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SECONDARY HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN AN IMMUNO-COMPETENT PATIENT OF EXTRAPULMONARY TUBERCULOSIS

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ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) results when critical regulation of natural termination of immune/inflammatory responses is disrupted or overwhelmed. The predominant clinical findings of HLH are fevers (often hectic and persistent), pancytopenias, hepatitis and hepatomegaly and splenomegaly. The diagnosis is established by fulfilling one of the HLH 2004 criteria. A 55 years male patient presented with fever, abdominal pain and abdominal distension. Examination revealed cervical lymphadenopathy. and hepato-splenomegaly. Persistent pancytopenia was evident on laboratory investigation, USG showed multiple intra-abdominal lymphnode with necrosis. His bone marrow showed emperepolesis and haemophagocytosis and lymphnode biopsy showed tubercular lymphadenitis. Finally he was diagnosed as secondary HLH with extrapulmonary tuberculosis. Patient managed with Anti tubercular drug and steroid with satisfactory response.HLH is a fatal but curable if diagnosed early and rarely associated with extrapulmonary tuberculosis.

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INTRODUCTION

Macrophages, including kupffer cell and alveolar and bone marrow macrophages are the primary defence mechanism against exogenous pathogen. Macrophages when activated release pro-inflammatory cytokines like IL-1,8,12 and TNF-α, which contributes to pathogenesis of various acute and chronic diseases. Haemophagocytic lymphohistiocytosis (HLH) results when critical regulation of natural termination of immune/inflammatory responses is disrupted or overwhelmed. The predominant clinical findings of (HLH) are fevers (often hectic and persistent), pancytopenias, hepatitis and hepatomegaly and splenomegaly (Filipovich, 2009). Distinctions between primary (genetically determined) and secondary (acquired) forms of HLH have become increasingly blurred together as new genetic causes are identified. Certainly secondary or acquired HLH may be associated with infections (commonly the Epstein–Barr virus or EBV, bacteria, Rickettsia**,** etc.), hematological malignancies (mostly T/NK cell leukemias/ lymphomas), rheumatological/autoimmune disorders (so-called macrophage activation syndrome), etc (Gupta, 2010; Rouphael, 2007). To diagnose a case of HLH clinico-pathological criteria need to be fulfilled. The diagnosis is established by fulfilling one of the following HLH 2004 criteria: i) Positive family history or molecular diagnosis consistent with HLH (mutations of PRF, SAP, or Munc13-4 genes), ii) any five out of the following eight criteria: Prolonged fever, unexplained progressive cytopenias involving at least two cell lines (hemoglobin ≤90 g/L, platelet count ≤100 × 10^9/L, absolute neutrophil count <1× 10^9/L); splenomegaly; hyperferritinemia (≥500 ng/mL); fasting hypertriglyceridemia (≥265 mg/dL) or hypofibrinogenemia (≤1.5 g/L); histiocytic hemophagocytosis in bone marrow, liver, spleen, or lymph nodes without evidence of malignancy; low or absent NK cell cytotoxicity; and elevated soluble CD25 levels (≥2400 IU/mL of interleukin-2Rα chain) (Henter, 2007). Tuberculosis (TB) is epidemiologically one of the most important infections in Asian subcontinent especially in India.

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Prevalence of both pulmonary and extra-pulmonary tuberculosis (EPTB) is high in India approximately 2.5 million (https://tbcindia.gov.in/showfile.php?lid=3180). EPTB constituted about 15 to 20 per cent of all cases of TB. Tuberculosis may rarely be complicated by HLH, which may be diagnostically challenging to the treating physicians, and in the absence of early and definitive therapy may lead to significant morbidity and mortality (Brastianos, 2006). In this case report we have mentioned a rare case of HLH in an EPTB patients, managed with anti tubercular drug therapy (ATD) and Steroid and had a favourable outcome.

