Case Report**A Fatal case of Epstein-Barr Virus-Induced Haemophagocytic Lymphohistiocytosis in a young male****Gnanathayalan S W¹, Peranantharajah T¹, Sooriyakumar T¹**¹*Teaching hospital Jaffna***Abstract**

Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially lethal condition due to dysfunctional immune response causing severe inflammatory syndrome. Epstein-Barr virus (EBV) – induced HLH is a form of secondary HLH, a very serious presentation of an otherwise benign viral infection. Here we present a case of 31 year old previously healthy male with prolonged fever and constitutional symptoms, eventually diagnosed to have HLH secondary to EBV infection. He had refractory response to treatment regimen of etoposide and dexamethasone followed by Rituximab therapy and succumbed to septic shock.

Keywords

Epstein-Barr virus, Haemophagocytic Lymphohistiocytosis, Etoposide, Rituximab

Introduction

Most patients with EBV infection recover without major clinical consequences but few fatal complications have been well recognized. One of them is Haemophagocytic Lymphohistiocytosis (HLH). HLH is potentially life-threatening condition due to dysfunctional immune response leading to severe inflammatory response by release of inflammatory mediators from uncontrollably activated T-lymphocytes, Natural Killer cells and macrophages. [1] Different conditions including viral and bacterial infections, auto immune diseases and malignancies are well recognized causes of HLH. EBV-induced HLH is due to persistence

of virus in tissues and the outcome is particularly worse and refractory to standard treatment. [2]

Case Report

A previously healthy 31 – year – old male patient presented to us in August 2020 with history of intermittent fever with severe constitutional symptoms for three-week duration. Prior to this hospitalization he was treated for two episodes of short-lasting febrile illnesses as clinically typhus fever and dengue fever respectively. He did not have other systemic symptoms or features of auto immune rheumatic diseases. He never smoked or consumed alcohol and denied any illicit drug abuse or sexual promiscuity.

Physical examination revealed ill looking febrile patient with pallor and mild palpable splenomegaly. He did not have palpable peripheral lymph nodes or skin rashes. Neurological examination was normal.

Laboratory tests performed at the time of admission revealed pancytopenia (WBC 2890 cells/ μ L, hemoglobin 8.4g/dL, platelets 58 000 cells/ μ L) with normal coagulation profile. Other relevant initial data included high inflammatory markers (ESR 64mm/1st hour, CRP 188mg/L) and marginally elevated liver enzymes and Serum creatinine. Blood and urine cultures showed no growth. Abdominal Ultrasound scan revealed splenomegaly of 16cm. Peripheral blood smear was significant for atypical reactive lymphocytes.

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The bone marrow biopsy described increased lymphocytes including atypical lymphocytes and increased number and activity of histiocytes with features suggesting hemophagocytosis (Fig.1). As haemophagocytic phenomena were detected in bone marrow further investigations were performed and detected hyperferritinemia (>1000ng/ml) and hypertriglyceridemia (666.4mg/dl) supported the diagnosis of HLH, fulfilling 6 out of 8 criteria of HLH.

Figure 1:

Extensive investigations were arranged to find out the aetiology and positive IgM to EBV was identified with 2×10^6 copies of EBV DNA detected by EBV PCR. Other infective screening for cytomegalovirus, hepatitis B and C viruses, Dengue virus, COVID-19, malaria, HIV/VDRL, scrub typhus, Mycobacterium tuberculosis and leishmaniasis were all negative. Rheumatoid factor and Anti Nuclear Antibodies (ANA) were also negative. Thus, the diagnosis of EBV – HLH was established.

He was initiated on treatment according to HLH – 94 protocol with Dexamethasone and Etoposide, with IVIg as well. Unfortunately, IVIg and Etoposide could not be continued after second doses due to anaphylaxis to IVIg and worsening pancytopenia after initiation of etoposide. Then he was commenced on Rituximab.

But, in spite of Rituximab therapy he gradually deteriorated with ongoing intermittent fever spikes, worsening cytopenias requiring multiple blood product transfusions, and worsening liver and

renal functions. During the course flowcytometry was done in peripheral blood and hematological malignancy was excluded. He developed severe sepsis with pseudomonas growth in blood, needed pressor support ventilation and for a prolonged duration. Despite possible optimal efforts, he succumbed after two months of hospital management due to septic shock with multi organ dysfunction.

Discussion

HLH can be classified into a primary and a secondary form. Though it is difficult to distinguish between them clinically, the primary form usually affects younger children with genetic cause and the secondary type occurs due to immunologic stimulation from an underlying infection, malignancy or auto immune conditions. Epstein-Barr virus is the most common infectious agent causing HLH, especially in Asian populations. [3]

The diagnosis of HLH still remains a challenge. Many conditions like septic shock, catastrophic Anti phospholipid Syndrome (APLS) and Adult Onset Still Disease present in the similar way characterized by fever, arterial hypotension and multi organ involvement due to exaggerated inflammation. At the same time auto immune conditions and haematological malignancies also have clinical similarities to HLH and can also evolve into HLH. As the treatment varies among these conditions, a thorough evaluation for an underlying cause should always be performed.

According to HLH – 2004 guidelines, at least 5 of 8 criteria is required for the diagnosis of HLH. In our patient, we found fever, splenomegaly, pancytopenia, hyperferritinemia, hypertriglyceridemia and evidence of haemophagocytosis in bone marrow biopsy, fulfilling 6 out of 8 criteria, leading to the diagnosis.

The management of HLH is more challenging because of the complications of it being life threatening even with appropriate early therapeutic approach. An American study involving 73 adult patients with HLH concludes that sepsis and multi organ dysfunction as the two most frequent causes of fatality among HLH patients with one-year survival rate only 48%. [1]

Treatment of HLH according to HLH – 2004 protocol include the etoposide plus dexamethasone regimen used in HLH – 94 but incorporates cyclosporin as part of initial therapy. [4] However, cyclosporin is associated with Posterior reversible Encephalopathy Syndrome (PRES) and there is no strong evidence to support its benefits. In addition to this initial regime, treatment of rituximab may be useful for decreasing mortality in EBV – driven HLH as it destroys EBV infected B cells. [4] IVIg is also recommended for HLH when active EBV infection is confirmed by finding of more than 10 000 copies of EBV/mcg cellular DNA. Due to these facts, we chose HLH – 1994 treatment protocol with IVIg followed by Rituximab to our patient but unfortunately, we could not complete the course of IVIg and Etoposide as he developed serious side effects to both of them .

Conclusion

This case highlights the diagnostic and especially therapeutic challenges and complications of HLH, a potentially deadly disorder. Early recognition

and treatment improve survival though early diagnosis is challenged by various non – specific presentations.

References

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