



Case Report

Epstein-Barr virus-associated lymphoproliferative disorder mimicking Hodgkin's lymphoma in immunocompetent patients: A case report and literature review

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ABSTRACT

Epstein-Barr virus (EBV) is the most common infectious agent associated with hemophagocytic lymphohistiocytosis (HLH). This case report discusses a 24-year-old immunocompetent African male presenting with a five-month history of persistent high-grade fever, pancytopenia, and splenomegaly. Initial diagnostic evaluations, including bone marrow biopsy, suggested Hodgkin lymphoma; however, further lymph node biopsy, repeated bone marrow biopsy and comprehensive clinical assessment confirmed EBV-associated lymphoproliferative disorder with HLH. This case underscores the importance of thorough diagnostic approaches, incorporating multiple biopsy sites and advanced imaging, to differentiate between EBV-associated HLH and hematological malignancies such as lymphomas. Enhanced clinical awareness and understanding of HLH's diverse presentations are essential for timely diagnosis and effective management.

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1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition characterized by an abnormal immune response that leads to a severe inflammatory reaction.¹ HLH is typically classified as primary or secondary.^{1,2} Primary HLH, also known as familial hemophagocytic lymphohistiocytosis (F-HLH), is caused by genetic mutations that disrupt the function of cytotoxic T cells and NK cells. While secondary or non-familial HLH occurs due to external factors such as infections, hematologic malignancies, cancer, drug hypersensitivity, post-allogeneic hematopoietic stem cell transplantation (HSCT), rheumatologic diseases, or other underlying causes. Epstein-Barr virus (EBV) is the most common infectious agent associated with HLH.^{1–5}

EBV, a member of the Herpesviridae family, is linked to various lymphoproliferative diseases involving one or more types of lymphoid cells. EBV can infect B lymphocytes, resulting in EBV-associated HLH by activating CD8+ cytotoxic T lymphocytes, which triggers uncontrolled activation of macrophages.¹ EBV-associated HLH is often a clinical manifestation of EBV-associated lymphoproliferative disease.⁵ It is noteworthy that the literature indicates that hematologic malignancies such as lymphomas can also induce HLH with mechanisms that remain poorly understood.⁶

Distinguishing between lymphomas and EBV-associated HLH is challenging due to the numerous overlapping features of these two conditions,⁷ making the detection and rapid diagnosis of HLH a complex task. Here, we describe a case in which the diagnosis of EBV-associated HLH was delayed due to its resemblance to Hodgkin lymphoma. The aim is to highlight the diagnostic difficulties associated with

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EBV-related HLH and to enhance clinicians' knowledge of this complex clinical condition.

2. Case Presentation

A 24-year-old African man with no significant medical history presented to the emergency department with persistent fever, dry cough, malaise, and abdominal pain. His symptoms began five months prior while he was in Nigeria on leave, during which he received symptomatic treatment without improvement. He returned to Qatar three months ago with persistent fever, dry cough, malaise, and abdominal pain. Despite seeking medical assistance at various private clinics, his condition deteriorated. He reported a productive cough with greyish sputum and persistent generalized abdominal pain, particularly in the epigastric region and left upper quadrant over the past month. Additionally, he experienced undocumented weight loss and night sweats. There were no associated symptoms such as shortness of breath or chest pain. The patient did not smoke or consume alcohol, had no history of serious illness or surgery, and denied contact with sick people.

Upon arrival, the patient was febrile and pale. Physical examination revealed significant inspiratory crackles in the right middle lobe. Abdominal examination revealed a palpable spleen and diffuse abdominal pain with marked tenderness in the upper abdomen, without evidence of guarding or rebound tenderness.

Initial laboratory investigations revealed pancytopenia, elevated ferritin, deranged liver function tests (LFTs), increased lactate dehydrogenase (LDH), and elevated C-reactive protein (CRP), as detailed in (Table 1). Screening tests for autoimmune diseases and bacterial and viral serologies were negative. Sputum acid-fast bacilli, polymerase chain reaction (PCR), and culture were negative for tuberculosis. Peripheral blood smear for malaria parasites was also negative. Viral PCRs for hepatitis B, hepatitis C, COVID-19, HIV, and HSV were negative, while EBV PCR in blood was positive with a titre of 436,000 IU/mL.

Despite supportive management with paracetamol and broad-spectrum antibiotics, the patient continued to experience high-grade fever daily for 10 days post-admission. Given the persistent symptoms of fever and abdominal pain, an abdominal ultrasound was performed, revealing features suggestive of splenomegaly. Further radiological investigations, including CT scans of the thorax and abdomen, showed bilateral pleural effusion with partial basal collapse and consolidation, mild ascites, and splenomegaly.

