.1°C, respiration rate 24 breaths / min, SpO_2 97% (room air)
Blood pressure 165/92mmHg, heart rate 100 beats/min
Height 175.0cm, weight 83kg, BMI 27.1

Good general condition
Head and neck: no conjunctival congestion
No pharyngeal redness, no tonsillar enlargement
No cervical lymphadenopathy
Chest: normal heart and lung sounds
Abdomen: no spontaneous pain, decreased bowel peristalsis
Skin: no rash
[Inspection]
Table 2 Blood tests

Hematology			Biochemistry					
WBC	6,200	/μL	Na	138	mEq/L	HDL-Chol	27	mg/dL
Band	8.5	%	K	4.0	mEq/L	LDL-Chol	62	mg/dL
Seg	70.0	%	Cl	99	mEq/L	TG	92	mg/dL
Eosino	0.0	%	BUN	11.6	mg/dL	CRP	3.23	mg/dL
Baso	0.0	%	Cre	0.88	mg/dL	HbA1c	6.6	%
Mono	4.0	%	TP	7.7	g/dL	HIV-1/2 antibody	negative	
Lympho	17.5	%	Alb	4.0	g/dL			
Hb	17.2	g/dL	AST	30	IU/L			
Plt	16.4	$\times 10^4/\mu L$	ALT	19	IU/L			
			LDH	254	IU/L			
			ALP	253	IU/L			
			γ-GTP	67	IU/L			

[image]

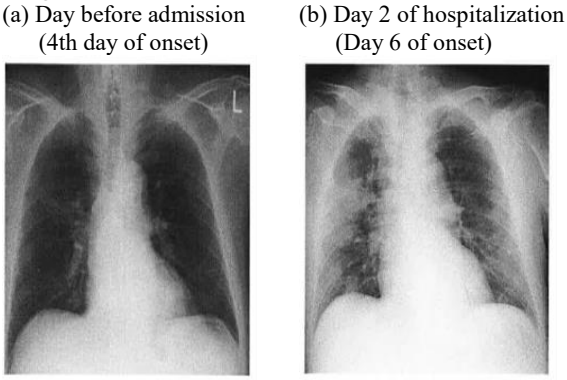


Fig. 2-1. Chest X-ray

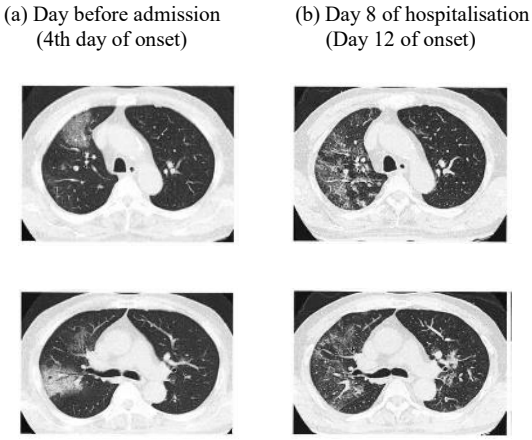
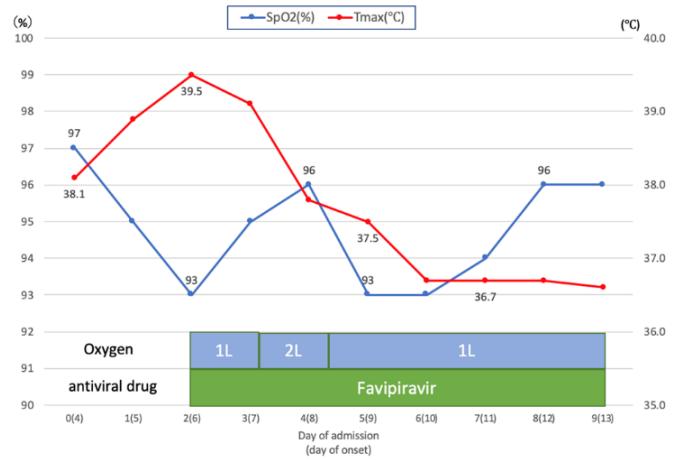


Fig. 2-2. Chest CT

[Progress after hospitalization]
The patient was relatively old in his 60s and had underlying diseases such as hypertension and diabetes, so we've regarded him as a high-risk patient since the first visit. Immediately after admission, his dietary intake had dropped and his general condition was poor. Oxygen administration was required on the second day, and the pneumonia image worsened on the image. Therefore, with the consent of the patient, off-label use of favipiravir was started through a procedure prescribed by the hospital. The dose was 3,600mg (1,800mg BID) on Day 1, followed by 1,600mg (800mg BID) from Day 2. Since the start of the drug, fever has been alleviated, and oxygenation and dietary intake have improved. Blood tests showed that granulocyte elevation, lymphocytopenia and thrombocytopenia were observed at the beginning of hospitalization, and then normalization of blood cell count and differentiation was observed after monocyte elevation. The leukocyte count itself has not increased throughout the course.



