

Hemophagocytic Lymphohistiocytosis in an 8-Month-Old Baby

Hanzelina*, Ketut Ariawati, Anak Agung Ngurah Ketut Putra Widnyana

Department of Child Health Medical Faculty Udayana University, Sanglah Hospital, Denpasar, Bali, Indonesia

Email address:

hanzel2gretel@gmail.com (Hanzelina), ketutari_hemato@yahoo.com (K. Ariawati), gungmanikledo@yahoo.co.id (A. A. N. K. P. Widnyana)

*Corresponding author

To cite this article:

Hanzelina, Ketut Ariawati, Anak Agung Ngurah Ketut Putra Widnyana. Hemophagocytic Lymphohistiocytosis in an 8-Month-Old Baby. *World Journal of Medical Case Reports*. Vol. 2, No. 2, 2021, pp. 19-24. doi: 10.11648/j.wjmcr.20210202.11

Received: April 29, 2021; Accepted: May 24, 2021; Published: May 31, 2021

Abstract: Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder with incidence 1 in 50.000 to 150.000 live births. HLH has high fatality rate and poor prognosis, therefore early recognition and diagnosis are necessary. Hereby we aimed to describe the clinical, examination and management aspects of HLH. An eight-month-old girl came with bloating stomach for 1 week and fever since 2 weeks before admission. She also had chronic suppurated otitis media in previous month. Patient has twin sibling, whom in healthy condition. Patient looked pale with distended abdomen. We found enlarge liver and spleen which were palpable 4 cm under the arch of costae and Schuffner IV, respectively. Multiple purpura were found on trunk, head and extremities. Laboratory tests revealed severe normochromic normocytic anemia, neutropenia, severe thrombocytopenia, hyperferritinemia and reactive anti CMV IgG. Blood culture resulted no growth. Urine culture revealed the growth of *Klebsiella pneumoniae*, first ear swab culture showed an isolated *Pseudomonas aeruginosa* and second ear swab culture with *Klebsiella pneumoniae*. The histopathologic examination from bone marrow aspiration revealed hemophagocytic histiocyte. Patient was given broad spectrum antibiotics and supportive therapy and oral dexamethasone after HLH was diagnosed. The patient was pronounced dead during second admission. HLH can be considered as one of the differential diagnosis in children with prolong fever, hepatosplenomegaly and cytopenia. Appropriate treatment protocol should be taken to avoid any complications.

Keywords: Children, Secondary HLH, Non-familial HLH

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder which caused by hyperinflammatory syndrome due to pathologic immune activation. It can be characterized by persistent spiky fever caused by tissue macrophage overabundance [1, 2]. There are two types of HLH: primary HLH and secondary HLH. Primary HLH is thought to be inherited in autosomal or X-linked genes. The secondary or acquired HLH, is caused by infection (49%), malignancy (27%) and autoimmune diseases (24%) [3]. The incidence of HLH is considerably rare with the confirmed cases globally range from 1 in 50.000 to 150.000 live births [1]. Data from Swedish national registry showed the incidence of primary HLH's was 1.5 cases per 1.000.000 live births within 2007 to 2011, furthermore Texas registry showed that 1 per 3000 children admitted with confirmed primary HLH [4]. Another nation-wide epidemiological data from Japan showed that the

annual incidence of HLH is estimated to be around 1 in 800.000 children per year [5]. Unfortunately in Indonesia, there has not been any epidemiological study about HLH yet, however, there was one confirmed case reported from a 12 years old girl in 2015 from West Java [6].

Histiocyte Society published the diagnosis criteria through standardized consensus in 1994 (HLH-94) and was revised in 2004 (HLH-2004). The criteria include consistent molecular diagnosis of HLH or 5 criteria from 8 symptoms which are fever higher than 38.3°C, splenomegaly, cytopenia (included 2 out of: hemoglobin <9g/dL; platelets <100.000/ml and neutrophils <1000/ml), hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL), hemophagocytosis in bone marrow/ spleen/ lymph node or liver, low/absent NK cell activity, ferritin more than 500 ng/mL and elevated soluble

CD25 [1, 4, 7]. It is extremely important to distinguish HLH as primary HLH or secondary HLH since the treatment would be completely different. The clinical manifestation of HLH often mimicking other diseases, which most of the patients came with unexplained persistent fever, enlargement of liver, spleen and cytopenia that can be manifested in anemia and/or spontaneous bleeding. However in condition that genetic testing is unavailable or inconclusive, clinical manifestation can be used to diagnose the HLH [1, 7, 8].

