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Hemophagocytic Lymphohistiocytosis (HLH): A Case Series and Review

Christine A. Garcia[1,*], Kester Haye[2], Theodore Gabig[3]

[1]Department of Internal Medicine, Stony Brook University, Stony Brook, NY, US
[2]Department of Pathology, Stony Brook University, Stony Brook, NY, US
[3]Department of Medicine, Division of Hematology and Oncology, Stony Brook University, Stony Brook, NY, US
*Corresponding author: Christine.Garcia@stonybrookmedicine.edu

Abstract **Background** Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening emergency and any delay in diagnosis and/or treatment is associated with high mortality. It is rarely observed in adult patients. HLH has multifaceted clinical presentations with often non-specific signs and symptoms that are often found in other clinical conditions. Classical manifestations suggestive of HLH include fever, cytopenia (thrombocytopenia), liver dysfunction, presence of CNS symptoms and coagulopathy. Hepatic dysfunction and failure can also be a presenting manifestation of HLH and may greatly complicate the clinical course. **Case Presentation:** We present four cases of secondary HLH in adults with varying presentations with a variety of underlying triggers including EBV infection, T cell lymphoma and blinatumomab therapy. **Conclusion:** HLH has multifaceted clinical presentations with often non-specific signs and symptoms that are often found in other clinical conditions. Early recognition of HLH is critical in initiating therapy early on and preventing high mortality resulting from multi-organ failure.

Keywords: *hemophagocytic lymphohistiocytosis, hematology, malignancy, lymphoma, infections*

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1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation. HLH presents as a febrile illness associated with multiple organ involvement. Initial signs and symptoms of HLH can mimic common infections, fever of unknown origin, hepatitis, or encephalitis[1]. Although the incidence in the adult population is unknown, the number of cases reported in the literature has dramatically increased over the past 10 years. Given its rarity and scarcity of data, we present a series of cases of secondary HLH in adults with a variety of presentations and associations.

2. Case Presentations

2.1. Case Presentation 1

The patient is a 44 year-old African-American male with no previous medical history or surgeries, an active 1/3 pack-per-day smoker who presented with a constellation of symptoms including back pain, sharp headaches, nausea, vomiting, photophobia, diarrhea and nose bleeds worsening for the past 6 days. He denied any trauma, recent insect bites, tick bites, recent travel or sick contacts. Patient presented to the emergency room after 4 days of symptoms. He was diagnosed with pneumonia, urinary tract infection and possible viral syndrome, and discharged home on azithromycin and cephalexin. He returned to the hospital 2 days later as symptoms worsened. While in the emergency room, he was started on empiric antibiotics then developed respiratory distress and hypoxia requiring intubation and ventilator support. He developed polymorphic ventricular tachycardia (VT), requiring defibrillation and initiation of Amiodarone and Lidocaine intravenous (IV) drips. He was then transferred to the intensive care unit. The patient was noted to be hypotensive and started on vasopressors. Patient labs revealed no leukocytosis WBC 7.66 K/uL, microcytic anemia with hemoglobin 9 g/dl, hematocrit 24.3%, MCV 65.9 fL. Lactic acid was 2.7 mmol/L. His ferritin was noted to be elevated to 12,876 ng/mL and triglycerides 1,021 mg/dL, raising suspicion for HLH. Bone marrow biopsy was consistent with a diagnosis of HLH (Figure 1). Soluble interleukin (IL)-2 receptor (CD25) was elevated 2,860 pg/mL.

