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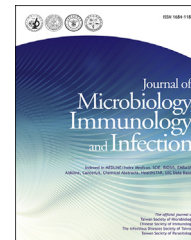
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Short Communication

Clinical manifestations and radiological features by chest computed tomographic findings of a novel coronavirus disease-19 pneumonia among 92 patients in Japan



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Abstract *Introduction:* The novel coronavirus disease (COVID-19) could cause a severe acute respiratory infectious disease, showing a high mortality rate of 12–45% among cases who required intensive care unit admission. COVID-19 pneumonia

Patients and methods: For the purpose of identifying clinical manifestations and radiological findings of COVID-19 pneumonia, we reviewed all cases of COVID-19 pneumonia which were published by the homepage of the Japanese Association for Infectious Diseases from Feb 5 2020 until April 30 2020, including our cases. All patients were diagnosed based on positive results of the novel coronavirus-real-time RT-PCR with chest computed tomography (CT) findings.

Results: A total of 92 patients were enrolled in this study. The median age was 66 years (range 16–92 years). For all, 50 (54%) were males. The most common underlying disease was hypertension in 32 (36%). Any comorbidity was seen in 60 (67%). The mortality rate was 4 (6%). In terms of clinical symptoms on an initial visit, fever and cough were confirmed in 66 (72%) and 37 (40%). Forty-three (47%) had no respiratory symptoms. As for radiological findings by chest CT scan, ground-glass opacities (GGOs), peripheral distribution, bilateral lung involvements were seen in 88 (96%), 76 (83%) and 78 (85%), respectively.

Conclusion: It is difficult to diagnose as COVID-19 pneumonia due to poor respiratory symptoms. Chest CT findings typically show GGO, peripheral and bilateral shadows. Patients should have

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chest CT performed if suspected for early diagnosis and therapeutic intervention, resulting in a favorable outcome and prevention of secondary nosocomial transmitted infection.

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Introduction

A novel coronavirus [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)], which initially appeared in December 2019 by Wuhan in China,¹ spread rapidly from China to Japan, Korea, other Asian countries, the United States of America (USA), European countries during only 3 months. The pandemic of a novel coronavirus disease (COVID-19) brought a crisis of human life and an economic burden worldwide. It is well known that SARS-CoV-2 has a high pathogenicity and therefore, COVID-19 could cause severe acute respiratory distress syndrome (ARDS), such as 13.8% cases with severe, and 6.1% with critical courses, showing a high mortality rate of 12–45% among cases with pneumonia requiring ICU admission.^{2,3} It is reported that different types of SARS-CoV2 such as type A, B and C are seen in Wuhan, Japan, USA, and European countries.⁴ These different types of virus could show different manifestations, radiological findings and pathogenicities each other.

Currently, the diagnosis as COVID-19 was based on positive result by SARS-CoV2- reverse-transcription polymerase chain reaction (RT-PCR) with clinical manifestations which are consistent with COVID-19. While early diagnosis of COVID-19 pneumonia is important for infection control to avoid secondary transmission by airborne and aerosol, PCR testing requires 4–5 working days for the final diagnostic decision. Due to this time lag from first visit to the final diagnosis, patients suspected with COVID-19 should be kept in isolation, resulting in an increase of medical staffs' labors. Viral pneumonitis generally shows diffuse GGO such as influenza pneumonitis. For the purpose of identifying radiological features of COVID-19 pneumonia by chest CT scanning, we reviewed all cases of COVID-19 pneumonia in Japan published previously by the homepage of the Japanese Association for Infectious Diseases (http://www.kansensho.or.jp/modules/topics/index.php?content_id=31#case_reports), including ours. This is the first report documenting clinical manifestations and radiological features of COVID-19 pneumonia in Japan.

Patients and methods

We present 8 COVID-19 pneumonia cases (Table 1) that we experienced during March 2020 and April 2020 and reviewed all cases previously published by the homepage of the Japanese Association for Infectious Diseases from Feb 5 2020 until April 30 2020,⁵ including ours to find clinical manifestations and radiological features of chest CT findings among COVID-19 pneumonia patients.

Patients' characteristics, clinical symptoms, radiological findings by chest CT images, treatment and outcome were evaluated. All cases were confirmed by real-time RT-PCR analysis of nasopharyngeal or throat swab specimens

according to a standard protocol. Cases who do not have information of chest CT findings were excluded. This study was approved by the Institutional Review Board of Aichi Medical University Hospital.

