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Case Report

Recurrence hospitalization due to SARS-CoV-2 infection on human immunodeficiency virus patients

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ABSTRACT

COVID-19 is a global health concern with varying severity. Moderate to severe cases require isolation for 10-20 days, and those with weakened immune systems (like HIV) should isolate for 20 days. Indonesia has a rising number of HIV cases. HIV-positive individuals have a higher risk of COVID-19 and may have lower antibody levels after vaccination. Two case studies of HIV-positive patients who contracted SARS-CoV-2 are presented. In case 1, a 29-year-old patient who received the COVID-19 vaccine and was on antiretroviral therapy was hospitalized three times with worsening symptoms, and unfortunately did not survive. In case 2, a 46-year-old patient with a history of tuberculosis and also on antiretroviral therapy was hospitalized twice, reporting mild symptoms, and did not experience any further symptoms related to COVID-19 after being discharged. Both patients tested positive for COVID-19 using rapid antigen tests and PCR tests and did not report any history of contact with COVID-positive individuals. These case studies highlight the challenges faced by HIV-positive individuals in managing COVID-19, and the need for continued research in this area. Immunocompromised COVID-19 patients need special isolation, even with mild symptoms. Longer isolation periods may be necessary, as studies show positive tests can still mean infectiousness. Viral culture tests can help identify contagious individuals who test positive on PCR tests. People with HIV may need a COVID-19 booster vaccine due to lower antibody levels after the initial vaccine. Further research is needed to develop antiviral treatments for COVID-19 infection in individuals with immunocompromised.

Keywords: COVID, HIV, COVID on HIV, Persistent virus shedding, Seroconversion, Immunocompromised

INTRODUCTION

In March 2020, the world health organization (WHO) declared the outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which originated in China, a pandemic and named it coronavirus disease 2019 (COVID-19). Despite the passage of two years, the COVID-19 pandemic continues to be a major global health concern, with WHO declaring it a global health emergency.[1,2] The clinical manifestation of COVID-19 varies from mild to severe. Most infected individuals may be asymptomatic or have mild flu-like symptoms. However, some cases may progress to moderate or severe illness, characterized by symptoms of lower respiratory tract involvement such as difficulty breathing, which can lead to respiratory failure, shock, and failure of multiple organs, resulting in death.[3] Individuals with moderate or severe COVID-19 should isolate for min 10 days. Those with severe COVID-19 may continue to be contagious beyond 10 days and may need to extend their isolation period up to 20 days. Individuals who have a weakened immune system should also isolate for a min of 20 days.[4]

Despite four decades of research and efforts to combat the human immunodeficiency virus (HIV) epidemic, the virus continues to be a major public health concern.[5,6] The joint united nations program on HIV/AIDS (UNAIDS) statistics show that an estimated 38.4 million (33.9 million-43.8 million) people were living with HIV and AIDS globally in 2021.[7] The number of HIV cases in Indonesia reached

its peak in 2019, with a total of 50,282 cases.[8] Effective antiretroviral therapy (ART) is necessary to prevent depletion of CD4 T-lymphocytes, which is caused by HIV, leading to weakened adaptive immune response.[9] Effective ART can help improve the cellular immune response, however, individuals living with HIV may still be at an increased risk for several infections such as *Pneumococcal pneumonia*, influenza, meningococcal disease, herpes virus infections, and tuberculosis.[10]

It is widely acknowledged that older adults, individuals with weakened immune systems, and those with underlying conditions such as hypertension, diabetes, and pre-existing respiratory and cardiovascular disorders are at a higher risk of severe illness requiring hospitalization and intensive care due to COVID-19 infection.[11,12] Additionally, people living with HIV (PLWH) often have an increased risk of COVID-19 due to overlapping risk factors, which tend to be higher than in the general population.[10] Due to varying levels of immune deficiency, the antibody levels and rates of seropositive for PLWH are lower than those of the general population after receiving the inactivated COVID-19 vaccine.[13,14]

CASE REPORT

Two cases were admitted to Wangaya general hospital Denpasar Bali from October 2022 to January 2023.

