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Case Study

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C/O Infectious mononucleosis- EBV/CMV associated with secondary HLH

Dr. Anil Batta[1], Umesh Kumar[2], Preeti Sharma[2]

[1]Professor, Dept. of Medical Biochemistry

[2]Tutor, Dept. of Medical Biochemistry

MM Institute of Medical Sciences & Research, Mullana-Ambala

Abstract

Epstein-Barr virus (EBV) is the main cause of infectious mononucleosis (IM), a self-limiting infection among immunocompetent patients. EBV is also implicated in the development of several malignancies. Hemophagocytic lymphohistiocytosis (HLH) is a potentially life-threatening syndrome of excessive immune activation that is most common in infants and young children, but it can affect patients of any age. We describe a case of a previously healthy 30-year-old female who presented with non-tender, enlarging, right cervical lymphadenopathy for over a year that was associated with significant weight loss, fevers, and night sweats. Two fine needle core biopsies showed inconclusive then reactive tissue, respectively. A third excisional biopsy demonstrated a reactive lymph node with EBV-positive IM. There was no evidence of lymphoma by histologic examination or flow cytometry. A diagnosis of chronic active EBV (CAEBV) was rendered. Subsequent lymph node debulking six months later showed classic Hodgkin lymphoma (CHL) positive for EBV. Patients with HLH can have a single episode of the disease or relapsing episodes, with relapses occurring most often in patients with familial HLH. The instigating trigger for an acute episode is often an infection or an alteration in immune homeostasis. The two broad categories of triggers include those that cause immune activation and those that lead to immune deficiency. The patient underwent chemotherapy with full treatment response. This is an unusual presentation of EBV infection that led to either a delayed onset or delayed diagnosis of CHL. Epstein-Barr virus (EBV) is regarded as the primary cause of infectious mononucleosis (IM) and is typically self-limiting among immunocompetent patients. Symptoms of IM include fever, fatigue, and lymphadenopathy/glandular adenopathy, with lymph node swelling most seen in the cervical region [12]. EBV can also cause chronic active Epstein-Barr virus (CAEBV) infection [10]. CAEBV is an uncommon disease that primarily affects children and is characterized by symptoms of fever, lymph node swelling, and hepatosplenomegaly with elevated liver serum transaminase levels [15]. Adult-onset cases may be more progressive and have a less favorable prognosis as compared to pediatric patients [1]. Currently, there is no established treatment regimen for this disease. Hematopoietic stem cell therapy (HSCT) has been a pivotal treatment and is the only known curative therapy, with varying degrees of success [5, 6, 15]. Acyclovir can theoretically be used for treatment of primary EBV infection but has no proven effect on CAEBV infection [3].

EBV is also implicated in the development of several lymphoproliferative disorders and lymphomas including Hodgkin's and non-Hodgkin's types [4]. More rarely, EBV infection can present with features of lymphoma without underlying malignancy [7]. Non-malignant EBV infection may have a different immunophenotypic profile than typical

classic Hodgkin lymphoma (CHL). On biopsy, it may mimic other types of lymphoma such as non-germinal center type diffuse large B-cell lymphoma as the atypical lymphoid infiltrates are MUM1/IRF4+, CD10-, and BCL-6- [7]. While the presentation of an enlarging neck mass accompanied by B symptoms of night sweats, fatigue, and weight loss is concerning for lymphoma, non-malignant EBV infection is a common imitator. We present an unusual case of the opposite scenario, where lymphoma mimicked EBV infection resulting in a delayed diagnosis of CHL.

Keywords: Epstein-Barr virus, IM, HLH, HSCT, CHL.

