

# Association of Langerhans Cell Histiocytosis with Chronic Active Epstein-Barr Virus Infection: Case Report and Review of the Literature

YH FANG, JG LOU, H ZHAO, J CHEN

## Abstract

Langerhans cell histiocytosis is a rare disease involving multiple systems in children. We report a case of Langerhans cell histiocytosis in a paediatric patient presenting with prolonged fever, enlargement of the cervical and abdominal lymph nodes, hepatosplenomegaly and anaemia. He was confirmed to have chronic active Epstein-Barr virus infection and Langerhans cell histiocytosis by abdominal lymph node biopsy, according to the diagnostic criteria for active Epstein-Barr virus infection and the histopathological criterion for Langerhans cell histiocytosis. The infiltration of Epstein-Barr virus in the Langerhans cell histiocytosis lesion was also detected. The diagnosis of Langerhans cell histiocytosis accompanied by chronic active Epstein-Barr virus infection is rare. The aetiology of Langerhans cell histiocytosis is obscure. However, the role of Epstein-Barr virus infection in the pathogenesis of several diseases has been postulated because higher frequencies of Epstein-Barr virus have been detected in blood or tissue samples from patients with these diseases compared with those from the unaffected individual. However, the relationship between Epstein-Barr virus infection and Langerhans cell histiocytosis remains unclear. Reports of the presence of Epstein-Barr virus in Langerhans cell histiocytosis tissues are controversial. In our case, Epstein-Barr virus infection might have participated in the development of Langerhans cell histiocytosis, according to the patient's clinical history and the infiltration of Epstein-Barr virus in the Langerhans cell histiocytosis lesion.

## Key words

Aetiology; Fever; Lymph nodes

## Introduction

Langerhans cell histiocytosis (LCH) is a rare disease occurring in children that involves the bones, skin, soft tissue, and other organs. It has highly variable clinical manifestations, ranging from solitary lytic bone lesions to diffuse organ involvement. The aetiology of LCH remains

obscure. Here, we report an LCH patient with an Epstein-Barr virus (EBV) infection diagnosed with chronic active EBV infection (CAEBV).

## Case Report

A one-year-old boy was admitted to our ward with a complaint of a recurrent fever lasting for 23 days. He was diagnosed with pneumonia and EBV infection at a local hospital. A complete blood count revealed five per cent abnormal lymphocytes and an elevated IgM antibody titre against EBV. He recovered after treatment with intravenous antibiotics. However, he developed another fever 15 days later. He was admitted to our ward for prolonged fever after being administered intravenous antibiotics and ganciclovir for four days at a local hospital and two days at our outpatient clinic.

Department of Gastroenterology, Children's Hospital, Zhejiang University School of Medicine, 3333 Bin Sheng Road, Hangzhou 310051, China

