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REVIEW ARTICLE

Pathogenesis and FDG-PET/CT findings of Epstein–Barr virus-related lymphoid neoplasms

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Abstract Epstein–Barr virus (EBV) is one of the most common viruses, infecting more than 90% of the adult population worldwide. EBV genome is detected in some lymphoid neoplasms. Not only their histopathological subtypes, but also their backgrounds and their clinical courses are variable. A number of B-cell lymphoproliferative disorders associated with the immunocompromised state are related to EBV infection. The incidences of these disorders have been increasing along with generalization of organ transplantations and use of immunosuppressive treatments. Furthermore, some EBV-positive lymphoma can also occur in immunocompetent patients. While evaluating patients with generalized lymphadenopathy of unknown cause by positron emission tomography/computed tomography with 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG-PET/CT), the possibility of lymphoid neoplasms should be considered in some patients, and a careful review of the background and previous history of the patients is necessary. In this review article, we describe the pathogenesis of EBV-related lymphoid neoplasms and then present FDG-PET/CT images of representative diseases. In addition, we also present a review of other EBV-related diseases, such as infectious mononucleosis and nasopharyngeal carcinoma.

Keywords Epstein–Barr virus · FDG-PET/CT · Lymphoproliferative diseases · Lymphoma

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Introduction

Epstein–Barr virus (EBV) is one of the most commonly occurring viruses, infecting more than 90% of the adult population worldwide through contact with oral secretions [1, 2]. When reflecting on the historical background of EBV, we need to start with the description by Burkitt in 1958 of a common cancer affecting children in equatorial Africa, which subsequently came to be known as Burkitt lymphoma (BL) [3]. In 1964, Epstein and Barr identified herpes virus-like particles by electron microscopy in a cell line established from a BL biopsy specimen [4]. These findings represent the first discovery of an oncovirus. In 1970, Zur Hausen et al. demonstrated that EBV infection was a common feature in patients with undifferentiated nasopharyngeal carcinoma (NPC) [5]. Subsequent studies have shown EBV infection to be associated with a variety of other human tumors, including some lymphoid neoplasms.

Although EBV-related lymphoid neoplasms can occur in immunocompetent patients, the incidence of EBV-related lymphoid neoplasms associated with immunocompromised state has been increasing along with generalization of organ transplantations and use of immunosuppressive treatments. With the increasing frequency of use of positron emission tomography/computed tomography with 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG-PET/CT), nuclear medicine physicians and radiologists are increasingly faced with the opportunity of

evaluating FDG-PET/CT images of patients with generalized lymphadenopathy of unknown cause. While interpreting the FDG-PET/CT images of such cases, the possibility of EBV-related lymphoid neoplasms needs to be considered in some patients. For rapid and appropriate diagnosis, not only careful evaluation of the PET/CT images, but also a review of the background and previous history of the patients is necessary.

First, in this review article, we describe the pathogenesis of EBV infection. Thereafter, we illustrate the FDG-PET/CT findings of representative EBV-related lymphoid neoplasms in immunocompetent and immunocompromised patients, with some explanations of their epidemiology and pathology. Finally, we review other EBV-related diseases which can serve as pitfalls in the diagnosis of lymphomas.

Pathogenesis of EBV infection

Epstein–Barr virus is a double-stranded deoxyribonucleic acid (DNA) virus of the herpes virus family [1, 6]. We have illustrated the pathogenesis of EBV infection in Fig. 1. Transmitted EBV via the saliva firstly infects resting B cells or epithelial cells localized in the oropharynx. The infected cells produce EBV which spread in the whole body. Then, the virus infects systemic B cells and causes the proliferation and activation of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells. The reaction is sometimes accompanied by severe systemic inflammation; lymphadenopathy, fever, and liver dysfunction, named infectious mononucleosis (IM). Although the primary infected cells are eradicated by these reactive CTLs, EBV persistently infects memory B cells throughout life without replication of the virus (latent infection).

To evade the attack of host's CTLs, the EBV gene expression in the resting memory B cell is limited to nine viral latent proteins [2]. These are six EBV nuclear antigens (EBNAs-1, -2, -3a, -3b, -3c, and -LP) and three latent membrane proteins (LMP-1, -2a, and -2b) [2]. Furthermore, the non-translated types of EBV-encoded ribonucleic acid (EBER) may be important for oncogenesis and resistance to programmed cell death or apoptosis [6].

According to the pattern of expression of the latent EBV genes, there are three distinct patterns of latency programs [2, 7]. Type 1 is selective expression of EBNA-1 which induces BL. Type 2 shows the expression of LMP-1 and LMP-2 in addition to EBNA-1. This pattern contributes to pathogenesis of some types of lymphoma, such as Hodgkin lymphoma (HL) and extranodal NK/T-cell lymphoma (ENKTL). Type 3, which is characterized by the expression of all EBNA and LMP families, is related to lymphomagenesis in immunocompromised patients, such as post-transplant lymphoproliferative disorders (PTLDs) and human immunodeficiency virus (HIV)-related diseases.

EBV-related lymphoid neoplasms in immunocompetent patients

The WHO classification of representative EBV-related lymphoid neoplasms in immunocompetent patients is shown in Table 1 [2, 8]. Most EBV-related lymphoid

