International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

It's Not Always Lupus

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Abstract: ***A 26-year-old female presented with fever on and off since last 5 months with weight loss and loss of appetite. Patient has history of infertility with one spontaneous abortion. Detailed history revealed history of recurrent aphthous ulcers, alopecia, low back ache and arthralgia. On examination patient appeared pale with rashes over her body. Patient had tachycardia with a systolic murmur. Cervical lymph nodes were palpable. Further workup showed persistent bicytopenia, hypertriglyceridemia and hepatosplenomegaly. A detailed evaluation with the help of the team from Rheumatology and Haematology, we concluded the final take on this rare presentation.***

Keywords: Systemic Lupus Erythematosus (SLE), Hemophagocytic lymphohistiocytosis (HLH), hepatosplenomegaly, H score, hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia, hemophagocytosis

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a severe clinical entity associated with high mortality in the adult population. HLH has been associated with infections, malignancy and autoimmune conditions such as Systemic Lupus Erythematosus (SLE), however this is often in the context of a disease flare. Currently, there are limited reports of inaugural SLE manifesting as HLH with a lack of consensus on treatment and management of these patients.

2. Case

We report a 26-year-old female patient with complaints of fever on and off since last 5 months along with weight loss and decreased appetite. Patient also had complaints of rashes mainly over the bilateral upper limbs, thighs and back which was maculopapular and non-blanching. At the time of admission, the patient appeared fatigued but nontoxic and in no acute distress. She was febrile with an oral temperature of 38.4°C. Her blood pressure was 112/59 mm Hg, her pulse was 126 per minute, her respiratory rate was 18 per minute, and her room air oxygen saturation was 100%. Patient had a past history of infertility and has been on treatment for last 1.5 years with history of recurrent aphthous ulcer and alopecia. Patient also complains of low back ache and arthralgia since last 6 months. Patient states a history of intrauterine foetal demise at 16weeks and had undergone evacuation and curettage. No history of any thrombotic event was elicited. On evaluation we noticed that the patient had cervical lymphadenopathy with history of cough with expectoration with bilateral crepitations and Ronchi. Patient appeared pale with tachycardia and soft systolic murmur in the mitral area. Abdomen was soft with slight tenderness in the right and left hypochondriac region with apparent hepatosplenomegaly. Routine labs were sent along with a USG abdomen which showed a haemoglobin level of 7.7gm% with a low TLC count (2600). Normocytic normochromic blood picture with anisopoikilocytosis and few tear drop cells were seen on peripheral smear. FERRITIN levels were raised (1971 ng/mL) with high Serum Triglyceride levels (245 mg/dL). USG Abdomen showed hepatosplenomegaly with some echotexture seen in the spleen with normal kidneys. Brucella serology was negative. Mantoux test was done which came to be negative. Renal function tests, Liver function tests and electrolytes were normal. Raised CRP levels (9.9 mg/L) and procalcitonin levels (1.97 mcg/L) with tenderness in the abdomen required a CT abdomen which showed splenic abscess in the cortical region with hepatomegaly. No feature of peritonitis was seen. Cultures were sent and patient was started on antibiotic coverage for the same. We involved the Rheumatologist as well as a Haematologist consultation. Provisional differential diagnosis of Systemic lupus erythematosus (SLE), Adult-onset Still's disease (figure 3)[6]and Hemophagocytic lymphohistiocytosis (HLH) (figure 2) was made. Rheumatoid factor was negative, ANA blot test showed positive nRNP/Sm and Ribosomal P-protein antigens while bone marrow study showed reactive marrow with evidence of mild hemophagocytosis. (Figure -1)

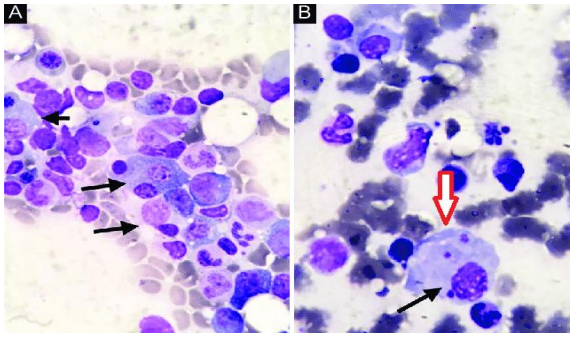

Figure 1: A - Bone Marrow Biopsy- B - Haemophagocytosis

Hemphagocytosis score (H score) was 225 points which pointed to a primary diagnosis of HLH. Persistent fever along with tenderness in the abdomen suggested another infective focus, probably the appendix for which the patient underwent Laparoscopic appendicectomy after blood transfusion. Plan to add steroids was withheld till the infective foci subsided and later patient was started on steroids after ruling out CNS infection with a CT brain.