2.2. Case Presentation 2

The second patient is a 27 year-old female with history of obesity and iron-deficiency anemia who presented with fevers up to 104F and pain located in the lower half of her bilateral lower extremities, hips, upper extremities and back. Six months prior to these symptoms, the patient noticed enlarged nodes in her neck and legs. She was subsequently treated with a short course of antibiotics for presumed infection and the nodularity eventually subsided. Past surgical history included an appendectomy. Family

history was significant for type 2 diabetes in her parents. On presentation, notable labs included ESR 88 mm/hr, CRP 10.1 mg/L, WBC 2.65 K/uL, and Hgb 11.2 g/dL. CT of the chest and abdomen revealed diffuse panniculitis without obvious mass. Additional infectious workup was grossly negative for Lyme, Rocky Mountain Spotted Fever, Babesia, Ehrlichia, Anaplasmosis, HIV and hepatitis. EBV IgG titer was elevated (>750 U/mL), but IgM negative. Fungal infection workup was also negative. Rheumatological workup showed negative ANA, anti-CCP, rheumatoid factor and ANCA 20:1. Initial excisional skin biopsy was negative for T-cell proliferation, and there was no evidence of lymphoma. Peripheral flow cytometry was negative for T-cell lymphoma, showing reactive/cytotoxic T-cells. Initially, there was suspicion for atypical erythema nodosum with an elevated ACE level 111 mcg/L and Vitamin D 1,25 131 pg/mL, concerning for sarcoidosis. The patient was treated with antibiotics, ibuprofen and acetaminophen, and was discharged with outpatient follow up. However, fevers (up to 105F) returned again two hours after discharge with associated nausea, poor oral intake, and night sweats. On her second presentation, bandemia was again noted on CBC with differential and ferritin was now elevated to 7788 ng/mL (previously 577 ng/mL) which peaked to 29,257 ng/mL. The elevated ferritin, elevated CRP of 27 mg/L and elevated hepatic AST and ALT without obvious infection or other etiology raised suspicion for HLH. Splenomegaly was not seen on the CT-scan. NK cell activity was found to be low, and bone marrow biopsy confirmed HLH.

2.3. Case Presentation 3

A 21 year-old Spanish speaking female from Ecuador with past medical history of salpingitis, HELLP (Hemolysis, Elevated liver enzymes and Low Platelet count) syndrome (2 years prior), and chronic hepatitis initially presented from an outside community hospital with fever, chills, bloody diarrhea, dizziness, diffuse myalgia, nausea, epistaxis and several weeks of lower extremity edema. Prior to her hospital presentation, she was seen by her primary medical doctor for elevated liver enzymes which improved with oral prednisone 20 mg PO daily for 4 days. She was found to be severely anemic (hemoglobin 5.1 mg/dL) with coagulopathy (INR 2.8) and evidence of worsening liver failure (decreased fibrinogen). She was transfused 7 units of packed red blood cells, 1 unit of cryoprecipitate, 4 units of fresh frozen plasma, and given methylprednisolone 40 mg daily, intravenous pantoprazole, pipercillin/tazobactam, and vitamin K. The patient was hemodynamically unstable with repeated melanotic bowel movements requiring IV fluids and vasopressors. Patient was found to have EBV hepatitis (EBV PCR + 3,270,000 copy/mL) and subsequently started on rituximab and steroids. She received only 3 doses of rituximab then developed hemodynamic instability and poor response. CMV titers were found to be positive, and gangiclovir was initiated. The hospital course was further complicated by hematochezia after embolization of right ileocolic artery followed by severe ischemic colitis for which she underwent right hemicolectomy with end ileostomy and mucous fistula. Small bowel enteroscopy showed 2 ulcers with visible vessels which were successful clipped. Further evaluation revealed soluble IL-2 (CD25) 1,835 pg/mL, elevated ferritin with peak 9,479 ng/mL, triglycerides 494 mg/dL, fibrinogen 124 mg/dL and LDH 825 IU/L. Liver biopsy showed patchy mild to moderate medium and large droplet steatosis. Portal tracts were expanded by a chronic inflammatory infiltrate composed predominately of lymphocytes with occasional plasma cells. There was moderate sinusoidal and lobular inflammation with sinusoidal erythrophagocytosis and sinusoidal congestion. Reticulin and trichrome stains highlighted mild periportal fibrosis. A PAS-D stain shows scattered PAS-D positive material in Kupffer cells. A special stain for iron was negative. Bone marrow biopsy showed hypocellular marrow with hemophagocytosis and tri-lineage maturation. The aspirate showed macrophages with engulfed erythroid precursors, red cells, neutrophils and apoptotic bodies.

