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Editorial

Inundate and Deluge-Hemophagocytic Lymphohistiocytosis

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Editorial

Hemophagocytic lymphohistiocytosis is a pathological syndrome constituted of defective Natural Killer (NK) cell or T cell function engendering unchecked secretions of cytokines and end organ damage on account of accompanying immune activation.

Hemophagocytic lymphohistiocytosis is categorized into congenital, genetic or primary and acquired or secondary subtypes. Immune activation with consequent hyper-cytokinemia induces histiocytic infiltration within reticuloendothelial organs along with hemophagocytosis of erythrocytes, leukocytes, platelets and precursor cells. Untreated primary and secondary hemophagocytic lymphohistiocytosis is invariably associated with disease associated mortality. However, adoption of contemporary therapeutic protocols document 5 year survival rates of ~ 54%. Familial or primary hemophagocytic lymphohistiocytosis is a progressive, autosomal recessive condition characteristically occurring within young age. The disorder exemplifies decimated NK cell function and frequently detected mutations within perforin gene.

Contingent to concordant genetic modifications, the autosomal recessive familial or primary hemophagocytic lymphohistiocytosis demonstrates cogent subtypes denominated as FHL1 to FHL5. Besides, familial hemophagocytic lymphohistiocytosis may be associated with primary immunodeficiency syndromes as Chédiak-Higashi syndrome, Griscelli syndrome type 2, Hermansky-Pudlak syndrome type 2 or X-linked lymphoproliferative disorder subtype 1 and subtype 2 [1,2].

Familial hemophagocytic lymphohistiocytosis predominantly incriminates young children whereas acquired hemophagocytic lymphohistiocytosis is commonly encountered within adolescents or adults. A specific racial or gender predilection is absent.

Secondary or acquired hemophagocytic lymphohistiocytosis arises in response to immune triggers comprised of infection, malignant conditions, rheumatologic disorders or inflammatory disorders and is preponderantly denominated as Macrophage Activation Syndrome (MAS) [1,2]. Secondary or acquired hemophagocytic lymphohistiocytosis is frequently associated with immunodeficiency, normal or decimated quantifiable NK cells and normal manifestation of perforin. The condition may be induced by exposure to infectious agents, malignant neoplasms, graft versus host disease or exceptionally with HELLP syndrome constituted of haemolysis, elevated liver enzymes and decreased platelet count.

Hemphagocytic lymphohistiocytosis commonly incriminates reticuloendothelial organs as the bone marrow, spleen, hepatic parenchyma and lymph nodes. Infrequently, sites such as cutaneous surfaces, subcutaneous tissue, pulmonary parenchyma, meninges or cerebrospinal fluid may be implicated [1,2].

Hemophagocytic lymphohistiocytosis is posited to arise due to functional failure of NK cells which induce apoptosis of target cell, eradicate the antigenic stimulus and terminate precise inflammatory response. Enhanced T helper cell 1(Th1) response engenders elevated levels of Tumour Necrosis Factor alpha (TNF-α) and Tumour Necrosis Factor gamma (TNF-γ) with consequent emergence of pancytopenia. Upregulation of serum ferritin appears secondary to elevated levels of heme-oxygenase. Hepatosplenomegaly may ensue on account of organ infiltration with activated lymphocytes and histiocytes. Besides, pyrexia may be induced by secretion of Interleukin 1 (IL1) and Interleukin6 (IL6) [1,2].

Contingent to specific genetic alterations, familial hemophagocytic lymphohistiocytosis is subdivided into cogent subtypes as ~FHL1 wherein genetic malformation is currently unidentified although documented to be situated upon chromosome 9q21_3-22. ~FHL2 wherein an estimated 50% instances demonstrate genetic malformations within PRF1 gene. ~FHL3 wherein roughly 50% instances enunciate chromosomal alterations within UNC13D gene. ~FHL4 wherein around 50% instances depict genomic malformation within STX11 gene. ~FHL5 wherein nearly 50% instances exhibit genomic malformation within STXBP2 gene [1,2]. Secondary or acquired hemophagocytic lymphohistiocytosis may exemplify missense or splice-site modifications confined to PRF1, MUNC13-4 and STXBP2 genes. Hemophagocytic lymphohistiocytosis is posited to arise due to genetic or acquired impaired cytotoxic function of T lymphocytes and NK cells. The inherited, autosomal recessive, familial hemophagocytic lymphohistiocytosis appears associated with genetic mutations confined to perforin and diverse genes [1,2]. Secondary hemophagocytic lymphohistiocytosis may induce familial hemophagocytic lymphohistiocytosis or may trigger diverse clinical symptoms as ~infection predominantly induced by viruses as Epstein Barr virus or cytomegalovirus ~malignant neoplasms preponderantly as NK / T cell neoplasms comprised of extra-nodal NK / T cell lymphoma, nasal subtype or cutaneous gamma / delta T cell lymphoma ~rheumatologic or autoimmune diseases ~immunosuppression ~exceptionally discerned with gestation or HELLP syndrome [1,2]. Incriminated paediatric subjects characteristically manifest a genetic defect indicative of familial hemophagocytic lymphohistiocytosis which necessitates appropriate discernment or exclusion. Adult subjects demonstrating hemophagocytic lymphohistiocytosis require investigation and exclusion of accompanying malignant disorder [3,4].

