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A RARE CASE OF EPSTEIN BAR VIRUS (EBV) INDUCED SECONDARY HEMOPHAGOCYTIC LYMPHOHISTYOCYTOSIS (HLH)

Paediatrics

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ABSTRACT

Background: Hemophagocytic lymphohistiocytosis (HLH) is rare but very severe clinical syndrome of hyperinflammation caused by a dysfunctional deficient down regulation of immune response, which leads to potentially life threatening complications. Viral infections with Epstein-Barr virus (EBV) are a well-recognised trigger of HLH but the treatment of such cases is not well-defined. **Clinical Description:** We describe here a case of 7years old female who developed hepatosplenomegaly and lymphadenopathy that later developed haemorrhagic manifestations, pyomeningitis as neurological manifestation of HLH, who Despite of giving aggressive treatment with multiple agents succumbed to illness. **Management:** Treatment of secondary HLH can be achieved with the help of the standard HLH-2004 regimen. However, the medication protocol needs to be adapted depending on its cause. **Conclusion:** This case report aims to underline the diagnostic challenges of HLH, potential of primary EBV infection to cause fulminant HLH, as well as its potentially lethal, haemorrhagic complications. There is meaningful work to continue in the HLH field, and unremitting efforts that are underway will continue to improve patient outcomes.

KEYWORDS

Epstein-Barr virus, Haemophagocyticlymphohistiocytosis (HLH), Hepatosplenomegaly, Haemorrhage

INTRODUCTION:

Hemophagocytic syndrome is a hyperinflammatory condition caused by highly stimulated but dysregulated and often ineffective immune responses. Its cardinal features are unremitting fever, cytopenias, hepatosplenomegaly, widespread histiocytic tissue infiltration, coagulopathy, and elevations in typical biomarkers, including ferritin and soluble interleukin-2 (IL-2) receptor (sIL-2R). Patients can also develop rash, hepatitis, disseminated intravascular coagulation, acute liver failure, central nervous system (CNS) involvement, multiorgan failure, and other problems, too often including death. There are 2 major forms of hemophagocytic syndrome: a primary (hereditary) form which occurs in early childhood, and a secondary (reactive) form which occurs at any age and is probably much more frequent than the primary form. The high mortality rate makes prompt recognition and treatment of this hyperinflammatory syndrome essential. [1-6]

We describe here a case of 7 years old female who developed hepatosplenomegaly and lymphadenopathy that later developed and haemorrhagic manifestations, pyomeningitis as neurological manifestation of HLH, This case report aims to underline the diagnostic challenges of HLH.

CASE DESCRIPTION:

Presenting Concerns

A 7years old female without having any significant past history presented with fever for 1month high grade ,intermittent, associated with chills), decreased appetite for 15 days, headache for 10days with cough for 2days.

Clinical Findings On Admission–

she was found to be febrile with temperature 38.6C with heart rate 112/min. Significant finding involved presence of pallor with palpable hepatosplenomegaly with bilaterally multiple lymph node enlargement in neck (at submental, submandibular, jugular, and posterior triangle region).There is no family history of any autoimmune or haematological disorder.

Diagnostic Focus And Assessment And Course Of Illness.

Patient was admitted and iv antibiotics (inj. Ceftriaxone) was started. FNAC done for lymphadenopathy suggestive of chronic reactive hyperplasia. Chronic infection (tuberculosis, seropositive) was ruled out. Patient had high grade fever spikes 1-2 /day. patient also developed signs of meningeal irritation .CSF examination suggestive of pyomeningitis . Antibiotics upgraded to inj. meropenem and vancomycin and planned for MRI. MRI brain showed mild meningeal enhancement along bilateral cortical sulci and subarachnoid process. Along with this course patient also advised to start AKT (anti tubercular treatment).

In spite of treatment disease did not subsided and she developed high grade fever of 105-106F continuous for 6-12hours. tablet prednisolone started . repeat investigation showed decreased cell lines bicytopenia with HB -4.6 for which RCC transfusion done .blood culture came negative.

Infectious disease specialist opinion taken ,advised to stop antibiotic and AKT in view of no clear evidences of bacterial infection. Due to its high prevalence in determining HLH, infection with various viral agents, including EBV needed to be searched for. Numerous investigations were carried out to look for HLH. (Detailed Investigations in Table No.1)

Table No.1 On Admission Investigations

INVESTIGATION	RESULT
HEMOGRAM	
Hb	gm/dl
TLC	8600/mm3
Platelets	332000 /mm3
ESR	142 sec
RENAL FUNCTION TEST	
S. Creatinine	0.4mg/dlC
S. Calcium	8.4mg/dl
CRP	71
LIVER FUNCTION TEST	
ALT	24

