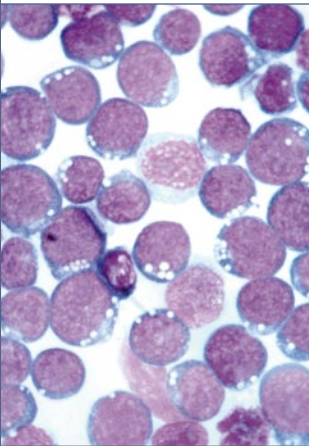


Epstein-Barr Virus Overview

ABOUT THE VIRUS

Epstein-Barr virus (EBV) is an omnipresent member of the Herpesviridae family. It is a linear, double-stranded DNA virus with an icosahedral capsid. EBV is also known as HHV-4. EBV is a member of the Gammaherpesvirinae subfamily, along with HHV-8. The virus was discovered in 1964 by Drs. Epstein and Barr, after whom it was named. The virions which make up EBV are hexagonal nucleocapsids, with a complex surrounding envelope. EBV is most commonly found in B lymphocytes and also in epithelial cells of the nasopharynx. The virus has also been seen in epithelial cells, T lymphocytes, smooth muscle cells and follicular dendritic cells. EBV enters the B lymphocyte and the viral DNA forms a self-replicating circular episome within the cell nucleus. EBV establishes latency in the B lymphocytes following primary infection. As B lymphocytes proliferate, the number of cells available to carry the virus increases. In an immunocompetent individual, specific cytotoxic T lymphocytes control the amount of B cell proliferation. In an immunocompromised patient, a latent EBV infection can reactivate and potentially cause lymphoproliferative disease, which can progress to a malignancy. This is due to a lack of T cells to control the EBV driven proliferation of B cells.



This histological slide, stained with H&E, is of the Epstein-Barr virus.

Courtesy of National Cancer Institute.

CLINICAL MANIFESTATIONS

EBV is the causative agent of heterophile-positive infectious mononucleosis, which is most commonly seen in young adults or older adolescents. In transplant patients, EBV is the most common cause of post-transplant lymphoproliferative disorder (PTLD).

EBV antibodies are found in 90-95% of virtually all populations by the time they reach adulthood. In developed countries, approximately 50% of the population seroconverts before the age of 5. Childhood primary EBV infections are usually asymptomatic. Between the ages of 10 and 20, a second wave of seroconversion typically occurs. When adolescents or adults experience a primary EBV infection, it takes the form of infectious mononucleosis (IM), which most often manifests itself clinically in individuals who are not exposed to EBV until their second decade of life. IM typically presents with sore throat, fever, lymphadenopathy and enlarged spleen. This disease is generally self-limiting and lasts approximately 2-4 weeks. Immunocompetent individuals usually do not experience additional complications, but some develop a chronic, persistent manifestation of the disease which can involve significant organ system dysfunction and last over 6 months.

Immunocompromised patients, such as hematopoietic stem cell transplant (HSCT) patients and solid organ transplant patients, are at risk for EBV-associated lymphoproliferation. EBV-induced proliferation may lead to PTLD. Transplant patients who are seronegative at the time of transplant are at highest risk for PTLD. If patients experience a primary EBV infection while being treated with immunosuppressive drugs, the risk of developing PTLD is dramatically increased. This is particularly common in the pediatric transplant population.

Additional risk factors for development of PTLD in the HSCT population include the intensity and duration of immunosuppressive therapy, unrelated donor, T-cell-depleted allografts, use of antithymocyte globulin and immunosuppression to prevent graft-versus-host disease (GVHD). If lymphoproliferative disease develops in HSCT patients with GVHD, the prognosis is quite poor. The disease can manifest itself in forms ranging from benign polyclonal hyperplasia to malignant lymphoma. HIV patients sometimes develop non-malignant lymphoproliferative diseases, such as follicular hypoplasia, primary lymphoid hyperplasia and oral hairy leukoplakia, as well as lymphoid, muscular and epithelial cell malignancies.

LABORATORY DIAGNOSIS

Heterophile antibodies are present in approximately 90% of the population presenting with IM in the second decade of life. However, in children younger than 5 years of age, the heterophile antibody will often be negative. Testing for these antibodies has been important to the diagnosis of IM. In some cases of IM and other EBV-associated illnesses, testing for EBV-specific antibodies has been shown to be useful. It is important, particularly in the pediatric population, to ascertain the EBV serostatus prior to transplantation, since seronegative patients are at significantly higher risk for PTLD when they acquire an EBV primary infection. Antibody testing is not useful for diagnosis or monitoring of PTLD. Molecular testing methods that facilitate early detection of EBV replication can facilitate early intervention, with the goal of restoring adequate function of the immune system to control EBV replication. For these reasons, real-time quantitative PCR is considered the best option for detecting and monitoring the overall EBV burden (viral load). Although both PBMCs and plasma are useful material for detection of EBV in immunocompromised patients, a higher positive predictive value for PTLD is achieved if plasma is used. Due to the highly sensitive nature of quantitative real-time PCR, latent EBV can be detected when testing specimens containing PBMC, which is not useful for the physician.

TREATMENT

Most cases of IM require only supportive care, as over 95% of patients recover without therapy or complications. Each individual should limit his or her activity level to comfortably tolerable, and heavy lifting should be avoided to prevent spleen ruptures in patients with splenomegaly.

The usefulness of antiviral therapy to treat immunocompromised patients with EBV has not been supported by sufficient clinical evidence to become a frequently recommended option. Acyclovir has benefited some HIV patients with EBV-related diseases, but results in the literature are mixed. Additional agents have been shown to have antiviral activity against EBV, but only in vitro. Rituximab, a chimeric anti-CD20 monoclonal antibody developed for the treatment of B cell lymphoma, has been utilized with some success to curb the proliferation of EBV driven proliferating B cells. Currently, the best approach appears to be restoration of T cell function by reduction of immunosuppression, to as great of an extent as possible. Other experimental approaches that may prove promising include tumor-directed monoclonal antibodies and EBV-specific cytotoxic T cells.

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