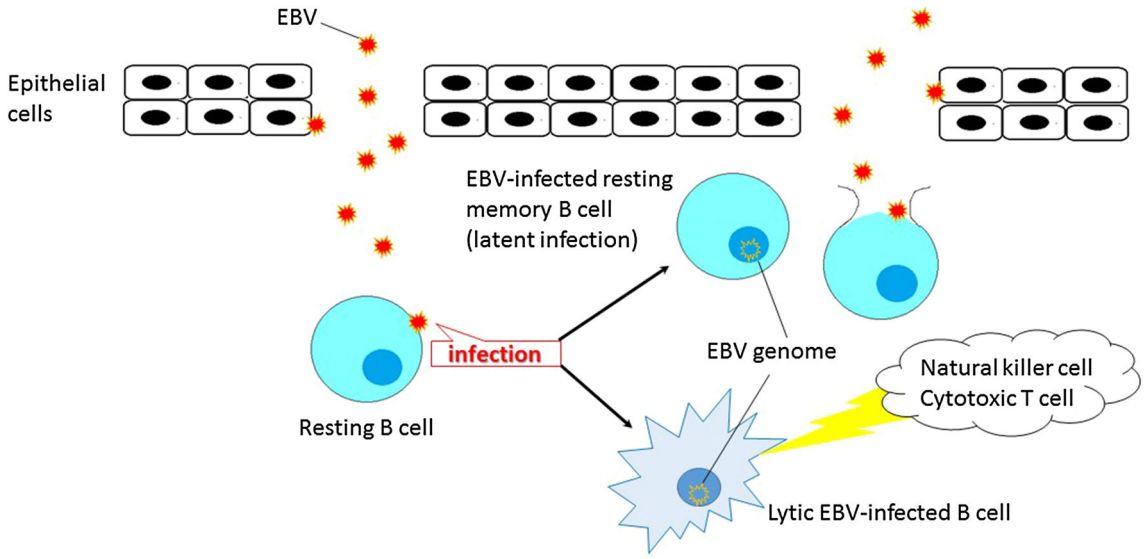

Fig. 1 Pathogenesis of Epstein–Barr virus (EBV) infection. EBV is transmitted via saliva and directly infects resting B cells. Although natural killer (NK) cells and cytotoxic T cells suppress primary infected B cells, some infected B cells shift to the state of latent infection. Some B cells or epithelial cells in the oropharynx reveal lytic infection. They reproduce viral particles and shed them into the saliva, which perpetuates transmission of the infection to other people

neoplasms are highly FDG-avid. In the following sections, we will explain some types of EBV-related lymphoid neoplasms, with representative FDG-PET/CT images of some cases.

Burkitt lymphoma (endemic and sporadic)

BL is considered as a prime example for *c-myc*-induced lymphomagenesis [9] and EBV may increase the likelihood of genetic accidents giving rise to the translocation, or may complement the activity of c-Myc [2]. The EBV positivity rate differs between endemic BL (100%) and sporadic BL (20–30%) [2]. Because of the fast growth of the tumor, with a potential doubling time of 24 h, BL can rapidly result in serious clinical conditions, such as airway compromise, cavernous sinus invasion, and spinal cord compression [1]. Chemotherapy with or without rituximab, an anti-CD20 monoclonal antibody, is highly effective, regardless of the EBV positivity status [2].

Because all BL lesions are highly FDG-avid [10, 11], FDG-PET/CT is useful for initial staging [12] and for monitoring the response to therapy [13] (Fig. 2).

Classical Hodgkin lymphoma

The EBV positivity rate is 40% [2]. The hallmark of HL, Reed–Strenberg (R–S) cell, needs NF-κB function for its survival. In EBV-infected cases, LMP1 activates NF-κB by mimicking an activated CD40 receptor [14]. A recent study showed that plasma EBV DNA is a useful biomarker for predicting the outcome in patients with advanced HL [15]. Especially in the early stage HL patients, EBV infection affects the shorter survival [16]. Although chemotherapy for both EBV-positive and EBV-negative cases of HL is currently identical and results in long-term remissions in most patients [2], concurrent radiotherapy is recommended for early stage HL [17].

Regardless of the positivity for EBV, HL lesions are also highly FDG-avid as BLs [10] (Fig. 3). FDG-PET/CT is useful not only for the initial staging, but also for monitoring of the early response to therapy and predicting the prognosis [18–20]. Recently, however, El-Galaly et al. [21] have reported a high negative predictive value (99%) of FDG-PET/CT for detecting bone-marrow involvement. Furthermore, in their study, the findings of bone-marrow biopsy did not change therapeutic strategy. Considering those results, international working group recently suggested that bone-marrow biopsy is no longer indicated if FDG-PET/CT is performed in cases of HL [22].

Pyothorax-associated lymphoma (PAL)

PAL is one of the representative types of diffuse large B-cell lymphomas (DLBCL) associated with chronic inflammation described in the WHO classification [8]. The EBV-positive rate in DLBCL is estimated as at most about 70% [2]. Pleural lymphoma develops in 2.2% of patients with chronic pyothorax. Most patients have a more than 20-year history of chronic pyothorax or having received an artificial pneumothorax for the treatment of lung tuberculosis, and tuberculous pleuritis is a risk factor for the development of lymphoma even in immunocompetent patients [1, 23] (Fig. 4).

FDG-PET/CT is useful for management of PAL, including for radiotherapy planning, and also for the detection of residual disease after treatment [24, 25].

EBV-positive DLBCL, not otherwise specified

Although the 2008 WHO classification included a provisional entity "EBV-positive DLBCL of the elderly", this was replaced by "EBV-positive DLBCL, not otherwise specified (NOS)" in the 2016 revision, because it may occur in younger patients [8]. It is characterized by EBV-positive monoclonal large B-cell proliferation, and usually occurs in patients older than 50 years of age with no known immunodeficiency or history of lymphoma [26]. Although therapeutic approach for DLBCL, namely, administration of a combination of rituximab and anthracycline-based

Table 1 WHO classification of representative EBV-related lymphoid neoplasms in immunocompetent host

B cell
Burkitt lymphoma
Classical Hodgkin lymphoma
Diffuse large B-cell lymphoma (DLBCL) associated with chronic inflammation
EBV-positive DLBCL
Lymphomatoid granulomatosis
NK/T cell
Extranodal NK/T-cell lymphoma, nasal type
Aggressive NK cell leukemia
Systemic EBV-positive T-cell lymphoma of childhood

