

# Young Woman With Recurrent Autoimmune Hemolytic Anemia And Covid-19: A Case Report

Hatano Wahyu Riyanto<sup>a</sup>, Indro Buono<sup>b\*</sup>

<sup>a</sup> *hattanova@gmail.com*

<sup>a</sup> *SidoWaras Hospital, Mojokerto City 61381, Indonesia*

## Abstract

**Introduction:** The clinical manifestations of autoimmune hemolytic anemia can be moderate or severe but if the anemia is associated with infection with the SARS-CoV-19 virus it can lead to higher rates of paralysis or even death. In this case, a young woman experiencing recurrent autoimmune hemolytic anemia accompanied by infection with the SARS-CoV-19 virus is a new case.

**Case Report:** A 20-year-old young woman came to our emergency department with a complaint of a limp body with fever for 1 day. The patient looks pale, tired and lethargic. Menstrual history  $\pm$  2 weeks. The patient had a history of autoimmune hemolytic anemia, 11 months ago. Lab tests showed hemoglobin (Hb) 3.7 g/dl, RT-PCR (+), x-ray photos of thorax appeared normal. Patients are given 4 prc transfusion bags in 1 day Hb increased to 10.1 g/dl. We performed an examination of the removal of peripheral blood and obtained the results of agglutination (+), spherocytes (+), polychromate (+), microcytocytes (+). Direct Coomb's Test (+). Patients diagnosed with AIHA and therapy with dexamethasone 5 mg IV as much as 3x / day. After 4 days, the patient goes home without any complaints.

**Conclusion:** SARS CoV-2 infection during this pandemic can be considered a recurrent AIHA trigger in adolescent women, besides that it can increase comorbidities, also cause a more severe inflammatory response, and injuries to organs, when compared to those that patients do not suffer from anemia.

Keywords: Young woman, Autoimmune hemolytic anemia, Pandemic, COVID-19, Corticosteroid

## INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is a hemolytic disease whose pathophysiology is based on an autoimmune process. Red blood cells are formed normally, but undergo a process of premature destruction due to damage acquired in the circulation. AIHA occurs when a patient's own immune system produces antibodies and attaches to red blood cells, causing red blood cells to burst excessively, resulting in a decrease in red blood cells, and the bone marrow cannot compensate for the destruction of red blood cells that are too damaged. blood cells.<sup>1</sup>

The lifespan of normal red blood cells is 120 days after they are removed from the bone marrow. In the absence of a disease process, red blood cells are removed from the circulation by phagocytosis in the spleen and liver. The premature breakdown of red blood cells is called hemolysis. Hemolytic anemia occurs if before that age the erythrocytes become damaged which can be caused by intracorporeal and extracorporeal

factors. Patients with hemolytic anemia generally come with complaints of fatigue, headache, palpitations, chest pain, complaints of heart failure, and ischemia of the central nervous system.<sup>1</sup>

The AIHA classification is generally based on the cause, namely primary or idiopathic which occurs without underlying disease and secondary when associated with an underlying disease process and drug induced. Another classification that is often used is based on the optimal temperature required for auto antibodies to become active, known as warm autoantibodies and cold autoantibodies.<sup>1</sup>

Teenage girls are prone to anemia because they lose a lot of blood during menstruation. Rematri who suffer from anemia are at risk of developing anemia during pregnancy. This will have a negative impact on the growth and development of the fetus in the womb and have the potential to cause complications in pregnancy and childbirth, and even cause the death of mother and child.<sup>6</sup>

The People's Republic of China reported a case of unexplained pneumonia to the World Health Organization on December 31, 2019. The outbreak is known as coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>4</sup>

The Indonesian Ministry of Health reported that as of July 20, 2020, the total number of confirmed cases of COVID-19 globally had reached 14,043,176, infecting 215 countries worldwide. Of these, 597,583 deaths were reported. The COVID-19 death rate in Indonesia is quite high (4.8%) compared to the world average of 4.3%.<sup>3</sup>

To determine someone who has COVID-19, a PCR swab examination is needed, the latest research results show that some cases can show persistent positive results even though there are no symptoms. Research in Korea showed that although no replicative virus was found 3 weeks after the onset of the first symptoms, SARS-CoV-2 RNA was still detectable in RT-PCR examination specimens for up to 12 weeks. For COVID-19 survivors, the latest research also shows that there is a possibility for reinfection because the COVID-19 antibodies in the body are expected to disappear in 3 to 12 months. In April 2020, America's first confirmed case of SARS-CoV-2 reinfection was reported. Therefore, even though he has been declared cured of COVID-19, he still has to carry out health protocols.

