

## Original article

# Anaplastic large cell lymphoma with concomitant Hemophagocytic Lymphohistiocytosis (HLH): hyperinflammation and capillary leakage syndrome

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**Abstract:**

*In our 19 years' experience at King Chulalongkorn Memorial Hospital, we were able to observe 21 pediatric cases with anaplastic large cell lymphoma (ALCL). Of these 21 cases, 4 (19% of ALCL cases) had concurrent hemophagocytic lymphohistiocytosis (HLH). All developed fever, lymphadenopathy and exaggerated signs of capillary leakage syndrome such as generalized edema, pleural effusion or ascites. The hyperinflammation was demonstrated with fever, hypoalbuminemia and elevated inflammatory markers. A high index of suspicion is warranted to recognize concurrent HLH when patients develop cytopenia, splenomegaly, liver dysfunction and pleural or pericardial effusions. For HLH with unknown etiology but with lymphadenopathy, lymph node biopsy should be considered as a part of secondary HLH workup to rule out malignancy-associated hemophagocytic syndrome. Treatment with lymphoma-directed therapy should not be contraindicated once a diagnosis of ALCL is made. Instead, one should be cautious whenever a hyperinflammatory state and multi-organ dysfunction exists because HLH-sensitive agents such as corticosteroid, etoposide, cyclosporin A, cyclophosphamide and others should be urgently administered. The mortality was quite high (50%) in our institution. Initial treatment with HLH protocol saved the lives of the other 2 patients (50%), both of whom were cured later with lymphoma-directed protocol.*

**Keywords :** ● Anaplastic large cell lymphoma ● Capillary leakage syndrome ● Hyperinflammatory state  
● Malignancy-associated hemophagocytic lymphohistiocytosis ● Histiocytotic syndrome

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## นิพนธ์ต้นฉบับ

# Anaplastic large cell lymphoma (ALCL) ร่วมกับ Hemophagocytic Lymphohistiocytosis (HLH): ภาวะอักเสบรุนแรง (hyperinflammation) และการรั่วของหลอดเลือดฝอย (capillary leakage syndrome)

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## บทคัดย่อ

จากการทบทวนย้อนหลัง 19 ปี ณ โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย พบผู้ป่วยมะเร็งต่อมน้ำเหลืองเด็กชนิดอะนาพลาสติค (anaplastic large cell lymphoma (ALCL)) จำนวน 21 ราย ในจำนวนนี้พบ 4 ราย (ร้อยละ 19) มีภาวะ hemophagocytic lymphohistiocytosis (HLH) ร่วมทุกรายมีอาการไข้ ต่อมน้ำเหลืองโตและมีการรั่วของหลอดเลือดฝอย การรั่วของหลอดเลือดฝอย (capillary leakage syndrome) ได้แก่ บวมทั่วตัว น้ำในเยื่อหุ้มปอดและน้ำในช่องท้อง ภาวะอักเสบรุนแรง (hyperinflammation) ได้แก่ ไข้ อัลบูมินต่ำและการเพิ่มขึ้นของค่าการอักเสบ (inflammatory markers) ควรสงสัยว่ามีภาวะ HLH ร่วมกับ ALCL เมื่อมีการสร้างเซลล์ระบบเลือดผิดปกติ (cytopenia) ม้ามโต ค่าการทำงานของตับผิดปกติและน้ำในเยื่อหุ้มปอดหรือหัวใจ สำหรับผู้ป่วย HLH ที่ไม่ทราบสาเหตุแต่ตรวจพบต่อมน้ำเหลืองโตควรพิจารณาการตัดต่อมน้ำเหลืองเพื่อตรวจทางพยาธิวิทยาหาสาเหตุว่าเกิดจากมะเร็ง (malignancy-associated hemophagocytic syndrome) หรือไม่ การรักษามะเร็งต่อมน้ำเหลืองด้วยสูตรยาเคมีบำบัด (lymphoma-directed therapy) ไม่ควรถือเป็นข้อห้ามเมื่อแรกวินิจฉัย ALCL แต่ควรระมัดระวังว่าเมื่อมีภาวะอักเสบรุนแรง (hyperinflammation) และอวัยวะล้มเหลวหลายระบบ (multi-organ dysfunction) จาก HLH ร่วม การให้ยาเคมีบำบัดที่ตรงกับ HLH (HLH-directed therapy: corticosteroid, etoposide, cyclosporin A, IVIG, cyclophosphamide และอื่นๆ) อาจมีความจำเป็นเร่งด่วนกว่า การพบภาวะ ALCL ร่วมกับ HLH ณ โรงพยาบาลจุฬาลงกรณ์พบอัตราการเสียชีวิตสูงถึงร้อยละ 50 การเริ่มต้นรักษาด้วยยาเคมีบำบัดที่ตรงกับ HLH (HLH-directed therapy) สามารถทำให้ผู้ป่วย 2 รายที่เหลือ (ร้อยละ 50) พ้นจากภาวะ HLH ก่อนรักษามะเร็งด้วยยาเคมีบำบัด (lymphoma-directed therapy) จนหายขาดต่อไป