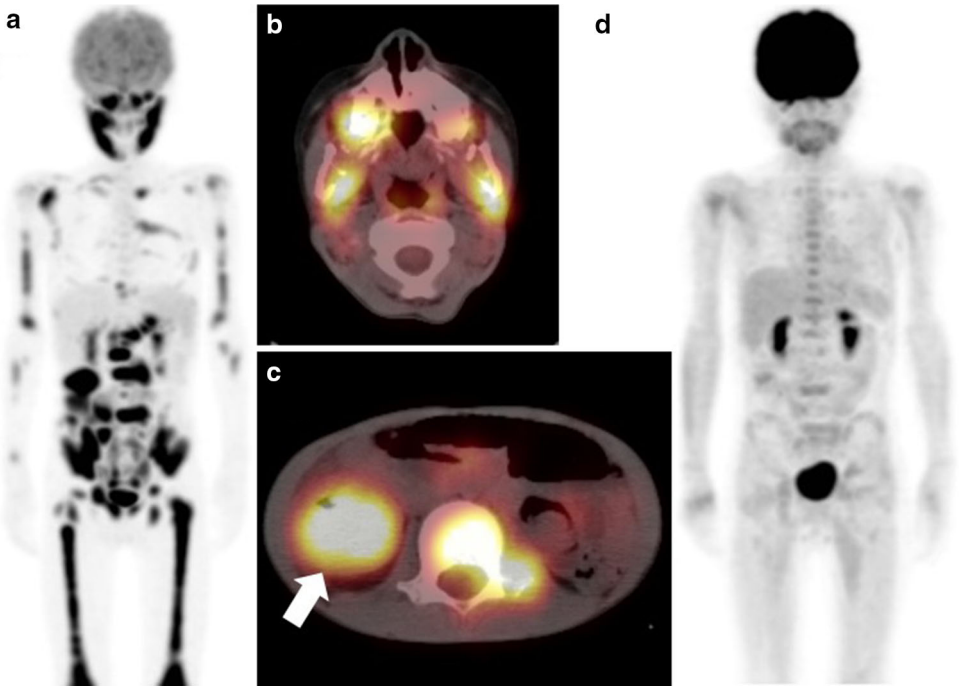

Fig. 2 Burkitt lymphoma in 9-year-old boy. **a** Maximum intensity projection (MIP) image of FDG-PET/CT showed multiple bone-marrow lesions. The maximum standardized uptake value (SUV_{max}) was 12.1 in the lesion in the L2 vertebral body. **b** Fused PET/CT image showed osteolytic changes in some of the lesions. **c** PET/CT also showed a tumor in the ascending colon (*arrow*). **d** Complete response was confirmed by posttherapeutic FDG-PET/CT

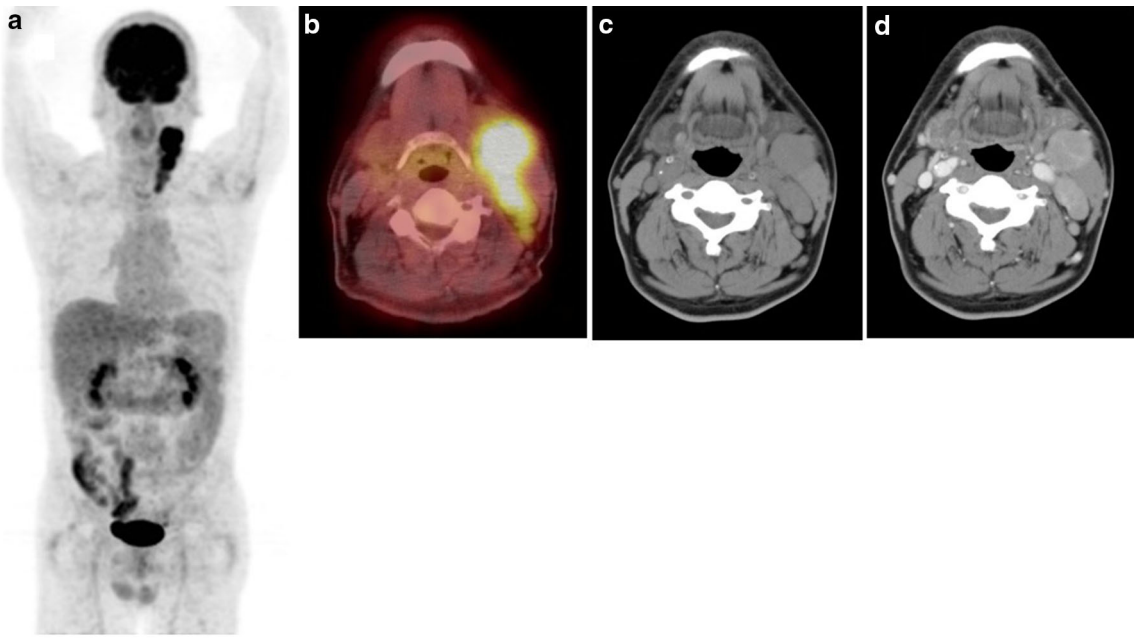

Fig. 3 Hodgkin lymphoma in a 56-year-old man. **a**, **b** FDG-PET/CT showed multiple enlarged lymph nodes in the left neck showing high FDG uptake ($SUV_{max} = 10.6$). **c** These enlarged lymph nodes showed isodensity to the muscles on plain CT, and **d** homogeneous enhancement on contrast-enhanced CT

chemotherapy, does not differ according to the EBV positivity status, EBV-positive DLBCL is associated with a worse prognosis as compared to EBV-negative DLBCL [27]. In addition, expression of CD30 has been shown to be associated with an adverse outcome [28].

Although there have been few case reports, most lesions are highly FDG-avid [10] (Fig. 5) and FDG-PET/CT is useful for clinical management of these patients, just as in patients with other DLBCLs. There have not been studies which compared FDG-PET/CT findings between EBV-positive and EBV-negative DLBCL. However, nodal and extranodal necrosis, which is reported as more frequent in patients with EBV-positive DLBCL, may contribute to the differential diagnosis [29].

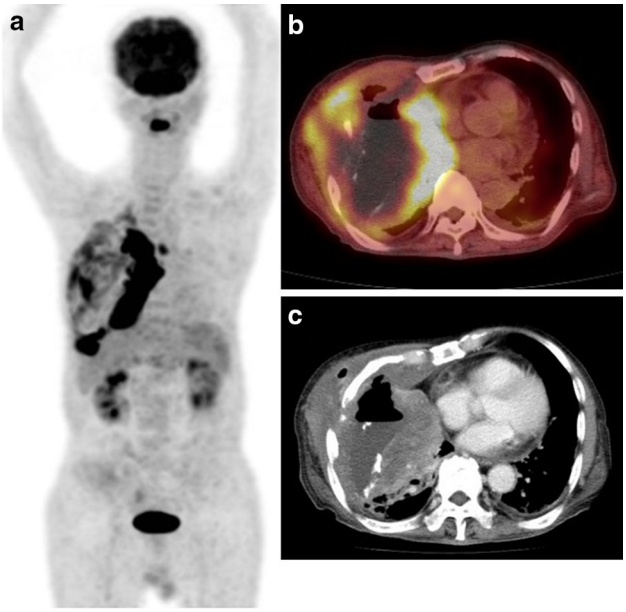

Fig. 4 Pyothorax-associated lymphoma in an 85-year-old man. The patient had undergone thoracoplasty for tuberculous pleuritic 60 years ago. **a**, **b** FDG-PET/CT showed chronic pyothorax in the right thorax and a diffusely spreading tumor along the right pleura, which showed elevated FDG uptake ($SUV_{max} = 13.1$). **c** On contrast-enhanced CT, the solid component of the tumor showed heterogeneous enhancement, concordant with the elevated FDG uptake