The mechanism of reducing hemoglobin (Hb) levels in COVID-19 patients is very limited. The spike protein CD147 present in the virus is reported to play a role in the attachment of the virus to red blood cells, which causes red blood cells to release Hb. The released Hb will be broken down into heme and globin. It has been reported that viral proteins such as Orflab, ORF3a, and ORF10 can bind to porphyrins in heme to form complexes, leading to heme destruction.

Molecular modeling has also been reported as a determinant of the incidence of AIHA in COVID-19 infection. Ankyrin-1 (ANK-1) is a protein on the red blood cell membrane and has the same epitope as the Spike protein in SARS-CoV-2, so the destruction of red blood cells is part of the patient's immune defense mechanism, resulting in a decrease in Hb levels.

## CASE REPORT

A 20-year-old female patient came to the emergency department of the Sido Waras Hospital complaining of feeling weak for the last 1 day accompanied by fatigue and paleness. No nausea or vomiting. There are no dizziness. The patient also complained of fever for 2 days, fever ups and downs. There is no cough, nor runny nose. The patient has not taken the medicine at all. Menstrual history for  $\pm 2$  weeks without stopping. History of gravis anemia 11 months ago. There is no history of hypertension or diabetes. The patient has no history of taking drugs.

Based on the patient's medical records, it was found that the patient had experienced the same complaint about 11 months ago. At that time, the patient was carried out a complete blood examination with low Hb results, in addition to that a stool & urine examination was carried out complete with normal results then the patient was carried out an edge blood removal examination with a positive Direct Coomb's Test. Conclusion

the patient suffers from autoimmune hemolytic anemia (AIHA). When patients were toddlers or teenagers before, they had never suffered like this.

From the physical examination, the typical symptoms of anemia are obtained. When examined moderately ill patients with mentis compost awareness, anemic in both eye mucosa, blood pressure 110/70 mmHg, pulse 78 x/min, respiratory rate 20 x/min, temperature 36.7 °C with oxygen saturation 98% without additional breathing apparatus. The patient has no tightness, cyanosis or jaundice. Symmetrical chest no wound, additional breathing sounds or additional heart sounds. There is neither ronkhi nor wheezing. Normal intestinal noise, soepel. Warm acral all 4 extremities and no decrease in skin elasticity. An X-ray of the thorax was performed on the patient, but no abnormalities were obtained.

A laboratory examination is carried out, namely a complete blood test. from the results of laboratory examinations obtained a decrease in hemoglobin by 3.7 g / dl (13.5-17.5 g / dl) with hyperpolioperative normosistic anemia, hematocrit 13% (34.9-44.5%). Then the patient is carried out blood transfusions as many as 4 bags.

A laboratory examination is carried out, namely a complete blood test. from the results of laboratory examinations obtained a decrease in hemoglobin by 3.7 g / dl (13.5-17.5 g / dl) with hyperpolioperative normosistic anemia, hematocrit 13% (34.9-44.5%). Then the patient is carried out blood transfusions as many as 4 bags.

After a blood transfusion was performed on the 2nd day a complete blood laboratory examination was carried out again and D-Dimer. After performing a blood transfusion, there was an improvement and increase in hemoglobin by 10.1 g /  $\mu$ L (13.5-17.5 g / dl) normochrome normociter and hematocrit 31.2 % (34.9-44.5%). The results of D-dimer 517 (<500) indicate the presence of viscosity in the blood vessels. In addition, the patient is examined for peripheral blood smears.

The results of the peripheral blood removal examination obtained the presence of agutination (+), morphologically obtained spherotic (+), polychromation (+), tear drop cells (+), eliptosites (+), microcytes (+). So it can be concluded that the patient suffers from autoimmune hemolytic anaemia (AIHA) with a differential diagnosis of secondary AIHA due to systemic lupus erythratosus (SLE). Follow-up examination is carried out reticulocyte check with a result of 11%. With the results of direct coomb's test is also positive 4. To get rid of the diagnosis of secondary AIHA appeal due to systemic lupus erythratosus (SLE) it is necessary to do an ANA Test. But due to cost limitations, the examination was not carried out.

