Am J Nucl Med Mol Imaging 2022;12(4):129-137
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0145903

Case Report

A rare B-cell type chronic active Epstein-Barr virus infection patient mimicking lymphoma on ^{18}F-FDG PET/CT and literature review

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Received August 13, 2022; Accepted August 15, 2022; Epub August 20, 2022; Published August 30, 2022

Abstract: A 13-year-old girl suffered from worsen snoring and persistent bilateral nasal congestion for one year. Paranasal sinus computed tomography (CT) and magnetic resonance imaging (MRI) found nasopharyngeal passages and sinus were occupied with soft tissues and bilateral neck enlarged lymph nodes 6 months ago. Tumor markers were normal. The titers of anti-Epstein-Barr virus (EBV) IgM, anti-EBV IgG, early antigen (EA) IgG, and Epstein-Barr nuclear antigen (EBNA) IgG increased. 2-Deoxy-2-[fluorine-18]-fluoro-D-glucose (^{18}F-FDG) positron emission tomography combined with CT (PET/CT) revealed thickened soft tissues in nasopharynx and oropharynx, enlarged multiple lymph nodes in the neck, bilateral armpits, abdominal cavity and retroperitoneum, and pelvic cavity, diffuse thickening of the gastric wall of the antrum with hypermetabolism. According to the age, situation, regions, and abnormal FDG uptake, an initial diagnosis of EBV-related lymphoma was made. However, the pathological results of the nasopharyngeal mass and the abdominal lymph node confirmed the final diagnosis of a B-cell type chronic active Epstein-Barr virus disease (CAEBV), a rare type of EBV associated lymphoproliferative disorder (LPD). After receiving adoptive immune cells therapy, the EBV load decreased. At present, the patient is being followed up.

Keywords: Epstein-Barr virus (EBV) associated lymphoproliferative disorders, chronic active EBV disease, ^{18}F FDG, PET/CT, B cell

Introduction

Epstein-Barr virus (EBV) infection affects more than 90% of the population in the world and results in various lymphoproliferative disorders (LPDs) [1]. Chronic active EBV disease (CAEBV) is a rare subtype of LPDs presenting with persistent or recurring infectious mononucleosis-like symptoms including fever, lymphadenopathy, hepatosplenomegaly, and liver dysfunction, with high EBV-DNA in the peripheral blood or infected tissues [2]. The incidence rate of CAEBV has increased in these years with reports of 23.8 cases per year in Japan and the prognosis is unsatisfactory due to the systemic involvement and lack of effective treatment regimen [3]. So far, 2-Deoxy-2-[fluorine-18]-fluoro-D-glucose (^{18}F-FDG) positron emission tomography combined with CT (PET/CT) has played a more and more important role in the early diagnosis, localization of lesions, staging, and monitoring diseases, especially in cancers and hematological diseases. Here, we presented a CAEBV case mimicking lymphoma in ^{18}F-FDG PET/CT that provide accurate guidance information for biopsy.

Case presentation

A 13-year-old girl presented with worsen snoring and persistent bilateral nasal congestion for one year. She had hematuria 4 months ago and the routine urine test found abnormal red blood cell (RBC) (+++) and protein (PRO) (+++). Her immunological profile was positive for anti-Sjogren's syndrome A (SSA)/Ro60 and anti-SSA/Ro52 antibodies, as well as antinuclear antibodies (ANA) at a titer of 1/320. Three months ago, a swollen mass in the right neck was accidentally found. After hospitalization, laboratory tests showed the increased titers of anti-EBV IgM (43.90 U/mL), anti-EBV IgG (> 750.00 U/