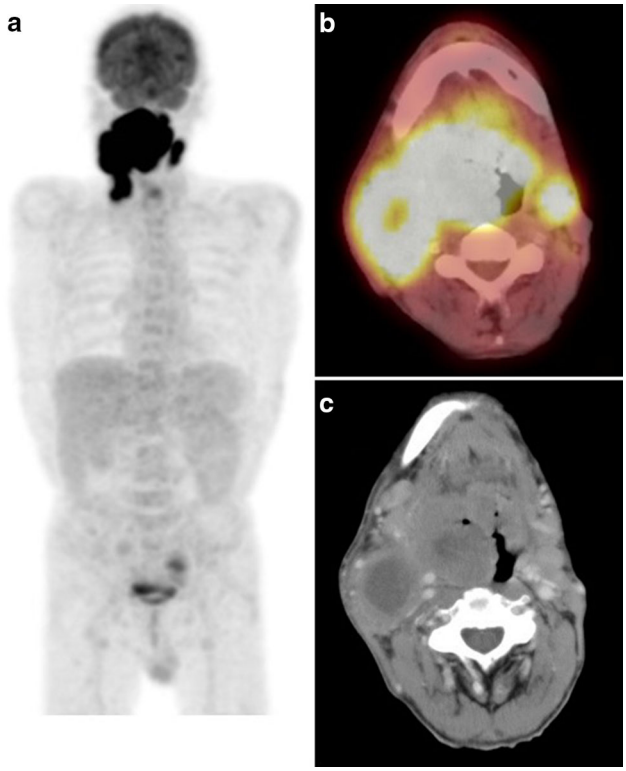

Fig. 5 EBV-positive DLBCL of the elderly in a 67-year-old man. **a**, **b** FDG-PET/CT revealed markedly elevated FDG uptake in the oropharyngeal mass and lymph nodes of both sides ($SUV_{max} = 24.7$). **c** On contrast-enhanced CT, some lymph nodes were found to contain low density areas, suggestive of necrosis or cystic degeneration. Although it was difficult to differentiate the disease from oropharyngeal carcinoma with lymph node metastases by imaging alone, biopsy confirmed the diagnosis of EBV-positive DLBCL

Lymphomatoid granulomatosis (LYG)

Lymphomatoid granulomatosis is a rare type of EBV-related lymphoproliferative disorders (LPDs) characterized by atypical lymphoid cell infiltration of an organ, most frequently the lungs [30, 31]. High-grade LYG is known to be associated with inferior outcomes and needs aggressive therapy according to the treatment protocol for high-grade B-cell lymphomas [30]. Siegloch et al. recommended high-dose chemotherapy followed by stem cell transplantation (SCT) for LYG cases with refractory diseases or multiple relapses [32].

Although there are few reports discussing the FDG-PET/CT findings of LYG, Chung et al. reported two cases with bilateral pulmonary nodules which showed elevated FDG uptake [31]. We have illustrated a case of DLBCL associated with LYG in Fig. 6, although the FDG uptake in the lung nodule was not so high in this case.

Extranodal NK/T-cell lymphoma, nasal type

ENKTL most often occurs in immunocompetent middle-aged men of Asian, Native American, or Central/South American descent, and the neoplastic cells are positive for EBV [2]. Because radiotherapy concurrent with or followed by chemotherapy has become the standard of treatment for limited-stage diseases [33], accurate staging is mandatory. For advanced-stage and relapsed or refractory disease, L-asparaginase, which exerts its anti-tumor effect by asparagine starvation of the tumor cells which show low expression levels of asparagine synthetase, has been reported to be effective [2, 33].

Most lesions of ENKTL are highly FDG-avid [10, 34, 35] (Fig. 7). Existence of a correlation has been reported between the FDG uptake and extent of local invasion, and thereby the survival outcomes [36, 37].

EBV-related lymphoid neoplasms in immunocompromised patients

The WHO classification of representative EBV-related lymphoid neoplasms in immunocompromised patients is shown in Table 2 [2, 8]. For appropriate diagnosis of these disorders, a careful review of the background and previous history of the patients is essential. We will discuss three types of EBV-related lymphoid neoplasms below.

