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CASE STUDY OF PEDIATRIC EBV INFECTION LEADING TO ENCEPHALITIS, SECONDARY HLH, AND GUILLAIN- BARRÉ SYNDROME

[1]Almohaisin Abdullah Adel, [2]Al Turki Shams Ahmad, [3]AlQahtani Mohammed Azib, [4]Alzahrani Saleh Mousa, [5]Aldahoos Mohammed Abdulrahman

[1]Imam Abdulrahman Bin Faisal University (IAU)

Abstract:

Ebestien-barr virus (EBV) is a wide spread herpesvirus, with up to 95% exposure rate in the adult population. Less than 10% of exposed population develop clinical manifestation. EBV infection is usually a benign infection, but in rare cases it can cause complications with lasting effects. EBV is also a very rare cause of encephalitis, accounting for less than 5% of clinical viral meningoencephalitis cases. It is also very rare for such a commonly presenting virus to cause secondary Hemophagocytic lymphohistiocytosis (HLH),or Gillian barre syndrome (GBS), not to mention fatality.

We describe a case of a 5 years old girl who presented initially with acute otitis media (AOM) at top of chronic and Infectious mononucleosis with expected discharge after IV antibiotic course, from that point she rapidly deteriorated with development of EBV complications in the form of encephalitis and then developed GBS and secondary HLH, she died after one month of admission due to these complications.

Although each of described rare complication is documented in literature, the combination of all of these findings was not reported previously.

Key words: *EBV, encephalitis, HLH, GBS.*

Corresponding author:

Almohaisin Abdullah Adel,

Imam Abdulrahman Bin Faisal University (IAU).

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INTRODUCTION:

Epstein-Barr virus (EBV) is a herpesvirus that is found in more than 90% of adult population and is spread by close contact between EBV shedders and susceptible individuals. Most of people carrying EBV stay asymptomatic for life[1,2]. Antibodies against EBV are present with in approximately 90 to 95 percent worldwide.[1,2] Childhood acquired EBV is a subclinical in most cases; the clinical manifestation of EBV acquired in childhood is less than 10% of exposure, and Infectious mononucleosis (IM) represent majority of the clinical presentation.[3]

IM manifests primarily as lymphadenopathy that's associated with fever, and pharyngitis in most cases, atypical lymphocytosis is found in some of the patients.[4,5,6].

CASE REPORT:

A 5 year old girl, known to have chronic otitis media with effusion on myringotomy tubes, and had recurrent chest infections. She was admitted to the hospital with fever and AOM on top of chronic for intravenous antibiotics. During hospitalization period, she had persistent fever. She developed cervical lymphadenopathy, and splenomegaly. She had elevated liver transaminases, and she was positive for EBV antibodies from blood. Few days later she started to have headache, became lethargic. On examination: she was drowsy, with right facial nerve palsy, decreased deep-tendon reflexes (DTR) and was unable to walk. She was transferred to critical care unit due to decrease level of consciousness ,GCS was less than 8. Computed tomography (CT) brain was done and showed mastoiditis and pan-sinusitis. CSF analysis revealed pleocytosis with normal CSF protein-at the beginning- and glucose, negative gram stain and cultures, EBV PCR was positive from CSF. So she was started on acyclovir and High doses dexamethasone. Brain MRI with and without contrast was unremarkable. During her hospital stay she developed pancytopenia in which the diagnosis of leukemia vs HLH was raised. So she Bone marrow aspiration was negative for hemophagocytosis, and malignancy ruled out.

EBV induced secondary HLH was highly suggested from clinical signs and lab tests (**Tables 1 and 2**). Pancytopenia ,hepatitis, low fibrinogen, high ferritin, high triglyceride, and low NK cells. Intravenous immunoglobulins were started and referral was arranged to a more specialized center for immunological and oncological management. But unfortunately, patient condition deteriorated and ended by cardiac arrest.

