

## CASE REPORTS

# Hemophagocytic lymphohistiocytosis

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## Abstract

A case of hemophagocytic lymphohistiocytosis in the Third Affiliated Hospital of Inner Mongolia Medical University was collected and analyzed on the basis of diagnosis, physical examination and treatment. Misdiagnosis of hemophagocytic syndrome is very common since it is a rare disease. So this paper aims to enhance the doctors' awareness of hemophagocytic syndrome during clinical practice.

**Key Words:** Hemophagocytic lymphohistiocytosis, Clinical, Case discussion

## 1 Medical record

A 1.5-year-old female patient with 8 days' history of fever was admitted to our hospital on January 28. She had continuous high fever for 8 days, especially in the afternoon and night, with the highest temperature of 40.4°C, prior to her admission. The patient was taking cefuroxime sodium and potassium sodium dehydroandrographolide succinate for three days in the clinic without much improvement. The patient was then given gamma globulin, methylprednisolone sodium succinate, fructose and anti-infection *etc.* in hospital for 4 days, which proved ineffective. The patient appeared drowsiness, less statements, poor appetite, no cough nor dyspnea, without the symptoms of rash, epistaxis, gum bleeding, joint swelling, activities by limited, nausea, vomiting and the abdominal pain and diarrhea. There was no specialness about past history, family history and history of vaccination. Her parents also denied consanguineous marriage. Examination at the local hospital including: Cardiac enzymes test: CK-MB 27.3-66.8 U/L, LDH 818 U/L, HBDH 656.3 U/L; Routine blood test: WBC  $2.03-4.7 \times 10^9/L$ , RBC  $3.01-4.37 \times 10^{12}/L$ , L 50%-55.7%, N 36.9%-41.4%, PLT  $12-31 \times 10^9/L$ , Hb 81-114 g/L, HCT 22.1%-31.8%, MCV 72.8-78 fl, MCH 26-26.9 pg; Immune

globulin: IgA 0.42 g/L, IgG 5.27 g/L, IgM 0.98 g/L; Coagulation tests: PT 13.5 s, APTT 69.9 s, Fbg 2.9 g/L, TT 12.6 s, Plasma D-Dimer 0.6 mg/L; Liver function: ALT 48 U/L, TC 0.84 mmol/L, ALB 23.4 g/L, serum iron 15.4  $\mu\text{mol/L}$ . Echocardiography: heart structure, size, form and the valve activities were all normal; Chest X-ray (lying posture): the texture of double lung were increased, and fuzzy, visible high density fuzzy of small spots, the right lung field with increased density. The right phrenic angle was slightly dull. Thoracic ultrasound: anteroposterior diameter of the right chest about 42 mm was detected, the left and right diameter of fluid sonolucent area was about 13 mm; ultrasound of liver, gall bladder and spleen indicate gall bladder, spleen was normal, liver enlargement over 2 cm-3 cm of the ribs.

## 2 Physical examination

The result of physical examination indicated: T 38°C, poor spirit and reaction, drowsiness, smooth breathing, 36 times/min, anemia appearance, no rash nor obvious enlargement of body superficial lymph nodes, the right rib clearance was broaden; percussion for right lung: dullness,

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double lung respiratory sounds were rough, right lung respiratory sounds were decreased, bubbling rale, powerful heart sound, regular rhythm, heart rate 123 beats/min, soft abdominal, liver enlarged to 4.5 cm over the ribs, 4 cm over the processus xiphoideus, spleen enlarge to 4 cm over the ribs with medium texture and blunted edge. Slightly swollen of double lambs and instep, little depression under slightly pressure, various joints were no redness, swelling, heat and pain and limited mobility, no abnormalities of the nervous system.