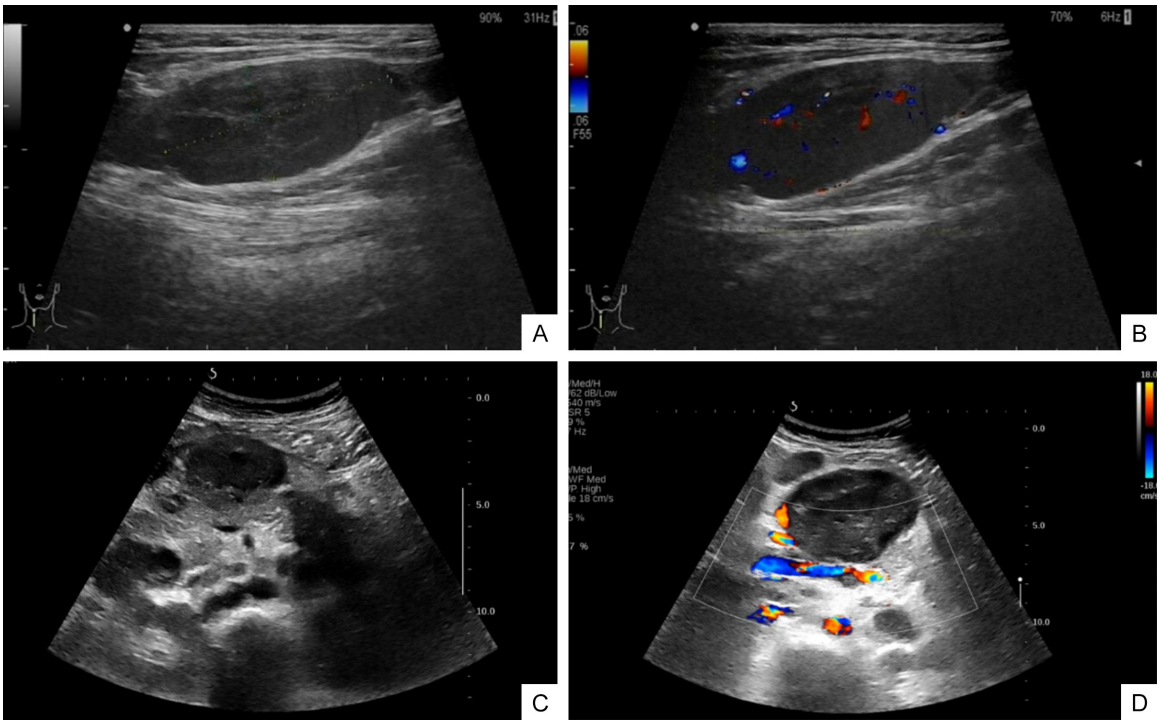

Figure 1. Ultrasound images. A, B. Multiple enlarged lymph nodes with heterogeneous hypoechoic manifestations were discovered in bilateral neck and the lymph node in the right neck was larger, about 2.9 × 1.4 cm in size. The right armpit lymph node was enlarged, about 1.4 × 1.0 cm in size. C, D. Multiple hypoechoic nodules and masses were discovered in the abdominal cavity and retroperitoneum, of which the largest is 7.3 cm × 5.4 cm, found with clear borders.

mL), anti-early antigen (EA) IgG (> 150 U/mL) and EBNA IgG (276.00 U/mL), indicating previous EBV infection and active proliferation of EBV. The number and percentage of neutrophils decreased, but the number and percentage of lymphocytes and monocytes increased. The routine urine test showed RBC (+++) and PRO (+). Her immunological profile was positive for anti-SSA antibodies and ANA at a titer of 1/1000, and was negative for anti-double-stranded DNA (anti-dsDNA) antibodies, indicating lupus erythematosus and lupus nephritis.

