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【 ORIGINAL ARTICLE 】

Clinical and Microbiological Features of Asymptomatic SARS-CoV-2 Infection and Mild COVID-19 in Seven Crewmembers of a Cruise Ship

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Abstract:

Objective To describe the clinical features and clinical course of individuals diagnosed with asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or mild coronavirus disease (COVID)-19.

Patients The study participants consisted of 7 crewmembers of the passenger cruise-liner, *Diamond Princess*, who were admitted to our hospital after becoming infected with SARS-CoV-2 aboard the ship.

Methods The data on patient background and biochemical test results were obtained from the patients' medical records. All patients had a chest X-ray, and a throat swab and sputum samples were sent for culture on admission.

Results The median age of the 7 patients, of whom 4 were male and 3 were female, was 39 years (range: 23-47 years). On admission, none of them had fever, but 4 (57%) had a cough. None of them showed any signs of organ damage on laboratory testing. Chest X-ray showed pneumonia in one individual, which resolved spontaneously, while the other 6 had normal chest X-ray findings. Culture of throat swabs and sputum samples revealed that 4 patients (57%) had bacterial upper respiratory infections (*Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*). The period from a positive polymerase chain reaction (PCR) test to negative conversion ranged from 5 to 13 days, with a median of 8 days.

Conclusion Healthy young adults without risk factors who acquire SARS-CoV-2 infection may have an asymptomatic infection or may experience mild COVID-19. In addition to obesity, an older age, underlying illness, and being overweight can lead to a risk of exacerbation; thus, hospital management for such individuals may be desirable. Culturing respiratory samples may be useful for diagnosing secondary bacterial pneumonia.

Key words: coronavirus disease 2019, COVID-19, severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, sputum culture, secondary bacterial infection

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Introduction

The novel coronavirus disease (COVID-19) has spread from Wuhan, Hubei Province, China, since December 2019 (1). On March 11, 2020, the World Health Organization declared it a pandemic (2). We herein report on 7 patients who ranged from asymptomatic to mildly ill, and who

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Table 1. Patient Characteristics, Clinical Features, and Imaging Findings.

Patient	Age (years)	Sex	Over-weight†	Smoking history	BT >37.5°C	Respiratory symptoms	Past medical history	CXR	Days to negative PCR†††	Days to discharge
1	45	M	-	-	No	Cough	Hyperuricemia	-	6	7
2	47	M	-	-	No	Cough	Cerebral hemorrhage	-	8	8
3	23	M	-	-	No	Cough	-	-	8	8
4	39	M	-	-	No	-	Hypertension	-	8	8
5	32	F	-	-	No	-	-	-	6	8
6	28	F	-	-	No	-	Interstitial nephritis	-	5	8
7	39	F	+	-	No	Cough	Dyslipidemia	+††	13	12

BT: body temperature, CXR: chest X-ray

† Overweight is defined as a BMI>25.

††Patient 7's chest X-rays and chest computed tomography images are shown in Figure.

††† The day of a positive PCR test is defined as day 1.

all had minimal symptoms but were positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on polymerase chain reaction (PCR) test. They were among the crewmembers of the cruise-ship *Diamond Princess* who were diagnosed with COVID-19 and transported to our hospital after the ship arrived in Yokohama Port on February 3, 2020. As of March 10, 2020, 696 passengers were diagnosed with COVID-19, of whom 328 (47.1%) were asymptomatic. According to a report from China, among the 44,672 patients with COVID-19 who had pneumonia, young people under the age of 50 years accounted for almost half the cases (46.4%), but the mortality rate was quite low at 7.0% (percentage of the total deaths) (3). Most of the severely ill patients were the elderly or immunocompromised, and most of the young, healthy people successfully recovered from a mild illness. There have been few reports on the clinical features of mild COVID-19 and asymptomatic SARS-CoV-2 infection (4). The purpose of this report is to describe a cluster of seven cases of asymptomatic or mild SARS-CoV infection detected by screening.