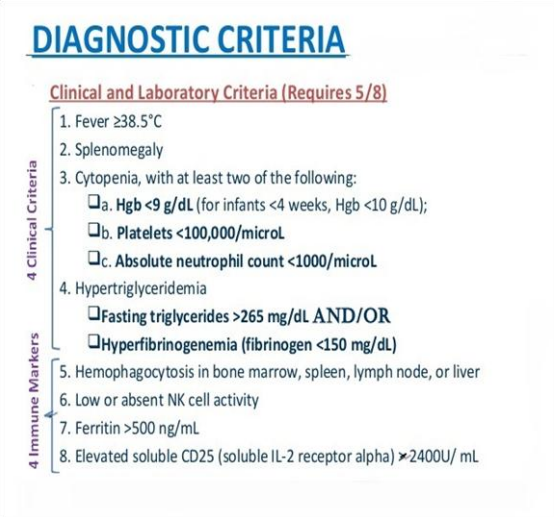

Figure 2

Yamaguchi classification criteria for adult Still's disease (ASD)
Diagnosis of ASD
At least 5 criteria, including 2 major criteria, and no exclusion criteria
Major criteria
Fever ≥39°C lasting 1 week or more
Arthralgias/arthritis lasting 2 weeks or more
Typical skin rash*
White blood cell count ≥10,000/mm³ with neutrophils ≥80%
Minor criteria
Pharyngitis or sore throat
Lymphadenopathy
Hepatomegaly or splenomegaly
Liver enzyme abnormalities (transaminitis)
Negative for rheumatoid factor and antinuclear antibodies
Exclusion criteria
Absence of infection
Absence of malignant diseases
Absence of inflammatory disease
* Maculopapular, nonpruritic, salmon-pink rash with concomitant fever spikes.

Figure 3

3. Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a constellation of symptoms caused by dysregulated hyperinflammation and cytokine storm, resulting in a life-threatening syndrome. HLH is classified into primary (familial) and secondary etiologies (infection, autoimmune conditions, drugs and malignancy).[1] Clinically and biochemically, the hallmark features include hepatosplenomegaly, fever, hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia and pancytopenia[2]. Case reports involving new diagnosis of SLE as the onset of HLH is limited [3,4]. Hyperferritinemia has been cited as the best parameter to distinguish between active SLE flare and HLH-associated SLE with a sensitivity and specificity of nearly 100% [1]. However, hyperferritinemia in the HLH-94 study indicated that in the pediatric population, ferritin level > 500 mcg/L was 100% sensitive for HLH but less specific; whereas ferritin > 10,000 mcg/L was 90% sensitive and 96% specific for HLH [1].In the adult population, the correlation between hyperferritinemia and HLH is less clear, particularly with the presence of an overlapping autoimmune condition such as SLE. More recently, a group from France has published the "HScore", a well-validated scoring system for the diagnosis of HLH [1]. The scoring system incorporates parameters including organomegaly, ferritin, ALT, degree of cytopenia, fibrinogen, fever, and hemophagocytosis with a HScore > 250 conferring 99% probability of HLH and a score < 90 at < 1% probability. Interestingly, for case 1 the HScore was calculated as 225 (conferring 96-98% probability of HLH). In the future, the HScore may be a useful clinical parameter to help tease out active SLE from HLH-associated SLE. Classically, treatment of primary HLH is directed towards use of the HLH-2004 protocol including etoposide, dexamethasone, cyclosporine, consideration of intrathecal methotrexate and finally with hematopoietic stem cell transplantation. Treatment of secondary HLH is less clear, but ultimately relies on treatment of the primary auto-immune disease. In the two cases presented, SLE was the process associated with HLH and corticosteroids were rapidly initiated, in keeping with previously described cases [5].Because of the high mortality risk of HLH, the absence of rapid improvement of symptoms, even in the context of non-severe manifestations of SLE, requires aggressive immunosuppression with cyclophosphamide and frequently the addition of biologics such as Anakinra (IL1 inhibitor), infliximab (TNF inhibitor) and alemtuzumab (CD52 inhibitor).

4. Conclusion

HLH has been associated with infections, malignancy and autoimmune conditions such as Systemic Lupus Erythematosus (SLE), however this is often in the context of a disease flare. Currently, there are limited reports of inaugural SLE manifesting as HLH with a lack of consensus on treatment and management of these patients.

Abbreviations
CRP: C-reactive protein
ANA: Anti-nuclear antibody
HLH: Hemophagocytic lymphohistiocytosis
SLE: Systemic lupus erythematosus
***TNF*:** Tumor Necrosis Factor
IL1: Interleukin 1

5. Acknowledgement

The photograph of the excisional biopsy sample is courtesy of Department of Pathology, Bharti Vidyapeeth Hospital, Pune.

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Author Profile

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