HLH has high fatality rate and poor prognosis [1], it is estimated that the 5 years overall survival is 54% with 94% death occur in the first 8 weeks, therefore early recognition and diagnosis become necessary [1, 4]. We report a case of HLH which presented in 8 months old baby whom was previously healthy. The objective of this case report is to describe clinical, examination and management aspects of HLH.

2. Case

An eight-month old girl came to emergency room of Sanglah Hospital on December 12th 2019 with chief complaint was bloating stomach. The parent mentioned that bloating stomach had been suffered since a week before admission. Additionally, the parent mentioned that her stomach got bigger everyday which caused constipation. Patient also had constant high fever for two weeks with highest temperature was 39.9°C. Fever was suspected caused by recurrent infection of her ears which already treated by ENT doctor. The infection of ears was getting better but the fever still persisted. Patient had reddish spot on her stomach and expanded to hands and legs. Patient also looked pale since one month before admission and the complete blood test showed anemia hypochromic microcytic which was suspected caused by physiology and infection. Patient has twin sibling, whom is healthy. There was no history of congenital anomalies in her family. There was no history of parental consanguineous marriage. No history of illness or consuming any medicine during pregnancy period were noted. There was no abnormality during pregnancy or delivery. Patient had normal growth and development before she was sick.

Patient was fully alert when admitted, her body temperature was 36.7°C, respiratory rate was 34 times per minutes and heart rate was 110 beats per minute and 98% oxygen saturation within the room air. Her head was normal in shape. There were pale conjunctiva, jaundice sclera without sunken eyes and conjunctival injection. The pupils light reflex were normal and size were equal. The left ear got mucoid discharge, while her nose was normal. There were multiple petechiae on her palate without gum bleeding or ulcer. There was no lymph node enlargement on the neck or supraclavicular. The chest was symmetrical both on rest and movement. Breath sound was bronchovesicular without rales or wheezing. The first and second heart sound were normal, regular and no murmur. There were no lymph nodes enlargement on both of axilla. Abdomen was distended with ascites. Bowel sound was still normal. During abdominal palpation we indentified

hepatomegaly which liver could be palpated 4 cm below the arch of costae and splenomegaly which was classified as schuffner IV. Skin turgor was normal. There were no edema on extremities or lymph nodes enlargement on both of inguinal. Anal and genital examinations were normal. There were multiple purpura on the patient's trunk, head and extremities (figure 1). Anthropometric status based on waterlow from mid upper arm circumference was 73% (moderate malnutrition), the height/age base on WHO chart was -3SD and classified as stunting.

Laboratory test revealed severe normochromic normocytic anemia (Hemoglobin 4.71 g/dL), severe thrombocytopenia (Platelet $30.1 \times 10^3/\text{mL}$), leukopenia ($3.67 \times 10^3/\mu\text{L}$), neutropenia ($0.89 \times 10^3/\mu\text{L}$), elevated reticulocyte count (8.4%) and corrected reticulocyte count (3.5%), elevated liver enzyme (SGOT 38.2 U/L; SGPT 46.50 U/L), elevated on both direct and indirect bilirubin (5.66 mg/dL and 0.75 mg/dL respectively) and hypoalbuminemia (2.3 g/dL). Kidney function test was normal. Laboratory resulted elevated the CRP level (99.34 mg/L) and procalcitonin (4.02 ng/mL). Fibrinogen and triglyceride were normal, 196 mg/dL and 159 mg/dL respectively. Ferritin level showed hyperferritinemia (506.1 ng/ml). A reactive CMV IgG was also found during the screening. Blood culture showed an isolated *Bacillus* sp., that possibly grew from specimen contamination. Urine culture revealed the growth of *Klebsiella pneumoniae*. We also performed ear swab twice with first result on December 2019 showed an isolated *Pseudomonas aeruginosa* and for the second time result on February 2020 showed isolated *Klebsiella pneumoniae*. Abdominal X-ray revealed ascites (figure 2). Abdominal ultrasound revealed hepatosplenomegaly (figure 3). Furthermore histopathologic examination from bone marrow aspiration on the 27th of January 2020, demonstrated hemophagocytic histiocyte, showed by orange arrow (figure 4). She fulfilled five criteria from 8 criteria of HLH such as fever, splenomegaly, cytopenia, hyperferritinemia and from histopathologic examination found hemophagocytic histiocyte. Finally HLH was established as diagnosis since February 2020.