Materials and Methods

Study design and participants

This study was conducted as a single-center, retrospective study. The 7 individuals with SARS-CoV-2 infection were *Diamond Princess* crewmembers and were admitted to our hospitals from February 24 to March 7, 2020. Our hospitals are regional core general hospitals with 1,033 beds and 413 beds, respectively.

Ethical issues

All the procedures followed were in accordance with the Declaration of Helsinki. The study protocol was approved by the Kitasato University Hospital ethics review board. The requirement for informed consent was waived because this was a retrospective study.

Procedures

The data on the presence or absence of fever and respiratory symptoms, medical history, blood counts, and biochemical test results were obtained from patient medical records. All patients had chest X-rays, culture of a throat swab, and sputum sample performed on admission. They were followed up until March 2, 2020. In addition, the time for the conversion of the PCR test of SARS-CoV-2 of the throat swab was investigated. The patients did not require medical treatment and were discharged once they tested negative for SARS-CoV-2 on PCR.

Qualitative detection of SARS-CoV-2

Throat swab samples were collected with a sterile swab, and RNA was extracted using the QIAamp Viral RNA Mini Kit (QIAGEN, Cat. No. 52904). Genetic identification of SARS-CoV-2 was performed using a 2-step real-time (RT)-PCR method to detect two specific gene regions of SARS-CoV-2: open reading frame 1a (ORF1a) and spike (S).

Statistical analysis

The patient characteristics and laboratory values were reported using simple descriptive statistics (frequencies, percentages, medians), and there was no hypothesis testing.

Results

Patient characteristics

The characteristics of the 7 patients, of whom 4 (57%) were male and 3 (43%) were female, are shown in Table 1. Their ages ranged from 23 to 47 years, with a median of 39 years. None of them had a fever on admission, but 4 (57%) had a cough. One patient (Patient 7, a 39-year-old woman) had pneumonia of both lower lobes and the right upper lobe of the lung on the chest X-ray taken on admission (Figure A) in addition to being overweight (BMI 28.6). None of the patients had gastrointestinal symptoms such as diarrhea

