
بسم الله الرحمن الرحیم

Severe refractory Langerhans Cell Histiocytosis (LCH) in an infant with association of Haemophagocytic Lymphohistiocytic syndrome (HLH)

P. Eshghi* ,F.Malek,Z.Khafafpour

***Prof. of Pediatric Hematology and Oncology**

Mofid Children`s Hospital

Iranian Children`s Health Institute

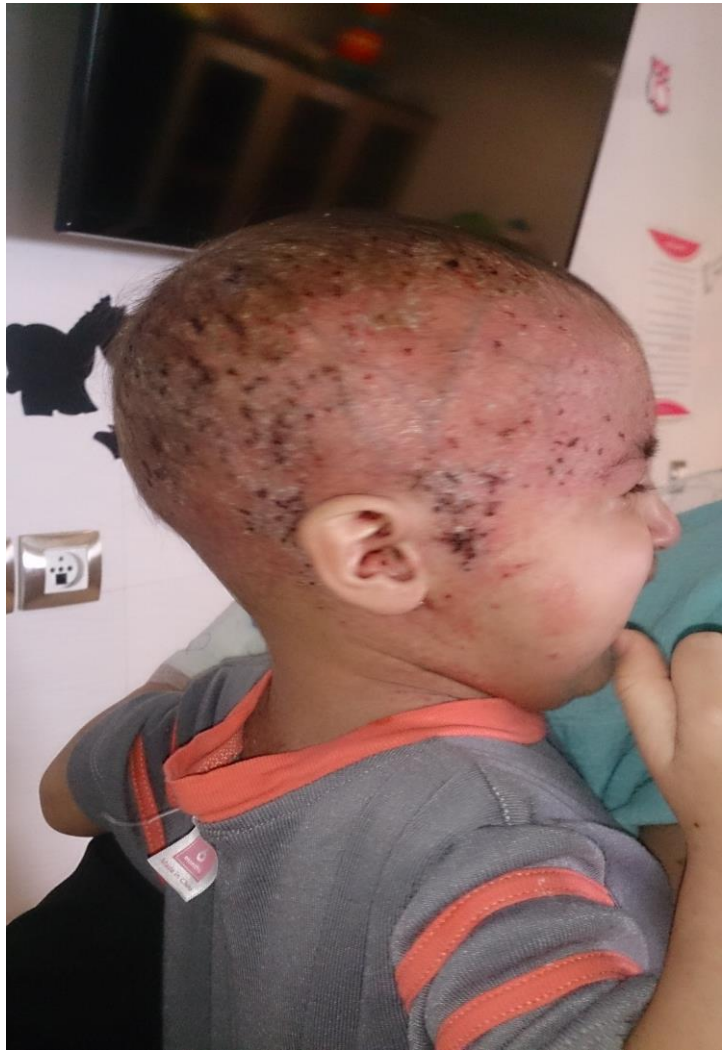
Pediatric Congenital Hematologic Disorders Research Center,

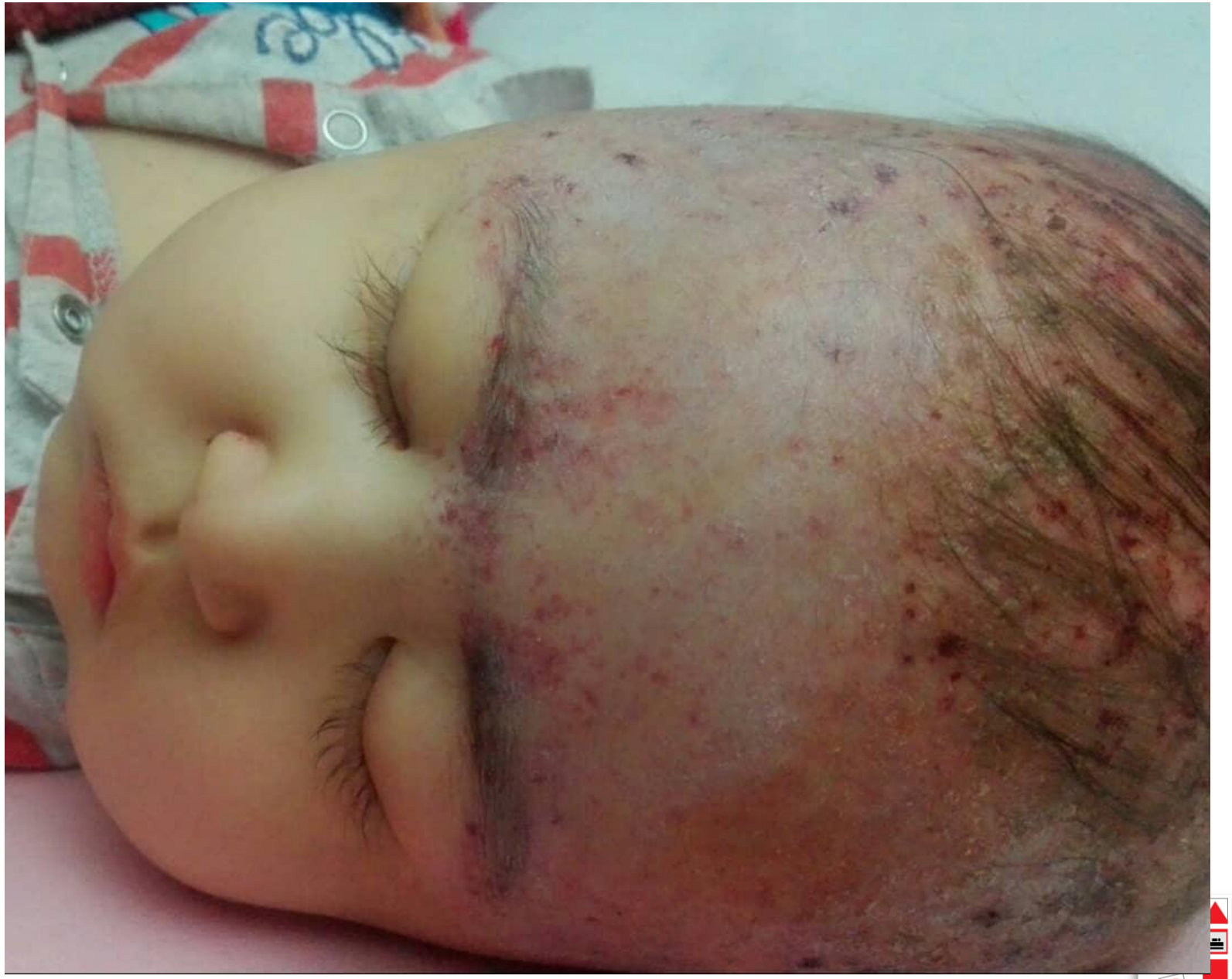
Shahid Beheshti University of Medical Sciences