Case 1: Three times hospitalization due SARS-CoV-2 infection within the past two months

A 29-year-old man who is HIV-positive was hospitalized three times in the last two months due to SARS-CoV2 infection. His first hospitalization occurred on November 16th, 2022. Prior to the hospitalization, he reported experiencing fever and cough for the past three days, as well as fatigue, nausea, and loss of appetite. The patient has been receiving antiretroviral therapy (ARV) from a tertiary hospital for the past 1.5 years. History of contact with COVID positive individual was denied and he has already received two doses of COVID vaccine in 2021. Upon examination, the patient was found to have a fever (38ºC), tachycardia (heart rate of 110 bpm), slightly increased respiratory rate (23 times/m), and normal blood pressure. He was fully alert during his first admission. Minimal rhonchi were present in both lungs and a chest X-ray showed infiltrate in both lung (Figure 1 A). An antigen swab for SARS-CoV-2 was positive on the day of admission and was confirmed by a PCR test (Table 1). Laboratory findings also revealed leucopenia (white blood count of 3090), anemia (hemoglobin of 5.3), and hyponatremia (sodium level of 125) (Table 2). Diagnosis for this HIV patient included COVID-19, anemia, and hyponatremia. Patient treated with Favipiravir 1600 mg twice a day on the first day, followed by a maintenance dose of 600 mg twice a day for days 2-5. Symptomatic and supportive treatment was also administered, along with need for four blood transfusions. On 7th day of admission, patient was discharged in good condition.

The patient's second admission occurred on December 23rd, 2022 with the same diagnosis as the previous hospitalization, but with symptoms that had worsened. The patient appeared exhausted, had a fever, a cough, and difficulty expelling phlegm. The patient's intake was low and they were suffering from malnutrition. A SARS-CoV-2 antigen swab was positive again and confirmed by a PCR test, which was treated with Remdesivir with loading dose and continue with maintenance dose for four days. During the hospitalization, nor-epinephrine was required to maintain blood pressure and a nasal cannula at 3 LPM was used to maintain oxygen saturation. Minimal rhonchi were present in both lungs and a chest X-ray showed bilateral infiltrate (Figure 1 B). The patient was also treated with double antibiotics, levofloxacin and doripenem, administered intravenously for 7 days. Corticosteroid was given this time. The anemia (hemoglobin of 7.33) was treated with two bags of blood transfusion. At the end of the hospitalization period (day 9), the patient was stable enough to continue treatment at home. The patient's family was educated that the patient's condition may not fully return to normal due to the COVID-19 infection.

The patient returned for his third admission for COVID-19 infection on January 10th, 2023, this time with a deterioration of consciousness since the previous day. Over the past week, the patient had not consumed any calories and had not taken his antiretroviral medication (ARV). He had become lethargic with a high fever. The patient's breathing was uncomfortable and required high-flow nasal cannula (HFNC) to maintain oxygen saturation. The patient was treated in the ICU setting this time. The chest X-ray has worsened and there is more infiltrate present in both lung lobes (Figure 1 C). Positive antigen of SARS-COV-2 showed positive and confirmed by a PCR test. The antiviral treatment administered was Remdesivir with no loading dose, at 100mg per day. Antibiotics chosen were levofloxacin and Meropenem. Unfortunately, the patient passed away next day after this third admission.

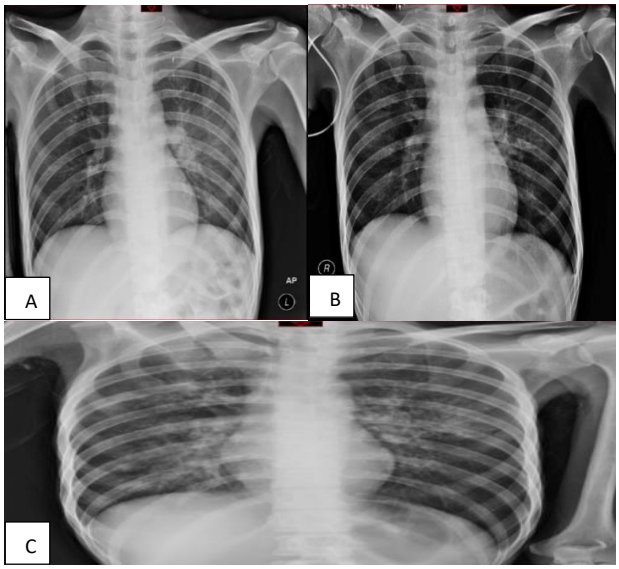

Figure 1 (A-C): Serial of chest X-ray.