Paranasal sinus computed tomography (CT) showed soft tissue shadows filling bilateral nasal passages, nasopharynx, and paranasal sinuses with distinct incrassation of nasopharynx soft tissues and involvement of bilateral pharyngeal recesses, the pharyngeal opening of auditory tubes and tubal torus. Magnetic resonance imaging (MRI) displayed nasopharynx space occupying lesions, at the size of 6.78 × 6.24 × 2.45 cm, with multiple bilateral neck and submandibular enlarged lymph nodes, the largest of about 3.47 × 2.04 cm. Multiple enlarged lymph nodes were discovered in the neck, right armpit, and abdomen by ultrasonography (**Figure 1**). To further evaluate the whole-body situation, ^{18}F-FDG PET/CT was performed. Both nasopharynx and oropharynx cavities were filled with soft tissues with high FDG uptake at a maximum standardized uptake value (SUVmax) of 7.7, while the bilateral maxillary sinus showed no FDG-avid. Besides, the thickened gastric wall of the antrum with high FDG uptake was also revealed with SUVmax of 4.9. Multiple enlarged lymph nodes in the neck, bilateral axilla, abdominal cavity, retroperitoneum, and pelvic cavity with high FDG uptake were observed with the highest value of SUVmax of 7.1. A low-density area in the lymph nodes indicated necrosis inside (**Figure 2**).

Based on the findings of PET/CT, biopsies of the nasopharyngeal mass and enlarged abdominal lymph nodes were performed, respectively. A biopsy of the nasopharyngeal mass revealed Epstein-Barr virus-encoded small RNA (EBER) in situ hybridization (ISH) was positive in partial cells and immune histochemical (IHC) results

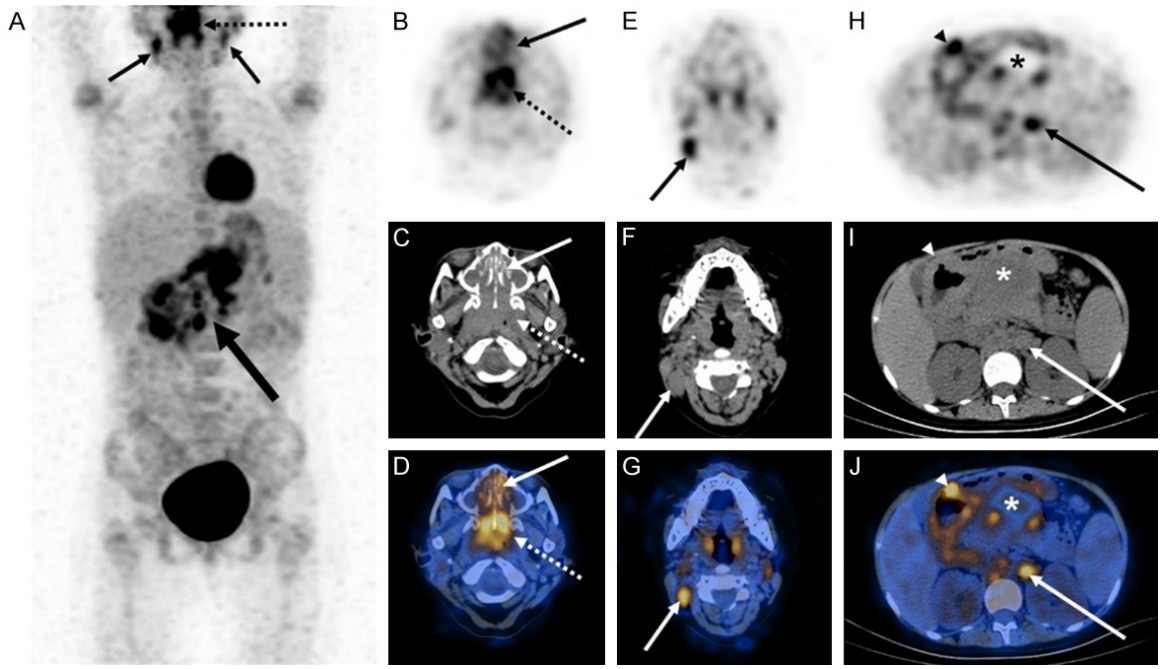

Figure 2. ^{18}F-FDG PET/CT images. A. The whole-body maximum intensity projection displayed FDG-avid lesions in the regions of maxillofacial (dashed arrow), bilateral neck (short arrows), and abdomen (long arrow). B–D. Both nasopharynx (solid arrow) and oropharynx (dashed arrow) cavities were filled with soft tissues with increased FDG uptake in these lesions while the bilateral maxillary sinus showed no FDG-avid. E–G. Enlarged lymph nodes (arrows) in the bilateral neck with increased FDG uptake. H–J. Enlarged lymph nodes (long arrows) in the abdominal cavity and retroperitoneum and the thicken gastric wall of the antrum (short arrows) with high FDG uptake. A Low-density area (asterisk) in the lymph nodes indicated necrosis.

