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A Hematopathology Case Study of Familial Hemophagocytic Lymphohistiocytosis (HLH)

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ABSTRACT

Hemophagocytic lymphohistiocytosis is a rare hematologic disorder caused by dysregulated immune activation and carries a high rate of mortality. It is categorized broadly into Primary (Familial) and secondary types. The recent classification of histiocytoses by Histiocytic society has placed Hemophagocytic lymphohistiocytosis in the "H" group. Greater awareness of Familial hemophagocytic lymphohistiocytosis is required among clinicians and pathologists for early diagnosis and a better survival. Here we report a case of Familial hemophagocytic lymphohistiocytosis correlating with clinical history, family history, bone marrow findings and genetic tests.

KEYWORDS: Hemophagocytic lymphohistiocytosis, Familial hemophagocytic lymphohistiocytosis

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INTRODUCTION

HLH is an aggressive life threatening syndrome of excessive immune activation, mostly affecting infants from birth to 18 months of age and also observed in children and adults of all ages. It occurs as familial and can be triggered by a variety of events that disrupt immune homeostasis. It is a reactive process, that results from prolonged and excessive activation of antigen presenting cells like macrophages, histiocytes and CD 8+ T cells. Hemophagocytosis is mediated through CD 163 heme scavenging receptor and is a hallmark of activated macrophages/histiocytes. Fever, splenomegaly, hepatomegaly lymphadenopathy,skin rashes, jaundice, cough, breathing difficulty are the clinical presentation of HLH. Due to life threatening nature of disease, early diagnosis and immunosuppressive therapy are extremely important.

CASE REPORT

A two month old female child, second born of a non consanguineous marriage, presented with complaints of fever and breathlessness for 1 week duration and later symptoms worsened and went to the stage of shock. There is family history of sibling death due to multiple organ failure syndrome or sepsis or hepatosplenomegaly. Examination revealed fever and hepatosplenomegaly. Blood investigation reports showed Anemia, Thrombocytopenia, elevated serum ferritin (Table 1). Direct coombs test was negative. She was treated with inotropes and other supportive management and child expired after two days. Bone marrow examination and liver biopsy examinations were done. The child was suspected to be affected with hemophagocytic lymphohistiocytosis and molecular test was done (table-2)

Table -1 Blood investigation results

Blood investigation	Result
Hemoglobin	**1.2 g/dL**
Total WBC count	**2800 / micro L**
Platelet count	**38000 / micro L**
PCV	3.6%
MCV	94.4 fL
MCH	30.7 pg
MCHC	33.3 g/dL
RDW - CV	17.8%
RDW - SD	58.3fL
Serum Ferritin	**More than 2000 ng/ mL**
Serum Triglycerides	**375mg /dL**

S. Calcium	9 mg/dL
S. Phosphate	4.7mg/dL
SGOT	206U/L
SGPT	186U/L

PERIPHERAL SMEAR REPORT

RBC – Normocytic normochromic anemia

WBC – Count markedly reduced and no atypical cells seen.

Differential count – Neutrophils – 3%, Lymphocytes – 97%

PLATELET – Count markedly reduced (less than 15000/ mm3)

BONE MARROW STUDY (Both bone marrow aspirate and bone marrow trephine biopsy)

Bone marrow study showed Trilineage hematopoiesis with megaloblastic maturation, shift to left in myeloid series and macrophage proliferation with evidence of hemophagocytosis.Impression – Correlating with clinical history and possibility of Hemophagocytic lymphohistiocytosis. (figure 1-6)

Figure 1, figure 2 and figure 3 - Bone marrow aspirate smear showing phagocytosis of marrow cells by macrophage