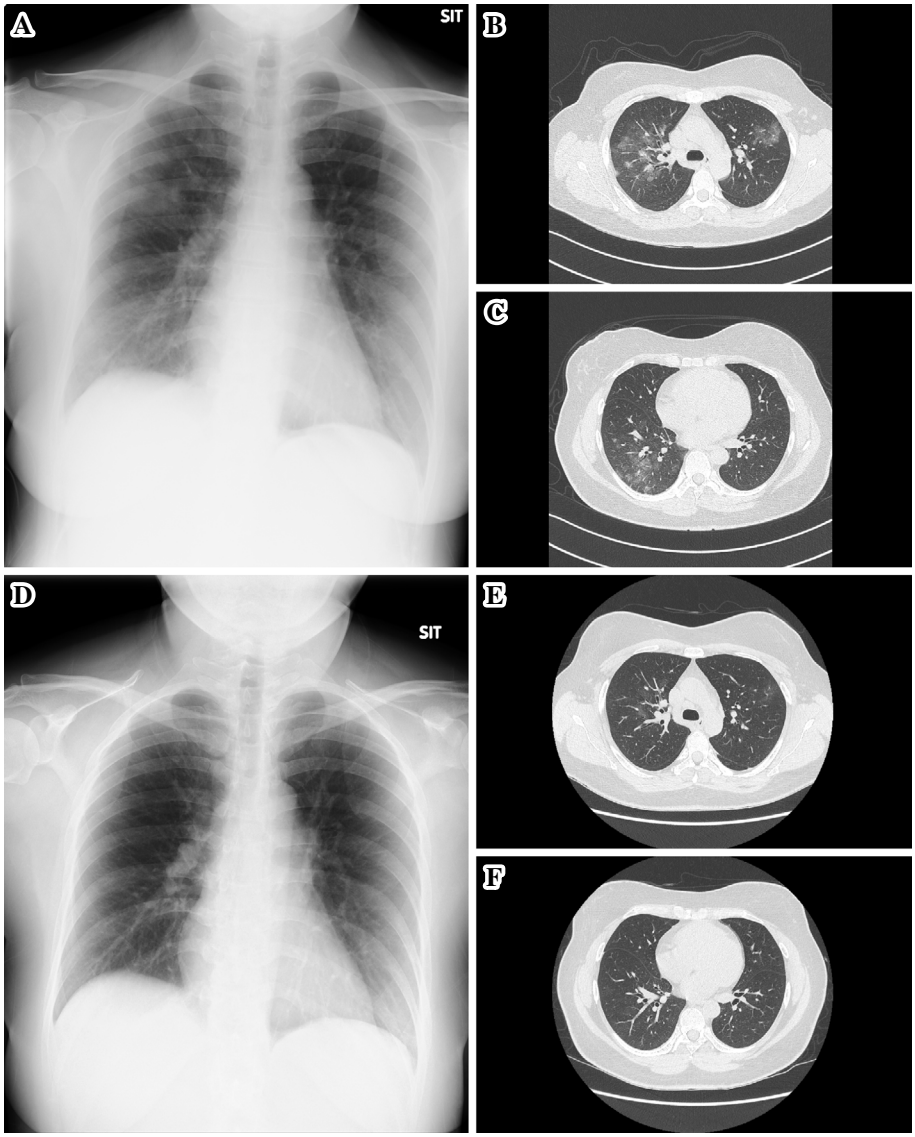

Figure. **Changes in the lungs of Patient 7 on chest X-ray and a chest computed tomography (CT) scan. A patchy ground-glass opacification was found in the upper lobes of both lungs superiorly and lower lung margin dorsal superiorly on hospital day 3. On hospital Day 10, the chest CT scan showed a marked improvement in the ground-glass shadow. A: Chest X-ray on hospital Day 2; B and C: A chest CT scan on hospital Day 3; D: Chest X-ray on hospital Day 9; E and F: Chest CT scans on hospital Day 10.**

or an absence of taste and/or smell. One patient (Patient 4, a 39-year-old man) had hypertension, but none of the other patients had any comorbid conditions known to affect the prognosis of COVID-19. No patient had a history of smoking.

Complete blood count and blood biochemistry

Table 2 shows the results of the complete blood counts and blood biochemistry tests that were performed on admission. None of the patients had any abnormalities on a complete blood count or any evidence of hepatic or renal impairment. The patient with pneumonia diagnosed on chest X-ray (Patient 7) had a high C-reactive protein level; and one patient (Patient 4) had a high serum ferritin level, but all the other laboratory test results were normal.

Culture of respiratory samples

Table 3 shows the results of the culture of sputum and throat swab specimens. Three patients had only normal commensal bacteria detected in both the pharynx and sputum. However, 4 patients had bacterial pathogens on sputum culture. The bacterial pathogens included *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*.

Clinical course of pneumonia in Patient 7

Patient 7 had had a fever of >38℃ until 2 days before admission. Figure B, C show the chest computed tomography (CT) images of Patient 7 on hospital Day 3. A patchy ground-glass opacification was found in the upper lobes of both lungs superiorly and lower lung margin dorsal superi-

Table 2. **Patients' Complete Blood Count and Blood Biochemistry Results.**

Patient	WBC (/μL)	Neut (/μL)	Lymph (/μL)	AST (U/L)	ALT (U/L)	BUN (mg/dL)	Cr (mg/dL)	CRP (mg/dL)	IgG (mg/dL)	FER (ng/mL)
1	6,100	3,142	2,385	17	27	14	0.99	0.03	-	-
2	7,800	4,376	2,660	22	34	11	0.92	0.22	1,269	**674**†
3	8,100	3,386	2,997	27	53	13	1.04	0.17	-	-
4	7,200	3,859	2,333	28	37	11	0.88	0.04	1,110	130
5	6,300	3,893	1,997	12	17	14	0.79	<0.03	1,488	27
6	6,200	3,776	1,829	37	41	3	0.60	<0.03	1,127	<4
7	7,500	4,448	2,415	29	27	9	0.61	**1.29**‡	-	-

