International Journal of Advances in Medicine
Kondam A et al. Int J Adv Med. 2022 Oct;9(10):1064-1068
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20222407

Case Report

Adult hemophagocytic lymphohistiocytosis triggered by disseminated tuberculosis and *Klebsiella pneumoniae* co-infection in an immunocompetent individual-a diagnostic challenge

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Received: 18 August 2022
Accepted: 15 September 2022

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ABSTRACT

Here in we report a diagnostically challenging case of adult hemophagocytic lymphohistiocytosis (HLH) triggered by disseminated tuberculosis and *Klebsiella pneumoniae* co-infection in an immunocompetent Individual. She was a young female presented with complaints of fever, abdominal pain and jaundice. Her evaluation showed cytopenias, hyperbilirubinemia, transaminitis, and hepatosplenomegaly. She progressed to have multi-organ involvement in the form of myocarditis, pleural effusion. Provisional diagnosis of fever with unknown origin and sepsis with multiple-organ dysfunction was made and evaluated for the same. Rapid clinical deterioration with evaluation for sepsis being normal prompted for considering HLH in the differential diagnoses, bone marrow and other criteria have been met resulting in confirmation of the same. Without prior past or family history of HLH, secondary HLH was suspected and substantial evaluation for possible triggers was made, and concomitantly immune suppression was started with corticosteroids. Disseminated tuberculosis was diagnosed and concomitantly *Klebsiella pneumoniae* was isolated from the bronchioalveolar lavage cultures. As there was no significant immune response culmination, intravenous immunoglobulins were added along with the treatment for possible triggers-tuberculosis and *Klebsiella* simultaneously. Patient showed significant improvement with this approach. In conclusion management of HLH is different from conventional sepsis and the treatment for each cause of HLH also varies. Furthermore, this case report stresses on the importance for initiating treatment rapidly and tailored approach of management therapy for each case.

Keywords: HLH, *Klebsiella pneumoniae*, Disseminated tuberculosis

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare hyperinflammatory syndrome characterized by excessive activation of macrophage and T-cells, causing excessive cytokines production and subsequent immune-mediated injury of different body organs.[1] It usually occurs secondary to malignancy, infections, or autoimmune disorders. HLH is marked by cytopenias and signs and symptoms of systemic inflammation related to macrophage activation.[2] This diagnosis is gaining importance as its presentation is quite similar to sepsis and sepsis-like conditions and can get overlooked easily. Disseminated tuberculosis occurs by hematogenous spread of *Mycobacterium tuberculosis* from lung and may involve bone, bone marrow, central nervous system, liver, spleen, skin etc. Patients usually presented with fever, anorexia, respiratory ailments in most of the cases. HLH might rarely complicate the clinical course of disseminated TB. Recent literature review by Padhi et al reported only 63 cases of tuberculosis-associated HLH up to year 2014.[3] *Klebsiella pneumoniae* is a serious gram-negative bacillus commonly causing hospital acquired pneumonia, urinary tract infections and so sepsis and multi-organ dysfunction. However, *Klebsiella pneumoniae* was associated to

activate HLH in only few cases.[4,5] *Klebsiella* infection as an added trigger along with disseminated tuberculosis makes this case unusual and challenging. With these viewpoints, here we aimed to present a rare case of adult HLH triggered by disseminated tuberculosis and *Klebsiella pneumoniae* co-infection in an immunocompetent individual.

CASE REPORT

Miss S, in early 20s, presented with complaints of fever since last 3 weeks, abdominal pain since last 5 days and jaundice since last 2 days. She had high grade, continuous fever with chills one week prior to presentation, which was then associated with abdominal pain-insidious onset, diffuse, mild, non-radiating, not related to food, not associated with any vomiting or altered bowel movements. Patient was admitted to a high-dependency unit, her blood tests showed bicytopenia, later pancytopenia and multi-organ involvement.

