Case Report

Hemophagocytic Lymphohistiocytosis: A Series of Five Clinical Cases in Adult Patients at a Single Institution with a Review of the Literature

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Abstract

Context: Hemophagocytic Lymphohistiocytosis or the "Hemophagocytic Syndrome" is a spectrum of disorders of regulatory immunomodulatory pathways inciting phagocytosis of hematopoietic cells resulting in end-organ damage. The condition appears in both heritable and non-heritable forms from a multitude of possible environmental triggers, most notably infection. The condition often results in a fatal outcome without prompt diagnosis and treatment. Cases in children have been reported much more frequently and classically than in adult patients. **Case Report:** In this case series we examined five such cases in adult patients that were found at our institution in a window as small at 2 years with more cases having presented since the time of this writing. In these cases, likely triggers were found ranging from infectious, drug-inducing and even underlying malignancy. The condition can be diagnosed by a set of laboratory and physical criteria (Hemophagocytic Lymphohistiocytosis -2004). Treatment ranges from immunosuppressive agents to chemotherapeutic approaches with variable success. **Conclusion:** Clinicians must maintain a higher index of suspicion in cases presenting with ominous symptomatology to ensure a prompt diagnosis and effective treatment of this potentially deadly condition.

Keywords: Bone marrow, hematopoietic cells, hemophagocytic lymphohistiocytosis, hemophagocytic syndrome

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a spectrum of various conditions affecting regulatory pathways. HLH is characterized by a constant activation of CD8+ T lymphocytes and natural killer (NK) cells to enact phagocytosis of hematopoietic cells and resulting in organ damage, affecting mainly bone marrow, liver and nervous system. The manifestations are often induced by a preceding infectious process.[1,2] HLH is seen more commonly among children with relatively fewer cases diagnosed in adults. This is believed to be due somewhat to under-recognition. HLH contains two different conditions that may be difficult to distinguish from one another: A primary autosomal recessive form, familial HL (FHL) and a secondary HLH (sHLH).[1,3] Prompt diagnosis and treatment is essential to prevent a fatal outcome. In this case series, we report on five distinct cases of sHLH in adult patients arising from various triggers. Laboratory trends were included in this writing for informational purposes where available. All of these cases occurred at our institution between the years 2012

Access this article online

Quick Response Code:

Website: www.najms.org

DOI: 10.4103/1947-2714.166225

How to cite this article: Thomas D, Shah N, Patel H, Pandya T, Gauchan D, Maroules M. Hemophagocytic lymphohistiocytosis: A series of five clinical cases in adult patients at a single institution with a review of the literature. North Am J Med Sci 2015;7:415-20.

and 2014. As of this writing, we have continued to see cases in additional patients.

Case Presentation

Case 1

A 24-year-old Hispanic female from the Dominican Republic with past medical history of pregnancy-induced hypertension presented to our institution with complaint of left-sided flank pain over the past 3 weeks. The pain was described as highly severe and sharp. She also noticed a bump over the left side of her back below the costovertebral angle. She visited the emergency department twice during these 3 weeks with conservative management and discharged home. She complained of subjective fever, nausea, vomiting, dysuria, dry cough and rash during the current visit. She smokes 3 cigarettes per day and used to drink alcohol many years ago but denied current use. On presentation, vitals were temperature of 103.1 degrees, a respiratory rate of 20 and heart rate of 142. On physical exam, there was a macular rash noted on the left upper chest, left back, both thighs and upper extremities with no lymphadenopathy.

She continued to have fever spikes, and remained tachycardic; her white blood cell (WBC) count remained elevated with bandemia. Procalcitonin was elevated. Laboratory values were trended as seen in Table 1. Eventually the patient was transferred to intensive care unit (ICU) for severe sepsis. The patient was found to have bilateral axillary lymphadenopathy and cervical lymphadenopathy, and on computed tomography (CT) scan, left inguinal lymphadenopathy with increased splenomegaly. Gallium scan was done, which showed increased bone marrow uptake, suspicious for elevated levels of serum iron. HLH was suspected but bone marrow biopsy was not performed at that time as the patient was too unstable.

Chemotherapy was started, including two doses of Etoposide, Dexamethasone 20 mg IV daily for 2 weeks and also intravenous immunoglobulin (IVIg) 30 gm IV daily for 5 days. Soluble interleukin (IL)-II receptor assay was 7867.00 pg/mL (reference range: 622 to 1619 pg/mL), confirming the diagnosis. Bone marrow biopsy showed normocellular bone marrow having increased numbers of histiocytes with hemophagocytosis. HLH was thought to be likely secondary to Still's disease vs. viral infection (Human herpes virus-6).

