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Case Report

Respiratory Distress due to Significant Hepatosplenomegaly Revealing Acute Leukemia Complicated by Macrophage Activation Syndrome

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- Acute leukemia
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- Hepatosplenomegaly

Abstract

Macrophage Activation Syndrome (MAS) or Hemophagocytic Lymphohistiocytosis (HLH) is an anatomoclinical entity characterized by the phagocytosis of blood cells by macrophages in response to a supra-physiological stimulation of phagocytic cells by a cytokine storm [1].

It is a rare entity (incidence: 1 in 800,000 in the pediatric population [2]), but a severe condition [3] considered a diagnostic and therapeutic emergency.

Its diagnosis is based on a combination of clinical, laboratory, and histopathological evidence [3].

Here, we report the case of a 3-year-old child admitted to our department for management of respiratory distress due to significant hepatosplenomegaly, revealing acute leukemia complicated by MAS.

ABBREVIATIONS

MAS: Macrophage Activation Syndrome; HLH: Hemophagocytic Lymphohistiocytosis; CBC: Complete Blood Count; MCV: Mean Corpuscular Volume; MCHC: Mean Corpuscular Hemoglobin Concentration; CRP: C - reactive protein; CT scan: Computerized tomography scan; AST: Aspartate transaminase; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; IFN-gamma: Interferon gamma;

INTRODUCTION

Macrophage Activation Syndrome (MAS) is a rare condition related to dysregulation of the immune system, resulting in excessive activation of macrophages that phagocytose red blood cells, white blood cells, and platelets.

Macrophage Activation Syndrome or Hemophagocytic Lymphohistiocytosis (HLH) can occur in both adults and children [4]. The clinical and laboratory signs associated with this condition are nonspecific, but their combination should raise suspicion and lead to a histopathological examination to search for hemophagocytosis in the bone marrow, spleen, or liver [5,6]. It is a rare but severe condition with a poor prognosis and still unclear treatment guidelines [6,7]. The added value of our work is to report a case of reactive MAS due to acute leukemia, revealed by significant dyspnea-causing hepatosplenomegaly.

CASE PRESENTATION

The patient, Y.K., is a 3-year-old child with a history of second-degree consanguinity among parents, presenting with a 2-month history of fever, cutaneous-mucosal pallor, fatigue, respiratory discomfort, and initially neglected bone pain.

He presents to the emergency department of the Children's Hospital in Rabat with worsening clinical symptoms, fever of 39°C, and tachypnea of 39 cycles/minute, showing signs of respiratory distress with a Silverman score of 4 (moderate flaring of the nostrils, intercostal retractions, and expiratory groaning audible without xiphoid funneling or thoraco-abdominal swinging), and oxygen saturation of 93% in ambient air.

On abdominal examination, there is marked abdominal distension with significant hepatomegaly of 14 cm and splenomegaly reaching the umbilicus (the liver and spleen not being palpable in a 3-year-old child under physiological conditions).

Chest X-ray is normal, complete blood count (CBC) shows severe leukocytosis at 47,000/mm3 without neutropenia, along

with bicytopenia including normochromic normocytic anemia [hemoglobin = 5.9 g/dL, mean corpuscular volume (MCV) = 83 um3, mean corpuscular hemoglobin concentration (MCHC) = 27.9 pg/L, reticulocyte count = 20,000/mm^3], and thrombocytopenia at 12,000 cells/mm^3.

C-reactive protein (CRP) is elevated at 150 mg/L.

The patient is stabilized, put on high-flow oxygen therapy, and started on antibiotics targeting the lungs.

Further investigation includes a bone marrow examination (after platelet and fresh frozen plasma transfusion), revealing a blast infiltration of the marrow up to 83%. The diagnosis of acute leukemia is thus established.

In response to the increased hepatomegaly, additional blood biochemistry tests are requested, along with a thoraco-abdominal CT scan.

The biochemistry tests reveal an elevated AST level at 194 IU/L (5 times the upper normal value), normal ALT level, elevated LDH level at 17,019 U/L (17 times the upper normal value). Triglycerides are measured at 2.71 g/L (Normal value: <2.5 g/L), fibrinogen is at 0.3 g/L (below the lower normal value of 1.5 g/L), and ferritin is at 37,000 µg/L (74 times the normal value) in favor of macrophage activation syndrome according to the criteria of Henter and Horne (Figure 1).