demonstrated cluster of differentiation 3 (CD3) (+++), CD20 (partial +), CD15 (-), CD30 (a few +), CD38 (partial +), CD68 (partial +), CD34 (-), Ki67 (about 60% +). The pathological results of enlarged abdominal lymph nodes showed that the lymph nodes infiltrated with small to medium-large heterotypic lymphocytes, with irregular nuclei, granular karyoplasm, and plasmacytoid differentiation with massive coagulative necrosis. IHC staining results demonstrated CD20 (+), CD3 (+), KP1 (+), CD138 (++), CD79a (+++), BCL2 (+), multiple myeloma oncogene 1 (MUM1) (+++), and Ki-67 40% (**Figure 3**). Both antigen receptor gene rearrangement of immunoglobulin heavy chain and T-cell receptor showed germline configuration by a polymerase chain reaction, which excluded clonal expansion of B cells or T cells. According to the clinical and pathological manifestations, the final diagnosis of B-cell chronic active EBV disease (CAEBV) was considered. After the diagnosis, the patient received donor lymphocyte infusion, an adoptive immune cell therapy. 109 mL and 101 mL of her mother's irradiated peripheral blood were infused respectively in which lymphocytes accounted for 66.8% at concentrations from 5.8 × 10^9/L to 7.6 × 10^9/L. After these treatments, her EBV load decreased (**Table 1**). At present, the patient is being followed up.

Discussion

EBV-associated LPDs are highly heterogeneous disease, classified into B-cell LPDs, T/NK-cell LPDs and immunodeficiency-related LPDs, ranging from reactive lymphoproliferative lymphadenitis to lymphomas [1]. CAEBV consists of B-cell types and T/NK cell types and is a rare life-threatening condition related to acute EBV infection and persistent EBV infection (more than 3 months) in patients with unknown immunodeficiency [4]. The vulnerable groups of CAEBV are children and young adults with a mean age of onset of 11.3 years in Asia and 19 years in the United States [5]. CAEBV shows a significant geographic preference for East Asia and usually involves T or NK cells in Asian patients while EBV has always been detected in B cells in United States patients with CAEBV [6-8]. Patients usually show remarkably increased EBV DNA, antibodies to EBV, EBV-positive tissues, and clinically present with fever, liver

