

Hemophagocytic Lymphohistiocytosis (HLH) – The Great Mimicker: Case Report

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Abstract Rationale and objective: HLH is the aggressive proliferation of activated macrophages and histiocytes phagocytosing blood cells. [1] This report demonstrates the clinical and laboratory approach and therapeutic management to a patient suspected of HLH. Case: This is a case of an 18-year old female with nine-month history of on and off fever. She was previously admitted and diagnosed with erythema nodosum probably secondary to pulmonary tuberculosis, congenital heart disease, atrial septal defect. She was discharged but there was still note of intermittent fever, tachycardia, progressive edema on upper and lower extremities, and increasing abdominal girth, hence readmission. Initial laboratory work up showed anisopoikilocytosis with a predominance of microcytic, hypochromic red blood cells, schistocytes and elliptocytes were seen with few burr cells and nucleated RBCs, normal WBC count, and with toxic granulation. Bone marrow aspiration was done revealing erythrophagocytosis and hemophagocytic lymphohistiocytosis. Patient was started with cotrimoxazole and fluconazole, induction therapy with corticosteroid-dexamethasone, chemotherapy with etoposide and cyclosporine, and blood transfusion. Clinical signs, symptoms, and laboratory parameters improved. Discussion and Summary: HLH does not have specific manifestations as it is capable of mimicking other diseases which contributes to its high mortality rate. With this, a high index of suspicion and a thorough clinical, immunological, and genetic workups are required. As in our patient, HLH should be considered when there is persistent high fever and cytopenias. With prompt recognition and appropriate treatment, prognosis may be improved.

Keywords: hemophagocytic lymphohistiocytosis, acquired, familial, perforin

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1. Introduction

1.1. Definition and Pathophysiology

Historically, HLH was first described in 1952 by Farquhar and Claireaux who termed the disease familial hemophagocytic reticulosis. They described HLH as progressive erythropenia with or without decreasing levels of granulocytes and thrombocytes with a reactive bone marrow. Organomegaly was noted in the liver, spleen, and lymph nodes with subsequent significant degree of intoxication and relapsing fever. [2]

Moreover, HLH is also thought to having an uncontrolled immune activation characterized by proliferation of morphologically benign lymphocytes and macrophages

that secrete high amounts of inflammatory cytokines. [3] In more recent studies, it was reported that the pivotal cause of HLH is the identification of the cytotoxic pathway mutations due to the impairment in the function of cytotoxic T lymphocytes (CTLs) and NK cells. [4] Impairment in the immunologic functions of CTLs and NK cells was thought to be the cause of hypercytokinemia. [5]

1.2. Epidemiology

HLH is thought to affect patients in same degree regardless of the age, sex, and race. [6] Incidence is reported to be 1.2 cases per million-persons per year less than the age of 15 years in Sweden, [7] 1 in 800,000 in Japan [8], and 7.5 in 10,000 in Turkey. [9] To date, there is still no established global incidence of HLH due to the current improvements in terms of diagnosing the disease.

1.3. Classification

HLH can be classified into two different forms: primary or familial and secondary or acquired. The primary or familial form is an autosomal recessive disorder common in children and is more prevalent with parental consanguinity. [9,10,11] Meanwhile, the secondary or acquired form is more common in adults and thought to occur after strong immunologic activation, systemic infection, immunodeficiency, or underlying malignancy. [10,11] Moreover, acquired or secondary HLH can further be subcategorized: infection-associated HLH, malignancy-associated HLH, and autoimmune disease-associated HLH. [12,13] It was noted that regardless of the form of HLH, patients manifest with fevers, hepatosplenomegaly, and cytopenias. [11]

1.4. Diagnosis

HLH oftentimes presents with nonspecific signs and symptoms contributing to it being underrecognized as well as the lack of gold standard confirmatory test. [1,14,15] In 2004, the Histiocyte Society released a diagnostic criteria for which was subsequently challenged due to the lack of specificity among critically ill patients. [16] This criteria include the following parameters: fever of more than seven days; palpable splenomegaly; cytopenias involving at least two lineages of peripheral blood; marked increased in ferritin ($>10,000$ $\mu\text{g/L}$); hypertriglyceridemia with or without concurrent hypofibrinogenemia; hemophagocytosis in the bone marrow, spleen, or lymph nodes; low or absent NK-cell activity determined by the 51-Cr release assay; and high levels of sCD25. [6,17] To establish the diagnosis of HLH, five out of the eight parameters should be met except for those with confirmed genetic mutations who do not need to meet the minimum number of abnormal parameters. [17] Unfortunately, soluble CD25 (sCD25) and 51-Cr release are not readily available to most of the institutions discounting for early diagnosis and therapy. [18] Recently, a modification to the 2004 diagnostic criteria was proposed because it does not include the macrophage activation syndrome (MAS). [19] With the proposed revision of the diagnostic criteria, marked increase in CRP with moderate cytopenias, reduced erythropoiesis, increased granulopoiesis, and a high level of interleukin 1-beta is thought to be more suggestive of MAS. [20]