Results

A total of 92 patients from 55 case reports were enrolled in this study. Table 1 shows patients' characteristics and clinical outcomes. The patients were 50 males (54%) and 42 females (46%). The median age was 66 years (16–92 years). Twenty-eight patients (30%) had a close contact with someone with COVID-19. There were no obvious history of exposure in 21 (23%).

The most frequent underlying diseases was hypertension in 32 (36%), followed by diabetes mellitus in 18 (20%). As for clinical symptoms, fever was seen the most frequently in 66 (72%), followed by cough in 37 (40%), general fatigue in 33 (36%). Radiological findings were shown in Table 2. Ground-glass opacities (GGOs) and mixed lesions with GGOs and lobular shadows were seen in 88 (96%) and 27 (29%), respectively. Neither mass shadows nor tree-in-bud appearances were seen in all patients. The predominant pattern observed was bilateral in 78 (85%), unilateral lung involvements in 14 (15%) and peripheral distribution in 76 (83%). Patchy shadows were found more frequently in 20–39 year old-patients than in others (≥ 40 years) (50% vs. 8%, $p = 0.008$ by Fisher's exact test). The mean timing for CT scan after the onset of signs and symptoms was 6.1 days. There was no correlation between the timing after the onset and any radiological features. There was no difference of timing of CT scan between bilateral and unilateral findings (6.1 vs. 6.1 days, $p = 0.956$). We could not find any correlation between the underlying diseases and the radiological features. As for the correlation between the radiological features and the outcomes, a diffuse pattern is more frequently seen in the death group than in the survival group even though there was no statistical difference (100% vs. 56%, $p = 0.082$). There was no correlation between other patterns and the outcomes (data not shown).

As for the initial treatment, lopinavir/ritonavir was used the most frequently in 28 (34%), followed by ciclesonid in 26 (32%). Favipiravir was prescribed in 18 (22%). Combination therapy with 2 more agents and no therapy were seen in 45/81 (56%) and 14/82 (17%), respectively. In terms of outcomes, 14 patients (17%) required mechanical ventilations, 61/65 (94%) were survived and 4/65 (6%) died. Twenty-eight patients moved to another institute or under treatment.

Discussion

Typical tomographic findings of COVID-19 pneumonia are GGOs, peripheral distribution and bilateral lung involvements^{6,7} as same as the result of our study. Notably,

Table 1 Reviewed patients' characteristics and clinical manifestations (n = 92).

Variables	Number (% except for age)
Median age (range, years)	66 (16–92)
Male gender (%)	50 (54)
Smoking history	
Current smoker	5 (5)
Ex-smoker	17 (18)
Never smoker	36 (39)
Unknown	34 (37)
Infectious routes	
Cruise ship	25 (27)
Music club, bar, night club	3 (3)
Travel history	6 (7)
Nursing home	10 (11)
Sick contact	28 (30)
Other	2 (2)
Unknown	21 (23)
Underlying diseases (n = 90)	
Any	60 (67)
Heart disease	7 (8)
Chronic respiratory disease	10 (11)
Diabetes mellitus	18 (20)
Malignancy	11 (12)
Chronic kidney disease	4 (4)
Chronic hepatic disease	4 (4)
Hypertension	32 (36)
Hyperlipidemia	14 (16)
Cerebrovascular disease	8 (9)
Collagen vascular disease	4 (4)
Symptoms on diagnosis	
Fever (≥ 37.5 °C)	66 (72)
Cough	37 (40)
Sputum	4 (4)
Sorethroat	15 (16)
Runny nose	9 (10)
Dyspnea	13 (14)
General fatigue	33 (36)
Headache	5 (5)
Anorexia	10 (11)
Diarrhea	10 (11)
Stomachache	2 (2)
Consciousness disturbance	2 (2)
Nausea/vomit	5 (5)
Headache	13 (14)
Taste disorder	5 (5)
Olfactory disorder	3 (3)
Respiratory rate ≥ 22 (/min)	10/69 (14)
Respiratory failure [SpO ₂ <90% (room air)]	11/90 (12)
Fine crackles on auscultations	10/68 (15)
Treatment (n = 82)	
Prednisolone	16 (20)
Hydroxychloroquine	11 (13)
Lopinavir/ritonavir,	28 (34)
Macrolides	16 (20)
Neuraminidase inhibitors	7 (9)
Ciclesonide,	26 (32)
Camostat	5 (6)

Table 1 (continued)

Variables	Number (% except for age)
Nafamostat	2 (2)
Favipiravir	18 (22)
Baloxavir	2 (2)
Kampo medicine	6 (7)
Sivelestat	3 (4)
Hemodialysis	2 (2)
Intravenous immunoglobulin	3 (4)
Intratracheal intubation and mechanical ventilation	14 (17)
Outcome* (n = 65)	
Survival	61 (94)
Death	4 (6)

SpO₂, oxygen saturation.

