

A Case Report of Confirmed COVID-19 In Acute Lymphoblastic Leukemia in Childhood

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Abstract

Introduction: Confirmed COVID-19 case is defined as positive reverse transcriptase polymerase chain reaction (RT-PCR) tests of viral RNA in person with or without clinical symptoms. Patients with leukemia may be at a higher risk to developing COVID-19 infection associated with their underlying disease and chemotherapy treatment, and also also developed severe disease more rapidly compared with healthy person. The aim of this case report is to describe an 11-year-old girl with confirmed COVID-19 and comorbidities of acute lymphoblastic leukemia.

Case Presentation: A girl 11 years 10 months old was clinically diagnosed as confirmed COVID-19 and Acute Lymphoblastic Leukemia (ALL) based on positive RT-PCR SARS CoV2 swab test and bone marrow puncture (BMP). The main complaint was weakness since 2 days ago, she had slight anosmia and dry cough since 1 days. The history of fever, dyspnoea, and spontaneous bleeding were absent. She had normal urination and defecation. Hepatosplenomegaly was found on physical examination. The laboratory result found the complete blood count (CBC) slightly leukopenia, antibody of COVID-19 test was reactive IgG and positive swab RT-PCR SARS CoV2 test. The first BMP result was ALL FAB L2. From the chest x-ray showed infiltrates in both of lungs.

Conclusion: This is a case reported of Acute Lymphoblastic Leukemia with confirmed COVID-19 in a girl 11 years 10 months old and diagnostic approach based on RT-PCR SARS CoV2 and BMP.

Keywords: Confirmed COVID-19, Acute Lymphoblastic Leukemia, Childhood.

1. Introduction

The novel beta coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially described in Wuhan, China, in December 2019. Since then, more than 2.5 million people worldwide have been infected with coronavirus disease 2019 (COVID-19), and more than 170,000 have died (Li et al. 2020). In Indonesia, there are 4,533 new confirmed cases of COVID-19 and total positive cases of COVID-19 were 1,636,792 cases until this April, 2021. About 25–50% of people are exposed to COVID-19 infection were asymptomatic, while symptomatic clinically infected people from mild symptoms of dry cough, fever, and malaise to severe complications such as life-threatening pneumonia, acute respiratory distress syndrome, neurologic dysfunction, disseminated intravascular coagulopathy (DIC), and cardiomyopathy leading to cardiac arrest, multiorgan failure, and ultimately death. Infected patients with cancer had higher rates of severe illness (intensive care unit admissions, invasive ventilation, or death) compared with others (Du et al, 2020). Children are at risk of being infected with Covid-19. Among these children, the largest proportion about 84% is in the age between 9-19 years group range. In the United States, prevalence cases of children were < 15% in age range of 0-12 months, 26% for age 1-9 years and 59% for age 10-17 years (Lu et al, 2020).

The first transmission to humans is thought to be due to direct contact. The largest transmission route from human-to-human transmission is droplet secretions of the respiratory tract in the form of coughing or sneezing. Early in infection, SARS-CoV-2 targets cells such as nasal, bronchial epithelial cells and pneumocytes by viral protein spike (S) structure that binds to the angiotensin-converting enzyme 2 (ACE-2) receptor. Transmembrane serine protease type 2 (TMPRSS2), which is present in host cells will promotes viral uptake by cleaving ACE-2 and mediates the entry of the coronavirus into host cells. Severe lymphopenia can occur in individuals with COVID-19 when SARS-CoV-2 infection kills T lymphocytes of humoral and cell mediated immunity, destroys lymphopoiesis and increases lymphocyte apoptosis. In the later stages of infection, SARS-CoV-2 will infect pulmonary capillary endothelial cells that provokes an inflammatory response and triggers the entry of monocyte s and neutrophils. Autopsy studies have demonstrated widespread alveolar wall thickening with mononuclear cells and macrophages infiltrating the air space in addition to endotheliitis (Jayaweera et al, 2020).

Patients with leukemia are often immunosuppressed, myelosuppressed, and may have low immunoglobulin levels, so they are a higher risk to developed critical ill condition more rapidly compared with healthy person (Belson et al, 2007). Here, we report the case report of a girl 11 years 10-month-old in Acute Lymphoblastic Leukemia with confirmed COVID-19 with antibody of COVID-19 was reactive IgG, swab RT-PCR SARS CoV2 test was positive.