Differentials of tropical illnesses like, typhoid, leptospirosis, dengue hemorrhagic fever, rickettsial infections, malaria and acute cholangitis, viral hepatitis, COVID-19 and other common fever of unknown origin causes-tuberculosis, infective endocarditis and autoimmune conditions were considered and worked up for the same. Electrocardiogram showed sinus tachycardia and 2D echocardiogram showed no clot/vegetations. infective endocarditis was ruled out. Differentials of disseminated tuberculosis and hematological malignancies were still considered. Bone marrow studies were performed as pancytopenia was worsening. Bone marrow showed normocellular marrow with normal maturation of all cell lines, good number of hemophagocytic histiocytes with engulfed hematopoietic cells (erythroid, myeloid and platelets) consistent with secondary HLH. No abnormal cells or granulomas were noted on bone marrow biopsy. With Epstein Barr virus (EBV) and cytomegalovirus (CMV) infections being common triggers for secondary HLH, blood sample for PCR was sent and came negative. As HRCT thorax showed right upper lobe consolidation, Mantoux test, sputum for aerobic culture and staining for AFB and GeneXpert for *Mycobacterium tuberculosis* (M. Tb) were sent and were negative. Bronchoscopy was performed and M. Tb was detected in the lavage fluid via GeneXpert in low amounts without any rifampicin resistance.

Patient's reports were reviewed and fulfilled 6 out of 9 criteria according to HLH 2004, suggesting secondary HLH; Fever-104° F, hepatosplenomegaly-radiological evidence, bicytopenias- Hb:8.1 g%, platelets:31000 cells/mm^3, hypertriglyceridaemia-470 mg/dL and hypofibrinogenaemia-137.8 mg/dL and bone marrow showed hemophagocytic evidence (Figure 1), with elevated ferritin-3756 ng/ml.

NK cell activity, soluble CD25, and CXCL9 could not be performed due to non-availability of testing facilities. Broncho-alveolar lavage fluid cultures grew *Klebsiella pneumoniae*. Therefore, we have concluded that the co-infection of tuberculosis and *Klebsiella* were possible triggers for activation of HLH in this case.

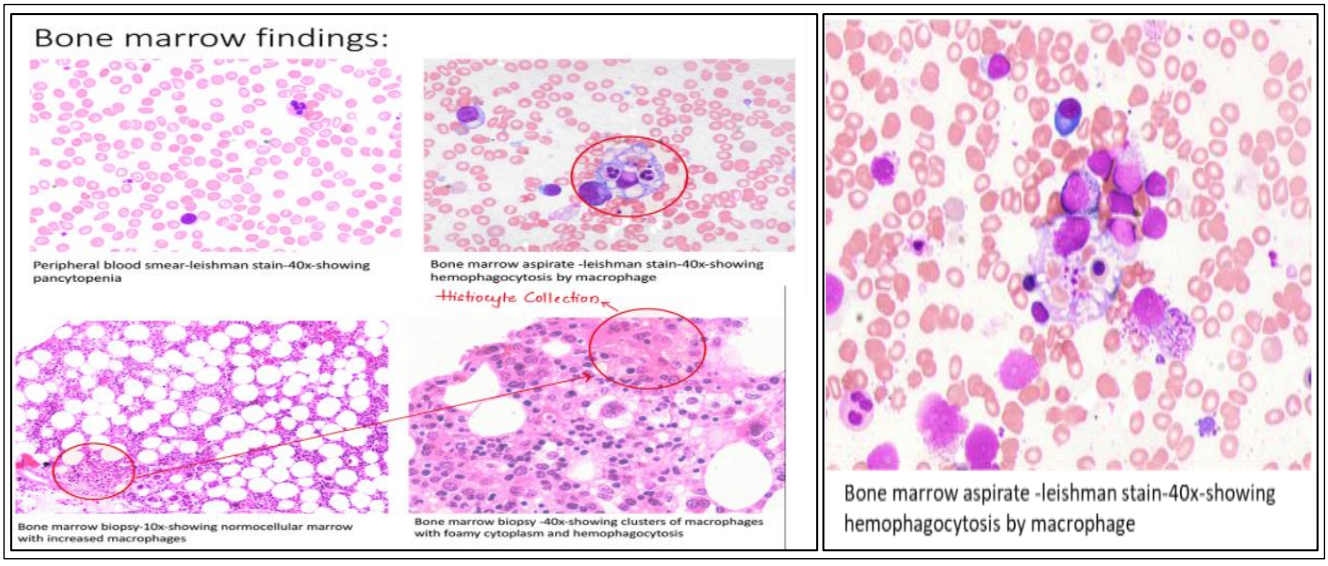

Figure 1: Hemophagocytic evidence.