Total bilirubin	0.3
ANEMIA PROFILE	
Sickling	Negative
S. Iron	16
TIBC	169
S. Ferritin	>1000
LDH	1222
URINE EXAMINATION	
Routine microscopy	Negative
Culture sensitivity	Negative
SEROLOGICAL EXAMINATION	
Dengue IgM	Negative
S. Widal	Negative
TB PROFILE	
Montoux test	Negative
Sputum CBNAAT	Negative
Serostatus	Negative
VIRAL MARKER	
Hepatitis a	Negative
Hepatitis b	Negative
Hepatitis c	Negative
Hepatitis e	Negative
RADIOLOGICAL INVESTIGATIONS	
USG abdomen +pelvis	Mild hepatosplenomegaly with varying sized LN mesenteric (17x7)mm2 and paraortic (18x5)mm2
USG NECK	Multiple varying sized LN bilaterally involved IB (20x10)mm2 , II (15x9)mm2, III (14x8) mm2 , IV and posterior triangle (13x8)mm2
SPECIFIC TEST FOR EBV VIRUS	
EBV VCA IgG	POSITIVE
EBV EBNA Ig G	NEGATIVE
EBV VCA IgM	NEGATIVE
BRUCELLA IgG	NEGATIVE
BRUCELLA IgM	NEGATIVE
RA FACTOR	NEGATIVE
ANA	NEGATIVE
BONE MAROW BIOPSY	NO EVIDENCE OF HEMOPHAGOCYTOSIS

In our patient's case, we found 5 criteria, which were consistent with a HLH diagnosis: fever, splenomegaly, and cytopenia of 2 lineages in the peripheral blood, hypertriglyceridemia, hyperferrinemia evidence of hemophagocytosis in the bone marrow aspirate and hyperferritinemia. IL-2 receptor and NK cell activity could not be performed, as they were not available in our hospital. The only significant finding was her EBV VCA IgG was positive with negative EBV EBNA.

A bone marrow biopsy was done however it did not show any evidence of hemophagocytosis. Also flow cytometry showed no evidence of haematological malignancy. In view of all investigations main cause for patients HLH was presumed to be EBV infection in absence of no other clear diagnosis.

She continued to deteriorate and developed two episodes of seizures (GTCS type) within 24 hours. Initially loaded with inj. Phenytoin .also patient had high grade fever with tachycardia (HR- 180-190/min) with tachypnoea. Patient start bleeding from nose and mouth, immediately shifted to intensive care unit and intubated. In view of this inj. Etoposide, inj. IVIG, inj. Dexamethasone given. Pressure support (inj. Dobutamine) started, antibiotics upgraded to inj.polymixim B, inj. Linezolid and inj. Methylprednisolone was given .as there was decreased cell lines on hemogram inj. Filgrastim started.

Patient started having fresh bleed from endotracheal tube and nasogastric, PT INR was highly deranged therefore advised fresh frozen plasma transfusion thrice a day along with transfusion of red cell concentrates and platelets .as there was hypofibrinogenemia cryoprecipitate transfusion done. Also patient became icteric repeat investigations suggestive of HB- 7.8gm/dl, TLC- 300, platelets -17000 with CRP -134, ALT -275, serum total bilirubin -11 with direct component 9.1

It is known that Complications of HLH can endanger life, even with proper, early therapeutic approach. Several case reports have described severe epistaxis as initial manifestations or aggravations of HLH, in patients with pancytopenia. A study cites intracranial, gastrointestinal, and diffuse alveolar haemorrhage among one third of the patients with fatal outcome, are described to have direct relation with the severity of thrombocytopenia and hypofibrinogenemia. [16]

Similarly, our patient developed a serious nasopharyngeal bleeding and pulmonary haemorrhage, in the circumstances of pancytopenia, hypofibrinogenemia and modified coagulation parameters.

Outcome

Despite of giving aggressive treatment with multiple agents, Patient deteriorated succumbed to illness.

DISCUSSION:

Hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome of hyperinflammation caused by a dysfunctional deficient down regulation of immune response, which leads to potentially life threatening complications. [9, 10, 11] HLH can be further divided into primary and secondary HLH. Primary HLH or familial HLH (FHLH) autosomal recessive disorder resulting from various genetic mutations is rare [12] and it is further described into 5 different types, FHLH-1 to FHLH-5. [13]

Secondary HLH also known as malignancy-associated hemophagocytic syndrome (MAHS) or virus-associated hemophagocytic syndrome (VAHS) [12,14,15] is described patient develop HLH like features associated with strong immunologic trigger such as infection, malignancy, or autoimmune disease in the absence of any frank genetic predisposition , While Secondary HLH can occur with any malignancy or any infection, More commonly it includes infection caused by DNA viruses Such as EBV, cytomegalovirus, and adenovirus, Epstein–Barr virus is considered to be the most frequent infectious factor associated with HLH, especially in Asian populations. Although the incidence of HLH has not been documented in many countries, a national study performed in Japan discovered a frequency of EBV infection as high as 40% among all patients diagnosed with HLH. [16]