2. Case

A girl aged 11 years 10 months old, came to the paediatric hematologic oncology clinic H. Adam Malik General Hospital on December 3, 2020 with the main complaint of weakness for 2 days before being admitted to the hospital without weakness in the hands and feet nor numbness. She had slight anosmia for 1 days ago and dry cough, without fever. No spontaneous bleeding such as bleeding gums, nosebleeds and bruises and shortness of breath. Normal urination and defecation. She was the previous patient in the paediatric oncology division of RSUP HAM with a diagnosis of ALL on chemotherapy standard risk consolidation phase at week 8. The previous chemotherapy was methotrexate intrathecal (MTX), vincristine, leunase, mercaptopurine. The history of mother going out of town was denied. The mother never tested the rapid antigen or antibody examination of COVID-19.

Physical examination on the chest she's not experienced dyspnoea with respiratory rate was normal and from auscultation, rales was absent. Hepatosplenomegaly was found on the patient. From the laboratory result showed anti COVID-19 result was reactive Ig G and positive swab PCR SARS Co-V-2 test. Inflammation marker were white blood cell 3.430 /uL, procalcitonin 0,03 ng/mL, erythrocyte sedimentation rate (ESR) 25 mg/dL, ferritin 681 ng/mL from the chest x-ray showed infiltrate in the bilateral perihilar (figure 1). First bone marrow puncture (BMP) was done on September 30, 2020 with result ALL FAB L2, second BMP on 27 November 2020 with result ALL complete remission. This patient had gotten Vitamin C 1000 mg daily, Zinc 20 mg daily and Mercaptopurine (6MP) 50mg daily.

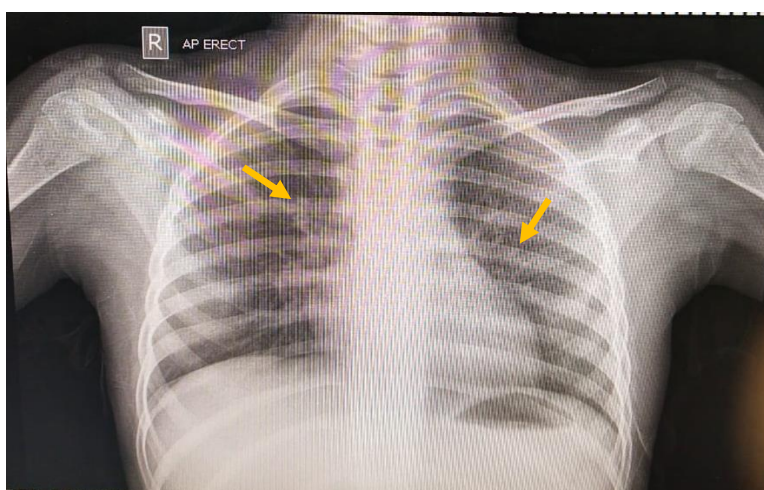


Fig. 1. Infiltrate appears in the bilateral perihilar and right pericardial.

3. Discussion

COVID-19 is an infection caused by the β -Corona virus family of coronavirus and belongs to subfamily Orthocoronavirinae, ordo Nidovirales, and subfamily includes α - coronavirus, β - coronavirus, γ - coronavirus, and delta coronavirus. Data from China has shown that older adults, especially those with serious health conditions, are at a higher risk for severe COVID-19-related illness and death than younger people. Almost all children are at risk of being infected with Covid-19 (Zhu et al, 2020). The first transmission to humans is thought to be due to direct contact. Particles of droplets are $> 5\mu\text{m}$ in size, and can occur in people within 1 meter. Airborne transmission by particles with size $<5\mu\text{m}$ can occur during medical procedures such as intubation, tracheostomy or nebulizing, so if necessary this action must be carried out in a negative pressure room (Wiersinga et al, 2020).