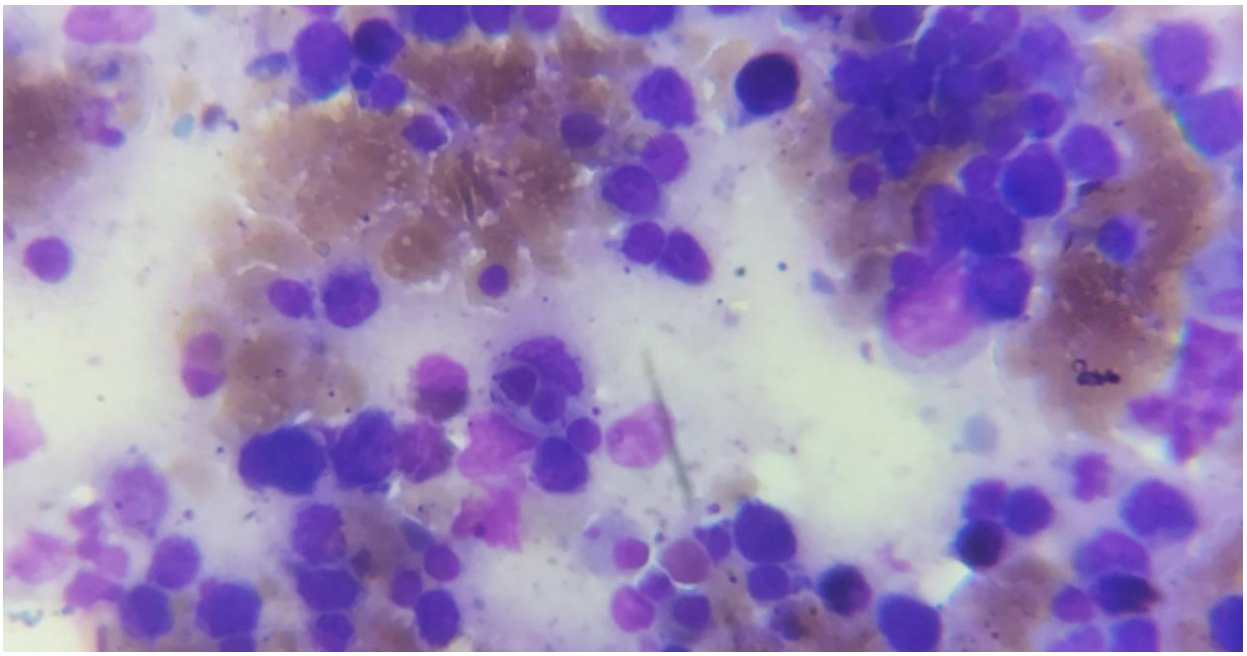

Figure -1

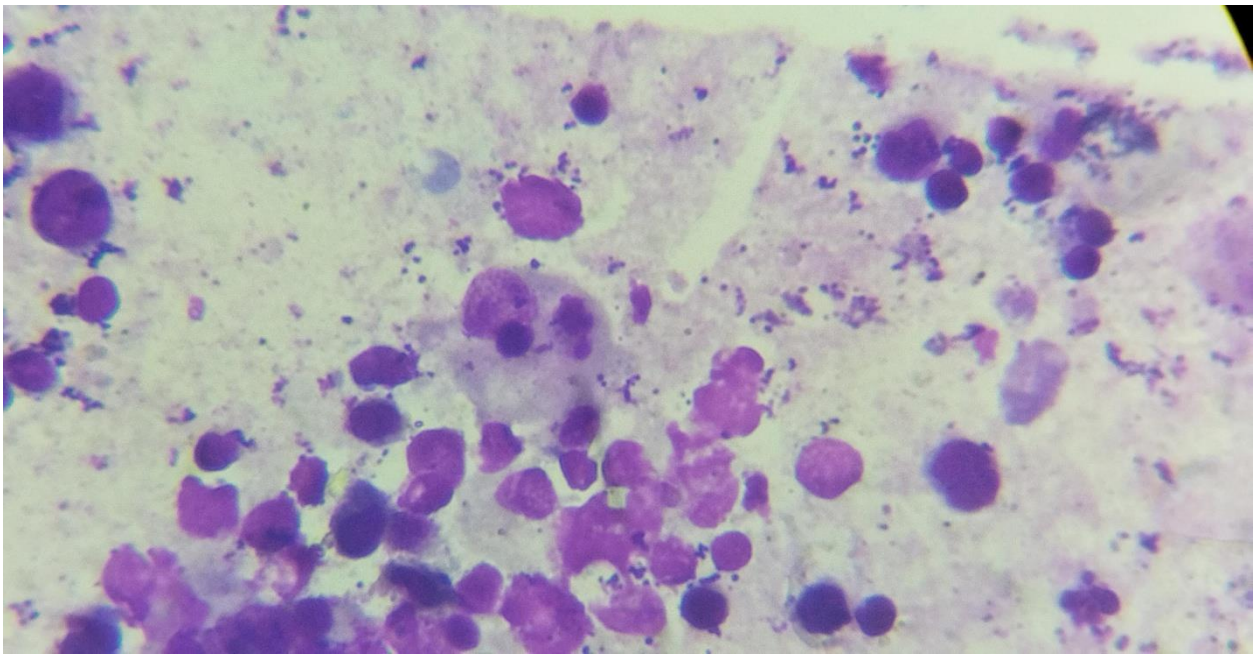

Figure 2 - Bone marrow aspirate smear