YH FANG (方優紅) MD

JG LOU (樓金珩) MD

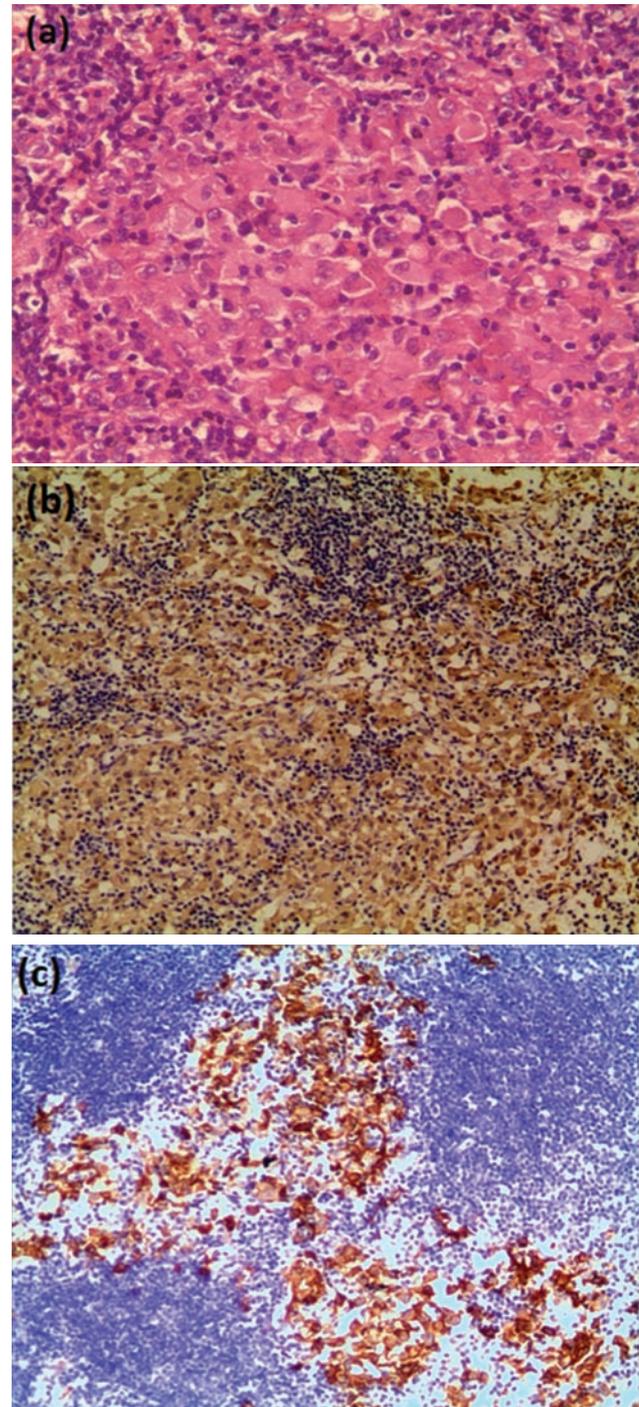
H ZHAO (趙泓) MD

J CHEN (陳潔) MD

Correspondence to: Dr YH FANG

Received November 16, 2014

The vital signs of the patient were normal, and the cervical lymph nodes were enlarged; the largest size observed on physical examination was 1 cm x 0.5 cm. His spleen was enlarged (3 cm below the ribs). The other physical examination results were normal. His complete blood count showed the following: a white blood cell count of  $7.02 \times 10^9/L$  (40.4% neutrophils), a haemoglobin level of 79 g/L, a platelet count of  $236 \times 10^9/L$ , a C-reactive protein (CRP) level of 52 mg/L, and an erythrocyte sedimentation rate of 27 mm/h. The cytokine IL-6 level was elevated, and the IL-10 and INF- $\gamma$  levels were normal. The albumin level was 26.6 g/L, and the triglyceride and alanine aminotransferase levels were normal. The IgG antibody titre against EB viral capsid antigen (VCA)-IgG was positive, the VCA-IgM titre was negative, and the early antigen (EA)-IgG and EA-IgM titres were also negative. EBV-DNA was not detected in the peripheral blood. Chest CT suggested pneumonia, and abdominal CT showed splenomegaly. The patient was diagnosed with EBV infection and pneumonia at admission. He received intravenous cefuroxime for six days, and we added intravenous ganciclovir on the fifth day after admission. However, he continued to have a fever, and an elevated CRP level. We changed the antibiotic treatment from cefuroxime to piperacillin/tazobactam for seven days and then to azithromycin for five days. We also administered the patient intravenous immunoglobulin to treat the EBV infection. However, his condition did not improve. The anti-EBV antibody levels were rechecked at 12 days after admission. VCA-IgG was still positive, and EA-IgG became positive. Ultrasonic examination showed hepatosplenomegaly and enlargement of the portal lymph nodes on the fifteenth day after admission. We found some haemorrhagic rashes on his trunk on the twentieth day, and a smear of the rashes tissue revealed the presence of histiocytes. The patient underwent abdominal lymph node biopsy via laparoscopy after 19 days of admission. The biopsy results showed the presence of  $2.6 \times 10^5/L$  and  $1.2 \times 10^4/L$  EBV-DNA copies in the lymph nodes and ascites, respectively. Histopathological examination demonstrated an infiltration of langerhans cells (LC) that stained positive for S100 and CD1a (Figure 1). The patient was diagnosed with CAEBV and LCH, and therapy was abandoned. We checked on the patient's condition by telephone after he went home ten months later and found that he continued to have fever with progressive hepatosplenomegaly and cervical lymph nodes and that he was not receiving any therapy.



