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EPSTEIN-BARR VIRUS-DRIVEN T-CELL LYMPHOMA WITH HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: A LIFE-THREATENING DISORDER EXTENDING BEYOND CHILDHOOD

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ABSTRACT

An 18-year-old previously healthy Filipino male presented with abdominal pain, vomiting, dyspnoea and fever. Initial investigations revealed severe hepatosplenomegaly, pancytopaenia, elevated liver enzymes, coagulopathy and extremely high ferritin levels. Bone marrow biopsy confirmed an abnormal CD8+ T-cell population with haemophagocytosis. Extensive workup was performed, and he was ultimately diagnosed with haemophagocytic lymphohistiocytosis (HLH) secondary to Epstein-Barr virus-positive T-cell lymphoma of childhood (EBV-TCL), a rare and aggressive malignancy. Despite the initiation of modified dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide (SMILE) chemotherapy along with high-dose glucocorticoids, the patient did not respond to the treatment and expired. This case underscores the critical importance of early recognition and prompt intervention in EBV-TCL-associated HLH which is a unique condition and a rare entity. The diagnosis of this entity can be particularly challenging, given its rapid progression and high mortality rate. Therefore, timely diagnosis and the initiation of appropriate therapy are essential for improving patient outcomes. General medicine providers play a key role in identifying warning signs to avoid delays in treatment initiation.

KEYWORDS

Epstein-Barr virus, T-cell lymphoma, childhood, haemophagocytic lymphohistiocytosis

LEARNING POINTS

- EBV-associated T-cell lymphoma with haemophagocytic lymphohistiocytosis can affect not only children but also adolescents and young adults, highlighting the need for awareness of the high fatality risk.
- Early recognition of EBV-associated haemophagocytic lymphohistiocytosis (EBV-HLH) is crucial; when a patient presents with fever, pancytopaenia and hepatosplenomegaly.
- Future prospective studies are warranted to determine the treatment strategy and the optimal patient population that requires early bone marrow transplantation when initial treatment is inadequate.

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INTRODUCTION

Systemic EBV-positive T-cell lymphoma (EBV-TCL) of childhood is a rare and highly aggressive disorder that primarily affects children, adolescents and young adults, with a higher incidence observed among individuals of Asian and Native American[1] ethnicity, which has been categorised into the spectrum of EBV-related T-cell lymphoproliferative disorders of childhood according to the World Health Organization (WHO) classification[1]. It is characterised by the monoclonal proliferation of EBV-infected cytotoxic T cells and is often associated with a fulminant clinical course, frequently complicated by haemophagocytic lymphohistiocytosis (HLH)[2]. HLH associated with EBV infection can progress rapidly, with clinical presentation that includes high fever, skin rash, pulmonary infiltrates, jaundice, hepatosplenomegaly, cytopaenia, coagulopathy and haemophagocytosis[3]. Although typically considered a childhood disease it also affects older patients, with a median age of diagnosis of around 20 years[1]. Given its rarity, with only 17 cases reported in the previous literature and its poor prognosis, often resulting in death within weeks[4], this condition presents considerable diagnostic and therapeutic challenges. This report underscores the need for clinical awareness of EBV-associated T-cell lymphoma with haemophagocytosis, especially when considering HLH in differential diagnosis, and highlights the importance of further investigation into this rare and often fatal entity.