**คำสำคัญ :** ● มะเร็งต่อมน้ำเหลืองชนิดอะนาพลาสติค ● การรั่วของหลอดเลือดฝอย ● ภาวะอักเสบรุนแรง

● ภาวะ HLH ที่มีสาเหตุจากมะเร็ง ● กลุ่มอาการ histiocytosis

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## Introduction

The anaplastic large cell lymphoma (ALCL) classified in a group of mature T-cell neoplasm may have a presentation as Hemophagocytic Lymphohistiocytosis (HLH).<sup>1</sup> With 19 years' experience in our institute, we found that combined ALCL and HLH might cause more severe inflammation and fluid leakage into the third space. Both have pathogenesis and clinical lapses with each other making accurate diagnosis a challenge. Due to the exaggerated hyperinflammatory state, HLH-directed therapy may be considered before lymphoma-directed treatment. Thus, HLH existing identification might be essential for the initial protocol decision.

The ALCL associated with HLH has also been shown to affect morbidity or mortality causing 50% (2/4) survival in our institute and 60-67% survival in a related study.<sup>2,3</sup> The poor prognostic factors of both also lapse. For isolated HLH was at a very young age, neurologic involvement, slow decline of ferritin after treatment, malignancy-associated HLH and other signs<sup>4</sup>, while isolated ALCL, comprises thoracopulmonary or bone marrow involvement and advanced stages.<sup>5</sup>

The perforin (*PRF1*) tumor suppressor gene<sup>6</sup>, which has pore-forming toxin properties, is a well-known pathogenesis of familial HLH. Patients with ALCL also have a higher probability of the mono-allelic germline variant than healthy individuals.<sup>7</sup> In the same way, biallelic germline mutation was found in multiple types of lymphoma including ALCL without HLH.<sup>8</sup> The defect in *PRF1* may tend to cause ALCL and HLH together.

## Methods

From 2002 to 2021, we collected 21 cases of patients with ALCL at ages between 2 and 17 years old. The data were collected using a search by ICD-10 together with a review of medical documentation. Four (19%) of 21 patients received a diagnosis associated with HLH. The *PRF1* protein detection by immunohistochemistry was performed in cases 1 and 2. The *PRF1* gene sequencing was performed in case 2.

## Results

Summaries of the four cases were compared in Table 1. The age of onset was late childhood at 6-11 years old, and fever (4/4) was the leading symptom. Enlarged lymph nodes (3/4) were palpated in most cases except for the first of which lymphadenopathy was evident only using abdominal ultrasonography. Hepatosplenomegaly (2/4) presented in some cases. The subjects usually presented cytopenia (4/4) of more than two cell lineages. Elevated inflammatory marker (3/3), pleural effusion (4/4) and ascites (3/3) were found. The median ferritin was 3,186.5 µg/L considered elevated but descriptively low compared with the other HLH etiology. The diagnosis of ALCL was made using lymph node histology unveiling atypical cells (4/4) with immunohistochemistry positive for CD30 (4/4) and ALK (4/4). The perforin immunostaining was positive (2/2), and HLH criteria were completed in most cases (3/4). The fourth case comprised neurological involvement. No definite infection/ autoimmune/ familial history of HLH was found during ALCL diagnosis and Epstein-Barr Virus (EBV)-DNA was negative (0/2). The HLH-directed protocol was initiated for the first two cases. The lymphoma-directed treatment was prescribed for the rest but with disappointing consequences. As expected, the causes of death were due to multi-organ failure both from hypercytokine or direct organ infiltration by histiocytes presented as cardiogenic shock, disseminated intravascular coagulation (DIC), pulmonary hemorrhage and seizure.

