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REVIEW

Spectrum of Epstein-Barr virus-related diseases: a pictorial review

**Eriko Maeda · Masaaki Akahane · Shigeru Kiryu
Nobuyuki Kato · Takeharu Yoshikawa · Naoto Hayashi
Shigeki Aoki · Manabu Minami · Hiroshi Uozaki
Masashi Fukayama · Kuni Ohtomo**

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Abstract Epstein-Barr virus (EBV) prevails among more than 90% of the adult population worldwide. Most primary infections occur during young childhood and cause no or only nonspecific symptoms; then the virus becomes latent and resides in lymphocytes in the peripheral blood. Inactive latent EBV usually causes no serious consequences, but once it becomes active it can cause a wide spectrum of malignancies: epithelial tumors such as nasopharyngeal and gastric carcinomas; mesenchymal tumors such as follicular dendritic cell tumor/sarcoma; and lymphoid malignancies such as Burkitt lymphoma, lymphomatoid granulomatosis, pyothorax-associated lymphoma, immunodeficiency-associated lymphoproliferative disorders, extranodal natural killer (NK) cell/T-cell lymphoma, and Hodgkin's lymphoma. The purpose of this article is to describe the spectrum of EBV-related diseases and their key imaging findings. EBV-related lymphoproliferative disorders and lymphomas are especially common in immunocompromised patients. Awareness of their clinical settings and imaging spectrum contributes to early detection and early treatment of possibly life-threatening disorders.

Key words Epstein-Barr virus · EBV-associated gastric carcinoma · Follicular dendritic cell tumor · Lymphoma · Lymphoproliferative disorder · Immunodeficiency

E. Maeda (✉) · M. Akahane · N. Kato · T. Yoshikawa · N. Hayashi · S. Aoki · K. Ohtomo
Department of Radiology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
Tel. +81-3-5800-8666; Fax +81-3-5800-8935
e-mail: emaeda-tky@umin.ac.jp

S. Kiryu
Department of Radiology, Institute of Medical Science, The University of Tokyo, Tokyo, Japan

M. Minami
Department of Radiology, Tsukuba University Hospital, Tsukuba, Japan

H. Uozaki · M. Fukayama
Department of Pathology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Introduction

Epstein-Barr virus (EBV) was first identified in 1964 by Epstein's group in a cell line derived from Burkitt lymphoma.[1] EBV is an enveloped herpesvirus with double-stranded DNA infecting only humans.[1] EBV is one of the most common viruses, infecting more than 90% of the adult population worldwide.

EBV infection is transmitted by salivary contact. Most primary infections occur during young childhood and cause no or only nonspecific symptoms, whereas infections during late adolescence or in adults can result in infectious mononucleosis. Once infection takes place, EBV becomes latent and resides in lymphocytes in the peripheral blood, rendering the infected individual a lifelong EBV carrier.[1] Carriage of EBV causes no serious consequences in most cases, so long as the virus exists in an inactive, latent form. On rare occasions, the latent virus becomes active and plays a role in the pathogenesis of chronic active infection or epithelial, mesenchymal, and lymphoid malignancies (Table 1).

In this article, the spectrum of EBV-related diseases is discussed in the following order: chronic active EBV infection and EBV-related epithelial, mesenchymal, or lymphoid malignancies.

Table 1. Spectrum of Epstein-Barr virus-related diseases

Acute form of infection
Infectious mononucleosis
X-linked lymphoproliferative syndrome
EBV-associated hemophagocytic syndrome
Gianotti-Crosti syndrome
Chronic form of infection
Chronic active EBV infection
Epithelial malignancies
Nasopharyngeal carcinoma
Gastric carcinoma
Lymphoepithelioma-like carcinoma (salivary glands, thymus, lung)
Mesenchymal malignancies
Follicular dendritic cell tumor/sarcoma
Leiomyomas/leiomyosarcomas in immunocompromised patients
Lymphomas and lymphoproliferative disorders
Burkitt lymphoma
Lymphomatoid granulomatosis
Pyothorax-associated lymphoma
Primary effusion lymphoma
Extranodal NK cell/T-cell lymphoma, nasal type
Hodgkin's lymphoma
Diffuse large B-cell lymphoma
CD30+/Ki-1+ anaplastic large-cell lymphoma
T-cell-rich B-cell lymphoma
Angioimmunoblastic lymphoma
Lymphoproliferative disorders in immunocompromised patients
Primary immunodeficiency-associated
Human immunodeficiency virus-associated
Posttransplant condition
Methotrexate-induced
Senile EBV associated lymphoproliferative disorder

EBV, Epstein-Barr virus; NK, natural killer

Chronic active EBV infection

The process of EBV infection and the pathogenesis of EBV-related diseases are briefly illustrated in Fig. 1.[1–3] A primary EBV infection during the first or second decade of life, or even earlier, can result in infectious mononucleosis (IM). Most patients recover from IM without any sequelae, although a variety of complications can occur, such as splenic infarction and rupture (Fig. 2), upper airway obstruction, and neurological complications.[4,5] EBV can cause chronic infections in individuals without apparent immunodeficiency. This condition is called chronic active EBV (CAEBV) infection. CAEBV infection, characterized by chronic or recurrent infectious mononucleosis-like symptoms, basically affects children and young adults.[6] In the traditional description by Straus, CAEBV infection fulfills the following three criteria: (1) severe illness lasting more than 6 months that began as a primary EBV infection or is associated with grossly abnormal EBV antibody titers; (2) histological evidence of major organ involvement, such as interstitial pneumonia, hypoplasia of some bone marrow elements, uveitis, lymphadenitis, persistent hepatitis, and/or splenomegaly; and (3) increased quantities of EBV in affected tissues, which can be reliably assessed with the peripheral blood specimen by a quantitative polymerase chain reaction (PCR).[6,7]

Fever, liver dysfunction, splenomegaly, lymphadenopathy, thrombocytopenia, and anemia are the common symptoms of CAEBV infection.[6] Radiologists should be aware of the association of CAEBV infection with a high incidence of life-threatening complications, such as hemophagocytic syndrome (21%), coronary aneurysms mimicking Kawasaki disease (21%), lymphomas and lymphoproliferative disorders (16%), interstitial pneumonia (12%), central nervous system (CNS) involvement (7%), and intestinal perforation (4%).[6] This reference does not specify computed tomography (CT) findings of interstitial pneumonia associated with CAEBV infection, but another study reported bilateral nodular pulmonary lesions. Therefore, radiological characteristics of CAEBV infection-associated interstitial pulmonary disease may be different from those of ordinary interstitial pneumonia and await further investigation.[8] CNS involvement includes Mollaret's meningitis, recurrent meningitis, cerebellitis, myochronic attacks, chronic meningoencephalitis, and acute disseminated encephalomyelitis (ADEM).[9] Differences between imaging findings of these conditions associated with CAEBV infection and those in other situations have not been described. Patients with CAEBV infection may present calcifications in the basal ganglia that are characteristically bilateral and symmetrical.[10]

Epithelial malignancies

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma, the most common nasopharyngeal malignancy in adults, is strongly associated with EBV (Fig. 3). Histologically, the World Health Organization (WHO) classification categorizes nasopharyngeal carcinoma into three classes depending on the degree of keratinization and differentiation (Table 2). Differentiated nonkeratinizing tumor, which is squamous cell carcinoma without keratinization, is the least common histology. Undifferentiated nonkeratinizing carcinoma, a form of squamous cell carcinoma, is the most common histology in both the United States and endemic areas, but the prevalence of this histology within nasopharyngeal carcinoma is higher in endemic areas. Among undifferentiated nonkeratinizing carcinomas, the mass intermixed with dense infiltration of benign T