The patient became more stable and was started on Cyclosporine 100 mg PO daily. Her condition continued to improve and she was discharged home with a diagnosis of HLH secondary to Still's disease on PO Cyclosporine, Dexamethasone and Bactrim. Patient has good follow up with Hematology-Oncology and Rheumatology clinic and was admitted in-patient twice after this admission for exacerbation of Still's disease. She continues to do well with outpatient follow-up.

Case 2

A 33-year-old male also from the Dominican Republic with no past medical history presented to our institution with complaint of headache for 3 days, which was generalized, 8/10 in severity at worst and associated with nausea, vomiting, diarrhea, altered mental status with difficulty finding words as per wife and also multiple mosquito bites. The patient had just returned from a trip to the Dominican Republic nine days prior.

Table 1: Laboratory Trends in Case 1

Day	1	2	6	11	14	20	23
WBC (4.5-11.0) K/mm^3	18.5	14.2	17.2	30.9	20.9	6.4	3.7
Hb (12.0-16.0) g/dL	12.4	10.6	11.4	9.8	10.0	9.4	9.2
Platelets (140-440) K/mm^3	197	176	218	151	174	286	209
BUN (7-23) mg/dL	7	5	6	7	38	11	–
Creatinine (0.60-1.30) mg/dL	0.81	0.61	0.63	0.46	0.74	0.34	–
AST (13-39) U/L	73	–	–	167	367	37	–
ALT (7-52) U/L	20	–	–	20	67	27	–
ALP (34-104) IU/L	65	–	–	179	138	80	–
Ferritin (6.9-283.0) ng/mL	–	4783	–	–	>75,000	6748	1748
Triglycerides (<150) mg/dL	–	–	–	473	1436	157	160
Total Protein (6.4-8.4) g/dL	7.4	–	–	4.5	5.6	5.9	–
Albumin (3.5-5.7) g/dL	3.6	–	–	1.7	1.9	2.5	–
Total Bilirubin (0.3-1.1) mG/dL	0.40	–	–	1.2	1.1	1.4	–
LDH (140–271) U/L	–	–	–	1634	2117	470	332
Lactic Acid (0.5- 2.2) mmol/L	0.7	1.0	2.0	1.2	–	–	–
Procalcitonin (<0.50) ng/mL	–	0.63	4.2	7.12	–	–	–

On presentation, vitals included a temperature of 105 degrees, respiratory rate of 22, pulse 102, blood pressure 135/78 and pulse oximetry of 99% on room air. On physical exam, the patient had bibasilar rales, was alert, awake and orientated to place and person but not to time.

The patient was admitted after Dengue serology came back positive. He had an episode of epistaxis and hematemesis and continued to remain unstable and was transferred to intensive care. Laboratory values were trended as seen in Table 2. Bone marrow biopsy showed normocellular bone marrow showing increased number of histiocytes containing hemophagocytosed materials. The diagnosis of HLH was made based on these findings on consultation with the reading pathologist.

Chemotherapy was started the following day. Etoposide with Dexamethasone along with plasmapheresis and IVIg were included in the regimen. The patient also received several units of blood products including single donor platelets (SDP), fresh frozen plasma (FFP), packed red blood cells (PRBCs) and cryoprecipitate. Despite these measures, PT/INR and aPTT remained high. The patient went into acute oliguric renal failure and received hemodialysis. Patient continued to have spike in temperature. He developed pancytopenia and was started on Neupogen. On the ninth day of admission, the patient had a seizure. He was made do not resuscitate (DNR) by the family, went into asystole and passed away.

Case 3

A 58-year-old Caucasian male with past medical history of hypertension, hypertriglyceridemia, chronic atrial fibrillation, coronary artery disease (CAD) s/p coronary artery bypass graft (CABG), ischemic cardiomyopathy and past surgical history of pacemaker/defibrillator placement presented to our institution with complaint of shortness of breath for about a week prior to admission. In the emergency room, the patient was noted to be febrile. His heart rate and blood pressure, however, were acceptable. On the chest X-ray, he was noted to have bilateral infiltrates. He was hypoxemic on room air. Lab reports were notable for thrombocytopenia and leukopenia as well as marked elevation of his liver transaminases and an elevated CPK level. Values are trended in Table 3. The patient was started on non-invasive ventilation with BiPAP. The initial presumed diagnosis was diffuse bacterial pneumonia. He was started on broad spectrum antibiotic therapy.