### Case 1

A 6-year-old Thai girl with a history of ALCL stage III, ALK+ postchemotherapy treatment with event-free for 15 months initially presented with fever and generalized edema for three days. The physical examination also revealed abdominal distension but without lymphadenopathy. Five of eight HLH criteria were met consisting of fever, pancytopenia, elevated serum ferritin, hypertriglyceridemia and presence of hemophagocytes as shown in Table 1 and Figure 1. Further study with an ultrasound abdomen revealed multiple small intra-abdominal

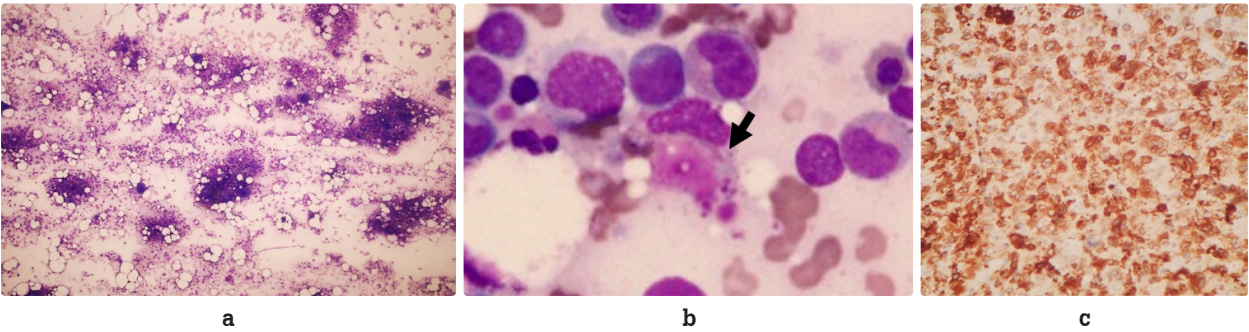
**Table 1** Clinical characteristics, laboratory workup and treatment of four cases of ALCL with HLH

|                                                   | Case 1                          | Case 2                                                    | Case 3                          | Case 4                                       |
|---------------------------------------------------|---------------------------------|-----------------------------------------------------------|---------------------------------|----------------------------------------------|
| Age (year)                                        | 6                               | 6                                                         | 10                              | 11                                           |
| Sex                                               | Female                          | Female                                                    | Male                            | Female                                       |
| Presenting symptoms                               |                                 |                                                           |                                 |                                              |
| - Fever                                           | Yes                             | Yes                                                       | Yes                             | Yes                                          |
| - Weight loss                                     | No                              | Yes                                                       | No                              | No                                           |
| - Drenching night sweats                          | No                              | Yes                                                       | No                              | No                                           |
| - Generalized edema                               | Yes                             | Yes                                                       | No                              | No (with SVC synd.)                          |
| - Palpable LN/mass                                | No                              | Yes                                                       | Yes                             | Yes                                          |
| Physical examination                              |                                 |                                                           |                                 |                                              |
| - Hepatomegaly                                    | No                              | Yes                                                       | Yes                             | No                                           |
| - Splenomegaly                                    | No                              | No                                                        | Yes                             | No                                           |
| - Lymphadenopathy/mass                            | No                              | Yes                                                       | Yes                             | Yes                                          |
| - Skin lesion                                     | No                              | No                                                        | No                              | No                                           |
| Laboratory investigation                          |                                 |                                                           |                                 |                                              |
| - Hemoglobin (> 11.5 g/dL)/Hct (> 35%)            | 8.3/23                          | 7.3/-                                                     | 9.5/28.5                        | 7.1/22.8                                     |
| - WBC/ANC (> 4,000/> 1,500 cell/mm <sup>3</sup> ) | 2,460/1,250                     | 9,970/5,980                                               | 2,260/1,570                     | 19,690/17,090                                |
| - Platelet (> 150,000 cell/mm <sup>3</sup> )      | 19,000                          | 29,000                                                    | 166,000                         | 26,000                                       |
| - Serum ferritin (< 500 µg/L)                     | 6,284                           | 1,438                                                     | 3,186.5                         | Elevated                                     |
| - Fibrinogen (> 1.5 gm/L)                         | 1.87                            | 6.3                                                       | 2.89                            | 2.54                                         |
| - Triglyceride (< 265 mg/dL)                      | 311                             | 331                                                       | 208                             | 80                                           |
| - EBV-DNA (copies/mL)                             | < 316                           | < 316                                                     | -                               | -                                            |
| - PT/PTT (10.8-13.9/26.6-40.3 secs)               | 12.6/32.2                       | 16/28.8                                                   | 14.8/45.1                       | 13.7/22.1                                    |
| - LDH (< 240 U/L)                                 | 293                             | 558                                                       | 875                             | 461                                          |
| - hs-CRP (< 5 mg/L)                               | 64.58                           | 76.66                                                     | -                               | > 160                                        |
| - ESR (mm/hr)                                     | 12                              | -                                                         | -                               | 47                                           |
| - AST/ALT (< 45 U/L)                              | 46/44                           | 33/20                                                     | 269/216                         | 144/80                                       |
| - Alb (gm/dL)                                     | 2.1                             | 2.4                                                       | 3.5                             | 2.5                                          |
| Primary lesion                                    | Intraabdominal LN               | Intrathoracic and intraabdominal LN                       | Left leg and inguinal LN        | Lung and mediastinal mass                    |
| Imaging: fluid                                    | - Pleural effusion<br>- Ascites | - Pericardial effusion<br>- Pleural effusion<br>- Ascites | - Pleural effusion<br>- Ascites | - Pericardial effusion<br>- Pleural effusion |
| Staging <sup>a</sup>                              | Stage III                       | Stage III                                                 | Stage III                       | Stage IV                                     |
| Perforin by IHC, gene sequencing:                 | Perforin+ by IHC                | Perforin+ by IHC,<br><i>PRF1</i> sequencing:<br>wild type | Perforin: not tested            | Perforin: not tested                         |
| HLH criteria <sup>b</sup>                         | 5 of 8                          | 5 of 8                                                    | 5 of 8                          | 4 of 8                                       |
| Time from medical attention to                    |                                 |                                                           |                                 |                                              |
| - Lymph node biopsy (days)                        | 4                               | 17                                                        | 17                              | 12                                           |
| - Bone marrow biopsy (days)                       | 3                               | 9                                                         | 45                              | 12                                           |
| Metastasis                                        |                                 |                                                           |                                 |                                              |
| - Nervous systems                                 | -                               | No                                                        | -                               | Yes                                          |
| - Bone                                            | -                               | -                                                         | -                               | -                                            |
| - Bone marrow                                     | No                              | No                                                        | No                              | No                                           |