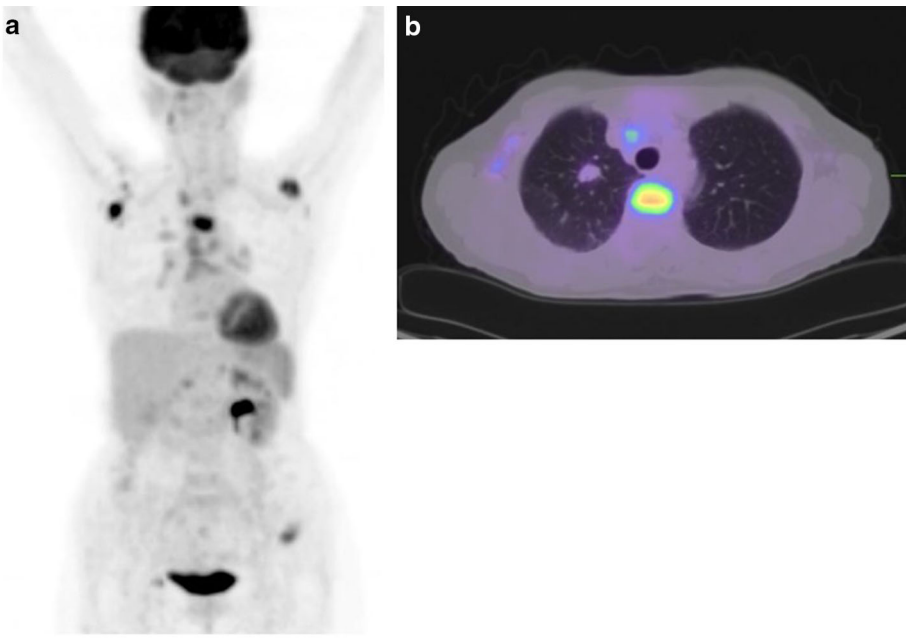

Fig. 6 Lymphomatoid granulomatosis (LYG) in a 40-year-old woman. **a** MIP image of FDG-PET/CT showed elevated FDG uptake in the axillary nodes of both sides and in the vertebral lesion. **b** Fused PET/CT image showed a nodule in the right lung with minimal FDG uptake. Right upper lobectomy and axillary lymph node biopsy were performed, and the histopathological diagnosis was DLBCL accompanied by pulmonary LYG lesion in the right lung

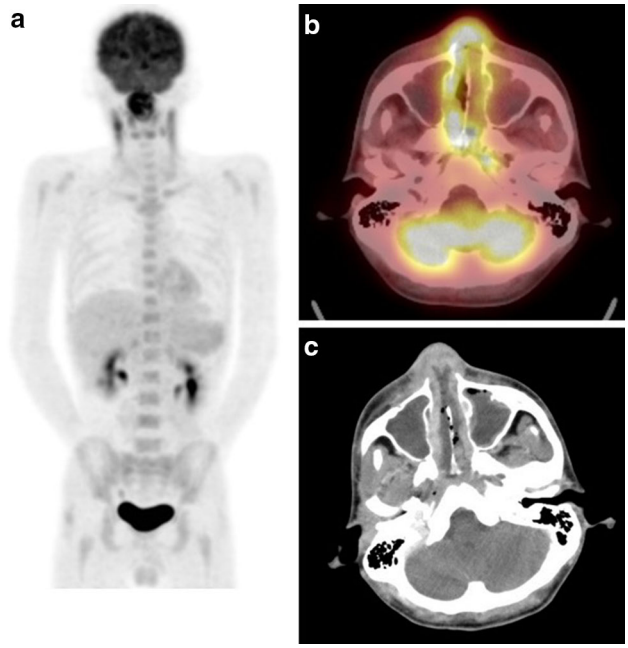

Fig. 7 Extranodal NK/T-cell lymphoma, nasal type in a 29-year-old man. **a**, **b** FDG-PET/CT showed elevated FDG uptake in the nasal cavity mass ($SUV_{max} = 8.3$) and cervical lymph nodes of both sides ($SUV_{max} = 5.5$). Although elevated FDG uptake was also detected in the bone marrow (**a**), bone-marrow biopsy failed to confirm involvement of the bone marrow. **c** Nasal cavity mass showed strong peripheral enhancement on contrast-enhanced CT

Post-transplant lymphoproliferative disorders (PTLDs)

PTLDs develop as a result of EBV-induced transformation of B cells in the setting of impaired anti-EBV cellular immunity induced by iatrogenic immunosuppression after transplant therapy [2]. Not only B-cell type, but also T-cell-type PTLDs can develop after transplantation, and their EBV positivity was 70 and 90%, respectively [2]. T-cell-type PTLDs are quite rarer. The risk of PTLDs is increased when an EBV-negative recipient receives a transplant from an EBV-positive donor [38]. The overall prevalence following solid organ transplantation ranges from 1 to 20%, with the highest rates in recipients of intestines and lungs [39]. EBV-positive PTLDs typically occur in the first year after transplantation [39]. The most effective intervention known until date for PTLDs is reduction of immunosuppression, while relapse is not rare [38, 39].

Most PTLDs lesions are FDG-avid (Fig. 8). Panagiotidis et al. reported a sensitivity and specificity of FDG-PET/CT of 88.2 and 91.3%, respectively, for the diagnosis of PTLDs [40]. As compared to the conventional imaging methods, FDG-PET/CT may be more useful to detect occult lesions, particularly extranodal lesions [41].

Lymphoma associated with HIV infection

Loss of immune surveillance of EBV-driven B-cell transformation leads to the development of lymphomas because of the decrease of CTLs [1]. Many subtypes of lymphoma associated with HIV infection have been described. In particular, primary effusion lymphoma and plasmablastic lymphoma of the oral cavity are known as lymphomas occurring more specifically in HIV-positive patients [42]. EBV positivity differs depending on the histology of the tumor. Although the overall positivity rate of EBV in HIV-related lymphomas is about 60% [1], primary central

Table 2 WHO classification of representative EBV-related lymphoid neoplasms in immunocompromised host

Post-transplant lymphoproliferative disorders (PTLDs)
Lymphomas associated with human immunodeficiency virus (HIV) infection
Burkitt lymphoma (HIV)
Hodgkin lymphoma (HIV)
Primary effusion lymphoma
Plasmablastic lymphoma
Lymphoproliferative diseases associated with primary immune disorders
Other iatrogenic immunodeficiency-associated lymphoproliferative disorders