Based on the clinical and adjunctive examination, the patient was diagnosed with HLH, severe normochromic normocytic anemia, severe thrombocytopenia, chronic suppurated otitis media (CSOM), intrahepatic cholestasis due to *Klebsiella pneumoniae*, moderate malnutrition and stunting. Patient had been given broad spectrum antibiotic. In the beginning of treatment, she got ceftriaxone for ten days, then changed to cefoperazone-sulbactam combine with amikacin for three days. After urine culture showed *Klebsiella pneumoniae*, the antibiotics were changed to meropenem. Beside antibiotic, she also got packed red cell (PRC), thrombocyte concentrate transfusion, ursodeoxycholic acid and albumin. From ENT division, she got ear toilet and ofloxacin ear drops. She also started dexamethasone 0.5 mg TID since the diagnosed of HLH was established. After her condition got better, she was discharged from hospital on February 22nd 2020.



Figure 1. Multiple purpura on patient's skin.



Figure 2. Abdominal X-Ray.

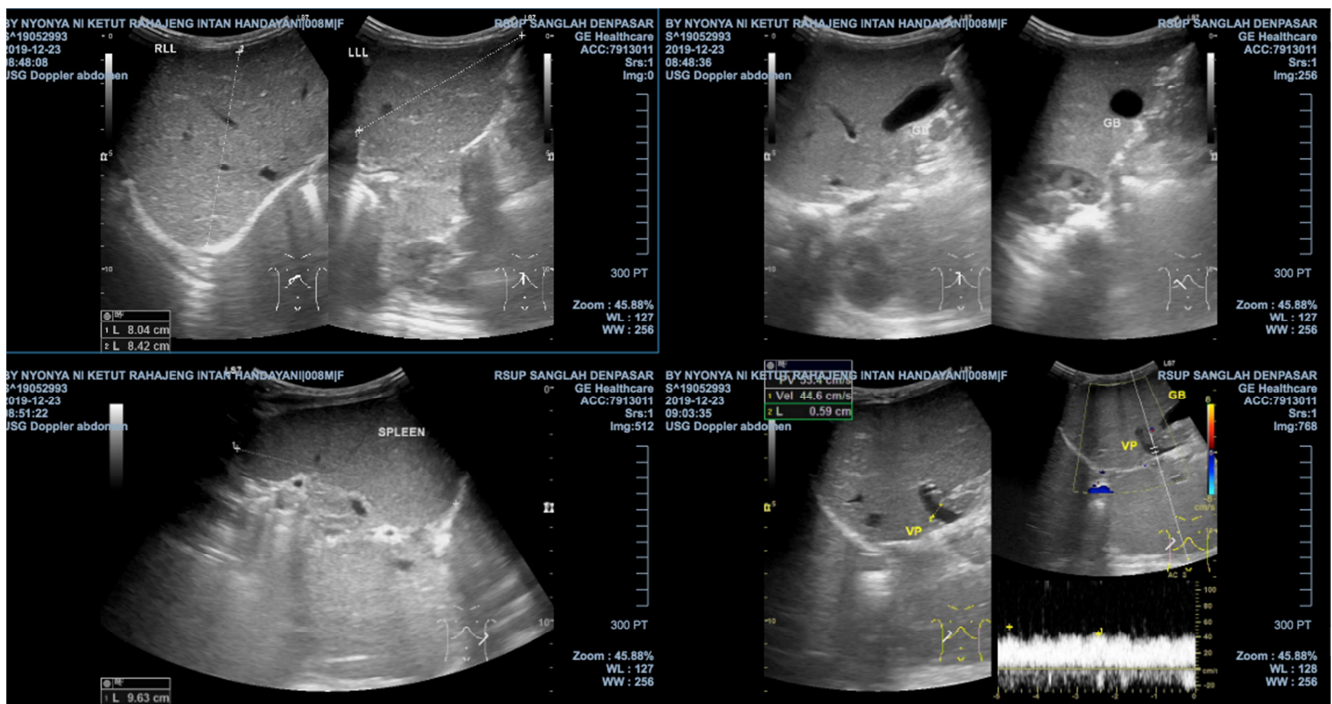


Figure 3. Abdominal Ultrasound.