Case 2: Hospitalized twice of SARS-CoV-2 infection within the past two months

A 46-year-old man with HIV-positive was hospitalized twice in the last two months due to SARS-CoV-2 infection. His first hospitalization occurred on August 17th, 2022. He presented with dyspnea, fatigue, and mild fever for 2 days before admission. The patient had been receiving ARV therapy for the past 4 years and had a history of tuberculosis 3 years ago. He had no history of contact with COVID-positive individuals and had received two doses of the COVID vaccine in the previous year. On examination, the patient had a mild fever (37.5 ºC), slight tachycardia (108 bpm), blood pressure 97/63 mmHg, and tachypnea (28 times/minute). Rhonchi were present in both lungs, and a chest X-ray showed infiltrate in both lungs (Figure 2 A). An antigen swab for SARS-CoV-2 was positive on the day of admission and was confirmed by a PCR test (Table 3). Laboratory findings were significant, including a drop in hemoglobin to 9.4 mg/dl, hypokalemia (potassium level of 2.7), and hyponatremia (sodium level of 129) (Table 4). Blood gas analysis showed increased pCO_2 with normal pH. Diagnosis for this HIV patient included COVID-19, anemia, hypokalemia, and hyponatremia. The patient was treated with remdesivir 200mg on the first day and 100 mg/day for next 4 days. Antibiotic Levofloxacin was given intravenously for 5 days. Symptomatic and supportive treatment was also administered, along with 4 blood transfusions and electrolyte imbalance correction. On seventh day of admission, patient was discharged in good condition. A week after discharge, patient returned to the clinic in good condition and chest X-ray showed no signs of pneumonia.

The patient's second admission occurred on September 29th, 2022 with a diagnosis of COVID-19 with anemia, similar to the previous hospitalization. The patient presented with a cough with phlegm, but no dyspnea this time, as well as fever and fatigue. A SARS-CoV-2 antigen swab was positive and confirmed by a PCR test (Table 3). He was treated with Favipiravir 1600 mg twice a day on the first day, followed by a maintenance dose of 600 mg twice a day for days 2-5. No oxygen therapy was needed during this hospitalization. On examination, no rhonchi were present this time, and a chest X-ray showed only fibro-infiltrates (Figure 2 C). The patient received prophylactic ceftriaxon, administered intravenously for 7 days. The anemia (hemoglobin of 8.7) was treated with one blood transfusion. At the end of the hospitalization period (day 7), patient was much better and was discharged. The patient returned to the clinic for follow-up visit two weeks after being discharged and reported having no respiratory symptoms and displaying good vital signs, however, the RAT and PCR tests still returned positive results.

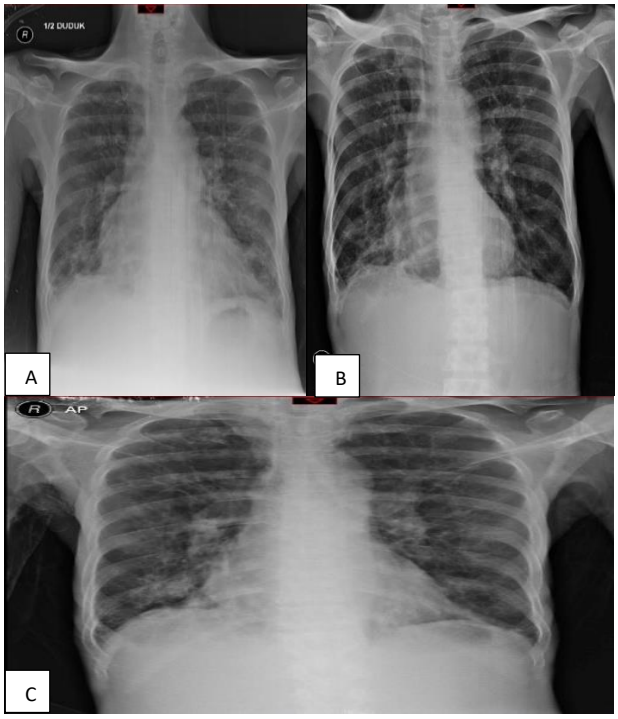

Figure 2 (A-C): Serial of chest x-ray.

Table 1: Antigen and PCR results.

Variables	1st admission (November 16th, 2022)	2nd admission (December 23rd, 2022)	3rd admission (January 10th, 2023)
Rapid antigen	Positive	Positive	Positive
PCR	Positive, Gen ORF1b: 18.51, Gen RdRP: 21.63	Positive, Gen ORF1b:17.00, Gen RdRP:21.11	Positive, Gen ORF1b:21.75, Gen RdRP:24.46

Table 2: Laboratory findings.

Variables	November 16th, 2022	November 21st, 2022	December 23rd, 2022	December 31st, 2022	January 10th, 2023
White blood count (10×3/uL)	3.09	3.30	7.62	6.44	7.20
Hemoglobin (g/dL)	5.3	9.8	10.2	10.4	9.8
Hematocrit (%)	15.1	27.3	29.9	30.6	26.5
Platelets (10×3/uL)	451	275	235	83	57
Neutrophil (%)	85.7	74.8	87.7	87.1	60.8
Lymphocyte (%)	11.2	8.2	5.1	7.3	33.5
Neutrophil/ lymphocyte ratio (%)	7.65	9.15	17.13	11.94	1.82

Continued.