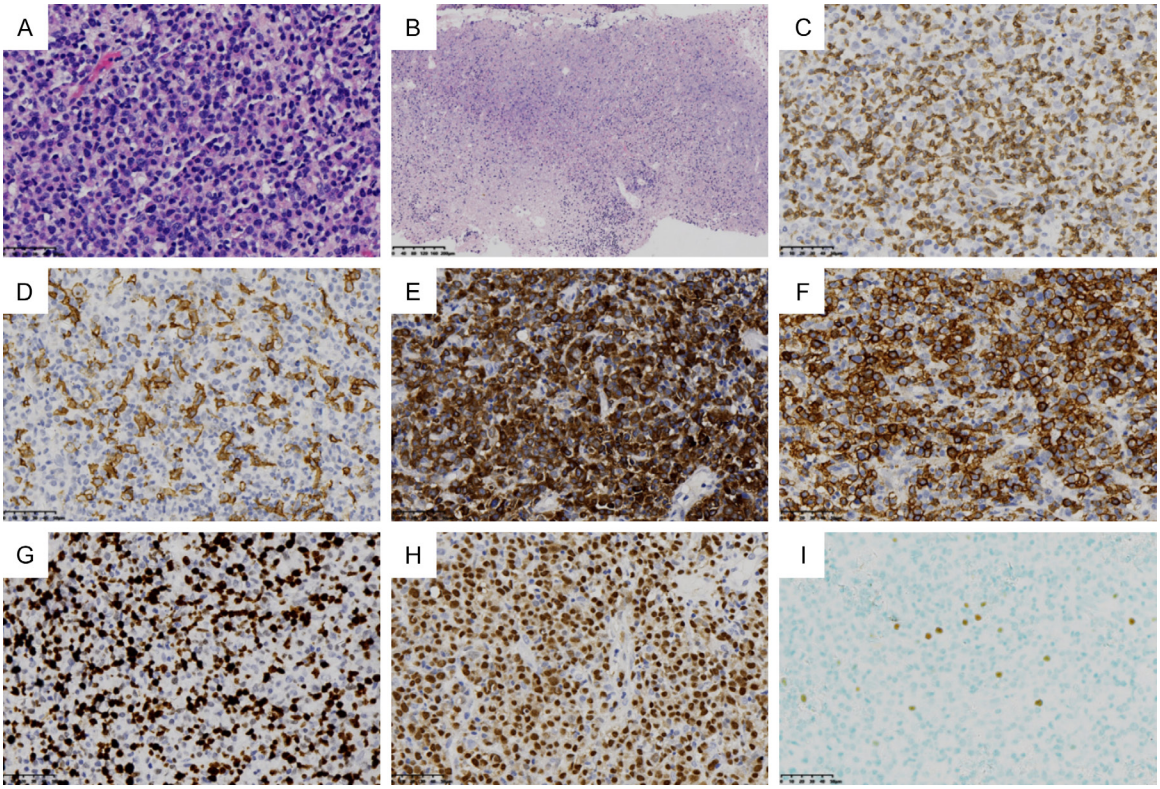

Figure 3. Histologic, immunohistochemical, and in situ hybridization (ISH) features of core needle biopsy of abdominal lymph nodes. (A) Hematoxylin-eosin (HE) staining showed that the lymph nodes were infiltrated with small to medium-large heterotypic lymphocytes, with irregular nuclei, granular karyoplasm, and remarkable plasmacytoid differentiation (magnification, × 400). (B) Coagulative necrosis could be seen (HE staining; magnification, × 200). In immunohistochemical staining, the cells were consisting of mixed small T lymphocytes, B lymphocytes and plasmacytoid cells with moderate proliferation activity, which were variably positive for CD3 (C), CD20 (D), CD79a (E), CD138 (F), Ki67 (G) and MUM1 (H) [magnification (C-H) × 400]. (I) EBER ISH showed partial positive cells (magnification, × 400).

dysfunction, lymphadenopathy, hepatosplenomegaly, and pancytopenia [6, 9]. Here, we reported a 13-year-old girl with worsen snoring and persistent bilateral nasal congestion and diagnosed with a B-cell type CAEBV.

A literature search was performed on the PubMed database from 2008 to 2022, using the keyword "chronic active Epstein-Barr virus infection (CAEBV) and PET/CT". There were eight cases of CAEBV with PET/CT findings. The basic information and PET/CT manifestations of CAEBV are summarized in **Table 2** [10-17]. Some studies have found that CAEBV infection occurs mostly in men [5, 18]. However, of the eight case reports mentioned in our case literature, the gender showed no difference (4 male vs 4 female). CAEBV is a disease that is more common in children and adolescents, while reports of adult-onset are increasing [19]. Of the above eight patients, children and adolescents constitute the majority, and the age of onset is 2-45. Patients with CAEBV usually show persistent inflammatory clinical manifestations, including fever, general malaise, progressive skin lesions, etc. As EBV can infect and proliferate various types of lymphocytes in different parts, the lesions can occur in almost every organ, such as the spleen, liver, bones, or muscle. In our case, the lesions located in the nasopharyngeal cavity, lymph nodes, and gastric wall that are different from other cases. The role of ^{18}F-FDG PET/CT for CAEBV cases was the whole-body evaluation of abnormality of FDG-avid lesions, as well as the guidance for the biopsy for further histological examination. In this case, the puncture biopsy was guided through the high FDG-avid lesions on PET/CT. And the results both suggested CAEBV, making the diagnosis more accurate. EBV-related intestinal lesions could also be better detected by