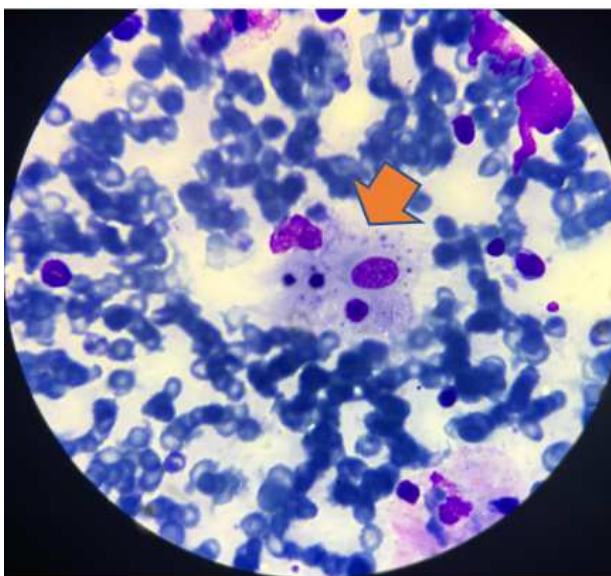


Figure 4. Histopathologic result from bone marrow aspiration.

Patient was admitted for the second time on 6th of March 2020 with chief complaint difficult to breath accompanied by fever for 3 days before admission. Patient was diagnosed with hospital acquired pneumonia, HLH, chronic suppurated otitis media (CSOM), intrahepatic cholestasis due to *Klebsiella pneumonia*, moderate malnutrition, stunting. On the 14th March, the breathlessness got worsen and on the 15th March, patient condition deteriorated due to the desaturation (SpO₂ 76%) before she was being admitted to the Pediatric Intensive Care Unit (PICU). About one hour after being moved to the PICU, patient experienced apnea, bradycardia and desaturation, thus we performed cardiopulmonary resuscitation with positive pressure ventilation and injection of adrenaline 0.1 ml intravenously. The resuscitations was performed for three cycles until patient was pronounced dead at 16th of March, 00.55 Central Indonesian Region Times.

3. Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a rare

disorder which can be characterized by persistent spiky fever caused by tissue macrophage overabundance [1, 2]. HLH incidence is considerably rare with the confirmed cases globally range from 1 in 50.000 to 150.000 live births [1]. Based on national epidemiological data in Japan, there was only a slight difference between an incidence of HLH amongst male and female with the ratio of 0.94, in addition, the vast majority of the patients were children less than 15 years of age including infants less than 1 year of age. Secondary HLH due to viral infection dominated the cases accounting for 53.1% of total cases [5]. In this case, patient was eight months old girl with HLH without any evidences of genetic mutation and have twin whom is perfectly normal. Patient also had history of hospitalization with some infections a month prior to the hospital admission.

Secondary HLH can be precipitated by infection, malignancies and autoimmunity [9]. Some data shows that 41% of HLH cases were caused by primary infection [10]. Systemic infection from viral or bacterial activates the immune system causing lymphoid depletion hence lead to over activation of macrophage [9]. Some pathogen that are known for their ability to cause HLH including *Leishmania spp*, *Toxoplasma gondii*, *Bacillus spp*, *Streptococcus spp*, *Pseudomonas spp*, EBV, CMV, HIV, H1N1, SARS and other parasites such as protozoa and fungi [8, 9]. Local infection is still debatable to cause the strong systemic T Cell in HLH, thus it is estimated that systemic persistent infection is the one that can stimulate immune respond that lead to HLH [11]. During infection, virus can stimulate and activate CD8⁺ T cells to undergo unregulated polyclonal expansion and permanent activation that lead to excessive macrophage activation and hemophagocytosis [12]. There are various mechanisms that can be done by the virus, especially CMV in order to cause HLH. CMV can trigger pattern recognition receptor (PRRs) including TLRs, NOD-like receptor and RIG-I like receptor, causing stimulation towards innate immunity. During some period of time, it causes the exhaustion of bone marrow which induce aplastic anemia and bone marrow failure. It contributes to cytopenia in HLH. CMV also naturally infects and establishes latency in dendritic cell and macrophages, hence permitting virus to take control over antigen presentation. Indirectly, CMV is able to downregulate p53 that control Bcl-2 proteins causing inhibition of mitochondrial apoptosis thus contribute to cytokine storm. CMV, along with EBV are capable to mimic the host immune respond, produce IL-10 that is able to suppress T-cell and reduce NK cell cytotoxicity [11, 12]. In this case, patient has undergone several screenings to reveal any evidences of infection such as toxoplasmosis, rubella and CMV. The reactive result from the CMV IgG demonstrated the history of chronic infection of CMV in this patient. In addition her blood culture revealed *Bacillus spp* that suspected as contaminant, urine showed *Klebsiella pneumoniae* and ear swab showed *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. On the last hospitalization patient also suffered from bacterial pneumonia. The non-reactive result of CMV IgM create a debatable fact that it is unlikely for the CMV to