Histopathologic diagnosis of HLH include aggregation of lymphocytes and mature macrophages exhibiting hemophagocytosis which can be seen in the bone marrow, spleen lymph nodes, liver, skin, lungs, meninges, and CSF. [21,22,23,24] However, it was later on noted that histopathologic or biopsy results were unnecessary for confirming the disease as biopsy specimens initially present with negative results. [15,23]

Genetic aberrations in HLH primarily include mutation in perforin gene 1 (*PRF1*) [25] which is thought to be located at chromosome 9q21. [26] It is known that perforin plays an important role by creating pores in the target cell leading to its osmotic lysis and responsible for the uptake of granzymes that will catalyze protein degradation. [27] This mutation also involves other genes

such as *UNC13D* (FHL3) [28], *STX11* (FHL4) [29], and *STXBP2* or *UNC18B* (FHL5). [30]

Early diagnosis of HLH remains a challenge up to present which puts emphasis on having a high level of suspicion regarding early detection of HLH and equally important to institute early therapy [15].

In our case, the patient fulfilled six out of the eight clinical criteria: fever, splenomegaly, pancytopenia, hypertriglyceridemia, increased serum ferritin, hypofibrinogenemia, and histologic finding of hemophagocytic cells in the bone marrow. All of these confirm the diagnosis of hemophagocytic lymphohistiocytosis in our patient.

2. Case History

We presented here a case of an 18-year old female who came in for consult due to nine-month history of on and off fever.

Nine months prior to admission, the patient had intermittent febrile episodes (T_{max} 39), self-medicated with paracetamol which afforded relief. Associated symptoms include bilateral knee joint pains and body malaise. There was no note of other symptoms such as cough, colds, abdominal pain, dyspnea, dysuria, diarrhea. Patient also self-medicated with liniments and oils which afforded relief. The condition was also associated with multiple nodular, non-erythematous, non-pruritic rashes on both lower extremities. The mother considered the condition as systemic viral illness, hence no consult was done.

Eight months prior to consult, fever persisted but no cough and colds. Consult was with their family physician wherein workups were done revealing unremarkable urinalysis; leukopenia (2.46), RBC (4.08) and hemoglobin (100) on CBC. The patient was then referred to a haematologist in a tertiary hospital, CBC with peripheral blood smear was done with an impression of iron deficiency anemia. The patient was given unrecalled medications. Fever still persisted prompting for admission. Serial workups were done: CBC, PC revealed bicytopenia (WBC 2.37 and RBC 4.08); BUN (3.57 [normal]); CREA (61 [normal]); TSH (1.381 [normal]); CRP (52 [high]); unremarkable serum electrolytes; total protein-globulin (34 [high]); ALB (38 [normal]); ANA (1:1); anti-dsDNA (normal); ESR (38 [high]); ASO (624 [high]); IgA (3.02 [normal]); ALT (81 [high]); AST (88 [high]); and 2D-echo (68%). Lastly, chest X-ray revealed pulmonary tuberculosis on the right lobe and with negative sputum for AFB for 2 collections.

The patient was discharged after four days with final diagnosis of erythema nodosum probably secondary to pulmonary tuberculosis; congenital heart disease, atrial septal defect sp secundum s/p atrial septal defect, patch (17 April 2017). Thirteen days after, the patient was referred to a cardiologist for follow up. On examination, there was a note of edema and multiple nodules on both upper and lower extremities, hence referred to a rheumatologist. The patient was started with anti-tuberculosis (FIXCOM) medications for two weeks and continued methylprednisolone.

