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Case report

Severe Epstein–Barr virus-associated hemophagocytic syndrome in six adult patients

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Abstract

Background: EBV associated hemophagocytic syndrome (HPS) is an aggressive and potentially life-threatening condition. So far, most EBV associated HPS has been characterized mainly in infants and children in Asian countries.
Results: Here, we report six cases of EBV associated HPS occurring in previously healthy adults in a non-endemic area within a short period of 3 years. All patients presented with fever, hepatosplenomegaly and pancytopenia as well as disturbed liver function tests and coagulopathy. Half were diagnosed as having lymphoma. While EBV-specific serological assays were non-diagnostic in four of the six patients, the presence of EBV DNA in plasma allowed the diagnosis of EBV associated HPS in all patients.
Conclusion: EBV associated HPS may be more prevalent in non-Japanese adults than was previously considered. Screening for hemophagocytic syndrome, in adults as well as in children, should include real-time PCR for EBV.

Keywords: Hemophagocytosis; Epstein–Barr virus; Adults

1. Introduction

Hemophagocytic syndrome (HPS) is an aggressive and potentially life-threatening condition. Patients with this unusual syndrome present with fever, generalized lymphadenopathy, hepatosplenomegaly, pancytopenia and hypertriglyceridemia. Disturbed liver function tests, as well as coagulopathy, are prominent features (Yoshioka et al., 2003). There are two distinct entities among HPS patients. One is primary or familial (the X-linked lymphoproliferative disorder) and the second is sporadic or reactive type (Su and Chen, 1997). The reactive type of HPS may be associated with infections, autoimmune disorders or malignancies. Among the infections associated with HPS, Epstein–Barr virus (EBV) is a prominent causative agent (McClain et al., 1981).

The pathogenesis of EBV-associated HPS remains poorly understood. As opposed to latent and lytic EBV infection, which affect B cells and nasopharyngeal epithelial cells, respectively (Straus et al., 1993), EBV-associated HPS involves direct infection of T- or NK-cells (Kasahara et al., 2001; Quintanilla-Martinez et al., 2000; Su and Chen, 1997). A proposed mechanism is that proliferation of EBV-infected T-cells, selectively upregulates the expression of tumor necrosis factor-alpha, interferon-gamma and other cytokines, which in turn stimulate histiocytes and macrophages (Imashuku et al., 1999; Larroche and Mauthon, 2004; Lay et al., 1997) resulting in uncontrolled accumulation of activated T-lymphocytes and histiocytes in multiple organs (Henter et al., 1991).

Thus far, EBV-associated HPS has been described mainly in infants and children in Asian countries (Imashuku et

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al., 2003). Here, we describe six adult patients with EBV-associated HPS who presented at the Hadassah University Hospital in Jerusalem between August 2004 and May 2007.

2. Case reports

Case 1. A previously healthy 27-year-old male presented with fever of 1-week duration. On physical examination he had jaundice and hepatosplenomegaly without lymphadenopathy. His initial laboratory tests revealed 451,000 /mm^3 platelets, 30,000/mm^3 white blood cells (WBC), creatinin 137 μmol/L, abnormal liver function tests with LDH 3088 units/L, GGTP 400 units/L, alkaline phosphatase 400 units/L, ALT 100 units/L, AST 100 units/L, albumin 26 gr/L, total protein 73 gr/L, total bilirubin 1032 μmol/L, direct bilirubin 712 μmol/L and coagulopathy with prolonged INR (2 units). During the hospitalization course his hemoglobin dropped from 14 to 5.5 g/dL with positive Coombs test, IgM cold agglutinins and anti-EBV serology was compatible with primary EBV infection, revealing positive IgM and IgG for viral capsid antigen with subsequent seroconversion of EBNA IgG. EBV viral load as measured by real time PCR was 90,000 DNA copies/ml plasma (Table 1). No source of bacterial infection was found on multiple blood, sputum and urine cultures. Bone marrow smear revealed hemophagocytosis. The patient was treated with high dose steroids and plasmapheresis with only transient improvement, and required repeated administration of packed red blood cells. Five days after his admission, the patient developed multi-organ failure and he died.

Case 2. A 34-year-old healthy male was admitted with fever and pancytopenia which developed 1 month prior to his admission. On physical examination he had hepatosplenomegaly without lymphadenopathy. Laboratory results revealed pancytopenia with hemoglobin of 7.9 g/dL, 1500/mm^3 WBC with 700/mm^3 neutrophils, 60/mm^3 platelets, elevated LDH (923 U/L) and negative serology for HAV, HBV, HCV and CMV. He developed anasarca, pruritic rash, jaundice, disseminated intravascular coagulation, renal failure and lung infiltrates. He subsequently required ventilation at the intensive care unit. No source of infection was found. Bone marrow biopsy revealed agranulocytosis, dyserythropoiesis, megaloblastic changes, hemophagocytosis, histiocyte proliferation with malignant appearing lymphocytes which stained for S100, and were negative for CD 56. Molecular analysis revealed a T-cell receptor rearrangement. The atypical lymphoid cells in the skin stained positive for EBV (latent membrane protein antigen) by in situ hybridization (Fig. 1). Cytogenetics reveled trisomy 3. EBV serology revealed viral capsid antigen IgG. The EBV viral load obtained was 300,000 copies/ml (Table 1). The patient was diagnosed with EBV-positive T-cell lymphoma. He was started on vincristine, cyclophosphamide and VP 16, but worsening multi-organ failure

Table 1
Patients' information

Case no.	Ethnic origin	Age	Sex	Pathology	EBV DNA viral load (copies/ml)	EBV serology	Therapy	Outcome
1	Jewish	27	M	HPS	90,000	VCA IgG+, IgM+, EBNA IgG seroconversion	Supportive	Fatal
2	Jewish	34	M	T-cell lymphoma	300,000	VCA IgG+, IgM−, EBNA IgG−	Vincristine, cyclophosphamide VP 16	Fatal
3	Jewish	70	M	HPS	550	VCA IgG+, IgM−, EBNA IgG+	Supportive	Fatal
4	Arab	16	F	Hodgkins disease	10,000	VCA IgG+, EBNA IgG−, IgM−	Combination chemo and acyclovir	Alive at 2 years follow up
5	Arab	31	M	HPS	3000	VCA IgG−, IgM−, EBNA IgG−	Supportive	Fatal
6	Jewish	55	M	Anaplastic large T-cell lymphoma lymphocytic variant	21,000	EBNA IgG+, VCA—not done	Supportive	Fatal

Abbreviations: VCA, viral capsid antigen; HPS, hemophagocytic syndrome; EBV, Epstein–Barr virus; EBNA, Epstein–Barr nuclear antigen.