A Challenging Case of Haemophagocytic Lymphohistiocytosis (HLH) Secondary to CMV Infection in an Adolescent with B-acute Lymphoblastic Leukemia

Sir,

We report a case of secondary haemophagocytic lymphohitiocytosis (HLH) associated with cytomegalovirus (CMV) infection in a patient of pre-B-acute lymphoblastic leukemia (pre-B-ALL). An 18-year female with pre-B-ALL in minimal residual disease (MRD)-negative complete remission (CR) post BFM 2000 induction was admitted with a febrile illness. She received broad spectrum anti-bacterials as well as antifungal medications, based on a suspicion of fungal infection on CT scan of sinuses and chest and raised serum galactomannan. She developed viral exanthem with a rash on upper torso and upper limbs with a very high titer of CMV PCR (93,600 copies/ml); for which, she received IV ganciclovir. However, she deteriorated rapidly with respiratory failure, leading to intubation and admission to intensive care unit (ICU). With continuous fever spikes, her liver function tests (LFTs) started to derange with peak total bilirubin of 10.04 mg/dl and mild transaminitis, despite cessation of all potential liver toxic medications. Meanwhile, she was requiring transfusion support for severe anemia and thrombocytopenia. She had worsening Glasgow coma scale (GCS) and tachypnea due to hepatic encephalopathy with very high ammonia levels (346 ug/dl). Given the persistent fevers, anemia, thrombocytopenia and rapidly deteriorating LFTs, she was suspected to have HLH secondary to CMV infection. Serum ferritin was raised at 7,628 ng/ml. Triglycerides were 1,108 mg/dl, and lactate dehydrogenase (LDH), 510 U/L. Bone marrow trephine biopsy revealed marked histiocytic infiltrate albeit without classic haemophagocytosis (Figure 1). CT scan of abdomen revealed mild ascites, hepato-splenomegaly and bilateral renal swelling, likely due to an infiltrative process. She was commenced on dexamethasone and weekly etoposide with prompt response after the first dose with rapid lysis of fever, improvement in cytopenias, ferritin, triglycerides and LFTs. CMV PCR went down from 93,600 copies/ml to undetectable level. She was subsequently extubated after 18 days and discharged back to the ward.

HLH is a life-threatening hyper-inflammatory disorder.[1] Timely diagnosis is crucial as untreated HLH leads to multi-organ damage with very poor outcome. The diagnosis of HLH is made by utilising 'HLH-2004 diagnostic criteria'[2] by finding five out of eight features (Table I).[3] HLH is quite underdiagnosed in critically ill patients. Secondary HLH is associated with a variety of infections, autoimmune and malignant conditions.[4] It is essential to have a high index of suspicion, especially in immunocompromised patients with persistent fever and pancytopenia non-responsive to antibiotics. Early treatment of the underlying condition often leads to clinical improvement.[5] Further work-up, such as serum ferritin and triglycerides, should be done immediately and treatment for HLH should be commenced early without waiting for bone marrow biopsy or other definitive work-up.

Table I: Diagnostic criteria for hemophagocytic lymphohistiocytosis.

Clinical criteria:
1. Fever: (≥38.5°C)
2. Splenomegaly
Laboratory criteria:
3. Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood):
1. Hemoglobin (<9g/dl)
2. Platelets (<100 x 109/L)
3. Neutrophils (<1.0 x 109/L)
4. Hypertriglyceridemia: (fasting triglycerides ≥3.0 mmol/L and/or hypofibrinogenemia (Fibrinogen ≤1.5 g/L)
5. Hyperferritinemia: (≥500 ug/L).
6. Elevated soluble CD25 (≥2400 U/ml)
7. Histopathologic criteria: Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy.
8. Reduced or absent natural killer cell cytotoxicity.

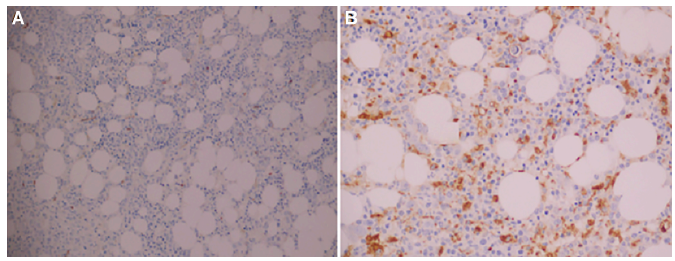

Figure 1: Bone marrow biopsy slides with CD 68 (A) and CD34 staining (B) showing histiocytosis.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

CL, MAJ, SWIB: All authors have contributed substantially to the conception of the work; acquisition, analysis, and interpretation of data for the work; drafting the case and discussion; revising it critically for important intellectual content; and the final approval of the version..

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