Original Research Article

A case of pyrexia of unknown origin, latent mycobacterial tuberculosis infection with haemophagocytic lymphohistiocytosis - A rare association

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Abstract

Background: Haemophagocytic lymphohistiocytosis (HLH), previously named as Macrophage Activation Syndrome is a rare but potentially fatal disease of normal but overactive histiocytes and lymphocytes that commonly appears in infancy although it has been seen in all age groups. Fever, hepatosplenomegaly, pancytopenia, lymphadenopathy, and rash often comprise the initial presentation. Cutaneous involvement occurs in as many as 65% of patients. Here we report a rare case of Pyrexia of Unknown Origin with LTBI associated with HLH.
Keywords: HLH, IGRA, LTBI.

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INTRODUCTION

A 70-year-old male, resident of Baruipur, retired businessman was admitted with a history of 45 days fever associated with marked weight loss and weakness. The fever was intermittent in nature. He is a known diabetic on OHA. His clinical examination was significant for mild pallor and a moderate splenomegaly which was soft, non-tender. No evidence of lymphadenopathy was noted. No icterus. He was initially admitted at a private hospital for 2 weeks where he was investigated extensively but the patient continued to be febrile. Upon admission all routine blood tests along with cultures were sent for. Urine c/s showed growth of klebsiella sensitive to only Colistin. A Procalcitonin was sent for which was highly positive >5.21. The patient was started on Colistin and a repeat procalcitonin showed a slight decrease in its values. The patient however continued to be febrile. Haematological findings were Hb- 8.2, TC- 5860, plt- 1.7lacs, ESR- 20. Her routine blood biochemistry revealed mild hyponatremia, Na-124, rest being within normal limits. A LFT revealed mild transminitis. All other routine tests for a febrile state including Dengue, Malaria were normal. A sputum for AFB and Grams stain Culture sensitivity was also negative. A CXR was done which was normal. A serology for HIV, HbsAg, HCV was negative. A scrub tyohus IgM was also negative. A USG Whole Abdomen revealed mild hepatosplenomegaly. An Echocardiography did not reveal any evidence of infective endocarditis and had a normal ventricular function. Even after seven days of Colistin therapy and sloght decrease in procalcitonin levels the patient continued to be febrile and toxic in appearance. In view of this presentation a search for a rare cause needed to be kept in mind.

- With a pyrexia of unknown origin state so far, a PET CT was planned for which revealed FEW

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SMALL LYMPH NODES IN CERVICAL, PAROTID AND PORTOCAVAL REGION – LIKELY INFECTIVE/INFLAMMATORY.

- The patient continued to be febrile and had persistent tachycardia and started developing cough

A repeat sputum for AFB was sent which was negative.

- A EBV VIRAL CAPSID Ag IgM –was NEGATIVE

With persistent febrile episodes , cough and progressive weight loss we decided to send a blood for IGRA and ANA.

- Blood for IGRA was strongly positive; value was 185.55; normal value is <14.0 and ANA was negative

On further enquiry, family members reported that their domestic help suffered from pulmonary tuberculosis 18 months back. With this report, we started the patient on Anti Tubercular Therapy. However even after 10 days of ATD, the patient continued to be febrile with peak temperatures reaching to around 100*F.

A bone marrow aspiration revealed haemophagocytosis. With haemophagocytosis on bone marrow a blood for Triglyceride, Fibrinogen, Ferritin and D-dimer was sent for.

- Fibrinogen – 161.4 (170-400)
- Triglyceride - 488 (50- 200)
- Ferritin > 1650
- D-dimer- 5772 ng/mL (<500)
- We consulted a haematologist who advised us to start the patient on oral steroids. As per his advise, we started the patient on Tablet Dexamethasone 4mg – twice daily regimen along with ATD.
- So with the reports we diagnosed it as
- HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN A CASE OF LATENT TUBERCULOSIS INFECTION

