

Misleading Diagnosis of Radiological Imaging of COVID-19 Pneumonia During Pandemic Era: Risk on the Existence of CMV Infection

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ABSTRAK

Coronavirus disease 2019 (COVID-19) adalah sebuah penyakit pernapasan akut yang sangat menular akibat virus Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2). Presentasi klinis COVID-19 antara lain demam, batuk non-produktif dan sesak napas. Meskipun diagnosis ditegakkan dengan mendeteksi ribonucleic acid (RNA) virus melalui metode reverse transcription-polymerase chain reaction (RT-PCR), CT scan memiliki peranan penting dalam deteksi dan tatalaksana COVID-19 terutama pada daerah yang prevalensinya tinggi. CT scan memiliki sensitivitas yang tinggi, namun spesifisitasnya rendah karena gambaran pneumonia COVID-19 seperti ground glass opacities (GGO) dan konsolidasi juga dimiliki oleh berbagai penyakit lain, salah satunya adalah infeksi sitomegalovirus (CMV). Tujuan laporan kasus ini adalah untuk meningkatkan kewaspadaan terhadap penyakit lain yang memiliki gambaran radiologis yang serupa dengan COVID-19, terutama pada pasien dengan imunodefisiensi yang rentan terhadap infeksi virus seperti infeksi CMV agar keterlambatan penanganan penyakit dapat dicegah.

Kata kunci: respiratory medicine, radiologi, ilmu penyakit dalam.

ABSTRACT

Coronavirus disease 2019 (COVID-19) is an acute respiratory disease which rapidly disseminated due to Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2) virus. Clinical presentations of COVID-19 are fever, non-productive cough, and dyspnea. Although the diagnosis establishment is done by detecting the viral ribonucleic acid (RNA) through reverse transcription-polymerase chain reaction (RT-PCR) method, CT scan has an important role in detection and treatment of COVID-19 especially in high prevalence regions. Chest CT scan has high sensitivity yet low specificity because there are a lot of other pathological spectrums that also present features of COVID-19 such as ground glass opacities (GGO) and consolidation, one of them is CMV infection. The objective of this case report is to raise vigilance towards other diseases that have radiological image similarities with COVID-19, especially in the immunocompromised patients who are susceptible to viral infections like CMV infection so that the delay in the disease treatment can be prevented.

Keywords: respiratory medicine, radiology, internal medicine.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an acute respiratory disease which rapidly disseminated due to Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2), a virus that originated from the Coronaviridae family. COVID-19 should be suspected if the patient has a history of respiratory tract symptoms such as fever, cough, runny nose, sore throat accompanied by a history of travel to a country or a region with local transmission; or a history of contact with probable case or COVID-19 confirmed case. COVID-19 is diagnosed by detecting ribonucleic acid (RNA) virus from reverse transcription-polymerase chain reaction (RT-PCR) method.^{1,2}

Several literatures revealed that chest CT scan has an important role in early detection and treatment of COVID-19.^{1,3,4} Chest CT scan findings in the early course of COVID-19 is ground-glass opacity (GGO) with or without consolidation in the posterior and peripheral part of the lung, but in the later course of the disease, consolidation, reticular opacity, crazy-paving pattern, reversed halo sign and vascular enlargement are more often found. GGO is defined by a hazy opacity that blurs the bronchial structure or vessels beneath.¹

Chest CT scan has high sensitivity but also low specificity because there are a lot of other pathological spectrums which can cause similar radiological findings in COVID-19 including GGO, consolidation, interlobular septal thickening and reticular opacities. Those findings are often found in viral/bacterial/fungal pneumonia, interstitial lung

disease, pneumonitis due to hypersensitivity, and even lung edema.^{1,5} Therefore, in this COVID-19 pandemic era, we should not forget other diseases that can cause similar presentations of COVID-19 pneumonia on chest CT scan. In this article, 3 cases of cytomegalovirus (CMV) pneumonia with similar chest CT scan findings to COVID-19 pneumonia were reported.