DISCUSSION:

The initial presentation of this patient -fever,Upper respiratory infection, and lymphadenopathy-give us differential of possible etiologies such as streptococcal pharyngitis , EBV, cytomegalovirus, acute HIV infection, and rarely toxoplasmosis. Among pediatric age group, EBV infection can cause otitis media, gastroenteritis, upper respiratory tract infection, and IM.[9] EBV infection can be responsible for many uncommon complications such as pneumonia, myocarditis, pancreatitis, mesenteric adenitis, myositis, glomerulonephritis, and hepatitis. Neurologic complications of primary EBV infection includes seizure , altered level of consciousness , meningoencephalitis ,Guillain-Barré syndrome, facial nerve palsy, transverse myelitis, peripheral neuritis, and optic neuritis. Although meningoencephalitis is the most common neurological complication of EBV, it is only represents less than 5% of all viral meningoencephalitis etiologies.[7,8,12]

Hematologic sequels of EBV infection include Hemophagocytic lymphohistiocytosis (HLH), hemolytic anemia, aplastic anemia, thrombocytopenia, thrombotic thrombocytopenia purpura, and disseminated intravascular coagulopathy .HLH is not common, but when seen, it often results into mortality. HLH can be primary presentation or can be secondary to hyper-cytokinemia triggered commonly by factors like sever EBV infection.[17] Pathophysiology of this immunological phenomena is characterized by exaggerated immunology recruitment of macrophages and lymphocytes with central role of T cell in the process.[13,14] Patients with this uncommon syndrome present with fever, generalized lymphadenopathy, hepatosplenomegaly, hepatitis, pancytopenia, coagulopathy.[15,16]

HLH diagnosis is frequently missed in early phases and sometimes cannot be reached until detailed autopsy study is done due to lack of specific genetic or biologic markers.[13] Hemophagocytosis was present at diagnosis in 75% of patients. Most common secondary cause of HLH is viral infections which is the cause in 41% of the cases, with EBV infection being the most prevalent factor.

Diagnostic criteria for HLH is suggested by Stringent is used for identification of patients screening. The criteria includes fever, splenomegaly, cytopenia in two lines of cell, hypertriglyceridemia, and/or hypofibrinogenemia, and hemophagocytosis without evidence of malignancy.

A case series of 23 cases identified most common presenting features of HLH to be fever, hepatospenomegaly, lymphadenopathy, and profound depression of blood counts respectively. Generally it has poor prognosis , and may be complicated by

coagulation abnormalities, hepatic dysfunction and renal failure.[14]

In our case, the patient presented with infectious mononucleosis and developed neurological complication in a short period in the form of facial nerve palsy, acute meningoencephalitis, and absent DTR high suspicion of Guillain-Barré syndrome , altered level of consciousness and seizures.It also has association with lymphoproliferative disorders.HLH should be raised if the patient had the following Diagnostic criteria: familial disease/known genetic defect in the familial type, and five of the following eight criteria: fever for 7 days; splenomegaly; cytopenia of two or more cells lines (hemoglobin, 9 g/dL [4 weeks, 10 g/dL]; platelets, 100 109 /L; neutrophils, 1 109 /L); hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides, 3 mmol/L; fibrinogen, 1.5 g/L); ferritin, 500 g/L; sCD25, 2400 U/mL; decreased or absent natural killer (NK) cell activity; hemophagocytosis in bone marrow, cerebral spinal fluid, or lymph nodes. 4 Supporting evidence for this diagnosis includes cerebral symptoms, cerebrospinal fluid with moderate pleiocytosis, and/or elevated protein. Often, there are increased serum transaminases, bilirubin, and lactate dehydrogenase.Specific to FHL, they also our patient had fever more than one week, cerebral symptoms, splenomegaly, cytopenia in three cell lines (red blood cells, neutrophils, and platelets), elevated liver transaminases, hypofibrinogenemia.However the bone marrow was negative for heamophyphagocytosis and negative family history.

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Tables and legends:

Investigation (Table 1)

Date	Hemo globin g/dL	White blood cell k/ul	Platelet k/ul	Fibrogen	Ferritin Range (5-205)	GOT (AST) u/L	GPT (ALT) u/L	Triglyceride mg/dL	Immunoglobulins 22 Oct 2018
6 Oct 2018	11.3	5.8	154	-----	----	253	273	----	IgA 2416 (mg/dl) IgE 2.99 (mg/dl) IgG 1968 (mg/dl) IgM 239 (mg/dl)
14 Oct 2018	7.3	3.7	142	----	----	106	06	----	
22 Oct 2018	6	2	110	107	3117	84	47	291	
30 Oct 2018	7.6	2.1	68	----	----	60	48	----	
6 Nov 2018	9.6	1.6	53	387	2381	47	52	163	
10 Nov 2018	9.4	4	20	----	23824	216	125	---	

CSF analysis(Table 2)

	Appearance	RBC	WBC	CSF Glucose	CSF Lymph	Plasma cell	Protein CSF
13 OCT 2018	Pale-yellow ,hazy	489	77	56	85%	---	81
24 Oct 2018	Colorless and clear	6	238	50	62%	37%	194