### 3 Laboratory examination

Routine blood test: WBC  $1.1-5.2 \times 10^9/L$ , PLT  $5-20 \times 10^9/L$ , Hb 55-88 g/L, Peripheral blood smear: ST 12%, S 46%, L 36%, M 4%, WYL 2%, Ret 0.002-0.006, the shape and size of mature erythrocyte was normal, vacuole, toxic granulation and sporadic platelets could be detected; blood gas analysis: pH 7.281-7.488,  $PCO_2$  22.2-36.8 mmHg,  $PO_2$  31.6-57.6 mmHg, BE 4.0-14.2 mmol/L,  $HCO_3^-$  10.2-27.3 mmol/L,  $SO_2$  48.7%-97.4%; ESR 24 mm/h. Four items infection: HBsAg negative, HCV-IgG negative, HIV negative, ATV-TP negative,  $K^+$  2.2-4.6 mmol/L,  $Na^+$ : 128.6-133 mmol/L,  $Cl^-$  90.9-101.0 mmol/L, Glu 7.92-12.5 mmol/L,  $Ca^{2+}$  1.83-1.95 mmol/L; Liver function: ALT 205 U/L, AST 373 U/L, TG 2.97 mmol/L, ALB 29.1 g/L, TP 50.2 g/L; Coagulation tests: PTA 65.2%, APTT 31.0 s, TT 29.8 s, Fbg 0.57 g/L, D-dimer 1.5 mg/L, serum ferritin 390.2 g/L; Cardiac enzymes test: LDH 832.0 U/L, HBDH 650.0 U/L. Blood culture: No bacterial growth; immunoglobulin IgG 15.72 g/L, IgA 0.15 g/L, IgM 0.44 g/L. Stool routine: Positive occult blood; Abdominal ultrasound: Enlargement of the liver and spleen occurs, edema of gallbladder wall, right pleural effusion, seroperitoneum (medium), EB-DNA:  $6.6 \times 10^6/L$ ; Bone marrow puncture: visible of 5.6% irregular cells, like reticuloendothelial cell, biopsy, active proliferation; positive EB IgG, positive EB IgM, negative MP IgG, negative MP IgM.

### 4 Primary diagnosis

- (1) Hemophagocytic lymphohistiocytosis:
  - Familial hemophagocytic lymphohistiocytosis?
  - Infection-related hemophagocytic lymphohistiocytosis?
- (2) Bronchopneumonia, right pleural effusion
- (3) Thrombocytopenia peliosis?

### 5 Diagnosis and treatment

The patient was treated with Azithromycin, Ceftazidime, Acyclovir and complementary drug (albumin, gamma globulin) since her admission. She received platelet transfusions

and packed red cells to prevent hemorrhage in advance. She then had methylprednisolone. Meanwhile, body temperature and calorie should be paid more attention, and the equilibrium of fluid-electrolytes should be preserved. A consultation regarding the diagnosis of the disease, from the department of hematology, respiratory, medical oncology, clinical laboratory, and gastroenterology was held on January 31, by Shanghai children's Medical Center and preliminary confirmed diagnosis for familial hemophagocytic lymphohistiocytosis (HLH). Additional drug agents, including ganciclovir and cyclosporine A, was employed but was proved noneffective. She was presented with continued fever, moaning, ravings, agitation and severe edema, ascites was detected. On the morning at 5 o'clock on February 1, the patient had the symptom of dyspnea and tachypnea (R 80-90/min, regular rhythm). Besides that, flaring of the nares and cyanosis were presented, three concave showed positive. Oxygen supply by CPAP to improve ventilation was performed. The patient's heart rate was 220 beats/min, respiratory rate 40-50 times/min (breathing like sighed), cyanosis, limb ends were cold at the night on February 1. Persistent oxygen supply by CPAP (mixed oxygen concentration 60%,  $SpO_2$  fluctuated 70%) continued. No reaction of pressure on the orbita and insensitive light reflex of pupils, the patient exhibit with heart failure and respiratory failure. The parents gave up the rescue for the patient. Unfortunately, the patient was dead after 20 minutes. The cause of her death: familial hemophagocytic lymphohistiocytosis, heart failure, respiratory failure.