The patient's respiratory status continued to deteriorate and he was intubated. Throughout the course of hospitalization, spontaneous breathing and pupillary responses were intact; however, his gag and cough reflexes were absent. The patient was started on broad spectrum antibiotics. He developed acute renal failure early during hospitalization and hemodialysis was started. He later developed hypotension requiring the use of pressor medications. The patient remained thrombocytopenic and although he had no evidence of bleeding, platelets were transfused. He subsequently developed gastrointestinal bleeding secondary to stress ulceration as well as prior use of anti-platelet drugs and thrombocytopenia. The patient received multiple units of packed cells. Ferritin level was markedly elevated at over 12,000 and viral-associated hemophagocytic syndrome was suspected. Bone marrow biopsy was performed, which showed mildly hypocellular bone marrow showing mild increase in histiocytes with hemophagocytosis.

Table 2: Laboratory trends in case 2

Day	1	2	3	4	9	10
WBC (4.5-11.0) K/mm^3	4.5	4.8	7.9	7.5	0.9	1.2
Hb (12.0-16.0) g/dL	14.9	17.8	12.4	8.9	4.7	8.1
Platelets (140-440) K/mm^3	29	13	14	21	69	63
BUN (7-23) mg/dL	11	10	35	52	50	50
Creatinine (0.60–1.30) mg/dL	1.14	1.22	3.01	5.36	7.72	8.05
AST (13-39) U/L	874	1807	15,560	19,416	1242	–
ALT (7-52) U/L	358	655	4100	4320	262	–
ALP (34-104) IU/L	60	63	56	83	83	–
Ferritin (6.9-283.0) ng/mL	> 15,000	59,666	84,367	100,281	10,100	14,325
Triglycerides (<150) mg/dL	175	194	132	461	180	420
Total Protein (6.4-8.4) g/dL	6.8	7.0	6.6	6.7	4.5	–
Albumin (3.5-5.7) g/dL	3.7	3.9	3.1	3.5	3.1	–
Total Bilirubin (0.3-1.1) mG/dL	0.9	1.5	4.0	5.9	13.5	–
LDH (140-271) U/L	1361	3652	14,100	17,858	–	4569
Lactic Acid (0.5-2.2) mmol/L	1.4	–	–	9.2	6.6	–
Procalcitonin (<0.50) ng/mL	1.05	–	–	–	7.20	–

Table 3: Laboratory trends in case 3

Day	1	3	5	9
WBC (4.5-11.0) K/mm^3	1.8	3.3	6.4	10.5
Hb (12.0-16.0) g/dL	13.9	14.3	12.6	6.7
Platelets (140-440) K/mm^3	55	60	31	41
BUN (7-23) mg/dL	41	35	99	95
Creatinine (0.60–1.30) mg/dL	1.50	1.20	4.20	3.50
AST (13-39) U/L	–	1075	437	85
ALT (7-52) U/L	–	460	225	69
ALP (34-104) IU/L	–	159	98	56
Ferritin (6.9-283.0) ng/mL	–	–	12,019	2085
Triglycerides (<150) mg/dL	–	–	993	–
Total protein (6.4-8.4) g/dL	–	4.7	3.9	4.1
Albumin (3.5-5.7) g/dL	–	2.1	1.5	2.0
Total bilirubin (0.3-1.1) mG/dL	–	5.2	5.0	7.70
LDH (140-271) U/L	–	2310	–	–
Lactic acid (0.5-2.2) mmol/L	2.3	–	–	–
Procalcitonin (<0.50) ng/mL	2.23	2.56	2.83	4.06

The patient's condition continued to deteriorate. In the second week, the patient developed massive hemoptysis as well as bleeding from IV sites suggestive of disseminated intravascular coagulation (DIC). Cardiac arrest soon followed. Cardiopulmonary resuscitation efforts were unsuccessful. The patient soon after expired.

Case 4

A 28-year-old Hispanic male presented to our institution with a complaint of multiple intermittent episodes of fever that began roughly 2 weeks prior to presentation accompanied by profuse night sweats without rigors. The patient was born in Mexico and has lived in the U. S. for the past 13 years. He had not recently traveled outside the U. S. He denied any contact with sick people, history of transfusions, use of herbal medicines, and changes in routine or eating habits. He had never experienced any similar episodes in the past and reported being generally healthy. He reported taking Ampicillin 500 mg tablets for a total of six doses sporadically over the 2-week period that was given to him by a friend. He also took Acetaminophen as directed when needed. The patient had fever with temperature 102.5 in the emergency department. His initial physical examination was entirely benign.