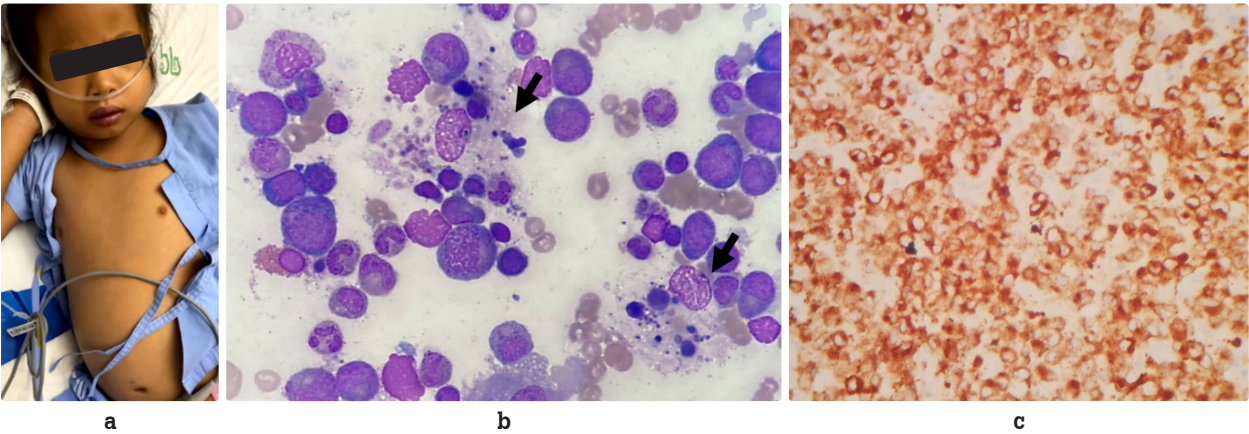
**Table 1** Clinical characteristics, laboratory workup and treatment of four cases of ALCL with HLH (continue)

|             | Case 1                           | Case 2                                                                                                                          | Case 3                                                                                                                                        | Case 4                                                                           |
|-------------|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Protocol    | HLH-directed (IVIG/<br>Dexa/CYA) | HLH-directed (IVIG/<br>Dexa/CYA)<br>→ Lymphoma-<br>directed (Ifo/Eto/<br>Dexa/MTX/AraC<br>alternate with CPM/<br>Doxo/Dexa/MTX) | Lymphoma-directed<br>(CPM/Eto/Dexa/MTX<br>alternate with Cb/<br>AraC/Dexa/MTX) →<br>HLH-directed (IVIG/<br>Dexa/Eto) → Lym-<br>phoma-directed | Lymphoma-directed :<br>(CPM/Eto/Dexa/MTX<br>alternate with Cb/<br>AraC/Dexa/MTX) |
| Progression | Death at diagnosis               | Remission at 1 year                                                                                                             | Remission at 17 years                                                                                                                         | Death at diagnosis                                                               |

**Abbreviation:** AraC: cytarabine; Cb: carboplatin; CPM: cyclophosphamide; CT: computed tomography; CYA: cyclosporin A; Eto: etoposide; Dexa: dexamethasone; Doxo: doxorubicin; HC: hydrocortisone; Ifo: ifosfamide; IHC: Immunohistochemistry; IT: intra-theal; IVIG: intravenous immunoglobulin; MTX: methotrexate; MP: methylprednisolone; VCR: vincristine  
<sup>⊞</sup>According to Murphy staging system; <sup>γ</sup>According to HLH-2004 diagnostic criteria; <sup>#</sup>The NK cell function analysis and soluble CD-25 are not available in treatment institute.