CASE ILLUSTRATION

Patient I

A 66 year old woman came to the hospital on March 26th 2020 with a difficulty of breathing since 2 weeks prior to admission. The patient has a history of diabetes mellitus (DM) type 2, hypertension, ischemic stroke and permanent pacemaker (PPM) insertion due to Sick Sinus Syndrome. The physical examination obtained blood pressure (BP) 152/89 mmHg, pulse 74 beats per minute, respiratory rate (RR) 22 times per minute, and body temperature 36°C. Laboratory examination showed an elevated C-reactive protein (CRP) 115.1 mg/dL (**Table 1**). The chest x-ray showed bilateral infiltrates with pleural effusion in the left lung.

The patient was given meropenem 1 g i.v. t.i.d, rivaroxaban 10 mg p.o. o.d., adalat OROS 30 mg p.o. o.d., atorvastatin 10 mg p.o. o.d. Thoracocentesis was performed on the patient and then the obtained pleural fluid was checked for culture examination, cytology, and adenosine deaminase (ADA).

On the 3rd day of care, the patient felt strenuous shortness of breath and O₂ saturation

Table 1. Clinical Data of the Case.

	Patient I	Patient II	Patient III
Sex	Female	Female	Male
Age (years)	66	60	63
Comorbidities	DM, hypertension, ischemic stroke, PPM insertion due to Sick Sinus Syndrome	SLE, heart failure	Vasculitis, hypertension
Chief complaint during admission	Shortness of breath	Shortness of breath	Fever
Chest x-ray	Bilateral infiltrates with left pleural effusion	Bilateral infiltrates and cardiomegaly	Bilateral diffuse consolidation
Chest CT scan	Bilateral diffuse ground glass opacities and consolidation in the left lung	Consolidation in the left lung	Bilateral ground glass opacities, consolidation, reticular opacities and pleural effusion

dropped to 83-88%. The patient was suspected for worsening pneumonia due to TB. Levofloxacin 1 x 750 mg IV was then added to the treatment list. Chest CT scan was also performed on the patient with a result of diffuse GGO in both sides of the lungs and consolidation in the left lung (Figure 1).

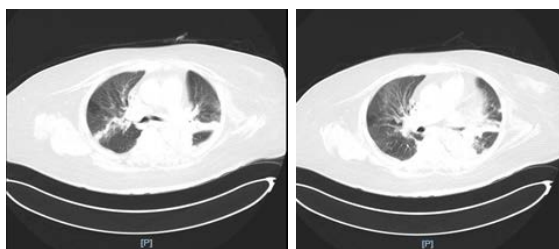


Figure 1. CT scan showed bilateral diffuse GGO and consolidation in the left lung.

On the 5th day, the patient's condition did not get any better, therefore the patient was suspected for COVID-19 based on the CT scan result. The patient was planned for rapid serological test for SARS-CoV-2 antibody and oropharyngeal swab twice. Rapid serological test was non reactive. Other examinations such as ADA resulted in 8 IU/L, culture examination found no microorganism and pleural fluid cytology found no malignancy.

Due to hypotension with a systolic pressure of 70 mmHg on the 8th day of care, the patient was moved to ICU. The patient was given some additional drugs: hydroxychloroquine 400 mg p.o. b.i.d., n-acetylcysteine 1200 mg i.v. o.d., meropenem was stopped and replaced by tigecycline 100 mg i.v. o.d. loading dose then 50 mg i.v. b.i.d.

From the 1st and 2nd oropharyngeal result which came out on the 13th day, SARS-CoV-2 was found negative and from the blood PCR test for CMV DNA, it was found positive with CMV count of 7.3×10^3 copies/mL. Subsequently, hydroxychloroquine was stopped and the patient began to be treated with ganciclovir 250 mg i.v. b.i.d. Unfortunately, the patient passed away on the next day.

Patient II

A 60 year old woman came to the hospital on April 28th 2020 with shortness of breath since

a week prior to hospitalization. The patient also complained feeling of nausea and vomit. There were no cough and fever. The patient has a history of valvular heart disease since 2010. The patient has also been suffering from systemic lupus erythematosus (SLE) since 2017. Prednison 3 mg p.o. t.i.w., hydroxychloroquine 200 mg p.o. o.d. and mycophenolic acid 180 mg p.o. b.i.d. has been routinely consumed for the past 1 year.

