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An unusual presentation of Hemophagocytic Lymphohistiocytosis – A rare but potentially fatal entity

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is an autoimmune phenomenon characterized by reactive hyperactivity of cytotoxic T cells and histiocytes, leading to hypercytokinemic injury to cells and organ system, which leads to multiorgan dysfunction and ultimate failure. We had a patient 26 year old female, with no comorbidities came with very late presentation of psoas abscess (trauma related). On presentation she was encephalopathic hence she got mechanically ventilated. Her lab investigations showed bicytopenia, coagulopathy, hyperbilirubinemia (indirect) with mild transaminits and normal renal parameters. She was started on empirical antibiotics and source control was done. Despite adequate source control, she continued to deteriorate. Pus culture showed E.coli and negative for TB. On extensive evaluation, she was found to have dengue IgM positive. Through out the course she was normothermic. On further evaluation on Day 5, she was found to have normal LDH levels, hypofibrinogenemia and hypertriglyceridemia. Imaging done showed hepatomegaly with normal sized spleen. On day 6, she started to develop bilateral lowerlobe consolidations. On suspicion of HLH, we did bone marrow aspiration that was consistent with hemophagocytosis. We planned to start her on Dexamethasone, but she unfortunately succumbed to death due to underlying sepsis and multiorgan failure. Early suspicion of HLH didn't arise because of normothermia, very mild transaminits, hyperbilirubinemia and normal sized spleen. Thus, clinical presentation of HLH is variable and early suspicion of this life threatening condition is warranted.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an autoimmune phenomenon characterized by reactive hyperactivity of cytotoxic T cells and histiocytes, leading to hypercytokinemic injury to cells and organ system, which leads to multiorgan dysfunction and ultimate failure. The aetiology of HLH may be classified as genetic (primary) and acquired (secondary). Secondary HLH occurs in the settings of infections, systemic connective tissue disease and lymphoid malignancies. The usual clinical presentation

will be fever associated with multiple organ involvement/failure.

Case Report

We had a patient 26 year old female, with no comorbidities came with very late presentation of psoas abscess (trauma related). On presentation she was afebrile, encephalopathic and hypotensive. Hence she was started on Noradrenaline and got mechanically ventilated. Her lab investigations showed bicytopenia (TLC-2750, Neutrophils – 1560, platelets - 76000), coagulopathy, hyperbilirubinemia (indirect) with mild transaminitis and normal renal parameters. ABG showed mild lactic acidosis. Her chest X-ray was within normal limits. Her SOFA score was 16. MRI done showed irregular collection in the right iliopsoas muscle extending to quadratus lumborum. She was started on empirical antibiotics (MEROPENAM) and source control was done on day 1, followed by VAC dressing on day 4. Despite adequate source control, she continued to deteriorate. Pus culture showed E.coli and negative for TB. On extensive evaluation, she was found to have incidental dengue IgM positive. Through out the course she was normothermic.

On further evaluation on Day 5, she was found to have normal LDH levels, hypofibrinogenemia(120mg/dl), Hyperferritinemia (>2000 µg/L) and hypertriglyceridemia(347mg/dl). Imaging done showed hepatomegaly with normal sized spleen. As she was not tolerating enteric feeds, she was started on TPN. Blood and ET cultures were sterile.

On day 6, she started to develop hypoxia. CT done showed bilateral lower lobe consolidation with surrounding ground glass opacities. On suspicion of HLH, we did bone marrow aspiration that was consistent with hemophagocytosis. She fulfilled 5 out of 8 criteria and her HScore (6) was 210 points (88 to 93% probability of hemophagocytic syndrome). (**Figure 1**)

