Hypercoagulation state in infant with COVID-19: a case report

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ABSTRACT

Background: COVID-19 pandemic is not over yet, and the clinical manifestations of this newly emerged disease vary due to the rapid mutation of SARS-CoV-2 as its causative agent. The SARS-CoV-2 infection will stimulate the release of proinflammatory cytokines in large amounts, which further leads to hypercoagulation. The aim of this study is to describe a case of COVID-19 with hypercoagulation and what can be done to prevent serious complications.

Case: A 1.5-month-old baby boy presented with a complaint of coughing for 10 days. He was accompanied by persistent fever, diarrhea, and vomiting, but no shortness of breath or rhinorrhea was reported. It was known that his parents, whom he was living with, were self-isolating due to COVID-19. On physical examinations, his vital signs were within normal limits except for axillary temperature, which was tested at 38.3°C. Laboratory results showed a prolongation of coagulation time (PT: 8.3 seconds, APTT: 23.2 seconds), elevated D-Dimer (>10,000 ng/mL), and a positive COVID-19 PCR test. He was diagnosed with a hypercoagulation state in severe COVID-19 and received both supportive and anticoagulant therapy. His condition improved, and he was discharged in good condition after 12 days of hospitalization.

Conclusion: In order to get good outcomes, thorough examinations and comprehensive management have to be ensured in patients with a hypercoagulation state due to severe COVID-19.

Keywords: Anticoagulant, COVID-19, D-Dimer, Hypercoagulation, SARS-CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first described as pneumonia of unknown etiology in Wuhan, China, in December 2019 and is now a pandemic. COVID-19 is an infectious disease caused by SARS-CoV-2, which is classified under the genus Betacoronavirus (Sarbecovirus subgenus) of the Coronaviridae family.¹,² SARS-CoV-2 is the seventh coronavirus that has been identified and known to infect humans.³

From China, COVID-19 has spread to various countries in a short time.³ Globally, there were 209,876,613 COVID-19 confirmed cases, with the number of deaths as much as 4,400,284 until August 12/8/21.³ Based on data recorded by the American Academy of Pediatrics (AAP), there was an average of 5,864 COVID-19 child cases out of 100,000 children in the population, and it was stated that there was a 5% increase in pediatric cases of COVID-19 over the last 2 weeks (29/7/21-12/8/21).³ In Indonesia, there were a total of 3,979,456 COVID-19 confirmed cases and 126,372 death cases, the proportion of cases in children aged 0–5 years was 2.9%, and children aged 6–18 years was 10%, with the number of deaths in children was 0.5% in each age group.⁴

The clinical manifestations of SARS-CoV-2 infection range from asymptomatic infection to severe disease.¹,⁵ In children with severe disease, laboratory tests act as an indicator to monitor the disease severity.⁶–⁷ Elevated LDH, CRP, PCT, D-dimer, and PT results in severe disease are often found consistently.⁶–⁷ Pediatric patients have fewer comorbidities and complications compared to adults.⁶–⁷ Some diseases that may exacerbate SARS-CoV-2 infection in children are asthma, congenital heart disease, and immunosuppressive conditions.⁶–⁷ Management in pediatric patients includes antiviral therapy, empiric antibiotic treatment, nutritional support therapy, and symptoms relief.⁸

CASE PRESENTATION

A one-and-a-half-month-old baby boy was brought by his mother to the emergency room with a complaint of coughing for 10 days. The baby coughed most of the time, and it was getting worse that he became restless and sleepless. An additional complaint was diarrhea 4 days before with a frequency of more than four times a day, watery, no pulp, yellowish in color, and no mucus or blood. Continuous fever in the last 3 days was reported, which subsided only when taking medicine. He also vomited 3–4 times a day in the last couple of days, especially when drinking milk. His parents tested positive for the COVID-19 PCR test and were self-isolating since then.

On physical examinations, he was alert with a heart rate of 150 times/minute, respiratory rate of 56–60 times/minute, an axillary temperature of 38.2°C, and oxygen saturation of 96% (room air). No liver or spleen enlargements were found.

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Other general and systemic examinations revealed no abnormality.

Initial laboratory tests showed hemoglobin of 11.1 g/dL, leukocytes of 10.400/mm³, lymphocytes of 45.5%, neutrophils of 31.3%, and platelets of 291,000/mm³. Complete blood count re-evaluation was done, and we found platelet level decreased to 183,000/mm³ and neutrophil to lymphocyte ratio was 0.91. Blood coagulation tests showed PT of 8.3 seconds, APTT of 23.2 seconds, and D-dimer of >10,000 μg/L. Other tests were done, and the results were stated as follows: SGPT 65 U/L, SGPT 81 U/L, serum creatinine 0.3 mg/dL, sodium level 142 mmol/L, potassium 5.4 mmol/L, chloride 102 mmol/L. SARS Cov-2 PCR test showed a positive result. A chest x-ray was done, and it showed pneumonia characteristics.