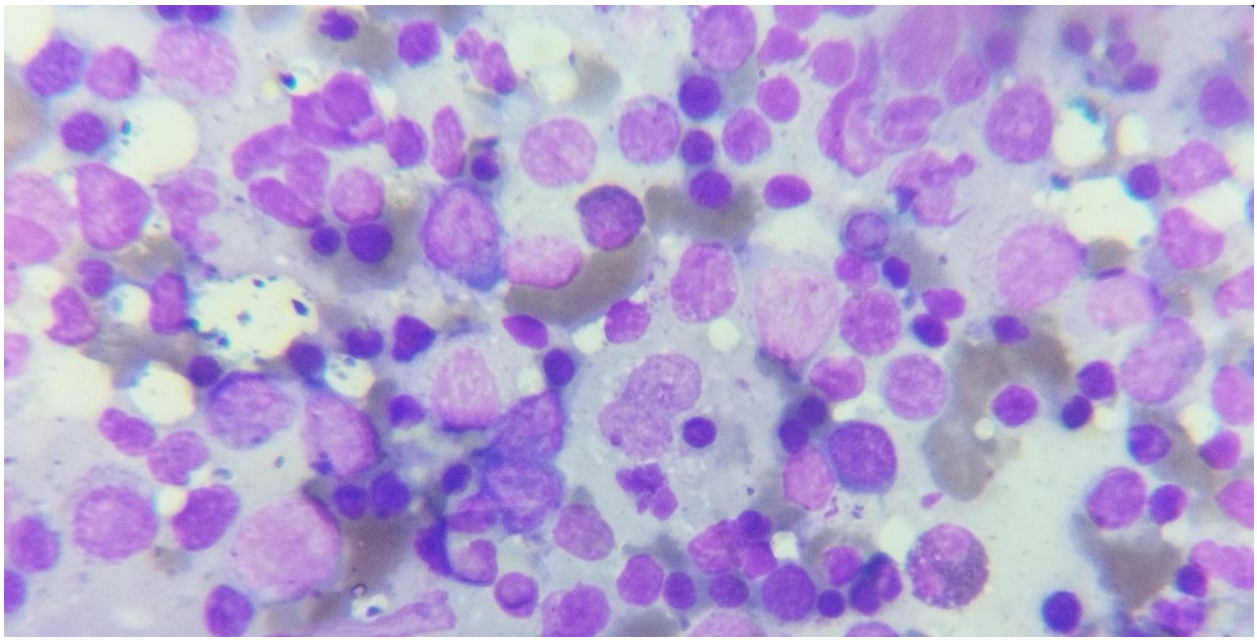

Figure 3 – bone marrow aspirate smear

4,5&6 – bone marrow biopsy showing hemophagocytosis (H &E, 400x)