Variables	November 16th, 2022	November 21st, 2022	December 23rd, 2022	December 31st, 2022	January 10th, 2023
Blood glucose (mg/dL)	109	103	75	105	304
Sodium (mmol/L)	125	131	124	132	121
Potassium (mmol/L)	4.1	4.2	4.5	4.2	5.4
Chlorida (mmol/L)	99	101	95	100	92
CRP (mg/L)	45		80		105

Table 3: Antigen and PCR results.

Variables	1st admission (August 17th, 2022)	2nd admission (September 29th, 2022)	Two weeks after discharged from 2nd admission (October 20th, 2022)
Rapid antigen	Positive	Positive	Positive
PCR	Positive, Gen ORF1b:26.53, Gen RdRP:25.92	Positive, Gen ORF1b:24.93, Gen RdRP:26.69	Positive, Gen ORF1b:22.74, Gen RdRP:24.34

Table 4: Laboratory findings.

Variables	August 17th, 2022	August 23rd, 2022	September 29th, 2022
White blood count (10×3/uL)	4.86	3.14	4.17
Hemoglobin (g/dL)	9.4	10.1	8.7
Hematocrit (%)	29.4	30.9	26.2
Platelets (10×3/uL)	165	150	141
Neutrophil (%)	81.7	81.5	84.2
Lymphocyte (%)	8.0	4.8	5.5
Neutrophil/ lymphocyte ratio (%)	10.18	17.07	15.26
Blood glucose (mg/dL)	125	103	85
Sodium (mmol/L)	129	132	130
Potassium (mmol/L)	2.7	3.3	3.5
Chlorida (mmol/L)	103	101	95
D-dimer (µg/ml)	661.2		
CRP (mg/L)	25		20

DISCUSSION

The COVID-19 outbreak is a significant global health concern, with a wide range of clinical manifestations that range from mild to severe. While many infected individuals may not have any symptoms, or may have mild flu-like symptoms, some cases may develop into more moderate or severe illness, characterized by symptoms such as difficulty breathing and the potential for respiratory failure, shock, and organ failure, which can lead to death.[1-3] People with compromised immune systems and underlying health conditions, including hypertension, diabetes, and respiratory or cardiovascular issues, are at a higher risk of experiencing severe illness from COVID-19 that may require hospitalization or intensive care.[11,12] Additionally, people living with HIV (PLWH) may also be at increased risk of COVID-19 due to overlapping risk factors that tend to be higher than in the general population.[10] Furthermore, due to varying levels of immune deficiency, the antibody levels and rates of seropositivity for PLWH may be lower than those of the general population after receiving the inactivated COVID-19 vaccine.[13,14] As seen in the two cases above, PLWH were repeatedly hospitalized due to SARS-CoV-2 infection within two months, despite receiving the two doses of COVID-19 vaccine.

It is estimated that individuals are most contagious around 4 days after contracting SARS-CoV-2.[15] This, along with the high rate of positive antigen test results in the 5-9 days following symptom onset, highlights the importance of proper and consistent mask use during this time. Even though they are likely to be infectious to others, people are recommended to wear a well-fitting mask and avoid contact with those at high risk of severe disease for 10 days after being infected, even if they end isolation after 5 days.[16] Individuals diagnosed with moderate or severe COVID-19 should self-isolate for at least 10 days. However, those with severe symptoms may still be able to spread the virus beyond that time frame and may need to continue isolation for up to 20 days. Individuals with compromised immune systems should also self-isolate for a minimum of 20 days.[4] As demonstrated in the cases above, despite isolating them for more than 20 days, the antigen test results remained positive, in conjunction with positive PCR results. It is important to note that these guidelines may not apply for immunocompromised patients who may need more time for the virus to clear from their system.[17]

