Epstein–Barr Virus Infection Masquerading as Acute Leukemia: A Report of Two Cases and Review of Literature

Puneet Chhabra · Arjun Dutt Law · Upender Sharma ·
Vikas Suri · Manupdesh Singh Sachdeva · Savita Kumari ·
Subhash Varma · Pankaj Malhotra

Received: 18 August 2012 / Accepted: 4 October 2012 / Published online: 25 October 2012
© Indian Society of Haematology & Transfusion Medicine 2012

Abstract Epstein–Barr virus (EBV) is the first herpes virus to be completely sequenced. It is implicated in diseases from the benign infectious mononucleosis to malignant nasopharyngeal carcinoma, Burkitt’s lymphoma and primary CNS lymphoma in AIDS patients. It has also been found to be associated with some miscellaneous diseases like chronic fatigue syndrome, multiple sclerosis etc. however causality still remains an issue of debate. As the virus mainly targets the lymphomonuclear cells and the reticuloendothelial system of the body, its various manifestations are often mistaken as leukemic malignancies. We report two such cases of young adults who had been diagnosed as having acute

leukemia on the basis of atypical cells in the peripheral blood. One patient later turned out to be a classical infectious mononucleosis and second patient had EBV associated hemophagocytic lymphohistiocytosis syndrome.

Keywords Epstein–Barr virus · Acute leukemia · Infectious mononucleosis · Hemophagocytic lymphohistiocytosis

Introduction

Epstein–Barr virus (EBV) causes a spectrum of diseases in human beings. Infectious mononucleosis commonly occurs in adulthood and presents as fever, generalized lymphadenopathy and sore throat [1]. Patients can also present with a maculopapular rash, jaundice, constitutional symptoms or even the complications associated with the infection. The disease is usually self limiting in most cases. EBV is also the most common infectious trigger of hemophagocytic lymphohistiocytosis [2, 3]. The presentation of both diseases mimics lymphoreticular malignancies and frequently it can be mistaken for leukemia and lymphomas.

Case Report

Case 1

A 32 year old male admitted with complaints of fever and jaundice for 1 week. He was being treated with ceftriaxone and amoxicillin for enteric fever in an outside medical facility. Following this he developed a generalized maculopapular rash. His peripheral blood film showed a high proportion of atypical lymphoid cells and he was told to have

P. Chhabra · A. D. Law · V. Suri · S. Kumari ·
S. Varma · P. Malhotra (✉)
Department of Internal Medicine, PGIMER,
Chandigarh 160012, India
e-mail: malhotrapankaj@hotmail.com

P. Chhabra
e-mail: puneet.pgi@gmail.com

A. D. Law
e-mail: Arjun.d.law@gmail.com

V. Suri
e-mail: Surivikas9479@gmail.com

S. Kumari
e-mail: Savita349@yahoo.com

S. Varma
e-mail: suvarma@hotmail.com

U. Sharma
Department of Pathology, PGIMER, Chandigarh 160012, India
e-mail: upenderkaushik@gmail.com

M. S. Sachdeva
Department of Hematology, PGIMER, Chandigarh 160012,
India
e-mail: drmanupdeshpgi@yahoo.co.in

acute leukemia and was referred to us for further management. At presentation he was febrile, and general physical examination revealed the presence of pallor, icterus, generalized lymphadenopathy and a maculopapular rash on the trunk, both upper limbs and palms. Abdominal examination revealed a firm, mildly tender liver 6 cm below the right costal margin, rest of the systemic examination was normal. Investigations revealed raised WBCs with atypical/transformed lymphocytes ranging from 60 to 70 % on various occasions (Fig. 1), biochemical investigations revealed conjugated hyperbilirubinemia (6.6/4.9 mg/dL) and transaminitis (OT/PT-198/323U), alkaline phosphatase was 321 U, albumin and coagulation profile were normal. HbsAG, anti HCV and Elisa for HIV were negative. Peripheral blood smear did not show the presence of malarial parasite, widal and rickettsial serologies were also negative. Urine and blood cultures were sterile. IgM anti viral capsid antigen for EBV was positive. The patient was managed conservatively. He became afebrile over 1 week, rash gradually subsided, WBC counts came down with decrease in the percentage of atypical cells in peripheral smear and a downward trend of bilirubin and OT and PT levels in blood. The patient was followed up in the outpatient department after 1 month and had regression of the lymph node enlargement as well as normalization of his WBC counts.

Case 2

A 15 year old female was admitted with high grade fever for 2 weeks with no localizing symptoms. She had been diagnosed as acute leukemia on basis of FNAC from an enlarged lymph node in an outside medical facility and referred to us for further management. Examination

Fig. 1 Microphotograph showing atypical lymphocyte which is larger in size than normal mature lymphocyte and has less dense nuclear chromatin with moderate amount of cytoplasm (Leishman's 400×)