The thoraco-abdominal CT scan shows no abnormalities in the thoracic region but reveals significant homogeneous hepatomegaly measuring 16 cm and splenomegaly measuring 9 cm.

Therefore, we have a 3-year-old child, born to second-degree consanguineous parents, admitted in respiratory distress with significant hepatosplenomegaly, and whose further investigations reveal acute leukemia complicated by macrophage activation syndrome (MAS) (Figure 2).

DISCUSSION

Macrophage activation syndrome (MAS), also known as hemophagocytic lymphohistiocytosis (HLH), is a medical condition characterized by excessive and inappropriate activation of phagocytic cells, particularly macrophages. It is a complex pathology that is not yet fully understood. However, two etiopathogenic models [8], are currently highlighted:

The cytotoxicity defect model

This is the predominant model, where a defect in cytotoxicity (congenital or acquired) of NK cells and CD8 T-cells leads to their excessive proliferation without a resolution phase due to their lack of efficiency. This results in a supra-physiological secretion of IFN-gamma, a macrophage-activating cytokine, leading to overstimulation of macrophage cells [8,9]. In response to this excessive and dysregulated secretion, macrophages start to phagocytose blood cells, leading to hemophagocytosis.

The inflammasome activation model [8,10]

This is a more recent model (2014), and is less common. Within certain cells such as macrophages, neutrophils, and enterocytes, there is an intracellular inflammasome. When the cell comes into contact with a sensor (a microbial molecular structure), the inflammasome is activated, which in turn cleaves procaspase 1 into caspase 1. This cleaved caspase is responsible for the secretion of cytokines, including IL-18, which induces the secretion of IFN-gamma. This model explains some cases of MAS without a cytotoxicity defect in NK and CD8 cells.

Two etiological entities are found in cases of MAS/HLH:

- Primary hemophagocytic lymphohistiocytosis (HLH), an autosomal recessive disease, most commonly observed in children.

- Reactive (secondary) hemophagocytic lymphohistiocytosis (HLH) in response to an underlying pathology [11], such as infections (mainly viral: EBV, HIV...; bacterial: BK and others; parasitic: toxoplasmosis, malaria...), malignancies or solid cancers, chronic inflammatory diseases (collagenosis: SLE...; chronic inflammatory rheumatism: PR, Still's disease...), or sometimes related to medication use. These cases are most commonly found in adults.

However, it is important to consider that these two entities exist on a continuum:

- Some cases of primary HLH may manifest later in adulthood.

- Some cases of reactive HLH can be observed in children (as in the case of our patient).