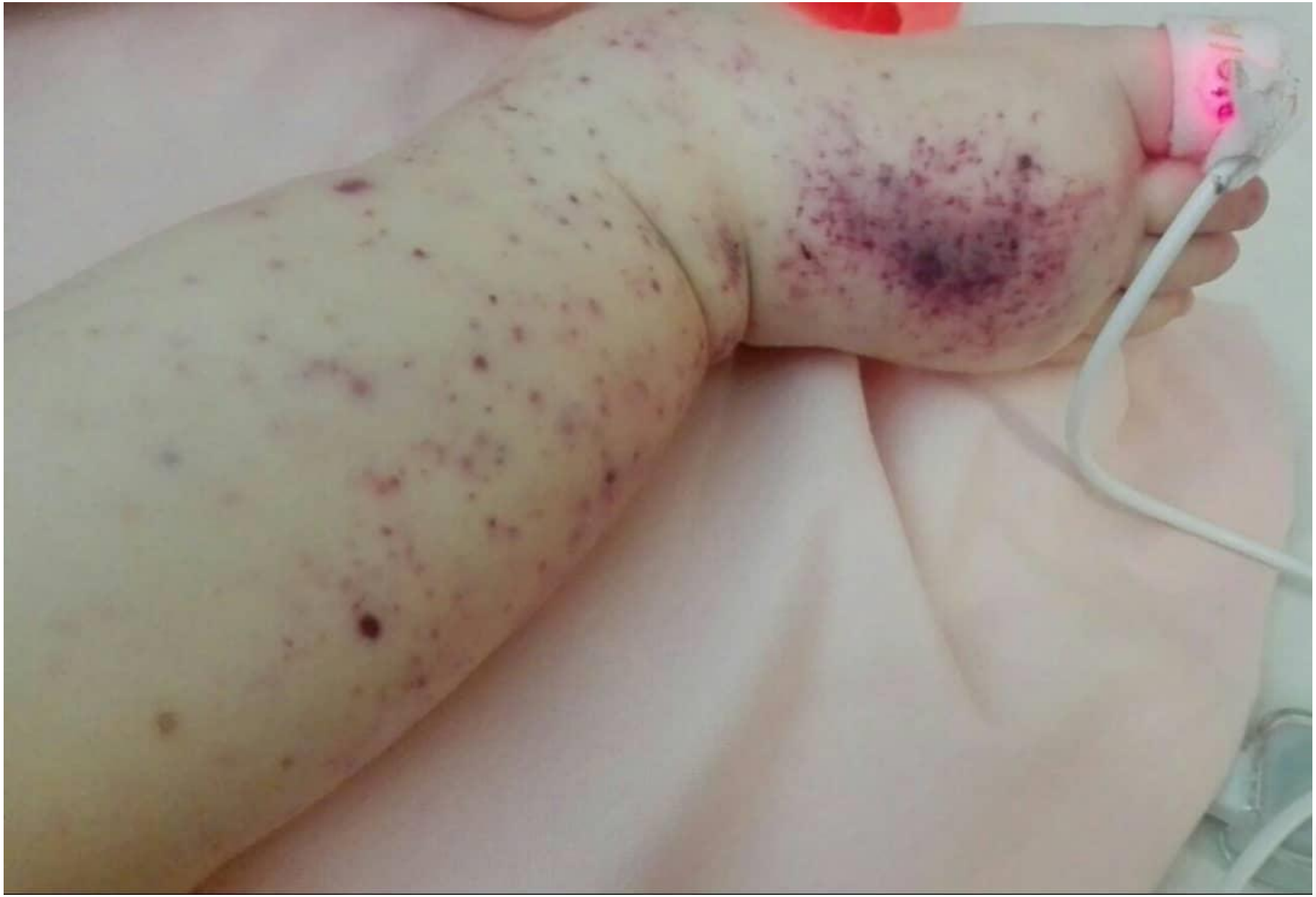
Case Presentation

- A 10 month-old boy , the first child of non-consanguineous and healthy parents was admitted in our ward for further evaluation.

- presented with recurrent fever (>38.5°) and generalized sever echzematoid bleeding dermal rash,since 6 months ago
- Physical examination revealed splenomegaly, respiratory distress and also generalized edema.







Diagnostic Lab data

WBC	1300/µl
Neut	32%
Hb	6.4g/dl
Hct	22
Plt	$45000 \times 10^4 / \mu l$

TG	296 mmol/ml
Ferritin	800mg/dl
Fibrinogen	80mg/dl
Total protein	2.7 g/dl
Albumin	1.8 g/dl

- At very beginning patient was suspicious to suffer from an immune deficiency, hence peripheral CD flowcytometry and other tests were administered without any specific finding.

NBT	100%
IgG	449
IgA	71
IgE	8

CD18	CD 11a	CD11b	CD11c	CD56	CD4	CD8	CD4l8
NL	NL	NL	NL	NL	38	20	2

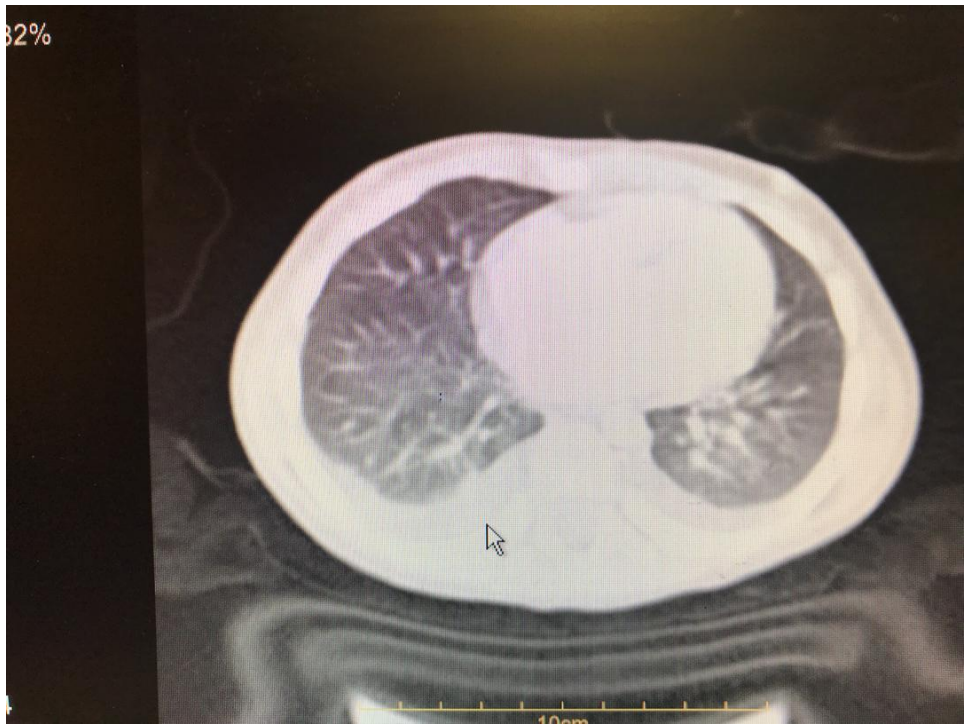
Laboratory Findings ending to Diagnosis

- Virological assay:
  - HCV : neg
  - HIV Ab : neg
  - HBS Ag : neg
  - HBSAB :> 200
  - CMV PCR :neg
  - EBVPCR :neg