Introduction

Epstein-Barr virus (EBV) is regarded as cause of infectious mononucleosis (IM) and is typically self-limiting among immunocompetent patients. Symptoms of IM include fever, fatigue, and lymphadenopathy/glandular adenopathy, with lymph node swelling are mostly seen in the cervical region [12]. EBV can also cause chronic active Epstein-Barr virus (CAEBV) infection [10]. CAEBV is an uncommon disease that primarily affects children and is characterized by symptoms of fever, lymph node swelling, and hepatosplenomegaly with elevated liver serum transaminase levels [15]. Adult-onset cases may be more progressive and have a less favorable prognosis as compared to pediatric patients [1]. Currently, there is no established treatment regimen for this disease. Hematopoietic stem cell therapy (HSCT) has been a pivotal treatment and is the only known curative therapy, with varying degrees of success [5, 6, 15]. Acyclovir can theoretically be used for treatment of primary EBV infection but has no proven effect on CAEBV infection [3]. EBV is also implicated in the development of several lymphoproliferative disorders and lymphomas including Hodgkin's and non-Hodgkin's types [4]. More rarely, EBV infection can present with features of lymphoma without underlying malignancy [7]. Non-malignant EBV infection may have a different immunophenotypic profile than typical classic Hodgkin lymphoma (CHL). On biopsy, it may mimic other types of lymphoma such as non-germinal center type diffuse large B-cell lymphoma as the atypical lymphoid infiltrates are MUM1/IRF4+, CD10-, and BCL-6$^-$ [7]. While the presentation of an enlarging neck mass accompanied by B symptoms of night sweats, fatigue, and weight loss is concerning for lymphoma, non-malignant EBV infection is a common imitator. We present an unusual case of the opposite scenario, where lymphoma mimicked EBV infection resulting in a delayed diagnosis of CHL.

Presenting Complaints

- Fever for ten days was: up to 103^0F, available chills
- Loose stools for eight days: 10-15 times/day, small volume, foul smelling, abdominal discomfort, and tenesmus presentation.
- Oral ulcers associated with pain throat for 5 days.
- No h/o cough /shortness of breath/hematuria/proteinuria, dysuria.
- No h/o decreased jaundice, anorexia, loss of weight/ hematemesis/Malena.
- No h/o headache/loss of consciousness/ dizziness/ no other h/o connective tissue disorder.
- No h/o decreased urinary output/ hematuria/ proteinuria/dysuria.
- History, Personal and family history: not significant

Treatment history: For these above complaints, she visited a local hospital where she was put on antibiotics (Ceftriaxone). Following initiating IV fluids/ antibiotics, she noticed generalized swelling/ redness over the arm, lower limb, and trunk. Subsequently, she was referred to PGI, Chandigarh.

On examination

The patient was alert, cooperative and conscious and well oriented to time and place, **Blood pressure** 100/70 mm of Hg, PR-120/minute, Spo_2: 98% on RT

Temperature: Afebrile. B/L pedal pitting oedema up to knee, **generalized lymphoedema,** generalized lymphadenopathy involving B/L cervical axillary, and inguinal regions, maximum size 2x2 cm in cervical region, No pallor, icterus, cyanosis and clubbing, **Skin**: Generalized erythema, palmoplantar hypererythema, oral ulcers, angular cheilitis. **Abdomen**: soft, non-tender, liver palpable 3ctal margin, liver span 16 cm below right costal margin, tip of spleen palpable, bowel sounds normal. **Respiratory system**: B/L vesicular breath sounds heard **CVS**: S_1/S_2 normal, no s3/murmur CNS GCS-E4V5M6, pupils B/L normal in size and reactive to light, No focal deficit.