Treatment

Patient was started on injectable ceftriaxone for enteric fever initially, as she continued to have high-grade fever, antibiotic was hiked to piperacillin-tazobactam on day 3 of presentation. Steroids-12 mg of dexamethasone/day was started on day 4 when hemophagocytosis was seen on bone marrow. Fever spikes came down temporarily. As the broncho-alveolar lavage was suggestive of tuberculosis, patient was started on modified anti-tubercular therapy (ATT) on day 8 of hospitalization with injectable amikacin-500 mg/day, oral ethambutol- 800 mg/day, oral

levofloxacin-500 mg/day intravenous dexamethasone was continued. High grade fever spikes recurred again and rheumatologist opinion was sought and initiated on intravenous immunoglobulin-2 mg/kg-100 mg divided over 5 days. Fever spikes subsided. However, inflammatory markers and serial liver function tests were not improving and meanwhile lavage fluid cultures grew multi-drug resistant *Klebsiella pneumoniae* in more than 100000 CFUs. Patient was started on injectable meropenem-1 g IV 8th hourly for 14 days. Patient started improving clinically, became afebrile, with serial declining trend of hyperbilirubinemia (Graph 1) and transaminases (Graph 2), and hence was initiated on isoniazid and tolerated well. Her platelets normalized soon after immunoglobulin therapy (Graph 3). However, counts (Graph 4) and haemoglobin (Graph 5) showed only mild improvement as shown in Figure 2. Patient was discharged with ATT-isoniazid, ethambutol, levofloxacin and amikacin and planned to initiate rifampicin at next review.