**Figure 1** Case 1: a) Bone marrow aspiration on Wright's stain under low power (10x objective) resolution shows decreased cellularity and inadequate megakaryocytes. b) On Wright's stain under 100x objective shows histiocyte with hemophagocytic activity (arrow). c) Lymph node immunohistochemistry shows positive perforin cytoplasmic stain of medium-to-large atypical cells.



**Figure 2** Case 2: a) The patient had upper lid and facial swelling, pleural effusion requiring oxygen support and abdominal distension with ascites. b) Bone marrow aspiration on Wright's stain under 100x objective resolution shows histiocytes with hemophagocytic activities (arrow). c) Lymph node immunohistochemistry shows positive perforin cytoplasmic stain of large, atypical cells. Permission for photo publication was obtained from the patient's guardians.

lymph nodes. Biopsy confirmed recurrent ALCL, ALK+ with immunohistochemistry staining: CD3-, CD4+, CD5-, CD8-, CD15-, CD20-, CD30+, CD43-, AE1/AE3-, ALK+, EBV(LMP)-, EMA+, Granzyme B+, Perforin+, Ki67+(80%), TIA1+ and PLAP-. The HLH-directed protocol was initiated. Unfortunately, she suddenly had dyspnea and persistent hypotension with an extremely poor ejection fraction on the echocardiogram. The child finally experienced cardiac arrest presumed due to HLH-induced cytokine-releasing syndrome with multi-organ failure.

### Case 2

A 6-year-old Thai girl without underlying disease presented prolonged high grade fever and abdominal tenderness for one month. The physical examination revealed generalized edema and enlarged liver. Computed tomography (CT) chest and abdomen demonstrated multiple intrathoracic and intra-abdominal lymph nodes. Five of eight HLH criteria were met consisting of fever, bicytopenia, elevated serum ferritin, hypertriglyceridemia and hemophagocytic activity on bone marrow examination as shown in Table 1 and Figure 2. Supraclavicular lymph node biopsy was performed and demonstrated ALCL, ALK+ with immunohistochemistry staining: CD2-, CD3-, CD4+, CD5+, CD8-, CD20-, CD30+, CD43+, CD45+, ALK+, AE1/AE3-, Granzyme B+ and Perforin+. Genetic test using *PRF1* sequencing was performed revealing wild-type alleles. HLH treatment was initially started, followed by the lymphoma-directed therapy using the ThaiPOG ALCL protocol.<sup>9</sup> The patient was in complete remission after one year of treatment.

### Case 3

A 10-year-old, previously healthy Thai boy presented a tender left leg mass, marked abdominal distension and high grade fever for three weeks. On physical examination, he presented generalized lymphadenopathy and hepatosplenomegaly. The lymph node incisional biopsy revealed ALCL, ALK+ with histiocytic proliferation and hemophagocytes. Immunohistochemistry staining was performed showing CD3+, CD15-, CD20-, CD30+, CD43+, CD45RO+, CD68-, ALK+, EMA+, TIA1+ and Perforin: not

tested. Bone marrow study showed hemophagocytic activity without lymphomatous involvement. Initial treatment with lymphoma-directed therapy with ThaiPOG ALCL protocol<sup>9</sup> was promptly started. Four weeks later, he still exhibited progressive cytopenia. A repeat marrow study showed a similar result of increased histiocytes with hemophagocytic activities. Five of eight of HLH criteria were met consisting of fever, splenomegaly, bicytopenia, elevated serum ferritin and hemophagocytosis as shown in Table 1. Hydrocortisone was started initially as a part of the HLH treatment protocol. Within 1 week, the complete blood count improved to the normal range. HLH treatment was continuously stepped up and resumed by lymphoma protocol.<sup>9</sup> Follow-up for 17 years demonstrated no recurrence of lymphoma and no long term complications.