Diagnostic criterion of hemophagocytic lymphohistiocytosis as configured in 2004 (HLH 2004) and updated in 2007 necessitates molecular evaluation of familial hemophagocytic lymphohistiocytosis or manifestation of minimally five of eight diagnostic criteria denominated as ~fever ~splenomegaly ~cytopenias with minimal incrimination of 2 lineages confined to peripheral blood ~haemoglobin < 9.0 gram/decilitre ~platelets < 100 x 10^9/Litre ~neutrophils < 1.0 x 10^9/Litre ~hypertriglyceridemia or hypofibrinogenemia with •fasting triglycerides ≥ 265 milligram/decilitre •fibrinogen ≤ 1.5 grams/Litre ~documented hemophagocytosis within bone marrow, spleen or incriminated lymph nodes ~minimal or absent NK cell activity ~serum ferritin ≥ 500 μgram/Litre ~soluble CD25 ≥ 2,400 Units/millilitre. Besides, instances of familial hemophagocytic lymphohistiocytosis appear to be devoid of malignant metamorphosis. Additionally, absence of hemophagocytosis upon microscopic assessment appears non concurrent to and may not exclude hemophagocytic lymphohistiocytosis [3,4].

Hemophagocytic lymphohistiocytosis demonstrates an abrupt onset of Systemic Inflammatory Response Syndrome (SIRS) comprised of clinical symptoms as unremitting pyrexia, malaise, rash, hyperbilirubinemia, myalgia, hepatosplenomegaly, generalized lymph node enlargement and accompanying mono-cytopenia, bi-cytopenia or pancytopenia. As hemophagocytic lymphohistiocytosis delineates cogent clinical symptoms as pyrexia, malaise, cutaneous rash, myalgia, hepatosplenomegaly, hyperbilirubinemia, generalized lymph node enlargement or neurologic symptoms, mono-lineage or bi-lineage cytopenias and pancytopenia may ensue. Hemophagocytosis emerges as a cyclical phenomenon wherein demonstration of hemophagocytosis remains superfluous in order to establish hemophagocytic lymphohistiocytosis. An estimated 60% subjects exemplifying sepsis are accompanied by non-specific hemophagocytosis [3,4]. Upon microscopy, bone marrow aspirate and obtained smears appear as an optimal site to visualize and evaluate hemophagocytic histiocytes. Hepatic sinusoids can exemplify histiocytes accompanied with erythrophagocytosis. Splenic white pulp appears atrophic and enunciates extensive infiltration of histiocytes incorporated with erythrophagocytosis. Lymph nodes demonstrate specific alterations contingent to disease stage where ~preliminary disease is associated with an intense immunoblastic response ~delayed stage is accompanied by lymphoid depletion along with massive infiltration of nodal sinusoids with benign histiocytes and foci of erythrophagocytosis [3,4].

Keywords: Kangaroo Mother Care; Neonates; Growth; Outcome; Cameroon

Abbreviations

JIA: Juvenile Idiopathic Arthritis; IL: Interleukin; CAR T: Chimeric Antigen Receptor T-cell; BiTE: Bispecific T-cell Engager

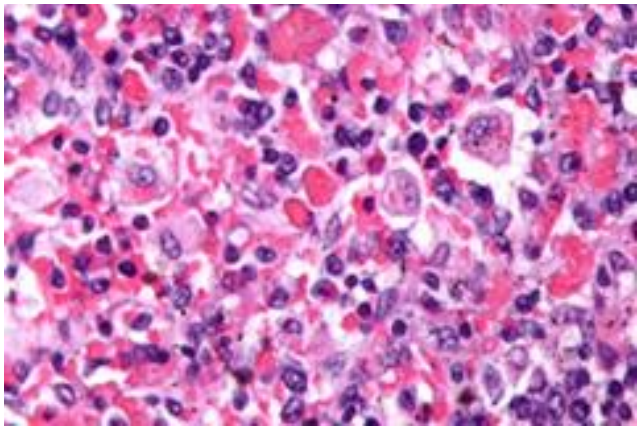

Figure 1: Hemophagocytic lymphohistiocytosis demonstrating mononuclear and multinucleated histiocytes exhibiting focal red cell ingestion.