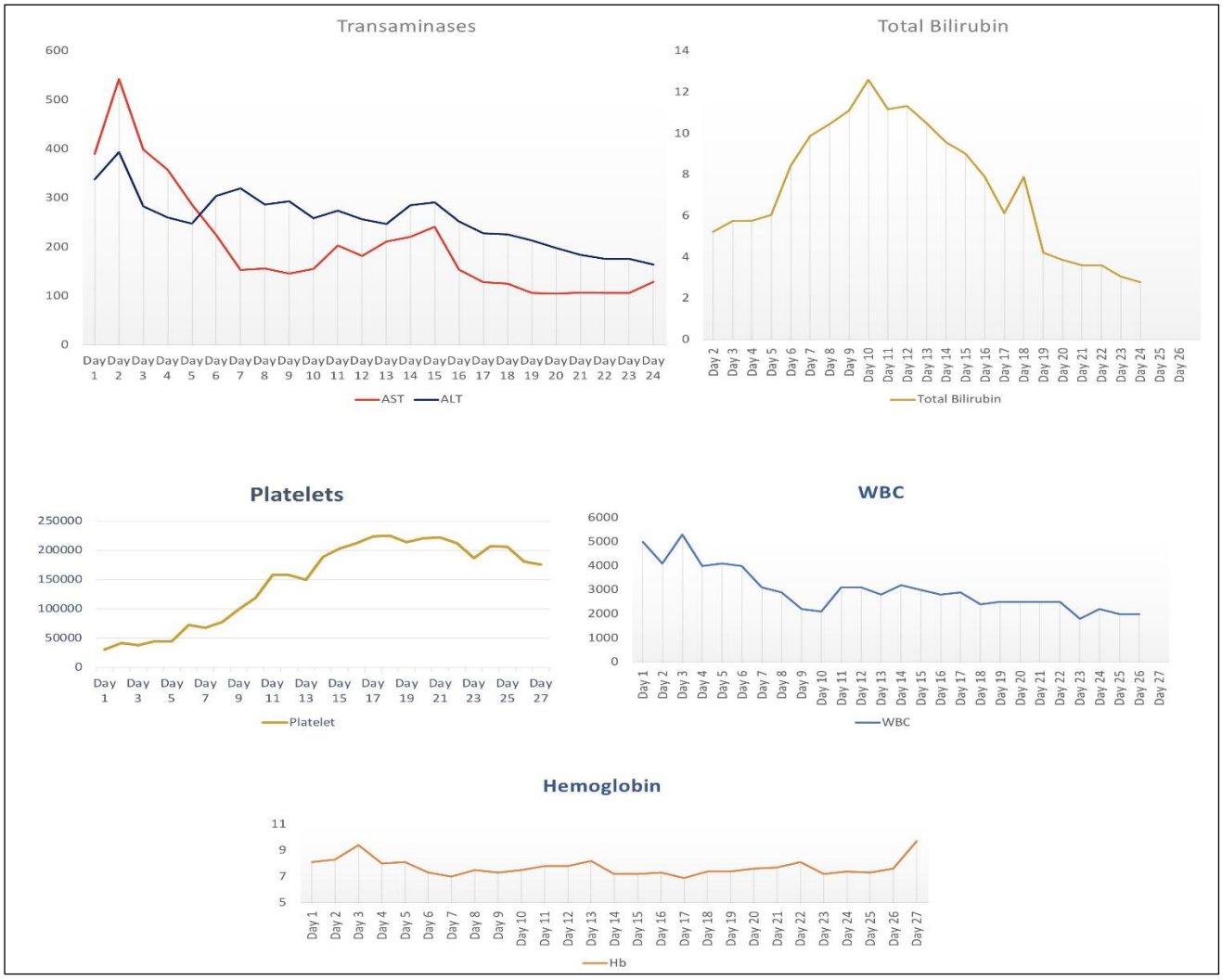

Figure 2: Blood parameters.

Outcome and follow-up

Patient was started on modified ATT-isoniazid-75 mg/day on day 8, ethambutol-800 mg/day, levofloxacin 500 mg/day and injection amikacin-500 mg/day. She was started on half the recommended dosage of isoniazid in view of deranged liver function. She tolerated the drug well; dose was increased to 150 mg/day and patient was discharged home on day 27 of hospitalisation and advised to review after one week for liver function and hemogram monitoring. Her body weight was 33 kg at discharge and had easily noticeable icterus. She reviewed in our outpatient department after 7 days. Her body weight increased to 36 kg and jaundice decreased. Her blood investigations were as follows; hemoglobin-10.5 g%, total counts-3600 cells/mm^3, platelets-204000 cells/mm^3, total bilirubin-1.77 mg/dL, aspartate transaminases-62 IU/L, alanine transaminases-94 IU/L, CRP-5.99 mg/L. Amikacin was stopped, she was started on full dose isoniazid-300 mg/day, oral syrup rifampicin at 100mg/day and dose was gradually increased to 200 mg/day over 1 week. She was continued on oral prednisolone in gradual tapering doses. She was followed up again after a week and weight stayed the same, but jaundice disappeared completely. Rifampicin was increased to 300mg/day after

liver functions improved; total bilirubin-0.88 mg/dL, aspartate transaminases-43 IU/L, alanine transaminases-63 IU/L. She's currently doing better symptomatically and advised to review after 1 month.

DISCUSSION

HLH was first described in the year 1952 by paediatricians. It is at the severe end of spectrum of hyper immune inflammatory diseases. It can be either primary (familial) or secondary (acquired).[2] The decision to start HLH-treatment should be based more on strong clinical suspicion, rather than on unequivocal evidence. The heterogeneity of the triggers in these conditions makes it clear that a "one size fits all" protocol does not apply for secondary HLH.[6] In patients with secondary HLH, treatment of underlying cause can lead to resolution of HLH. Paediatric protocols HLH-94 and HLH-2004 have been developed specifically for children, a substantial percentage of whom suffer from hereditary HLH. In both HLH-94 and HLH-2004, daily dexamethasone (10 mg/m^2 per day weeks 1-2; 5 mg/m^2 per day weeks 3-4; 2.5 mg/m^2 per day weeks 5-6; 1.25 mg/m^2 per day week 7, and tapering during week 8), and etoposide (VP-16) (150 mg/m^2, twice weekly weeks 1-2, then once weekly) is administrated during the initial therapy. The continuation therapy for both protocols consists of Dexamethasone every second week (10 mg/m^2 per day for 3 days), Etoposide (150 mg/m^2) every second week, and cyclosporine A (aiming at 200 µg/L trough value).[7] The HLH-94 protocol, perhaps with individual adaptation, is indicated for treatment in severe adult HLH with unknown trigger, known hereditary severe HLH and relapsed HLH (relapse is confirmed only when all strict criteria are met and infectious episodes that mimic HLH are excluded). In patients with a transient episode of HLH (like infection associated HLH), pulsed treatment with corticosteroids or immunoglobulins alone often is sufficient to control HLH.[6]

