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Case Report

Hemophagocytic lymphohistiocytosis in a HIV positive patient associated with *Pneumocystis Jirovecii* pneumonia and hepatitis C infection

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation with a high mortality rate. According to the literature, HLH in Human Immunodeficiency Virus (HIV) infected patients has not been reported in Sri Lanka. In HIV positive patients, HLH can be triggered either due to HIV per say or due to opportunistic infections (OI) or due to immune reconstitution inflammatory syndrome following initiation of ART. Here, we discuss a HIV positive patient who is having HLH with Pneumocystis jirovecii pneumonia (PJP) and hepatitis C infections. Our aim is to emphasize the importance of considering possible HLH in patients with HIV.

Key words: Hemophagocytic lymphohistiocytosis (HLH) ,Human Immuno Deficiency Virus (HIV) , Acquired Immuno Deficiency Syndrome(AIDS), Immune Reconstitution Inflammatory Syndrome(IRIS), Anti retroviral treatment (ART),opportunistic infections(OIs)

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare life-threatening syndrome driven by unregulated hyperactive T-lymphocytes and macrophages causing hematopoietic cell phagocytosis and excessive release of inflammatory cytokines (1, 2). It can be genetic (primary HLH) or acquired (secondary HLH) (1, 2). The latter is secondary to immunological dysregulation induced by infections, malignancies, or autoimmune conditions (2). In HIV infected patients HLH can be triggered by HIV infection either in acute seroconversion stage or in AIDS stage, due to opportunistic infections (OI) or due to immune reconstitution inflammatory syndrome following initiation of ART (3). The diagnosis of HLH in patients with HIV is challenging and requires a high index of suspicion. This is because various clinical and laboratory abnormalities listed in the diagnostic criteria for HLH can be seen with advanced HIV. Moreover, hemophagocytic syndromes can mimic sepsis and other conditions that are often encountered in patients with HIV.

Case Presentation

A 42-year-old male, presented to a base hospital in Kegalle district, Sri Lanka, with loss of appetite and loss of weight for the last 18 months, non-productive cough with shortness of breath for three months and fever for more than three weeks duration. He didn't have any abdominal pain, nausea, diarrhea, headache, neck stiffness, or vision changes. He was also complaining of a rash on the scalp and exposed parts of the body. On arrival he was febrile (39C^{o}), wasted and was having pruritic papular urticaria and extensive seborrheic dermatitis of the scalp. He was pale without icterus and was having non tender firm discrete lymphadenopathy on the cervical, inguinal and axillary regions. Respiratory, abdominal, cardiovascular, musculoskeletal and central nervous systems examination were normal. He was investigated for pyrexia of unknown origin (PUO).

With high suspicion of sepsis, he was started on intravenous Ceftriaxone and oral Clarithromycin after the baseline investigations outlined in table 01.

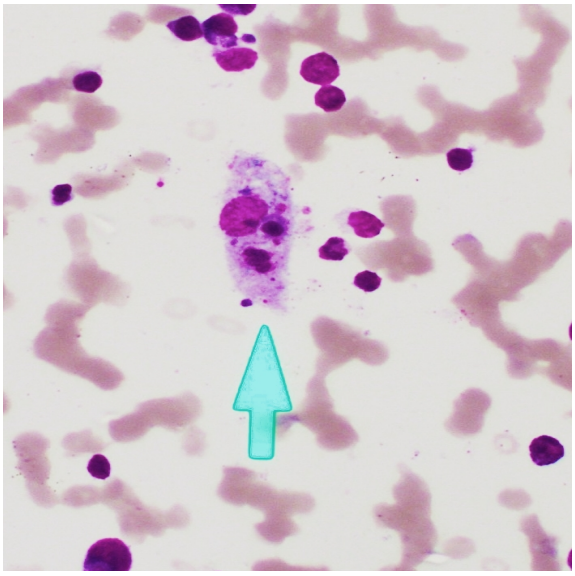
Table 1: Baseline investigations

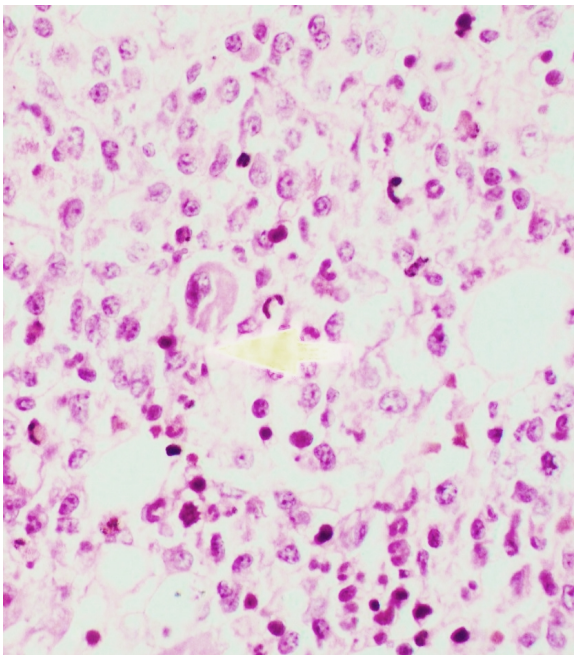
Laboratory tests	**Patient laboratory values**	**Reference laboratory values**
Hemoglobin, g/dL	7.9	11-15
Neutrophils , 109/L	0.49	2-7
Platelets, 109/L	94	150-450
Creatinine, mg/dL	0.97	0.6- 1.1
AST, units/L	42.3	9-35
ALT, units/L	16.5	10-40
Total bilirubin, mg/dL	1.05	0.1-1,2
LDH u/L	1569	0-243
ESR	125mm/1st hour	
CRP, mg/L	34	0-5
UFR	normal	
Sputum for acid fast bacilli (AFB)	negative	
Sputum for Genexpert	Negative for MTB	
Blood culture	Positive for coliforms	
Blood picture	Pancytopenia	
2D Echo	LVF>60%. No echo evidence of infective endocarditis	
USS abdomen	Sub centimetre size para aortic lymph adenopathy and splenomegaly	

However, the patient didn't respond to the first line, or second line antibiotics and fever continued. Cervical lymph node biopsy was attempted but failed and his HIV test became positive. Treatment for Pneumocystis jiroveci pneumonia (PJP) was started as the patient was having typical symptoms with characteristic x ray findings. HRCT was not done due to non-availability.