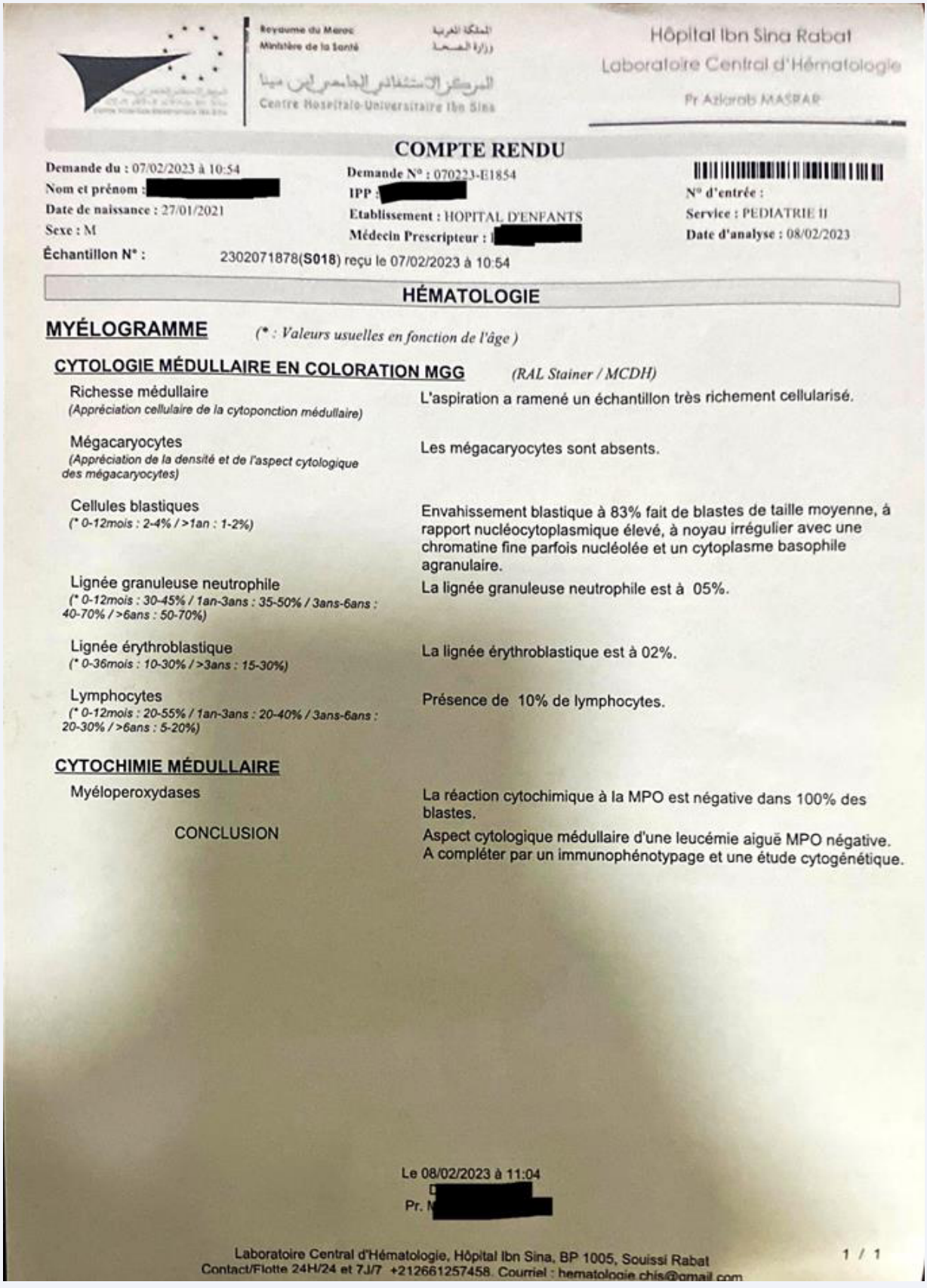
Clinically, the manifestations of MAS/HLH are nonspecific:

MAS is clinically characterized by prolonged fever and hepatosplenomegaly. Cutaneous manifestations (erythema, purpura, edema), respiratory manifestations (pulmonary infiltrates), or neurological manifestations (rare) may also be present [1,3,12]. In our patient's case, he presented with a fever at 39°C, hepatosplenomegaly, and respiratory symptoms.

Biochemically, cytopenia involving at least two of the three blood cell lineages is observed. The association of hyperferritinemia and hypertriglyceridemia is nearly constant and reflects macrophage activity [13]. Disruption of liver parameters and hypofibrinogenemia are also frequently observed. In our patient, all the aforementioned biochemical criteria were present.

The search for medullary hemophagocytosis is systematic [14]. However, due to its low sensitivity (70-83%) and specificity (60%), its presence is neither sufficient nor necessary to establish the diagnosis of HLH [14,15]. In our case, hemophagocytosis was not found in the medullary examination.

The HLH-2004 criteria were established for the diagnosis of



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Laboratoire Central d'Hématologie
Pr Azlarab MASRAR

COMPTE RENDU

Demande du : 07/02/2023 à 10:54
Nom et prénom : [redacted]
Date de naissance : 27/01/2021
Sexe : M
Demande N° : 070223-E1854
IPP : [redacted]
Etablissement : HOPITAL D'ENFANTS
Médecin Prescripteur : [redacted]
N° d'entrée :
Service : PEDIATRIE II
Date d'analyse : 08/02/2023

Échantillon N° : 2302071878(**S018**) reçu le 07/02/2023 à 10:54

HÉMATOLOGIE

MYÉLOGRAMME

(: Valeurs usuelles en fonction de l'âge)*

CYTOLOGIE MÉDULLAIRE EN COLORATION MGG

(RAL Stainer / MCDH)