Physical examination obtained BP 70/40 mmHg, pulse 150 bpm irregular, RR 34 times per minute, O_2 saturation 98.5%. From chest examination, bilateral wet coarse rhonchi was acquired. Laboratory examination showed lymphopenia of $0.57 \times 10^9/L$, NLR of 13.5, elevated CRP of 13.5 mg/L, elevated procalcitonin of 0.51 ng/mL. Chest x-ray revealed infiltrates in both sides of lungs and cardiomegaly (Figure 2). Chest CT scan was also performed on patient with a result of consolidation in the left lung (Figure 3).

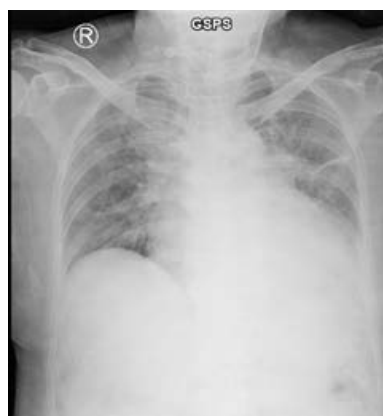


Figure 2. Infiltrates in both sides of lungs and cardiomegaly revealed on chest x-ray.

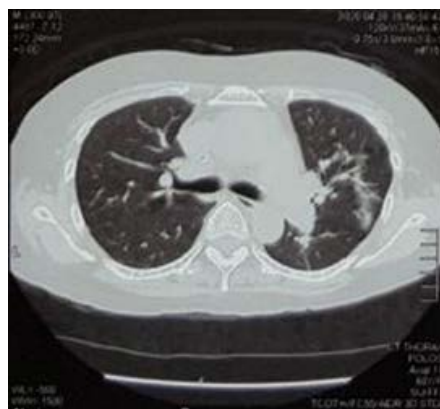


Figure 3. Consolidation in the left lungs from chest CT scan.

Table 2. Laboratory Examination Results.

Laboratory Results (normal value)	Patient I	Patient II	Patient III
Hemoglobin (g/dL, 11.5-15)	12.4	8.4	11.8
Thrombocyte (x 10 ⁹ /L, 150-350)	153	199	291
WBC count (x 10 ⁹ /L, 3.5-9.5)	10.5	9.7	25.7
Neutrophil (x 10 ⁹ /L, 1.8-6.3)	7.41	7.7	19.8
Lymphocyte (x 10 ⁹ /L, 1.1-3.2)	2.27	0.57	1.25
Neutrophil lymphocyte ratio	3.2	13.5	15.84
CRP (mg/L, 0-5)	121	17.34	108.9
Procalcitonin (ng/mL, 0-0.05)	0.02	0.51	4.02
IgM anti CMV (<0.7 U/mL)		0.2	
IgG anti CMV (<0.5 U/mL)		691.3	
PCR DNA CMV	Positive, 7.3 x 10 ³ copies/mL	Positive, 1.06 x 10 ⁴ copies/mL	Positive, 9.5 x 10 ³ copies/mL
pH (7.35-7.45)	7.37	7.43	
pCO ₂ (35-45 mmHg)	50	24.3	
pO ₂ (80-100 mmHg)	110	216.5	
HCO ₃ ⁻ (22-26 mmHg)	27.9	16.5	
SO ₂	97.1	98.5	
Rapid Serological Test SARS-CoV-2	Non reactive	Non reactive	Non reactive
RT-PCR swab SARS-CoV-2	Negative	Negative	Negative

Initial diagnoses of the patient were a suspected case of COVID-19, cardiogenic shock, heart failure, atrial fibrillation with normal ventricular response (AF-NVR) and SLE. The patient was given dobutamine drip 3 mg/kgBW/hour, ceftriaxone 2 g i.v. o.d., azithromycin 500 mg p.o. o.d., warfarin sodium 2 mg p.o. o.d., bisoprolol 5 mg p.o. o.d., digoxin 0.125 mg p.o. o.d., methylprednisolone 4 mg p.o. o.d., and allopurinol 100 mg p.o. o.d.

Rapid serological test for SARS-CoV-2 antibody was non reactive. RT-PCR swab was done 3 times and all the results were negative. On the 11th day, IgG anti-CMV was checked and the result was 691.3 u/mL. On the 21st day, CMV DNA resulted in 1.06 x 10⁴ copies/mL. On the 25th day, the patient's condition was getting better and then discharged for ambulatory care.