- Electrolytes WNL
- SGOT : 15
- SGPT : 13
- T.BIL :0.9
- D.BIL : 0.4
- PT PTT: WNL
- CSF Analysis: Normal
- BG :O +
- Coombs : neg
- G6PD Sufficient
- BUN 11 , Cr 0.4

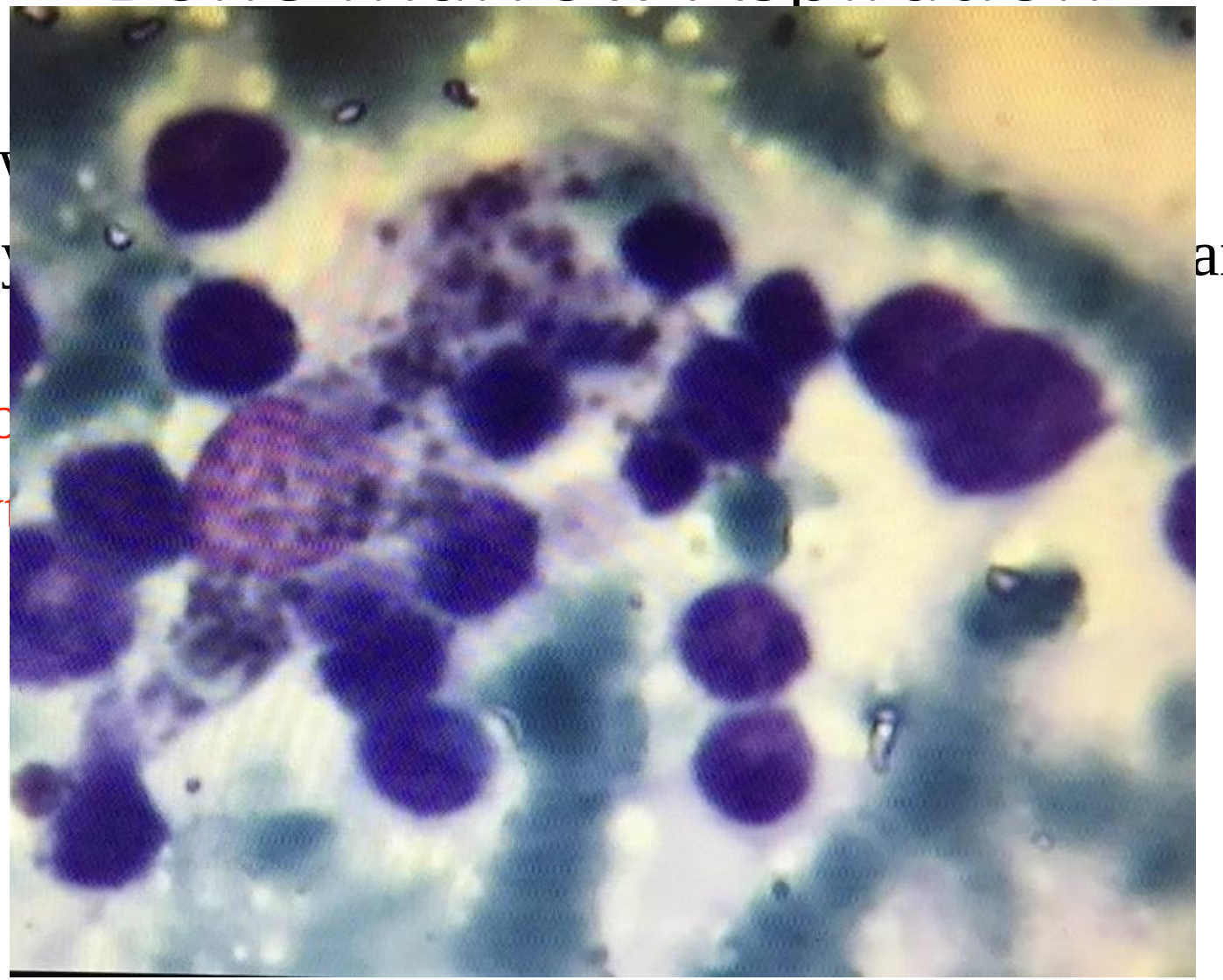
Imaging

- Abdominopelvic ultrasonography revealed Splenomegaly, Liver had normal size and echo , other findings were not specific
- Normal bone survey in X-ray
- CXR and CT scan both revealed diffuse ground glass densities bilaterally



Bone Marrow Aspiration

- Cellularity v
- Myeloid,Ery ange without dyspoiesis.
- Hemophago
- CD Flowcyt



Skin Biopsy

- Sections show skin tissue infiltrated by Langerhans cells with eosinophilic Cytoplasm,oval nuclei with Longitudinal groove.Some inflammatory cells are present
- IHC study
  - **S100 : Positive**
  - Pan CK :Negative
  - **CD 68 Postive**
  - **CD 1a Positive**
- Diagnosis : Langerhans cell histiocytosis of skin lesion

Table 1. Diagnostic criteria for HLH used in the HLH-2004 trial*

The diagnosis of HLH† may be established:

A. Molecular diagnosis consistent with HLH: pathologic mutations of *PRF1*, *UNC13D*, *Munc18-2*, *Rab27a*, *STX11*, *SH2D1A*, or *BIRC4*

or

B. Five of the 8 criteria listed below are fulfilled:

1. Fever ≥ 38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)
   - Hemoglobin < 9 g/dL (in infants < 4 weeks: hemoglobin < 10 g/dL)
   - Platelets < 100×10^3/mL
   - Neutrophils < 1×10^3/mL
4. Hypertriglyceridemia (fasting, > 265 mg/dL) and/or hypofibrinogenemia (< 150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Low or absent NK-cell activity
7. Ferritin > 500 ng/mL‡
8. Elevated sCD25 (α-chain of sIL-2 receptor)§

*Adapted from Henter et al.[7]

†In addition, in the case of familial HLH, no evidence of malignancy should be apparent.