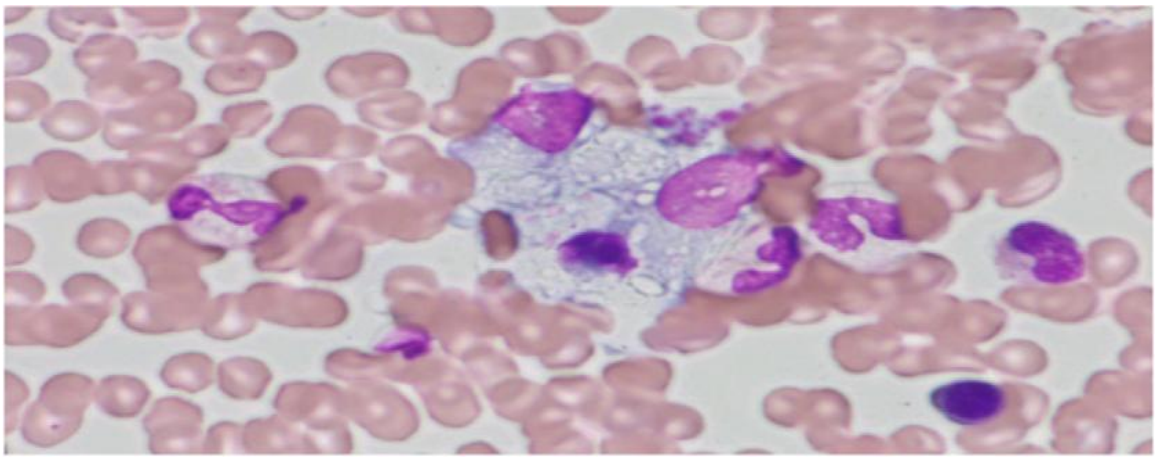

Fig.1: Bone marrow aspiration Bone marrow aspiration performed on hospital day 7 shows phagocytosis of neutrophils and platelets.

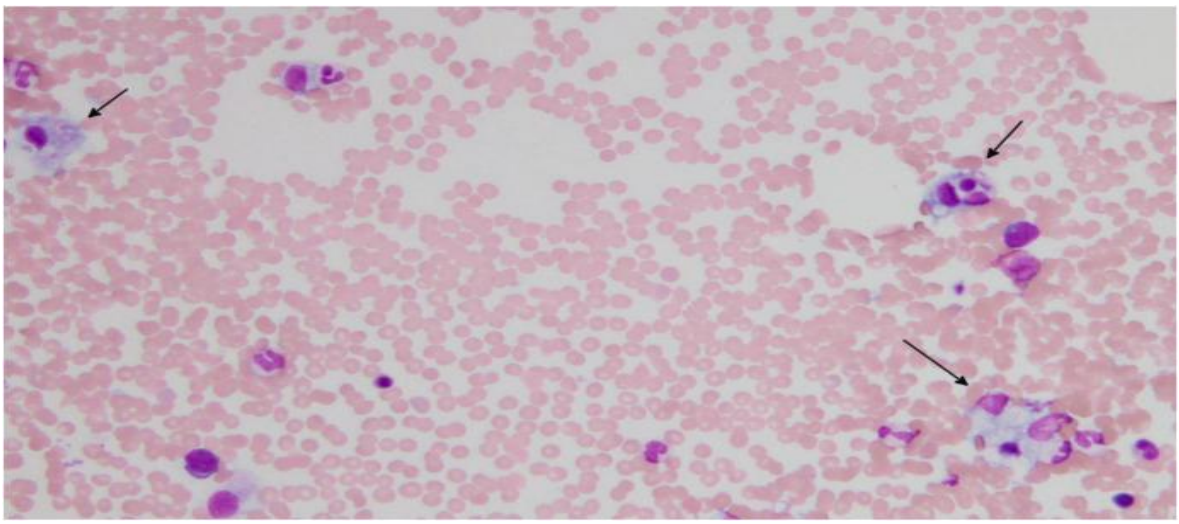

Fig.2. Bone marrow aspiration Hemophagocytosis were shown in three cells per low-power field.