Patient III

The third patient is a 63 year old man who came to the hospital on July 3rd 2020. The patient complained about fever since 3 days prior to admission, along with shortness of breath and worsening cough since a day beforehand. The patient was referred from another hospital which located 700 km from our hospital due to

suspicion of pulmonary embolism and sepsis caused by complicated urinary tract infection (UTI). The patient had already been catheterized upon arrival. The patient did not experience any dizziness, headache, chest pain, epigastric pain, nausea and vomitus. The patient has a history of vasculitis and asthma that occasionally occurs in the past 2 years. The patient also has a history of hypertension. The patient routinely consumes hydroxychloroquine 200 mg p.o. o.d, imidapril 10 mg p.o. o.d., and amlodipine 10 mg p.o. o.d. The patient had been treated with methylprednisolone for vasculitis but it had already been stopped since 8 months before admission. The patient has allergies on several drugs including levofloxacin, ciprofloxacin, cefadroxil, cefixime and mefenamic acid. The patient also has contrast allergy and seafood allergy. In the previous hospital, the patient had already been given nebulization of salbutamol, furosemide 40 mg i.v. o.d., enoxaparin sodium 0.6 U i.v. o.d., fondaparinux 2.5 mg s.c. o.d., and meropenem 1 g i.v. o.d.

From the physical examination, several datas were obtained. The BP was 151/87 mmHg, pulse 95 beats per minute regular, RR 20 times per

minute, pulse oxymetry 95%. Minimal rhonchi on the left lung was found from chest examination. Laboratory examination showed leukocytosis of $25.7 \times 10^3/\text{mm}^3$, lymphocyte count of $1.25 \times 10^9/\text{L}$ (normal), NLR of 15.84, elevated CRP of 108.9 mg/dL, elevated procalcitonin of 4.02 ng/mL. Chest x-ray showed diffuse consolidation in both sides of the lungs (**Figure 4**). CT scan revealed GGO, consolidation and reticular opacities in both sides of the lungs, along with bilateral pleural effusion (**Figure 5**).



Figure 4. Diffuse consolidation of both lungs found in chest x-ray.

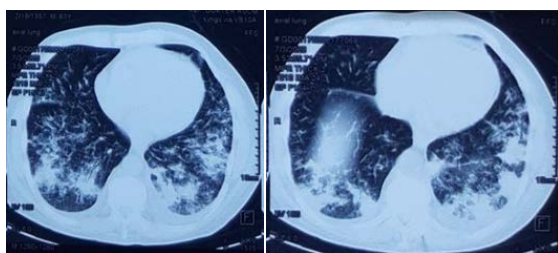


Figure 5. CT scan showed GGO, consolidation and reticular opacities in both sides of the lungs.

When the patient was admitted to the ward, the patient was diagnosed with bacterial pneumonia with differential diagnosis of fungal and viral pneumonia, along with leukocytoclastic vasculitis and controlled hypertension. The patient was given paracetamol 1 g i.v. t.i.d. prn., meropenem 1 g i.v. t.i.d., methylprednisolone 62.5 mg i.v. o.d., nebulization of salbutamol : budesonide 1:1 mL b.i.d, and esomeprazole 40

mg i.v. b.i.d. While being treated in the ward, several drugs were added to the treatment list: n-acetylcysteine 5 g i.v. o.d., fluconazole 150 mg i.v. o.d., fondaparinux 2.5 mg s.c. o.d, hydroxychloroquine 200 mg p.o. o.d., imidapril 10 mg p.o. o.d., and amlodipine 5 mg p.o. o.d. On the 2nd day of care, the patient felt strenuous shortness of breath and O_2 saturation dropped to 92-93%.

In this COVID-19 pandemic era, this kind of situation leads to suspicion of COVID-19 thus the patient was tested for rapid serological test for SARS-CoV-2 antibody, nasopharyngeal and oropharyngeal swab. From the previous hospital, rapid serological test had already been done twice which both resulted in non reactive. On the 2nd day of care in our hospital, rapid serological test showed non reactive for SARS-CoV-2 antibody. RT-PCR examination on nasopharyngeal and oropharyngeal swabs came out negative on the 4th day of care. On the next day, several laboratory examinations were carried out to search for the pneumonia etiology, one of them was CMV DNA examination with PCR method. On the 6th day of care, the result turned out to be positive. A couple days later, the result of quantitative PCR examination for CMV DNA was obtained and the CMV count was 9.5×10^3 copies/mL. Hence, the patient was given ganciclovir with the loading dose of 250 mg i.v. b.i.d. and the maintenance dose of 250 mg i.v. o.d.. The patient's condition improved and the patient was discharged on the 16th day for ambulatory care.