Case details

A 55 years non-diabetic, non-hypertensive, non-smoker, non-alcoholic male patient, resident of an urban area and shopkeeper by profession, presented to us with history of low grade fever predominantly evening rise for last 4 months, dull aching right upper abdominal pain for last one month and progressively increasing abdominal distension for last 15 days. Patient was apparently well 6 months back with history of minor ailments in past. He gradually developed anorexia with progressive weight loss . There was also associated low grade fever with evening rise and sweating (fever was high grade since last one week) without any history suggestive of cough, burning urination, body ache, arthalgia/arthritis, skin rash or gastro intestinal disturbances. When we examined the patient we found, his higher mental functions were normal with perfect orientation to time place and person. Speech was also normal. His built was average with a subnormal nutritional status. His abdomen was distended. There was moderate pallor, tachycardia, and temperature of 100°F with other vitals within normal limit. Systemic examination revealed lymphadenopathy involving left posterior triangle with matted and fixed lymph nodes with firm consistency. Liver was palpable 3 cm below costal margin with firm consistency moderately tender and 2 cm spleen was palpable below costal margin. Chest examination revealed no mediastinal dullness with bilateral vesicular breath sound and no adventitious sound. Other systemic examinations were non-contributory. Depending on our clinical assessment of lymphadenopathy with hepato-splenomegaly and anaemia we planned for following investigations.

i) **Complete Blood Count:** (as in Table 1)
ii) **Liver Function Test:** (as in Table 2)
iii) USG of Abdomen showed multiple hypo-echoic lymph nodes in the hilum of spleen, in the porta hepatis and in mesentery and pre and para-aortic region with evidence of necrosis.
iv) **Chest X-ray:** Unremarkable.
v) Urea and creatinine value on the day of admission and thereafter: (as in Table 3)
vi) **Lymph node biopsy:** Lymph node biopsy from left posterior triangle of neck (Station V) had shown that there was presence of multiple epitheloid granulomas with langhan's type of giant cell and extensive caseaous necrosis suggestive of Tubercular lymphadenitis. (Figure 1)
vii) **Bone marrow examination:** Bone marrow trephine biopsy showed that bone marrow was hypocellular, myelopoiesis is markedly reduced. Most of the cellularity is accentuated by erythroid progenitor cells with dystrophic changes. Megakaryocyte number has also been reduced. Some reticulum shows haemophagocytes and emporepolesis. (Figure 2 and 3)
viii) **Biochemical Parameters of inflammatory disease:**
Ferritin: 4600 mg/dl.
Triglyceride: 350 mg/dl.
Fibrinogen: 80 mg/dl.
ix) Autoimmuno marker: ANA, RA factor and Anti CCP was negative
x) HIV I and II negative.

So on the basis of clinico-laboratory data we have diagnosed this patient as having tubercular lymphadenitis with secondary haemophagocytic lymphohistiocytosis.

Table 1. Complete blood count day wise

Day	Hb (g/dl)	TC (dl)	DC	Platelets (dl)
1st	7.6	5000	N 25 L70	48000
4th	7.6	2500	N 30 L60	20000
6th	6.6	1700	N30 L60	10000
9th	6.6	2600	N10 L83	20000
11th	5.8	1800	N15 L82	16000
16th	8.5	3500	N45 L45	36000
24th	10.0	5500	N62 L28	150000

Table 2. Liver function test date wise

Day of Presentation	Liver Function Test
Day 1st	Bilirubin: 0.5, SGOT:36, SGPT: 48, Alkaline Phosphatase: 117, Total protein: 7.8,Serum Albumin: 3.4,Globulin: 4.4.
Day 5th	Bilirubin: 0.9, SGOT:58, SGPT: 27, Alkaline Phosphatase: 97, Total protein: 6.3,Serum Albumin: 3.0,Globulin: 3.3.
Day 10th	Bilirubin: 0.3, SGOT:11, SGPT: 12, Alkaline Phosphatase: 47, Total protein: 6.3,Serum Albumin: 3.0,Globulin: 3.3.
Day 15th	Bilirubin: 0.8, SGOT: 26, SGPT:34, Alkaline Phosphatase: 84, Total Protein: 5.8, Serum Albumin: 3.5, Globulin: 2.3.