Richesse médullaire *(Appréciation cellulaire de la cytoponction médullaire)*	L'aspiration a ramené un échantillon très richement cellularisé.
Mégacaryocytes *(Appréciation de la densité et de l'aspect cytologique des mégacaryocytes)*	Les mégacaryocytes sont absents.
Cellules blastiques *(* 0-12mois : 2-4% / >1an : 1-2%)*	Envahissement blastique à 83% fait de blastes de taille moyenne, à rapport nucléocytoplasmique élevé, à noyau irrégulier avec une chromatine fine parfois nucléolée et un cytoplasme basophile agranulaire.
Lignée granuleuse neutrophile *(* 0-12mois : 30-45% / 1an-3ans : 35-50% / 3ans-6ans : 40-70% / >6ans : 50-70%)*	La lignée granuleuse neutrophile est à 05%.
Lignée érythroblastique *(* 0-36mois : 10-30% / >3ans : 15-30%)*	La lignée érythroblastique est à 02%.
Lymphocytes *(* 0-12mois : 20-55% / 1an-3ans : 20-40% / 3ans-6ans : 20-30% / >6ans : 5-20%)*	Présence de 10% de lymphocytes.

CYTOCHIMIE MÉDULLAIRE

Myéloperoxydases	La réaction cytochimique à la MPO est négative dans 100% des blastes.
CONCLUSION	Aspect cytologique médullaire d'une leucémie aiguë MPO négative. A compléter par un immunophénotypage et une étude cytogénétique.

Le 08/02/2023 à 11:04
Pr. [redacted]

Laboratoire Central d'Hématologie, Hôpital Ibn Sina, BP 1005, Souissi Rabat
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Figure 1 Myelogram report in support of acute leukemia.

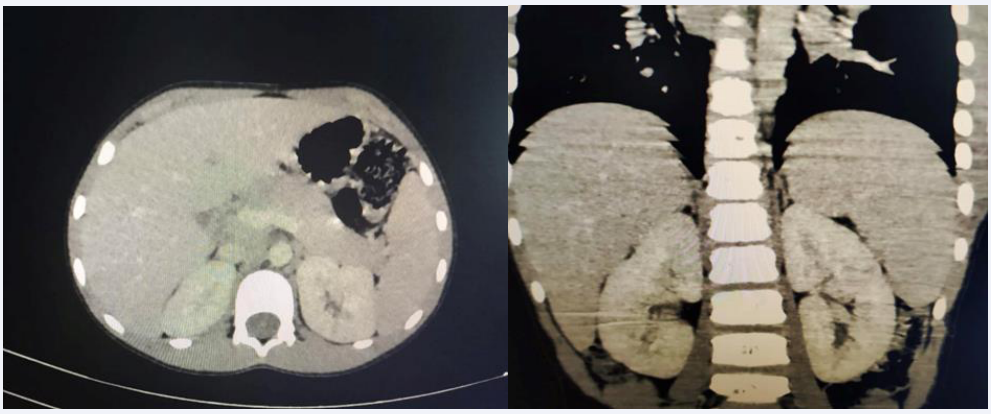

Figure 2 CT scan images showing significant hepatosplenomegaly.

HLH-2004 diagnostic criteria

Any five of:
- Fever >7 days
- Splenomegaly
- Cytopenia—any two of:
  - Haemoglobin <9 g/dl
  - Platelets $<100 \times 10^9$/ml
  - Neutrophils $<1 \times 10^9$/ml
- Hypetriglyceridaemia and/or hypofibrinoginaemia (fasting triglycerides ⩾3 mmol/l, fibrinogen ⩽1.5 g/l)
- Low or absent natural killer cell activity
- Ferritin >500 ng/ml
- Soluble CD25 ⩾2400 U/ml
- Haemophagocytosis in the bone marrow, spleen or lymph nodes

Figure 3 HLH-2004 Criteria for the Diagnosis of Macrophage Activation Syndrome.

MAS. According to Henter J-I, Horne A [7], 5 out of 8 criteria are required to establish the diagnosis. In our case, 5 out of the 6 criteria investigated are present: fever, bicytopenia, hyperferritinemia, hypofibrinogenemia, and splenomegaly. Hemophagocytosis was not found in the bone marrow examination (Figure 3).

Three complementary therapeutic approaches should be implemented [6,7]:

- Symptomatic treatment: Treatment of cytopenias through transfusions, correction of electrolyte imbalances, etc.

- Etiological treatment: Anti-infective treatment, anti-cancer treatment, etc.

- Treatment of the MAS itself: To counteract the cytokine storm, the latest recommendations propose the use of Etoposide for its anti-cytotoxic T lymphocyte action.