CASE DESCRIPTION

An 18-year-old previously healthy Filipino male presented with a five-day history of acute right upper quadrant tenderness, vomiting, dyspnoea and fever. He self-administered a few tablets of acetaminophen the day prior for fever relief. Denying any recent medication changes, herbal supplement intake, substance use or significant family medical history, the patient exhibited physical findings of scleral icterus and right upper quadrant tenderness. Initial laboratory investigations revealed acute renal failure, anion gap metabolic acidosis, elevated transaminase and bilirubin levels, coagulopathy and pancytopaenia, summarised in *Table 1*. Computed tomography of the abdomen and pelvis with intravenous contrast confirmed severe hepatosplenomegaly without bile duct dilatation or gallstone, prompting admission to the intensive care unit. The patient met sepsis criteria at first and was started on empirical antibiotic with ceftriaxone, metronidazole, vancomycin, doxycycline and ganciclovir, although the source of infection remained. A chest X-ray showed a small amount of right pleural effusion. Given leucopoenia with a white blood cell count of 2.04 $\times 10^3$/µl and an absolute neutrophil count of 610 cell/µl, a viral aetiology was highly likely. Further investigation indicated a positive EBV DNA polymerase chain reaction and detection of anti-EBV VCA IgM antibodies. Additionally, ferritin levels exceeded 100,000 ng/ml, triglycerides measured 406 mg/dl, fibrinogen was 91 mg/dl and soluble interleukin-2 receptor (soluble CD25) was 36,464.5 pg/ml. The clinical course was complicated by multisystem organ failure and vasodilatory shock. Suspecting haemophagocytic syndrome, a bone marrow biopsy with flow cytometry was performed, revealing an immunophenotypically abnormal CD8+ T-cell population in immunohistochemical staining. It demonstrated prominent CD8+ and CD68 histiocytic infiltrates with haemophagocytosis *(Fig. 1A)*, along with positivity for CD2, CD3 *(Fig. 1B)* and TIA-1. Epstein-Barr encoding region in-situ hybridisation was positive in the neoplastic T cells *(Fig. 1C)*.

Based on clinical and histopathological findings, along with adherence to HLH-2004 criteria, a diagnosis of haemophagocytic lymphohistiocytosis (HLH) secondary to EBV-positive T-cell lymphoma of childhood was established. Inpatient chemotherapy with modified SMILE regimen (dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) was initiated promptly. Due to pancytopaenia and coagulopathy, the patient required frequent transfusions of blood products. His respiratory function deteriorated, necessitating intubation and mechanical ventilation, with progressively worsening desaturation. The patient was considered ineligible for extracorporeal membrane oxygenation support due to multisystem organ failure and refractory thrombocytopaenia. Ultimately, despite treatment efforts, the patient did not recover and passed away in hospital on day 26.

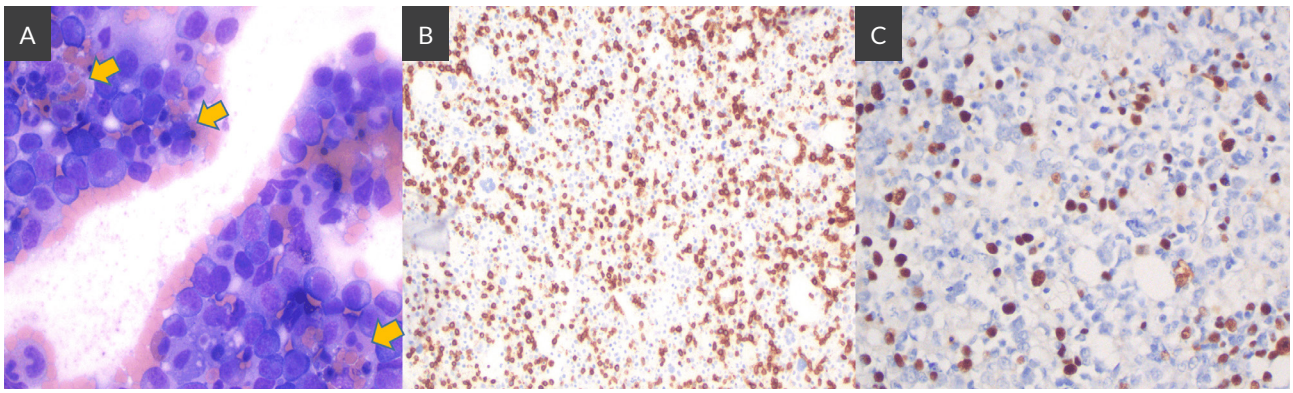

Figure 1. Histopathology imageges showing A) Several haemophagocytic cells are identified in the bone marrow (orange arrows); B) Atypical lymphocytes are positive for T-cell marker CD3 with cytotoxic phenotype; C) Epstein-Barr encoding region in-situ hybridisation is positive in the neoplastic T cells.