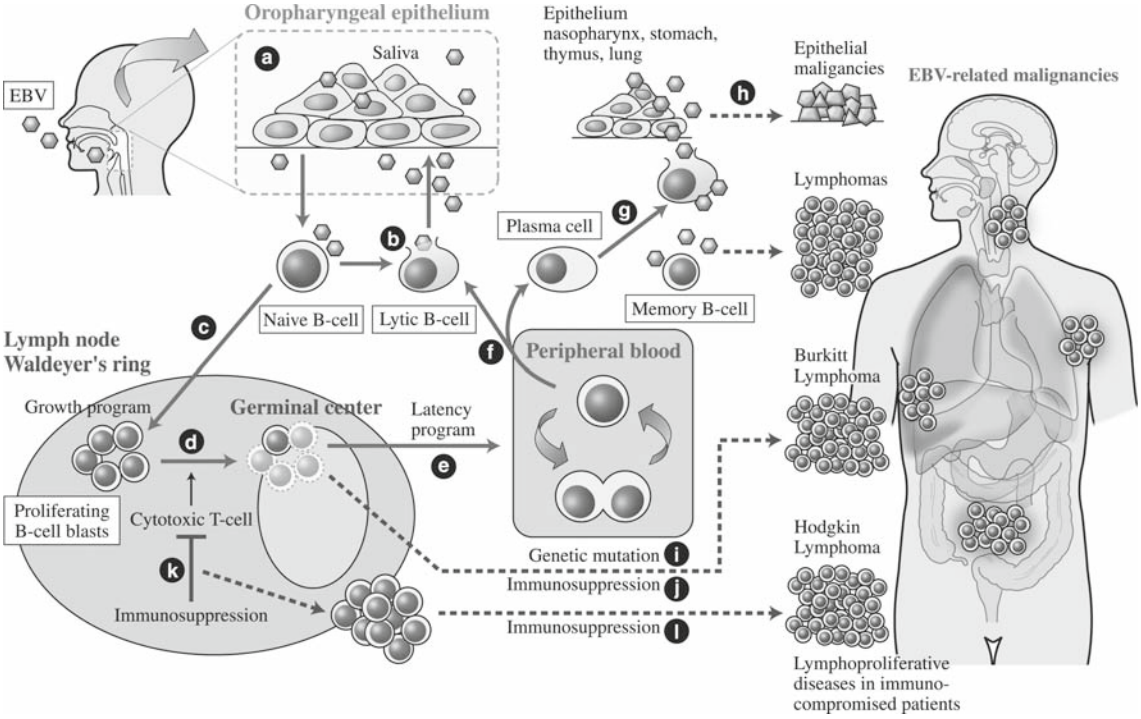

Fig. 1. Epstein-Barr virus (EBV) infection and pathogenesis of EBV-related diseases. EBV is transmitted from host to host via saliva. The virus primarily infects oropharyngeal epithelium or naive B cells infiltrating mucosa (**a**). EBV-infected B cells enter either the lytic cycle or the latent cycle. In the lytic cycle, viral particles are reproduced and shed into saliva, again infecting other mucosal cells and lymphocytes (**b**). EBV-infected B cells entering the latent cycle migrate back into the lymphoid tissue (**c**). There, lymphocytes enter the growth program, become blasts, and undergo proliferation. A considerable ratio of the proliferated lymphocytes is eliminated by cytotoxic T cells before and through a germinal center reaction (**d**). Thereafter, the infected B cells express the latency program. In this program, expression of antigen molecules that induce cytotoxic response by infected-B-cell-specific T cells is ceased, and the infected B cells become resting memory B cells (**e**). This way, EBV evades surveillance by the immune system, accomplishing lifelong infection in resting memory B cells. EBV-infected memory B cells persist at a frequency of 1–50/10^6 B cells in the peripheral blood and act as a long-term reservoir for the virus. Occasionally, EBV-infected memory B cells replicate the virus and release infectious viruses into saliva (**f**). Some EBV-infected memory B cells differentiate into plasma cells. The EBV is also released from plasma cells, entering the lytic cycle as they migrate into peripheral tissues (**g**). EBVs released from B cells in the lytic cycle are considered to be the viral source in EBV-related epithelial neoplasms, such as nasopharyngeal and gastric carcinomas (**h**). EBV-associated Burkitt lymphoma is thought to occur when the germinal-center B-cell blasts are stuck at the proliferative stage because of activated c-*myc* oncogene (**i**). EBV-associated Hodgkin's lymphoma is considered to arise from EBV-infected B cells blocked at the germinal center as a result of cellular mutation (**j**). In the immunosuppressive state, lymphocytes that should be destroyed in the germinal center are rescued in the absence of cytotoxic T cells (**k**). This circumstance is thought to give rise to lymphoproliferative diseases in immunocompromised patients (**l**)

Table 2. WHO classification of nasopharyngeal carcinoma and prevalence of EBV in each subtype[10,11]

WHO classification	EBV (+) rate	Incidence (%)			Extensive local growth (%)	Lymph node metastasis (%)
		USA	Japan	Southern China		
Keratinizing SqCC		25	25	2	76	29
Nonkeratinizing carcinoma						
Differentiated	Variable[a]	12	75	3	55	70
Undifferentiated	Almost 100%	63		95		

WHO, World Health Organization; SqCC, squamous cell carcinoma
[a] Almost always positive in endemic areas, often positive in intermediate-incidence areas, occasionally positive in low-incidence areas

cells is known as lymphoepithelioma.[11] The EBV-positive rate varies with the histology of the tumor and the geographic profile (Table 2).[12,13] Nonkeratinizing carcinoma shows a stronger association with EBV than keratinizing carcinoma. Regarding gross morphology, we found no reported difference between keratinizing and nonkeratinizing carcinomas or between EBV-positive and EBV-negative tumors. On the other hand, clinical

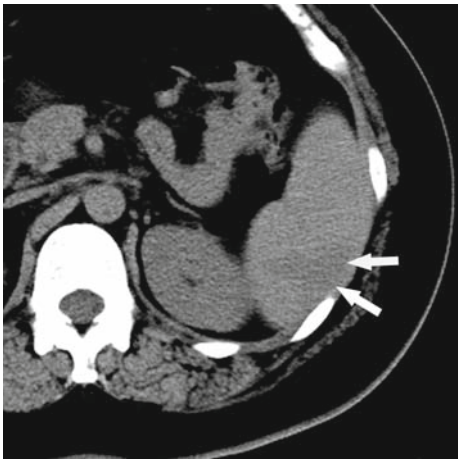

Fig. 2. Splenic infarction in a 29-year-old woman with infectious mononucleosis. The patient presented with fever of 38.9°C (102°F) and acute upper left quadrant pain after 7 days of remittent fever and chills. Noncontrast computed tomography (CT) shows a wedge-shaped area of low density in the dorsal portion of the spleen (*arrows*)

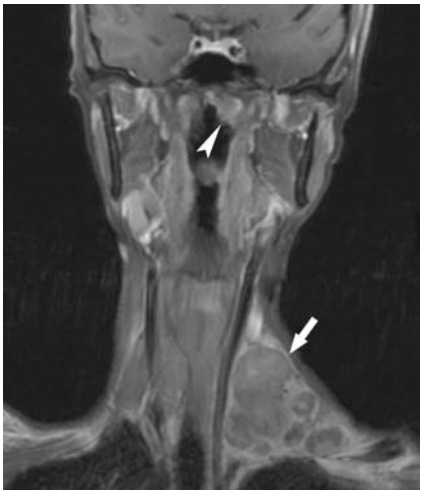

Fig. 3. Biopsy-proven EBV-positive undifferentiated nasopharyngeal carcinoma in a 38-year-old woman with a left supraclavicular mass. She was treated with combined radiotherapy and chemotherapy and has been well without relapse so far. Contrast-enhanced coronal T1-weighted magnetic resonance (MR) image shows massively enlarged left supraclavicular lymph nodes (*arrow*) and a small nodule on the left side of the nasopharynx representing the primary tumor (*arrowhead*)

behavior does differ to some extent between keratinizing squamous cell carcinoma and nonkeratinizing carcinoma (Table 2). Focal or diffuse thickening of the nasopharyngeal mucosa and cervical lymphadenopathy are the most common presentations of nasopharyngeal carcinoma.[14] Keratinizing squamous cell carcinoma shows a higher propensity for locally advanced growth, such as direct infiltration into the skull base or perineural spread toward the cavernous sinus and brain stem. Nonkeratinizing carcinoma is more commonly associated with lymph node metastasis, and even subtle primary tumors can cause extensive lymphadenopathy (Fig. 3).[12]

EBV-associated gastric carcinoma

EBV-associated gastric carcinoma (EBVaGC) occurs worldwide, with the reported incidence varying from 5.2% to 16.0%.[15] EBVaGC constitutes the largest group of EBV-associated malignancies and is now recognized as a distinct entity with distinct molecular and clinicopathological features.[16] Various subtypes show an association with EBV, and more than 80% of lymphoepithelioma-like carcinomas and about 10% of gastric carcinomas not otherwise specified are EBV-associated.[16] Lymphoepithelioma-like carcinoma (also called gastric carcinoma with lymphoid stroma) is a relatively infrequent subtype characterized by an extreme degree of lymphocyte infiltration resembling EBV-associated nasopharyngeal carcinoma.[17]