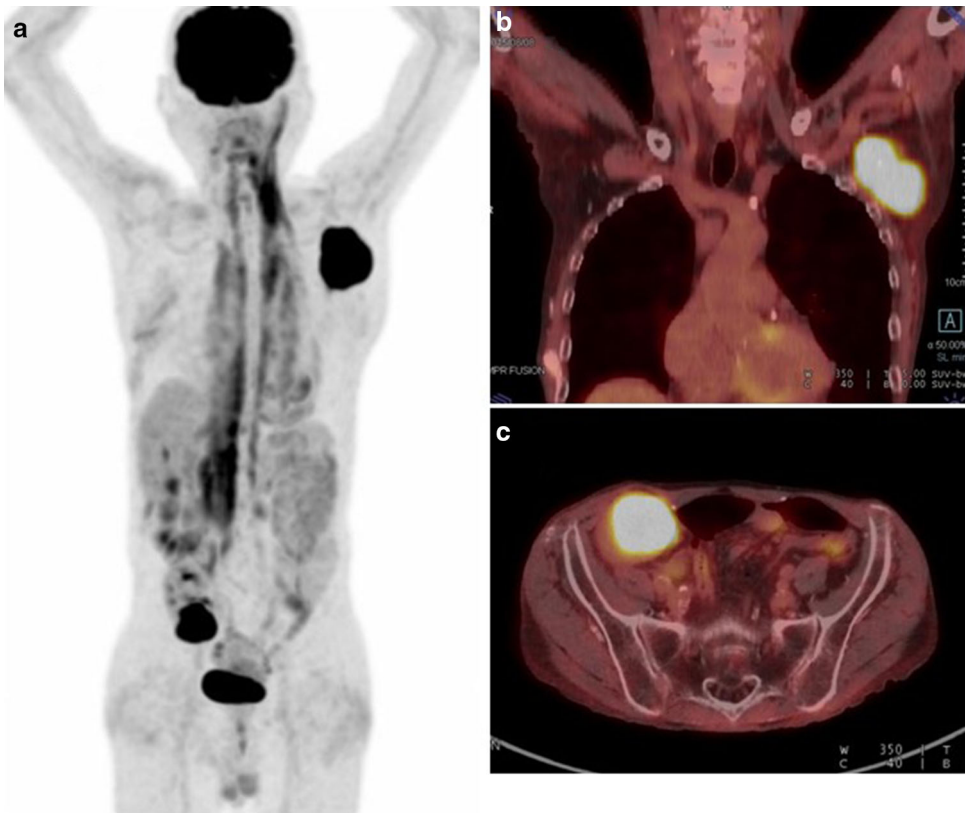

Fig. 8 Post-transplant lymphoproliferative disorders in a 65-year-old man. The patient had undergone kidney transplantation for chronic nephritis 12 years previously. **a–c** FDG-PET/CT showed left axillary lymphadenopathy ($SUV_{max} = 15.1$) and a tumor below the transplanted kidney ($SUV_{max} = 16.5$) which showed elevated FDG uptake. These lesions shrank only when immunosuppressive drug doses were reduced. FDG uptake along the vertebrae was physiological uptake in the back muscles

nervous system lymphoma (PCNSL) and plasmablastic lymphoma show a positive detection rate of 100% [2].

Although there have been few studies conducted to evaluate the usefulness of FDG-PET/CT, this imaging modality is considered to be useful for staging, restaging, and surveillance for HIV-related lymphoma of various histologic subtypes [43].

Other iatrogenic immunodeficiency-associated lymphoproliferative disorders (LPDs), previously known as methotrexate (MTX)-related LPDs

Methotrexate is one of the most commonly used drugs in the treatment of rheumatoid arthritis. Inhibition of T-cell activation and suppression of T-cell expression of the intercellular adhesion molecule by MTX are the main causes of MTX-related LPDs [44]. Recently, the disorders also arise in patients treated with anti-tumor necrosis factor α (TNFα) antagonists. Spontaneous regression is seen after the withdrawal of MTX, especially in EBV-positive cases (about 40–50%) [2, 42] (Fig. 9), whereas regression after drug discontinuation seldom occurs in patients who developed the disorders following anti-TNFα antagonists.

FDG-PET/CT allows clinical assessment of MTX-related LPDs and their recurrent lesions [45, 46]. However, degree of FDG uptake in the lesion before the withdrawal of MTX is not useful to predict complete response after the withdrawal of MTX [46].

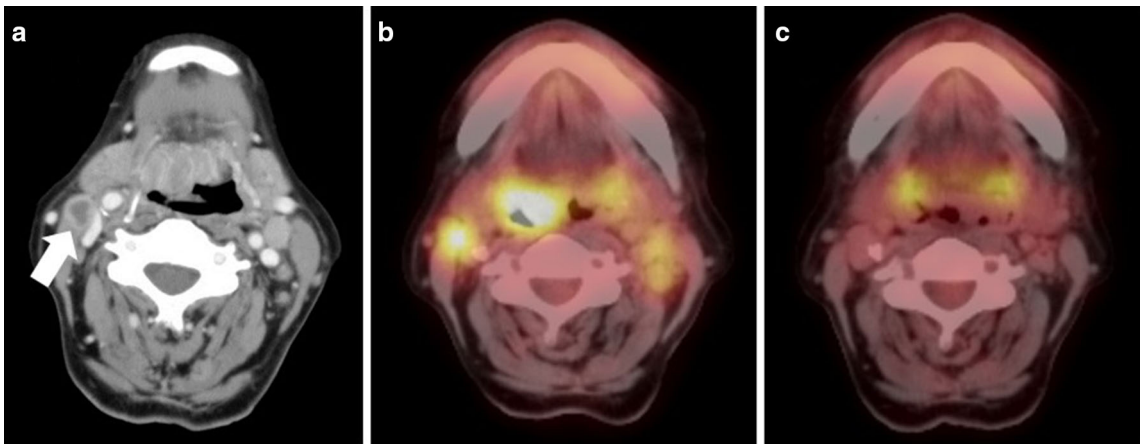

Fig. 9 Other iatrogenic immunodeficiency-associated lymphoproliferative disorders in a 77-year-old man. The patient had received methotrexate (MTX) for more than 20 years as treatment for rheumatoid arthritis. **a** Contrast-enhanced CT showed an oropharyngeal mass and bilateral cervical lymphadenopathy. Some of the lymph nodes contained low density areas, suggestive of necrosis or cystic degeneration (*arrow*). **b** FDG-PET/CT revealed elevated FDG uptake in these lesions ($SUV_{max} = 14.9$ in the oropharyngeal mass). **c** Although these lesions shrank after the withdrawal of MTX, the clinician judged this as only a partial response because of residual FDG uptake in the tonsils. The patient was then administered rituximab-based chemotherapy