Complete blood count	Results	Reference range
WBC (103/µl)	2.04	3.84–9.84
Neutrophil (%)	30	34–72
Lymphocyte (%)	19	12-44
Monocyte (%)	3	0–12
Eosinophil (%)	0	0–7
Basophil (%)	0	0–2
Metamyelocyte (%)	3	0
Hb (g/dl)	8.3	13.7–17.5
HCT (%)	22	40.1–51
MCV (fl)	79.2	79.4–98.4
MCH (pg)	29.3	26–34
MCHC (g/dl)	37.1	32–36
RDW (%)	14.3	11.6–14.4
Plt (103/µl)	30	151–424
Biochemical findings	**Results**	**Reference range**
BUN (gm/dl)	25	6–23
Cr (gm/dl)	2.8	0.6–1.4
Na (mEq/l)	138	133–145
K (mEq/l)	3.6	3.3–5.1
Cl (mEq/l)	96	95-108
HCO3 (mEq/l)	18	21–30
TP (gm/dl)	4.7	6.4–8.3
Alb (mg/dl)	2.8	3.5–5.2
AST (IU/l)	763	0–40
ALT (IU/l)	181	0–41
ALP (IU/l)	113	35–129
T-Bil (mg/dl)	5.4	0–1.2
DBI (mg/dl)	3.5	0–1
Triglyceride (mg/dl)	406	<150
TSH (uIU/ml)	3.4	0.5–4.5
Autoimmune workup findings		
ANA	< 40	
Anaemia workup findings	**Results**	**Reference range**
LDH (IU/l)	> 2,500	135–350
Haptoglobin (mg/dl)	< 10	30–200
Iron, total (ug/dl)	253	45–160
IBC (ug/dl)	< 270	228–428
Saturation (%)	> 93.7	20–50
Ferritin (ng/ml)	> 100,000	30–400
Soluble interleukin 2 receptor (pg/ml)	36,464.5	175.3–858.2
Coagulation profile	**Results**	**Reference range**
PT	24.6	
PTT	62.3	
INR	2.3	
Fibrinogen (mg/dl)	91	150-250
Infectious workup findings	**Results**	**Reference range**
EBV Ab to VCA, IgM (U/ml)	> 4	< 0.8
EBV Ab to early Ag, IgG (U/ml)	6.7	< 0.8
EBV Nuclear Ag, IgG (U/ml)	< 0.2	< 0.8
EBV Ab to VCA, IgG (U/ml)	< 0.2	> 0.8
EBV DNA, QN PCR (cpy/ml)	> 2,000,000	
HIV-1 RNA (copies/ml)	Negative	
HSV	Negative	
CMV DNA (quantitative)	Not detected	
Hepatitis A IgM	Negative	
Hepatitis B surface antigen	Negative	
Hepatitis B core IgM	Negative	
Hepatitis B core IgG	Negative	
Hepatitis C antibody	Negative	
Typhus fever IgM	Not detected	
RMSF IgM	Not detected	
Brucella Ab	Negative	
SARS-CoV-2 RNA	Negative	

DISCUSSION

Systemic EBV-associated T-cell lymphoma of childhood (EBV-TCL) is a rare condition that has been classified, although its incidence remains unclear. Previous studies have reported only 17 cases following acute EBV infection, which revealed a high prevalence in the Asian population[3]. Our patient was a Filipino who was born and raised in the Philippines and moved to Hawaii at the age of 11. It remains unclear whether genetic factors associated with the Asian population contribute to the development of this condition. Additionally, the majority of reported cases have emerged from Eastern Asia, particularly Japan and Taiwan[1]. This geographical distribution suggests potential genetically determined defects in T-cell responses to EBV among certain populations. The median age at diagnosis for EBV-TCL is 20 years[1], with a range of 0 to 45 years, and the condition is more prevalent in males, with a male-to-female ratio of 11:6[3]. Common presentations of systemic EBV-associated T-cell lymphoma of childhood (EBV-TCL) include hepatosplenomegaly, fever and pancytopaenia[2]. However, the clinical presentation can often mimic sepsis, potentially delaying diagnosis. In our case, the patient presented with fever, right upper quadrant pain, jaundice and abnormal liver function tests, which could be confused with a biliary tract infection, similar to a previously reported case initially misdiagnosed as this[5].