Regarding clinical features, some authors have reported that EBVaGCs tend to locate in the proximal stomach in contrast to ordinary gastric carcinomas.[18] Multiplicity and remnant carcinoma is common with EBVaGCs,[18] with about 35% of remnant carcinomas found to be associated with EBV.[16] Therefore, for proven or suspected EBVaGC, a thorough endoscopic investigation before deciding the extent of surgical resection as well as careful follow-up with endoscopy and endosonography are warranted.[19,20] Certain morphological features are also linked to the presence of EBV in gastric carcinomas. Early EBVaGCs tend to present as superficial depressed tumors with well-demarcated submucosal nodules at endosonography, reflecting the expansive growth pattern of carcinomas with lymphoid stroma.[20,21] Submucosal EBVaGCs with expansive growth present a significantly larger thickness-to-length ratio than ordinary lesions.[20] A small number of submucosal EBVaGCs are associated with infiltrative growth.[21] A large percentage of the advanced lesions present as ulcerated carcinomas without definite limits, which is thought to represent advanced carcinomas derived from superficial, depressed early EBV-associated lesions.[19] Some form a well-circumscribed mass with a large thickness-to-length ratio, or they may appear as a bulging mass[15] (Fig. 4). The bulky masses may represent the extreme forms of expansive growth and may be a form of a characteristic morphology of advanced EBV-associated gastric carcinomas.

The incidence of lymph node metastasis in EBVaGCs is reported to be lower than in ordinary gastric carcinomas.[16] Reactive hyperplasia is frequent in the regional

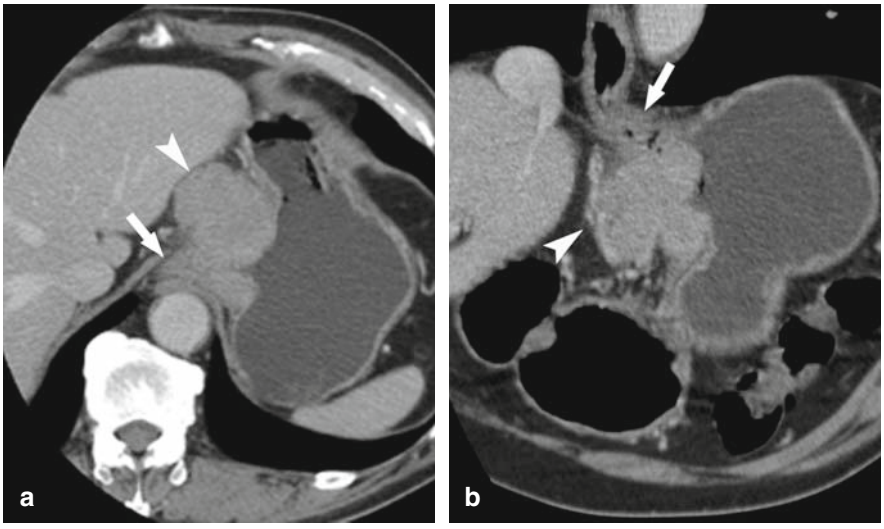

Fig. 4. EBV-associated gastric carcinoma in a 64-year-old man. Reformatted oblique axial image (**a**) and oblique coronal image (**b**) of contrast-enhanced CT scans show circumferential thickening of the junctional area extending into the esophagus (*arrows*) and a bulky portion projecting from the lesser curvature with a clear fat plane around the lesion (*arrowheads*). Despite the extensive appearance of the tumor, there was no serosal involvement on the pathology investigation

Table 3. Comparison of conventional and IPT-like FDC tumor[20,21]

Parameter	Conventional FDC tumor	IPT-like FDC tumor
Sex	No sex predilection	Female predominance
Location	Lymph nodes, extraabdominal extranodal sites	Exclusively intraabdominal
Systemic symptoms	Usually asymptomatic	Common
Clinical behavior	Variable, can be aggressive	Indolent; can be cured surgically
EBV	<4%	Always positive
Histology	Storiform, fascicular, and diffuse growth with a sprinkling of lymphocytes	Inflammatory pseudotumor-like morphology tumor cells with prominent infiltration of inflammatory cells and more dispersed tumor cells

IPT, inflammatory pseudotumor; FDC, follicular dendritic cell

lymph nodes of EBVaGCs regardless of the presence or absence of metastasis.[21] EBVaGCs are associated with a better prognosis than ordinary gastric carcinomas—irrespective of the presence of lymph node metastasis.[16] In summary, location in the upper part of the stomach, a large thickness-to-length ratio, and a bulky portion projecting from the gastric wall suggests the presence of EBV in gastric carcinoma.

Mesenchymal malignancies

Follicular dendritic cell sarcoma/tumor

Follicular dendritic cell (FDC) sarcoma/tumor is a rare neoplasm characterized by neoplastic proliferation of spindle to ovoid cells showing morphological and phenotypic features of FDCs, the cells that function as antigen-presenting cells.[22] FDC sarcomas/tumors (conventional FDC tumors), as a whole, present in lymph nodes in one-half to two-thirds of cases, with the cervical nodes being the most common site.[22] A wide variety of extranodal sites have been reported, such as the tonsil, spleen, oral cavity, gastrointestinal tract, liver, soft tissue, skin, and breast.[22] FDC tumors occur in association with the hyaline vascular-type Castleman's disease in 10%–20% of cases.[22] Systemic symptoms are uncommon in extraabdominal tumors. However, intraabdominal FDC tumors constitute a form of true neoplastic inflammatory pseudotumor with prominent infiltration of inflammatory cells and more dispersed tumor cells. Such a variant, inflammatory pseudotumor (IPT)-like FDC tumor, forms a distinct clinicopathological entity; it is usually accompanied with systemic symptoms and is invariably associated with EBV. The differences between conventional and IPT-like FDC tumors are summarized in Table 3.

FDC sarcomas/tumors form a solitary round or ovoid circumscribed mass with pushing borders rather than permeative borders[23] (Fig. 5). The IPT-like FDC tumor is reported to be a hepatosplenic tumor 3.5–22.0 cm in size.[24] IPT-like FDC tumors have a tan-colored cut surface and typically present with irregular patchy areas of necrosis or hemorrhage, which can be extensive.[24] The IPT-like FDC tumor appears as a solitary, well-circumscribed low-density mass on plain and con-

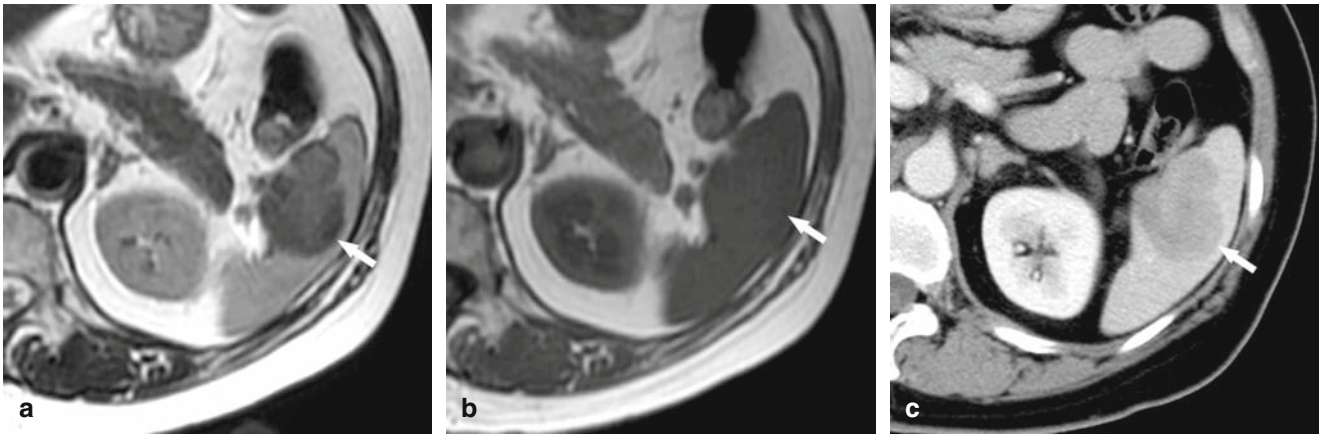

Fig. 5. EBV-associated splenic follicular dendritic cell tumor in a 57-year-old woman. The splenic mass was incidentally discovered during a routine abdominal ultrasonography examination. **a** This T2-weighted MR image shows a lobulated splenic mass hypointense to the spleen (*arrow*). **b** The T1-weighted MR image shows a lobulated splenic mass isointense to the spleen (*arrow*). **c** Contrast-enhanced CT scan shows the mass with less prominent enhancement than the spleen (*arrow*)