Corticosteroids hold utmost importance as anti-inflammatory drugs for HLH. Due to its better penetration into the CSF (cerebrospinal fluid), dexamethasone may be superior. Less severe cases can be treated with corticosteroids and immunomodulatory drugs such as cyclosporine A or intravenous immunoglobulins. Therapeutic dosing for immunoglobulins requires high doses (up to 1.6 g/kg over 2-3 days) and acts through diverse mechanisms- Fc-receptor blockade, inhibition of complement activation, or neutralisation of cytokines. Immunoglobulins are used in combination with Corticosteroids (prednisolone 1-3 mg/kg/day), and continue replacement therapy is given in cases with Ig-deficiency. However, in macrophage activation syndrome (MAS), a pulse of high-dose corticosteroids with or without cyclosporine-A is effective in most patients. Lately anticytokine treatment has also been used successfully.[8] Early initiation and appropriate ATT (Anti Tubercular Therapy) is the key to prevent HLH in patients with tuberculosis and is the cornerstone of TB-HLH treatment. Early immunosuppression was found to improve overall survival rates in Tb-HLH. The mortality in patients who did not receive ATT is reported to be 100%, while ATT in combination with immunotherapy can reduce the mortality rate by 40% to 60%.[9,10]

Here in our case, patient is a young, nil-comorbid female who presented with acute to sub-acute history of fever followed by abdominal pain and jaundice. Her blood tests showed bicytopenia, later pancytopenia and multi-organ involvement. Though the clinical presentation was consistent with sepsis and multiple-organ involvement, high ferritin levels directed towards considering HLH as an alternative diagnosis and was confirmed with bone marrow and other supportive blood parameters.[11] The classical HLH-94/HLH-2004 protocols were not adopted for management. Patient was started on IV dexamethasone to suppress the hyper inflammation, simultaneously while aggressively evaluating for the trigger that led to this condition.

Once tuberculosis was identified as the probable trigger, immediate anti-tubercular treatment has been started to eliminate the offending trigger. However, due to underlying hepatitis standard full-line treatment could not be given. Meanwhile patient's response to the treatment was declining and as she developed fever again, we added immunoglobulins at higher dose for elimination of activated immune cells and suppressing hyper inflammatory response. In evaluation for possible triggers, she also had infection with multi-drug resistant, carbapenem sensitive *Klebsiella pneumoniae* and after starting meropenem, patient started to show rapid response clinically.

Terminating the inflammatory response prior to progression into a severe/irreversible state was critical in the management of this patient. The case also depicts the infrequent presentations of common diseases. It emphasizes the importance of considering broad differential diagnoses and adopting aggressive diagnostic approach to make a prompt diagnosis to intervene early in the course of disease and alter the clinical outcomes and complications.

CONCLUSION

There should be a high degree of suspicion for HLH, especially in cases presenting as sepsis with cytopenias in intensive units to not miss the diagnosis as the disease natural course is mostly fatal and should be targeted before irreversible multi-organ damage occurs. The management of HLH is different from conventional sepsis and the treatment for each cause of HLH also varies. Furthermore, this case report stresses on the importance for initiating treatment rapidly and tailored approach of management therapy for each case.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Kondam A, Prabhu M, Shreesha N, Vidarshan M, Lakshmi S. Adult hemophagocytic lymphohistiocytosis triggered by disseminated tuberculosis and *Klebsiella pneumoniae* co-infection in an immunocompetent individual-a diagnostic challenge. Int J Adv Med 2022;9:1064-8.