This condition poses a diagnostic challenge for clinicians when identifying haemophagocytic lymphohistiocytosis (HLH) and determining the primary aetiology. Clues for diagnosing HLH include elevated ferritin and triglyceride levels, alongside low fibrinogen levels and cytopaenia, according to the HLH-2004 criteria[6]. In patients exhibiting hyperinflammatory status and cytopaenia who do not respond to broad-spectrum antibiotics, alternative diagnoses, including HLH secondary to atypical infections or malignancies, should be considered. A multidisciplinary approach is essential for accurate diagnosis; in this case, consultations with infectious disease, hepatology and haematology teams were crucial. This collaboration facilitated an early suspicion of HLH, allowing for timely treatment according to HLH protocols while awaiting confirmation through pathology and specific investigations, including soluble IL-2 receptor (sIL-2R = sCD25). It is important to be aware that younger patients may develop a particularly aggressive form of the disease known as fatal haemophagocytosis syndrome, which can result in mortality within weeks of diagnosis[3]. A review of the literature indicates that among 17 reported patients,

Abbreviations: Hb, hemoglobin; WBC, white blood cell; HCT, hematocrit; Plt, platelet; Na, sodium; K, potassium; Cl, chloride; Cr, serum creatinine; TSH, thyroid stimulating hormone; TP, total protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; T-Bil, total bilirubin; ANA, anti-nuclear antibody; LDH, lactate dehydrogenase; IBC, iron binding capacity; EBV, Epstein-Barr virus; Ab, antibody; VCA, viral capsid antigen; Ag, antigen; HIV, human immunodeficiency virus; HSV, Herpes simplex virus; CMV, cytomegalovirus; RMSF, rocky mountain spot fever; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1. Main laboratory data.

15 ultimately passed away due to complications associated with this condition[4].

This EBV-TCL is characterised by the monoclonal expansion of EBV-infected T cells, often exhibiting an activated cytotoxic phenotype. The pathogenesis of EBV-TCL-associated HLH involves a complex interplay of immunological factors – a severe systemic inflammatory disorder, driven by the uncontrolled activation of the immune system. EBV infection is theorised to hyperactivate T cells, leading to uncontrolled cytokine release, particularly interferon gamma (IFN-γ) and interleukin (IL-18)[7]. This cytokine storm disrupts normal immune function, promoting excessive macrophage activation and haemophagocytosis; the hallmark feature of HLH, where macrophages engulf healthy blood cells. These cytokines contribute to a cascade of immune activation and inflammation, resulting in the multisystem organ dysfunction that is emblematic of HLH[8]. Additionally, impaired natural killer cell cytotoxicity due to EBV-driven T-cell proliferation further contributes to uncontrolled immune activation and tissue damage[9]. The triggers for this dysregulation can vary, with primary EBV infection in children or underlying lymphoma in adults being notable precipitating factors. Malignancy-associated HLH requires urgent interventions for the primary disease, although only a few patients have clinical responses. For EBV-TCL, various chemotherapy regimens, including the CHOP-like regimen SMILE and asparaginase-based treatments, have been employed with limited success[10,11]. The modified SMILE regimen with dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide is used in natural killer and T-cell lymphoma with increased intensity[12]. However, even these modifications have not significantly improved outcomes, as evidenced by the rapid deterioration and expiry of the patient described.

Novel therapeutic strategies are actively being explored to improve outcomes for HLH. While clinical trials in this have faced challenges to incorporate an adequate number of patients given the severity and paucity of diseases, interferon-gamma inhibitions and janus kinase (JAK) inhibitors have been considered for refractory cases to manage uncontrolled activation of T cells and macrophages[13]. Refractory HLH cases should require early allogeneic bone marrow transplant service consultation, especially in young and fit patients[14].

CONCLUSION

This case highlights the significant challenges to identifying HLH in undiagnosed haematologic malignancy, EBV-TCL. While patients with malignancy-associated HLH are known to be associated with a poor prognosis, clinicians should be reminded of the importance of early recognition of HLH when patients have cytopaenia and signs of hyperinflammatory status, and fail to respond to conventional broad-coverage antibiotics.

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