‡Although the HLH-2004 protocol uses ferritin > 500 ng/mL, we generally view ferritin > 3000 ng/mL as concerning for HLH and ferritin > 10 000 as highly suspicious.[8]

§Elevations above age-adjusted, laboratory-specific normal levels (defined as > 2 SD from the mean) appear more meaningful than the original designation of > 2400 U/mL because of variations between laboratories.[17]

Table 1

Parameters Included in the Adapted HLH-2004 Guidelines and H-Score and the Number of Points Associated With Each Criterion for Scoring[a]

Parameter	Adapted HLH-2004 Guidelines	H-Score
Fever (°C)	0 (<38.5) or 1 (≥38.5)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
Splenomegaly	0 (no) or 1 (yes)	
Organomegaly		0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
Cytopenia	0 (one lineage) or 1 (two or three lineages)[b]	0 (one lineage), 24 (two lineages), or 34 (three lineages)[c]
Ferritin (ng/mL)	0 (<500) or 1 (≥500)	0 (<2,000), 35 (2,000-6,000), or 50 (>6,000)
Triglycerides (mmol/L)	0 (<3) or 1 (≥3)	0 (<1.5), 44 (1.5-4), or 64 (>4)
Fibrinogen (g/L)	0 (>1.5) or 1 (≤1.5)[d]	0 (>2.5) or 30 (<2.5
Hemophagocytosis in bone marrow	0 (no) or 1 (yes)	0 (no) or 35 (yes)
Aspartate aminotransferase (IU/L)		0 (<30) or 19 (≥30)
Known underlying immunosuppression		0 (no) or 18 (yes)

5 out of 6 criteria

199 H-score POINTS

HLH, hemophagocytic lymphohistiocytosis.

[a]Data are presented as number of points, with values in parentheses.

[b]Defined as hemoglobin less than 90 g/L, platelets less than 100×10^9/L, and neutrophils less than 1.0×10^9/L.

[c]Defined as hemoglobin 92 g/L or less, platelets 110×10^9/L or less, and leukocytes 5×10^9/L or less.

[d]The point is not added if there is already one point for triglycerides.

France Debaugnies ,et al. Am J Clin Pathol 2016;145:862-870

Table 4

Sensitivity, Specificity, and Percentage of Accurate Classification for the Adapted HLH-2004 Guidelines and the H-Score With Adapted Cutoff in the Discrimination of Patients With HLH From Control Groups[a]

	HLH Children vs Control Group, %			HLH Adults vs Control Group, %		
Characteristic	Sensitivity	Specificity	Accurate Classification	Sensitivity	Specificity	Accurate Classification
At initial presentation						
Adapted HLH-2004 guidelines (at least four of six criteria)	**81**	**100**	95	75	92	80
Adapted HLH-2004 guidelines (at least five of six criteria)	25	100	82	55	100	80
H-score >169	63	91	84	65	90	76
H-score >120	**100**	**80**	64	95	73	73
H-score >138	65	89	86	**90**	**79**	86
Maximal score value[b]						
Adapted HLH-2004 guidelines (at least four of six criteria)	88	93	92	90	73	78
Adapted HLH-2004 guidelines (at least five of six criteria)	44	100	88	**80**	**96**	91
H-score >169	81	89	88	90	73	78
H-score >141	**100**	**88**	90	95	56	69
H-score >185	69	91	86	**85**	**88**	87

HLH, hemophagocytic lymphohistiocytosis.

[a]Bold values represent the highest value of the sum of sensitivity and specificity.

[b]Maximal score value was determined using the diagnostic confirmation data set consisting of extreme values reached during the episode for each parameter.

France Debaugnies ,et al. Am J Clin Pathol 2016;145:862-870

Diagnosis

- ❑It is only a **Multisystemic-LCH** involving risk organs
- ❑It is a coincident of **Primary HLH** and **Multisystemic-LCH**
- ❑It is a **secondary HLH** due to **Multisystemic-LCH** involving risk organs

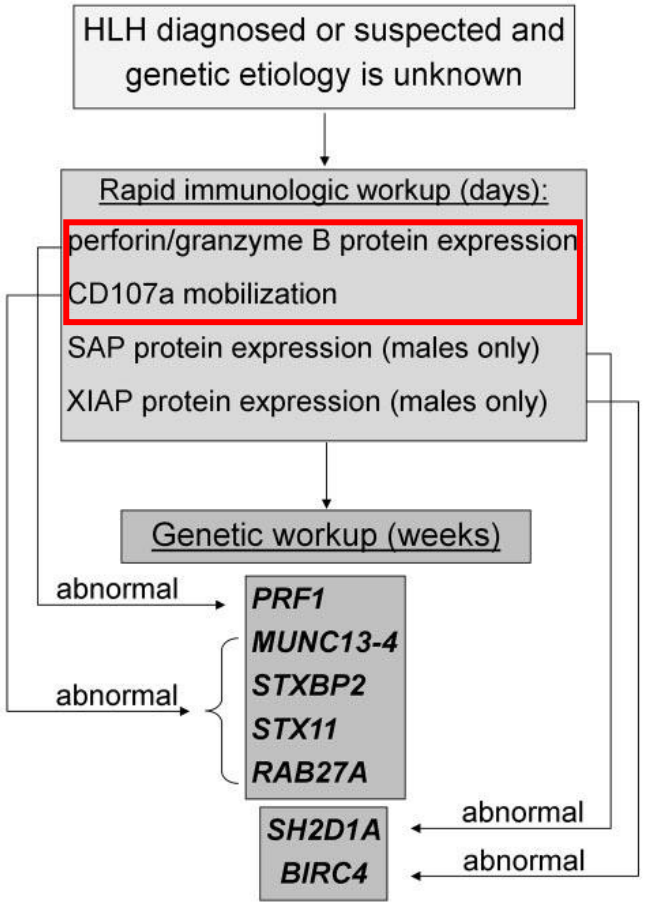
Immunologic and genetic workup of HLH

JORDAN et al ,BLOOD, 13 OCTOBER 2011 VOLUME 118, NUMBER 15

Table 4. Frequency of HLH-associated gene mutations by age in North American patients

Age at referral	No. of HLH patients	*PRF1*	*UNC13D*	*STXBP2*	*STX11*	*RAB27A*	Mutation identified, %
< 1 mo	58	16	5	0	0	0	45
2 mo to 1 y	100	23	15	1	0	0	39
1-2 y	55	7	4	0	0	0	20
> 2 y	263	7	3	2	2	1	6

Data from Judith Johnson and Kejian Zhang.