DISCUSSION

HLH should be considered as a differential diagnosis in patients with tuberculosis who present with cytopenia(s), organomegaly, and coagulopathy. The existing literature points to the fact that TB-HLH may have an unpredictable and/or unfavorable outcome with or without ATT. Early diagnosis and initiation of ATT, even in the presence of disseminated disease, might alter the final outcome in these cases. First-line antituberculous drugs such as rifampicin have enzyme-inducing activity, which can lower the efficacy of drugs such as cyclosporine and etoposide used in the HLH 2004 protocol. Besides, HLH *per se* leads to significant derangement of liver functions, making the administration of ATT as well as etoposide difficult. HLH may even be exacerbated after initiation of ATT, which may be challenging to treat.[2,3] Therefore, it is open to speculation whether HLH *per se* or the delay in initiation of ATT is the predictor of unfavorable outcome in these cases. The best approach would be determination of treatment priorities based on the clinical condition of the patient and individualization of the treatment plan according to clinicolaboratory parameters, as was evident in our case. Finally, the utility of the HLH 2004 protocol in patients with TB-HLH seems to be controversial at present, and warrants larger future prospective studies. Highly elevated ferritin is strongly associated with HLH and its levels may provide a prognostic marker. Lin *et al.* suggested that a rapid rate of fall in ferritin levels following therapy initiation was associated with decreased mortality.[4] However, Park *et al*. in their cohort of 23 patients with secondary HLH found that the rate of decline in ferritin was not associated with survival, and that high fibrinogen at the time of diagnosis was significantly associated with survival.[5]

Table 1: Revised diagnostic guidelines for haemophagocytic lymphohistiocytosis

The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled
1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (five out of the eight criteria below):
A. Initial diagnostic criteria (to be evaluated in all patients with HLH)
Fever
Splenomegaly
Cytopenias (affecting 2 of 3 lineages in the peripheral blood):
Hemoglobin <90 g/l (in infants <4 weeks: hemoglobin <100 g/L)
Platelets <100X10^9/L
Neutrophils <1.0 X10^9/l
Hypertriglyceridemia and/or hypofibrinogenemia:
Fasting triglycerides >3.0 mmol/l (i.e. >265 mg/dl)
Fibrinogen <1.5 g/l
Haemophagocytosis in bone marrow or spleen or lymph nodes
No evidence of malignancy
B. New diagnostic criteria
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin<500 mg/l
Soluble CD25 (i.e. soluble IL-2 receptor) 2.400 U/mL

Primary or genetic HLH is inherited in an autosomal recessive or X linked fashion and can be further divided into familial hemophagocytic lymphohistiocytosis and X linked lymphoproleferative syndrome. In familial form the clinical syndrome of HLH is the primary and only manifestation.[6] Onset of the disease is seen during the first year in 70% children. Acquired forms may develop because of strong immunological activation of the immune system caused by severe infection and malignancy. In infection associated hemophagocytic syndrome triggering agents belong to Herpes group, especially EBV and CMV. Some malignant diseases like lymphomas which can develop before or during treatment are associated with

acquired form. Much data is not available about the incidence in children and adults but from available literature it appears to be more common than previously believed. A study done in Sweden reported 32 children with FHL. The incidence was 1.2/1,000,000 children per year.

REFERENCES

1. Morrell DS , Pepping MA , Scott JP , *et al.*. Cutaneous manifestations of hemophagocytic lymphohistiocytosis . Arch Dermatol. 20002 Sep . 138(9);1208-12 [Medline]
2. Seminari E, Contardi G, Rubert L, Fronti E, Comoli P, Minoli L, *et al.*. Tuberculosis-induced haemophagocytic syndrome in a patient on haemodialysis treated with anti-thymocyte globulin. Int J Tuberc Lung Dis. 2014;18:248–9. [PubMed] [Google Scholar]
3. Balkis MM, Bazzi L, Taher A, Salem Z, Uthman I, Kanj N, *et al.*. Severe hemophagocytic syndrome developing after treatment initiation for disseminated Mycobacterium tuberculosis: Case report and literature review. Scan J Infect Dis. 2009;41:535–7. [PubMed] [Google Scholar]
4. Lin TF, Ferlic-Stark LL, Allen CE, Kozinetz CA, McClain KL. Rate of decline of ferritin in patients with hemophagocytic lymphohistiocytosis as a prognostic variable for mortality. Pediatr Blood Cancer. 2011;56:154–5. [PMC free article] [PubMed] [Google Scholar]
5. Park HS, Kim DY, Lee JH, Lee JH, Kim SD, Park YH, *et al.*. Clinical features of adult patients with secondary hemophagocytic lymphohistiocytosis from causes other than lymphoma: An analysis of treatment outcome and prognostic factors. Ann Hematol. 2012;91:897–904. [PubMed] [Google Scholar]
6. Farquhar JW and Claireaux AE. Familial hemophagocytic reticulosis. Arch Dis Child.1952;27:519-525.

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