### Case 4

An 11-year-old Thai girl without underlying disease presented high grade fever, cough, dyspnea and facial edema for four days. Physical examination showed a large ill-defined mass at the left back measuring 6 cm. in diameter. Blood chemistry revealed calcium: 14.2 mg/dL, phosphate: 2 mg/dL and parathyroid hormone (PTH): 4.76 pg/mL (15-65). The presentation was highly suspicious of cancer-producing PTH-related peptides but without proven investigation. Calcitonin was started. CT chest revealed two large left lower and right upper lung masses with a cavity. Mass wall histology was obtained and found to be compatible with ALCL, ALK+ with immunohistochemistry staining: CD3+, CD15-, CD20-, CD30+, CD45+, AE1/AE3-, ALK+, EMA-, HCG-TIA1+, vimentin+ and Perforin: not tested. Four of eight of HLH criteria were met which could not be diagnosed including fever, bicytopenia, elevated serum ferritin and hemophagocytes on bone marrow examination as shown in Table 1. Nevertheless, severe bicytopenia without lymphomatous involvement in bone marrow was likely suggestive of hemophagocytosis syndrome and needed to be repeated. Dexamethasone was started for superior vena cava syndrome treatment just before the lymphoma-

directed therapy with ThaiPOG ALCL protocol.<sup>9</sup> Recurrent generalized tonic-clonic convulsions were reported, and neurologic involvement was diagnosed. Septic shock with uncontrolled disseminated intravascular coagulation (DIC) was observed and pulmonary hemorrhage with cardiac arrest was noted.

### Discussion

A comparison of ALCL with or without HLH clinical characteristics is demonstrated in Table 2. The co-existence of five factors including splenomegaly, cytopenia, liver dysfunction, pleural and pericardial effusions might imply coincidental HLH in ALCL and were quite rare in ALCL alone.<sup>10</sup>

**In the case of a large mass presentation** similar to our third and fourth cases, HLH might be obscured. Fever was not a good clue to consider HLH involvement because the B symptoms were found in nearly one half of ALCL without HLH.<sup>10</sup> A study on adolescent and adult lymphoma also documented that fever, hepatosplenomegaly, cytopenia, bone marrow involvement, elevated Lactate Dehydrogenase (LDH) (> 1,000 U/L) and liver dysfunction (aspartate transaminase or alanine transaminase > 40 U/L) were significantly found more in lymphoma-associated HLH than lymphoma alone.<sup>11</sup>

**In the case of HLH without obvious etiology** similar to our first and second cases, the diagnosis of HLH was obvious. However, the co-existence of ALCL was challenged. In Table 2, no difference is shown between nonmalignant HLH as compared with lymphoma and HLH. Our recommendation is, if the HLH is of unknown etiology and generalized lymphadenopathy is evident, lymph node biopsy may be beneficial to rule out the coincidence of lymphoma and should be counted as a part of a secondary HLH workup. Because isolated HLH also had lymphadenopathy, the decision for biopsy should be weighted by clinical correlation and complication of the invasive procedure. Missing the lymphoma diagnosis is also hazardous as this may cause partial

treatment of cancer by HLH chemotherapy.

Without a palpable lymph node, imaging such as an ultrasound abdomen or CT chest remains not recommended if HLH is obvious. Positron emission tomography (PET)-CT was widely accepted in Hodgkin's disease and diffuse large B-cell lymphoma for accurate baseline tumor staging and prognostic evaluation.

One report of 50 children with ALCL found that malignancy-associated HLH accounted for 12% of all ALCL cases.<sup>10</sup> Another report of 21 childhood and adolescents receiving a diagnosis of malignancy-associated HLH at the first presentation found that 23% of cases (5 of 21 cases) were induced by ALCL.<sup>3</sup> The HLH may appear initially at the first presentation or during chemotherapy.<sup>3</sup>

Cytokine overproduction, especially interleukin (IL)-6, IL-2R, IL-10, tumor necrosis factor receptor 1 (TNF-RI) and macrophage inflammatory protein-1 $\alpha$ , was demonstrated in ALCL more than in other B-cell neoplasms.<sup>2</sup>

The typical capillary leakage syndrome may have generalized edema, weight gain, hypotension, hypoalbuminemia or oliguria. The leakage syndrome from HLH was proposed to be due to excessive inflammatory cytokines damaging the vascular endothelial cells. This was exaggerated combined with ALCL resulting in severe clinical manifestation.

Immunohistochemistry with perforin staining is a choice for screening germline bi-allelic mutations. Evidence from a small study showed that the absence of perforin staining on liver tissue with HLH involvement is associated with homozygous and compound heterozygous *PFR1* mutation in all two cases. However, other hemizygous carriers (0 of 2) could not be identified.<sup>12</sup> Moreover, some *PRF1* mutations may produce normal quantitation and protein malfunction may also have false-positive expression.<sup>13</sup> Currently, no known case of familial HLH was reported to have subsequent lymphoma; although, a report described a family with one case of familial HLH (bi-allelic *PRF1* mutation: A91V/R410W) and four cases of hereditary cancers (renal/prostate/gastric

