

Macrophage Activation Syndrome: A form of Hemophagocytic Lymphohistiocytosis; when the Immune System goes Rogue

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Abstract: The authors presented three different cases with hemophagocytic lymphohistiocytosis syndrome. The HLH syndrome is trigger in the three cases with different disease process involving; Rheumatological disease (SLE), malignancy (renal cell carcinoma), and influenza infection with H1N1. All cases presented with fever and multi-organ involvements, high ferritin level, and evidence of phagocytosis of the normal blood cells by macrophages as well as infiltration of the affected organs by activated lymphocytes and histiocytes. The three cases are considered as a form of secondary HLH. One case made a full recovery and the other 2 cases succumbed to their disease. No case was treated with hematopoietic cell transplant.

Keywords: hemophagocytic lymphohistiocytosis, macrophage activating syndrome, systemic juvenile idiopathic arthritis, hyperferritinemia, hypofibrinogenemia, liver failure.

1. CASE ONE PRESENTATION

The patient is 35-year old female with a history of SLE which has not been well controlled. She is admitted for a flare characterized by inflammatory arthritis, an active malar rash, and progressive lower extremity edema as well as proteinuria. She is found to have an acute kidney injury (AKI) and significant proteinuria. Soon after admission, she begins developing fevers, confusion, and acute respiratory failure requiring mechanical ventilation. Her daily laboratories show a rapidly progressive pancytopenia, a significant transaminitis, and worsening renal failure. Her erythrocyte sedimentation rate (ESR) is decreasing and a disseminated intra-vascular coagulopathy (DIC) panel is positive. Her Ferritin is 1,000,000,000. Bone marrow examination revealed the presence of hemophagocytic lymphohistiocytosis (HLH).

2. CASE TWO PRESENTATION

A 62-year old Caucasian male with no significant past medical history, presented to the hospital with 2 weeks of fever, not feeling well, hematuria and loss of appetite. Examination revealed left renal mass, and moderate hepatomegaly. The ultrasound examination of the kidney confirmed large irregular renal mass involving the upper and mid-portion of the left kidney that invaded the capsule of the kidney and indented the pelvi-

calyceal system. Urine cytology confirmed the presence of renal cell carcinoma. His laboratory revealed significant anemia with hemoglobin of 7.2 g/L, thrombocytopenia of 76,000/L and leucopenia of 2,300 WBC/L. His ferritin level was high of 70,000ng/ml. The patient had high liver enzymes (AST, ALT, and GGT, 2-3 times the upper limit of normal). His total bilirubin was 4.2mg/dl, hypofibrinogenemia of <1.5g/L, and mild disseminate intra-vascular coagulopathy (DIC) with increased prothrombin time, and partial thromboplastin time (PT, aPTT), and D-Dimers. Liver biopsy following the correction of coagulopathy revealed evidence of HLH.

3. CASE THREE PRESENTATION

A 43-year old female with history of alcohol and drug abuse admitted to the hospital with deteriorating mental status and acute respiratory failure secondary to H1N1 viral infection. She was intubated and mechanical ventilated for respiratory failure. She was treated for H1N1 infection and respiratory failure and her laboratory revealed DIC like picture, pancytopenia, hypofibrinogenemia, elevated liver enzymes, hyperbilirubinemia, and rhabdomyolysis resulting in acute renal failure. She was placed on renal replacement therapy. Later in her disease course her bone marrow examination showed evidence of

hemophagocytic activities with multi-organ involvement and hyper-stimulation of the immune system with cytokine storm. Unfortunately, the patient had cardiac arrest and succumbed to her disease in her 12th day in the ICU.

4. DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) is an excessive immune activation with rapidly progressive course and life threatening syndrome. Rapid initiation of treatment is essential for the survival of the affected individuals.

The syndrome of HLH can be

1. Primary or familial when it is associated with gene mutation that is responsible for one of the several immune-deficiency syndromes (FHL1-5, XPL1, 2, GS2, MAGT1 etc.).
2. Secondary or acquired HLH without a known familial mutation; usually affects adults and those whom a clear trigger of HLH episode has been identified (viral infection, autoimmune disease, lymphoma etc.).
3. Macrophage Activation Syndrome: A form of secondary HLH due to an underlying Rheumatological disease. It is characterized by severe inflammatory response caused by immune system over activation leading to cytokine storm. The overactive macrophages start to engulf red blood cells (RBCs), platelets, white blood cells, and other cells leading to Inflammation within vital organs causing widespread organ damage.

Pathophysiology

- Immunologic abnormalities
 - Activated macrophages which secrete excessive amounts of cytokines, causing severe tissue damage.
 - Natural killer (NK) cells and cytotoxic lymphocytes (CTLs) are unable to eliminate damaged, stressed, or infected host cells and macrophages in response to infection, or malignant cells.
 - The failure of NK and CTLs to eliminate activated macrophages via a perforin-dependent cytotoxicity, coupled with macrophage over activity leads to release of high levels of interferon gamma and other cytokines which are considered a primary mediator of tissue damage (1-7)

- Hemophagocytosis
 - The macrophages jobs are antigen presentation, cytokine production, and phagocytosis of host cells.
- Cytokine storm
 - Interferon gamma, tumor necrosis factor alpha, interleukins (IL) e.g. IL-6, IL-10, IL-12 and soluble IL-2 receptor (CD25) (8-10).
 - IL-16 and IL-18 are also high in some cases, (11, 12)
- Triggers
- Genetics
- Immune deficiency syndromes

Epidemiology

- Primary HLH (familial), occurs in pediatric age group, the highest incidence in those less than 3 months old, and the male to female ratio is 1:1 (13, 14). However, the genetic abnormality can be diagnosed in adults as old as 70 years (15-17). Up to 25% of HLH cases are familial and are autosomal recessive inheritance (18).
- Secondary HLH including macrophage activation syndrome (MAS) is usually associated with triggers e.g. viral infection, malignancy, and Rheumatological diseases. This type of HLH occurs frequently in adults.