DISCUSSION

COVID-19 pneumonia is a novel acute respiratory disease which has been disseminated rapidly and has similar clinical presentations to other viral pneumonias.⁶ Epidemiologically, COVID-19 often happens in male about 40-60 years old with history of residing or travelling into the area of epidemic. In other hand, viral pneumonia often occurs in children, rarely found in adults or in the communities and its prevalence also spikes in the certain season. The occurrence of viral pneumonia depends on the virulence of the virus, transmission route, age and the host's immunological status.⁷

COVID-19 clinical manifestations are mainly fever, non-productive coughs and shortness of breath.^{6,8} Those symptoms are similar to viral pneumonia symptoms in general including coughs, dyspnea, fever and pleuritic chest pain. Coughs in viral pneumonia are mainly non-productive, but if there were sputum production, the sputum would be scant and watery in contrast to bacterial pneumonia that presents with mucopurulent sputum.⁶ Clinical presentations of viral pneumonia alone may not distinguish the specific cause of the viral pneumonia. Nevertheless, COVID-19 has some symptoms that are rarely found in other viral pneumonia such as anosmia, dysgeusia and gastrointestinal symptoms.^{9,10}

Laboratory findings that are often found in COVID-19 are normal or low white blood cell (WBC) count, lymphopenia, elevated CRP, elevated lactate dehydrogenase (LDH), and elevated erythrocyte sedimentation rate (ESR).^{7,8} In viral pneumonia, WBC count may increased, normal or decreased, but increased WBC count is often associated with bacterial pneumonia. Elevated CRP is also found in viral pneumonia even though it is not a sensitive nor specific finding.¹¹ Similar to clinical presentations, general parameters that are measured in the laboratory such as complete blood count and differential count cannot differentiate the specific cause of pneumonia, but can only raise the tendency of the cause of infection whether if it is viral or bacterial. Because of that, specific laboratory examinations must be conducted to detect the specific cause of pneumonia.

Radiological features of COVID-19 found in chest CT scan are multiple and bilateral GGO with or without consolidation in the posterior, basal and peripheral part of the lungs. Other finding which is often found after GGO and consolidation is reticular opacities that appear due to a complex network of interlobular and intralobular septal thickening. Crazy paving pattern, reversed halo sign and air bronchogram are also found in chest CT scan. The features that are rarely seen in COVID-19 are widespread GGO, lymphadenopathy and pleural effusion.^{1,5}

RT-PCR examination is a specific laboratory examination that has to be conducted on

COVID-19 suspected patients because it is the gold standard in COVID-19 diagnosis establishment,¹ but it requires a lot of time—a day or even more—in order to get the result especially in the early of pandemic.⁷ During COVID-19 pandemic era, chest CT scan has a vital role in diagnosing COVID-19 and monitoring the patient's clinical course.^{1,3} GGO, one of the most often radiological finding of COVID-19, appears on the chest CT scan in the early course of the disease (0-4 days after the symptom onset).¹² The existence of that finding in high risk patients may raise the suspicion and vigilance towards COVID-19.³

According to the multinational consensus statement from the Fleischner Society,¹³ chest CT scan is indicated if the patient presents with moderate to severe COVID-19 symptoms regardless of the RT-PCR result. Asymptomatic patients or patients with mild symptoms are not indicated for chest CT scan examination. If the chest CT scan resulted in suggestive of COVID-19, that patient must be admitted, isolated, and the RT-PCR examination must be performed in order to establish the diagnosis.^{7,13,14}

Based on the systematic review done by Böger B et al,² chest CT scan has high sensitivity about 89.8% to 93.7% (mean = 91.9%), in contrast to its low specificity around 21.0% to 29.5% (mean = 25.1%). Low specificity of chest CT scan is caused by the CT scan features of COVID-19 that are also found in other lung diseases, ranging from pneumonia caused by virus, bacteria, fungi, pneumonitis caused by hypersensitivity, to lung edema.⁵ In imaging diagnosis, COVID-19 is hardly distinguishable from its differential diagnoses particularly viral pneumonia.⁷ Because of that, it is important to identify viruses that can also cause the radiological features of COVID-19 pneumonia.