**Table 2** Recognition of ALCL with HLH compared with nonmalignant HLH, isolated ALCL and all lymphomas with HLH

|                                             | Nonmalignant HLH                         | Isolated ALCL             | ALCL with HLH |                          | All lymphoma with HLH                                                        |
|---------------------------------------------|------------------------------------------|---------------------------|---------------|--------------------------|------------------------------------------------------------------------------|
|                                             |                                          |                           | KCMH          | Previous study           |                                                                              |
| HLH-2004 criteria                           |                                          |                           |               |                          |                                                                              |
| - Fever                                     | 98% <sup>17</sup>                        | 57% (25/44) <sup>10</sup> | 100% (4/4)    | 100% (6/6) <sup>10</sup> | 100% (28/28) <sup>11</sup>                                                   |
| - Splenomegaly                              | 68.1% (47/69) <sup>18</sup>              | 5% (2/44) <sup>10</sup>   | 25% (1/4)     | 67% (4/6) <sup>10</sup>  | 86% (19/22) <sup>18</sup>                                                    |
| - Cytopenia                                 | 94% <sup>18</sup>                        | 7% (3/44) <sup>10</sup>   | 100% (4/4)    | 83% (5/6) <sup>10</sup>  | 100% (28/28) <sup>11</sup>                                                   |
| - Hemophagocytosis                          | 53.6% (37/69) <sup>18</sup>              | 7% (2/27) <sup>10</sup>   | 100% (4/4)    | 100% (6/6) <sup>10</sup> | 73% (16/22) <sup>18</sup>                                                    |
| - Hypofibrinogenemia (< 1.5 g/L)            | 92% <sup>19</sup>                        | 8% (3/39) <sup>10</sup>   | 0% (0/4)      | 80% (4/5) <sup>10</sup>  | 43% (12/28) <sup>11</sup>                                                    |
| - Hyperferritinemia (> 500 µg/L)            | 97% <sup>19</sup>                        | 25% (1/4) <sup>10</sup>   | 100% (4/4)    | 100% (4/4) <sup>10</sup> | 100% (28/28) <sup>11</sup>                                                   |
| - Hypertriglyceridemia (> 265 mg/dL)        | 64% <sup>19</sup>                        | 13% (1/8) <sup>10</sup>   | 50% (2/4)     | 60% (3/5) <sup>10</sup>  | 79% (22/28) <sup>11</sup>                                                    |
| Median ferritin (> 500 µg/L)                | 3,562.0 <sup>18</sup>                    |                           | 3,186.5       |                          | 1,148.5 <sup>18</sup>                                                        |
| Elevated CRP                                |                                          |                           | 100% (3/3)    |                          | 58% (7/12) <sup>20</sup>                                                     |
| Liver dysfunction <sup>a</sup>              | 67% (Transaminase > 60 IU/L)             | 5% (2/44) <sup>10</sup>   | 75% (3/4)     | 67% (4/6) <sup>10</sup>  | 40% (11/28) <sup>11</sup>                                                    |
|                                             | 18% (TB > 2 mg/dL) <sup>19</sup>         |                           |               |                          |                                                                              |
| Lung infiltrates                            | 30% (Respiratory symptoms) <sup>19</sup> | 9% (4/44) <sup>10</sup>   |               | 67% (4/6) <sup>10</sup>  |                                                                              |
| Lymphadenopathy                             | 39% <sup>19</sup>                        | 94% (17/18) <sup>21</sup> | 75% (3/4)     |                          | 39% (11/28) <sup>11</sup>                                                    |
| Pleural effusion                            | 38% (26/69) <sup>18</sup>                | 5% (2/44) <sup>10</sup>   | 100% (4/4)    | 33% (2/6) <sup>10</sup>  | 13.6% (3/22) <sup>18</sup>                                                   |
| Pericardial effusion                        |                                          | 0% (0/44) <sup>10</sup>   | 75% (3/4)     | 33% (2/6) <sup>10</sup>  |                                                                              |
| CNS disease                                 | 36% <sup>19</sup>                        | 0% (0/44) <sup>10</sup>   | 25% (1/4)     | 50% (3/6) <sup>10</sup>  |                                                                              |
| Bone marrow lymphoma involvement            |                                          | 12% (5/43) <sup>10</sup>  | 0% (0/4)      | 67% (4/6) <sup>10</sup>  | 57% (16/28) <sup>11</sup>                                                    |
| Prognosis KCMH study: survival              |                                          |                           | 50% (2/4)     |                          |                                                                              |
| Study A <sup>3</sup> : 6-mo survival        |                                          |                           |               | 60% (3/5)                | 14% (1/7, T-ALL), 71% (5/7, B-lineages malignancy), 38% (3/8, HLH during Tx) |
| Study B <sup>2</sup> : up to 10-yr survival |                                          |                           |               | 67% (4/6)                | 92% (22/24, B-NHL, T-LBL, B-LBL)                                             |
| Study C <sup>18</sup> : mean survival       | 35.09±2.19 mo                            |                           |               |                          | 26.9±3.82 mo (p = 0.055)                                                     |
| Study D <sup>10</sup> : 5-yr EFS            |                                          | 59-60%                    |               | 67-68% (p = 0.914)       |                                                                              |