The Clinical Feature of HLH

- Fever, which is associated with multiple organ involvement (93%), (19, 20)
- Hepatomegaly (95%)
- Lymphadenopathy (33%)
- Neurological symptoms (33%), like
 - Sensorineural deafness, change in mental status, posterior reversible encephalopathy syndrome (PRES), seizure, ataxia, encephalitis, demyelinating peripheral neuropathy
- Rash in (31%)
- Splenomegaly (97%)
- Hypo-gammaglobulinemia, diarrhea, bleeding, gram negative sepsis.
- Laboratory abnormalities
 - Cytopenia- anemia, thrombocytopenia, leucopenia

- High serum ferritin levels, usually >3000ng/mL (21) (the presence of Cytopenia, high ferritin, elevated sIL-2R and sCD163 in patients with HLH excluded other causes of high ferritin).
- Hepatitis (high AST, ALT, GGT, LDH, bilirubin, increased triglycerides, abnormal coagulation parameters, DIC and high D-dimers) (22). Liver biopsy is likely to show lymphocytic infiltrations with chronic persistent hepatitis with periportal lymphocytic infiltration (23).
- Other abnormalities
- Acute respiratory distress syndrome (ARDS)
- Severe hypotension
- Renal dysfunction with hyponatremia secondary to syndrome of inappropriate ADH (SIADH)
- Skin manifestation, rash, erythema, petechiae, and purpura
- Bleeding from altered coagulation secondary to liver failure, thrombocytopenia from bone marrow failure, and platelets functional defects
- Associated diseases (14, 24-31);
- Infection, especially viral, Epstein-Barr virus (EBV), CMV, parvovirus, varicella-zoster virus, influenza (H1N1), human herpes virus-8, HIV
- Malignancy
- Lymphoid cancers, T, NK, and anaplastic large cell lymphomas, leukemia (31-38), large B cell lymphoma, myeloid malignancy, and solid tumors (18, 33, 39-41).
- Rheumatological disease (MAS) (42-44):
- Systemic juvenile idiopathic arthritis (sJIA)
- Still's disease of adults
- SLE
- Rheumatoid arthritis
- Mixed connective tissue diseases
- Antiphospholipid syndrome
- Sjogren syndrome
- Vasculitis
- Immune-deficiency disorders;
- Associated with mutations in primary HLH (45-50)

- Acquired immune deficiencies (HIV/AIDS, hematopoietic cell transplantation, solid organ transplants (31, 51, 52)
- Lymphoproliferative disease (53-55)
- Administration of anti-thymocyte globulin, splenectomy (56).

The Presentation of the Syndrome is Usually Dramatic with

- Fever
- Hepatosplenomegaly
- Cytopenia
- Low ESR due to hypofibrinogenemia and high CRP
- Elevated ferritin levels
- Elevated LDH
- High triglyceride levels
- Bleeding disorders with high PT, aPTT, and high D-dimers, low fibrinogen level (DIC-like picture)
- Hemophagocytosis on the bone marrow aspirate or liver biopsy when possible
- Underlying predisposing diseases, infection, Rheumatological disease or malignancy

The Syndrome can be Diagnosed with Presence of Constellation of Signs and Symptoms Listed Above with the Followings

- High ferritin levels usually >3000ng/ml (high sensitivity and specificity)
- Elevated soluble CD25 (soluble IL-2 receptor alpha)
- Phagocytosis with Cytopenia
- Low ESR and high CRP
- Abnormal liver function tests with coagulopathy
- Hypofibrinogenemia with high D-dimers

All the three cases presented have had many features of the syndrome with multi-organ system involvements, evidence of coagulopathy, high ferritin levels, Cytopenia, and most importantly the biopsy of the affected organs showed phagocytosis of the blood cells. The rapidly progressive course, and the high mortality associated with HLH along with delay in the diagnosis contribute to the dismal outcome of the condition if HLH-specific therapy could not implemented as soon as possible.

Treatment of the syndrome consists of supportive therapy with blood products transfusion, treatment of the underlying infection, autoimmune disorders, and malignancy alone with HLH specific therapy consists of;

- Etoposide and dexamethasone at tapering doses over 8 weeks
- Intra-thecal methotrexate and hydrocortisone if CNS is involved
- Hematopoietic cell transplant may be needed
- Refractory disease to induction therapy is treated with anti-CD52 monoclonal antibody almetuzumab, before transplant
- Median survival for patients with HLH is approximately 50%. Poor prognostic factors include younger age, CNS involvement, and failure of therapy to induce a remission prior to HCT.

5. CONCLUSION

The syndrome of HLH, including MAS is characterized by fevers, confusion, dyspnea, abdominal pain and pancytopenia, along with high ferritin levels, severe transaminitis, AKI, DIC. Diagnosis via bone marrow biopsy or biopsy of other involved organ would show evidence of hemophagocytosis. These changes are primarily occurs in lymph organs like lymph nodes, spleen, bone marrow, and liver, but other organs can be involved. If not treated, the disease leads to patient demise from coagulopathy and multi organ failure.

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