### 6 Discussion

#### 6.1 Dr. Fang Zhou

*Dr. Fang Zhou is a chief physician of Pediatrics at the third affiliated hospital of Inner Mongolia Medical University, specializing in children's blood disorders.*

It is sometimes difficult to establish the diagnosis of HLH, and the combination of the physical symptoms and certain laboratory tests is required. A set of diagnostic criteria was recommended by the Histiocyte Society<sup>[1]</sup> for use in the HLH-2004 research protocol. This includes diagnosis of a specific gene defect and/or the presence of at least five of the following eight criteria: (1) Fever (2) Splenomegaly (3) Cytopenias affecting at least two of three lineages in the peripheral blood: Hb < 90 g/L (in infants less 4 weeks: Hb < 120 g/L), PLT <  $100 \times 10^9/L$ , Neutrophils <  $1.0 \times 10^9/L$  (4) Hypertriglyceridemia  $\geq 3.0$  mmol/L, hypofibrinogenemia  $\leq 1.5$  g/L (5) Haemophagocytosis in the bone marrow, spleen or lymph nodes (6) Low or absent natural killer cell activity (7) Ferritin  $\geq 500 \mu g/L$  (8) Soluble CD25 (soluble IL-2 receptor)  $\geq 2.4 \times 10^6$  U/L.

The patient in this case was with these symptoms: (1) fever (2) splenomegaly (3) peripheral blood Hb 55 g/L, PLT

$5 \times 10^9/L$ , WBC  $1.1 \times 10^9/L$ , decreased (4) triglycerides 2.97 mmol/L, fibrinogen 0.57 g/L. They are in line with four of eight criteria. Besides that, the patient was also presented with lung disease, enlarged liver and spleen, abnormal liver function, enzyme abnormalities and neurological symptoms. Moreover, he was 1.5 years old (younger than 2 years old) with rapid progression, which was diagnosed as primary (familial) HLH.

It is difficult to determine the diagnosis of HLH as primary or secondary since genetic testing is not widely carried out. It is generally believed that onset before the age of 2 is primary HLH, whereas onset after 8-year-old is more likely to be secondary HLH, onset at 2-8 the age depends on clinical manifestations and judgment.<sup>[2]</sup> And the identification between HLH and malignant tissue cell diseases is required. The diagnosis of malignant tissue cell diseases relies on the number of abnormal cells, such as phagocytic-histiocytic cell and multinucleated giant cells in the bone marrow. While the diagnosis of HLH depends on establishment of malignant tissue cell cloning marks.<sup>[3]</sup>

It is a life-threatening disease with rapid progression and high mortality. The clinician should raise awareness and vigilance for this kind of disease, and early diagnosis and treatment is essential. The main treatment includes steroid therapy, high-dose intravenous gamma globulin, hepatoprotective, anti-infection and symptomatic treatment. Cyclosporin-A is reported to add in and combine with G-CSF treatment.<sup>[4]</sup> The main causes of death: hemorrhage, infection, multiorgan failure and disseminated intravascular coagulation.<sup>[5]</sup>

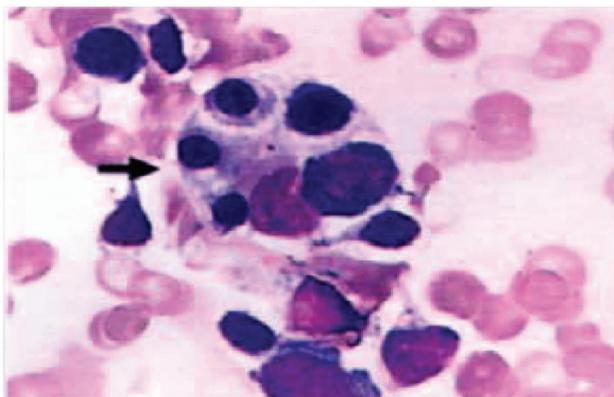
### 6.2 Dr. Jinli Hao

*Dr. Jinli Hao is the deputy director of paediatrics at the third affiliated hospital of Inner Mongolia Medical University, whose research interests are child development, children with hematological malignancies and newborn.*

