Review Article

Medical Progress

EPSTEIN–BARR VIRUS INFECTION

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THE Epstein–Barr virus (EBV) was discovered 36 years ago by electron microscopy of cells cultured from Burkitt's lymphoma tissue by Epstein, Achong, and Barr.[1] Four years later, in 1968, EBV was shown to be the etiologic agent of heterophile-positive infectious mononucleosis.[2] EBV DNA was detected in tissues from patients with nasopharyngeal carcinoma in 1970.[3] In the 1980s, EBV was found to be associated with non-Hodgkin's lymphoma and oral hairy leukoplakia in patients with the acquired immunodeficiency syndrome (AIDS).[4,5] Since then, EBV DNA has been found in tissues from other cancers, including T-cell lymphomas and Hodgkin's disease.[6,7]

EBV is one of the most successful viruses, infecting over 90 percent of humans and persisting for the lifetime of the person. EBV is closely related to viruses present in Old World nonhuman primates, including EBV-like viruses of chimpanzees and rhesus monkeys. For example, the rhesus monkey virus and EBV share similar sequences and genetic organization, and they maintain persistent infection in the oropharynx and in B cells.[8] Thus, EBV probably evolved from a nonhuman-primate virus.

VIROLOGIC FEATURES

Replication

EBV is a member of the herpesvirus family. The viral genome is encased within a nucleocapsid, which is, in turn, surrounded by the viral envelope. Before the virus enters the B cell, the major envelope glycoprotein, gp350, binds to the viral receptor, the CD21 molecule (the C3d complement receptor),[9] on the surface of the B cell. Other factors in addition to CD21 are important for infection. The major-histocompatibility-complex (MHC) class II molecule serves as a cofactor for the infection of B cells.[10] Patients with X-linked agammaglobulinemia lack mature B cells, and their B cells cannot be infected with the virus either in vitro or in vivo.[11]

The EBV genome consists of a linear DNA molecule that encodes nearly 100 viral proteins.[12] During viral replication, these proteins are important for regulating the expression of viral genes, replicating viral DNA, forming structural components of the virion, and modulating the host immune response. Infection of epithelial cells by EBV in vitro results in active replication, with production of virus and lysis of the cell.[13] In contrast, infection of B cells by EBV in vitro results in a latent infection, with immortalization of the cells. After infecting B cells, the linear EBV genome becomes circular, forming an episome, and the genome usually remains latent in these B cells. Viral replication is spontaneously activated in only a small percentage of latently infected B cells.

Infection of humans with EBV usually occurs by contact with oral secretions. The virus replicates in cells in the oropharynx, and nearly all seropositive persons actively shed virus in the saliva.[14] Although earlier studies indicated that the virus replicated in epithelial cells in the oropharynx,[15] and investigators postulated that B cells were subsequently infected after contact with these cells,[16] other studies suggest that B cells in the oropharynx may be the primary site of infection[17,18] (Fig. 1).

Latent Infection

Resting memory B cells are thought to be the site of persistence of EBV within the body.[20] Shedding of EBV from the oropharynx is abolished in patients treated with acyclovir, whereas the number of EBV-infected B cells in the circulation remains the same as before treatment.[21] In addition, the observation that EBV can be eradicated in bone marrow–transplant recipients who have received therapy that ablates their hematopoietic cells, but not their oropharyngeal cells,[22] provides further evidence that B cells are the site of EBV persistence. In normal adults, from 1 to 50 B cells per million in the circulation are infected with EBV, and the number of latently infected cells within a person remains stable over years.[20,23]

Of the nearly 100 viral genes that are expressed during replication, only 10 are expressed in latently infected B cells in vitro.[12] Two types of nontranslated RNA, six nuclear proteins, and two membrane proteins are expressed in these latently infected B cells. By markedly limiting viral gene expression during latency, EBV reduces the number of viral proteins that