Viral clearance in the respiratory tract typically occurs within 21 days.[18] However, a certain percentage of patients with SARS-CoV-2 infection may experience persistent viral shedding (PVS) lasting up to 60-80 days after diagnosis.[19,20] Recent literature shows that PVS is defined as detection of SARS-CoV-2 RNA for a median of 21 days after symptom onset.[18] A study by Vena et al found that PVS did not seem to be related to age or sex. However, individuals with immunosuppression were found to have a sevenfold increased risk of PVS (p=0.019).[17] The findings of this study align with those observed in the cases above, where individuals with immunocompromised status and SARS-CoV-2 infection exhibit prolonged symptoms and a higher frequency of hospitalization compared to the general population, likely due to PVS. The study also observed a higher likelihood of PVS in patients with high levels of IL-6 at the time of diagnosis. This supports recent research that suggests high levels of IL-6 during antiviral immune responses may inhibit the ability of cytotoxic T lymphocytes to effectively clear the virus.[17,21] Although we did not measure IL-6 levels in these patients, it is known that various inflammatory mediators, including IL-6, can induce the liver to produce CRP, a plasma protein.[22] Thus, we assessed the severity of the cases by measuring CRP values, which is a reliable indicator for early detection. As mentioned previously, patient 1 had a higher CRP value than patient 2, indicating greater severity and that may indicate ongoing inflammation. It's important to note that while PVS may indicate the presence of the virus, it is not clear if it means that the virus is still active and able to be transmitted. Studies have suggested that the infectiousness of SARS-CoV-2 may decrease significantly between 8-18 days after symptom onset, even if the virus can still be detected by reverse transcriptase-polymerase chain reaction (RT-PCR) test.[23] The cycle threshold (Ct) was highly accurate in determining the presence of live virus. A Ct < 25 had a 90% success rate in predicting live virus. On the other hand, a Ct > 25 was 100% accurate in predicting negative viral culture.[24]

The literature review found other ten cases of immunocompromised patients in whom live virus was detected more than 10 days after the onset of infection, in most cases after more than 20 days (median: 46.5 days; range: 17-119). It's important to note that PVS of live virus was observed not only in severely ill patients but also in those with mild or asymptomatic infection.[25] PLWH may have lower antibody levels and rates of seropositivity compared to the general population after receiving the inactivated COVID-19 vaccine. This is due to the varying levels of immune deficiency that PLWH may experience. These lower antibody levels can potentially impact the level of protection provided by the vaccine.[13,14] Similar to the two patient cases, even after being vaccinated, they still contracted COVID-19 at a moderate to severe degree.

Rapid antigen test (RAT) has been found to have a higher positive predictive value for detecting live virus in viral culture than RT-PCR and can be an effective tool for determining the duration of infectiousness.[26] It can be can be a useful tool in guiding recommendations for isolation after SARS-CoV-2 infection.[16] The SARS-CoV-2 virus can generally be detected in viral culture up to 10 days after symptom onset.[27] Studies show that individuals 2-3 days before the onset of symptoms and during the first 5-7 days of illness have the highest viral loads and are most likely to transmit the virus to others.[28] Approximately 50% of antigen tests are positive between 5-9 days after infection, but the percentage of positive results decreases during this period, particularly after asymptomatic infection, prior infection, and in people who have completed a primary COVID-19 vaccine series. "Prolonged antigen positivity" refers to RAT positivity lasting longer than 14 days from the onset of symptoms or from the first positive COVID-19 test, whichever occurs earlier. A study by Sasikumar found that the average duration for RAT negativity was 12.9 days, but in 23.4% of patients, it took more than 14 days for the RAT to become negative.[29] Those two patients experienced prolonged antigen positivity, as we can see on the Table 1 and Table 3.

Many antigen-based rapid diagnostic tests (Ag-RDTs) can detect more than 90% of cases with high viral loads, such as Ct values less than 25-30, that are typically seen in the early days following the onset of symptoms.[30] WHO recommends that SARS-CoV-2 Ag-RDTs that meet the minimum performance requirements of at least 80% sensitivity and 97% specificity compared to a nucleic acid amplification test (NAAT) reference assay can be used to diagnose SARS-CoV-2 in suspected COVID-19 cases.[30] In our setting, Wangaya public hospital, the antigen test kit used is from Arkan medical and it has a sensitivity of 93.33% and specificity of 100% for PCR with CT value of ≤ 25, and sensitivity of 13.33% and specificity of 100% for PCR with CT value >25.

CONCLUSION

In conclusion, special attention should be given to isolation precautions for individuals who are immunocompromised and have SARS-CoV-2 infection, particularly in hospital settings, even if they only have mild symptoms. Previous studies have shown a correlation between antigen positivity and infectiousness in COVID-19 therefore a longer isolation period should be considered for these individuals compared to those with a competent immune system. Furthermore, viral culture may be useful in determining the potential contagiousness of individuals with prolonged PCR COVID-19 positivity.

Additionally, due to the lower antibody levels and rates of seropositivity for people living with HIV (PLWH) after receiving the inactivated COVID-19 vaccine, it is crucial for PLWH to receive a booster vaccine. Further research is needed to develop antiviral treatments for COVID-19 infection in individuals with immunocompromised.

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