Genetics and HLA testing

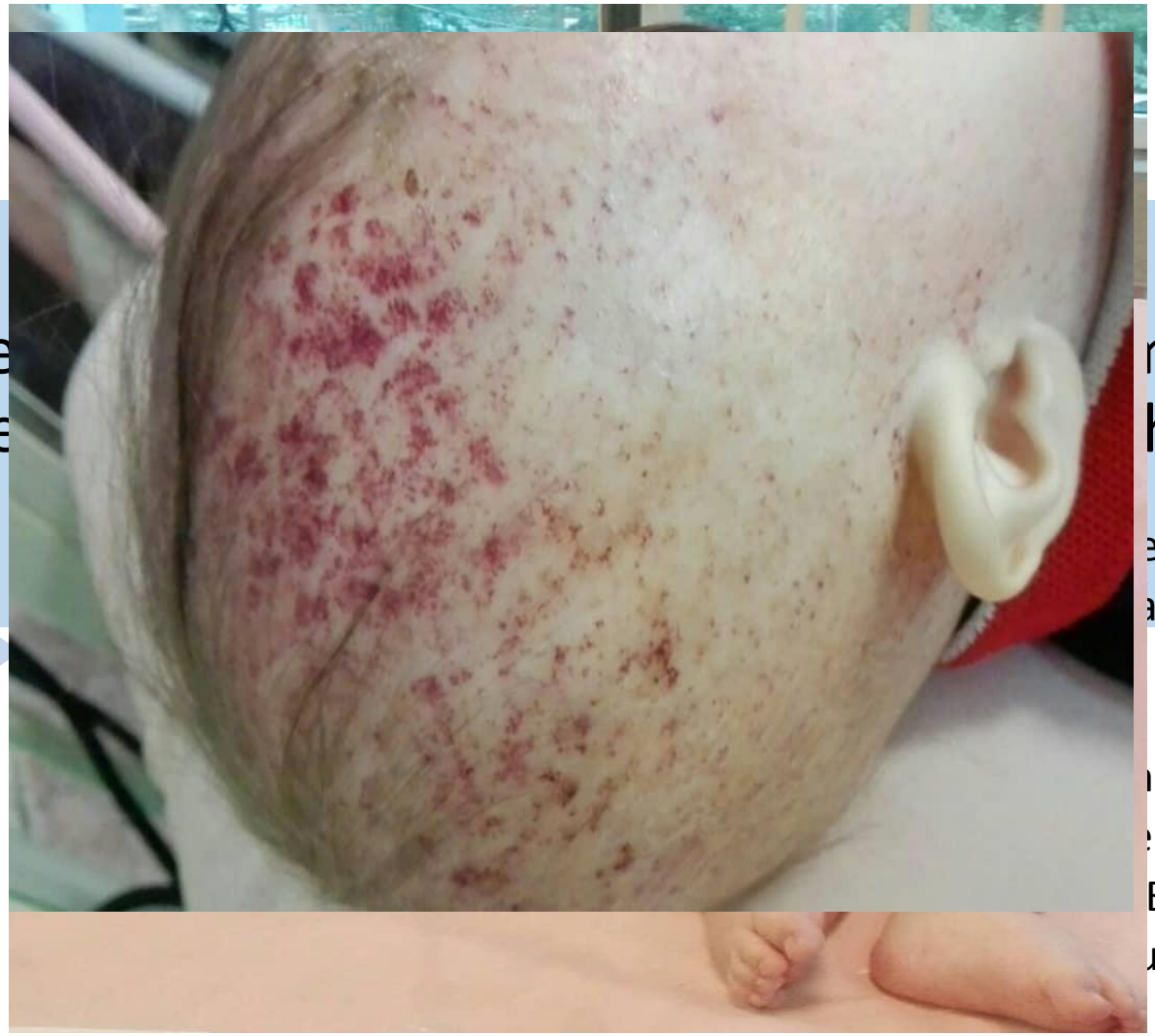
- A genetic analysis is not practical in all cases in developing countries, especially **in case of suspected**

Treatment of HLH were initiated **without requesting specific HLH mutation** due to relating HLH to underlying LCH

- However, it is mandatory in children with :
  - CNS involvement,
  - relapsing/refractory disease,
  - disease with significant multiorgan involvement
  - children born to consanguineous parents/ with positive family history.

Treatment:
First 6 weeks

Induction of HLH 2004



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Treatment:

Intensified treatr

- Weekly VP16 + CSA
- Weekly Vnb+MTX 5
- Supportive therapy

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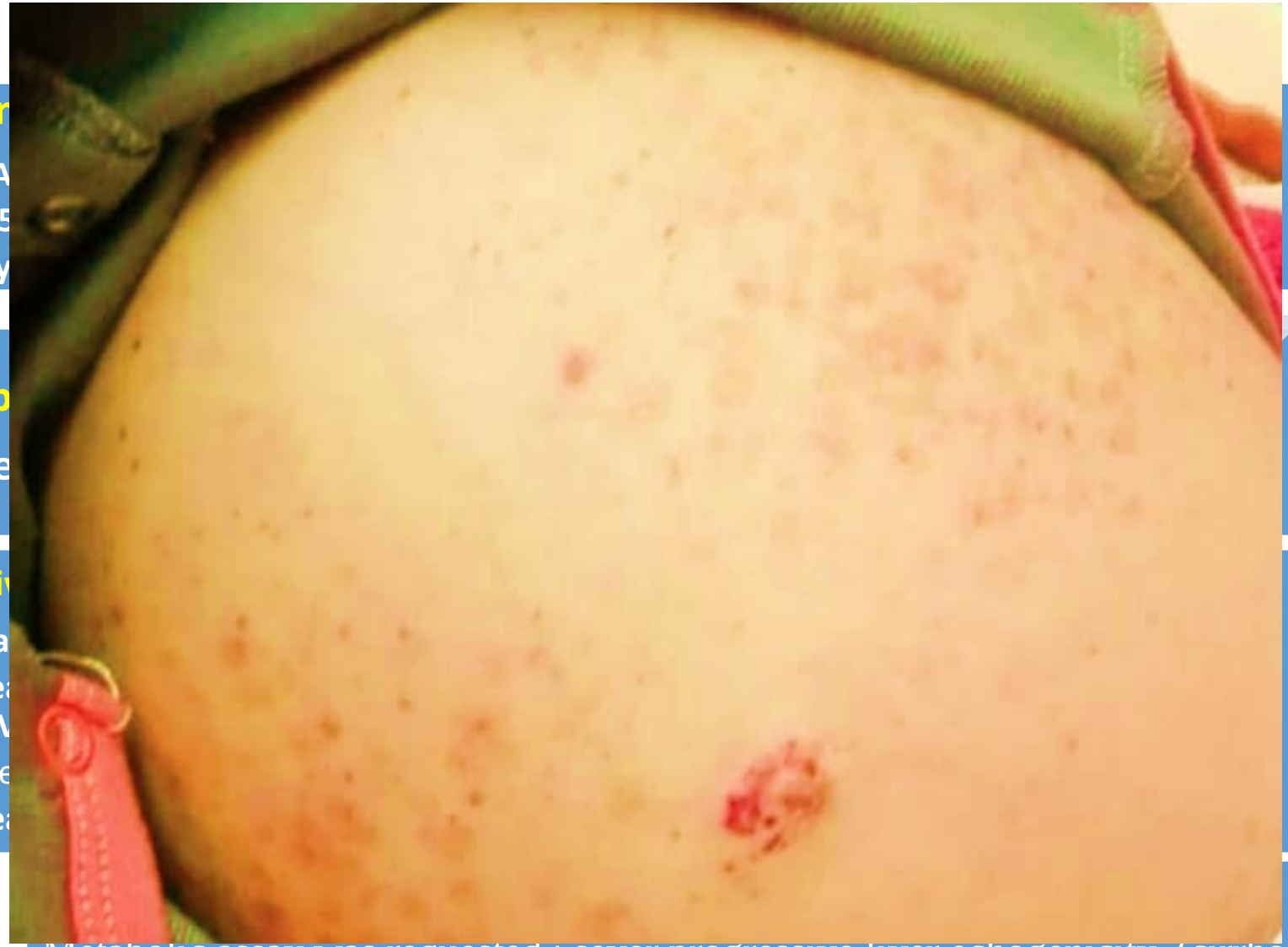
- Increa



Metabolic assay was requested : sever progressive liver echogenicity (cirrhosis?!)