2.4. Case Presentation 4

The fourth patient is a 58 year-old woman with a history of relapsed Pre-B Acute Lymphocytic Leukemia (ALL) with CD22 positive blasts on flow cytometry and bone marrow biopsy. Cytogenetics revealed deletion of 9q34 (ABL1) and Philadelphia chromosome was absent. Lumbar puncture was negative for CNS involvement. After completion of 4 cycles of cyclophosphamide, vincristine, doxorubicin and dexamethasone (HyperCVAD) with intrathecal cytarabine (AraC), the patient had persistent residual disease. She was then treated with salvage clofarabine, cytarabine and dexamethasone chemotherapy. A repeat bone marrow biopsy confirmed refractory ALL with 76% blasts. The patient received one cycle of Methotrexate, Oncovin, PEG-I-Asparaginase, Dexamethasone (MOAD salvage therapy) and again had persistent bone marrow disease. Third line salvage chemotherapy with Blinatumomab therapy was initiated with levetiracetam seizure prophylaxis. On day 12 of blinatumomab, the patient developed fever, rash, and decreased responsiveness and blinatumomab was discontinued. The neurological signs progressed over the following 24 hours to confusion, expressive aphasia, stupor and coarse tremors of arms and feet. The patient's altered mental status was concerning for neurotoxicity versus cytokine macrocytic activation syndrome (MAS) secondary to blinatumomab. Ferritin levels were elevated to 15,114 ng/dl and triglycerides peaked at 991 mg/dL.

3. Discussion

3.1. Diagnostic Criteria for HLH and Therapeutic Guidelines

Henter's modified criteria establishes clinical and laboratory diagnostic criteria for the diagnosis of HLH (Table 1) [1]. Patients must meet molecular diagnosis for HLH or five out of the eight criteria for diagnosis: fever, splenomegaly, cytopenias affecting ≥2 lineages, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis (in bone marrow, spleen, or lymph node), hyperferritinemia, impaired NK cell function, and elevated soluble CD25 (sCD25) (i.e., sIL2R). Transaminitis, coagulopathy, hyponatremia, edema, rash,

hypoalbuminemia, elevated lactate dehydrogenase (LDH), elevated C-reactive protein, elevated D-dimer, increased very low-density lipoprotein, decreased high-density lipoprotein, elevated cerebrospinal fluid protein and cells, and neurologic symptoms ranging from focal deficits to altered mental status are additional findings. Elevated ferritin occurs in most patients with HLH but it is nonspecific. The published criteria use a ferritin cutoff value of ≥500 µg/L when diagnosing HLH, based on the HLH-94 study that showed a sensitivity of 84% [1].

A retrospective analysis at Texas Children's Hospital performed by Allen et al reported that a maximum ferritin level higher than 10 000 µg/L had a 90% sensitivity and 98% specificity for HLH [2]. In another study of 113 patients identified with ferritin levels >50,000 µg/L, only 19 had HLH. Serum ferritin elevation more than 5 times this level is associated with a variety of disorders and is not predictive of HLH [3].

Table 1. Modified Criteria for the Diagnosis of HLH [1]

Molecular diagnosis compatible with hemophagocytic lymphohistiocytosis
At least five out of the eight following criteria:
Fever
Splenomegaly
Cytopenia (involving at least two lines)
Hemoglobin <9 g/dL or <10g/dL in newborn babies
Platelets <100 x 10^9/L
Neutrophils <1.0 x 10^9/L
Hypertriglycerides (>265 mg/dL) or hypofibrinogenemia (<150mg/dL)
Evidence of hemophagocytosis in a bone marrow, liver or node biopsy
Decreased or absent NK-cell activity
Elevated ferritin >500 ug/L
Elevated soluble IL-2 receptor alpha (> 2400 U/mL)

Table 2. Clinical and laboratory characteristics of four adult patients with Hemophagocytic Lymphocytic (HLH)