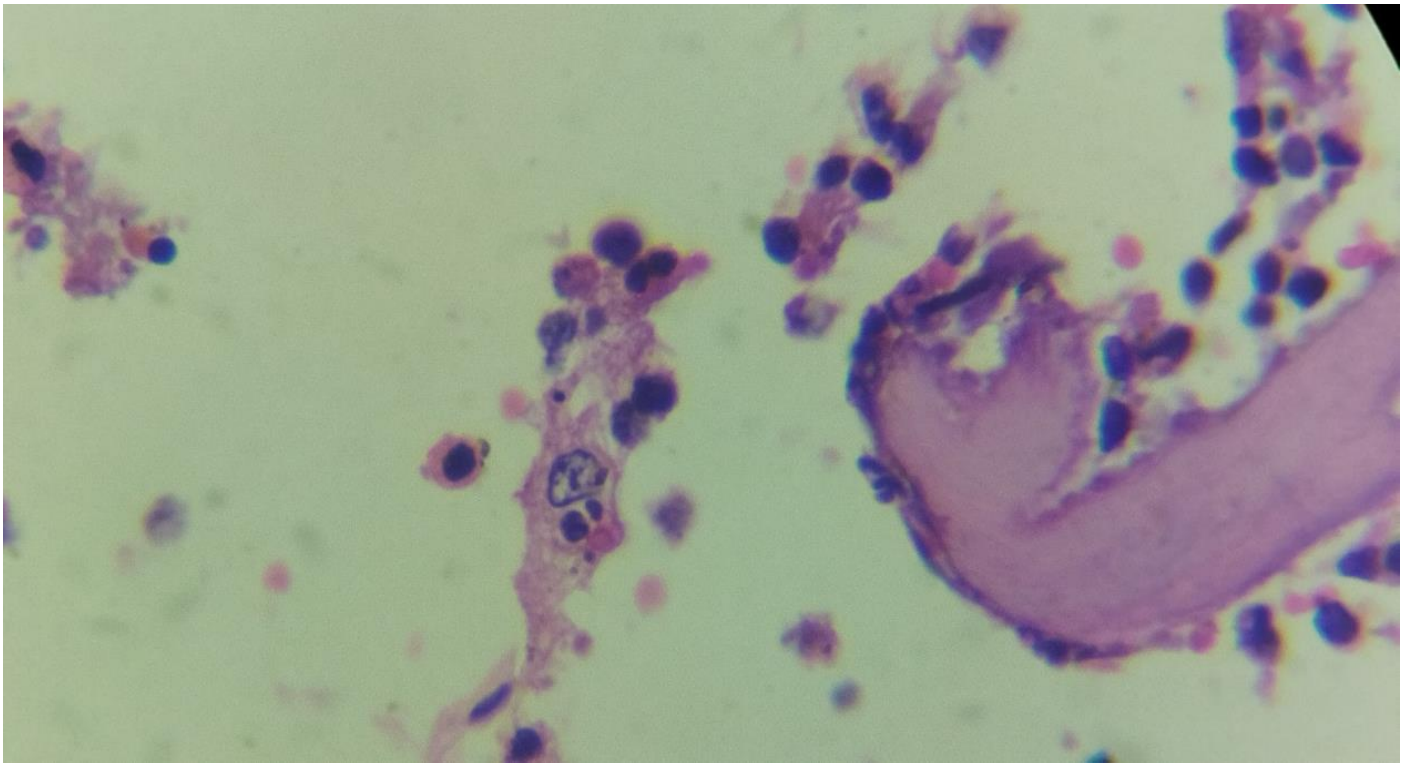

Figure - 4

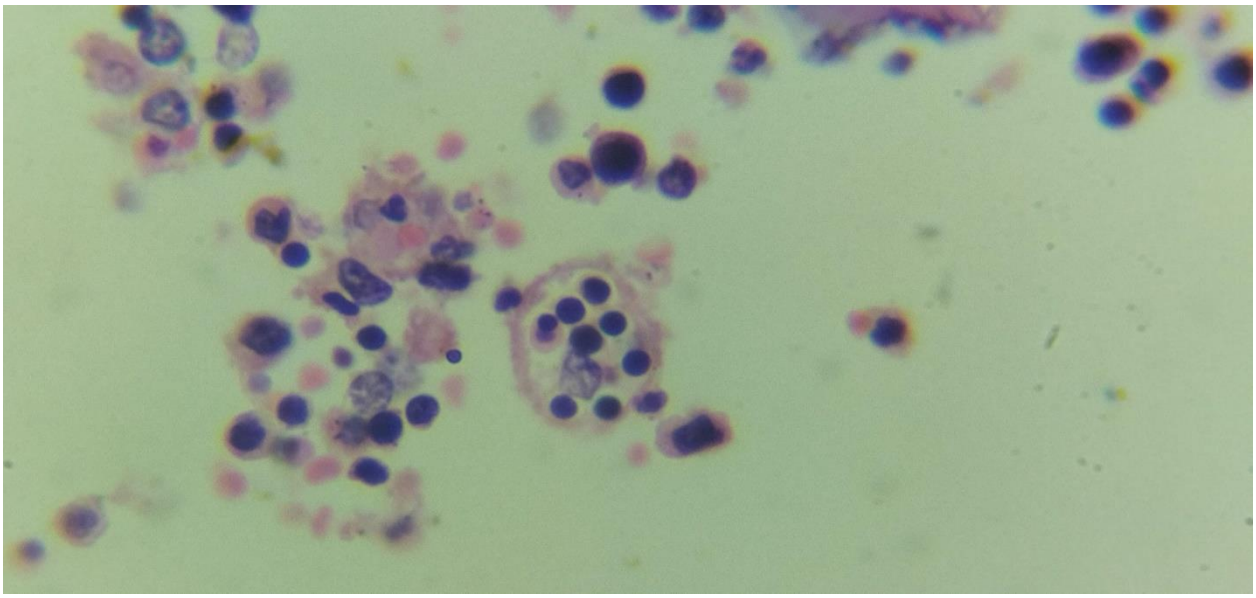

Figure - 5

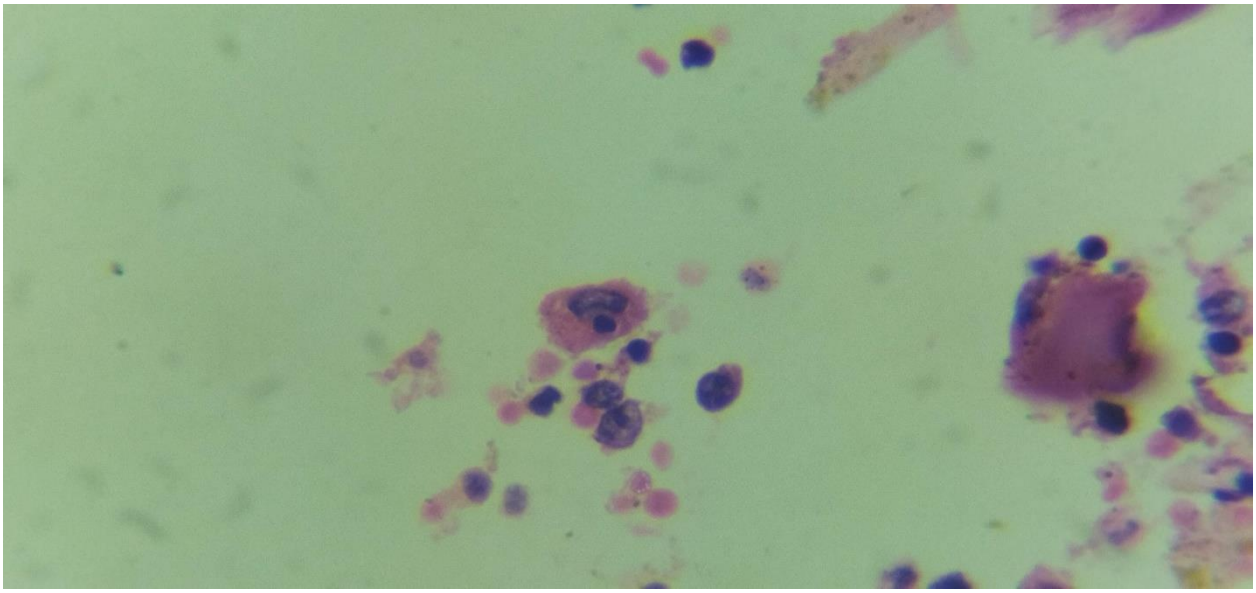

Figure - 6

LIVER BIOPSY REPORT

Liver biopsy showed sinusoidal expansion with increased number of histiocytes and lymphocytes and many histiocytes exhibits hemophagocytosis. Immunohistochemistry markers – CD 68 highlighted in histiocytes.Impression – correlating with clinical history, laboratory investigations and bone marrow findings consistent with Hemophagocytic lymphohistiocytosis.

DNA TEST REPORT

Table- 2

Gene (transcript)	Location	Variant	Zygosity	Disease	Inheritance	classification
STXBP2(+) (ENST00000044179.6)	Exon 4	c.194G>A(p.**Arg65Gln**)	Heterozygous	**FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS – 5 WITH OR WITHOUT MICROVILLOUS INCLUSION DISEASE**	Autosomal recessive	Likely pathogenic
	Exone 19	c.1730G>**A(p.Gly577Asp)**	Heterozygous			Likely pathogenic

DISCUSSION