Seven months prior to readmission, still with intermittent fever, the patient was admitted in another tertiary hospital due to the progression of edema on both upper and lower extremities and with tachycardia, there was no associated dyspnea, night sweats, cough, colds, dysuria, sore throat, anorexia, weight loss, and abdominal pain. Repeat chest X-ray then revealed normal chest findings. Repeat CBC still revealed bicytopenia. The patient was sent home after six days with a diagnosis of erythema nodosum; primary Koch's infection; s/p and repair, with home medications of digoxin, levofloxacin, ethambutol, and methylprednisolone. Skin/Nodule biopsy revealed skin and subcutaneous tissue with fibrosis and acute and chronic inflammation around sweat gland and fat; negative for bacteria, fungal elements, and AFB on special stains; and negative for granuloma or malignancy.

Six months prior to readmission, still with intermittent fever with associated increasing abdominal girth and increasing ALT (210) and AST (412) levels, there was no associated cough, colds, dysuria, and abdominal pain. consult done to a private physician, wherein abdominal ultrasound was done and revealed unremarkable results. The patient was diagnosed with primary Koch's infection; erythema nodosum. Methylprednisolone and anti-Koch's medications were continued. Whole abdominal ultrasound was done, revealing normal sonographic study of the liver, gallbladder, pancreas, spleen, kidneys and urinary bladder, non-dilated ureters, negative adnexae, non-dilated abdominal aorta, and negative for ascites and free pleural effusion.

On interval history, the patient still had intermittent febrile episodes, with moon face and puffy eyelids. Methylprednisolone was shifted to prednisolone tablet and was tapered. Anti-Koch's medications were continued.

Two weeks prior to readmission, the patient still with fever Tmax at 42C, with associated body weakness, anorexia, pallor, with increasing abdominal girth, palpable mass on the right upper quadrant of the abdomen on deep palpation, no changes in bowel habits noted, no dysuria, and no abdominal pain. Follow up with rheumatologist was done, with consideration of systemic lupus erythematosus. This time, ANA panel was done which revealed equivocal findings. Whole abdominal CT scan was also done which revealed *enlarged liver (18cm) but with normal parenchymal attenuation. Its border is smooth and sharp with no focal lesions. The spleen is enlarged measuring cc10.88 x w10.52 x ap5.28 (hepatosplenomegaly) and contracted gallbladder.* There were subcutaneous edema and non-specific calcifications on bilateral breast. The rest of the pancreas, adrenal glands, stomach, bowel, bilateral kidneys, ureters, and urinary bladder were unremarkable.

With a negative ANA panel, SLE is unlikely, hence given clearance by the rheumatologist. The family was advised to rule out malignancy, hence referred to a haematologist-oncologist for further evaluation and management, hence admission.

3. Course in the Ward

Upon admission at our institution, the patient still presented with fever, which satisfied the patient under

fever-of-unknown-origin. She came in with all workups that were done following the algorithm of FUO. Upon admission, the following workups were repeated: CBC PC, urinalysis, PT, PTT, peripheral blood smear, serum electrolytes, AST, ALT, LDH, tumor markers (AFP, p53, and Her2Neu) and pregnancy test. Anti-Koch medications were continued.

On the first hospital stay, the patient was awake, coherent, and not in respiratory distress. The patient was requested for ultrasound of the breast and abdomen including the pelvis area. Other laboratory tests such as PT, PTT, total bilirubin, b1, alkaline phosphate, CBC with platelet count, ammonia, BUN, creatinine, TPAG, and peripheral blood smear were done. Vitamin K 1amp per IV for 3 days was started and plain cranial CT scan was also done. The patient was referred to Ophthalmology for fundoscopy.

PERIPHERAL BLOOD SMEAR: Anisopoikilocytosis with a predominance of microcytic, hypochromic red blood cells. Distinct amounts of schistocytes and elliptocytes and few amounts of burr cells and nucleated red blood cell count. White Blood Cell count is below normal with the predominance of segmenters with few stab cells. Positive for toxic granulation. No blast is seen. Platelet is adequate.

CRANIAL CT SCAN WITH CONTRAST: Normal results.

On the 2nd hospital day, FFP 1 unit was transfused. Additional laboratory workups were requested such as ferritin, lipid profile, hepatitis B profile, fibrinogen, ceruloplasmin, and copper determination. The patient was seen and evaluated by haematologist-oncologist with the consideration of lymphoma versus autoimmune disease to rule out HLH (lymphohistiocytosis).

On the 3rd to 9th hospital day, the patient was conscious, coherent, but still with on and off episodes of fever. The rest of the family members were advised to undergo Chest X-ray to rule out pulmonary tuberculosis in the family. This time, bone marrow aspiration was done revealing erythrophagocytosis, hemophagocytic lymphohistiocytosis, therefore diagnosis was revised to, hemophagocytic lymphohistiocytosis.