be the cause of HLH inspite of multiple blood transfusion and leucopenia which suppress cell mediated immunity. This could be predisposed the CMV infection further lead to the HLH [12]

HLH can manifest in various forms and often mimicking other diseases such as SIRS and Sepsis [10]. The most common symptoms of HLH in children are fever, hepatosplenomegaly and cytopenia. Fever occurs in 91% of the reported HLH cases in children despite the causes [13]. It can be caused by an overabundance of pyrogenic mediator including IL-1, IL-6 and TNF- α . Cytopenia can be manifested as pale and fatigue children, spontaneous bleeding or recurrent infections. Cytopenia is caused by the suppression of hematopoiesis by TNF- α and IFN- γ due to the cytokines storm [1, 7]. Furthermore, the enlargement of spleen and liver are caused by infiltration of the macrophages into those specific organs [1, 13]. In spite of the typical manifestation that has been mention in previous literatures, skin manifestation also has strong association with HLH which 6%-65% patient reported cutaneous eruption in secondary HLH [16]. Reported cutaneous finding included maculopapular rashes, generalized erythroderma, panniculitis, erythema morbilliform, petechiae and purpura [1, 5, 16]. Purpura often associated with thrombocytopenia that is going to be visible in the average platelet count of 25.000/L. It can also be assumed purpura is an indirect manifestation of cytopenia in HLH [14]. In this case, patient experienced prolonged fever, with enlargement of liver and spleen, also purpura on her entire body. Her blood examination revealed the platelet count 10.300/L.

Histiocyte Society first published the diagnosis criteria through a standardized consensus in 1994 (HLH-94) and gave an update in 2004 (HLH-2004). The criteria include a consistent molecular diagnosis of HLH or 5 criteria out of 8 symptoms which contain fever higher than 38.3°C, splenomegaly, cytopenia (included 2 out of: hemoglobin <9g/dL; platelets <100.000/ml and neutrophils <1000/ml), hypertriglyceridemia (fasting triglyceride >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL), hemophagocytosis in bone marrow/ spleen/ lymph node or liver, low/absent NK cell activity, ferritin more than 500 ng/mL and elevated soluble CD25 [1, 4, 10]. Cytopenia is caused by the suppression of hematopoiesis due to elevated level of TNF- α and IFN- γ that can also causing the apoptosis of blood cell precursors [1, 17]. Hypertriglyceridemia can occur due to suppression of lipase lipoprotein activity whereas hypofibrinogenemia is caused by secretion of plasminogen activator from macrophage that can cause hyperfibrinolysis [13]. Ferritin can be used as specific sign of HLH since it is released during cell breakdown [13, 15]. Ferritin is accumulated during the anti-inflammatory process of macrophage savaging of heme via CD163 receptor [10, 18]. A study revealed that serum ferritin greater than 2000 μ g/L has 71% sensitivity and 76% specificity in diagnosis of HLH, whereas the serum greater than 4780 μ g/L has 93% positive predictive value to predict death among patient with HLH [18]. To confirm the diagnosis, BMA has to be perform as gold standard examination in HLH. A figure of hemophagocytosis

cell that engulfed debris is illustrating the hemophagocytosis activity I HLH case [1, 15]. In this case, patient fulfilled 5 criteria out of the 8 mentioned above. She had prolonged fever with the highest peak 39.9°C, splenomegaly (schuffner IV), cytopenia with severe low hemoglobin, platelet and neutropenia, hyperferritinemia and also hemophagocytosis in her bone marrow that can be seen through the BMA.