SARS-CoV-2 targets cells such as nasal, bronchial cells and pneumocytes by viral protein spike (S) structure that binds to the angiotensin-converting enzyme 2 (ACE-2) receptor. Transmembrane serine protease type 2 (TMPRSS2), which is present in host cells especially alveolar type II epithelial cells will promotes viral uptake. Severe lymphopenia can occur in person with COVID-19 when SARS-CoV-2 infects and kills T lymphocytes of humoral and cell mediated immunity, destroys lymphopoiesis and increases lymphocyte apoptosis. In the later stages of infection, the integrity of the epithelial-endothelial barrier is compromised and SARS-CoV-2 infects pulmonary capillary endothelial cells, provokes an inflammatory response and triggers the entry of monocytes and neutrophils that causing alveolar wall thickening (Jayaweera et al, 2020).

According to research conducted by Bialek et al in 2020 that the predictor of the incidence of COVID-19 was age <1 year with comorbidities were admitted to ICU care in 15-62% of the total patients. Patients with leukemia often experience immunosuppression, myelosuppression, and have low levels of immunoglobulin, making them potentially more susceptible to COVID-19 infection and its complications. Patients with leukemia

have a higher risk of developing COVID-19 infection due to various factors related to the underlying diagnosis and treatment as well as factors related to the patient's condition as listed in Table 1 (Belson et al, 2020).

Table 1. Risk Factors of COVID-19 in Leukemia (Belson et al, 2020).

Risk Factor	Cause		
	Leukimia diagnosis	Treatment	Patient spesific
Neutropenia	X	X	
Leukopenia	X	X	
Hypogammaglobulinemia	X	X	
Depressed immune function	X	X	
Hypercoagulable state	X	X ^a	
Organ dysfunction (cardiac, renal, liver, pulmonary)	X	X	X
Comorbid conditions			X
Age			X

COVID-19, coronavirus disease 2019. ^a With asparaginase treatment.

Chemotherapy is the drugs to destroy cancer cells. It usually works by keeping the cancer cells from growing, dividing, and making more cells. However, the drugs used for chemotherapy are powerful, and can still cause damage to healthy cells. Methotrexate (folic acid antagonist) and mercaptopurine, are belongs to the class of antimetabolites that work to inhibit DNA synthesis. Vincristine is belonging to the class of alkaloids vinca that inhibit microtubule formation in mitotic spindle, resulting an arrest of dividing cells at the metaphase stage. Asparaginase / leunase is an enzyme that breaks down asparagine. Unlike normal cells, ALL cells are unable to make their own asparagine. So asparaginase stops the cancer cells from dividing and growing (Ariawati et al, 2007). However, these chemotherapies have common side effect of myelosuppression, alopecia, and mucositis that increased risk of infection due to decrease white blood cells level. Each type of leukemia can also be associated with a risk to COVID-19 infection due to the course of the disease or associated therapy. These risk factors are presented in table 2 (Jianping et al, 2020).

Table 2. Specific risk factors for leukemia against COVID-1911 infection (Jianping et al, 2020)

Leukemia type	Possible risk factors
ALL	Myelosuppression due to underlying disease and treatment Hypogammaglobulinemia Impaired B-cell function due to CD20-targeted monoclonal antibodies Prolonged steroid exposure Pulmonary and renal impairment due to methotrexate therapy Cardiac dysfunction due to anthracycline exposure Increased risk of COVID-19-associated thrombosis with asparaginase
AML	Myelosuppression due to underlying disease and treatment Cardiac dysfunction due to anthracycline exposure Pulmonary injury due to midostaurin
CML	Cardiac injury due to dasatinib, nilotinib, ponatinib Pulmonary injury due to dasatinib Increased risk of COVID-19-associated thrombosis with ponatinib and nilotinib
CLL	Hypogammaglobulinemia Impaired B-cell function due to CD20-targeted monoclonal antibodies Impaired innate immune response as well as B-cell and T-cell function with BTK inhibitors
MDS	Myelosuppression due to underlying disease and therapy Impaired neutrophil and T-cell function Potential increase risk of COVID-19 associated hyperinflammation due to baseline elevated IL-1, IL-6, TNF, and other cytokines Renal, cardiovascular, or other comorbidities due to underlying comorbidities
MPN	Risk of thrombosis in myeloproliferative disorders Rare but potential risk of cytokine reaction with abrupt discontinuation of JAK inhibitor Potential increased risk of COVID-19-associated hyperinflammation due to baseline elevated IL-1, IL-6, TNF, and other cytokines

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; COVID-19, coronavirus disease 2019; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms.

