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Case Study

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HLH SYNDROME – UNCOMMON ENTITY WITH OVERLAP PRESENTATION. A CASE REPORT

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH), is an uncommon hematologic disorder seen more often in children than in adults. It is a life-threatening disease of severe inflammation caused by uncontrolled rapid increase of activated lymphocytes and macrophages, leading to cytokine storm syndromes. There are inherited and non-inherited (acquired) causes of hemophagocytic lymphohistiocytosis (HLH) (we can omit this line). We report an unusual presentation of HLH and it's management in a previously healthy gravid lady.

KEYWORDS: Hlh, Cytokine Storm, Etoposide, Steroid, Rituximab.

CASE REPORT

37 year old Philippino, gravida 2, para 1 presently(×) 15 weeks, previously healthy presented to obs and gyn hospital (OB&G) on 29/10/2019, with C/O (complaints of) high grade fever, dry cough, generalized body pain and frequent episode of bleeding from nose. On presentation in Latifa Hospital, she was tachycardic, tachypnic, and hypotensive. Her initial labs, investigations) showed pancytopenia, deranged LFT and coagulation profile. She was transferred to our center with a provisional diagnosis of viral hemorrhagic fever. She works as a food handler in a local bakery, with no previous significant medical history and her previous pregnancy was normal.

On arrival it was noted that along with the above symptoms she had severe abdominal pain with tenderness, palpable spleen and liver, normal heart sounds with basal crackles in lungs on auscultation. She underwent emergency ultrasonography which revealed acalculous cholecystitis, hepato-splenomegaly, and bilateral pleural effusion. Her labs were consistent with pancytopenia, deranged LFT, abnormal coagulation profile, reduced fibrinogen levels, elevated triglycerides and upward trend of(raised) ferritin. A provisional diagnosis of HLH was made in view of clinical, lab, USG findings.

Her breathing problem(difficulty) gradually worsened requiring elective intubation and mechanical ventilation as, a her clinical and chest x-ray findings were consistent with ARDS. Post stabilization, she was referred to hemato-oncologist confirmed diagnosis of HLH was made based on bone marrow biopsy which showed bone marrow with triliniage hematopoiesis with myeloid hyperplasia and evidence of hemophagocytic activity, CD20 showed many positive B cells, many mature T cells positive for CD3(faint) were seen, cytokeratin was negative, CD68 stains most of cells comprising noted cellularity(40-50%) and CD34 did not show increased blasts(<1%). EBV DNA PCR was positive.

She was immediately started on Methylprednisolone 1000 mg iv daily and Etoposide100 mg iv. The following day she developed abdominal pain with undergarments soaked with clotted blood. Bedside USG and Doppler showed absence of fetal heart sound. She underwent pharmacological termination followed with evacuation of conceptual products. Bleeding and coagulation abnormalities were corrected with PRBC, FFP, and platelet transfusions. Her pan-cultures were negative.

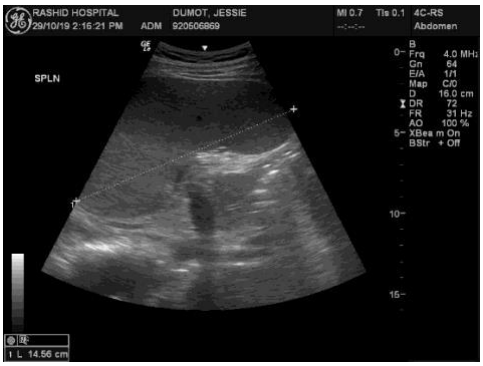
During her admission she was in(multiorgan failure) ARDS, severe sepsis, septic shock and acute renal failure requiring inotropic support, lung recruitment with high

PEEP and low tidal volume ventilation, and continuous renal replacement therapy. She was treated with empirical antibiotics (meropenem, levofloxacin, teigecycline, and septrin).