Latest guidelines for management and therapy for HLH was updated by Histiocyte Society in 2004 (HLH-24). The protocol include 8 weeks of initiation therapy with etoposide (VP-16) and dexamethasone along with intratracheal methotrexate for patient with central nervous system manifestation [16, 17, 18]. Broad spectrum antibiotics, prophylactic cotrimoxazole, oral antimycotic, antiviral and IVIG should be considered during the initial phase [16]. Patient will be assessed after 8 weeks of therapy, their condition will be assessed from body temperature (<37.5°C), no splenomegaly, no cytopenia, normal level of triglyceride (<265 mg/dL), fibrinogen (>150 mg/dL), ferritin (<500 ng/mL) and no abnormality in CSF fluid [16]. Patient without familial HLH are recommended to start the continuation therapy after 8 weeks of initial therapy regardless of the result of evaluation with VP-16, dexamethasone and cyclosporine [16, 17]. If patient has completed the resolution of the disease, therapy can be stopped, however if the disease has not resolved, hematopoietic cell transplantation can be considered for patient with familial HLH especially if the compatible donor is available [16, 18]. This protocol has induction rate 58.9% after initial therapy with the overall 3 years survival is 73.9% [17]. In this case, patient was still in her 8 weeks of initial therapy with dexamethasone 0.5 mg every 8 hours and broad spectrum antibiotics.

The prognosis of secondary HLH is relatively poor with only 55% survival within 3 years after diagnosis. Early mortality has been related mostly to the source of infection [13]. More importantly, HLH that is caused by viral infection tend to have worse prognosis and associated with decreased survival [11]. In this case, the primary cause of patient's death was respiratory failure due to pneumonia. Patient died after being hospitalized for 9 days and 3 months after the first onset of HLH manifestation. It is important to predict the prognosis of HLH patient in order to give more aggressive and appropriate treatment approach for the patient. Recently a study stated that patients with non-malignancy associated HLH do not have better prognosis but having a relatively better survival in clinical practice. Higher DIC score, lower albumin, hemoglobin and platelet are a negative prognosis factors in HLH [19] which are align with our case.

From this case, we conclude that we should consider HLH as one of the differential diagnoses in children with symptoms of prolong fever, hepatosplenomegaly and cytopenia. Awareness of this may reduce pain and avoid any delay in treatment. Once HLH is diagnosed, appropriate treatment protocol measures should be undertaken to avoid complications.

4. Conclusions

An eight months old girl came to hospital with the chief

complaint was bloated stomach since one week before admission. Her stomach kept getting bigger by days and patient had difficulty in defecation. Patients also had constant high fever for two weeks with highest temperature reached 39.9°C before admitted. Fever was suspected caused by recurrent infection of ear and already treated by ENT doctor. Patient was the first child of a twin in the family, no history of congenital anomalies in her family. Her twin is also perfectly normal and does not experience similar symptoms as her. Physical examination showed significant for jaundice sclera with pale conjunctiva, abdominal distension, ascites, hepatomegaly and splenomegaly. Liver can be palpated 4 cm under the arch of costae and spleen was enlarged (schuffner IV). In addition multiple purpura were found on her trunk, head and extremities. Laboratory test revealed severe normochromic normocytic anemia and severe thrombocytopenia, elevated liver enzyme, elevated on both direct and indirect bilirubin, hypoalbuminemia. Patient had an elevated CRP and procalcitonin. Ferritin level was checked and showed hyperferritinemia. Reactive anti CMV IgG also found during the screening. Urine culture revealed the growth of *Klebsiella pneumoniae*. She also performed ear swab twice with result isolated *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. The histopathologic examination from bone marrow aspiration demonstrated hemophagocytic histiocyte. She fulfilled five criteria from 8 criteria of HLH such as fever, splenomegaly, cytopenia, hyperferritinemia and from histopathologic examination found hemophagocytic histiocyte. She got broad spectrum antibiotic and supportive therapy. She also got dexamethasone orally. She pronounced dead one month later on the second admission due to the pneumonia.