The patient was diagnosed with severe COVID-19 with a hypercoagulation state and was treated at the Pediatric Intensive Care Unit (PICU). He received 2 – 4 liters/minute of oxygen using a nasal cannula, a remdesivir loading dose of 5 mg/kg followed by a dose of 2.5mg/kg every 24 hours, and ceftriaxone 50 mg/kg every 12 hours. The doctor decided to administer enoxaparin 0.5 mg/kg every 24 hours subcutaneously. Additional drugs were given, such as intravenous dexamethasone 0.15 mg/kg every 24 hours, paracetamol drop, zinc syrup and vitamin D3 supplementation. The patient was hospitalized for 12 days and was discharged in good condition with a heart rate of 100 bpm, respiratory rate of 38 times per minute, a temperature of 36.5°C, and oxygen saturation was 98%.

**DISCUSSION**

COVID-19 is a respiratory disease caused by the SARS-CoV-2, an enveloped single-stranded RNA virus, which is easily transmitted from human to human (mostly through droplets); and currently known that the transmission can also be through contact with the membrane. This virus gets into human cells by binding to the ACE2 receptor, facilitated by the membrane protease TMPRSS2, replicates within the cell and is then released by the cells into the body, where it inactivates or destroys the host cells. ACE2 and TMPRSS2 receptors are co-expressed in the lung, heart, gut, smooth muscle, liver, kidney, neurons, and immune cells. This may explain the potential for multi-organ injury recently observed in pediatric patients. In the lung, the binding of viral ACE2 receptors on alveolar epithelial cells and alveolar macrophages causes alveolar damage. This virus is also believed to affect immune system function and has been shown to increase the expression of the proinflammatory cytokine IL-6 and the chemokines MCP1, CXCL1, CXCL5, and CXCL10 in lung tissue.

Since the declaration of the COVID-19 pandemic in early 2020 until 2021, many cases have been found in infants. The disease ranges from mild to severe symptoms and requires special treatments due to complications involving multiple organ systems. Based on the classification made by Ikatan Dokter Anak Indonesia (IDAI), this patient was classified as severe COVID-19 because it involves various organ systems, such as gastrointestinal and hematological systems.

Based on the history of this patient, it was found that he was infected by SARS-CoV-2 from a family cluster. According to the obtained information, the patient’s father and mother were confirmed positive for COVID-19 and were undergoing quarantine. It was preceded by the grandparents experiencing COVID-19 symptoms. Close contact and living in the same house increased the risk of infants being infected with the SARS-CoV-2 virus.

Early identification and screening are necessary to prevent infants from SARS-CoV-2 infection because some patients can be asymptomatic. The patient in this report experienced coughing for 10 days accompanied by gastrointestinal symptoms such as vomiting and diarrhea. Several studies suggest that these gastrointestinal symptoms are related to the SARS-CoV-2 antibodies, which are formed at the time of infection. In pediatric patients, respiratory symptoms such as coughing and shortness of breath are rare, but gastrointestinal symptoms such as diarrhea, nausea, vomiting and loss of appetite are more common, but if there are gastrointestinal symptoms accompanied by a history of contact with COVID-19 patients, screening must be carried out.

From the results of the patient’s laboratory examination, it was thought that the shortened coagulation time was associated with hyperactivation of the complement system, which contributed to the tendency to thrombosis. SARS-CoV-2 is an extracellular RNA virus that has been identified as a natural factor VII-activating protease cofactor and a natural procoagulant by enhancing the autoactivation of proteases of the intrinsic blood clotting pathways such as factors XI and XII. Neutrophil extracellular traps (NETs), which are extracellular networks of chromatin, protein, and antimicrobials were released by neutrophils to prevent infection. By activating platelets through intrinsic and extrinsic pathways, inflammation and thrombosis can be initiated by NETs.

Based on various studies that have been carried out on children with mild to severe COVID-19, different laboratory results were obtained compared to adult patients. In pediatric patients with severe disease, leukocyte levels tend to be normal or even elevated. In addition, lymphocyte levels appear to be normal, in contrast to adult patients who tend to decrease. This may be due to the relative immaturity of the children’s immune systems, which allows for differences in viral susceptibility or response to infection. So that in pediatric patients, leukocytes cannot be an indicator of the disease severity.

It is well known that hypercoagulation in COVID-19 patients is caused by the SARS-CoV-2 virus attaching to the ACE-2 receptor, causing angiotensin II to bind to the cellular receptor angiotensin II type 1a receptor in the lungs, causing acute lung injury along with the occurrence of diffuse alveolar damage. This results in fibrin deposition, hyaline membrane deposition and microvascular thrombus. Acute lung injury in COVID-19 patients shows deposits of fibrin in the pulmonary microcirculation and clinically may occur in various organs such as the heart and kidneys.