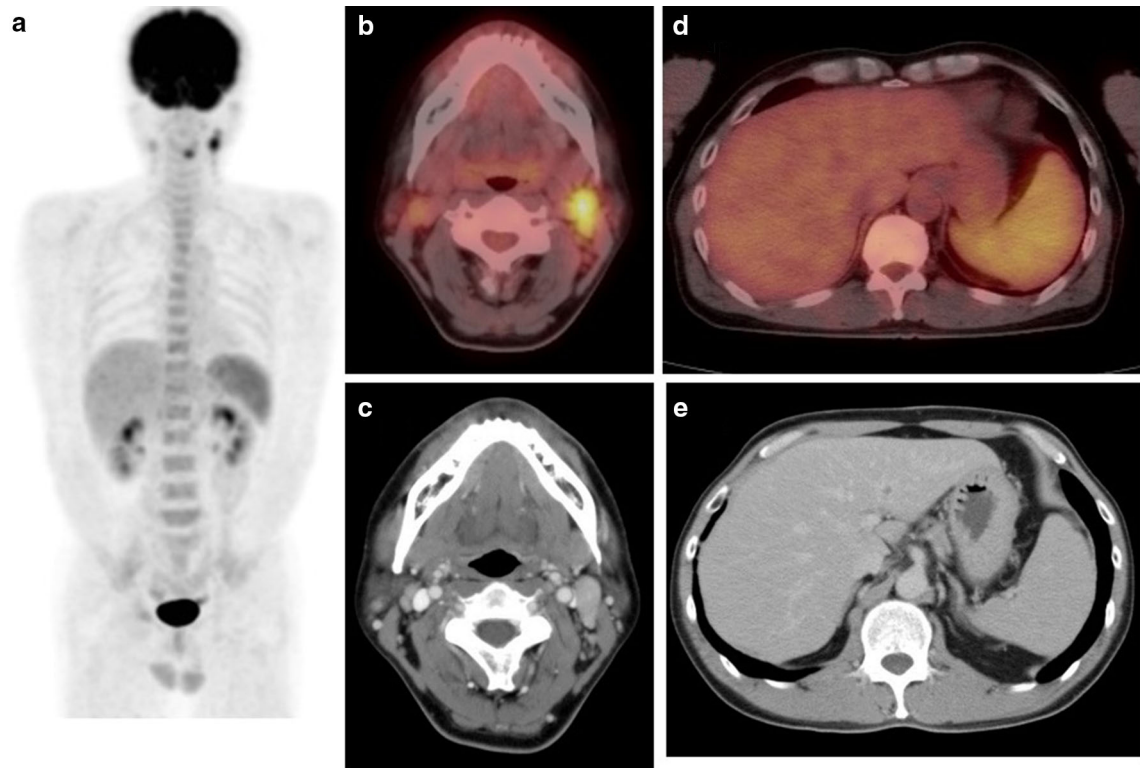

Fig. 10 Infectious mononucleosis in a 51-year-old man. The patient presented with a 1-week history of fever and left cervical lymphadenopathy. **a** MIP image of FDG-PET/CT showed hot spots in the left neck and elevated FDG uptake in the spleen and bone marrow. **b** Left cervical lymphadenopathy with elevated FDG uptake was confirmed on the fused PET/CT images ($SUV_{max} = 8.4$). **c** Lymph nodes showed homogeneous enhancement on contrast-enhanced CT. **d** FDG uptake in the spleen exceeded that in the liver, hence judged as representing pathological uptake. **e** However, contrast-enhanced CT did not show splenomegaly or any abnormal enhancement in the spleen

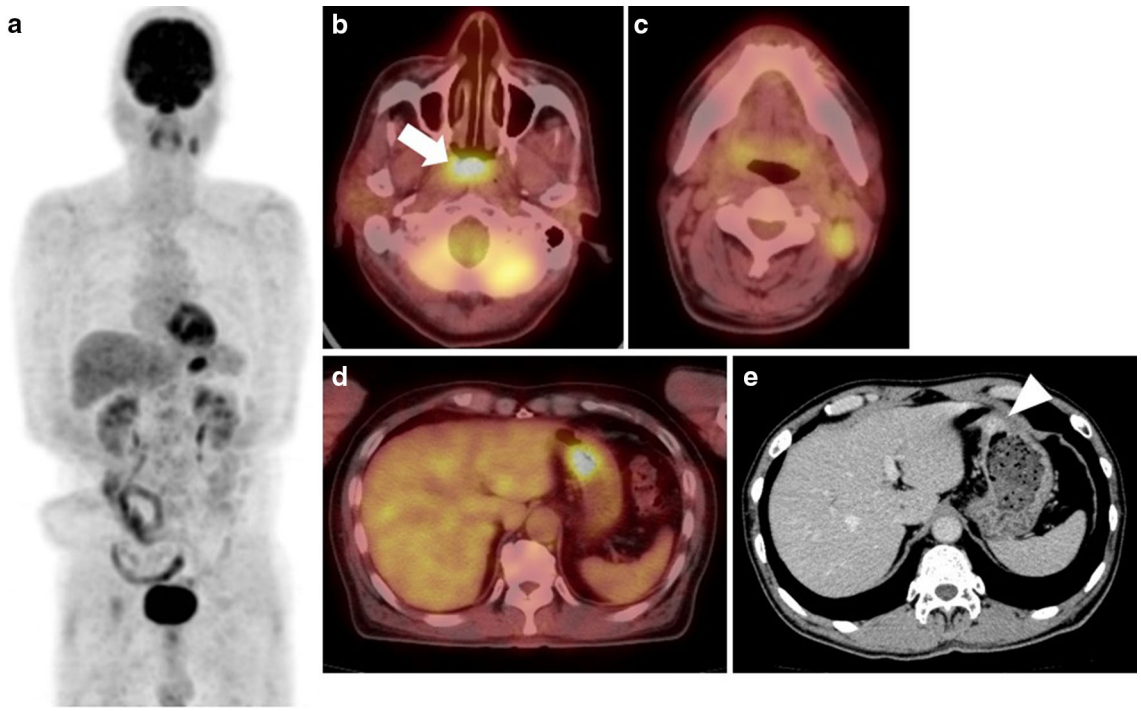

Fig. 11 Coexistence of nasopharyngeal carcinoma and gastric carcinoma in a 61-year-old man. **a–c** FDG-PET/CT confirmed the primary nasopharyngeal lesion ($SUV_{max} = 5.9$) (**b**; *white arrow*) and left cervical lymph node metastasis ($SUV_{max} = 3.5$). **d** In addition, increased gastric FDG uptake suggestive of a gastric carcinoma was also unexpectedly discovered at the same time ($SUV_{max} = 6.1$). **e** Although it would have been difficult to point out prospectively, limited enhancement in the gastric corpus was confirmed by contrast-enhanced CT (*white arrowhead*). Although tests for markers of EBV infection were not performed in this case, a relationship is well known to exist between EBV and gastric carcinoma [1]

Pitfalls

Infectious mononucleosis (IM) and NPC are representative pitfalls, as they can be misdiagnosed as EBV-related lymphoid neoplasms. Because the seroprevalence of EBV antibody has recently declined in young individuals [47], more patients with IM may be referred for FDG-PET/CT in clinical practice. It is difficult to distinguish between NPC and lymphoma based on the FDG-PET/CT findings alone. Nevertheless, we should suggest the accurate extent of the disease from the findings on FDG-PET/CT, even if the histopathological diagnosis is yet to be established.