Our patient received transfusions and correction of hydroelectrolyte imbalances (including the correction of frequent hyponatremia in cases of macrophage activation syndrome). However, Etoposide could not be administered due to its unavailability in our facility. The anticancer treatment could not be initiated. On day 3 of admission, the patient developed an altered level of consciousness with pupillary asymmetry. A cerebral computed tomography (CT) scan was performed, revealing an extradural hematoma with cerebral herniation, likely related to the profound thrombocytopenia, leading to the patient's death on the same day.

MAS is a rare but severe condition with a high mortality rate: 20 to 88% according to studies [16]. Some American series report a median survival of 2 months.

The following factors are associated with poor prognosis [17]:

- Age > 30 years

- Neoplastic etiology

- Platelets < 100,000

- Ferritin > 500 kg/L.

Our patient had 3 out of 4 risk factors: Neoplastic etiology, thrombocytopenia, and significantly elevated ferritin.

In conclusion, macrophage activation syndrome (MAS) is a medical condition characterized by excessive activation of phagocytic cells. The clinical and laboratory signs are nonspecific, but their combination should raise suspicion for the diagnosis. A febrile bi- or pancytopenic presentation associated with tumor syndrome strongly suggests the diagnosis. Three therapeutic approaches should be simultaneously implemented: management of MAS itself, etiological treatment, and symptomatic treatment. Early recognition and awareness of MAS are crucial [3], for early diagnosis and appropriate management.

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REFERENCES

1. Boussaadni YE, Benajiba N, Bousfiha AA, Ailal F. Syndrome d'activation macrophagique compliquant une lymphohistiocytose familiale. Pan Afr Med J. 2017; 26: 93
2. Penel-Page M, Ben Said B, Phan A, Hees L, HartmannMerlin C, Girard S, et al. Pièges diagnostiques d'un syndrome d'activation macrophagique. Arch Pédiatrie. 2017; 24: 254-259.
3. Lerkvaleekul B, Vilaiyuk S. Macrophage activation syndrome: early diagnosis is key. Open Access Rheumatol Res Rev. 2018; 10: 117-128.
4. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014; 383: 1503-1516.
5. Berrady R, Bono W. Le syndrome d'activation lymphohistiocytaire (SALH). Ann Fr Anesth Réanimation. 2014; 33: 26- 32
6. Borgia RE, Gerstein M, Levy DM, Silverman ED, Hiraki LT. Features, Treatment, and Outcomes of Macrophage Activation Syndrome in Childhood-Onset Systemic Lupus Erythematosus. Arthritis Rheumatol. 2018; 70: 616-624.
7. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007; 48: 124-131
8. Bracaglia C, Prencipe G, De Benedetti F. Macrophage Activation Syndrome: different mechanisms leading to a one clinical syndrome. Pediatr Rheumatol Online J. 2017; 15: 5.
9. Yang SL, Xu XJ, Tang YM, Song H, Xu WQ, Zhao FY, et al. Associations between inflammatory cytokines and organ damage in pediatric patients with hemophagocytic lymphohistiocytosis. Cytokine. 2016; 85: 14-17.
10. Tomasik J, Basak GW. Inflammasomes-New Contributors to Blood Diseases. Int J Mol Sci. 2022; 23: 8129.
11. Risdall RJ, McKenna RW, Nesbit ME, Krivit W, Balfour Jr HH, Simmons RL, et al. Virus-associated hemophagocytic syndrome: a benign histiocytic proliferation distinct from malignant histiocytosis. Cancer. 1979; 44: 993-1002.
12. Karras A, Hermine O. Hemophagocytic syndrome. Rev Med Interne. 2002; 23: 768-778
13. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014; 66: 2613-2620.
14. Favara BE. Histopathology of the liver in histiocytosis syndromes. Pediatr Pathol Lab Med. 1996; 16: 413-433.
15. Créput C, Galicier L, Buyse S, Azoulay E. Understanding organ dysfunction in hemophagocytic lymphohistiocytosis. Intensive Care Med. 2008; 34: 1177-1187.
16. Rebecca DB. Bonny R1, Moh EN1, Ake YL1, Kouassi AKS1, Midékor-Gonébo K1, et al. Difficultés diagnostiques du syndrome d'activation macrophagique chez l'enfant. Rev int sc méd -RISM-2016; 18, 4: 298-300.
17. Kaito K, Kobayashi M, Katayama T, Otsubo H, Ogasawara Y, Sekita T, et al. Prognostic factors of hemophagocytic syndrome in adults: analysis of 34 cases. Eur J Haematol. 1997; 59: 247-253.