Case #	1	2	3	4
Gender	Male	Female	Female	Female
Age at diagnosis	44	27	21	58
Fevers	Yes	Yes	Yes	Yes
Splenomegaly	No		Yes	No
Cytopenias (2 of 3 lineages)	WBC 7.66 g/dL Hgb 9 g/dL	WBC 2.65 g/dL Hgb 11.2 g/dL	WBC 3.81 g/dL Hgb 1.8 g/dL Platelets 67 K/uL	WBC 3.95 g/dL Hgb 9.6 g/dL Platelets 26 K/uL
Ferritin (>500 ug/L)	12,876 ng/mL	29,257 ng/mL	9,479 ng/mL	15,114 ng/mL
Fibrinogen (<1.5 g/L)	529 mg/dL	N/A	124 mg/dL	N/A
Triglycerides (>3mmol/L)	1,021 mg/dL	265 mg/dL	494 mg/dL	991 mg/dL
Soluble Interleukin 2 receptor (CD25) >2400 U/mL	2860 pg/mL	N/A	1,835 pg/mL	N/A
Low or absent NK cell activity	N/A	Low	N/A	N/A
Lactic acid	2.7 mmol/K	3.1 mmol/K	3.5 mmol/K	1.4 mmol/K
Hemophagocytosis in bone marrow	Yes	Yes	Yes	No
Associated infections/ malignancy	None	Subcut. Panniculitis T- cell lymphoma	EBV	ALL
Type of therapy/ outcome	Dexamethasone, Etoposide / Alive at present	Dexamethasone /Alive at present	Deceased	Dexamethasone/ Alive at present

Findings suggestive of HLH include fever, cytopenia (thrombocytopenia), markedly elevated ferritin, and the presence of CNS symptoms. Although analysis of bone marrow aspirate is commonly used to diagnose HLH, it has a sensitivity of around 60% [4]. Therefore, a negative bone marrow biopsy analysis should not preclude initiation of therapy it there is a high clinical suspicion and laboratory evidence of HLH [5]. Nearly all patients in this series with HLH had very high ferritin levels, hepatitis manifested by elevated liver function tests, increased triglycerides and abnormal coagulation parameters (especially elevated D-dimer) caused by hepatic dysfunction (Table 2).

Table 2 reviews the clinical and laboratory characteristics of four adult patients with HLH**.** In **case 1,** the patient underwent extensive infectious workup was completed which was negative for Legionella and pneumococcal urinary antigens, Lyme, Babesia, HSV, Parvovirus, CMV. Ferritin was 12,876 ng/mL. Triglycerides were elevated to 1,021 mg/dL. Bone marrow biopsy was completed and confirmed HLH (Figure 1).

Figure 1: Bone marrow biopsy findings in HLH

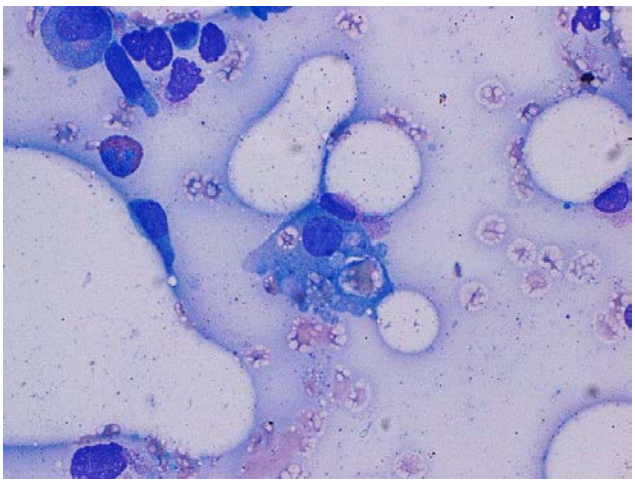

Figure 1A. Wright-Giemsa stain of a bone marrow aspirate smear. The yellow arrow indicates a multi-vacuolated macrophage with phagocytized mature red blood cells (600x).