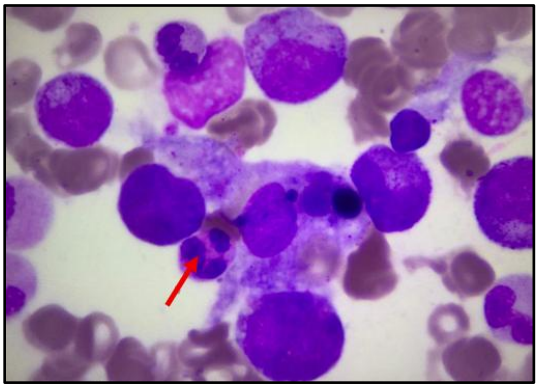

Figure 1: *Macrophages with Hemophagocytic activit*

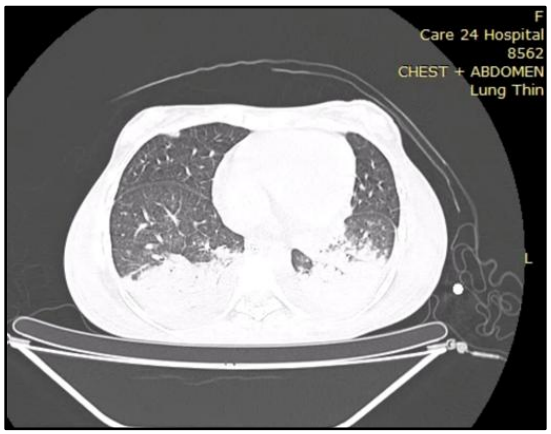

Figure 2: *Bilateral lower lobe consolidation*

We planned to start her on Dexamethasone, but she unfortunately succumbed to death due to underlying sepsis and multiorgan failure. Early suspicion of HLH didn't arise because of normothermia, very mild transaminits, hyperbilirubinemia and normal sized spleen. Thus, clinical presentation of HLH is highly variable.

Discussion

HLH is a rare complication of dengue infection and can be often missed if not suspected because it may mimic sepsis syndrome. As per HLH-2004 diagnostic criteria,

HLH is diagnosed when at least five of the eight criteria listed are fulfilled. These criteria are fever, splenomegaly, cytopenia affecting at least two of three lineages in peripheral blood, ferritin ≥500 μg/L, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent natural killer (NK) cell activity, and high level of soluble interleukin-2 receptor alpha chain (CD25).[1] Our patient had Hscore of 210 points.[6] (**Table 1**)

Table 1: *HScore*[6]

Parameter H Score[12]	**Criteria for scoring**
Known underlying immunosuppression	0 (no) or 18 (yes)
Temperature (°C)	0(< 38.4), 33(38.4-39.4), or 49(> 39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
No of cytopcnias	0 (!lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin (ng/ml)	0 (< 2,000), 35 (2.000-6.000), or 50 (> 6,000)
Triglyceride (mmoles/liter)	0 (< 1.5), 44 (1.5-4), or 64 (> 4)
Fibrinogen (gm/liter)	0 (> 2.5) or 30 (s 2.5)
Serum glutan1ic oxaloacetic	0 (< 30) or t9 (30)
Hernophagocytosis features on bone marrow aspirate)	0 (no) or 35 (yes)

HLH is a hyperinflammatory state that induces cytokine storms, leading to multiorgan dysfunction. Clinically, HLH presents with nonspecific signs of systemic inflammation, including prolonged fever, cytopenias, hepatosplenomegaly, and elevated inflammatory markers like ferritin. Neurological symptoms, liver dysfunction, and respiratory distress may also occur. The bone marrow in HLH shows macrophage-derived phagocytosis of blood cells.[2] In adults, the presentation is often obscured by another confirmed multiorgan system process, eg, malignancy, sepsis, or an autoimmune process. A high index of suspicion should be maintained in any patient who presents with multiorgan failure with associated cytopenias, coagulopathy, and failure to improve with standard treatment.[7]

Lung involvement in HLH is not frequently described. In a study of 219 patients with HLH, 54% had lung involvement. The patients with lung involvement had serious multiorgan dysfunction.[3] The various radiologic findings included were centrilobular nodules, consolidations, ground-glass opacities, septal thickening, pleural effusions, and mediastinal lymphadenopathy. Our patient had six out of eight criteria for HLH with pulmonary involvement in the form of ground-glass opacities, consolidations, and septal thickening.

HLH is, by definition, a multiorgan pathology with disease occurring indiscriminately due to widespread, deregulated immune system activity. Lungs can develop acute respiratory distress syndrome, hearts can be affected by myocarditis with its complications, and kidneys can suffer microangiopathies, brains can succumb to fatal meningoencephalitis, and livers can acutely fail. Not a single major organ system is spared the devastating effects of this disease. The majority of patients who die from the disease die as a result of hemodynamic collapse.[7]

The treatment approach of HLH is targeted first toward the inciting event, which may be a viral infection, autoimmune disorder, or malignancy. The

HLH-94 protocol states that induction therapy with etoposide is indicated in malignancy-associated HLH or where there is evidence of clinical deterioration. Other therapies are corticosteroids, intravenous immunoglobulin, and cyclosporin. Allogenic stem cell transplantation is reserved for refractory cases.[4-5]

Conclusion

Hemophagocytic lymphohistiocytosis is an immunologically mediated inflammatory response to viral infections, immune disorders, and malignancy. From our case we conclude that 1) Though EBV is the most common viral infection known to cause HLH, dengue-indued and bacterial infections induced HLH can also occur. 2) Pulmonary involvement though rare but can occur in HLH. 3) The clinical presentation of HLH is highly variable with salient features being absent. Thus, early suspicion of this life-threatening condition is warranted.

Source of Funding

None.

Conflict of Interest

None.

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