Patients during treatment in addition to being given PRC blood transfusions were also given IV PZ fluid therapy, 3x500mg antrain injection, 3x50mg ranitidine injection, 2x4mg ondansentrone injection, 3x500mg transamine injection, cefriaxone 2x1gr injection, dexamethasone 3x5mg injection, 1x1200mg favirapir injection on day 1, the next day 2x600mg. The patient is also carried out a PCR swab test on the first day of coming to the IGD with the results (+). The 6th day of the inpatient was also carried out a PCR test swab examination with the result (-). The patient's condition has improved and there are no complaints so he is allowed to return home after the 6th day of hospitalization.

## DISCUSSION

The COVID-19 pandemic caused significant mortality and morbidity. Clinical manifestations of COVID-19 patients have a wide scope, ranging from asymptomatic, pneumonia, severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis to septic shock.<sup>10</sup> Clinical manifestations of anemia, in many cases have been reported in COVID-19 patients with severe illness.<sup>11</sup>

Patients of the age of 20 years with a history of menstruation for 2 weeks do not stop, accompanied by fever, no nausea, vomiting , tightness of complaints in his chest. On physical examination, anemia was obtained, no tachycardia, hypoxia or tachypnea . There was also no additional sound in the lungs or heart. Laboratory examinations show severe anemia with high reticulocytes. X-ray examination of the thorax did not

find any abnormalities. PCR Swab Examination (+) with good swab through nasopharyngeal & oropharyngeal. Patients for 6 days from the time the patient was treated from March 17, 2022 to March 23, 2022, the patient was given 4 transfusion blood bags, there was an increase in Hb from 3.7 g / dl to 10 g / dl. During therapy to the patient there is an improvement in the condition.

Peripheral blood removal examination was carried out to see the typical erythrocyte form for various hemolytic anemias, in patients a typical spherocyte formation was obtained in patients with hereditary spherocytosis with the conclusion that patients suffered from autoimmune hemolytic anemia (AIHA) with a differential diagnosis of the presence of secondary AIHA from systematic lupus erythematosus (SLE).

Anemia that appears in patients with suspicion of the process of hemolysis must be done anti globulin test (direct coomb's test) which if a positive result is obtained then the pesien suffers from AIHA, but keep in mind that not all AIHA shows positive results. As well as to get rid of differential diagnosis of secondary AIHA due to SLE, an ANA test must be performed. To get rid of the diagnosis of anemia appeal caused by worm infection, a stool examination must be carried out, to find out the eggs or worms.<sup>1</sup> But because of the limited cost, the examination is not carried out.

AIHA is a hemolytic state whose pathophysiological basis is through autoimmune processes.<sup>1</sup> But the underlying mechanism of autominmunity from SARS-COV-2 infection is not yet unexplained. In another case report, 7 patients from 6 hospitals in France and Belgium reported the appearance of AHAI during COVID-19 infection accompanied by previous comorbidities (hypertension, diabetes militus and chronic renal failure). The average time between the onset of COVID-19 symptoms and the onset of AIHA is 9 days (range 4-13 days).<sup>11</sup>

The mechanism of hemoglobin (Hb) reduction in COVID-19 patients is very limited. The spike-CD147 protein present in the virus reportedly plays a role in the virus's attachment to red blood cells, which causes red blood cells to release Hb. Liu et al. report that the virus first infects cells with ACE2 receptors, including immune cells. Immune cells produce antibodies and viral proteins. Antibodies and erythrocytes produce immune hemolysis, or erythrocytes infected by the Spike-CD147 pathway, at which point Hb attaches and attacks to produce toxic and inflammatory derivatives. This mechanism occurs because several viral proteins can individually bind porphyrins to form their respective complexes. At the same time, the proteins orflab, ORF3a and ORF10 can synergistically attack heme in Hb. Deoxyhemoglobin is more susceptible to viral attacks than oxidized Hb. Such an attack will result in a decrease in hemoglobin, which carries oxygen and dioxidized carbon. Lung cells are toxic and inflammatory due to the derivatives produced by the attack, which ultimately produce a glass-like appearance (ground glass appearance). Capillaries break easily due to inflammation. Proteins such as fibrinogen fill the capillary cracks of coagulation reactions.<sup>8</sup>