The patient was started with cotrimoxazole and fluconazole. Induction therapy was also started with corticosteroid-dexamethasone 13.6mg, and chemotherapy with etoposide 250mg (100mg/5ml) and cyclosporine (6mg/kg) 100mg/capsule with continuous correction of anemia and thrombocytopenia with blood transfusion of PRBC and cryoprecipitate.

Our patient completed the following Protocol: Etoposide 250mg (100/ml 12.5 Incorporate 250ml D5.03 NaCl for 2 cycles) twice a week (Monday and Tuesday). The patient was able to complete six cycles of etoposide. Currently, patient continued her secondary level of schooling with regular follow-ups with her hematologist-oncologist for possible recurrence and surveillance.

4. Conclusion

HLH is a rare, but likely underdiagnosed progressive disease with multi-organ involvement. It is a dreadful disease mimic. The mortality is uniformly high and timely

diagnosis is imperative. Since it has no specific signs and symptoms, initial symptoms of HLH may be non-specific and misleading. Therefore, a high index of suspicion through clinical, immunological, and genetic workup are required. Infections are common triggers in both genetic and acquired HLH.

HLH should be considered in a patient presenting with prolonged high fever, splenomegaly, and cytopenias. There have been recent advances in understanding the pathogenesis of genetic HLH, for which genetic tests are available and treatment protocols have shown to improve prognosis.

Prompt initiation of adequate treatment is the key to survival. However, despite important advances in therapy, the overall survival rates remain unsatisfactory. Early recognition and treatment of HLH are still highly associated with mortality in up to 60%. Though rare, the disease is usually considered when majority of the diagnostic criteria are seen in the patient, which may be late in the course after considering other differential diagnoses. It is, therefore, crucial to educate our fellow clinicians about the increasing prevalence of the disease and how it could start as a usual case of prolonged fever. Early diagnosis and management may improve prognosis. To the best of our knowledge, our patient was one of the survivors of this rare disease as most cases we have seen in other institutions in the Philippine-based journal reviews, most of the patients suspected and/or diagnosed with HLH succumb to death.