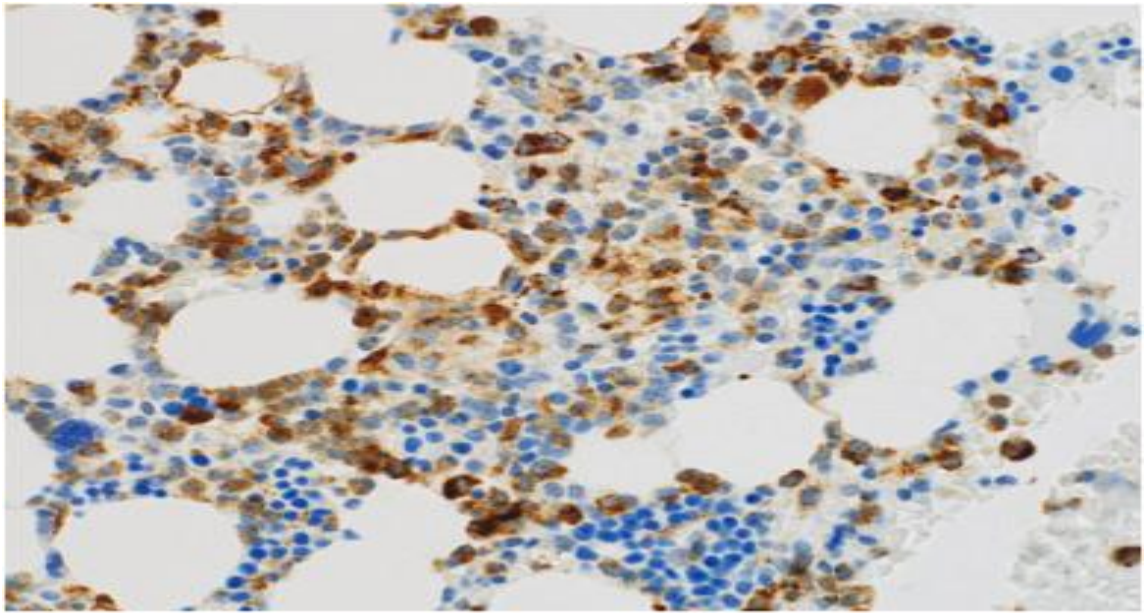

Fig. 3. CD68 stain CD68 stain shows numerous CD68 positive macrophages.

Investigations

Date	8/6/22	10/6/22	14/6/22	16/6/22
Hemoglobin (g/dL)	9.9	9	7.6	8.2
TLC	33,200	32,100	29,400	73,800
DLC N/L/M	34/58/5	36/51/11	38/38/8	52/27/15
Platelet count ($x10^3$)	222	185	146	178
Na/K	137/3.5	134/3.7	134/4.3	133/5.98
Urea/Creatin	26/0.67	18/0.63	21/0.7	24/1.73
AST/ALT/ALP	110/128	371/193/518	2491/599/720	36/1110/583
Bilirubin-Total/Direct	3.3/2.2	3.7/3.4	6.6/5.9	10.2/8.4
Total Protein/Albumin	4.4/2.2	4.8/2.0	6.6/5.9	7.2/1.8
Calcium/Phosphorus	7.0/1.2			7.5/10.4
PT/PTI/INRAPPTT	45/30/3.14/40	65/21/4.5/4.5		71/19/4.9/102
Fibrinogen (g/L)		2.94		1.0
D-dimer(ng/mL)		1002		1407
LDH (U/L)			1455	4301
CRP (mg/L)			163	112

ABG

Date	8/6/22	15/6/22	16/6/22 (Post dialysis)
pH	7.406	7.25	6.706
pCO_2	31	23	52.3
pO_2	68.4	44	68
HCO_3	19	9.9	6.4
Lactate	3.9	12.4	19.5