**Abbreviation:** ALCL: Anaplastic Large Cell Lymphoma; B-LBL: B-cell Lymphoblastic Lymphoma; B-NHL: B-cell Non-Hodgkin Lymphoma; CMV: Cytomegalovirus; CNS: Central Nervous System; EBV: Epstein-Barr Virus; EFS: Event Free Survival; HLH: Hemophagocytic lymphohistiocytosis; HSV: Herpes Simplex Virus; mo: month; KCMH: King Chulalongkorn Memorial Hospital; T-ALL: T-cell Acute Lymphoblastic Leukemia; T-LBL: T-cell Lymphoblastic Lymphoma; TB: Total bilirubin; Tx: Treatment; VZV: Varicella-Zoster Virus

<sup>a</sup>Liver dysfunction: Total bilirubin (TB) > 1 mg/dL, Serum albumin < 3.5 g/dL, Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) > 40 U/L

carcinoma with Acute Myeloid Leukemia (AML), Acute Lymphocytic Leukemia (ALL), Chronic Myelomonocytic Leukemia (CMML) and Glioma; both mono- or bi-allelic *PRF1* mutation).<sup>14</sup> Our second case underwent genetic testing for the *PRF1* gene sequencing and wild-type alleles were found. Immunohistochemistry of *PRF1*, just

like, western blotting, flow cytometry and genetic testing is an option but not mandatory for ALCL with HLH due to weak correlation and few evidence-based data.

In our practice, if HLH was more severe than ALCL and presented exaggerated the hyperinflammatory state and organ dysfunction, the HLH protocol (corticosteroid,

etoposide, cyclosporin A, cyclophosphamide, IVIG and others) is considered first before lymphoma-directed treatment (EICNHL-ALCL99).<sup>9,15</sup> In fact, we initially started one half of the cases with the HLH protocol and the other one half with the lymphoma protocol. However, the results were mixed with one case requiring rescue of lymphoma protocol with HLH treatment. Our mortality cases had rapid progression just after diagnosis were due to cytokine storms such as cardiogenic shock, DIC, seizure and pulmonary hemorrhage and not due to lymphoma complications such as tumor lysis or SVC syndrome. Thus, the use of lymphoma-directed therapy should not be contra-indicated once the diagnosis of ALCL has been firmly established. The use of HLH-directed therapy can also be considered among all patients satisfying the HLH diagnostic criteria. The decision should be based on the individual's most harmful condition. If the SVC syndrome or mass effect are most intense, the lymphoma-directed with HLH-sensitive agents might be switched/initiated in the conceptualized HLH-precipitative cause treatment. Further, if hypercytokine and capillary leakage are explicit, the HLH-directed treatment is the most appropriate to constitute the first protocol. In our case series, the prognosis of ALCL with HLH is poor comprising 50% mortality (2 of 4 cases), especially in the first month of treatment. Please note that for our mortality cases, both also had high risk features such as relapsed status on the first case and soft tissue/ neurological involvement on the fourth.

Because HLH universally affects the liver, chemo therapy/ immunosuppressive should be carefully prescribed as dose reduction, postponement or omission. These include etoposide in a part of the HLH-directed protocol and vincristine, doxorubicin, methotrexate and others in a part of the lymphoma-directed protocol.

Upfront combination with anti-CD30 monoclonal antibody (brentuximab vedotin) in adult CD30-positive peripheral T-cell lymphoma majority in ALCL was

reported to be superior in median progression-free survival compared with the conventional CHOP protocol (48.2 VS 20.8 months,  $p = 0.011$ ) with similar adverse events.<sup>16</sup> This should be considered especially in the case of the initially advanced stage of the disease. However, with the adverse reactions of brentuximab as fever and hypersensitivity, initial prescribing, in active HLH status, should be performed carefully.

### Conclusion

The diagnosis of combined ALCL with HLH remains challenging. The coincidence with HLH should be highly suspicious when patients develop cytopenia, splenomegaly, liver dysfunction and pleural and pericardial effusions. On the other hand, if HLH without etiology present includes only fever and cytopenia, an enlarged lymph node should be biopsied and considered as a secondary HLH workup, while the perforin study remains optional. When ALCL with HLH has severe hyperinflammation and capillary leakage syndrome, the HLH-directed protocol should be considered first before lymphoma-directed treatment. They should be performed cautiously because the mortality is quite high when these two conditions are combined.

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