To evaluate the pancytopenia and splenomegaly, hematological assessments, including bone marrow aspiration and biopsy, were performed. Bone marrow aspiration revealed histiocytes with active hemophagocytosis (Figure 1A and 1B). Bone Marrow

biopsy results were consistent with classical Hodgkin lymphoma, showing prominently increased histiocytes with evident hemophagocytosis, indicating Hemophagocytic lymphohistiocytosis (HLH) likely triggered by lymphoma and EBV infection (Figure 2 A–D). The patient continued to have fever and developed inguinal lymphadenopathy. A PET-CT scan was performed, which showed multiple severely hypermetabolic lymph nodes above and below the diaphragm and a 19 cm enlarged spleen. Results of a right inguinal lymph node biopsy indicated EBV-positive infectious mononucleosis, with immunohistochemical (IHC) staining showing that the large lymphoid cells were positive for CD30.

A second opinion was sought from the Mayo Clinic laboratories in the USA, which reviewed both the bone marrow biopsy and lymph node biopsy results. According to the Mayo Clinic experts, the lymph node biopsy was consistent with EBV-associated lymphoproliferative disorder, while the bone marrow biopsy showed increased histiocytes with heightened hemophagocytic activity, lymphohistiocytic infiltrate scattered with EBV-positive cells, and normocellular bone marrow with morphologically normal trilineage hematopoiesis. No overt lymphoma was identified. Based on the results of the repeated bone marrow biopsy, lymph node biopsy, and clinical and laboratory findings, the diagnosis of EBV-associated lymphoproliferative disorder with related HLH was confirmed.

The patient was treated with steroids, resulting in rapid improvement of his symptoms. The fever subsided, splenomegaly and lymphadenopathy, and a negative EBV PCR in blood

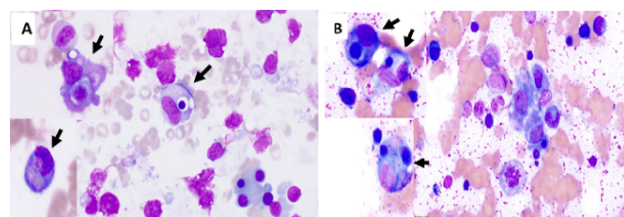


Figure 1: A. Bone marrow aspirate and B. touch slide showing histiocytes with active hemophagocytosis (arrowed cells). Wright stain x1000.

B. The infiltrate is composed mostly of lymphocytes (predominantly T-cells), histiocytes/macrophages, few plasma cells, and some abnormal large mononuclear cells with inclusion-like nucleoli and rare binucleated cells. H&E x1000. C. CD3 immunostaining highlights T-lymphocytes, and CD68 highlights histiocytes x200. D. CD30 immunostain highlights many positive. E. PAX5 immunostaining highlights positive cells with variable intensities.

Table 1: Laboratory Investigations

Parameters	Results	Reference Range
WBC	1.7	4.0–10.0 x10 ³ /uL
RBC	3.9	4.5–5.5 x10 ⁶ /uL
Hgb	10.8	13.0–17.0 gm/dL
Hct	31.6	40.0–50.0 %
MCV	80.6	83.0–101.0 fL
MCH	27.6	27.0–37.0 pg
MCHC	34.2	31.5–34.5 gm/dL
RDW-CV	14.7	11.6–14.0 %
Platelets	38	150–450 x10 ³ /uL
Absolute Neutrophil count Auto # (ANC)	0.7	2.0–7.0 x10 ³ /uL
Retic #	24.7	50–100 0 x10 ³ /uL
Retic %	0.6	0.5–2.5%
Urea	8.1	2.5–7.8 mmol/L
Creatinine	103	62–106 umol/L
Sodium	132	133–146 mmol/L
Potassium	3.7	3.5–5.3 mmol/L
Chloride	100	95–108 mmol/L
Bicarbonate	16	22–29 mmol/L
Calcium	2.31	1.6–3.24 mmol/L
Bilirubin T	88	0–21 umol/L
Bilirubin D	86	0–5 umol/L
Total Protein	60	60–80 gm/L
Albumin	28	35–50 gm/L
ALK phosphate	135	40–129 U/L
ALT	156	0–41 U/L
AST	285	0–40 U/L
LDH	926	135–225 U/L
Triglyceride	3.5	< 1.7 mmol/L
Iron	20	6–35 umol/L
TIBC	40	45–80 umol/L
Transferrin	1.6	2.0–3.6 gm/L
Fe% Saturation	50	15–45 %
Ferritin	7,963	38.0–270 ug/L
CRP	57.7	0.0–5.0 mg/L
Lipase	98	13–60 U/L
Prothrombin Time	10.8	1.0–3.0 x10 ³ /uL
INR	0.9	0.2–1.0 x10 ³ /uL
Fibrinogen	1.57	2.0–4.10 gm/L
APTT	31.9	0.02–0.50 x10 ³ /uL

Abbreviations: White Blood Cell (WBC), Red Blood Cell (RBC), Hemoglobin (Hgb), Hematocrit (Hct), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Red Cell Distribution Width-Coefficient of Variation (RDW-CV), Platelet Count (Platelets), Absolute Neutrophil Count (ANC), Estimated Glomerular Filtration Rate (eGFR), Alkaline Phosphatase (ALK phosphate), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH), Total Iron Binding Capacity (TIBC), C-Reactive Protein (CRP), Activated Partial Thromboplastin Time (APTT).