Treatment:
last 4weeks till now

Protocole:	Positive Points:	Negative Point
• 2 CDA(5mg/ Q3-4 W) • Continue H regimen IF • Supportive therapy + Albumin	condition • Billirubin decreased to 1.5-3mg/dl	ctory nemia • Refractory Anemia & thrombocytopenia

Metabolic screening assay suggested for Biotinidase deficiency:
More specific assays has been requested

Problem List

- Sever Multi system LCH refractory to treatment (skin,Spleen,liver,BM,Lung),No bone lesion
- Refractory HLH probably secondary to LCH ,OR coincidental primary HLH: looking forward of HLH Mutation evaluation & BRAF mutation
- Rapidly progressive Size and Hyperechogenisty of the liver + sever Hyperbilirubinemia + mild to moderate increase in LFT (transaminases ,PT and PTT) despite of the treatment (GI consultation proposed **possibility of Cirrhosis and recommended for liver biopsy**) :
  - VP16,VINB, MTX,CSA were holded due to Hyperbilirubinemia
  - Metabolic Consultation proposed Biotinidase deficiency
- Refractory hypoalbuminemia in spite of Normal LFT & no evidence of proteinuria & no evidence of protein loosing entropahy(diarrhea,lymphopenia)

Discussion

- Coincidence of LCH and HLH (primary OR secondary)
- Coincidence of OR correlation between metabolic disorders and HLH
- Next steps of treatment: HLH/ refractory LCH /HLH & refractory LCH/ HSCT

co-existence of LCH and HLH

- Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia characterized by the accumulation of CD1a+ CD207+ histiocytes.
- Hemophagocytic lymphohistiocytosis (HLH), a non-malignant histiocytic disorder, is typified by the accumulation and activation of CD8+ T cells and macrophages, which secrete high levels of pro-inflammatory cytokines.
- There are overlapping features between MS-LCH and HLH that make the clinical distinction between these disorders difficult
- The co-existence of LCH and HLH has been reported, albeit rarely, and is believed to be associated with a poorer outcome.

Blood 2016 128:707

Litterature review:
coincidence of secondary HLH and LCHL,

Krstovski N, Jankovic S, Janic D. Turk J Pediatr 2014; 56: 452-457.

- **A young girl who developed secondary HLH <u>while being treated</u> for relapsed multisystem LCH under the LCH III Protocol.**
- **She fulfilled 5 of 8 HLH-2004 criteria (fever, splenomegaly, pancytopenia, ferritin level >500 µ/l and sIL-2R >2400 IU/ml) and was successfully treated by the HLH-2004 Protocol for secondary HLH.**
- **She remains in good health, apart from insipid diabetes she developed as a complication of LCH.**
- **Considering that the occurrence of HLH in LCH patients has been reported before, the case history presented here yields additional support for the hypothesis that the pathogenesis of the two histiocytoses – LCH and HLH – may indeed overlap to a considerable extent.**

- Of 384 MS-LCH patients, 44 (11%) were identified with HLH,ranging in age from 15 days to 20.6 years (median, 1.12 years).
  - 40/44 cases of MS-LCH patients who also had HLH were females (n=27) and had accompanying risk organ (liver, spleen, and/or hematopoietic system involvement).
- A histiocytosis (LCH) patients tested for BRAF V600E mutation status, eight were found to be positive.
- The 3-year cumulative incidence of HLH (true or HLH-like) in MS-LCH was 16.8%.:
  - Twenty (45%) patients developed HLH (true or HLH-like) concurrent (±7 days) with LCH diagnosis, while 24 (55%) developed HLH >7 days before or after LCH diagnosis.
- Age <2 years, female gender, RO+ and lack of bone involvement at LCH diagnosis were each independently associated with **increased risk for HLH**
- Ferritin levels appear **to be lower** in comparison to patients who develop HLH in other contexts.

Hemophagocytic Lymphohistiocytosis (HLH) in Langerhans Cell Histiocytosis (LCH): A Multicenter Retrospective Descriptive Study

Deepak Chellapandian, Rui Zhang, Michael Jeng, Cor Van Den Bos, Vicente Santa-María López, Kai Lehmberg, Elena Sieni, Yini Wang, Taizo Allen Nakano, James Williams, Nicholas J. Fustino, Itziar Astigarraga, Ira Dunkel, Qi An, Cheng Cheng, Sheila Weitzman, Lillian Sung and Kim E. Nichols

Blood 2016 128:707

*14 centers and collected data on 384 MS-LCH patients aged less than 30 years and who were diagnosed between year 2000 and 2015.

- a case of a 4-month-old boy presenting with hypotonia, apnea, and fever
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- successfully treated with biotin-replacement therapy, upon which the hemophagocytic syndrome ceased.

Pediatr Blood Cancer 2012;59:191–193

BRIEF REPORT

Hemophagocytic Syndrome in a 4-Month-Old Infant With Biotinidase Deficiency

Fatih Kardas, MD,[1] Turkan Patiroglu, MD,[2] Ekrem Unal, MD,[2]* Samuel C.C. Chiang, MSc,[3] Yenan T. Bryceson, PhD,[3] and Mustafa Kendirci, MD[1]