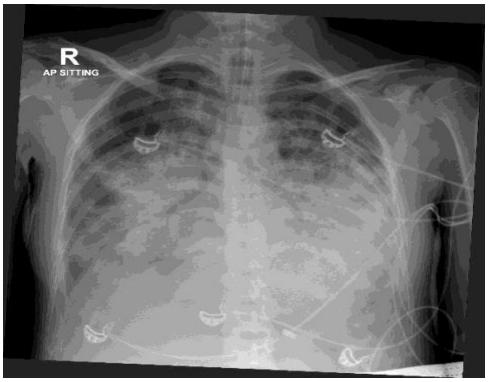
Her condition gradually improved and was successfully weaned off ventilator and dialysis.(after how many days) She was then transferred under care of hematology for further management. She was further treated with Rituximab and Ruxolitinib and was discharged in a stable condition on 03/02/2020.

Laboratory Findings

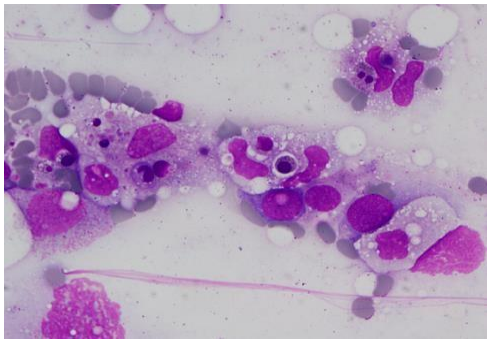
WBC	1.5
Hb	10
HCT	28.9
Platelet count	35
Creatinine	1.7
Sodium	128
Potassium	3.8
Urea	73
AST	656
Bilirubin	5.5
ALT	171
Alkaline phospatase	438
Ferritin	34308
Fibrinogen	180
PT	19.8
APTT	78
INR	1.63
Procalcitonin	7.37
Triglyceride	316



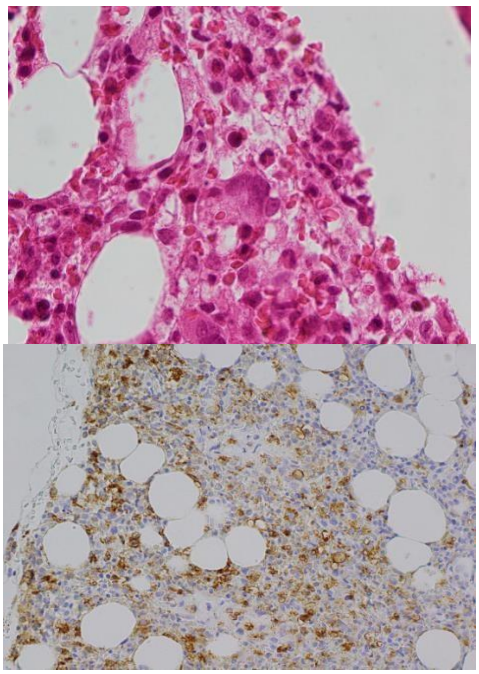
Splenomegaly on USG



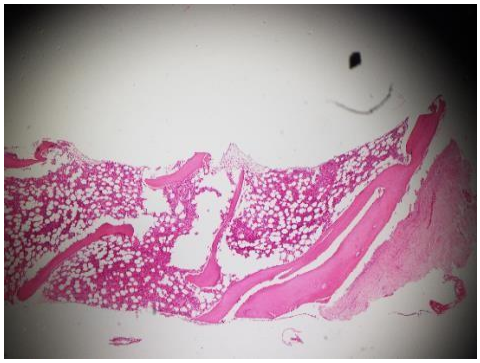
ARDS on chest X ray



Bone marrow aspirate and bone marrow trephine biopsy were examined and both showed bone marrow with trilineage hematopoiesis and definitive evidence of hemophagocytosis.



The bone marrow trephine showed a cellularity of 80% and showed several CD68 positive scattered histiocytes with definitive evidence of hemophagocytosis. The noted histiocytes are reactive appearing with no coffee bean nuclei noted with no cytoplasmic organism or viral inclusion seen.



The bone marrow aspirate shows several histocytes with many showing cytoplasmic vacuoles and hemophagocytosis. (Slides are shared courtesy Dr Rania Medhet Saleim).