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, Cr: creatinine, CRP: C-reactive protein, FER: ferritin, IgG: immunoglobulin G, Lymph: lymphocytes, Neut: neutrophils, WBC: white blood cells

All values are normal unless indicated otherwise.

† Above the normal range. The normal range for ferritin is 5–152(ng/mL).

‡ Above the normal range. The normal range for C-reactive protein is less than 0.14(mg/dL).

Table 3. **Patients' Throat Swab and Sputum Culture Results.**

Patient	Throat swab	Sputum
1	-	-
2	*Staphylococcus aureus*<10^3	*Staphylococcus aureus* 10^5
3	-	-
4	*Staphylococcus aureus* 10^5 *Streptococcus agalactiae* (Group B) 10^5	*Staphylococcus aureus* <10^3
5	-	Group C *Streptococcus* 10^6 *Haemophilus influenzae* 10^6
6	-	-
7	*Enterobacteria* species 10^4	*Klebsiella pneumoniae* 10^6

orly. On hospital Day 9, the pneumonia features of the chest X-ray image had improved (Figure D), and the serum C-reactive protein (CRP) value had normalized to 0.22 mg/dL. On hospital Day 10, the chest CT scan showed a marked improvement in the ground-glass shadow (Figure E, F). The patient did not experience any fever while in hospital, and her cough improved.

Polymerase chain reaction test and outcomes

All 7 patients were had two consecutive negative results for SARS-COV-2 using PCR test, performed on consecutive days, and were discharged without symptoms. The period from positive PCR test to negative conversion ranged from 5 to 13 days, with a median of 8 days.

Discussion

All 7 patients in this study had either an asymptomatic or mild infection and were discharged after they were confirmed as negative for SARS-CoV-2 by PCR test. Younger individuals generally have milder disease than do older individuals (5, 6). Patient 4 had a history of hypertension, which is considered a risk factor for severe disease (5). None of the patients showed either moderate or highly abnormal laboratory data for severity risk factors, such as increased leukocytes, inflammatory response, and liver dysfunction (5, 7). Patient 7 had typical chest CT findings for COVID-19, was the only patient with pneumonia, and recovered without invasive treatment (8-10). Of all cases, only patient 7 was overweight (BMI 28.6).

Obesity (BMI >30) is a risk for COVID-19 aggravation, according to the US Centers for Disease Control and Prevention (CDC) guidelines (11). The low obesity rate in Asian countries, including Japan, might have contributed significantly to the low rates of aggravation (12). Obesity is considered to be a risk factor owing to arteriosclerosis due to complications of lifestyle-related diseases, blood oxygen saturation due to poor ventilation, an impaired immune system function due to chronic inflammation, and involvement of the angiotensin-converting enzyme 2 (ACE 2) receptor (13-15). SARS-CoV-2 has been shown to invade cells via ACE 2 receptors present on the alveoli, and obese individuals express more ACE 2 receptors than normal-weight subjects (15-17).

Although the number of patients in this study was small, the results suggest that in addition to obese patients, even overweight persons with a BMI >25 may be at risk of aggravation. The number of people testing positive for SARS-CoV-2 continues to increase. Therefore, in the future, scarcities, such as a lack of hospital beds, will be expected; thus, it is necessary to make the hospitalization criteria stricter. Most asymptomatic infections remain asymptomatic and heal throughout the course of the infection, and these patients are generally not hospitalized (18). Currently, patients

on maintenance dialysis and cancer-bearing patients, who are at high risk of aggravation, are generally indicated for hospitalization even if they are asymptomatic; in addition, overweight patients might also be indicated.