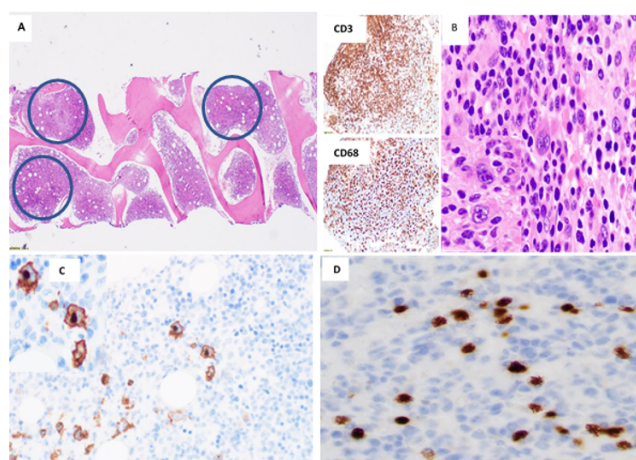


Figure 2: A. Bone marrow biopsy is hypercellular with multiple areas of abnormal infiltrate H & E. 40x.

3. Discussion

Epstein-Barr virus (EBV), a member of the Herpesviridae family, is carried by approximately 95% of the adult population worldwide. Most primary infections occur during childhood and frequently present without symptoms. However, infections in adolescents or young adults may lead to infectious mononucleosis (IM), which is marked by symptoms including fever, sore throat, swollen lymph nodes, and enlargement of the liver and spleen, along with high levels of atypical lymphocyte.⁸ While most cases of IM resolve spontaneously without sequelae, rare instances may progress during the acute phase to a life-threatening condition known as chronic active EBV infection (CAEBV).^{5–7} This systemic EBV-positive lymphoproliferative disorder is characterized by severe constitutional symptoms, systemic lymphadenopathy, and cytopenias lasting at least three months, and is associated with high blood EBV DNA levels in immunocompetent individuals.^{4,8,9} Our patient, a previously healthy young immunocompetent male, presented with fever for five months. His laboratory investigations revealed pancytopenia and high blood EBV DNA levels (EBV-PCR in blood was positive with a titre of 436,000 IU/mL).

In clinical scenarios where fever and pancytopenia persist for an extended period in the context of high blood EBV DNA levels, the differential diagnosis may include various conditions such as EBV-associated lymphoproliferative disorder, hematological malignancies, and disseminated cancers. Therefore, bone marrow studies and tissue biopsies are crucial for differentiating between these clinical entities, to establish the final diagnosis. In our case, bone marrow aspiration and biopsy, as well as right inguinal lymph node biopsy, were performed. Although the bone marrow aspiration suggested EBV-associated HLH, the bone biopsy indicated findings

consistent with Hodgkin lymphoma, suggesting lymphoma-associated HLH. Moreover, the right inguinal lymph node biopsy revealed EBV-positive infectious mononucleosis, with immunohistochemical (IHC) staining showing that the large lymphoid cells were positive for CD30. These findings were initially confusing, causing a delay in reaching a final diagnosis and leading to a potential diagnostic error.

Clinicians must distinguish EBV-associated lymphoproliferative disorder from other hematological malignancies like lymphomas due to EBV's role in various malignancies. However, differentiating between lymphomas and EBV-associated HLH is challenging due to the extensive overlap in disease characteristics.⁷ Therefore, obtaining multiple biopsy samples from various anatomical sites may help resolve this dilemma. In our case, we consulted experts at the Mayo Clinic and repeated the bone biopsy and inguinal lymph node biopsy. Based on the experts' opinion and the results of the repeat biopsies, a final diagnosis of EBV-associated lymphoproliferative disorder was established. Currently, there are no standardized guidelines for treating EBV-associated lymphoproliferative disorder.¹⁰ However, in our case, the patient exhibited a dramatic response to steroids, with resolution of fever, splenomegaly, and lymphadenopathy resolved, and EBV PCR in blood became negative.

4. Conclusion

All adult patients with prolonged cytopenia and fever that do not respond to antibiotics should be evaluated for HLH. Prompt hematologic consultation and consideration are essential for appropriate HLH work-up and diagnosis. It is challenging to differentiate between lymphoma and EBV-associated HLH because they share many similar disease characteristics. Therefore, repeating biopsies may help avoid misdiagnosis of lymphoma, whereas corticosteroids can be employed in the treatment of EBV-associated lymphoproliferative disorders with HLH.

5. Patient Consent

Written informed consent was obtained from the patient for the publication of this case report.

6. Authors' Contribution

All authors contributed to the completion of this work. The final manuscript was read and approved by all authors.

7. Source of Funding

None.

8. Conflict of Interest

None.

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