Prompt diagnosis and treatment of HLH is critical for the patient survival. Criteria for diagnosis of HLH are molecular diagnosis consistent with HLH or 5 out of 8 criteria (Revised diagnostic guidelines for Hemophagocytic lymphohistiocytosis). Molecular criteria (table 2)are any of FHL mutations – FHL1, FHL2, FHL3, FHL4 or FHL5. In familial HLH mutations of PRF1, UNC13D, MUNC18-2, Rab27a, STX11,SH2D1A or BIRC4 gene are seen. Peripheral smear shows cytopenia and bone marrow shows normocellular to hypocellular with erythroid suppression of erythropoiesis and myelopoiesis. Megakaryocytes are normal or reduced. Macrophages are markedly increased in marrow and demonstrate phagocytosis of platelets, red cells, white cells, immature myeloid and erythroid cells. Fibrin degradation products are positive suggesting consumptive coagulopathy. Serum triglyceride levels are elevated. Hemophagocytosis are also seen in kupffer's cells in liver, littoral cells in spleen and in macrophages of lymph nodes. Perl's stain demonstrates marrow macrophages with phagocytosis. CD68 highlights macrophages. In cases of suspected genetic causes , genetic testing will be performed. Without treatment familial HLH is rapidly fatal with a median survival of about two months.