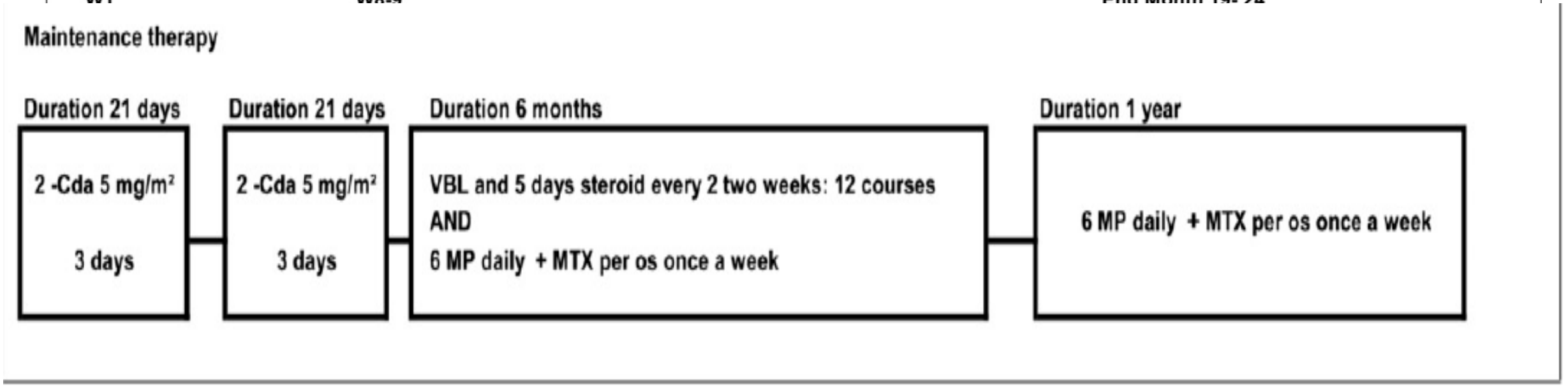
Hemophagocytic syndromes such as hemophagocytic lymphohistiocytosis (HLH) are life-threatening hyperinflammatory conditions caused by inherited or acquired immune disorders. Awareness of the clinical symptoms and diagnostic criteria for hemophagocytic syndromes is crucial to start timely life-saving therapy. We present a case of a 4-month-old boy presenting with HLH. However, the patient was subsequently diagnosed with biotinidase deficiency and was successfully treated with biotin-replacement therapy, upon which the hemophagocytic syndrome ceased. Subsequent laboratory evaluations revealed normal lymphocyte cytotoxicity and no mutations in genes associated with familial HLH were found. Biotinidase deficiency should be considered as a differential diagnosis of patients fulfilling HLH criteria. Pediatr Blood Cancer 2012;59:191–193.

Key words: biotinidase deficiency; children; hemophagocytic lymphohistiocytosis

Treatment paradox

- The certainty that the infant was diagnosed with LCH may lead physicians to fail to notice the developing secondary HLH or regard its symptoms and signs to the underlying disease:
  - Delay in treatment of HLH which may be life threatening
- More to add some crucial symptoms and signs of HLH, such as cytopenias and heptosplenomegaly, are also attributable to LCH too :
  - Missing to treat the primary disease which keep secondary HLH active and refractory

Scenario 1:
Treat as a refractory sever LCH



Oncology, CHU, Limoges, France; [8]Pediatric Hémato Oncology, CHU, Rennes, France; [9]Pediatric Hémato Oncology, CHU, Grenoble, France; [10]Pediatric Hematology Oncology, Universitets Hospital of Aarhus at Skejby, Aarhus, Denmark; [11]Pediatric Hémato Oncology, Hopital Jean De Flandre, CHU, Lille, France; [12]Pediatric Hematology Oncology, The Hospital for Sick Children, Toronto, ON, Canada; [13]Department of Women's and Children's Health, Karolinska Institute, Karolinska Univeristy Hospital, Stockholm Sweden; and [14]Department of Pediatric Oncology, Emma Children's Hospital/Academic Medical Center, Amsterdam, The Netherlands

Scenario 1:
Treat as a refractory sever LCH

Langerhans Cell Histiocytosis (LCH): Guidelines for
and Treatment for Patients Till the A

centre (evidence: D, agreement: 2). Therapeutic options (evidence: C) include combination chemotherapy with cladribine (2-CdA) and cytarabine (Ara-C) [39] or hematopoietic stem cell transplantation using reduced intensity conditioning regimen [40]. If there is evidence of disease progression in "non-risk organs," treatment with 2-CdA as monotherapy [41] or even with further courses of a combination of VBL and steroids should be considered.

arraga, MD,[3] Ev
hD,[7] Gritta Jan
Van Gool, MD,[1]
), PhD[4]* and fo

group of experts involved in the Euro Histio Net project who participated in national or international studies and in peer reviewed publications. Existing guidelines were reviewed and changed where new evidence was available in the literature up to 2012. Data and

publications hav
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Key words: clinical work-up; diagnosis; follow-up; guidelines; Lan

In 2010, Badalian-Very et al. [53], reported somatic mutations of the BRAF oncogene in about half of the LCH patients in their series, and this finding was recently confirmed by other teams [54,55]. This discovery may have a significant potential impact if we consider the possibility of treating LCH with the new class of BRAF inhibitors. However, this promising discovery will need to be verified and concretized before these drugs can be used for treatment of LCH. The group(s) of LCH patients who may benefit from BRAF inhibitor treatment must be determined and balanced with toxicities as in the case of melanoma [56,57]. Knowledge about drug schedule and safety, especially long-term effects [57] and mechanisms of resistance [58] must be acquired.

Progress may be expected from collaborations organized at national and international levels, among specialist groups and expert networks. Collection of tissue and blood samples in biobanks is essential for improving the understanding of the biology of this rare and fascinating condition. New international protocols will soon be opened and continue to represent an opportunity to develop global research in LCH (see www.histiocytesociety.org and www.histio.net).

Scenario 2:
Treat as a refractory sever LCH

How I treat

How I treat hemophagocytic lymphohistiocytosis

Conclusion:
HLH is fatal and should be treated regardless of its cause

Children, Toronto, ON

BLOOD, 13 OCTOBER 2011 • VOLUME 118, NUMBER 15

patients with suspected familial or reactive HLH.

diagnosis of primary or secondary HLH. Furthermore, a careful search for underlying disease triggers should be performed in all patients. Thus, initial treatment should not be delayed or altered based on these categories.