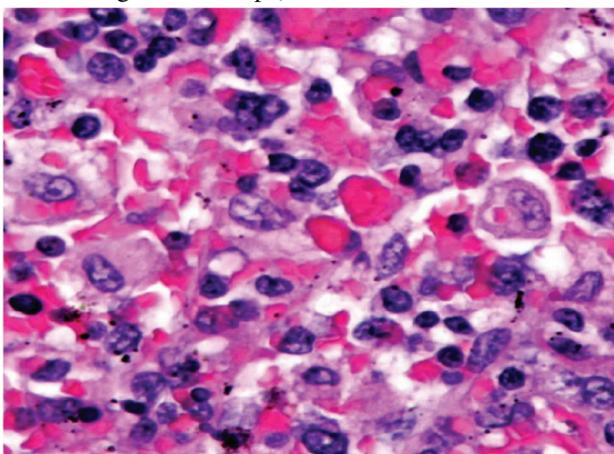
HLH is a polygenic immunodeficient disease. The diagnosis of HLH could be very challenging due to the lack of specificity of laboratory diagnostic methods, and misdiagnosis and missed diagnosis is common. The 1.5-year-old patient began with fever, and was gradually presented with lung damage, liver and spleen enlargement, liver dysfunction, nervous system symptoms, three-line reduction of peripheral blood cells, the minimum of Hb was 55 g/L, PLT  $5 \times 10^9/L$ , WBC  $1.1 \times 10^9/L$ ; triglycerides up to 2.97 mmol/L, fibrinogen was 0.57 g/L; hyponatremia, hypokalemia, hypocalcemia, hypoproteinemia, LDH 832 U/L. Bone marrow aspiration and biopsy revealed an active proliferation, visible 5.6% of irregular, similar to the reticuloendothelial cell. EB-DNA  $6.6 \times 10^6/L$ , EB-IgG, EB-IgM were all positive. The diagnosis of familial HLH was confirmed through remote consultation according to clinical diagnosis

standards, but lack of support from pathology results.

The bone marrow for patients with HLH was dominated by benign and large blood cells (see Figure 1, Figure 2). Phagocytic hyperfunction was founding rising, especially for mature or immature erythrocyte, white blood cells of morphological structural integrity and platelets, accompanied by increasing tissue cells. And the increased tissue cells were mainly differentiate mature or relatively mature cells. The level of alkaline phosphatase in peripheral blood neutrophil granulocyte was increased.



**Figure 1:** HLH bone marrow picture (HE staining, 400 times the light microscope)



**Figure 2:** HLH bone marrow picture (HE staining, 200 times the light microscope)

It is difficult to find hemophagocytosis during clinical practice just by positive results from bone marrow samples. Therefore, other organs such as the liver, spleen, lymph nodes, bone marrow, brain and spinal cord should be examined as well. In addition to the organs mentioned above, it could be found in the thyroid gland, lungs, heart, intestines, kidneys, and pancreas. Continuous bone marrow puncture can be conductive to establish a diagnosis. The following tips proposed in HLH-2004 can be powerful indicators for the diagnosis of HLH. (1) An increasing in cerebrospinal fluid of lymphocytes and (or) increased cerebrospinal fluid

protein. (2) Histological findings: similar chronic persistent hepatitis performance (biopsy). (3) Other clinical presentation and laboratory tests which consistent with the diagnosis of the disease include: meningeal syndrome, enlarged lymph nodes, jaundice, edema, rash, abnormal liver enzymes, hypoproteinemia, hyponatremia, very low density lipoprotein to raise and very high density lipoprotein to decrease. The patient was consistent with the diagnostic criteria on the basis of adequate clinical examination. It will be an assistant in the diagnosis by continuous bone marrow aspiration to find hemophagocytosis. The diagnosis of the disease may be confirmed if CSF examination was performed, which provides supporting evidence.