As a preventive measure against SARS-CoV-2, The CDC has proposed preventive measures for droplet infection and contact infection (19). In our hospital, in addition to preventive measures against droplet and contact infection, we also implemented airborne infection control measures using N95 masks to prevent aerosol generation to ensure the safety of healthcare workers (20). No staff members became ill. Clearly, adequate infection control significantly reduces the risk of infection (21). It is therefore necessary to consider each facility, especially from the perspective of the efficient use of medical resources.

For sputum cultures, bacteria that could cause bacterial pneumonia were isolated from 4 out of 7 patients (22, 23). Individuals with influenza virus infections have been reported to be more severe due to secondary bacterial pneumonia, and *Streptococcus pneumoniae* (29-48%) and *Staphylococcus aureus* (7-40%) are the most frequently identified bacteria (24, 25). Although less frequent, *Haemophilus influenzae* and *Pseudomonas aeruginosa* may also cause secondary bacterial pneumonia (26). *Klebsiella pneumoniae*, *Staphylococcus aureus,* and *Acinetobacter species* have also been reported to cause secondary bacterial pneumonia in patients with the Middle East respiratory syndrome (MERS), which is also caused by a coronavirus (27-29). In this study, *Staphylococcus aureus* was detected in 2 of 7 patients, and *Klebsiella pneumoniae* and *Haemophilus influenzae* were detected in 1 patient each. Secondary pneumonia caused by these bacteria following COVID-19 has been reported (30, 31).

Infections of the respiratory tract epithelium with respiratory viruses are known to cause damage to lower respiratory epithelial cells (32). Although the degree of lower respiratory epithelial damage varies according to the virus, this damage may enable bacteria to colonize the lower respiratory tract in healthy young individuals with COVID-19 (33-35). The immune reaction to SARS-CoV-2 infection is a 2-step reaction; during the non-severe infection phase, a particular adaptive immune reaction is necessary for viral clearance and the prevention of the disease from the progressive to the severe phase (36, 37). It has been noted that the adaptive immune reaction elicited toward a viral infection results in the failure of the host's innate immunity against a bacterial infection (35, 38, 39). Thus, secondary bacterial infections occur following the elimination of the virus from the lungs of patients with COVID-19. According to laboratory, clinical, and epidemiological studies, secondary bacterial infections can significantly increase the mortality rate in patients with viral infections (40, 41). In this study, none of the 4 patients in whom bacterial pathogens were isolated developed signs of secondary bacterial infections, such as fever or respiratory symptoms.

In this study, the sample size was small, and the cases were limited to individuals with asymptomatic infection or mild disease identified through screening. Despite the high death toll due to the COVID-19 pandemic, most individuals with SARS-CoV-2 infection develop mild disease. Knowledge of the determinants of severity of COVID-19 is limited. The frequency of secondary bacterial pneumonia following COVID-19 has been reported to be approximately 10%, which is lower than that for influenza (42). However, once secondary bacterial pneumonia develops, the risk of morbidity and mortality is high and it is a risk factor for exacerbation. Early proper antimicrobial treatment is needed to avoid secondary infections, and preclinical bacterial culture testing may help select the appropriate treatment.

In conclusion, these patients demonstrate that SARS-CoV-2 infection may cause mild disease and that patients with mild disease may recover without experiencing complications. As a risk factor for COVID-19 aggravation, being overweight should be considered as an indicator for hospitalization in addition to the patient's basic conditions, such as an older age, requiring maintenance dialysis, or having cancer. Even with the limited sample size of this study, bacteria were isolated from the lower respiratory tract of more than half the patients, and an analysis in a larger population is awaited to investigate the secondary bacterial pneumonia.

The authors state that they have no Conflict of Interest (COI).

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