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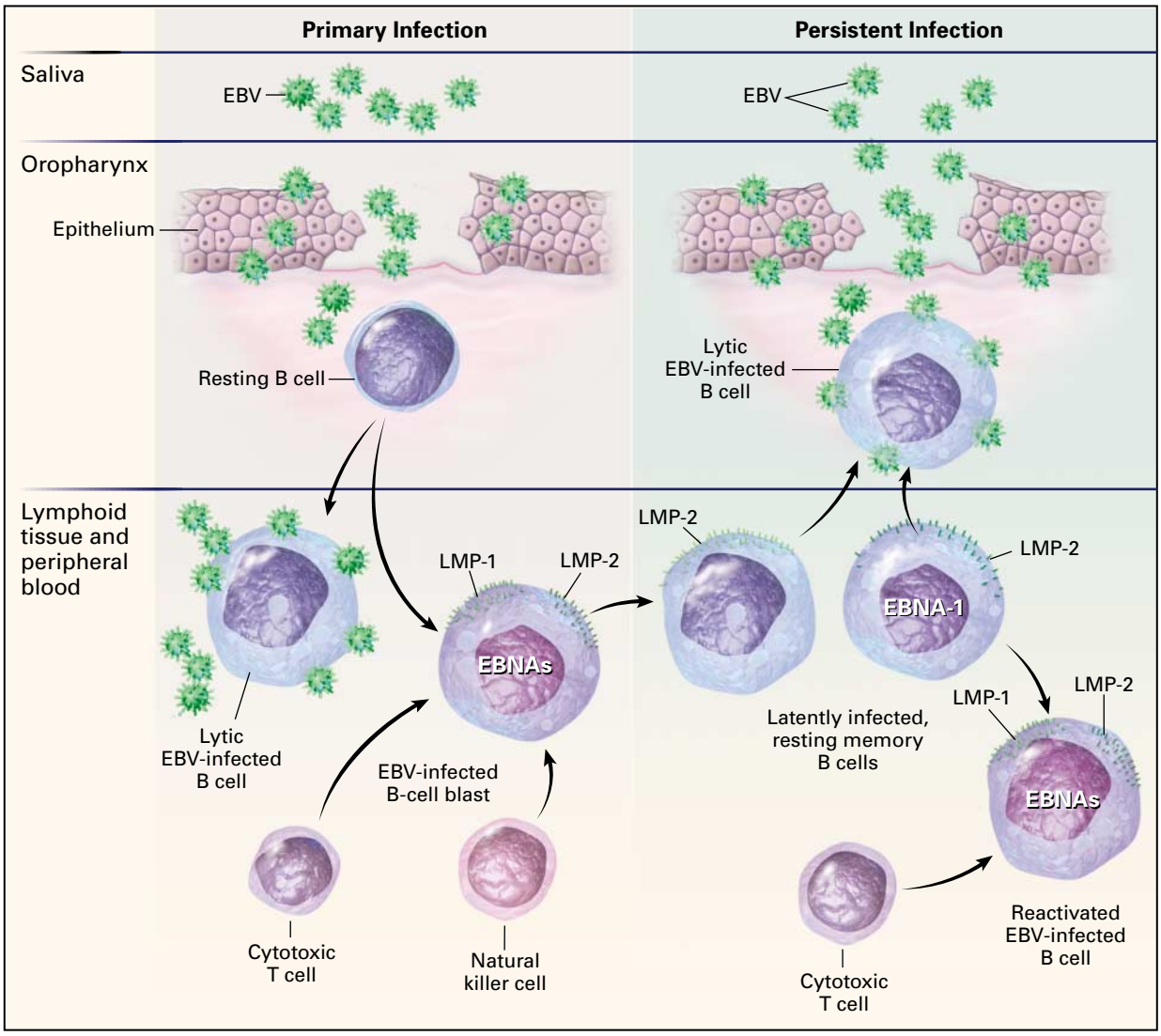

Figure 1. Model of Epstein–Barr Virus (EBV) Infection in Humans.