Table 4. WHO classification of Burkitt lymphoma[22]

Type of Burkitt lymphoma	EBV (+) rate (%)	Geographic distribution	Ages	Sites of involvement
Endemic	100	Malaria-endemic areas: Equatorial Africa, Papua New Guinea	4–7 years[a]	Jaws (33%–88%), facial bones Kidneys, iliocecal, ovaries, breasts
Sporadic	5–80	Worldwide	Children, young adults	Typically extranodal Abdominal (especially iliocecal) Jaw involvement less frequent CNS involvement in 13%–47%
Immunodeficiency associated	25–40	Worldwide		Frequently nodal, bone marrow

CNS, central nervous system
[a] It represents 80% of all childhood malignancies in endemic areas

trast CT.[25] At magnetic resonance imaging (MRI), the tumor is characterized by isointensity to splenic parenchyma on T1-weighted imaging, hypointensity to splenic parenchyma on T2-weighted imaging reflecting massive fibrous stroma, and delayed enhancement.[25]

Lymphoid malignancies

Burkitt lymphoma

Burkitt lymphoma (BL) is a highly aggressive B-cell lymphoma. All cases are associated with translocation of the *myc* oncogene into the region of active immunoglobulin gene-regulating elements. There are three clinical variants of BL, with different clinical, morphological, and biological characteristics: endemic BL, sporadic BL, and immunodeficiency-associated BL.[26,27] Each variant shows different positivity for the EBV (Table 4).

Endemic BL, as the name suggests, is the most common subtype of BL in malaria-endemic areas and is invariably associated with EBV. Involvement of the jaw is quite common in endemic BL, with a reported incidence of 33%–88%.[28] Other sites of frequent involvement include other facial bones, distal ileum, cecum, omentum, ovaries, kidneys, and breast.[26] In the areas where malaria is not endemic, sporadic BL is the ordinary subtype, and EBV is identified less frequently in sporadic BL.[29] The most frequent site of involvement is the ileocecal region, more specifically Peyer patches. The patients commonly present with abdominal masses in a form of either a well-circumscribed discrete mass or a diffuse ill-defined mass[30] (Fig. 6). Rapid growth of the abdominal mass often results in intestinal or urinary obstruction. Other abdominal CT findings include ascites, splenomegaly, hepatic lesions, renal abnormalities, and a thickened gastric wall.[30] Jaws, the most common site of involvement in endemic BL, are less frequently involved in

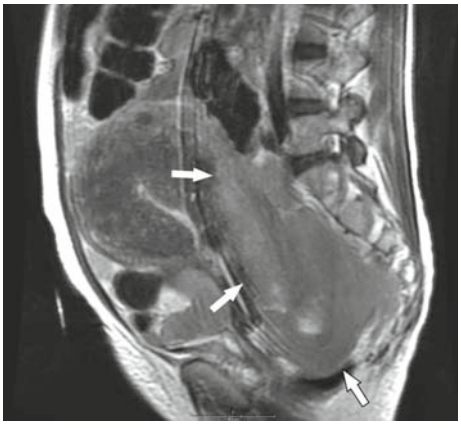

Fig. 6. EBV-positive sporadic Burkitt lymphoma in a 52-year-old woman. She was treated with chemotherapy, which resulted in a complete response. Sagittal T2-weighted MR image shows a soft tissue mass of heterogeneous intensity filling the pouch of Douglas (*arrows*). The border between the mass and uterus, which is enlarged with adenomyosis, is ill-defined

sporadic BL. In contrast to other non-Hodgkin's lymphomas, nodal presentation is uncommon with both endemic and nonendemic BLs.[26] In contrast, the presentation of immunodeficiency-associated BL, which usually occurs in association with the human immunodeficiency virus (HIV), is frequently nodal, commonly with bone marrow involvement.

Burkitt lymphoma is known to be the fastest growing tumor in humans, with a potential doubling time of 24 h. Therefore, the disease can rapidly result in airway compromise, cavernous sinus invasion, spinal cord compression, or other serious sequelae. Despite its aggressiveness, BL is highly sensitive to chemotherapy and its endemic and sporadic variants are potentially curable. At presentation, BL patients are found be in the localized stages in 30% of cases and in advanced stages in 70% of cases.[26] Treatment should be started as soon as possible owing to the high tumor burden of BL. Therefore, on the diagnosis of suspicious facial or abdominal lymphoma in children and young adults, radiologists should initiate a thorough investigation for disseminated disease.

Lymphomatoid granulomatosis

Lymphomatoid granulomatosis (LYG) is a rare lymphoproliferative disease characterized by a predominantly lymphocytic angiocentric and angiodestructive infiltrative process with accompanying plasma cells, histiocytes, and atypical reticuloendothelial cells.[31] The proliferating lymphocytes are B cells and are always infected with EBV, whereas EBV is absent in reactive T cells, which are usually present in higher numbers.[32] The proportion of EBV-positive B cells relative to the reactive lymphocyte background reflects the histological grade, and aggressive chemotherapy may be indicated for high-grade LYG lesions with marked proliferation of EBV-positive lymphoid cells. LYG can progress to malignant lymphoma in 12%–47% of patients and is often fatal.[33,34] Patients in an immunosuppressive condition are at increased risk of developing LYG.[34]

Lymphomatoid granulomatosis primarily presents in extranodal sites. The lungs are always involved, with other common sites being the CNS, skin, kidney, liver, lymph nodes, and bone marrow.[33] The patients have symptoms such as fever, cough, malaise, weight loss, shortness of breath, neurological symptoms, and chest pain.[31]

Lymphomatoid granulomatosis tends to affect the subintimal region of medium-sized arteries and veins, ultimately causing infarction, coagulative necrosis, and sometimes hemorrhage. In the lungs, the common findings are poorly marginated nodules and masses distributed along the bronchovascular bundle and interlobar septa (Fig. 7a).[35,36] Coagulative necrosis can cavitate the nodules, and resultant fibrosis can cause irregular linear opacities and architectural distortion.[36] In the CNS, the most common findings are multiple punctate and linear lesions of a few millimeters in diameter in the white matter of the cerebrum and cerebellum, basal ganglia, midbrain, and spinal cord, diffusely distributed along medullary vessels (Fig. 8). The lesions are usually hyperintense on T2-weighted MRI scans and often enhance on postcontrast images. Differential diagnoses of multiple punctate or linear enhancement include sarcoidosis, primary angiitis, granulomatous angiitis (Churg-Strauss syndrome), and intravascular lymphomatosis.[37] Other imaging findings include abnormal leptomeningeal and cranial nerve enhancement, enlargement and intense enhancement of the choroid plexus, and enhancing intracranial masses.[38] Nodular, necrotizing lesions are also found virtually throughout the body, including the kidneys, liver, spleen, and soft tissue (Fig. 7b,c).[31,34]

Pyothorax-associated lymphoma

Long-standing chronic empyema can be associated with non-Hodgkin's lymphoma and various other neoplasms, such as squamous cell carcinoma, mesothelioma, malignant fibrous histiocytoma, liposarcoma, rhabdomyosarcoma, angiosarcoma, and hemangioendothelioma.[39] Pleural lymphoma is reported to develop in 2.2% of patients with chronic empyema.[40] Pyothorax-associated lymphoma (PAL) is clinically aggressive and develops 22–55 years after formation of pyothorax.[41,42] The cause of pyothorax is tuberculosis in about three-fourths of the cases, although the cause is unknown in some cases.[39]