**Figure 1** Haematoxylin and eosin staining of lymph node biopsy showing the presence of langerhans cells with typical dendritic projections (a) (400 of original magnification). Immunohistochemical staining showing expression of S-100 (b) and CD1a antigen (c) (100 of original magnification).

## Discussion

This patient mainly presented with prolonged fever, enlargement of the lymph nodes, hepatosplenomegaly and anaemia. He was finally confirmed to have CAEBV and LCH by abdominal lymph node biopsy. We report this patient because of the rarity of the diagnosis of LCH accompanied by CAEBV; in addition, the detection of EBV in LCH lesions, as in our patient, seems to play a role in the development of LCH. CAEBV is characterised by chronic or recurrent symptoms of fever, hepatosplenomegaly, and liver dysfunction during the acute phase of infectious mononucleosis (IM). Unusually high titres of anti-EBV antibodies are detected in serum from CAEBV patients. The patient in this report had IM-like syndrome 23 days prior and presented with prolonged fever, hepatosplenomegaly, enlargement of the cervical and abdominal lymph nodes and anaemia. He tested positive for EA-IgG after 12 days. EBV-DNA copies were detected in the biopsy tissue and ascites. The patient was diagnosed with CAEBV according to the diagnostic criteria reported by Okano et al.<sup>1</sup>

LCH is a rare disease affecting children that involves the bone, skin, soft tissue, and other organs. It has highly variable clinical manifestations, ranging from solitary lytic bone lesions to diffuse organ involvement. Langerhans cells express CD1a and langerin (CD207), are positive for S-100 and contain Birbeck granules. The pathogenesis of LCH remains obscure, and it is unclear whether it is associated with infection. The patient in this report had multiple involved organs, including the liver, spleen, skin, and lymph nodes. Histopathological examination of the abdominal lymph node biopsy demonstrated an infiltration of large cells with pale cytoplasm and reniform nuclei that stained positive for S100 and CD1a. The diagnosis of LCH was established according to the histopathological criterion of the Histiocyte Society (2009).

Over 90% of the world's population have been infected with EBV. Primary EBV infection is usually asymptomatic, except for IM, which mainly occurs in children and young adults. B cells are the cellular targets of EBV in primary EBV infection. EBV-associated haemophagocytic histiocytosis (EBV-HLH) and chronic active EBV infection are rare. EBV typically infects T lymphocytes and natural killer (NK) cells and plays significant roles in the pathogenesis of these diseases.

In fact, the roles of EBV infection in the pathogenesis of several diseases have been postulated. EBV is more easily detected in blood or tissue from patients with these diseases