* Twenty-seven patients moved to other institutes or under treatment.

respiratory symptoms such as cough and sputum were seen in 36 (39%) and 4 (4%) respectively among the patients with COVID-19 pneumonia. Forty-three patients (47%) had no respiratory symptoms such as cough, sore throat, runny nose or dyspnea. This could be explained by that the clinical course of COVID-19 pneumonia would progress slowly in many cases, even if some cases have acute respiratory failure. Although all of coronavirus infections could cause cytokine storm, some reported that the pathophysiology of MERS and SARS-CoV differ from that of COVID-19.¹ The disease severity could depend on the correlation between the host immunity and the imbalance of helper T-cell 1 and 2. Therefore, it is reasonable that some pneumonia patients improved without any therapy.^{1,2} Some COVID-19 cases which were considered as light or moderate, unfortunately died. We worry that some COVID-19 patients who were misdiagnosed as not having pneumonia could develop acute respiratory failure, or cytokine release syndrome (CRS), resulting in unexpected deaths.

Different shadows could appear in different patients depending on the age and conditions. Immunological effect could be influenced differ in patients' ages and conditions. Some documented that predominant shadows in the right of the lung were seen among the patients. We could not find correlation between disease severity and the predominance of the lung side due to a lack of tomographic information.⁶

The patients in this review were older and have more comorbidities than those in previous studies.^{6,8} In this review, all patients who died were older than 75 years. Three of the patients had severe comorbidities (One had no information of underlying disease). We recommend that COVID-19 patients with risk factors who developed respiratory failure should receive chest CT scan to detect if they have pneumonia or not. While the standard treatment for COVID-19 is not yet established, the clinical trials of some promising antiviral drugs are ongoing. Early treatment for COVID-19 pneumonia could prevent the disease deterioration, resulting in favorable outcomes.

Fortunately, the mortality rate of COVID-19 in Japan is the lowest all over the world.⁹ This result may be attributable to the specific aspects in the Japanese healthcare

Table 2 Radiological features by chest CT findings.

Variables	Number (%)
Tomographic features	
Ground-glass opacity	88 (96)
Mixed lesion with GGO and lobular shadow	27 (29)
Peripheral distribution	76 (83)
Diffuse	60 (65)
Airspace consolidation	11 (12)
Nodule	2 (2)
Patchy shadow	11 (12)
Cavity	1 (1)
Tree-in bud appearance	0
Mass lesion	0
Bilateral	78 (85)
Unilateral	14 (15)
*Timepoint CT scan after onset of the symptoms and signs (mean days±SD)	6.1 ± 3.5

CT, computed tomography; GGO, ground-glass opacity; SD, standard deviation.

There was no correlation between the date after onset and any tomographic features. We could not find the correlation between underlying disease and tomographic features.

As for the correlation between radiological features and outcome, diffuse pattern is more frequently seen in death group than survival group even though there was no statistical difference (100% v.s. 56%, $p = 0.082$). Other patterns of CT scan.

* Timing CT scan after onset of the symptoms and signs were analyzed in 84 patients due to missing information.

system. Japanese medical service is based on a free-access policy and medical cost could be covered by a universal public insurance system for every citizen as well as for inhabitants from abroad. Thus, it is easier to perform CT scan in Japan than any other country. We believe that early diagnosis of COVID-19 pneumonia could contribute to a favor outcome. In order to reduce the risk of nosocomial infection and mortality of the disease, chest CT should be performed even though we are facing the escalation of medical costs and staff's labors.

There are some limitations in our study. First, this is a retrospective study in a small population. Second, this study was a case review of the literature in which clinical information might be insufficient. Third, this review has included only cases who showed positive SARD-CoV2-RT-PCR testing. Thus, these patients might not reflect the whole patients with COVID-19 pneumonia in the real world.

We concluded that COVID-19 pneumonia patients show typically GGO, peripheral, bilateral shadows in chest CT.

The patients should receive chest CT if COVID-19 is suspected for the early diagnosis and therapeutic intervention, resulting in a favor outcome and prevention of secondary nosocomial transmitted infection.

Declaration of competing interest

All co-authors have none declared.

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