On the other hand, we would like to discuss the FDG-PET/CT findings of chronic active EBV infection (CAEBV). To the best of our knowledge, there are no previous reports which showed characteristic FDG-PET/CT findings of CAEBV.

Infectious mononucleosis (IM)

During primary infection of EBV, NK cells and CTLs control proliferating EBV-infected B cells. It is considered that these cell-mediated immune responses result in the classical trial of IM symptoms, namely, pharyngitis, fever, and lymphadenopathy [48].

Some cases of IM with FDG-PET/CT findings similar to those of lymphomas have been reported [49–51] (Fig. 10). However, it is not difficult to distinguish IM from LPDs or lymphomas considering the clinical course, which clearly suggests an acute inflammatory disease.

Nasopharyngeal carcinoma (NPC)

Epstein–Barr virus released from lytic B cell is considered to be the viral source in EBV-related epithelial neoplasms, such as NPC [1]. It is impossible to distinguish between NPC and lymphoma based on the findings of FDG-PET/CT alone. However, we should be able to assess the accurate extent of the lesions, not only of the primary lesion, but also of the nodal spread, from the FDG-PET/CT findings, even if the histopathological diagnosis is not yet to be established. FDG-PET/CT is also useful for the evaluation of local recurrence or distant metastases [52, 53]. On the other hand, magnetic resonance imaging (MRI) is superior for the detection of intracranial extension [54].

We have shown a case in which NPC and gastric carcinoma incidentally coexisted in Fig. 11.

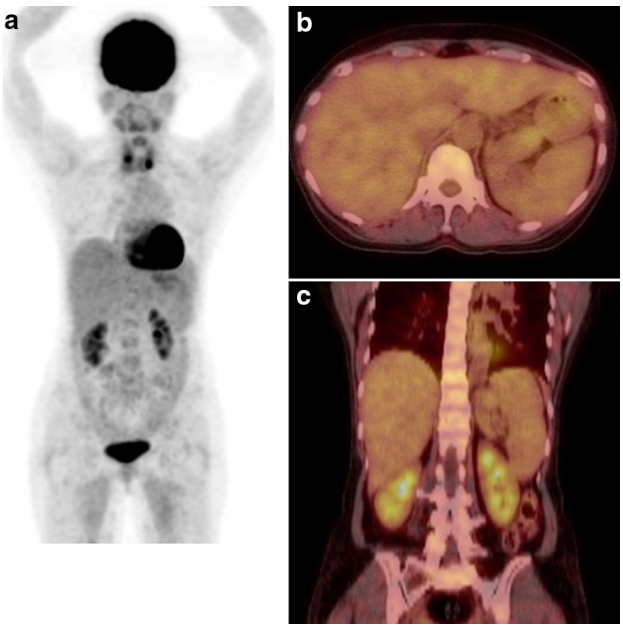

Fig. 12 Chronic active EBV infection (CAEBV) in a 62-year-old woman. This patient presented with fever of unknown origin. Physical examination revealed splenohepatomegaly. Laboratory data showed liver dysfunction and leukocytopenia. Finally, we diagnosed the patient as having CAEBV on the basis of detection of an increased load of EBV in the peripheral blood and confirmation of EBV infection in the T cells. **a–c** FDG-PET/CT showed splenohepatomegaly, with a craniocaudal length of the spleen and liver of 137 and 200 mm, respectively. However, both organs showed homogenous FDG uptake, compatible with physiological uptake. On the other hand, a MIP image showed hot spots in the thyroid (**a**), which were, however, confirmed as benign nodules after clinical follow-up

Chronic active EBV infection (CAEBV)

CAEBV is a rare disease characterized by inflammation, including fever, splenohepatomegaly, and lymphadenopathy, and so on, persisting for at least 6 months. In WHO classification revise in 2016, CAEBV was defined to have two characteristic skin disorders: hydroa vacciniforme-like LPD and severe mosquito bite allergy [8]. CAEBV is considered to be an EBV infection of the T or NK cells resulting in their activation and immortalization. Such EBV-infected T or NK cells finally become expanded monoclones, leading to the development of aggressive diseases, such as lymphoma or hemophagocytic lymphohistiocytosis [55]. Although CAEBV mainly affects children, adult-onset cases are also encountered [1, 55]. Recently, hematopoietic stem cell transplantation has been reported as an effective treatment for this condition [56].

As described above, most EBV-related LPDs or lymphomas show elevated FDG uptake, just like other malignant tumors. However, according to our review, one of the characteristic findings in CAEBV is that despite physical examination revealing the presence of lymphadenopathy and hepatosplenomegaly, these involved organs do not show elevated FDG uptake. Suspecting the possibility of CAEBV from the findings of FDG-PET/CT carried out for the investigation of related symptoms, including fever of unknown origin, may contribute to rapid diagnosis and prompt therapy.

We have shown a representative case of CAEBV in Fig. 12. However, further studies including many cases of CAEBV are needed to confirm our hypothesis.

Conclusions

Because most EBV-related lymphoid neoplasms are highly FDG-avid, FDG-PET/CT is a useful tool for evaluating the extent of involvement, as a surveillance tool for recurrent lesions, and for monitoring of the response to therapy. Although there are not specific FDG-PET/CT findings to EBV-related lymphoid neoplasms when encountering patients with generalized lymphadenopathy with elevated FDG uptake, we should take possibility of EBV-related lymphoid neoplasms into consideration in conjunction with a careful review of the background and previous history of those patients.

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