Table 1. Changes in EBV-DNA levels before and after the treatment in this case

		Before the treatment	One week after the first treatment	One week after the second treatment
EBV-DNA load (Copies/mL)	In plasma	1.50×10^3	9.47×10^2	3.07×10^3
	In peripheral blood lymphocytes	1.62×10^4	7.77×10^3	9.86×10^3

Table 2. Literature review of CAEBV cases with basic information and PET/CT manifestations

No.	References	Age (years)	Sex	Clinical symptom	Location	Imaging method	PET/CT manifestations
1	Akazawa et al. [9]	2	Male	Persistent fever	Right side of his neck; liver; spleen; bones	^{18}F-FDG PET/CT	Increased ^{18}F-FDG uptake
2	Hao et al. [10]	20	Female	Intermittent fever	Spleen; lymph nodes in the porta hepatis, splenic hilum, subcarinal and left inguinal region	^{18}F-FDG PET/CT	Increased ^{18}F-FDG uptake
3	Jin et al. [11]	9	Male	Intermittent fever	Cervical lymphadenopathy; liver; spleen	^{18}F-FDG PET/CT	Symmetric enlargement of the cervical lymphadenopathy and hepatosplenomegaly
4	Kong et al. [12]	9	Female	Facial rash, angio-edema, fevers, and night sweats	Subcutaneous soft tissues throughout the entire body, likely localized to white subcutaneous fat	^{18}F-FDG PET/CT	Diffuse increased ^{18}F-FDG uptake
5	Takano et al. [13]	45	Male	Fever and general malaise for 5 years	Whole left ventricular wall	^{18}F-FDG PET/CT	Increased ^{18}F-FDG uptake with mild heterogeneity (maximum at the lateral wall)
6	Wass et al. [14]	42	Male	Fever and a suspected epileptic seizure	Multiple bone marrow sites; thyroid; adrenal glands	^{18}F-FDG PET/CT	Increased ^{18}F-FDG uptake
7	Yang et al. [15]	7	Female	Fever	Multiple muscle groups, especially in the right upper arm, right thigh, left thigh, and right foot	^{18}F-FDG PET/CT	Heterogeneously ^{18}F-FDG uptake
8	Wang et al. [16]	17	Female	Persistent fever and severe dyspnea	Back; lower extremities; mediastinal and bilateral subaxillary lymph nodes	^{18}F-FDG PET/CT	Increased ^{18}F-FDG uptake (maximum standardized uptake value 0.9–4.3)

PET/CT. Focal bowel wall thickening with a remarkably increased FDG uptake indicates the lesion, which is difficult to be distinguished from physiological changes only by CT. Toriihara et al. [20] found that most CAEBV patients showed splenomegaly or hepatomegaly and the SUVmean of the spleen and the liver was 1.75 ± 0.72 and 1.92 ± 0.53, respectively, which were considered as low as physiological uptake. Their assessment demonstrated that low FDG uptake can distinguish CAEBV from lymphoma which shows high FDG uptake. It should be noted that there were still some patients' spleens presented with hypermetabolic activity, such as in this case. Therefore, for the children, and young adults with FDG high uptake and remarkable increased EBV levels, CAEBV should be considered and further differentiation should be made from lymphoma. In these situations, pathological examination helps to make the final diagnosis.