Angilleri et al, report the hypothesis that protein molecules on the erythrocyte membrane mimic ANK-1 with the same epitope as the Spike protein in SARS-CoV-2, so the destruction of erythrocytes as part of the patient's immune defense mechanism can lead to a decrease in Hb. ANK-1 levels are erythrocyte membrane proteins used for differentiation and function to provide the main connection between the membrane skeleton and the plasma membrane. They found that ANK-1 allegedly shared an immunogenic-antigenic epitope (the amino acid LLLQY) which is 100% identical to the surface of a SARS-CoV-2 glycoprotein called the spike protein. They determined that this epitope was part of the predicted immunogenic epitope spike 750-SNLLLQYGSFCTQL-763 by B cells using immune epitope databases and analysis sources.<sup>9</sup>

Corticosteroids are an important first line in AIHA. If the corticosteroid does not respond after 14 days of dosing, the corticosteroid can be lowered and then stopped. Corticosteroids such as prednisone 1 mg/kgBB/day divided by several doses, for 14 days when giving a good response (normal Hb, normal reticulocytes) are continued another 14 days then the dose is lowered slowly until the smallest dose in the absence of signs of hemolysis (Normal Hb, normal reticulocytes).<sup>1</sup> But for AIHA accompanied by COVID-19 infection according to research conducted by Lee et al, which reported that the administration of

corticosteroids at the beginning of coronavirus infection was associated with an increase in plasma viral load and should be avoided.<sup>12</sup> As for blood transfusions, they are given when there is very severe and life-threatening anemia.<sup>1</sup>

## CONCLUSION

Recurrent autoimmune hemolytic anemia with SARS CoV-2 virus infection is the first case to occur in a sane hospital. Sars CoV-2 virus infection during this pandemic can be considered as a recurrent AIHA minister in adolescent women, besides it can increase comorbidities, also cause a more severe inflammatory response, and organ injury, when compared to patients who do not suffer from anemia.

## REFERENCES

- Askandar T, Poernomo BS, Chairul E, Djoko S, Gatot S, et al. Book of Teaching Internal Medicine, Issue-2, Surabaya: Airlangga University Press, 2015.
- Prevalence of anemia in women of reproductive age (15-49), 2022. Available from: [https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-anaemia-in-women-of-reproductive-age\(-\)](https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-anaemia-in-women-of-reproductive-age(-)).
- Ministry of Health of the Republic of Indonesia; 2020. Available from: <https://covid19.kemkes.go.id/category/situasi-infeksi-emerging/info-corona-virus/#.X6dwjvkzblIU>, 20 August 2020.
- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for disease control and prevention. *JAMA*. 2020;323(13):1239-42. <https://doi.org/10.1001/jama.2020.2648> PMID:32091533.
- COVID-19 Governance Guidelines, Issue-4, 2022. Available from: <https://covid19.go.id/artikel/2022/02/03/pedoman-tatalaksana-covid-19-edisi-4>.
- Guidelines for prevention and countermeasures of anemia in adolescent girls and women of childbearing age, 2018. Available from: <https://promkes.kemkes.go.id/buku-pedoman-pencegahan-dan-penanggulangan-anemia-pada-remaja-putri-dan-wanita-usia-subur>.
- Ministry of Health of the Republic of Indonesia, 2022. Available from: <https://infeksiemerging.kemkes.go.id/dashboard/covid-19>.
- Liu W, Li H. COVID-19: Attacks the 1-beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. China: Sichuan University of Science and Engineering; 2020. Available from: <https://doi.org/10.26434/chemrxiv.12120912>.
- Angileri F, Legare S, Gammazza AM, Macario EC, Macario AJL, Cappello F. Is molecular mimicry the culprit in the autoimmune hemolytic anemia affecting patients with COVID-19? *Br J Haematol*. 2020;190(2):e92-3. Available from: <https://doi.org/10.1111/bjh.16883> PMID:32453861.
- World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Geneva: World Health Organization; 2020.
- Lazarian G, Quinquenel A, Bellal M, Siavellis J. Autoimmune haemolhemolyticia associated with Covid-19 infection. 2020. *Br J Haematol*. 2020;190(1):29-31.
- Lee N, Chan A, Hui D, Enders KO, Wu A, Chiu R. Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. *J Clin Virol*. 2004;31(4):304-9. Available from: <https://doi.org/10.1016/j.jcv.2004.07.006> PMID:15494274.