It also happens in infection with intracellular pathogens such as Leishmaniasis, and the list triggering HLH is extensive, causes can be further sub dived by seasonal infections (influenza viruses, tick-borne illnesses), geographic region illnesses (leishmaniasis and tick-borne illnesses), , and socioeconomic status (tuberculosis). Immune reconstitution inflammatory syndrome which has been associated with IL-18 has striking similarity to HLH. When HLH or a syndrome resembling HLH occurs in association with Pediatric rheumatic diseases or autoinflammatory diseases such as systemic-onset juvenile rheumatoid arthritis, Kawasaki disease, or systemic lupus erythematosus. it is often referred to as macrophage activation syndrome (MAS). [10,12,17]

The pathogenesis of FHLH involves a hyperactivity of CD 8 + T lymphocytes and macrophages due to an impairment of cytotoxic T cell and natural killer (NK) cell function. The latter play a key role in modulating the immune response, by inhibiting the activation of antigen-specific T cells. Overwhelming activation of macrophages and T cells leads to an increased expression of proinflammatory cytokines, with excessive circulatory levels leading to organ dysfunction and hematologic abnormalities. [11,17] In particular, Epstein–Barr virus (EBV), through its ability of activating CD 8 + T lymphocytes, can cause a hyperproduction of interferon-gamma (IFNg), which can trigger antigen-presenting cells. [18]

Regardless of the type of HLH, central nervous system (CNS) involvement has been reported in 10-73% of patients, either at initial presentation or during the course of the disease Neurological presentations are variable and include irritability, seizures, ataxia, cranial nerve palsies, meningism, signs of increased intracranial pressure, and altered consciousness. [19] The presence of CNS involvement at diagnosis is a poor prognostic sign, and requires prompt management. [20]

The diagnosis of HLH still remains a challenge, due to its nonspecific diagnostic criteria. Its similarity to sepsis is obvious due to some common features, such as fever and leukopenia. Hyperferritinemia

(acute phase reactant), low fibrinogen levels, and thrombocytopenia can also be found in sepsis, especially in the context of disseminated intravascular coagulation. An early differential diagnosis of the 2 conditions is mandatory for a proper therapeutic management, as sepsis therapy does not involve any of the chemotherapeutic agents, which can considerably improve survival of HLH. [21] Hematologic malignancies and autoimmune disorders can present clinical similarities to HLH, but can also evolve into HLH. Therefore, a thorough search for an underlying disease must always be conducted. [22]

Diagnostic criteria of HLH – (Table No.2)

Table No.2 HLH-2004 Diganostic Criteria [7]

HLH -2004 GUIDELINES 8 CRITERIA	CRITERIA FULFILLED IN OUR PATIENT
Fever Splenomegaly	√
Cytopenia in >=2 cell lineages	√
Haemoglobin <9 g/dL, in neonates <10 g/dL	√
Platelet count <100 X 103/mL	√
Neutrophil count <1 X 103/mL	X
Hypertriglyceridemia (> 265 mg/dL) Hyperferritinemia (> 500 ng/mL)	√
Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver	X
Low or absent NK-cell cytotoxicity	NOT DONE

List of diagnostic criteria for HLH that were used in the Histiocyte society HLH-2004 study [7]

(A) Genetic defect consistent with HLH or
(B) 5 out of 8 clinical and laboratory criteria fulfilled

- Fever
- Splenomegaly
- Cytopenia in >=2 cell lineages
- Haemoglobin <9 g/dL, in neonates <10 g/dL
- Platelet count <100 X 103/mL
- Neutrophil count <1 X 103/mL
- Hypertriglyceridemia (>265 mg/dL) or hypofibrinogenemia (>150 mg/dL)
- Hyperferritinemia (>500 ng/mL)
- Soluble CD25 >2400 U/mL (or elevated compared with laboratory- defined normal ranges)
- Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
- Low or absent NK-cell cytotoxicity

HLH typically presents with persistent fever, hepatosplenomegaly, and pancytopenia, Besides these features (at least two cellular lines in the peripheral blood), there are other criteria relevant for the diagnosis: hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow or spleen or lymph nodes, lack of evidence to support the presence of a malignancy, hyperferritinemia, low/absent activity of NK cells, and high levels of the interleukin 2 soluble receptor.