than in those from the unaffected individuals. EBV is associated with haematological diseases, such as systematic EBV-associated T/NK cell lymphoproliferative diseases, malignant lymphoma, and leukaemia, in addition to malignancies of epithelial cell origin. It typically infects CD4+T cells or NK cells in CAEBV patients. The development of T cell-type non-Hodgkin lymphoma or NK/T cell midline lymphoma has been reported in several patients with CAEBV. However, the aetiology of LCH remains unclear. Is EBV infection associated with LCH? In our case, both EBV and LC were detected in the patient's lymph nodes. Was it a coincidence or did EBV infection participate in the development of LCH? McClain et al<sup>2</sup> failed to find evidence of the EBV genomic material in 56 patients with LCH. Schenka et al<sup>3</sup> reported 117 biopsy specimens diagnosed as LCH, while EBV was not detected in Langerhans cells in any of the 117 specimens. Recently, Jeziorski et al<sup>4</sup> have shown that the prevalence, serological titres, and viral loads for EBV and other human herpes viruses do not differ between LCH patients and controls. None of the abovementioned studies found evidence of a relationship between EBV and LCH. In contrast, Shimakage et al<sup>5</sup> showed positive hybridisation signals for EBER1 ribonucleic acid by in situ hybridisation in paraffin sections from 17 patients with LCH. This group also examined 26 North American paediatric LCH patients, who were found to be positive for EBER1.<sup>6</sup> Further, a patient has been reported in the literature who was diagnosed with EBV-related HLH and subsequently developed LCH within a short period of time.<sup>7</sup> In addition, a CAEBV patient has been reported who subsequently developed bilateral orbital masses and was diagnosed with LCH,<sup>8</sup> suggesting that the EBV infected B-cells detected in the tissues of these patients may trigger the formation of Langerhans-like lesional cells and eventually the development of LCH in some cases. The different outcomes among studies may have been due to the varying regions studied or to the differing sensitivities of the detection methods used. Previous studies have demonstrated the infiltration of EBV-infected B-cells into LCH tissues, suggesting that interactions between EBV-infected B-cells and lesional cells might contribute to the pathological development of LCH. Egeler et al have indicated that the expression of CD40 and CD40 ligand (CD40L) in LCH lesions, along with CD40-CD40L interactions, might play important roles in activating both lesional cells of LCH (CD40+) and T-cells (CD40L+). This activation results in increases in the expression of costimulatory and adhesion molecules, proliferation, and the production of proinflammatory cytokines and proteolytic

enzymes, which are all features of LCH.<sup>9</sup> Imadone et al have implied that the main source of CD40L in LCH patients may be EBV-infected B-cells that infiltrate into LCH tissues because EBV infection induces the expression of CD40L on these cells. In conclusion, the patient in this report was diagnosed with CAEBV and LCH, and EBV infiltration was detected in the LCH lesion.<sup>10</sup>

A review of the literature has suggested that EBV infection might participate in the development of LCH in some cases.

### Declaration of Interest

We declare that we have no conflict of interests.

### References

1. Okano M, Kawa K, Kimura H, et al. Proposed guidelines for diagnosing chronic active Epstein-Barr virus infection. *Am J Hematol* 2005;80:64-9.
2. McClain K, Jin H, Gresik V, Favara B. Langerhans cell histiocytosis: lack of a viral etiology. *Am J Hematol* 1994;47:16-20.
3. Schenka AA, De Angelo Andrade LA, et al. Langerhans cell histiocytosis and its relationship with Epstein-Barr virus. *Hum Pathol* 2006;37:1508-9; author reply 1509-11.
4. Jeziorski E, Senechal B, Molina TJ, et al. Herpes-virus infection in patients with Langerhans cell histiocytosis: a case-controlled sero-epidemiological study, and in situ analysis. *PLoS One* 2008; 3:e3262.
5. Shimakage M, Sasagawa T, Kimura M, et al. Expression of Epstein-Barr virus in Langerhans' cell histiocytosis. *Hum Pathol* 2004;35:862-8.
6. Shimakage M. Langerhans cell histiocytosis and its relationship with Epstein-Barr virus-reply. *Hum Pathol* 2006;37:1509-11.
7. Lai CC, Huang WC, Cheng SN. Successful treatment of refractory Langerhans cell histiocytosis by allogeneic peripheral blood stem cell transplantation. *Pediatr Transplant* 2008;12:99-104.
8. Sakata N, Toguchi N, Kimura M, Nakayama M, Kawa K, Takemura T. Development of Langerhans cell histiocytosis associated with chronic active Epstein-Barr virus infection. *Pediatr Blood Cancer* 2008;50:924-7.
9. Egeler RM, Favara BE, Laman JD, Claassen E. Abundant expression of CD40 and CD40-ligand (CD154) in paediatric Langerhans cell histiocytosis lesions. *Eur J Cancer* 2000;36(16): 2105-10.
10. Imadome K, Shirakata M, Shimizu N, Nonoyama S, Yamanashi Y. CD40 ligand is a critical effector of Epstein-Barr virus in host cell survival and transformation. *Proc Natl Acad Sci U S A* 2003; 100:7836-40.