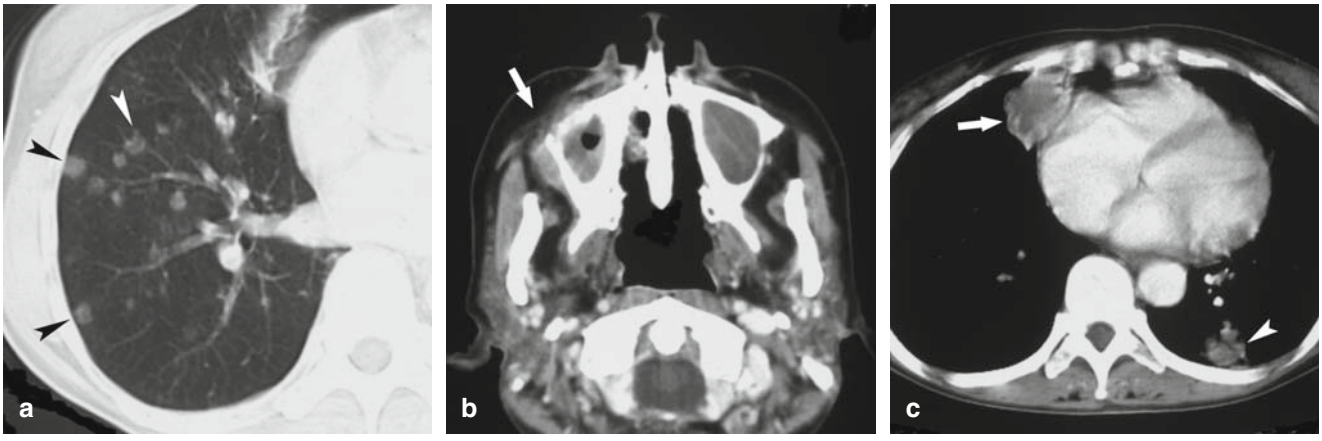

Fig. 7. EBV-positive lymphomatoid granulomatosis (LYG) in a 54-year-old woman. She was treated with chemotherapy. She has been well after a relapse followed by spontaneous regression. **a** CT of the chest in the lung window shows multiple ground-glass nodules in the right lower lobe (*arrowheads*). There was also an irregular mass seen with an air bronchogram in the right middle lobe (not shown). The pulmonary lesions of LYG typically involve the mid and lower lung fields. **b** Contrast CT of the face shows a bone-destructive mass involving the right maxillary sinus (*arrow*). **c** Contrast CT of the chest shows a pericardial mass with moderate peripheral enhancement (*arrow*). A pulmonary lesion is also seen in the left lung base (*arrowhead*)

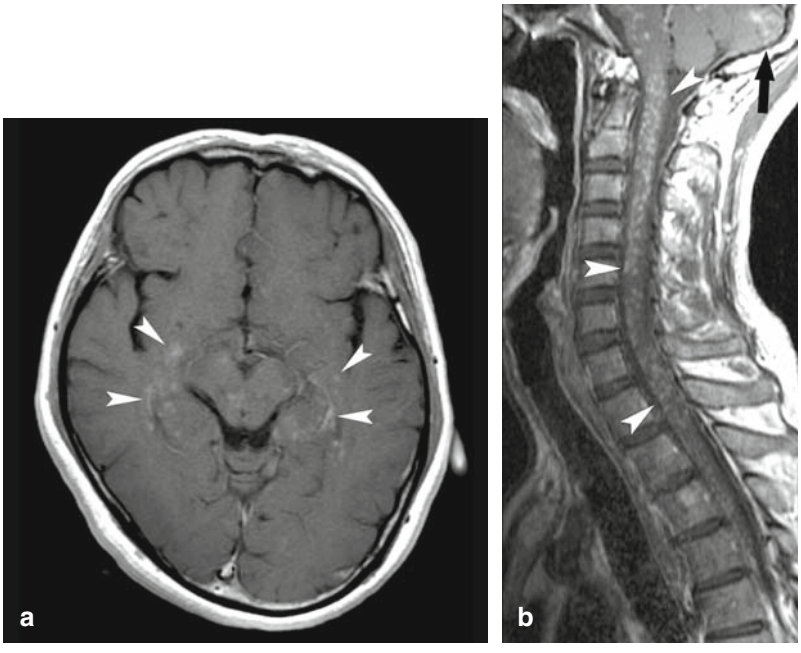

Fig. 8. Lymphomatoid granulomatosis in a 48-year-old man. **a**, **b** Contrast-enhanced axial T1-weighted MR images of the brain and sagittal T1-weighted MR images of the cervical spine show multiple punctate enhancing lesions in the white matter of the cerebrum (*arrowheads*), basal ganglia, midbrain, cerebellum (*arrow*), and spinal cord (*arrowheads*)

Male predominance has been reported, and artificial pneumothorax is known to be a strong risk factor for the development of PAL.[43] Owing to the high prevalence of tuberculosis and treatment with artificial pneumothorax in the past, most of the PAL cases have been reported in Japan. Patients present with pain in the chest, back, or shoulder; respiratory symptoms such as productive cough and dyspnea; and a chest wall mass.[42] EBV is found in almost all cases of PAL, whereas it is usually negative in patients with ordinary chronic empyema.[41,42]

Pyothorax-associated lymphoma is demonstrated as a soft tissue mass around an empyema (Fig. 9). It may cause osteolytic expansile lesions or bone erosion in the ribs. Important differential diagnoses include exacerbation of an empyema, especially empyema necessitatis, and soft tissue involvement of tuberculosis of the ribs or the chest wall; however, the differential diagnosis is often difficult because PAL infrequently infiltrates adjacent organs and demonstrates extensive necrosis or cystic degeneration.[41,44] Biopsy is necessary to confirm the diagnosis; and CT, MRI, and positron emission tomography

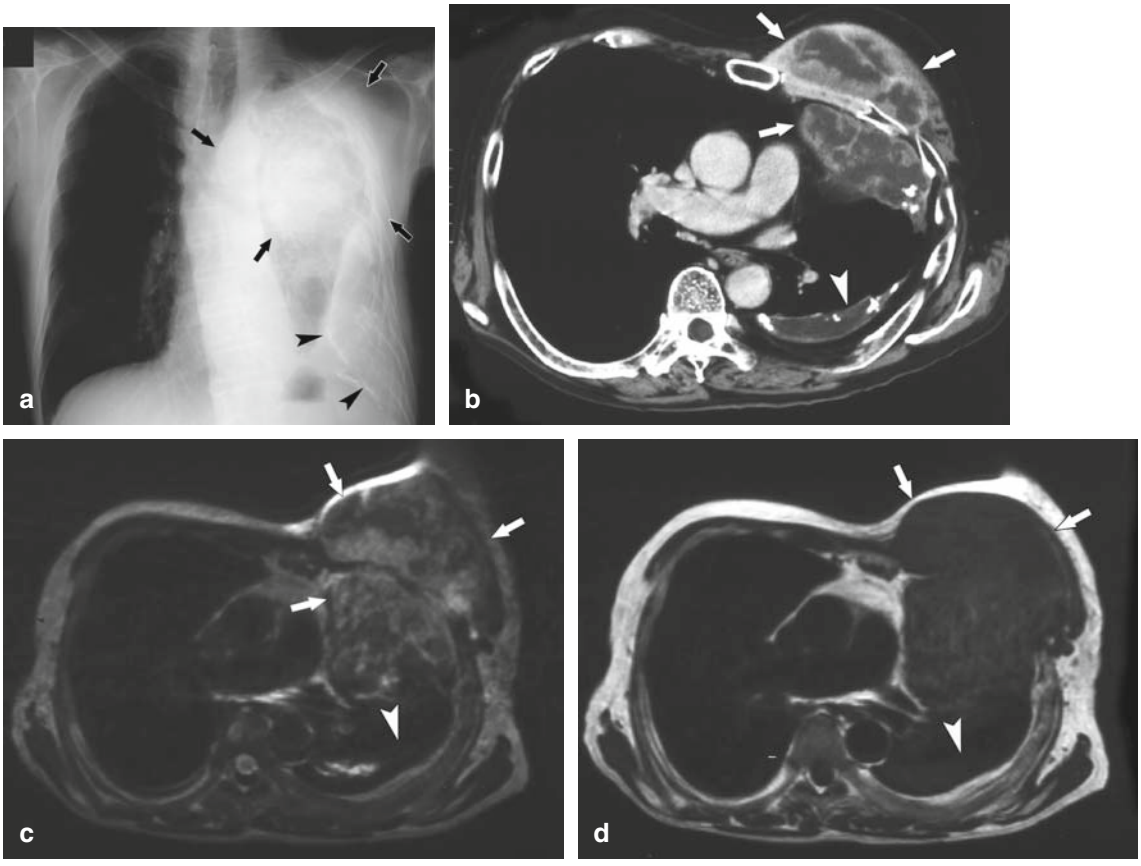

Fig. 9. Pyothorax-associated lymphoma in a 68-year-old man. The mass was painless and was firmly attached to the left chest wall. He had undergone artificial pneumothorax for tuberculous pyothorax 46 years ago. A diffuse, large B-cell lymphoma was confirmed at biopsy. **a** Chest radiograph shows a dense opacity in the left upper and middle lung fields with axillary opacification, indicating a chest wall mass (*arrows*). It is associated with pyothorax, which is demonstrated as a left inferior pleural mass with peripheral calcification (*arrowheads*). **b** Contrast CT shows a heterogeneously enhancing mass in the chest wall (*arrows*). The mass bulges out to both sides of the chest wall (*arrowhead*). The posterior portion of the mass with calcification had continuity with a pyothorax (not shown). **c** T2-weighted MR images shows a chest wall mass with heterogeneous signal intensity (*arrows*) and associated pyothorax (*arrowhead*). **d** T1-weighted MR images show a chest wall mass with heterogeneous signal intensity (*arrows*) and associated pyothorax (*arrowhead*). The bone marrow of the spine and ribs is also involved