Several viruses that can produce radiological features of COVID-19 such as GGO and consolidation are CMV, adenovirus, herpes simplex virus (HSV), influenza virus, parainfluenza virus, human meta-pneumovirus (HMPV), coronavirus, and respiratory syncytial virus (RSV). Nevertheless, those viruses show some radiological findings that are useful in differential diagnosis. In general, RSV shows

centrilobular nodules and area of consolidation which often distributed asymmetrically. GGO caused by adenovirus can be distributed in the lobular manner. Parainfluenza virus and HMPV can produce some centrilobular nodules with thickening bronchial walls. Influenza virus often shows nodule and tree in bud opacities. GGO due to HSV and CMV are involving >75% of lung area. Coronaviruses that are causing the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) can produce GGO, consolidation, septal thickening and air bronchogram that are similar to COVID-19. However, reversed halo sign has never been reported in SARS and MERS cases. The lung abnormalities in SARS are more often unifocal.^{1,5}

CMV is the main cause of morbidity in patients with immunodeficiency which occurs due to HIV or non-HIV such as autoimmune disease and post transplantation. CMV infection can happen in various organs particularly the eyes, GI tract, liver and lungs. CMV infection in lungs has similar clinical manifestations as COVID-19, there are fever, non-productive cough and shortness of breath. In contrast to COVID-19, the CMV infection only occurs in immunocompromised patients due to its opportunistic nature.¹⁵ CT imaging of CMV pneumonia are mainly bilateral GGO and consolidation along with poorly defined small centrilobular nodules. Thickened interlobular septum and pleural effusion are also found often.¹⁶ Centrilobular nodule image and pleural effusion are the features that distinguish CMV pneumonia from COVID-19. The diagnosis of CMV pneumonia is established by using polymerase chain reaction (PCR) method.¹⁵

In the case illustrations above, the first and the second patient had shortness of breath whereas the third patient had fever and shortness of breath. It is needed to be noted that all of the reported patients had comorbidities; the first patient had the PPM implantation done, the second and the third patient had autoimmune disease. These patients were included in the group that had a high risk of COVID-19 and all of them came to the hospital with symptoms that match the clinical presentation

of COVID-19, consequently they were suspected as COVID-19 cases. Chest CT scan result of patient I and III showed bilateral GGO and consolidation, while the patient II only showed unilateral consolidation. These results represent pneumonia suggestive of COVID-19. In further development, rapid serological test showed a non-reactive result for SARS-CoV-2 antibody and oropharyngeal swab RT-PCR examination resulted in negative for SARS-CoV-2. Soon after, a few follow up examinations were performed to evaluate the cause of pneumonia. One of them was CMV DNA examination which turned out to be positive in all cases. Diagnosis establishment for other diseases besides COVID-19 in these cases were slow.

During the COVID-19 pandemic, it is important to suspect a case when the CT imaging showed the features of COVID-19. However, the consideration of the patient's history of travel/epidemiology, clinical manifestations, and performing swab RT-PCR are needed by clinicians to establish the diagnosis.^{2,7,13} In this case report, all cases were initially suspected of COVID-19 because those patients were high risk of COVID-19 and all of them came with symptoms that match the clinical presentation of COVID-19, supported with their CT findings of pneumonia suggestive of COVID-19. Eventually, the cause of the disease in all of the reported cases was CMV. Hence, it is needed to be considered for clinicians to think about other differential diagnoses and to do further examinations to search for the disease etiology as soon as possible in order to achieve faster diagnosis establishment. Therefore, in specific conditions where other viral infections may occur such as in immunocompromised or transplant patients suspicion towards non-COVID-19 diseases must be properly considered.

CONCLUSION

While facing the COVID-19 pandemic, chest CT scan has an important role in COVID-19 detection due to its high sensitivity. However, chest CT scan has low specificity for COVID-19 because of several other diseases that have similar radiological features. This case report describes 3 cases of pneumonia CMV with

clinical presentations and chest CT scan results that resemble the clinical and radiological features of COVID-19. Therefore, we should not forget that other diseases may have similar radiological finding to COVID-19, especially in specific conditions such as immunocompromised patients, transplant patients or patients with comorbidities so that the delay in the treatment of other diseases including CMV does not occur.

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