revealed, pallor, generalized lymphadenopathy, hepatomegaly 6 cm below the right costal margin and splenomegaly 4 cm below the right costal margin. She had a maculopapular rash over the trunk and both upper limbs which developed after patient was given cefixime in the outpatient department. Investigations at presentation revealed pancytopenia with a hemoglobin of 9.1 gm/dL, total leucocyte counts of $1,200/\text{mm}^3$, absolute neutrophil count of $216/\text{mm}^3$ and a platelet count of $19,000/\text{mm}^3$. Considering the diagnosis of Febrile Neutropenia, she was started on injection ciprofloxacin and amikacin. Because of the persistence of high grade fever, cytopenias and splenomegaly she was worked up for Hemophagocytic syndrome. Triglycerides level were high (270 mg/dL) as was serum ferritin (4,650 ng/mL) and the patient had hypofibrinogenemia (1.4 units). Bone marrow revealed hemophagocytosis (Fig. 2). A diagnosis of hemophagocytic lymphohistiocytosis was made based on HLH 2004 criteria (6/9 criteria positive). Blood and urine cultures were sterile. As the patient continued to have high grade fever and no identifiable focus of infection, she was started empirically on amphotericin B following which she became afebrile. A work up for hemophagocytosis revealed IgG anti viral capsid antigen to be positive. It was decided to start the patient on etoposide, cyclosporine and dexamethasone as per HLH 2004 protocol however, as the patient had clinically improved, this was deferred. At discharge patient had regression of hepatosplenomegaly and lymph nodes. At the time of discharge, investigations revealed hemoglobin of 9.9 gm/dL, total counts of $4,500/\text{mm}^3$ with absolute neutrophil counts of $3,060/\text{mm}^3$ and platelet count of $2,40,000/\text{mm}^3$. Triglycerides also decreased to 240 mg/dL. The patient was followed up on an outpatient basis after 4 weeks and showed sustained clinical and hematological recovery.

Discussion

Epstein–Barr virus associated infectious mononucleosis is a benign syndrome characterized by proliferation of lymphomononuclear cells. Manifestations range from a non-specific constitutional syndrome to fever, rash, jaundice, hepatosplenomegaly and lymphadenopathy and rarely complications like autoimmune hemolytic anemia [4], splenic rupture and neurologic manifestations like bell's palsy, GB syndrome and meningoencephalitis [5]. Investigations reveal atypical lymphocytes in the peripheral smear which are CD8+ T cells as well CD16+ natural killer cells. These cells are also observed in other viral illnesses as well conditions such as toxoplasmosis [6].

Hemophagocytic lymphohistiocytosis is a syndrome characterized by proliferation of the histiocytes and dysfunction of the natural killer and cytotoxic T cells

Fig. 2 Microphotograph showing erythro and hemophagocytosis (MGG1000×)

commonly presenting as multiorgan failure due to infiltration of various organs of the body by mononuclear cells. The disease manifests as fever, pancytopenia and hepatosplenomegaly. Investigations reveal hypertriglyceridemia, hyperferritinemia, increased CD25 and hypofibrinogenemia. Some congenital syndromes linked with HLH like Chediak-Higashi syndrome, Griscelli syndrome-2 and X-linked lymphoproliferative disease etc. It is secondarily associated with variety of bacterial, viral and fungal infections. It is called macrophage activation syndrome when it is associated with autoimmune diseases. EBV associated hemophagocytic syndrome is seen most commonly between 1 and 2 years of age, however presentation in young adulthood is also reported. HLH is highly fatal if left untreated. According to HLH protocol 2004, patients with persistent or familial HLH should be treated with 8 weeks of cyclosporine, dexamethasone and etoposide [7]. However reports have shown improvement of EBV associated HLH without any treatment as occurred in our patient.

Lymphoproliferative diseases are a close mimicker of EBV associated syndromes, as the primary target of this virus are B cells but it also leads to proliferation of T cells as well. It was initially thought that Flow cytometry would solve the problem but it's not true. T cell lymphoproliferative disorders show down regulation of CD 7 as well as CD3 and CD4 on immunophenotyping but this can be seen in a lot of other conditions too [8, 9]. A quite good number of infectious mononucleosis patients show T cell clones which express HLA DR however this may also be seen in

some T cell lymphoproliferative conditions. So to make a definitive diagnosis of EBV associated syndromes requires a comprehensive battery of tests like peripheral smear examination, viral serologic markers, detection of viral DNA through PCR and careful interpretation of flow cytometry.

Conclusion

Epstein–Barr virus associated disorders may mimic haematological malignancies. EBV associated syndromes should always be considered in the differential diagnosis of patients presenting with fever, jaundice, hepatosplenomegaly and cytopenias. If at all there is a strong clinical suspicion of EBV associated condition, a detailed work up should be done before labelling the patient with a diagnosis of a lymphoproliferative neoplasm to avoid erroneous administration of hazardous chemotherapy. EBV associated hemophagocytosis may improve without therapy [10] and thus a careful close observation and follow up is required.

References

1. Hurt C, Tammaro D (2007) Diagnostic evaluation of mononucleosis-like illnesses. *Am J Med* 120(10):911
2. Fadilah SA, Raymond AA, Cheong SK et al (2001) Fatal hemophagocytic syndrome. *Med J Malaysia* 56(4):503–507
3. Maakaroun NR, Moanna A, Jacob JT, Albrecht H (2010) Viral infections associated with hemophagocytosis. *Rev Med Virol* 20(2):93–105
4. Karzon DT (1976) Infectious mononucleosis. *Adv Pediatr* 22:231–265
5. Grose C, Henle W, Henle G et al (1975) Primary Epstein–Barr virus infections in acute neurologic diseases. *N Engl J Med* 292:392–395
6. Wood TA, Frenkel EP (1967) The atypical lymphocyte. *Am J Med* 42:923–936
7. Weisberger J, Cornfield D, Gorczyca W, Liu Z (2003) Down-regulation of pan-T-cell antigens, particularly CD7, in acute infectious mononucleosis. *Am J Clin Pathol* 120:49–55
8. Gorczyca W, Weisberger J, Liu Z, Tsang P, Hossein M, Wu CD et al (2002) An approach to diagnosis of T-cell lymphoproliferative disorders by flow cytometry. *Cytometry* 50:177–190
9. Henter J-I, Horne AC, Arico M et al (2007) HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 48:124–131
10. Bakhshi S, Pautu JL (2005) EBV associated hemophagocytic lymphohistiocytosis with spontaneous regression. *Indian Pediatr* 42(12):1253–1255