Studies on sIL-2R $\alpha$  detection in HLH pediatric reports are fewer in China. The IL-2 receptor  $\alpha$  subunit is only expressed when lymphocyte is activated, part of the  $\alpha$  chain which is shed off from the cell membrane then released into the blood circulation to form sIL-2R $\alpha$ . Thus, sIL-2R $\alpha$  levels in serum is a sensitive quantitative index in the circulating lymphocyte activation. Yin Zhu, *et al.*,<sup>[6]</sup> from the Fudan University Affiliated Children Hospital, used the classical method of ELISA to test sIL-2R $\alpha$ , and found sIL-2R $\alpha$  was significantly higher in HLH, which could as an indicator of condition evaluation.

Familial HLH is an autosomal recessive genetic disease, whose diagnosis depends on positive family history or history of inbreeding. Due to the low incidence, the information of family history is not required, which increased the difficulty of diagnosis. It is generally believed that onset before age 2 is more likely to be familial HLH, while after age 8 is suggestive of secondary HLH. Therefore, the diagnosis of familial HLH is more emphasis on molecular testing and related genetic testing. There are several factors about molecules which relates to HLH and gene defects:<sup>[7]</sup> (1) Perforin gene mutations FHLH2. Step, *et al.* found perforin gene mutations in familial HLH patients in 1999. Currently, it was found that about 15%-50% in familial HLH patients were caused by perforin gene mutations.<sup>[8]</sup> When CTL cell and NK cell encountered target cell, cytolytic granules secreted out cells, and its perforin provided channel for granzyme B to enter target cell, then killed target cell. Perforin gene mutations resulted in the reduction of perforin formation. The killer function of CTL cells and the NK cells was decreased, leading to immune disorders which triggered HLH. (2) Mutation for UNC13D genes. It was discovered in 2003 that UNC13D genes mutations, located in chromosome 17q25, encoded protein Munc13-4, could also cause familial HLH. (3) STX11. The newly-discovered protein-encoding gene of syntaxin11 was related with the familial HLH. Presumably syntaxin11 protein may be involved in intracellular transport, but its exact function remains unknown.

There were respectively 20% and 10% of the familial HLH patients who had STX11, UNC13D gene mutation, 60%-

70% of the patients had XLP gene mutation according to the reports in the literature.<sup>[9]</sup> In addition to that, some surface markers serve as a predictor of gene defects, for example, the reduction of CD107a expression in NK cells suggests gene defects in Munc13-4 and Syntaxin11.<sup>[10]</sup> The rise for soluble CD163 level is found of specificity in the diagnosis of HLH.<sup>[11]</sup>

Severity of the HLH was positively correlated with release amount of cytokine. Yong-min Tang<sup>[12]</sup> believe that deficiency of immune-related genes and precipitating factors are closely related to two important mechanisms for pathogenesis of HLH. The immune system is difficult to remove pathogens and autologous antigen formed by aging tissue cell and death tissue cell, which lead to the continuous stimulation of immune system by antigenic material. Meanwhile, the T cells monocyte-macrophage secrete large amounts of cytokines, such as  $\gamma$ -IFN, IL-10, *etc.* While these cytokines can further activate the body's immune system, secrete larger amounts of cytokines, which forms a vicious circle. Consequently, excessive release of cytokines (also known as cytokine storms) can lead to damage of tissue cell and the incidence of HLH. Therefore cytokines is an important indicator of rapid diagnosis of HLH and the cytokines, such as  $\gamma$ -IFN and IL-10 cytokines, generated by familial HLH is of significance to identify familial HLH and AHLH.