Rapid HIV, syphilis and Monospot tests were negative. Levels were drawn for Acetaminophen and Salicylates, which were both undetectable. The patient was subjected to multiple viral, parasitic and bacterial testing, which noted multiple past exposures but no acute source of infection. Viral hepatitis profile was negative. Abdominal ultrasound was unremarkable. Chest X-ray showed no visual abnormalities of the heart and lungs. A CT of the abdomen and pelvis without contrast was also obtained, which noted no abnormalities. Liver biopsy was performed, which showed non-specific inflammatory changes. Lab tests were sent out for NK cell activity and anti-CD25, which noted decreased NK activity, establishing our diagnosis.

The patient received two doses of IVIg 900 mg and was immediately started on antibiotic prophylaxis with Cefepime 2 g, Vancomycin 1 g, and Doxycycline 100 mg every 12 hours. The patient was also placed on Dexamethasone initially at 20 mg and tapered throughout the stay. Cyclosporine 200 mg IV every 12 hours was then initiated. Within 1 week of treatment, the patient had remained afebrile for the majority of his stay and improvements were noted in his laboratory values, particularly with normalization of the aminotransferases and bilirubin levels as well as in the ferritin and lactate dehydrogenase. Triglycerides became elevated for a time but began to normalize as treatment continued. There was an appreciable improvement in his white blood cells up to 0.9 10^9/L during admission without improvement in neutrophil counts. The patient was subsequently transfused a total of four units of PRBCs and discharged on Cyclosporine 200 mg PO twice daily. At 1 week follow-up, the counts had improved white blood cells of 2.1 × 10^9/L with resolution of the neutropenia to 1.3 × 10^9/L and both LDH and ferritin levels had nearly normalized. The patient had no recurrences of fever. He presented again 3 months later. Initial laboratory values noted blasts in peripheral blood. Bone marrow biopsy was attempted multiple times but was unsuccessful. Peripheral blood was then sent for flow cytometry returning a diagnosis of acute lymphoblastic leukemia (ALL). Given the lack of another triggering event, our working hypothesis is that ALL itself was the trigger for this patient's HLH.

Case 5

A 43-year-old postmenopausal African American women with a past history of breast cancer presented to our institution with complaints of nausea, dizziness and lightheadedness for 2 weeks. She also reported a fever of 102 degrees, bleeding from the gums and some difficulty breathing. She had previously been evaluated and treated by us for her inflammatory breast cancer and had been receiving a neoadjuvant chemotherapy regimen prior to resection of the mass. Post-regimen, her repeat positron emission tomography scan showed worsening lymphadenopathy and the mass was deemed unresectable. On physical exam in the emergency department, it was noted that she had an abscess in the right axilla. CT of the chest showed left axillary lymph nodes, multiple lung metastases, small right pleural effusion and diffuse liver metastases. Lab work showed an elevated ferritin at 10,064 ng/mL. Ferritin levels were

measured in an anemia profile at 10,064 ng/mL upon admission. The patient was transfused with two units of platelets for concurrent thrombocytopenia (29,000/mm^3 and Vancomycin and Piperacillin/Tazobactam for the abscess in her right axilla. The patient was transferred to the ICU shortly after admission due to increased lethargy, tachycardia with rate of 145. Vital signs at this time included a temperature of 101.2 degrees, blood pressure 91/52, with saturation 97% on 2 liters per minute of Oxygen. Repeat blood work showed a white blood cell count of 4,300/mm^3, platelets 138,000/mm^3. Procalcitonin was 2.92. As per surgery, the right axillary area was packed with gauze, which had a clean wound base. Antibiotics were continued. Additionally, cancer antigen 27-29 was measured at 128.9U/mL, LDH at 2258U/L and fibrinogen at 345 mg%. Ferritin levels rose to 12,842 ng/mL from the previous day.

The following day, the patient had a temperature of 100.3 degrees, pulse 121 and blood pressure of 106/90; she was placed on palliative care thereafter, including pain management. An ultrasound of the liver was done due to elevated AST 308U/L and ALT 109U/L, which found hepatosplenomegaly with multiple hepatic lesions. A bone scan showed metastatic disease involving the right shoulder girdle, upper sternum, thoracic and lumbar spine, pelvis and right hip. LDH levels rose from 2,823 U/L to 3,072 U/L over the next 24 hours. During the same time frame, ferritin levels rose from 15,000 ng/mL to 26,210 ng/mL; triglycerides had remained elevated at 232 mg/dL and 235 mg/dL, respectively. Considering these laboratory values with the recent history of fever and ultrasound showing hepatosplenomegaly, the patient met the criteria for the diagnosis of HLH. No biopsy of the bone marrow was taken during this stay. The patient became nonverbal and confused. Her care was discussed with her family. She was made DNR and placed on a morphine drip. The patient expired later the same day.