In the oropharynx, EBV directly infects resting B cells or infects epithelial cells, which in turn infect B cells. During primary infection, EBV-infected B cells undergo lytic infection with production of virus or express the full complement of latent viral proteins. The latter cells are kept in check by natural killer cells and cytotoxic T cells. After convalescence, EBV is present in the peripheral blood in latently infected memory B cells that express latent membrane protein (LMP) 2 and possibly EBV nuclear antigen (EBNA) 1. The latter cells can undergo EBV reactivation and express other latent viral proteins, resulting in their recognition and destruction by cytotoxic T cells. Some latently infected cells undergo lytic replication in the oropharynx, resulting in production of virus with shedding of virus into the saliva or infection of epithelial cells with release of virus. Adapted from Cohen with the permission of the publisher.[19]

permit the recognition of infected cells by cytotoxic T cells.

The EBV nuclear antigen (EBNA) 1 protein binds to viral DNA and allows the EBV genome to be maintained in the B cell as a circular DNA episome (Fig. 2A).[24] EBNA-2 up-regulates the expression of EBV latent membrane protein (LMP) 1 and LMP-2, as well as cellular proteins that contribute to the growth and transformation of B cells.[25] The EBNA-3 proteins also regulate the expression of cellular genes,[26] whereas EBNA leader protein augments the ability of EBNA-2 to up-regulate LMP-1.

LMP-1 acts as an oncogene,[27] and expression of this protein in transgenic mice results in B-cell lymphomas.[28] LMP-1 induces a signaling response in cells that mimics a constitutively active form of the B-cell–surface molecule CD40.[29] LMP-1 binds to several of the tumor necrosis factor receptor–associated factors