Other investigation

PBF (15/6/22)- moderate anisopoikilocytosis, Normocytic normochromic red cells admixed with microcytes, macrocytes, ovalocytes and a few spherocytes. Leucoerythroblastic picture. Left shift is seen. Nucleated RBC -4/100 WBCs, Myelocytes-2, N48 L28 M19 E3, Neutrophils show cytoplasmic vacuolation. Platelets adequate; few forms and platelets clumps notes. **Malaria antigen Negative IgM Dengue (sent twice)** Borderline **IgM Leptospira** Negative **IgM Scrub** Negative **Widal test** Negative **Hepatitis A/Hepatitis E antigen Negative** **HIV/HBsAg/ Anti HCV-** Negative **Blood Culture** Sterile **Procalcitonin:** 3.72ng/ml (16/06/2022) **Iron Profile (15/06/2022**) **Serum Iron** -45 ug/dl **TIBC -** 153 ug/dl **Percentage saturation -**29.3% **Serum Ferritin**-687ng/mL Ferritin 11,778 (15/06/2022) Triglycerides 180 mg/dL **ANA-**Negative (Twice) **C3-** 16 mg/dL **C4**-13mg/dL	**Stool RME (twice) pus** cell +, no ova, cyst, atypical organism **USG Abdomen (8/06/2022)** Liver -18 cm, normal echotexture, outline normal, portal vein normal, spleen-13.9 Right kidney 9.5 cm, left kidney 8cm - both showing normal echogenicity, with normal CMD **CECT Abdomen (16/06/2022)** Hepatosplenomegaly mesenteric and retroperitoneal lymphadenopathy Mural thickening with the differential enhancement of large bowel loops - infective Moderate ascites **FNAC lymph Node (15/06/2022)-** left posterior cervical LN - reactive lymphoid hyperplasia **Bone marrow examination (16/06/2022**): hypercellular bone marrow show infection /sepsis- associated changes and evidence of increased Hemophagocytic activity

Course and management:

A30-year-old female with no previous comorbidities presented with fever and large bowel type of diarrhoea for ten type days. She was treated in another hospital with intravenous fluids and antibiotics, after which she developed oral ulcers and generalised erythema. CBC done there show 10.9/47,700/202 lakh with 28% blasts; hence she was referred to PGI. At PGIMER, on examination, she was found to have a generalized erythematous rash, palmoplantar hyperaemia, oral ulcers, generalized lymphadenopathy, and hepatosplenomegaly. Investigation: peripheral blood smear was suggestive of aa leucoerythroblastic picture and deranged liver function. With the working diagnosis of tropical illness-related liver dysfunction, started on ceftazidime and azithromycin. The possibility of EBV- related viral exanthematous reaction was also considered. Coagulopathy and diarrhoea episodes despite antibiotic treatment, while the evaluation for tropical illness, hepatotropic virus and blood culture were all negative. On 13/6/2022, liver function worsened further, the possibility of sepsis/drug induced/HLH was considered on 15/6/2022, she was started on dexamethasone (H Score-214); patient also developed anuria with VBG suggestive of severe metabolic acidosis and did not respond to IV fluids and diuretics. On 16/3/2022, she underwent hemodialysis. CECT done before hemodialysis revealed hepatosplenomegaly with some mural with some mural thickening of bowel loops. Post dialysis patients developed shock and inotropic support was started.

With suspicion of sepsis, antibiotics were hiked up to Meropenem and Vancomycin. Patients with HLH can have a single episode of the disease or relapsing episodes, with relapses occurring most often in patients with familial HLH. The instigating trigger for an acute episode is often an infection or an alteration in immune homeostasis. The two broad categories of triggers include those that cause immune activation and those that lead to immune deficiency. She underwent bone marrow biopsy s/o reactive marrow with secondary HLH. The hypotension continued to worsen, she also required intubation, and she succumbed to her illness on the same day.

Final diagnosis:

1. **Infectious Mononucleosis**- EBV/CMV associated with secondary HLH
2. **Underlying hematological malignancy**? Lymphoma
3. **Cause of death**: Refractory Septic Shock, Acute Pulmonary Thromboembolism

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