Discussion

We understand that HLH is a life-threatening disorder of uncontrolled immune system activation, which can have congenital or secondary forms. These can be seen in both children as well as adults.[1,3] The congenital form results from a range of genetic defects including several associated gene mutations such as PRF1 on 10q21, UNC13D on 17q25 and LYST on 1q41.[3] sHLH can develop as a result of strong immune system activation as mentioned above which frequently arises from infection, however our experience as well as other literature has noted that they can arise from almost any exogenous, rheumatic, or malignant process.[1-3] Both primary and secondary cases of this disorder can also be associated with several immunodeficiency syndromes such as Chediak-Higashi, Griscelli and X-linked lymphoproliferative syndrome with sporadic cases of sHLH seen in association; however, secondary acquired disease typically has no underlying syndromes.[3]

Diagnosis of this condition is based on clinical and laboratory evidence based on a set of criteria known as HLH-2004. This criteria is a revisal of initially agreed-upon guidelines that were established in 1991.[4] Clinical findings of fever, splenomegaly, cytopenia in at least two lineages, hypertriglyceridemia and hypofibrinogenemia with hemophagocytosis in the spleen or lymph nodes also now include hyperferritinemia, low or absent NK cell activity and elevated levels of sIL-2r with five of the eight criteria being met in order to establish diagnosis and those with molecular criteria bypassing this requirement.[4] Research continues to study this condition, and understanding of its pathophysiology continues to improve. In one such study by Jenkins *et al*., the role of sphingolipids was assessed. "Patients with HLH exhibited elevated levels of serum S-SMase activity, with concomitant elevations in several ceramide species and sphingosine, while levels of sphingosine-1-phosphate were significantly decreased. Importantly, the ratio of C16-ceramide:sphingosine was uniquely elevated in HLH patients that died despite appropriate treatment, but remained low in HLH patients that survived, suggesting that this ratio may be of prognostic significance."[5]

Treatment options remain limited but continue to evolve. The HLH-94 protocol includes early and aggressive management including ICU care as needed and there remains a strong role for supportive measures as well as chemotherapy including Etoposide and Dexamethasone.[6] These two were chosen over prednisone as central nervous system disease is relatively common, particularly in children and thus crosses the blood-brain barrier.[1,2] The proposed goal of therapy was either remission of the condition or stability until hematopoeitic stem cell transplant (HSCT) and alternatively bone marrow transplant (BMT) could be performed.[2,6] This was extensively studied in a trial of 113 subjects by Henter *et al*., in 2002 just prior to the revised HLH-2004 protocol where BMT followed HLH-94 treatment with good survival outcomes.[6] The 2004 protocol introduced HSCT formally and it has been noted that survival over that decade since the HLH-94 protocol in patients has improved. We understand the risks of utilizing some of the drugs noted in the treatment protocols for HLH and have tailored the treatments for each patient in this series based on the severity of their disease. As the 2007 study noted, this process is ongoing as we attempt to better understand the pathophysiology; participation in clinical trials by patients with HLH

has been encouraged by these previous studies.[2] Unfortunately there is still limited data on this condition in adults and trials have been difficult due to lower numbers of reported cases. Nearly all standard literature reviewed involved predominantly pediatric populations. One study in 2003 by Imashuku *et al*., looked at young adult patients with sHLH triggered by the Epstein-Barr virus (EBV). Patients who received Etoposide within 4 weeks of diagnosis had a good prognosis further establishing this drug's importance in the HLH treatment protocols. This was also a study done on patients versus a pediatric population, which noted nearly equivalent efficacy.[7]

Novel targets continue to be explored in HLH. Olin *et al*., investigated the use of anti-CD25 antibody daclizumab in the treatment of HLH in an adult patient.[8] This patient was EBV negative at diagnosis and first relapse. The condition was initially treated with steroids and immunosuppression with cyclosporine as was routinely done with some of our cases; however, cyclosporine had to be discontinued due to renal dysfunction and hyperkalemia. Daclizumab was instituted in the treatment of this patient with very promising results.[8]

As cases of this disease in adult patient remains less common than in the pediatric literature, due diligence must be maintained to diagnose and treat these patients aggressively to avoid organ damage and higher likelihood of mortality. The cases we present here were intended to add to the existing body of literature with the intent to raise awareness of this condition in adults. We suspect that it is likely that HLH continues to be underreported and given the cluster of cases that we have seen in our institution and with more numbers being diagnosed the condition may very well be much more common in adult patients than we think.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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