Atypical Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis simulating lymphadenitis on $^{18}$F-FDG PET/CT and its differential diagnosis

Abstract
Diagnosis of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) is challenging as its clinical presentation is atypical. Here we present a case of atypical EBV-HLH simulating lymphadenitis on fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT), with a view to consider this kind of EBV-HLH as a possible differential diagnosis in lymphadenitis. A 68 years old male who had episodic fever accompanied by weight loss and weakness for two weeks was studied. Finally, biopsies in bone marrow and spleen revealed hemophagocytic cells. He was diagnosed with EBV-HLH and treated with etoposide and prednisone. His condition started improving soon, and his abnormal laboratory findings were normalized at day 15. He remained in good clinical condition at 3 months follow-up after hospital discharge.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and potential life-threatening clinical syndrome that rapidly deteriorates and leads to multiple organ failure and death, due to uncontrolled proliferation of activated lymphocytes and the secretion of large amounts of inflammatory cytokines by histiocytes [1]. Hemophagocytic lymphohistiocytosis is broadly divided into two categories according to the cause of disease: primary and secondary or acquired. Primary HLH is due to genetic defects in cellular cytotoxicity, such as perforin defects, whereas secondary HLH is often associated with viral infections including Epstein-Barr virus (EBV), malignant tumors, and autoimmune diseases. Epstein-Barr virus is the most common infectious agent in patients with the viral-associated HLH [2].

The clinical features of EBV-HLH were high fever, cytopenia, liver dysfunction, hepatosplenomegaly, hypofibrinogenemia, and elevated serum triglycerides, similar to other types of HLH as defined by Henter et al. (1997) and Imashuku et al. (2002) [3, 4]. The diagnosis of EBV-HLH is based on a combination of clinical and laboratory criteria, including high EBV load [4]. Phagocytosis of bone marrow cells in otherwise normal bone marrow environment is a diagnostic cytoclogic finding [3]. A $^{18}$F-FDG PET/CT imaging may sometimes be performed before a bone marrow puncture-biopsy is completed since it is helpful for identifying the possible trigger (infection or malignant disease) and extent of secondary HLH [5]. A few cases of HLH with atypical clinical presentation have been reported in the literature [6, 7]. The diagnosis of atypical EBV-HLH is generally difficult because it shows basically similar symptoms to Hodgkin’s lymphoma (HL), non-Hodgkin’s lymphomas (NHL), infectious mononucleosis, etc [8]. We present a case of atypical EBV-HLH simulating lymphadenitis on $^{18}$F-FDG PET-CT, with the view to consider its different diagnosis.

Case Description

A 68 years old male who had episodic fever, which persisted despite antibiotic therapy accompanied by weight loss and weakness for two weeks was admitted to our hospital. He had unremarkable medical history, as for trauma, cancer, tuberculosis, and surgery.
At the time of admission, on physical examination, he had only an enlarged palpable spleen at 3.0cm below the costal margin and superficial lymph nodes in both axillae of 2.0cm in diameter. Ultrasound showed multiple enlarged lymph nodes, moderate splenomegaly and mild hepatomegaly without focal lesions. The patient had anemia, hyperferritinemia and normal kidney and liver function tests. C-reactive protein (CRP) was 10.0mg/L (normal range: 0-5.0) and D-dimer 2.38mg/L (normal range: 0-0.55) were slightly to moderately elevated. Furthermore, the real-time PCR detected a high copy number of EBV DNA (8.25×10^4 copies/μg DNA) in the peripheral blood mononuclear cells (PBMC). Immunofluorescence assays revealed a high titer of EBV-VCA-IgG (301.4 RU/mL, normal range: 0-16RU/mL), positive for EBV-VCA-IgA and EBV-ED/D-IgA, whereas negative for EBV-VCA-IgM. Additionally, viral work-up was negative for human immunodeficiency virus, hepatitis B virus and hepatitis C. Blood and urine cultures showed no growth. Tests for antinuclear antibody, double-stranded DNA antibody, anticyclic peptide containing citrulline, immunoglobulin A (IgA), IgG, IgM, and serum complement C3, C4 also were negative. No abnormalities were found in the chest X-rays, the echocardiogram and brain MRI. Fluorine-18-FDG PET/CT (Siemens Biograph mCT) was then performed after the IloVo injection of 212 MBq 18F-FDG and revealed mild 18F-FDG uptake in multiple enlarged lymph nodes and the enlarged spleen on the image of maximum intensity projection (MIP) (Figure 1E).

**Figure 1.** 18F-FDG PET/CT imaging of Atypical EBV-HLH of the lymph nodes and spleen. (A) Right supraclavicular regional lymph node; (B) Axillary lymph nodes; (C) Mediastinal lymph nodes; (D) Portacaval space lymph node and spleen; (E) MIP image.