On initial examination, the D-dimer was more than 10,000 μg/L. This may be related to an acute inflammatory reaction in which the liver synthesizes fibrinogen.
according to the degree of disease.\textsuperscript{19} It is also known that D-dimer is a product of fibrin degradation, which is broken down by plasmin in alveolar and low fibrinolytic activity, resulting in an increase in D-dimer level.\textsuperscript{19} It is also believed that the largest proportion of circulating D-dimer originates from the lesions located in the lungs.\textsuperscript{19}

Complement system activation is involved in the pathogenesis of hypercoagulation in SARS-CoV-2 infection.\textsuperscript{20,21} There is an interaction between activation of coagulation, initiation of tissue factor coagulation cascade, formation of thrombin, activation of Thrombin Activatable Fibrinolysis Inhibitor (TAFI), inhibition of fibrinolysis by TAFI, and several steps in the complement activation. This may explain the hypercoagulability state in COVID-19 and the increased incidence of thrombotic complications.\textsuperscript{20,21} In addition, it should be noted that the degree of fibrinolytic involvement varies with disease severity and may subsequently change transiently during the disease course.\textsuperscript{20,21} Thus, the therapeutic approach must be appropriately adapted to the phase of the clinical course.\textsuperscript{20-23}

In accordance with the management guidelines of COVID-19 in children in 2021 issued by the Ikatan Dokter Anak Indonesia (IDA), the current treatments were appropriate by giving broad-spectrum empirical antibiotics, such as ceftriaxone, to prevent and treat bacterial coinfection.\textsuperscript{5}

COVID-19 treatments are usually supportive, including prevention and management of complications. Remdesivir has shown to be beneficial in trials in adult patients that it is now available and approved by the FDA for emergency use in pediatric patients.\textsuperscript{4} Remdesivir works by inhibiting the replication of RNA-dependent RNA polymerase, stopping the synthesis of the SARS-CoV-2 virus in vitro and has been shown to reduce recovery time from COVID-19.\textsuperscript{4} From the research data, there were only a few pediatric patients who experienced adverse effects such as increased liver aminotransferase levels and anemia in these patients.\textsuperscript{4} It was found that hemoglobin levels tended to be the same as not affected by the use of remdesivir.\textsuperscript{4} Liver function tests, namely SGOT-SGPT, were done on this patient, and we did not find an increase in SGOT and SGPT levels more than 5 times the normal value level. In patients with 7 days of remdesivir therapy, clinical evaluations during administrations have always been carried out in order to result in a positive outcome.\textsuperscript{22}

For the treatment of prolonged coagulation time, enoxaparin therapy was given. Based on the COVID-19 management guidelines, enoxaparin therapy is given (low molecular-weight heparin/LMWH) in hemodynamically unstable MIS-C with cardiac involvement patients, DIC, pulmonary embolism, and life-threatening deep vein thrombosis.\textsuperscript{20,23} It can also act as a prophylaxis therapy in patients with MIS-C.\textsuperscript{23} Enoxaparin should not be given if there is active bleeding, history of heparin allergy or heparin-induced thrombocytopenia, history of previous bleeding, platelet count <25,000/mm\(^3\), uncontrolled hypertension, acute stroke, lumbar puncture or complete anesthesia procedure 4 hours earlier, and severe hepatic impairment.\textsuperscript{23} The enoxaparin administration must be discussed first with the COVID-19 treatment team at the respective hospital.\textsuperscript{23} The dose of enoxaparin as prophylaxis is 0.5 mg/kgBW every 24 hours SQ.\textsuperscript{23} The administration of anticoagulants was adjusted to the clinical and coagulation markers.\textsuperscript{4,23} In this case, the patient was treated with enoxaparin for 10 days, and the response was quite good, as evidenced by an improvement in the examination of the coagulation time during treatment. For other treatments, the patient was given supportive and symptomatic therapy such as antipyretics, vitamin D3 and zinc.

After 12 days of hospitalization, the patient’s conditions were getting better. The cough became less frequent, shortness of breath and fever were absent, and vomiting was also absent since the fourth day. The patient also met the discharge criteria, such as having no fever for more than two days and not using oxygen supporting devices for two days. This patient also had a good response to remdesivir and enoxaparin therapy which was in accordance with the guidelines issued by IDAI, but its use must be under close observation in the intensive room, and serial laboratory examinations must be carried out to monitor whether there is impaired renal, hepatic, hematological function during therapy.

CONCLUSION

Hypercoagulation states in pediatric COVID-19 cases may have a wide range of manifestations that require close observation in the intensive room and anticoagulant therapy to prevent worsening or complications. Assessment of complications can be seen from clinical manifestations and laboratory results.

ETHICS CONSIDERATION

The parents have given consent to participate and publish the data.

CONFLICT OF INTEREST

There was no conflict of interest in writing this study report.

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AUTHOR’S CONTRIBUTION

All authors contributed together to writing this study report, from the first step of proposal preparation, data collection and analysis until the preparation of the report in the form of publication.

REFERENCES


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