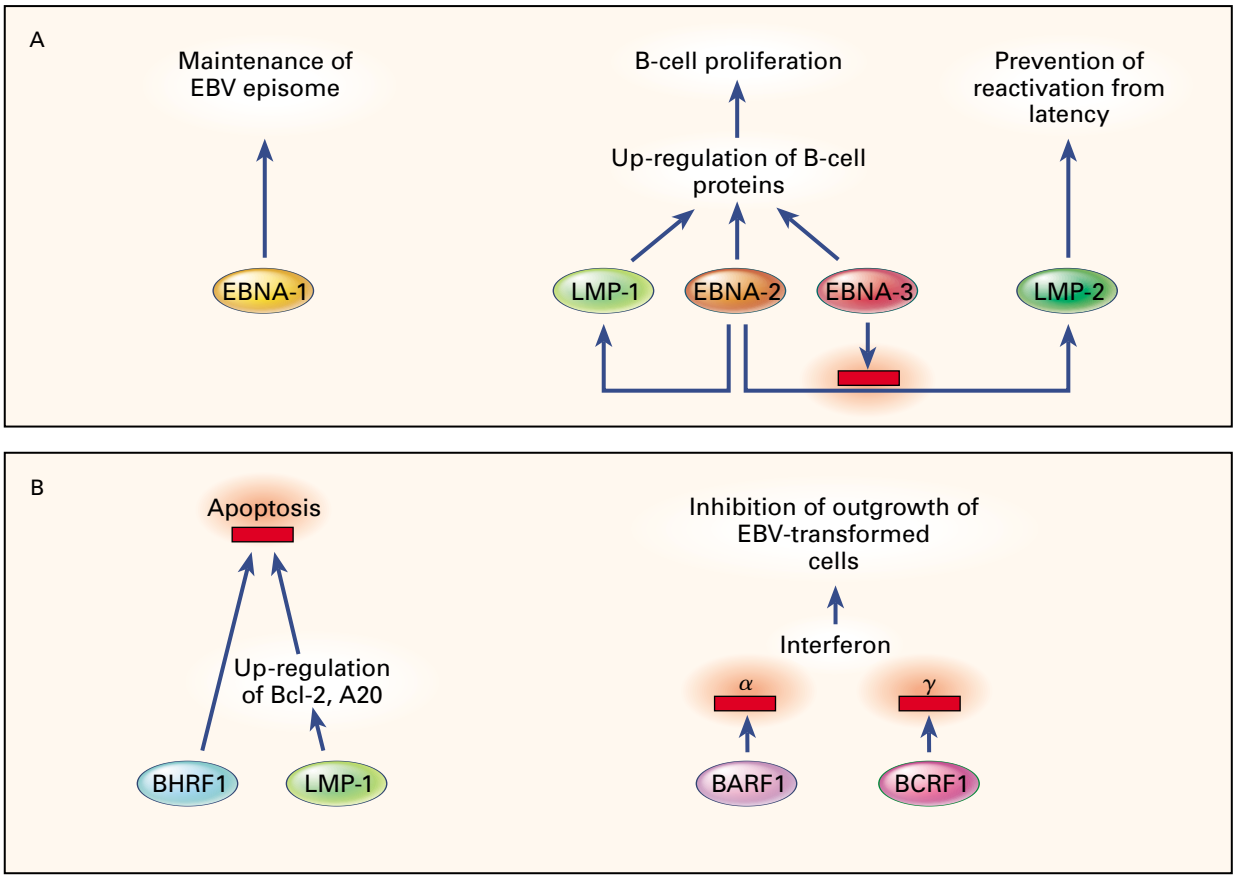

Figure 2. Activities of Selected Epstein–Barr Virus (EBV) Proteins That Are Important for Latent Viral Infection (Panel A) or Evasion of Host Immune Responses (Panel B).

In Panel A, EBV nuclear antigen (EBNA) 2 up-regulates the expression of latent membrane proteins 1 and 2 (LMP-1 and LMP-2, respectively). EBNA-3 is a set of three proteins: EBNA-3A, EBNA-3B, and EBNA-3C. EBNA-3B and EBNA-3C up-regulate the expression of some B-cell proteins, and all three EBNA-3 proteins inhibit the ability of EBNA-2 to up-regulate the expression of LMP-2. Panel B shows proteins that inhibit apoptosis or block the ability of interferon to inhibit the outgrowth of EBV-transformed B cells. Red bars indicate inhibition of activity.

both in vitro[30] and, in EBV-positive lymphomas, in vivo.[31] These activities result in activation of the nuclear factor-κB (NF-κB) transcription factor in vitro and in vivo, activation of c-*jun*, up-regulation of cellular adhesion molecules, cytokine production, and B-cell proliferation.

EBV LMP-2 prevents reactivation of EBV from latently infected cells by blocking tyrosine kinase phosphorylation.[32] Expression of LMP-2 in transgenic mice allows nontransformed B cells to survive even in the absence of normal B-cell–receptor signaling.[33] The nontranslated types of EBV-encoded RNA (EBER) do not encode proteins, but they may be important for oncogenesis and resistance to programmed cell death, or apoptosis.[34] Another viral RNA, BARF0, has been detected in latently infected B cells.[12] EBV-associated diseases generally show viral gene expression limited to one of three patterns of latency[35] (Table 1). In the first form, only EBNA-1 and EBER are expressed, whereas in the second form, EBNA-1, LMP-1, LMP-2, and EBER are expressed. In the third pattern, all the latency genes are expressed. A fourth pattern of latency is seen in B cells obtained from the peripheral blood of healthy persons infected with EBV in the past, in which only EBER and LMP-2, and in some studies, EBNA-1 RNA have been detected.[36]

IMMUNE RESPONSE TO EBV AND EVASION OF THE IMMUNE SYSTEM BY THE VIRUS

Infection of humans with EBV results in both humoral and cellular immunity to the virus. Although the finding of antibodies directed against viral structural proteins and the EBNAs is important for the diagnosis of infection, the cellular immune response is more important for the control of EBV infection.

TABLE 1. EXPRESSION OF EBV LATENT GENES IN DISEASE.*

PATTERN OF LATENCY	EBNA-1	EBNA-2	EBNA-3	LMP-1	LMP-2	EBER	DISEASE
Type 1	+	−	−	−	−	+	Burkitt's lymphoma
Type 2	+	−	−	+	+	+	Nasopharyngeal carcinoma, Hodgkin's disease, peripheral T-cell lymphoma
Type 3	+	+	+	+	+	+	Lymphoproliferative disease, X-linked lymphoproliferative disease, infectious mononucleosis
Other	±	−	−	−	+	+	Healthy carrier

*EBV denotes Epstein–Barr virus, EBNA Epstein–Barr virus nuclear antigen, LMP latent membrane protein, and EBER Epstein–Barr virus–encoded RNA. A plus sign indicates that the gene is expressed in the disease, a minus sign that it is not expressed, and the two together that the gene may or may not be expressed.