GENES KNOWN TO BE INVOLVED IN PRIMARY HLH

Table 3

HLH subtype	Gene / Protein	Location
FHL1	Unknown	9p21.3- locus 6
FHL2	PFR1	10q11-12
FHL3	UNC13D/Mun13-4	17q25
FHL4	STX11	6q24
FHL5	STXB2	19p13

REVISED DIAGNOSTIC GUIDELINES FOR HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

The diagnosis can be established if either no. A or 5 out of the 8 criteria B is fulfilled.

A. Molecular diagnosis consistent with HLH
B. Diagnostic criteria for HLH fulfilled
    1. Fever >38.5 °C
    2. Splenomegaly
    3. Cytopenias (affecting >2 of 3 lineages in peripheral blood)
       Hemoglobin <9g/dL(in infants with age less than 4 weeks – Hb <10 g/dL)
       Platelets - < $100x10^9$/L
       Neutrophils<$1x10^9$/L
    4. Hypertriglycerudemia / Hypofibrinogenemia- fasting teriglycerides >3 mmol/L, fibrinogen <1.5 g/L
    5. Hemophagocytosis in bone marrow or spleen or lymph nodes; no evidence of malignancy
    6. Low or absent natural killer cell activity
    7. Serum ferritin > 500 microgr/L
    8. Elevated soluble CD25 >2400U/mL

The poor prognosis of this syndrome suggests that patients should be treated with chemotherapy and immunotherapy .According to HLH 2004 protocols 8 weeks of therapy is given for secondary non genetic disease and for genetic disease stem cell transplantation is recommended.

CONCLUSION

Clinicians must possess a high index of suspicion for diagnosing Familial HLH amongst patients presenting with fever and cytopenia. Early diagnosis and treatment with chemotherapeutic agents or stem cell transplantation may reduce mortality of HLH. Improved utility of genetic testing should enable early diagnosis of Familial hemophagocytic lymphohistiocytosis in children for whom early hematopoietic stem cell therapy may be curative.

REFERENCES

I. Cornelia KnaakPeter Nyvlt[...]Gunnar Lachmann,Hemophagocytic lymphohistiocytosis in critically ill patients: Diagnostic reliability of HLH-2004 criteria and HScore,Critical Care (2020),10.1186/s13054-020-02941-3
II. Ryu YanagisawaYozo Nakazawa[...]Eiichi Ishii,Outcomes in children with hemophagocytic lymphohistiocytosis treated using HLH-2004 protocol in Japan,International Journal of Hematology (2019),10.1007/s12185-018-02572-z
III. Sandra AmmannKai Lehmberg[...]Stephan Ehl,Primary and secondary hemophagocytic lymphohistiocytosis have different patterns of T-cell activation, differentiation and repertoire,European Journal of Immunology (2017),10.1002/eji.201646686
IV. G. Naheed UsmaniBruce A. WodaPeter E. Newburger,Advances in understanding the pathogenesis of HLH,British Journal of Haematology (2013),10.1111/bjh.12293
V. Manisha MadkaikarSnehal ShabrishMukesh Desai,Current Updates on Classification, Diagnosis and Treatment of Hemophagocytic Lymphohistiocytosis (HLH),Indian Journal of Pediatrics (2016),10.1007/s12098-016-2037-y
VI. A. M.V.R. NarendraG. Varun Kumar[...]V. R. Srinivasan,Hemophagocytic lymphohistiocytosis,Indian Journal of Hematology and Blood Transfusion (2014),10.1007/s12288-012-0210-7

VII. Nobuhiro SuzukiAkira Morimoto[...]Eiichi Ishii,Characteristics of Hemophagocytic Lymphohistiocytosis in Neonates: A Nationwide Survey in Japan,Journal of Pediatrics (2009),10.1016/j.jpeds.2009.02.050