### 6.3 Dr. Yajing Zhang

*Dr. Yajing Zhang is a professor of Pediatrics at the third affiliated hospital of Inner Mongolia Medical University, whose research interests are diseases of newborns, children's growth and development.*

(1) Etiology and pathogenesis of HLH. HLH can be divided into primary and secondary according to the etiology. Primary hemophagocytic lymphohistiocytosis, also known as familial hemophagocytic lymphohistiocytosis, is autosomal recessive genetic disease, mainly seen among infants and young children with a prevalence of one over fifty thousand under 2 years old and high mortality. It has been demonstrated that the symptoms of 4 genetic abnormalities are much associated with the disease.<sup>[13]</sup> The possible mechanism was due to 10q21 perforin gene (Perforin, PRFI) mutation that caused some viruses and bacterial infections to lose control, resulting in high cytokine hypercytokinemia.<sup>[14]</sup> Secondary HLH is divided into infection hemophagocytic lymphohistiocytosis and tumor hemophagocytic lymphohistiocytosis, which is caused by various infections, connective tissue diseases, tumors and immune deficiency and its pathogenesis is related with immune system disorder in organism cell and Th1/Th2 imbalances.

This patient was 1.5 years old with no clear family history, and parents deny inbreeding. The result of serologic tests

included: EB virus VCA-IgM (+), VCA-IgG (+), EB virus DNA (+) were all for high titer which suggested active infection of EBV. However, it is difficult to determine whether it is primary or secondary due to our limited laboratory conditions, thus molecular biology was not conducted.

(2) This case conformed 4 items of the 8 diagnostic criteria. The child was presented with persistent fever, progressive enlargement of liver and spleen, dysfunction liver, blood three-line reduction and coagulation disorders at the early stage, followed by central nervous system symptoms, multiple organ failure and eventually died just for 13 days.

Significant hemophagocytic proliferation was not found on the bone marrow biopsy. Gupta, *et al.*<sup>[15]</sup> reported that about 70%-80% patients were with hemophagocytic phenomena in bone marrow at the early pathogenesis of HLH. The sensitivity of hemophagocytic phenomenon among adults is 76.7% in the diagnosis of HLH.<sup>[16]</sup> 91.8% of children with HLH were found hemophagocytosis on the initial bone marrow examination, while hemophagocytosis was not seen in disease progression.<sup>[17]</sup> Hemophagocytosis on bone marrow examination is not a reliable and absolute standard for the diagnosis of HLH, therefore the diagnosis of HLH could not be excluded given that hemophagocytic phenomenon was not found on in bone marrow diagnosis. Since HLH invasion was not uniformly distributed, bone marrow puncture and lymph nodes biopsy at different sites are required. However, further relevant examination was not done as the patient was in severe condition and died in 5 days since admission.

(3) Treatment guidelines according to International Association of tissue HLH-2004,<sup>[18]</sup> includes: 1) Initial induction therapy. Etoposide (VP216, or relevant VM-26) and steroid, combined with intrathecal therapy or not. 2) Maintenance therapy. Combine with cyclosporine-A pulse-dosing on the basis of VP-16 and dexamethasone. It is an important treatment for the majority of patients to reach a longer survival until matching bone marrow donor is found. 3) Bone marrow transplants and supporting therapy. Allogeneic bone marrow transplantation is the only method to obtain the best outcome. This patient was firstly treated with ceftazidime (Pfizer), azithromycin (zithromax), acyclovir anti-infection, glucocorticoid and methylprednisolone after admission. At first, she had 12 mg/(kg.d), qd, consecutively used for 3 days, then changed 30 mg/(kg.d), qd, consecutively used for 2 days. Gamma globulin of 400 mg/(kg.d) was employed, along with one time human albumin, platelet transfusion, and CRCs. On the 4th days since her admission, she had ganciclovir 5 mg/(kg.d), bid, and cyclosporine-A chemotherapy. The condition was without any improvement. The patient died on the next day.