(PET) with 2-[fluorine-18] fluoro-2-deoxy-D-glucose (FDG) are highly useful in evaluating the location and the amount of viable tumor cell.[45–47] Extrathoracic involvement affecting approximately half of the PAL cases tends to be extranodal, with reported sites being the brain, heart, stomach, adrenal gland, spleen, liver. and pancreas.[42,48]

Lymphoproliferative disorders in immunocompromised patients

Epstein-Barr virus is associated with an increase in incidence of various forms of lymphoproliferative disorders (LPDs) in immunocompromised patients. Loss of immune surveillance of EBV-driven B-cell transformation leads to LPDs. The abnormal proliferation of lymphoid cells ranges from benign hyperplasia causing IM-like syndrome to aggressive malignant lymphoma. LPDs in different clinical settings of immunodeficiency are constituted of different categories of neoplasms with variable prevalence of EBV.[49]

LPD in HIV patients

Patients with HIV infection are at a 60- to 200-fold risk of developing various lymphomas.[49] Lymphoma is the first acquired immunodeficiency syndrome (AIDS)-defining illness in 3%–5% of HIV patients.[49] A significant relation is known to exist among HIV disease status, subtypes of HIV-associated lymphoma, and EBV positivity (Table 5). The overall positivity of EBV in HIV-related lymphomas is about 60%.

HIV-related lymphomas tend to involve extranodal tissues, in particular the gastrointestinal tract, lungs,

Table 5. Immunological and EBV status in AIDS-related lymphomas[45,47]

Histology	Host's immunodeficiency	Incidence among HIV(+) patients (%)	EBV(+) rate (%)
Systemic AIDS-related lymphomas			
Burkitt lymphoma	Mild		
Classic BL		30	30
BL with plasmacytoid differentiation		20	50–70
Atypical BL		Less frequent	30–50
Diffuse large B-cell lymphoma			
Centroblastic type	Mild	25	30–40
Immunoblastic type	Marked	10%	90
AIDS primary CNS lymphoma—immunoblastic type (mostly)	Marked		100
Primary effusion lymphoma (PEL)	Marked	<5% of NHLs	90
Plasmablastic lymphoma of the oral cavity			>50

AIDS, acquired immunodeficiency syndrome; BL, Burkitt lymphoma; NHL, non-Hodgkin's lymphoma

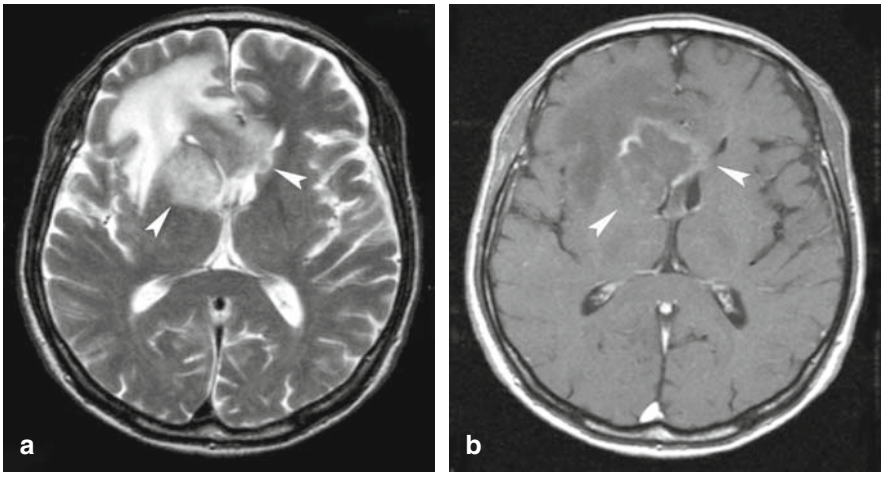

Fig. 10. Human immunodeficiency virus (HIV)-associated lymphoproliferative disease in a 66-year-old man. Stereotactic biopsy of the brain was performed, and the lesion proven to be EBV-positive diffuse large B-cell lymphoma. **a** T2-weighted MR image shows a heterogeneous mass in the head of the right caudate nucleus and the genu of corpus callosum (*arrowheads*). The lesion is associated with edema in the right frontal lobe. **b** Contrast T1-weighted MR image after administration of gadolinium shows peripheral enhancement in the mass in the head of caudate nucleus and the genu of corpus callosum (*arrowheads*)

liver, CNS, and bone marrow. The overall incidence of EBV-positive cells in HIV-related lymphomas is about 60%, but the incidence varies with the site and the subtype of lymphoma (Table 5).[49,50]

Primary HIV-related CNS lymphomas display imaging features unusual for CNS lymphomas in the general population; they mostly present as heterogeneous or ring-like enhancing lesions, typically isointense to gray matter on T2-weighted MR images, with perilesional edema and rapid progression[51] (Fig. 10). The lesions are often multifocal and frequently involve the basal ganglia, deep white matter, and periventricular regions. Differentiating HIV-related CNS lymphoma from toxoplasmosis, the most common HIV-related CNS infection, is often difficult and requires brain biopsy.

Primary effusion lymphoma (PEL) is a peculiar type of lymphoma affecting immunocompromised patients, especially those with HIV infection.[52] PEL is always associated with human herpesvirus (HHV-8)/Kaposi's sarcoma-associated herpesvirus (KSHV) and is commonly co-infected with EBV.[52] PEL arises in the body cavity and basically presents as a lymphomatous effusion without a contiguous mass, although it can be associated with an extracavitary solid form of lymphoma.[50] The prognosis of PEL is extremely poor. On imaging studies, PEL cannot be distinguished from persistent pleural effusion or ascites due to other causes.

Plasmablastic lymphoma of the oral cavity is another type of lymphoma occurring exclusively in HIV patients. It is a rapidly growing lymphoma localized in the oral cavity or the jaw. EBV is found in more than 50% of cases, but no association with HHV-8/KSHV has been reported.[49]

Posttransplant lymphoproliferative disorder

Posttransplant lymphoproliferative disorder (PTLD) is thought to result from iatrogenic immunosuppression and chronic antigenic stimulation from the engrafted organ after hematopoietic or solid organ transplantation. PTLD includes a wide spectrum of diseases ranging

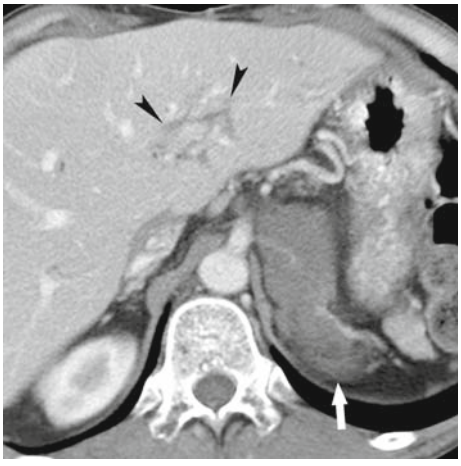

Fig. 11. EBV-positive posttransplant lymphoproliferative disease in a 33-year-old man who underwent cadaveric liver transplantation for primary sclerosing cholangitis. Contrast CT shows an ill-defined homogeneous mass along the splenic artery (*arrow*) and an ill-defined periportal mass in the grafted liver (*arrowheads*)

from polyclonal reactive lymphoid hyperplasia to monoclonal malignant lymphoma. About 80% of PTLDs are associated with EBV. The overall incidence of PTLD is about 1% in patients with hematopoietic cell transplantation and less than 2% in those with solid-organ transplantation: The former develops within the first 5 months, whereas the latter develops up to 5 years later (mean 48 months).[49] The incidence of PTLD after solid-organ transplant varies depending on the age of the recipient and the types of allograft.[53] In adults, it is more common after lung and small bowel transplantation.[53] PTLD is more common in pediatric patients, largely because children are more likely to be primarily infected with EBV via the graft.[53] The risk of developing PTLD is greatest during the first year after transplantation and declines thereafter.[53]