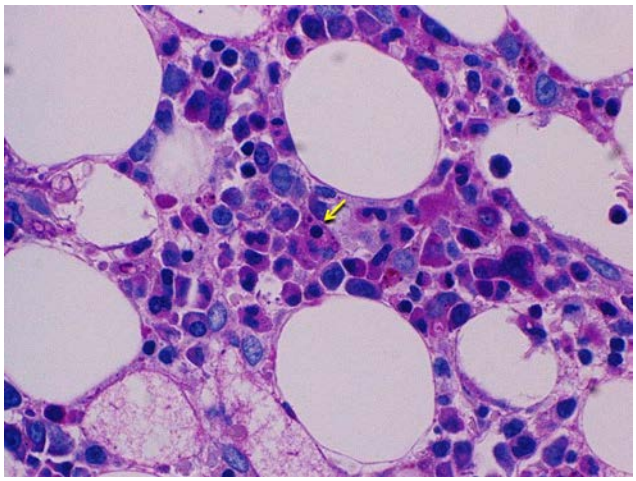

Figure 1B. A PAS-stain of the bone marrow core biopsy. The yellow arrow indicates a macrophage which phagocytized an immature red blood cell (600x).

In **case 2,** the patient was found to have an elevated triglyceride level 265 mg/dL, NK Function Low. Familial HLH (FHL types 2-5) resulted as negative. Viral workup showed EBV PCR negative, CMV PCR viral load and titers negative. Peripheral blood smear showed anisocytosis, bands with some toxic granulation, burr cells, and possible few tear drop cells. Skin biopsy revealed small to medium sized lymphoid cells with irregular and hyperchromatic nuclei, small nucleoli and small amount of cytoplasm with admixed histiocytes, and atypical lymphoid cells show rimming around the fat cells. Immunohistochemistry showed these atypical cells were positive for CD3, CD8 and TIA1 and negative for CD56. CD5 was partially lost on the atypical cells. CD4 was positive on some lymphocytes and macrophages, but the atypical cells appear largely CD8 positive. TCRy was positive on a subset of the atypical cells rimming around the fat cells, but the bF1 stain also stained some atypical cells, making it difficult to conclude a gamma delta vs alpha beta origin for the tumor cells. T-cell rearrangement study revealed > 90-95% of all TCRy gene rearrangements occurring in clonal T-cell proliferations consistent with histological diagnosis of subcutaneous panniculitis like T-cell lymphoma. Bone marrow biopsy revealed normocellular marrow with hemophagocytosis consistent with presumed clinical diagnosis of HLH in the presence of appropriate clinical findings that meet the diagnostic criteria for HLH syndrome. Her bone marrow was negative for lymphoma or negative for organisms. **Case 3** fulfilled 7 of the 8 criteria listed for diagnostic criteria: massive hepatosplenomegaly (liver, 3540 grams; spleen, 510 grams), elevated soluble Interleukin 2 receptor (CD25), elevated ferritin, fever (clinical), hypertriglyceridemia, hypofibrinogenemia, cytopenias affecting >2 lineages in the peripheral blood (WBC range 2.02-4.80 K/uL, absolute neutrophil count range 0.28-3.52 K/uL, platelets range 17-84 K/uL, hemoglobin 10 g/dL), persistent hepatitis (clinical signs of diffuse jaundice and scleral icterus with transaminitis: ALT 160 U/L, AST 271 U/L, ALP 271 U/L, T. Bili 15.5 mg/dL, D.Bili 13.2 mg/dl), and bone marrow, liver and spleen biopsy with hemophagocytosis. In **case 4,** analysis at the time of symptoms were suspicious for secondary HLH including elevated ferritin, triglycerides and LDH. Bone marrow biopsy was not performed at the time of symptoms.