DISCUSSION

HLH is a syndrome of excessive inflammation and tissue destruction due to abnormal immune activation. The hyperinflammatory/dysregulated immune state is thought to be caused by the absence of normal downregulation by activated macrophages and lymphocytes.

The cell types involved in the pathogenesis of HLH include the following.
Macrophages – In HLH, macrophages become activated and secrete excessive amounts of cytokines, ultimately causing severe tissue damage that can lead to organ failure.

Natural killer cells and cytotoxic lymphocytes - fail to eliminate activated macrophages. This lack of normal feedback regulation results in excessive macrophage activity and highly elevated levels of interferon gamma and other cytokines.

Hemophagocytosis — In addition to antigen presentation and cytokine production, macrophages can also phagocytize host cells. Hemophagocytosis refers to the engulfment of host blood cells by macrophages. Hemophagocytosis is characterized by the presence of red blood cells, platelets, or white blood cells (or fragments of these cells) within the cytoplasm of macrophages.

Hemophagocytosis can be observed in biopsies of immune tissues (lymph nodes, spleen, liver) or bone marrow aspirates/biopsies. Although it can be a marker of excessive macrophage activation and supports the diagnosis of HLH, hemophagocytosis alone is neither pathognomonic of, nor required for, the diagnosis of HLH.

Cytokine storm — The persistent activation of macrophages, NK cells, and CTLs in patients with HLH leads to excessive cytokine production (cytokine storm) by all of these cell types, and is thought to be responsible for multiorgan failure and the high mortality of this syndrome. Cytokines found at extremely high levels in the plasma of patients with HLH include interferon gamma (IFN gamma); tumor necrosis factor alpha (TNF alpha); interleukins (IL) such as IL-6, IL-10, and IL- 12; and the soluble IL-2 receptor (CD25).

Triggers — Patients with HLH can have a single episode of the disease or relapsing episodes, with relapses occurring most often in patients with familial HLH. The instigating trigger for an acute episode is often an infection or an alteration in immune homeostasis. The two broad categories of triggers include those that cause immune activation and those that lead to immune deficiency.

Immune activation from an infection is a common trigger both in patients with a genetic predisposition and in sporadic cases with no underlying genetic cause identified. The most common infectious trigger is a viral infection, especially Epstein-Barr virus (EBV) [2]. Primary EBV infection can trigger HLH in individuals with a defect in perforin-dependent cytotoxicity, as well as in those without a known predisposition; patients with X-linked lymphoproliferative disease (XLP) are at particularly high risk [23]. Many other infectious organisms are also implicated. Kawasaki disease, a common vasculitis of childhood, can also trigger HLH and can often be misdiagnosed initially.

The coexistence of immune dysregulation with unchecked inflammation distinguishes HLH from other syndromes of immune activation, immunodeficiencies, and inflammatory states.

HLH has been recognized as an inflammatory response for many conditions including autoimmune diseases, malignancies, and infections. It can be classified as primary and secondary. Primary also called as familial HLH, usually presents in childhood. It is associated with mutations in genes such as MUNC 13-4, perforin 1 (PRF1), Syntaxin-122 and Syntaxin-binding protein which can affect the cytotoxic function of T-lymphocytes and natural killer (NK) cells. Familial HLH can present as a sporadic case, but also few viral infections have also been implicated. Secondary HLH usually presents in the adulthood. It has many causes including autoimmune diseases, malignancies (commonly lymphomas) and underlying infections (mainly viral, which includes HBV, HIV, HBV, HCV and CMV). In secondary HLH few cases have been reported with genetic predisposition. Presenting features are similar to sepsis, TTP, acute liver failure and MODS.

A diagnosis of HLH, as determined by the Histiocyte Society in 2004, is based on the following criteria [7]:
Molecular diagnosis confirming HLH, and/or five of the following parameters.

1. Fever >38.5°C (>101.3°F)
2. Splenomegaly
3. Cytopenia (at least two cell lines are affected with adult hemoglobin <10 g/dl, platelets
4. <10,000/µl and absolute neutrophil count <1000/µl)
5. Elevated serum ferritin with ferritin >500 µg/l
6. Hypertriglyceridemia (with triglycerides levels >265 mg/dl) and/or hypofibrinogenemia (fibrinogen levels <1.5 g/L)
7. Hemophagocytosis in the bone marrow/lymph nodes/spleen
8. Low or absent NK cell activity
9. An increase in soluble CD25 (increase in soluble Il-2 receptor) >2,400 U/mL
10. Other common associations include rash, edema, hypoalbuminemia, hyponatremia, and elevated LDH levels.