The treatment above was merely symptomatic and supportive cure rather than the standardized treatment of HLH-2004. What we have learned from the case was that chemotherapy was necessary for critical sick patients even

though they did not meet the diagnostic criteria. They may have the opportunity to receive further treatment if they were treated over observation. The application of early HLH-2004 program was reported to carry out better effect on improving the survival rate of sick children. Early diagnosis and treatment, therefore, is of great significance.<sup>[19]</sup>

## 6.4 Dr. Huaixiu Yan

*Dr. Huaixiu Yan is a chief physician of hematology at the third affiliated hospital of Inner Mongolia Medical University, specializing in hematological disease.*

Currently, there is no specific treatment method for primary HLH or familial HLH except strengthening the supportive treatment and complications treatment. The fundamental cure is allogeneic hematopoietic stem cell transplantation. The causes of HLH should be explored on the basis of background disease.

### 6.4.1 Comprehensive treatment of familial hemophagocytic lymphohistiocytosis

(1) **Chemotherapy** Cytotoxic agents are the most commonly used for chemotherapy, such as vincristine combined with adrenocortical hormones agents. Repeated plasmapheresis or VP16, VM26 combined with adrenocortical hormones agents were employed. It is reported that application of VP16, adrenocortical hormones agents, intrathecal methotrexate (MTX) and cranial irradiation therapy got good results. Others suggest that low dose of those drugs be used for maintenance therapy.

(2) **Immunotherapy** Some patients achieved satisfactory results with treatment of cyclosporine A for familial HPS. Antithymocyte globulin (ATG) can induce remission as well.

(3) **Allogeneic hematopoietic stem cell transplantation** Though the chemotherapy above could ease illness, some even maintains the effect for 9 years, there is still no fundamental theory for familial HLH completely. Qingkui Liao<sup>[20]</sup> claimed that hematopoietic stem cell transplantation followed by cyclosporin A and VP16 for patients with HLH can greatly improve the prognosis of the disease on the International Symposium on pediatric hematological malignancies in Shanghai in 2000.

(4) **Therapeutic schedule** International Association of tissue cells proposed a treatment plan for familial HPS (HLH94) in 1994: Dexamethasone daily 10 mg/m<sup>2</sup> and VP16 weekly 150 mg/m<sup>2</sup> for 3 weeks, then reduce doses on the fourth week. Take VP16 medication once per 2 weeks combined with cyclosporin A for 5-6 mg/kg daily for a year since the ninth week. An injection of MTX is needed one time per 2 weeks for patients with neurological symptoms

before 8 weeks. Allogeneic hematopoietic stem cell transplantation is an optimal treatment for patients with familial history of HPS. However, treatment for patients with non-familial HPS should be suspended after 8 weeks according to the real condition.

#### 6.4.2 Comprehensive treatment of secondary hemophagocytic lymphohistiocytosis.

(1) **The corresponding treatment for associated infection of HLH** 1) Active resistance to infection. 2) Steroid therapy or high dose of methylprednisolone. 3) Large dose gamma globulin, iv, (mainly used in VAHS). 4) Inhibitors cyclosporin A which can inhibit the activation of T cell combined with G-CSF for VAHS, or antithymocyte globulin. 5) Direct antagonist cytokines TNF antibodies and IL-1 receptor antagonist. 6) It is suggested chemotherapy be applied to suppress or reduce the supply sources of lymphokine. It includes CHOP, CHOPE programmes or slow intravenous infusion of vincristine. Some reports demonstrate the best effect of etoposide (VP16) on unexplained severe HLH, EBV-AHS or LAHS. Analysis of the prognosis shows that it's necessary to apply chemotherapy for patients with HLH which not be identified along with MH.