Scenario 2:
continue to treat refractory HLH

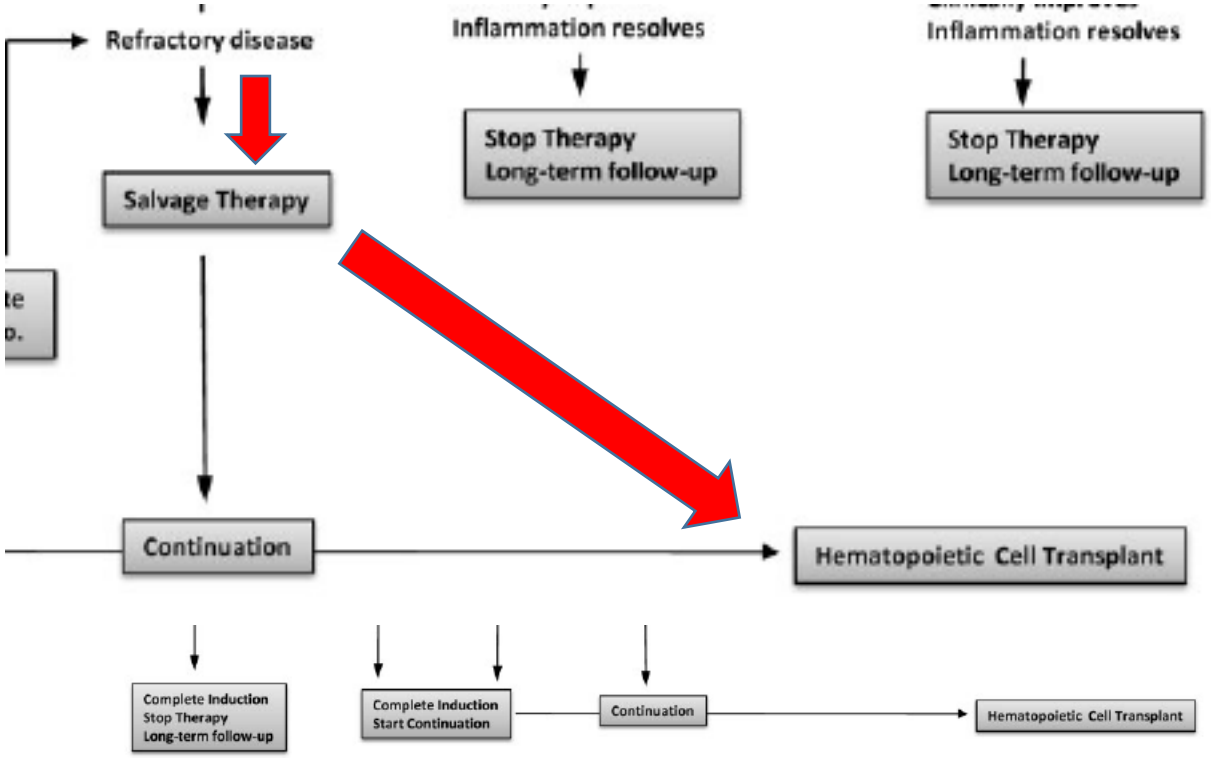
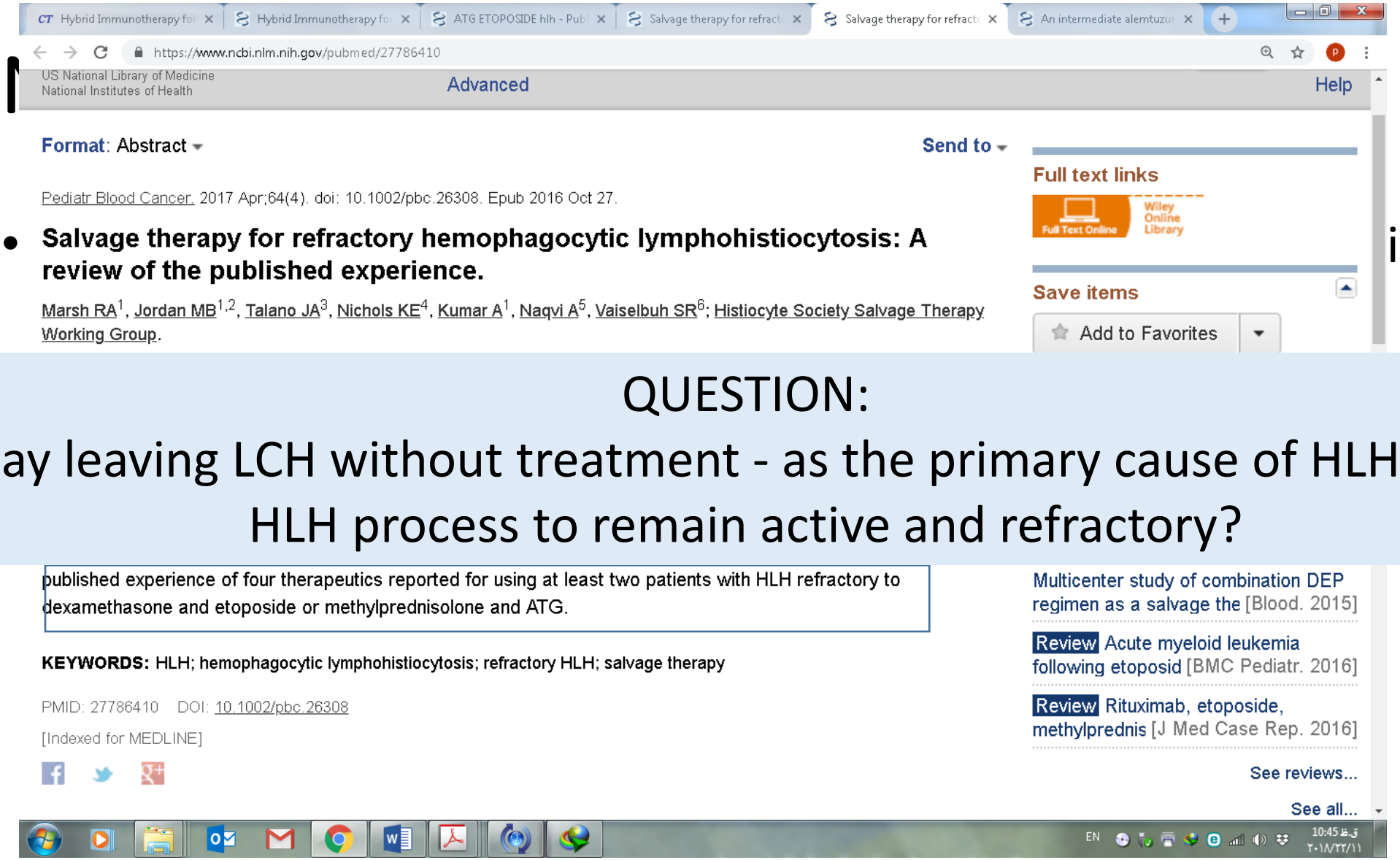


Figure 6. Treatment strategy for HLH. An algorithm for HLH treatment strategies in various clinical contexts.



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Pediatr Blood Cancer. 2017 Apr;64(4). doi: 10.1002/pbc.26308. Epub 2016 Oct 27.

Salvage therapy for refractory hemophagocytic lymphohistiocytosis: A review of the published experience.

Marsh RA[1], Jordan MB[1,2], Talano JA[3], Nichols KE[4], Kumar A[1], Naqvi A[5], Vaiselbuh SR[6]; Histiocyte Society Salvage Therapy Working Group.

published experience of four therapeutics reported for using at least two patients with HLH refractory to dexamethasone and etoposide or methylprednisolone and ATG.

KEYWORDS: HLH; hemophagocytic lymphohistiocytosis; refractory HLH; salvage therapy

PMID: 27786410 DOI: 10.1002/pbc.26308

[Indexed for MEDLINE]

Multicenter study of combination DEP regimen as a salvage the [Blood. 2015]

Review Acute myeloid leukemia following etoposid [BMC Pediatr. 2016]

Review Rituximab, etoposide, methylprednis [J Med Case Rep. 2016]

See reviews...

See all...

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QUESTION:

May leaving LCH without treatment - as the primary cause of HLH- lead HLH process to remain active and refractory?

Conclusion:

- Coincidence of LCH and HLH is rare but confusing in diagnosis and management
- Metabolic disorders should be kept in mind in any cases of HLH
- Liver dysfunction and sever hyperbilirubinemia is a great barrier for conducting the protocols
- A new integrating or hybrid regimen may be needed to manage refractory secondary HLH due to sever refractory LCH, without systemic toxicities