PTLD after hematopoietic cell transplantation presents as a widespread disease involving nodal and extranodal sites. PTLD after solid-organ transplantation frequently involves the allograft itself, which suggests a role of chronic antigen stimulation in the graft regarding lymphomagenesis[1] (Fig. 11). Other sites are also frequently involved, such as the gastrointestinal tract, liver, lungs, lymph nodes, bone marrow, skin, and CNS[49] (Fig. 11). The disease is limited to a single site in two-thirds of patients.[53] Systemic presentation of PTLD is variable; it includes fever (50%), lymphadenopathy (30%), weight loss, intestinal perforation (15%), and septic-shock-like systemic disease.[53]

Abdominal involvement is common after transplantation of abdominal organs such as the liver and kidney and the heart. Although PTLD has much in common with HIV-related lymphoma, hepatic involvement is more common with PTLD, whereas gastrointestinal lesions predominate with HIV-related lymphoma.[54] Patients present with abdominal pain, hepatosplenomegaly, gastrointestinal bleeding, jaundice, and an abdominal mass.[54] At CT, hepatic involvement manifests as one to more than twenty 1- to 4-cm low-attenuation nodules, a diffuse geographic or ill-defined infiltrate with hepatomegaly, or hilar involvement with soft tissues.[54] Splenic involvement usually presents as splenomegaly and occasionally with hypoattenuating lesions.[54] Gastrointestinal involvement manifest as circumferential wall thickening, aneurysmal dilatation of the involved loops, luminal excavation or ulceration, an eccentric polypoid mass, extramural extension, and intussusception.[54]

Renal PTLD tends to be unilateral and unifocal, more commonly affecting the native kidney rather than the graft.[54] The lesion appears as a round parenchymal hypoattenuating mass with a mean diameter of 3 cm.[54] A less common presentation is a diffuse infiltrate causing enlargement of the affected kidney, extending beyond the renal capsule.[54] Lymphadenopathy appears as a homogeneous 2- to 6-cm mass without necrosis.[54]

Pulmonary involvement tends to be asymptomatic. Intrathoracic involvement with PTLD presents as a solitary or multiple nodules of various sizes with smooth or irregular margins, an alveolar infiltrate, and lymphadenopathy.[55] The nodules predominantly involve middle and lower zones, with peribronchovascular and subpleural distribution.[55] The nodules may have a low-attenuation center, reflecting necrotic lymphoid tissue, and may be accompanied by ground-glass opacities that correlate with more sparse parenchymal infiltration by lymphocytes.[55] Nodules with halos mimic invasive aspergillosis, and alveolar PTLD mimics infection, especially when the disease is multifocal. A pulmonary infiltrate resistant to antibiotic therapy should raise suspicion.

Central nervous system involvement presents with new onset of seizures, focal neurological deficits, and altered mental status.[56] The CNS is affected without evidence of involvement of other organs, and high index of suspicion is required for early detection.[56] Supratentorial lesion of periventricular and subcortical distribution is common.[56] The disease tends to be aggressive, presenting with surrounding edema, hemorrhage, and ring enhancement associated with central necrosis, a feature unusual for CNS lymphoma in the general population.[56] Areas of hypercellularity present as hyperattenuation on noncontrast CT and hypointensity on T2-weighted MR imaging, which can help differentiating the disease from an abscess.[56]

Unlike CNS PTLD, head and neck PTLD is usually associated with thoracic and abdominal PTLD and

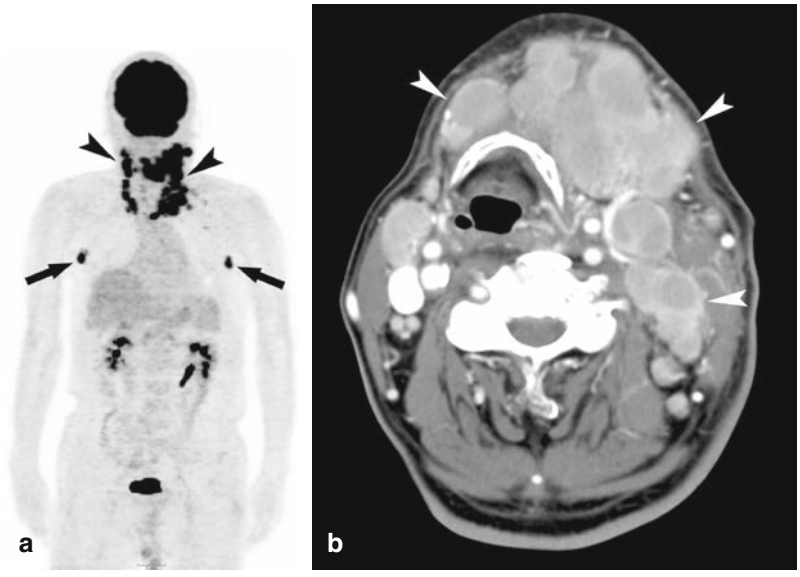

Fig. 12. Senile EBV-positive B-cell lymphoproliferative disorder in a 75-year-old man. He presented with an acutely enlarging cervical mass and was treated with chemotherapy. He has been in complete remission. **a** Positron-emission tomography (PET) image shows uptake of 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG) in the neck (*arrowheads*) and bilateral axilla (*arrows*). **b** Contrast CT of the neck shows conglomerated lymph nodes in the bilateral submandibular and jugular regions (*arrowheads*)

typically presents as a soft tissue mass resembling non-Hodgkin's lymphoma.[56] Head and neck PTLD in children frequently presents as IM-like illness with pharyngitis, tonsillar enlargement, and lymphadenopathy.[56] The differential diagnosis includes infection, especially fungus or cytomegalovirus, rejection, and drug-related toxicity; and clinically or radiologically antibiotic-resistant conditions should raise a suspicion of PTLD. Diagnosis of PTLD should be based on pathological investigation, preferably an excision biopsy specimen.[53]

Reducing immunosuppression to restore EBV-specific immunity, with close monitoring for acute rejection, is the key to successful management of PTLD. Chemotherapy and anti-B-cell antibodies may be used in combination with the reduction in immunosuppression. Surgery may be considered for localized PTLD. PTLD can be lead to remission with reduction in immunosuppression alone in 25%–63% of adults and in 40%–86% of pediatric patients.[53] The prognosis of PTLD not responding adequately to the reduction in immunosuppression is poor, with mortality exceeding 50%.[53]

Senile EBV-associated B-cell LPD

Senile EBV-associated B-cell LPD is a recently reported entity that affects patients over 60 years of age without any underlying immunodeficiency.[57] Age-related decline in EBV-specific cellular immunity may be associated with senile EBV-associated B-cell LPD. Senile EBV-associated B-cell LPD can be divided into two subtypes: large-cell lymphoma subtypes, which are histologically similar to diffuse large B-cell lymphoma, and polymorphic LPD subtypes, similar to Hodgkin's lymphoma, with Hodgkin- and Reed-Steinberg-like giant cells.[57] Both types of tumor often show angiocentric growth and extensive necrosis.[57] Patients present with lymphadenopathy, fever, malaise, and weight loss. Both nodal and extranodal involvement is common (Fig. 12). The large-cell lymphoma subtype has a significantly poorer prognosis than the polymorphic subtype.[57]

Extranodal natural killer cell/T-cell lymphoma, nasal type

Extranodal natural killer (NK) cell/T-cell lymphoma, nasal type, is a clinically aggressive lymphoma that predominantly involves extranodal sites, in particular the nasal cavity. Identical neoplasms primarily arising in other extranodal organs are known as the nonnasal type.[58] Extranodal NK/T-cell lymphoma, nasal type accounts for 45.2% of nasal and nasopharyngeal carcinomas and is the most common immunophenotype in the nasal and nasopharyngeal regions.[59] The reported mean age of patients of extranodal NK/T-cell lymphoma, nasal type is 53 years, which is about 10 years younger than that of B-cell lineage lymphomas arising in the nasal and nasopharyngeal regions.[59] Male predominance has been reported.[58] Extranodal NK/T-cell lymphoma, nasal type is common among Asians, Mexicans, and South Americans.[58] The frequency of extranodal NK/T-cell lymphoma is 2.6%–8.0% of all non-Hodgkin's lymphomas in endemic areas, whereas it is 0.17%–1.50% in Western populations.[59] Furthermore, extranodal NK/T-cell lymphoma, nasal type is almost consistently associated with EBV irrespective of the ethnic origin of the patient.[58,60] In contrast, extranodal NK/T-cell lymphoma

arising in other sites than the nose and nasopharynx shows an association with EBV in Asians, but the association is less clear for Caucasian populations.[58]