Bone marrow biopsy was conducted and samples were sent for TB culture, GeneXpert, AFB and histopathology. The investigations for TB came as negative from the bone marrow biopsy samples. HIV viral load was 16000 copies/ml and the CD4 count was 232 cells/ul. Anti-retroviral treatment was started one week after the PJP treatment and the regimen consisted of Tenofovir, Emtricitabine and Efavirenz. This regimen was started with the anticipation of starting anti TB treatment if the need arises. However, one week after commencing ART the fever spikes increased in magnitude and frequency. The liver enzyme levels increased by more than 10-fold from baseline and ART was withheld eight days after commencing it. Histopathological features of bone marrow biopsy showed moderately hyper cellular bone marrow with increased macrophage numbers and haemophagocytosis. He was also having increased triglycerides (407mg/L) and serum ferritin (>2000ng/ml) levels. As the patient met HLH-2004 diagnostic criteria, he was started on IV Dexamethasone 16 mg daily. Meanwhile, patient's liver and renal functions deteriorated. As the transaminases were more than 20 times higher than the upper normal limit, all the drugs except Dexamethasone was omitted and planned to reintroduce one by one. However, the patient's oxygen saturation, cardiac functions deteriorated further and was observed in high dependency unit till been transferred to ICU. Despite the resuscitation efforts, the patient passed away. The Hepatitis C antigen/antibody ELISA test came as reactive around one week after the death.

Figure 1: Bone marrow smears showing features of hemophagocytosis





Discussion

The diagnosis of HLH can be challenging, and it depends on clinical, laboratory, and histopathologic findings. Common laboratory findings include cytopenia, liver synthesis dysfunction, and elevated level of ferritin, triglycerides, and serum transaminases. Histopathology may show accumulation of lymphocytes and activated macrophages from various sites (4). The diagnosis of HLH requires a positive genetic workup or the presence of at least 5 clinical and laboratory criteria defined in HLH-2004 diagnostic criteria by the Histiocyte Society (5)

Table 2: HLH diagnostic criteria by the Histiocyte Society (2004)

Diagnosis of HLH requires one of the following criteria
Presence of molecular mutations* related to HLH Or Presence of five of the eight following criteria: • Fever (temperature ≥ 38.5°C) • Presence of splenomegaly • Cytopenia (affecting ≥ 2 cell lineages): a. Hemoglobin <9 g/dl b. Platelets <100 X 10^3/ml c. Neutrophils <1 X 10^3/ml • Hypertriglyceridemia (265 mg/dL or more) and/or hypofibroginemia (less than 150 mg/dl) • Low or absent NK T-cell** activity • Elevated ferritin more than 500 ng/ml • Elevated soluble form of DC25 (α-chain of SIL-2Rα*** • Histopathologic evidence of hemophagocytosis in bone marrow, spleen, liver or lymph node biopsy.

* PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4 ** Natural killer T-cell *** Soluble interleukin-2 receptor

HLH has a poor overall prognosis even with appropriate therapy, a more fulminant course of HLH may occur in HIV positive patients (6). HIV infection has been associated with HLH in several different ways. In the majority of such cases, AIDS acts only as the underlying disease setting in which an opportunistic infection triggers the onset of HLH. However, HIV itself, without opportunistic infections, has been attributed to be the cause of HLH in several reported cases. Hemophagocytic lymphohistiocytosis has also been described in the settings of immune reconstitution inflammatory syndrome (IRIS) and acute HIV infection (7).

Our patient was diagnosed as having secondary HLH based on the HLH-2004 criteria, in the setting of HIV, Hepatitis C and PJP infections. Immune over activation was present in our patient with fever, fatigue, and elevated inflammatory markers. However, it was not

entirely clear whether his presentation was solely related to HIV itself or associated with Hep C coinfection and PJP.

HLH needs to be considered and recognized early. Its overlap with other infectious processes renders its diagnosis more challenging as many infections can present with fever, splenomegaly, and high ferritin levels (8). Bone marrow biopsy is essential to diagnose HLH to detect hemophagocytosis and to exclude other causes of cytopenia. The main treatment for secondary HLH is to treat the underlying cause with good supportive care, however, immunosuppression is often required. Dexamethasone is the first-line drug used in the immunosuppression of secondary HLH cases according to the HLH-94 treatment protocol. In some cases, we may need to use etoposide and cyclosporine when dexamethasone fails to achieve the required response. Hematopoietic stem cell transplant may be an option for the definitive treatment of HLH in selected patients (9).

Conclusion

This case shows the clinical complexity and diagnostic challenges faced when HIV positive patients present with HLH. The identification of underlying etiologies is crucial for the proper management and treatment of HLH. In this case, the patient presented with fever, and was later found to have HIV with PJP and HCV infections. This highlights the importance of considering HLH in this patient population. The clinical picture is vague, including fever, hepatomegaly, splenomegaly, and pancytopenia. Lack of specific manifestations poses a challenge in establishing a definitive diagnosis. Further research is needed to better understand the pathophysiology and optimal management strategies for HIV/AIDS patients with HLH.

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