Table 3. Urea and creatinine value on the day of admission and there after

Day of presentation	Urea	Creatinine
Day 1st	23	0.9
Day 5th	16	0.7
Day 10th	31	1.0
Day 15th	36	0.8

Treatment

We have managed this patient with supportive care, blood transfusion, platelet transfusion systemic broad-spectrum antibiotics prior to confirmation of diagnosis. Following confirmation of diagnosis of tubercular lymphadenitis we have managed this patient with Anti tubercular drugs with daily

regimen and pyridoxine. When we have conclusive evidence that this patient is having secondary HLH, we have started Systemic corticosteroid with favourable response. On subsequent follow up after two weeks he has symptomatic improvement and two months later his haematological and biochemical parameters normalised. He continued his ATD for 6 months and unfortunately lost to follow up there after.

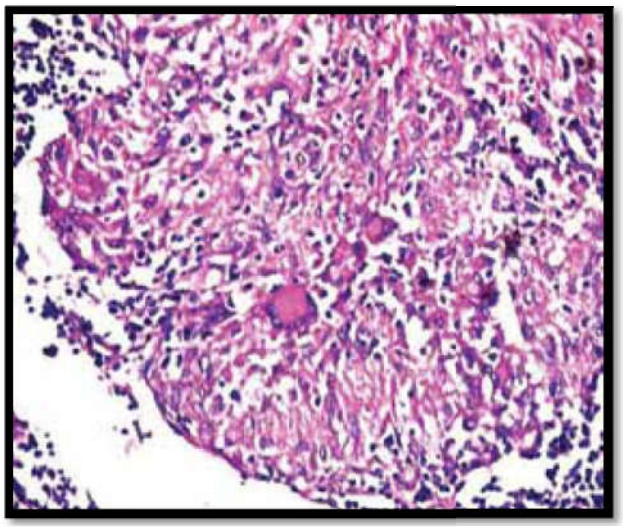

Figure 1. Lymphnode biopsy sample histopathology examination under microscope after haematoxylin eosin staining

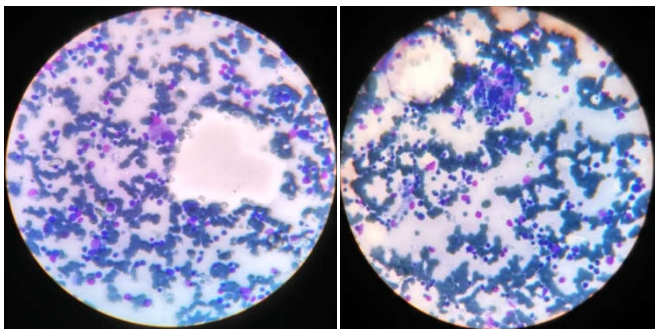

Figure 2. Bone marrow biopsy sample showing haemophagocytes and emperepolesis

DISCUSSION

Our patient presented with fever, abdominal pain and distension for quite some time with recent exacerbation. Examination imparted node left posterior triangle of neck nodes and hepato-splenomegaly and laboratory evaluation suggested persistent pancytopenia with no peripheral smear abnormal cells and elevation of inflammatory markers. Lymph node biopsy was suggestive of tubercular lymphadenitis. Bone marrow aspiration under persistent pancytopenia showed haemophagecytes with emporepolesis. Depending of this we have diagnosed this case as secondary HLH as per 2004 HLH criteria (Henter, 2007). HLH is a fatal condition, it has reported infrequently with EPTB. 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 response may be unpredictable with ATD in EPTB-HLH cases. Early diagnosis and initiation of ATD and steroid might have altered fatal out come in this patient. HLH may even be exacerbated after initiation of ATD, which may be challenging to treat (Seminari, 2014 and Balkis, 2009). We have reported this case of EPTB with secondary HLH diagnosed early and managed with ATD and steroid with favourable outcome.

Conclusion

HLH is a fatal condition, EPTB is less commonly consider as a precipitator of HLH. Management solely depends on early diagnosis and intervention by graded immunosuppression.

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