3.2. Triggers of Secondary HLH

Immune activation is typically initiated by an infection, most commonly viral infections, especially with Epstein-Barr virus (EBV). HLH has been associated with visceral leishmaniasis [6], CMV [6], EBV [6], varicella-zoster [7], acute viral hepatitis A [8], ulcerative colitis [9,10]. HLH has been reported in association with malignancies, most commonly lymphoid cancers, including T, NK, and anaplastic large cell lymphomas and leukemias. There are many known triggers of HLH including infectious diseases, tumors and autoimmune disease detailed in Table 3 [6-11].

In **case 2,** the patient had HLH associated with Subcutaneous Panniculitis T- cell lymphoma. In **case 3**, the patient was later found to have EBV infection. In **case 4,** the patient had known diagnosis of refractory ALL but subsequently developed non-specific symptoms including fevers, rashes, altered mental status, confusion shortly after starting blinatumomab therapy. No underlying trigger was found in **case 1**.

Table 3. Triggers of secondary HLH [6-11]

Infectious diseases	
Viruses	Herpes virus (EBV, CMV, HHV-8, HSV), HIV, HTLV, hepatitis virus (A, B,C), measles, parotitis, rubella, adenovirus, dengue, hantavirus, parvovirus B19, enteroviruses, influenza
Bacteria	*Staphylococcus aureus*, *Campylobacter* spp., *Fusobacterium* spp., *Mycoplasma* spp., *Chlamydia* spp., *Legionella* spp., *Salmonella typhi*, *Rickettsia* spp., *Brucella* spp., *Erhlichia* spp., *Borrelia burdorferi*, *Mycoplasma tuberculosis*
Fungi	*Candida* spp., *Cryptococcus* spp., *Pneumocystis* spp., *Histoplasma* spp., *Aspergillus* spp., *Fusarium* spp.
Parasites	*Plasmodium falciparum*, *Plasmodium vivax*, *Toxoplasma* spp., *Babesia* spp., *Strongyloides* spp., *Leishmania* spp.
Tumors	
Hematological	Lymphomas (T/NK cells, anaplastic large cell lymphomas, Hodgkin's), acute lymphocytic leukemia, multiple myeloma, acute erythroid leukemia
Non-hematological	Prostate cancer, lung cancer, hepatocellular carcinoma
Autoimmune diseases	
Macrophage-activation syndrome (MAS)	Juvenile chronic arthritis, Kawasaki disease, SLE, seronegative spondyloarthropathies
Other factors	Drug-related, pregnancy, vaccines, surgery, hemodialysis, ulcerative colitis

3.3. Subtypes of HLH

HLH has been categorized in primary or familial HLH (FHLH). Based on genetic etiology, FHLH has been subcategorized into five subtypes, FHLH-1 to FHLH-5 (Table 4).

Table 4. Classification of Primary HLH

Subtype	Mutation
Type 1 Familial HLH	Unknown
Type 2 Familial HLH	PRF1
Type 3 Familial HLH	UNC13D
Type 4 Familial HLH	STX11
Type 5 Familial HLH	STXBP2
Griscelli syndrome type 2	RAB27A
Chediak-Hagashi syndrome	LYST
Hermansky-Pudiak syndrome type 2	AP3B1
X-linked lymphoproliferative disease Type 1 Type 2	 SH2D1A BIRC4

The mutation in FHLH-1 has yet to be identified, but the defect was mapped to chromosome 9q21.3. FHLH-2 is attributed to mutations in the gene coding perforin (PRF-1) [12]. FHLH-3 is associated with mutations in the genes encoding Munc-13-4 (UNC13D)[13]. FHLH-4 is associated with mutations in genes encoding syntaxin 11 (STX11) [14] and FHLH-5 is associated with mutations in genes encoding syntaxin-binding protein 2 (STXBP2) [15]. HLH is also described in three disorders related to defects in granule trafficking that affect neutrophil and platelet dysfunction: Griscelli syndrome type II (RAB27A), Chediak-Higashi syndrome (LYST) and Hermansky-Pudlak syndrome type II (AP3B1).