The disease with nasal involvement commonly presents with nasal obstruction, swelling, epistaxis, and midfacial destruction. The tumor often grows in an angiocentric fashion, with prominent necrosis and vascular destruction; and it often ends in destruction of the medial region of the face, such as the hard palate, orbit, and nasopharynx (Fig. 13).[58] The disease may be disseminated to the skin and multiple organs, with a reported incidence of 16% (Fig. 14).[60] Lymph nodes are unusual as the site of initial presentation but are usually involved as a part of the disseminated disease. At imaging, nasal involvement present as a soft tissue mass arising from the nasal septum or turbinate. Tumors are typically locally aggressive, with involvement of adjacent bones, hard palate, orbit, and nasopharynx in more than 50% of cases.[61] Nodal involvement is relatively infrequent compared with that of diffuse large B-cell lymphoma, with a reported rate of 23%.[62] Systemic symptoms, such as fever, malaise, and weight loss, may be present in patients with multiorgan involvement.[60] Although the site of the tumor and its destructiveness are suggestive of NK/T-cell lymphoma, nasal type, these features are not specific. A long list of differential diagnoses should be considered: granulomatous disease (e.g., Wegener's granuloma, sarcoidosis), cocaine abuse, other lymphomas, granulomatous infection (e.g., allergic aspergillosis, leprosy, syphilis, tuberculosis), aggressive carcinomas (squamous cell carcinoma, adenoid cystic carcinoma), olfactory neuroblastoma, malignant melanoma, lymphoepithelioma, and rhabdomyosarcoma.[61,63] They cannot be reliably distinguished by imaging studies alone. Clinical information and histological confirmation are essential to confirm the diagnosis.

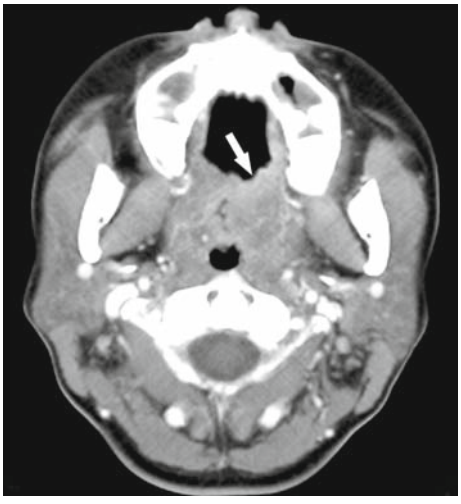

Fig. 13. Natural killer (NK) cell/T-cell lymphoma in a 43-year-old woman. Contrast CT of the face shows a bulky mass replacing the palate (*arrow*). The mass involved the left Rosenmuller fossa, palate, oropharynx, and left piriform sinus. There were associated bilateral deep cervical and accessory adenopathies and left supraclavicular adenopathy (not shown). The patient underwent allogeneic stem cell transplantation. Although she experienced a relapse after transplantation, she had a spontaneous complete remission and has been well ever since

Hodgkin's lymphoma

Hodgkin's lymphoma is a neoplasm of B-cells that usually arises in lymph nodes. It is histologically characterized by unique neoplastic cells called Hodgkin's and Reed-Steinberg cells (Fig. 15). The incidence of Hodgkin's lymphoma has not changed during the last six decades, in stark contrast with the constantly rising incidence of non-Hodgkin's lymphoma.[64]

Hodgkin's lymphoma is classified into two distinct entities: nodular lymphocyte predominant Hodgkin's lymphoma and classic Hodgkin's lymphoma. Nodular lymphocyte predominant Hodgkin's lymphoma makes up 5% of Hodgkin's lymphomas and is usually not

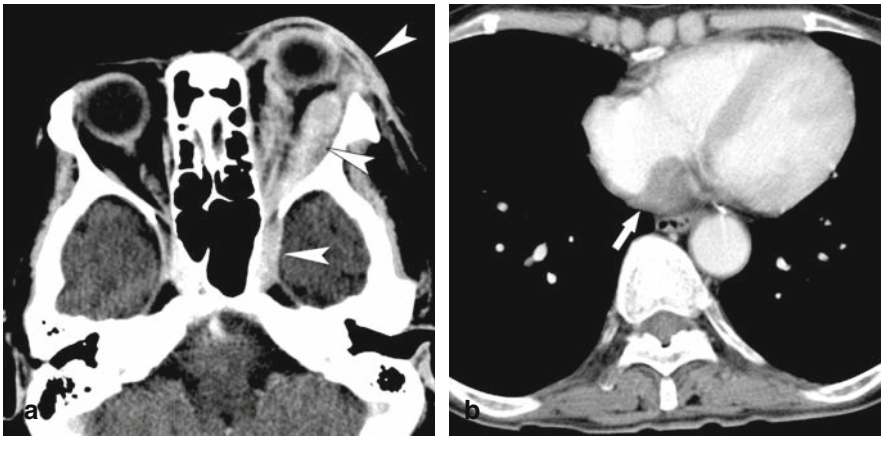

Fig. 14. NK/T-cell lymphoma in a 74-year-old woman who was treated with chemotherapy. **a** Contrast CT of the face shows an ill-defined mass in the left orbit resulting in exophthalmos (*arrowheads*). The tumor extends posteriorly along the rectus muscles into the cavernous sinus through the superior orbital fissure. **b** Contrast CT of the chest shows a mass protruding from the atrial septum into the right atrium (*arrow*)

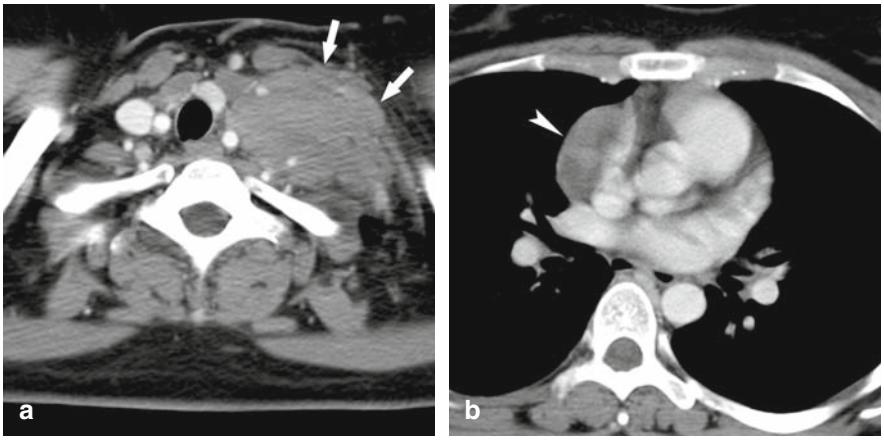

Fig. 15. EBV-positive Hodgkin's lymphoma in a 19-year-old woman. She presented with a neck mass and has been treated with chemotherapy. **a** Contrast CT of the neck shows massive left supraclavicular lymphadenopathy (*arrows*). **b** Contrast CT of the chest shows a convex mass compressing the right atrium (*arrowhead*)

associated with EBV.[65] Geographic differences in affected age and EBV positivity are known for classic Hodgkin's lymphoma. Hodgkin's lymphoma in North America has two age-incidence peaks in young and older adults.[64] Hodgkin's lymphoma is EBV-positive in 30% of the cases: 10%–40% of the nodular sclerosis subtype, the most common subtype, and 75% of the mixed cellularity subtype, the second most common subtype. For Hodgkin's lymphoma in some developing countries and in patients with HIV infection, the young adult peak is less prominent, and EBV is found in more than 90% of the cases.[64–66] The percentage of EBV-positive Hodgkin's lymphomas is reported to be age-dependent.[67] The prognostic significance of EBV status remains controversial, but a survival disadvantage in older EBV-positive patients appears to be consistent.[65,67] The differences in imaging findings of EBV-positive and EBV-negative Hodgkin's disease have not been reported.

Conclusion

Primary EBV infections mostly occur during young childhood and cause no or only nonspecific symptoms, but EBV can cause a wide spectrum of diseases in humans. Primary infections during late adolescence or in adults can manifest as an acute syndrome of infectious mononucleosis. Active infection rarely persists as chronic active EBV infection. EBV resides as a latent form in lymphocytes in the peripheral blood after a primary infection. Lifelong latent infection causes no serious consequences in most cases but sometimes causes various malignancies of epithelial, mesenchymal, or lymphoid tissues, especially in the setting of immunodeficiency. Awareness of lymphoproliferative disorders in immunocompromised patients and their spectrum contributes to early detection of these possibly life-threatening disorders.

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