day of admission(onset)	0(4)	1(5)	2(6)	3(7)	4(8)	5(9)	6(10)	7(11)	8(12)	9(13)
dietary intake(out of 10)	4	6	4	4	4	6	8	8	9	9
WBC	6,200		6,700		5,700		5,600		5400	
Band	8.5		7.5		9.0		0.0		5.5	
Seg	70.0		74.5		66.5		68.3		60	
Lympho	17.5		13.5		16.5		18.4		27	
Mono	4.0		3.5		8.0		9.9		6.5	
Plt	16.4		14.9		16.4		20.2		29.5	
Hb	17.2		16.0		15.7		14.9		15	

Discussion
The clinical course of 2 cases of COVID-19 pneumonia including favipiravir use at our hospital is reported. According to past reports, clinical symptoms often worsen on the 7th to 10th day after symptom onset [1)], and in patients aged 50 years or older with underlying diseases (hypertension, diabetes, cerebrovascular disorder), it has been reported that the risk of severe disease is high [2)]. In our hospital, we found that in patients who are in their 30s and younger, spontaneous fever persisted, but spontaneous remission was observed only with supportive care. In patients in their 60s and patients with a history of diabetes, oxygenation worsened after admission.
Blood tests have shown that lymphocytopenia is a predictor of severe disease [1)]. Examining the blood counts of the two cases reported in this report in a time series shows that when the respiratory condition worsens around the 7th day of symptom onset, the leukocyte count itself is normal, but increased segmental neutrophils and decreased lymphocyte and platelet count were observed. After that, after several days of monocyte increase, platelet recovery, normalization of differentiation, and stabilization of respiratory condition were observed. Changes in the CBC may be helpful in determining the clinical stage (acute exacerbation / recovery) of COVID-19 pneumonia patients (Fig.3).

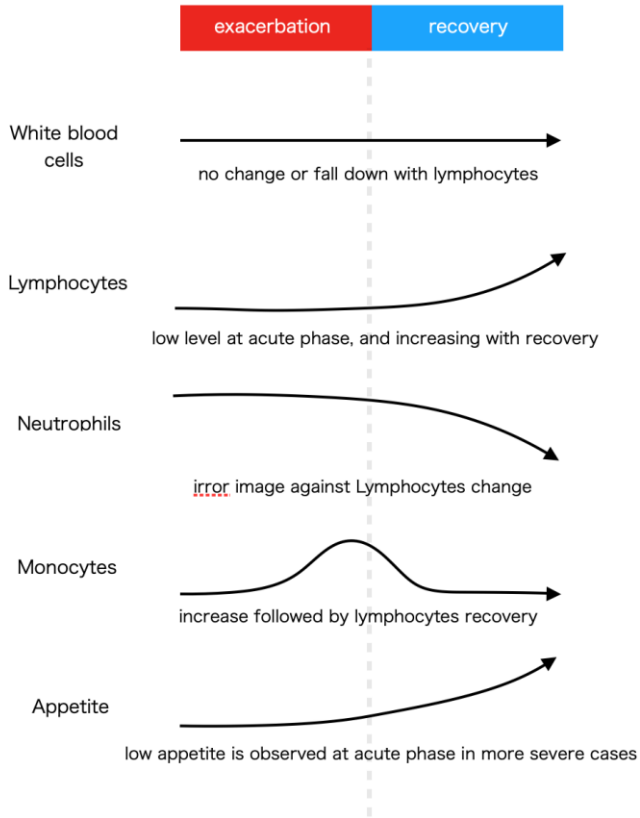


Fig. 3

In case II, with the support of the in-hospital approved off label drug use and with the support of the Ministry of Health, Labor and Welfare and FUJIFILM Toyama Chemical Co., the use of Fabipiravir could be started promptly as soon as hypoxemia appeared. Regarding the efficacy of favipiravir, the results of a randomized controlled trial (ChiCTR200030254) have been reported, and a significant difference in the improvement of symptoms on the 7th day in mild cases compared with Arbidol has been observed [3)]. Further knowledge of the timing of administration, prevention of illness, reduction of mortality, etc. has to be waited for, but it may be a message worth waiting for, for healthcare professionals and patients depending on future reports.
Knowledge about the diagnosis and treatment of COVID-19 is accumulating at a rapid pace. We believe that it will be necessary to share information on prevention, early diagnosis, and early treatment with the close cooperation of medical institutions, governments, and companies in order to improve the prognosis of patients.

Reference

1) Li Q, Guan X, Wu P, *et al*. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020; 382(13): 1199-1207.
2) Wang D, Hu B, Hu C, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus infected pneumonia in Wuhan, China. JAMA. 2020; 323(11): 1061-1069.
3) Chen C, Huang J, Cheng Z, *et al*. Favipiravir versus arbidol for COVID-19: A randomized clinical trial. medRxiv. 2020: 2020.03.17.20037432. doi:10.1101/2020.03.17.20037432.202