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

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.
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