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CASE REPORT

A CASE OF EBV ASSOCIATED REACTIVE HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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ABSTRACT

Hemophagocytic lymphohistiocytosis is an unusual syndrome characterized by fever, splenomegaly, jaundice and the pathological finding of hemophagocytosis (phagocytosis by the macrophages of erythrocytes, leucocytes, platelets and their precursors) in bone marrow and other tissues.HLH may be diagnosed in association with malignant, genetic or autoimmune diseases but is also predominantly linked with Ebstein-Barr Virus (EBV) infection. Hyperproduction of cytokines including interferon gamma and tumour necrosis factor-alpha by EBV infected T lymphocytes may play a role in the pathogenesis of HLH. Here we present a young female who presented with HLH associated with EBV infection. The rapid deterioration of clinical condition with multisystem involvement mandates a strong suspicion for the possibility of HLH. Such a clinical scenario in the presence of high ferritin and triglycerides with low fibrinogen helps in timely diagnosis and prompt initiation of immunosuppressant therapy; thereby improving the outcome of a fatal disease.

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INTRODUCTION

30 year old female patient with no known co-morbidities presented with fever for a week, high grade, intermittent associated with chills and rigors, cough with frank hemoptysis, minimal amount for 2 day, high coloured urine with burning micturition for 3-4 days. She developed oral ulcers along with perioral skin lesions for a week. She had irregular cycles with menorrhagia for the past 2-3 cycles. On examination she was febrile with temperature of 100 F. She had pallor and icterus but no significant lymphadenophathy. Her oral examination revealed healing vesicles of HSV. On examination she had bilateral lung crepitations and bronchospasm, liver was palpable 3 cms below the right coastal margin and spleen was just palpable. Her investigations revealed Hb of 5.7, TC was 6300 which dropped to 1700 after 2 days and platelets were 0.45. Peripheral smear showed normocytic, normochromic to microcytic, hypochromic RBC's, anisocytosis, spur cells, thrombocytopenia and occasional giant platelets. Her coagulation profile revealed PT - 48.9 (C-14.1), PTT – no clot and INR – 4.67. LFT showed T.Bilirubin - 4.12, D.Bilirubin - 2.98, SGOT-513, SGPT-242, ALP-307.

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Other investigations were S.ferritin – 2274, CPK – 909, LDH – 2321, Triglycerides – 256, S.fibrinogen – 157 (normal 250-520), FDP – 10.0 (normal <5). Serology for EBV revealed IgG- detected (35.71), IgM – not detected, DNA PCR – detected. Her CXR showed bilateral non homogenous opacities, suggestive of alveolar hemorrhages.

Shewas admitted to ICU, where she required NIV support followed by intubation in view of worsening breathlessness. She developed bleeding manifestations in the form of multiple generalized petechiae, mild hematuria and scanty gum bleeds. She received supportive transfusions with packed cells and fresh frozen plasma. In view of fever with thrombocytopenia, elevated ferritin and triglycerides, Hemophagocytic syndrome was suspected and the patient was started on steroid pulse therapy. With no significant improvement in her cell lines she was started on intravenous Cyclosporin. The patient responded well to Cyclosporin and was later switched to oral steroids.

DISCUSSION

HLH can be familial or sporadic (Farquhar and Claireaux, 1952; Janka, 2012). The sporadic form is mostly associated with viral infections (Janka *et al*., 1998). It is a syndrome of excessive inflamation and tissue destruction due to abnormal immune activation. Here cytotoxic T lymphocytes are abnormally activated which along with the natural killer cells

fail to eliminate the activated macrophages. Thus there is a lack of normal feedback regulation resulting in excessive macrophage activity and excess levels of INF- gamma, TNFα, IL-6,IL-18 (Verbsky and Grossman, 2006). Thus the cytokine storm is ultimately responsible for multiorgan failure and high mortality (Castillo and Carcillo, 2009). In addition, the macrophages also phagocytise the host cells. Hence we come across the presence of RBC's, platelets, WBC's inside the cytoplasm of the macrophages. The occurrence of HLH can be triggered by infections with EBV, Cytomegalovirus, HIV, Parvovirus 19 and certain fungal infections in the sporadic forms while it is associated with inherited immune deficiency syndromes, malignancy, rheumatological disorders like SLE, Stills disease, MCTD (Larroche *et al*., 2002; Deane *et al*., 2010).

DIAGNOSTIC CRITERIA FOR HLH (Henter *et al*., 1991; Henter *et al*., 2007)

Presence of five out of these eight findings are required for the diagnosis of HLH

- Fever >= 38.5C
- Spleenomegaly
- cytopenias affecting atleast two of three lineages in the peripheral blood
- hyperferritinemia >500ng/ml
- Hypertriglyceridemia (fasting TGL >265 mg/dl), and /or hypofibrinogenemia (fibrinogen <150mg/dl)
- Hemophagocytosis in bonemarrow, spleen or lymphnode
- Low or absent nk cell activity determined by the 51-Cr release assay
- High levels of sCD25

TREATMENT

Ebstein Barr virus associated HLH is almost universally fatal if left untreated (Buyse *et al*., 2010). Death usually results from haemorrhage, infection or multi organ failure. Chemotherapy with etoposide (which is toxic to macrophage) and dexamethasone is recommended (Imashuku *et al*., 2004; Imashuku *et al*., 2001). Intrathecal methotrexate is considered for the patients with neurological symptoms or persistent CSF abnormalities. Cyclosporine A immunotherapy is effective against T lymphocytes. Allogenic bone marrow transplant is the treatment of choice in patients with Familial HLH who attain remission.

Conclusion

When a patient presents with fever with pancytopenia, simple tests for serum ferritin, triglyceride and fibrinogen will strengthen the clinical suspicion and help in an early diagnosis and treatment initiation for HLH, thereby improving the clinical outcome of a fatal disease.

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