Treatment.

HLH is a progressive syndrome of unchecked immune activation and tissue damage. If left untreated, patients

with HLH survive for only a few months, due to progressive multi-organ failure. In 1994, the Histiocyte Society organized the first treatment protocol for HLH (HLH-94), which dramatically increased this survival rate to 54 percent with a median follow-up of six years. The greatest barrier to treatment and a successful outcome for individuals with HLH is a delay in diagnosis.

The goal of therapy for patients with HLH is to suppress life-threatening inflammation by destroying immune cells. Induction therapy based on the HLH-94 protocol consists of a series of weekly treatments with dexamethasone and etoposide (VP-16). Intrathecal methotrexate and hydrocortisone are given to those with central nervous system disease. After induction, patients who are recovering are weaned off therapy, while those who are not improving are continued on therapy as a bridge to allogeneic hematopoietic cell transplantation (HCT). HCT will be required in those with an HLH gene mutation, central nervous system disease, or disease relapse.

When HLH is triggered by an acute infection or other condition (eg, rheumatologic condition), treatment of the trigger is appropriate because this may remove the stimulus for immune activation. Patients who are less acutely ill and stable may be able to tolerate treatment of the triggering condition alone without HLH-specific therapy; this strategy may allow some patients to avoid potentially toxic therapy.

Our patient was treated with methyl prednisolone and etoposide on initial presentation and was then further treated with Rituximab and Ruxolitinib.

CONCLUSION

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation. It is most common in infants and young children but can affect patients of any age, with or without a predisposing familial condition. Most patients with HLH are acutely ill with multiorgan involvement. Common findings include fever, rash, hepatosplenomegaly, lymphadenopathy, neurologic symptoms, bi-cytopenia, high serum ferritin, and liver function abnormalities. Patients may have already experienced a prolonged hospitalization or clinical deterioration without a clear diagnosis before the possibility of HLH is raised. A priority should be placed on rapid evaluation, with the goal of starting treatment as soon as possible.

Many patients with HLH have a predisposing genetic defect, and/or an immunologic trigger, which can include infection, malignancy, rheumatologic disorder such as juvenile idiopathic arthritis, or another disorder associated with immune dysregulation. These genetic defects and immunologic triggers should be identified in all patients.

The initial evaluation includes a complete blood count with differential, coagulation studies, serum ferritin, liver function tests, triglycerides, blood cultures, and viral testing. The bone marrow should be examined for the cause of cytopenias, infectious organisms, hemophagocytosis, and macrophage infiltration; and sent for cultures. All patients should have a lumbar puncture with cerebrospinal fluid (CSF) analysis and magnetic resonance imaging (MRI) of the brain. Computed tomography (CT) scans of the neck, chest, abdomen, and pelvis or positron emission tomography (PET) scan should be done to evaluate for possible malignancy. For those with a high clinical suspicion, specialized testing of immunologic parameters and genetic testing are also indicated.

HLA typing is done in preparation for possible allogeneic hematopoietic cell transplantation.

The diagnosis of HLH is made by identifying a mutation in an HLH gene, or by fulfilling five of eight diagnostic criteria. Many patients fit only three or four of the eight criteria, yet have clinical evidence of HLH and require HLH-specific treatment. Modified diagnostic criteria may also be used. Hemophagocytosis, while often seen, is neither necessary nor sufficient for the diagnosis of HLH.

Patients should be urgently referred to a hematology or oncology specialist. Pretreatment testing of cardiac function and disease markers should be done in all patients. HLA typing of all patients and appropriate family members, and genetic testing of potential sibling donors should be sent in anticipation of possible hematopoietic cell transplant (HCT).

Poor prognostic factors include younger age, CNS involvement, and failure of therapy to induce a remission prior to HCT

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