Patients with CAEBV can develop systemic organ disease and it calls for more necessity for a thorough investigation and accurate lesion localization. In addition to PET/CT, conventional imaging methods are also essential in this disease, containing ultrasound, CT, and MRI. Ultrasound could be used for a preliminary estimate of the condition of hepatosplenomegaly and lymphadenectasis and presence of an arterial aneurysm. CT is helpful for the detection of characteristic lesions such as lymphadenopathy and hepatosplenomegaly and systemic multi-organ involvement including pulmonary, intestine, heart, and vessels [21]. CT can demonstrate occupying lesions with low density, dilation of vessels, and in the condition of patients presenting with interstitial pneumonia, patchy opacities with consolidation, and pleural effusion. What's more, the utility of CT in differential diagnosis and surveillance of complications and therapy response should be noticed [22-24]. A study revealed CT has become a significant method for detecting intestinal lesions and distinguishing intestinal involvement of CAEBV from inflammatory bowel

disease. The characteristics of CAEBV patients with intestinal involvement in CT enterography include colon involvement, segmental bowel wall thickening, asymmetric thickening, fat stranding, layered attenuation, and adenopathy [22]. MRI is most frequently employed for detecting brain lesions in CAEBV. Although central nervous system involvement only occurs in approximately 8.5% of all complications, it's fatal and progressive and predicts unfavorable outcome [7]. The features in head MRI include hyperintensity signal in the cortex and subcortical white matter on T2- and T1-weighted images, encephalanalosis, aneurysmal dilatation of arteries, with hemorrhage, ischemia and calcification in the basal ganglia [25, 26]. In addition, a case reported that cardiovascular MRI could effectively reveal early lesions and dynamic changes such as aneurysm and pericardial effusion and act as an outstanding method in the detection of cardiovascular diseases [27].

Pathological examination plays a vital role in the diagnosis of CAEBV since CAEBV infection is almost always accompanied by varying degrees of lymphoproliferation, closely relating to tissue damage [28]. Infiltration of lymphocytes in tissues is mainly distributed in the lymph node paracortical area, liver sinus, spleen red pulp area, and bone marrow cavity. Cells varied in size and atypia was not apparent [29]. EBER, a small noncoding RNA abundantly expressed in all cells transformed by EBV, has been used as a standard for the diagnosis of CAEBV. Patients with CAEBV are classified based on the type of EBV-infected cell into B cell, T cell, and NK cell types. In East Asia, T cell and NK cell types are common and most reported. When patients with T-cell type infection, CD3+ cells are the major group of cells. Patients are NK-cell-type infected when their CD56+ cells are the major group of cells infected with EBV. In cases of NK/T-cell type, both CD3+ cells and CD56+ cells are the major group of cells that harbored EBV. The difference in our case is that, as a rare B-cell type CAEBV, it mainly expresses B-cell-related immunohistochemical markers, containing CD20, CD79a, PAX5, etc. Clonality for CAEBV has been tested by PCR of the T cell receptor genes (for T cell CAEBV) or IgH genes (for EBV+ B cell disease) or on the terminal repeat structure of the EBV genome and most patients have clonal EBV [30, 31]. The clonality of EBV may be polyclonal, oligoclonal, or monoclonal, in which as the disease progresses from polyclonal lymphoid tissue proliferation to monoclonal illness, the degree of malignancy generally increases [32, 33].

As a rare disease type, clinical symptoms and laboratory examinations also provide useful information for diagnosis and differential diagnosis. According to criteria, CAEBV was diagnosed as follows: (1) Persistent or recurrent infectious mononucleosis-like illness or symptoms including fever, lymphadenopathy, pancytopenia, hepatosplenomegaly, persistent hepatitis, interstitial pneumonia for > 3 months; (2) Increased amounts of EBV detected by Southern blot hybridization, an unusual pattern of anti-EBV antibodies with increased anti-viral capsid antigen (VCA) and anti-early antigen (EA), EBER-positive cells in affected tissues or peripheral blood, or raised EBV-DNA ($\geq 10^{2.5}$ copies/mg) in peripheral blood; (3) Illness cannot be explained by known immunodeficiency, autoimmune disorders or malignancy [9, 34]. Anti-EBV titers to specific antigens are associated with different stages of infection. Persistently elevated diffuse EA IgG is associated with a chronic active infection, reinfection, or virus reactivation [35]. A finding of positive VCA-IgG and VCA-IgM is considered as evidence of an acute EBV infection. Negative VCA-IgM with positive VCA-IgG is usually considered a past infection. However, sometimes, positive VCA-IgM can be detected persistently for up to a year, thus, anti-EBNA is employed as a clear marker of late infection with its positivity considered a definite exclusion of acute EBV infection [36].