3.4. Macrophage Activation Syndrome (MAS)

When HLH arises in association with rheumatologic disease, it is termed macrophage activation syndrome (MAS). MAS is most commonly seen in association with adult-onset Still disease, systemic juvenile idiopathic arthritis, and systemic lupus erythematosus but has also been described in other rheumatologic conditions [16].

3.5. Treatment of HLH

Immediate goal of therapy is to reduce the hyperinflammation responsible for symptoms that are life-threatening. Early recognition and treatment with steroids or immunotherapy is needed to avoid mortality from multi-organ failure, sepsis and disseminated intravascular coagulation (DIC). Respiratory abnormalities often leads to an urgent need for ventilatory support and death from acute respiratory distress syndrome. Severe hypotension may require administration of one or more vasopressors. The standard treatment of HLH is etoposide in combination of steroids for further suppression of hypercytokinemia and inflammation. Etoposide inhibits topoisomerase II, leading to double-stranded DNA breaks [17]. Etoposide selectively depleted activated T cells leading to suppression of inflammatory cytokines and improved survival, suggesting that T-cell deletion, rather than suppression of activation, was most effective [18]. In addition, allogeneic hematopoetic stem cell transplant (HSCT) has become a mainstay of treatment in pediatric HLH and is increasingly used in adults with recurrent HLH or HLH with a known genetic predisposition. Patients with MAS should be treated initially with steroids alone and typically do not require etoposide. When response is inadequate, additional immunosuppressive agents that address the underlying rheumatologic disorder are recommended rather than HLH-specific therapy [19]. A schematic algorithm to the approach and treatment of adult HLH was proposed recently [19].

3.6. Outcomes and Follow-up

In **case 1**, the presence of persistent fever, elevated triglycerides and elevated level of ferritin all support the diagnosis of HLH. The patient was started empirically on IV dexamethasone while awaiting bone marrow biopsy. Bone marrow biopsy reveals presence of phagocytosis of platelets by macrophages consistent with HLH (Figure 1a and b). IL-2 soluble receptor CD25 returned elevated to 2860 pg/mL. Patient improved dramatically on intravenous corticosteroids, eventually was extubated and started on Etoposide. In case 2, the patient was diagnosed with Subcutaneous Panniculitis T-cell Lymphoma with HLH. She started on Doxil and then on DHAP. Plan was to switch to dose adjusted-EPOH for third cycle given her aggressive disease with concomitant HLH. She later was started on DHAP. In **case 3,** the patient had multi-organ involvement and developed DIC. Schistocytes were noted on peripheral smear and she subsequently expired. Autopsy confirmed HLH likely secondary to Epstein-Barr virus (EBV) infection with massive hepatosplenomegaly. In **case 4,** the patient's altered mental status was concerning for neurotoxicity versus cytokine MAS secondary to blinatumomab. The patient's levetiracetam dose for seizure prophylaxis was increased and she was started on dexamethasone 40 mg IVPB daily for 3 days for neurotoxicity related to blinatumomab. Routine EEG showed no seizures and generalized slowing. Symptoms eventually improved with intravenous dexamethasone over the course of 1 week with return to baseline mental status.

4. Conclusions

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening emergency and any delay in diagnosis and/or treatment is associated with high mortality. It most frequently affects infants from birth to 18 months of age, however the disease is rarely observed in children and adults.

HLH has multifaceted clinical presentations with often non-specific signs and symptoms that are often found in other clinical conditions. The same manifestations can be caused by the disorders that trigger HLH, such as sepsis or lymphoma. Classical manifestations suggestive of HLH include fever, cytopenia (thrombocytopenia), liver dysfunction, presence of CNS symptoms and coagulopathy. Hepatic dysfunction and failure can also be a presenting manifestation of HLH and may greatly complicate the clinical course. In addition, development of subtle or overt CNS findings may be related to CNS involvement in HLH [20].

Given the variety of presentations, clinicians need to be suspicious for patients presenting with a constellation of symptoms, both classical and atypical presentations, to recognize HLH and begin therapy early to prevent high mortality resulting from multi-organ failure.

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