(2) **Comprehensive treatment of tumor-associated hemophagocytic lymphohistiocytosis** Treatment program is depended by the type of disease. The main treatment is anti-infection and the anti-tumor for patients with immune defects and HLH occurred before the treatment. However, the treatment of anti-tumor should be suspended if HLH occurred after chemotherapy and tumor has eased. While anti-infection maintains by Cortin and the VP16. It should be cured according to damage level of cell factor if MAHS was with rapid progression.

HLH mostly carries poor prognosis, about half of all death cases with risk factors during hospitalization,<sup>[21]</sup> such as increased Total bilirubin, reduction of progressive platelets, anemia, and increased serum ALP. Death-related risk factors for less than 3 years of age include presence of disseminated intravascular coagulation (DIC), ferritin and increased  $\beta$ -2-microglobulin, jaundice and anemia with thrombocytopenia. HLH patients with risk factors should be treated with aggressive chemotherapy and supportive care. Poor prognosis of HLH is mainly due to the severity of potential diseases and degree of cytokine (cytokinestorm) after conditions deteriorated sharply so that the patient died within 4 weeks. The survivor's blood cell count will be recovered within 1-2 weeks and recovery for liver function needs a long time (3-4 weeks). Kaito, *et al.* reported that 14 cases survived, 20 cases (58.5%) died in 34 cases of HLH, and 13 cases (65%) were patients with unexplained HLH among 20 death cases. The patient in this case was with death-associated risk factors. Therefore, active resistance to infections, intravenous immunoglobulin and methylprednisolone impact, cyclosporine A, blood transfusion and supportive

treatment were applied, the disease was not be under control with rapid progression. Eventually, the patient died of heart failure and respiratory failure.

#### 6.5 Dr. Xin Chen

*Dr. Xin Chen is a chief physician of Paediatrics at the third affiliated hospital of Inner Mongolia Medical University, specializing in children's growth and development.*

The familial and secondary HLH are the most confusing in differential diagnosis of HLH, especially the identification for virus-associated HLH. It is because viral infections are associated with virus-associated HLH and often occurred in patients with familial HLH, and familial HLH is often induced by virus. Familial HLH is an autosomal recessive genetic disease. The diagnosis of the disease can be challenging if a requirement of family history was not performed. It is generally believed that patients under 2 years old are more likely to have familial HLH. Secondary HLH was suspected if the patients are 8 years older. While, the diagnosis depends on clinical manifestation for patients between 2-8 years old. It is regarded as familial HLH provided that the diagnosis could not be established. Then it should be identified from malignant histiocytosis, but both of them are all difficult to identify on the bone marrow X-ray, whereas the HLH is much more common than malignant histiocytosis. Rapid progression, severe liver function damage, bone marrow tissue cells with high degree of malignancy, especially liver, spleen or other organs found abnormal histiocytes were primary indicators of malignant histiocytosis, otherwise it should be diagnosed as HLH.<sup>[22]</sup>

HLH mostly carries poor prognosis, especially for familial HLH with short course. Patients with untreated familial HLH usually get 2-month survival period. While, the prognosis is greatly improved after chemotherapy since less than 10% of the patients' survival are more than 1 year. It is reported that some patients could live for 9 years after chemotherapy. However, allogeneic hematopoietic stem cell transplantation is the optimal treatment of familial HLH. HLH caused by bacterial infection usually carries better prognosis and prognosis for those caused by EB virus is the worst. The fatality rate of HLH caused by other viruses is generally 50%. The mortality rate of tumor-associated hemophagocytic lymphohistiocytosis is almost 100%.<sup>[2]</sup>

In summary, it is easy to misdiagnose or missed diagnose as this disease is rare. This paper aims to increase clinical physicians' awareness on HLH, especially for the grassroots hospital, through information analysis. Examination of serum ferritin, coagulation function, cellular immunity, lipid and repeated bone marrow puncture are required to improve prognosis when the patient is presented with unexplained reduction of two-line peripheral blood or three-line peripheral blood, enlargement of liver, spleen and lymph nodes.

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