Although the clinical tableau is very important in establishing a diagnosis, most professionals prefer to refer to the HLH-2004 diagnostic criteria before drawing a conclusion. [23]

According to the revised diagnostic criteria guideline of the HLH-2004 protocol, HLH is assumed if /that they have a predisposition to the syndrome of HLH.[23]It is particularly worth mentioning that the "pathognomonic" observation of hemophagocytosis is not required for a diagnosis and has poor sensitivity and specificity. [24]

Table No.3 H Score Calculation [8]

PARAMETER(CRITERIA FOR SCORING)	NO. OF POINTS
Temperature (°C)	49 (>39.4)
Organomegaly	38 (hepatomegaly and splenomegaly)
No. of cytopenias	24 (2 lineages)
Ferritin (ng/ml)	0 (<2,000)
Triglyceride (mmoles/liter)	64 (>4)
Fibrinogen (gm/liter)	0 (<2.5)
Serum glutamic oxaloacetic transaminase (IU/liter)	19 (>30)
Hemophagocytosis features on bone marrow aspirate	0
TOTAL POINTS	194
Probability of hemophagocytic syndrome	80%

Diagnostic criteria sets for reactive hemophagocytic syndrome have been proposed [25-30], but they suffer from substantial limitations, first, the weight of each criterion included in these scoring systems is unknown, and the proposed cut-off values were empirically defined. Second, some of the proposed criteria (e.g., natural killer cell activity, soluble interleukin-2 receptor level) cannot be measured in routine practice and may be of low interest for the diagnosis of the reactive form of the syndrome, hence non availability of activity paraclinical investigations are not accessible in many hospital settings and the wait for various laboratory results delays the HLH diagnosis and eventually the treatment.

H SCORE FOR HLH

Table 4. The H Score [8]

Parameter	No. of points (criteria for scoring)
Known underlying immunosuppression* Temperature (°C)	0 (no) or 18 (yes) 0(<38.4), 33 (38.4–39.4), or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
No. of cytopenias†	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin (ng/ml)	0 (<2,000), 35 (2,000–6,000), or 50 (>6,000)
Triglyceride (mmoles/liter)	0 (<1.5), 44 (1.5–4), or 64 (>4)
Fibrinogen (gm/liter)	0 (<2.5) or 30 (>= 2.5)
Serum glutamic oxaloacetic transaminase (IU/liter)	0 (<30) or 19 (>= 30)
Hemophagocytosis features on bone marrow aspirate	0 (no) or 35 (yes)
* Human immunodeficiency virus positive or receiving long-term immunosuppressive therapy (i.e., glucocorticoids, cyclosporine, azathioprine). † Defined as a hemoglobin level of 9.2 gm/dl and/or a leukocyte count of 5,000/mm^3 and/or a platelet count of 110,000/mm^3.	

As Shown In Table No.4 A new score has been developed for the diagnosis of reactive HLH in 2014 by the American College of Rheumatology, based on the HLH-2004 criteria, with the addition of liver involvement among relevant diagnostic elements. [8] The H-score is obtained depending on the severity of each of the clinical and paraclinical parameters evaluated. This score then translates into the individual probability of having secondary HLH. [8] Developed only for adult populations, this score can be a useful tool in Pediatric HLH as well, with a better diagnostic accuracy than the classical HLH-2004 criteria, according to a Belgian study. [31]

The H-score, which was more recently developed, seems to have a higher specificity than the HLH-2004 diagnostic guidelines. However, further studies need to be conducted in order to determine the optimal cut-off values. [8] Some authors state that this score is easier to apply into routine practice than the traditional criteria, as it can easily be accessed online(http://saintantoine.aphp.fr/score/) [32] As shown in Table No.3 , With the help of the same platform, we calculated the score using the parameters of our patient and obtained a probability of 83.72%.

Treatment Of HLH

Treatment of HLH should begin as soon as the syndrome has been recognized, with the caveat that steroids or chemotherapy should not begin until after evaluating for malignancy (with bone marrow, lymph node, tissue biopsy, etc.) so as not to interfere with diagnosis [24] Assessment for hemophagocytosis and staging for CNS involvement should not delay therapy.

The mainstays of HLH treatment consist of immunosuppressive and chemotherapeutic drugs and biologics that aim to dampen the cytokine storm and eliminate activated T-cell and Treatment of HLH should be coupled with prompt treatment of any identified underlying trigger. Rituximab can be helpful in the treatment of EBV-HLH. [24] Most patients should also receive aggressive antimicrobial prophylaxis directed against Pneumocystis jirovecii, general fungal organisms, and also viruses depending on previous exposures. IV immunoglobulin replacement is generally warranted. Patients with HLH can be critically ill and often need intensive care support in the early phase of diagnosis and treatment.

CONCLUSION:

Pediatric HLH is rare, remains a challenge as it is deadly disorder, it needs to be recognized promptly to be appropriately managed. This case report describes the clinical course of a patient who developed HLH post EBV infection, complicated by a massive nasopharyngeal bleed. Early recognition of the disease still remains a challenge, although Significant advances have been made in the last 20 years. There is meaningful work to continue in the HLH field, and unremitting efforts that are underway will continue to improve patient outcomes.

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