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References

- [1] Rosado F & A Kim. (2013). Hemophagocytic Lymphohistiocytosis: An Update on Diagnosis and Pathogenesis. *American Journal of Clinical Pathology*, 139(6): 713-727.
- [2] Farquhar JW & Claireaux AE. (1952). Familial haemophagocytic reticulosis. *Arch Dis Child*. 1952(27): 519-525.
- [3] Pearson C. (2015, April 14). A Case of EBV-Associated Hemophagocytic Lymphohistiocytosis [Scientific Abstract]. Abstracts from the 38th Annual Meeting of the Society of General Internal Medicine. *Journal of General Internal Medicine* 30, 45-551.
- [4] Janka G. Hemophagocytic lymphohistiocytosis: when the immune system runs amok. *Klin Padiatr*. 2009; 221: 278-285.
- [5] Grom AA. Natural killer cell dysfunction: a common pathway in systemic-onset juvenile rheumatoid arthritis, macrophage activation syndrome, and hemophagocytic lymphohistiocytosis? *Arthritis Rheum*. 2004; 50:689-698.
- [6] Janka GE. (2012). Familial and acquired hemophagocytic lymphohistiocytosis. *Annu Rev Med*. 2012(63): 233-246.
- [7] Henter JI, Elinder G, Soder O et al. (1991) Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. *Acta Paediatr Scand*. 1991; 80:428-435.
- [8] Ishii E, Ohga S, Imashuku S, et al. (2007). Nationwide survey of hemophagocytic lymphohistiocytosis in Japan. *Int J Hematol*. 2007; 86: 58-65.
- [9] Gurgey A, Gogus S, Ozyurek E, et al. Primary hemophagocytic lymphohistiocytosis in Turkish children. *Pediatr Hematol Oncol*. 2003; 20: 367-371.
- [10] George M. (2014). Hemophagocytic lymphohistiocytosis- review of etiologies and management. *Journal of Blood Medicine* 2014;5 69-86.
- [11] Khaliq M & Go R (2015, April 14). Secondary Hemophagocytic Lymphohistiocytosis: Rare Etiology of Hepatic Failure and Refractory Bleeding in Adults [Scientific Abstract]. Abstracts from the 38th Annual Meeting of the Society of General Internal Medicine. *Journal of General Internal Medicine* 30, 45-551.
- [12] Parodi A, Davi S, Pringe AB, et al. Macrophage activation syndrome in juvenile systemic lupus erythematosus: a multinational multicenter study of thirty-eight patients. *Arthritis Rheum*. 2009; 60:3388-3399.
- [13] Deane S, Selmi C, Teuber SS, et al. Macrophage activation syndrome in autoimmune disease. *Int Arch Allergy Immunol*. 2010; 153:109-120.
- [14] Buyse S, Teixeira L, Galicier L, et al. Critical care management of patients with hemophagocytic lymphohistiocytosis. *Intensive Care Med*. 2010; 36: 1695-1702.
- [15] Alencherril J., Barnes M., and Hunter L. (2015, April 14) A Surreptitious Diagnosis: Hemophagocytic Lymphohistiocytosis [Scientific Abstract]. Abstracts from the 38th Annual Meeting of the Society of General Internal Medicine. *Journal of General Internal Medicine* 30, 45-551.
- [16] Castillo L, Carcillo J. Secondary hemophagocytic lymphohistiocytosis and severe sepsis/systemic inflammatory response syndrome/multiorgan dysfunction syndrome/macrophage activation syndrome share common intermediate phenotypes on a spectrum of inflammation. *Pediatr Crit Care Med*. 2009; 10:387-392.
- [17] Janka GE, Schneider EM. Modern management of children with haemophagocytic lymphohistiocytosis. *Br J Haematol*. 2004; 124:4-14.
- [18] Arico M, Janka G, Fischer A, et al. Hemophagocytic lymphohistiocytosis: report of 122 children from the International Registry. FHL Study Group of the Histiocyte Society. *Leukemia*. 1996; 10:197-203.
- [19] Trizzino A, zur Stadt U, Ueda I, et al. Genotype-phenotype study of familial haemophagocytic lymphohistiocytosis due to perforin mutations. *J Med Genet*. 2008; 45:15-21.
- [20] Ravelli A, Grom AA, Behrens EM, et al. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment. *Genes Immun*. 2012; 13:289-298.
- [21] Lai S, Merritt BY, Chen L, et al. Hemophagocytic lymphohistiocytosis associated with influenza A (H1N1) infection in a patient with chronic lymphocytic leukemia: an autopsy case report and review of the literature. *Ann Diagn Pathol*. 2012; 16:477-484.
- [22] Foucar K, Reichard K, Czuchlewski D. *Bone Marrow Pathology*. 3rd ed. Chicago, IL: American Society for Clinical Pathology; 2010.
- [23] Hsi ED. *Hematopathology: A Volume in Foundations in Diagnostic Pathology Series*. London, UK: Churchill Livingstone; 2007.
- [24] Aronson IK, Worobec SM. Cytophagic histiocytic panniculitis and hemophagocytic lymphohistiocytosis: an overview. *Dermatol Ther*. 2010; 23:389-402.
- [25] Goransdotter Ericson K, Fadeel B, Nilsson-Ardnor S, et al. Spectrum of perforin gene mutations in familial hemophagocytic lymphohistiocytosis. *Am J Hum Genet*. 2001; 68: 590-597.
- [26] Ohadi M, Lalloz MR, Sham P, et al. Localization of a gene for familial hemophagocytic lymphohistiocytosis at chromosome

- 9q21.3-22 by homozygosity mapping. *Am J Hum Genet.* 1999; 64:165-171.
- [27] Lichtenheld MG, Olsen KJ, Lu P, et al. Structure and function of human perforin. *Nature.* 1988; 335:448-451.
- [28] Feldmann J, Callebaut I, Raposo G, et al. Munc13-4 is essential for cytolytic granules fusion and is mutated in a form of familial hemophagocytic lymphohistiocytosis (FHL3). *Cell.* 2003; 115:461-473.
- [29] Zur Stadt U, Schmidt S, Kasper B, et al. Linkage of familial hemophagocytic lymphohistiocytosis (FHL) type-4 to chromosome 6q24 and identification of mutations in syntaxin 11. *Hum Mol Genet.* 2005; 14:827-834.
- [30] Zur Stadt U, Rohr J, Seifert W, et al. Familial hemophagocytic lymphohistiocytosis type 5 (FHL-5) is caused by mutations in Munc18-2 and impaired binding to syntaxin 11. *Am J Hum Genet.* 2009; 85:482-492.



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