In selected transaxial PET-CT slices, increased 18F-FDG accumulation lesions were found to be present in multiple lymphadenic sites, including the right supraclavicular region (Figure 1A) with a maximum standardized uptake value (SUVmax) of 2.76, bilateral axilla with SUVmax of 4.51 (Figure 1B), mediastinum (2R/L) with SUVmax of 2.76 (Figure 1B, 1C), and portacaval space with SUVmax of 3.44 (Figure 1D), and splenomegaly (10.4×6.1×11.9cm) with SUVmax of 4.11 (Figure 1D). Almost all of lymph nodes showed heterogeneous mild 18F-FDG accumulation, most of them were mild enlarged (from 1.1×0.9cm to 2.0×1.2cm in size). These PET/CT findings suggested possible lymphadenitis. The patient only reported a 2 weeks history of moderate grade fever (38.5-39°C). Moreover, no signs of calcification or necrosis were found in the hypermetabolic lymph nodes and no obvious pulmonary abnormalities were observed on CT scans. A fine needle aspiration cytology of a lymph node in the right axilla showed a polymorphous cell population comprising of plasma cells, eosinophils, and histiocytes (Figure 2A). Based on the medical history, these findings of cytology and 18F-FDG PET/CT imaging, generalized lymphadenitis was first considered. To confirm the diagnosis, biopsies in bone marrow and spleen, and bone marrow aspiration smear were examined and these pathological findings revealed hemophagocytic cells (Figure 2B, and Figure 3). According to the HLH-2004 study group [9], the standard definition of HLH requires that at least five of the following clinical criteria are met as in our patient: fever, anemia, splenomegaly, hyperferritinemia and histological evidence of hemophagocytosis in bone marrow and spleen. Our patient also had copy number of EBV DNA in the PBMC. Thus, he was diagnosed with EBV-HLH [9]. The patient was treated with etoposide (150mg/m^2) twice a week (on day 4 and day 7) and prednisone (0.8mg/kg/day, orally) for two weeks, followed by only prednisone (0.8mg/kg/day, orally) from the third to the fourth week of hospitalization. After one week, the patient’s condition started improving progressively and her fever subsided. His abnormal laboratory findings, including EBV DNA copies number, at the time of admission decreased near to or within normal ranges. The patient was discharged after 4 weeks on further steroid course for 2 weeks. He remained in good clinical condition during 3 months follow-up after his discharge from the hospital. The patient provided a written informed consent for the case report. The consent procedure was approved by the Ethics Committee of Zhongshan Hospital Xiamen University.

**Discussion**

EBV-HLH is the most frequent subtypes of secondary HLH that more commonly observed in adults [1, 2]. EBV-HLH more commonly occurs in adult patients living in Asian counties, and accounts for approximately 40% of patients with HLH in Japan and Korea, 75% in China [10]. Zhizhuo H et al. (2012) [11] reported that a fraction of Chinese children with EBV-HLH have genetic defects in PRF1, UNC13D, and XIAP. Although our patient did not perform any gene tests, he was diagnosed a secondary HLH since he was an adult without familial HLH.

Early diagnosis and prompt treatment is essential in order to avoid a rapid and fatal outcome. Updated clinicopathologic criteria for the diagnosis of HLH described in HLH-2004 by the Histiocyte Society, have been widely accepted [9]. However, recent studies showed that HLH-2004 diagnostic criteria do not apply easily to many cases of secondary HLH, especially in atypical HLH, as it derived from the experience on paediatric patients with congenital HLH [1, 6]. Cattaneo C et al. (2016) [1] reported that in 35 patients with acquired HLH, hyperferritinemia, fever and splenomegaly were present in...
more than 90%, whereas other criteria were in only found in less than 70% of these cases (bone marrow hemophagocytosis in 51% of the cases). In other cases NK cell activity or soluble CD25 were difficult to be obtained timely and NK cells activity was reduced in five of seven patients. Importantly, HLH with atypical clinical presentation has attracted much attention in recent years [6, 7, 12, 13]. A few individuals with biallelic PRF1 mutations give rise to a variable spectrum of clinical presentations, without fulfilling the above diagnostic criteria for HLH, some of them are early-onset or later-onset HLH disease, and some are asymptomatic or atypical HLH cases, furthermore, some develop hematological malignancies [7, 12, 13]. Our patient presented atypical clinical presentation with a history of spiking fever for two weeks and did not have thrombocytopenia, hypertriglyceridemia, and hypofibrinogenemia, consistent with the previous studies [7, 13].

Some studies demonstrated that therapeutic regimens containing etoposide provided survival benefit in adults with EBV-HLH [16, 17]. The survival of the early etoposide treatment in young adults with EBV-HLH is significantly better than that of the no/late etoposide treatment, suggesting that etoposide might act by partly blocking EBV [16]. Phenotypically, EBV-HLH is a heterogeneous disorder with various symptoms, ranging from mild to severe. Furthermore, the clinical course of EBV-HLH is diverse and can range from self-limiting in some patients to severe/aggressive and fatal in others [18]. Therefore, prompt and appropriate therapeutic strategy should be established based on the laboratory findings at the time of diagnosis as in our patient.

In conclusion, EBV-HLH is a rare and potential life-threatening clinical syndrome, however, its incidence has recently been increasing. This case suggests that EBV-HLH should be considered as a possible differential diagnosis in patients who may not initially fulfill diagnostic criteria for HLH, or have multiple increased $^{18}$F-FDG lymphadenic uptake. Early histological examination after bone marrow biopsy should be emphasized in the diagnosis of this disease.

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**Bibliography**


Pierre Auguste Renoir. Girl with a fan. 1880.