The differential diagnosis of CAEBV should be made from infection mononucleosis (IM) and lymphoma. IM is caused by primary infection of EBV and mainly presents with fever, angina, hepatosplenomegaly and lymph node enlargement, liver function impairment, and the severe ones may be complicated by hemophagocytic lymphohistiocytosis, EBV encephalitis, or aneurysm. The whole blood and plasma EBV-DNA increased transiently. The above manifestations are difficult to identify from CAEBV, however, the course of CAEBV is typically more than three months, and the antibodies of EBV also contribute to the differential diagnosis. IM is usually positive for EBV-VCA-IgM or low-affinity VCA-IgG, which indicates a recent infection,

whereas CAEBV is usually positive for EBNA IgG and high-affinity VCA-IgG, which indicates a previous infection. Lymphoma, especially EBV-associated lymphoma, can also present with fever, hepatosplenomegaly, or even be complicated by hemophagocytic lymphohistiocytosis. Because both infection and the malignant tumor may show hypermetabolism on ^{18}F-FDG PET/CT, resulting in false-positive findings, the differential diagnosis mainly depends on histopathological examination [37].

Generally, the prognosis of CAEBV is poor with 15-year-overall survival of 59.7% in patients aged under 8-year-old and 27% above 8 [34]. In addition, T-cell CAEBV has a poorer prognosis than NK-cell CAEBV and B-cell CAEBV [6]. Numerous methods have been tried for the treatment including antiviral therapy (e.g. ganciclovir, acyclovir), immunoglobulin therapy that can neutralize the cell-viruses, immunosuppressive agents (e.g. corticosteroids, cyclosporine), immunomodulatory therapy and cytotoxic chemotherapy [38]. Unfortunately, none of these agents can reach a complete cure and they only temporarily induce remissions or just reduce symptoms in the majority of patients [38]. Hematopoietic stem cell transplant (HSCT) is extensively accepted as the only treatment to cure CAEBV [39]. Reports demonstrated that reduced-intensity conditioning allogeneic HSCT could achieve the eradication of EBV-infected neoplastic cells [40]. Adoptive immune cell therapies, for example, adoptive infusion of autologous lymphokine-activated killer cells, autologous EBV-specific cytotoxic T lymphocytes (CTLs), or donor human leukocyte antigen (HLA)-haploidentical lymphocytes infusion perform successfully in the treatment of posttransplant lymphoproliferative disease [38]. The utility of adoptive immunotherapy for CAEBV has been reported in several studies. In a study in the USA, most of the patients with mild/moderate CAEBV presented with symptom improvement and disease stabilization for 3 years after infusion of virus-specific CTLs while patients with severe CAEBV only experienced transient viral and immunological responses [41]. And a study showed high doses of mother's lymphocyte infusion could attain complete remission for 6–18 months in some patients [42]. In our case, EBV-DNA presented a continuous decrease after several lymphocyte infusion treatments, indicating a response to this adoptive cell therapy.

Conclusion

CAEBV is a rare disease with an unfavorable prognosis and should be properly diagnosed by clinical symptoms, laboratory examinations, imaging findings and pathological features. Conventional imaging is essential in this disease, containing ultrasound, CT, and MRI. PET/CT shows an important role in the evaluation of the whole body. For the children and young adults with FDG high uptake and remarkable increased EBV levels, CAEBV should be considered but further differentiation should be made from lymphoma. In these situations, pathological examination helps to make the final diagnosis.

Acknowledgements

This study was funded by the Beijing Science Foundation for Distinguished Young Scholars (JQ21025), the Peking University Medicine Fund of Fostering Young Scholars' Scientific & Technological Innovation (BMU2022PY006).

Disclosure of conflict of interest

None.

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