Patients who receive chemotherapy may have a higher risk of developing infective complications when compared to healthy people due to their greater level of immunosuppression. Even after cessation of their chemotherapy, immunosuppression is reported to last for several months although its duration is yet to be accurately determined. In addition, it is known that younger children have more persistent immune deficits following chemotherapy, and alterations of the immune system have been reported until 6–12 months following cessation of their chemotherapy. Therefore, many concerns have been raised on the potential risk that the current COVID-19 pandemic would behave in the same way as previous coronaviruses outbreaks when more severe respiratory illnesses and higher rates of hospitalization were registered in immunosuppressed children than in healthy children (Paul et al, 2020).

This patient was diagnosed with acute lymphoblastic leukemia by BMP since September 2020 with previous chemotherapy agent were methotrexate intrathecal (IT), vincristine and L-asparaginase / leunase and mercaptopurine. The serology of IgG anti Covid-19 was reactive. Based on the results of the chest radiograph shows bronchopneumonia although it is not suitable for clinical conditions. The patient admitted to the isolation room with confirmed COVID-19 infection based on the RT-PCR Covid-19 was positive and postpone the next chemotherapy. The number of confirmed cases COVID 19 in the paediatric hematology oncology department RSUP H Adam Malik to date were 4 patients. The laboratory result of the patient shows leukopenia that can caused by a previous chemotherapy agent (methotrexate IT, mercaptopurine, vincristine, asparaginase) which have common side effect of myelosuppression and basic underlying disease itself that increased risk of getting an infection due to low level of white blood cells. Asparaginase can increased risk of COVID 19 associated thrombosis. All of these were stopped except mercaptopurine. High level of ferritin from this patient may caused by COVID-19 infection although procalcitonin level was normal.

Hrusak et al reported that a boy 8-year-old undergoing myelosuppressive chemotherapy for T-cell acute lymphoblastic leukemia in Wuhan hospital developed respiratory distress and required mechanical ventilation. Another Reports from 25 countries around the world, covering a population of around 10,000 children and adolescents undergoing chemotherapy found that nine children tested positive for SARS-CoV-2 based on swab results (Hrusak et al, 2020). Eight of the nine cases had asymptomatic to mild symptoms. During the course of the patient's disease, C-reactive protein and interleukin-6 levels increase slightly, but high levels of ferritin. Another case was a child with ALL without typical symptoms and a COVID-19 swab was carried out (the parents were positive for COVID-19), the maintenance phase of antileukemia treatment was stopped until two negative results were obtained. Clinical symptoms of the patients gradually improve until they recover. However, it should be noted that there are some factors influencing the prognosis of patients with COVID-19; these can be seen in table 3 (Xia et al, 2020).

Table 3. Factors influencing the prognosis of COVID-19 (Brousseau et al, 2020).

Groups	Clinical features
Asymptomatic	Later seroconversion
Mild	Low fever, fatigue, dry cough, slight asthenia, increased CRP and ESR
Moderate	Increased CRP and ESR, increased ground-glass and infiltrating shadows in both lungs
Severe and critical	Dyspnoea, hypoxemia, ARDS, septic shock, metabolic acidosis, bleeding, coagulation dysfunction, increased troponin, increased CRP and ESR, increased D-dimer, decreased peripheral blood lymphocyte count, elevated inflammatory factors, increased ground-glass and infiltrating consolidation of lung, earlier seroconversion, high viral burden.

ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

The clinical symptoms of this patient, there was no fever, no cough, no anosmia and no shortness of breath. the patient only complained of weakness. From laboratory results show slightly leukopenia with neutrophil, lymphocyte counts, and procalcitonin within normal limit but the level of ferritin was slightly increased. On the chest radiograph there were no other abnormalities except bronchopneumonia, and also no interference from other organ systems while the patient was undergoing treatment in the isolation room. Based on these assessments, the patient has a good outcome.

4. Conclusion

This is a case reported of confirmed COVID-19 In Acute Lymphoblastic Leukemia in girl 11 years 10-month-old. Diagnostic approach confirmed COVID-19 based on RT-PCR SARS CoV2 swab test and ALL based-on BMP. This rapid antibody IgG was reactive with positive swab of RT-PCR SARS CoV2 test. The main

complaint was dry cough and weakness, as a sign of mild SARSCoV-2 infection with bronchopneumonia result in chest radiologic imaging. The laboratory result found the complete blood count (CBC) slightly leukopenia,

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