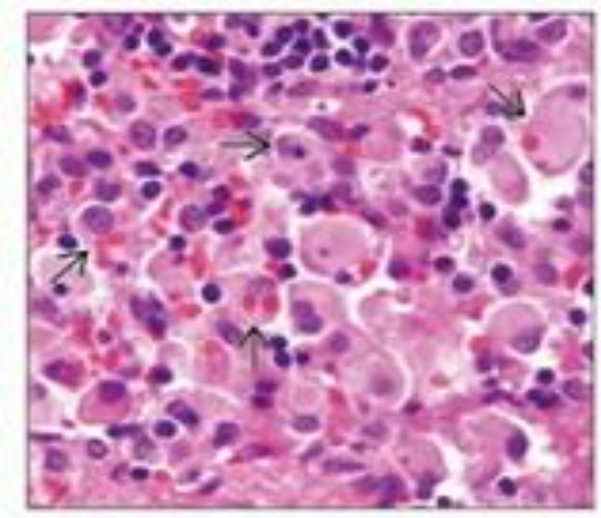

Figure 2: Hemophagocytic lymphohistiocytosis exemplifying numerous mononuclear histiocytes with multiple ingested red cells.

Hemophagocytic Lymphohistiocytosis	General Syndrome
Primary HLH	HLH driven by genetic inborn errors of immunity
Secondary HLH	HLH driven by environmental /acquired mechanisms as infection, malignancy, rheumatic disease
Familial HLH	HLH driven by genetic defects in PRF1, UNC13D, STX11, STXBP2 with profoundly impaired NK cell and CD8+ T cell cytotoxic function
Macrophage activation syndrome	HLH due to rheumatologic disease as systemic JIA or auto-inflammatory mutation, high IL8
Cytokine release syndrome	HLH due to CAR T cell or BiTE therapy

Table 1: Categories of Hemophagocytic Lymphohistiocytosis (HLH) [3,4].

Histiocytes configuring familial hemophagocytic lymphohistiocytosis demonstrate a characteristic phenotype with immune reactive CD11b, CD21, CD25, CD30, CD35, CD36 and S100 protein. In contrast, histiocytes may delineate absent or diminished intracellular staining for perforin, a feature which appears indicative of genetic mutations within protein encoding gene [5,6]. Upon flow cytometry, decimated expression of CD107a (LAMP1), confined to surface of cytotoxic NK / T-cells is observed. Additionally, few instances may depict decimated enunciation of CD5 and CD7, especially within circulating and bone marrow CD8+ T-cells. Hemophagocytic lymphohistiocytosis requires segregation from conditions such as sepsis, Myeloproliferative Neoplasm (MPN), myelodysplastic syndrome (MDS), Rosai-Dorfman disease, Langerhans cell histiocytosis, Leishmaniasis or histoplasmosis [5,6]. Biochemical evaluation exemplifies specific alterations as hypofibrinogenemia, hypertriglyceridemia, significantly elevated serum ferritin, elevated hepatic transaminases, elevated Lactate Dehydrogenase (LDH), elevated serum soluble CD25 or Interleukin 2 (IL2) receptor. Chromium 51 (51Cr) release assay depicts decimated or absent NK cell activity [5,6]. Upon plain radiography, features such as hepatosplenomegaly, generalized lymph node enlargement, pleural effusion accompanied by alveolar interstitial opacities, thickened gallbladder wall, hyperechoic renal parenchyma, ascites, nonspecific periventricular white matter abnormalities, decimated brain volume and enlargement of extra-axial fluid spaces may be discerned [5,6]. Secondary hemophagocytic lymphohistiocytosis mandates prompt therapeutic intervention of concurrent disease. As per HLH 2004 protocol, induction therapy with cyclosporine, corticosteroids and etoposide is necessitated for eight weeks. Adoption of cyclosporine inhibits activation of T-cells, corticosteroids suppress hyper-cytokinemia and etoposide obstructs cellular proliferation. Aforesaid therapeutic manoeuver exhibits a 5 year survival rate of ~ 54%. Additionally, stem cell transplantation can be employed for treating familial hemophagocytic lymphohistiocytosis [5,6]. Untreated hemophagocytic lymphohistiocytosis invariably demonstrates disease associated mortality. An estimated 80% instances of familial hemophagocytic lymphohistiocytosis may reoccur within infant phase. Delayed disease discernment, incrimination of multiple organs, hemophagocytic lymphohistiocytosis associated with Epstein Barr Virus (EBV) infection, accompanied by HELLP syndrome or occurring within third trimester of gestation with concurrent Epstein Barr viremia is associated with adverse prognostic outcomes [5,6].

Conflict of Interest

The author has no conflict of interest to declare.

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