References

- [1] McLean, J., Katebian, R., Suh, E., Mirza, K., Amin, S. (2019). Neonatal Hemophagocytic Lymphohistiocytosis. *Neo Reviews* 20 (6): 317-325.
- [2] Morimoto, A., Nazakawa, Y., Ishii, E. (2016). Hemophagocytic lymphohistiocytosis: Pathogenesis, diagnosis, and management. *Pediatric International*. 58: 817-825.
- [3] Wang, A., Pope, S., Weinstein, J., Yu, S., Zhang, C., Booth C., Medxhitov, R. (2016). Specific sequences of infectious challenge lead to secondary hemophagocytic lymphohistiocytosis-like disease in mice. *PNAS*: 1-16.
- [4] Allen, C., McClain, K. (2015). Pathophysiology and epidemiology of hemophagocytic lymphohistiocytosis. *Hematology*: 177-182.
- [5] Ishii, E., Ohga, S., Imashuku, S., Yasukawa, M., Tsuda, M., Miura, I., Yamamoto, K., Hirouchi, H. (2017). Nationwide Survey of Hemophagocytic Lymphohistiocytosis in Japan. *Int J Hematology*. 86: 58-65.
- [6] Dewi, Y., Sukorini, U., Budi, M., Intansari, U. (2015). Hemophagocytic Lymphohistocytosis (HLH) pada Severe Systemic Lupus Erythematosus (SLE) dengan Autoimmune Hemolytic Anemia (AIHA) refrakter. *OJS Universitas Gadjah Mada*.

- [7] Canna, S., Marsh, R. (2010). Rare Systemic Hematologic Disorders: Pediatric hemophagocytic lymphohistiocytosis. *The American Society of Hematology*. 15 (16): 1322-1343.
- [8] Garcia, C., Haye, K., Gahig, T. (2016). Hemophagocytic Lymphohistiocytosis (HLH): A Case Series and Review. *American Journal of Medical Case Reports*. 4 (3): 74-79.
- [9] Cascio, A., Pernice, K., Barberi, G., Biondo, C., Beninati, C., Mancuso, G., Morales, R., Iaria, C. (2012). Secondary hemophagocytic lymphohistiocytosis in zoonoses. A systematic review. *European Review for Medical and Pharmacological Sciences*. 16: 1324-1337.
- [10] Castillo, L., Carcillo, J. (2009). Secondary hemophagocytic lymphohistiocytosis and severe sepsis/systemic inflammatory response syndrome/multiorgan dysfunction syndrome/macrophage activation syndrome share common intermediate phenotypes on a spectrum of inflammation. *Pediatr Crit Care Med*. 10 (3): 367-372.
- [11] Brisse, E., Wouters, C., Andrei, G., Matthys, P. (2017). How viruses contribute to the Pathogenesis of Hemophagocytic Lymphohistiocytosis. *Frontiers in immunology*. 8 (1): 102-110.
- [12] Tumian, B., Wong, C. (2015). Pregnancy-related hemophagocytic lymphohistiocytosis associated with cytomegalovirus infection: A diagnostic and therapeutic challenge. *Taiwanese Journal of Obstetrics & Gynecology*. 54: 432-437.
- [13] Zerah, M., Witt, C. (2015). Cutaneous Findings in Hemophagocytic Lymphohistiocytosis. *Dermatology*. 230: 234-243.
- [14] Carthy, L., Fernandez, K., Antony, R. (2017). Challenges in the Diagnosis and Management of Pediatric Hemophagocytic Lymphohistiocytosis. *Clinical Pediatrics*. 1-7.
- [15] Grange, S., Buchonnet, G., Macari, E., Beduncau, G., Carpentier, D., Dehay, J., Girault, C. (2016). The Use of Ferritin to Identify Critically Ill Patients With Secondary Hemophagocytic Lymphohistiocytosis. *Critical Care Medicine*. 44 (11): 1045-1051.
- [16] Henter, J., Home, A., Arico, M., Egeler, M., Imashuku, S., Ledich, S., Clain, K. (2006). REVIEW HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis. *Pediatr Blood Center*.
- [17] Yanagisawa, R., Nakazawa, Y., Matsuda, K., Yasumi, T., Kanegane, H., Marimoto, A., Imaizumi, M. (2018). Outcomes in children with hemophagocytic lymphohistiocytosis treated using HLH-2004 protocol in Japan. *Int J Hemato*. 125-131.
- [18] Ehi, S., Astigaraga, I., Greenwood, T., Hiner, M., Horne, A., Henka, G., Rosee, P. (2018). Recommendations for the Use of Etoposide-Based Therapy and Bone Marrow Transplantation for the Treatment of HLH: Consensus Statements by the HLH Steering Committee of the Histiocyte Society. *Am Ascc Allergy*. 321-333.
- [19] Pan, H., Huo, Y., Sun, L. (2019). Comparison between clinical features and prognosis of malignancy- and nonmalignancy-associated pediatric hemophagocytic lymphohistiocytosis. *BMC Pediatrics*. 19: 468-475.