Natural killer cells and CD4+ and CD8+ cytotoxic T cells control proliferating EBV-infected B cells during primary infection.[37] In infectious mononucleosis, up to 40 percent of CD8+ T cells are targeted to one replicative EBV protein sequence, whereas 2 percent are targeted to one latent EBV protein sequence.[38] After recovery from acute infection, HLA-restricted cytotoxic T cells are important in controlling EBV, and CD8+ T cells are targeted to similar percentages of replicative and latent antigens.[39] Many of the cytotoxic-T-cell responses directed against latent proteins are targeted to the EBNA-3 proteins.

The ability of EBV to persist, despite potent immune effector responses against it, indicates that the virus has evolved strategies to elude the immune system. EBV encodes a cytokine and a cytokine receptor that may be important for modulating the immune system to allow persistent infection. The EBV BCRF1 protein shares 70 percent of its amino acid sequence with interleukin-10.[40] The BCRF1 protein mimics the activity of interleukin-10 by inhibiting interferon-γ synthesis by human peripheral-blood mononuclear cells in vitro (Fig. 2B).[41] The EBV BARF1 protein functions as a soluble receptor for colony-stimulating factor 1. Since colony-stimulating factor 1 normally enhances the expression of interferon-α by monocytes, BARF1 protein may function as a decoy receptor to block the action of the cytokine.[42] Because interferon-γ and interferon-α inhibit the outgrowth of EBV-infected cells in vitro, the BCRF1 and BARF1 proteins may help the virus to evade the host's immune system during acute EBV infection or reactivation of virus from latently infected cells.

EBNA-1 has been shown to block its own degradation by proteosomes in the cell.[43] Since viral proteins are normally broken down by proteasomes to peptides for presentation to cytotoxic T cells, the ability of EBNA-1 to inhibit its degradation may allow the protein to avoid triggering the activation of cytotoxic T cells.

EBV encodes at least two proteins that inhibit apoptosis. The EBV BHFR1 protein is a homologue of the human bcl-2 protein, which also blocks apoptosis,[44] whereas EBV LMP-1 up-regulates the expression of several cellular proteins that inhibit apoptosis, including bcl-2 and A20.[28]

EBV-infected Burkitt's lymphoma cells down-regulate the expression of several proteins that are important for killing by cytotoxic T cells. These include the transporter proteins associated with antigen processing that convey viral peptides from the cytoplasm to the endoplasmic reticulum for antigen presentation, cellular adhesion molecules that allow cells to contact each other, and MHC class I (but not class II) molecules that allow cytotoxic T cells to recognize virus-infected cells.[45]

CLINICAL SYNDROMES

Infectious Mononucleosis

Whereas most EBV infections of infants and children are asymptomatic or have nonspecific symptoms, infections of adolescents and adults frequently result in infectious mononucleosis.[46,47] Over 50 percent of patients with infectious mononucleosis manifest the triad of fever, lymphadenopathy, and pharyngitis; splenomegaly, palatal petechiae, and hepatomegaly are each present in more than 10 percent of patients. Less common complications include hemolytic anemia, thrombocytopenia, aplastic anemia, myocarditis, hepatitis, genital ulcers, splenic rupture, rash (Fig. 3C), and neurologic complications such as Guillain–Barré syndrome, encephalitis, and meningitis.

Most patients with infectious mononucleosis have leukocytosis with an absolute increase in the number of peripheral mononuclear cells, heterophile antibodies, elevated serum aminotransferase levels, and atypical lymphocytes. The atypical lymphocytes are primary T cells, many of which are responding to the EBV-infected B cells. Most of the symptoms of in-

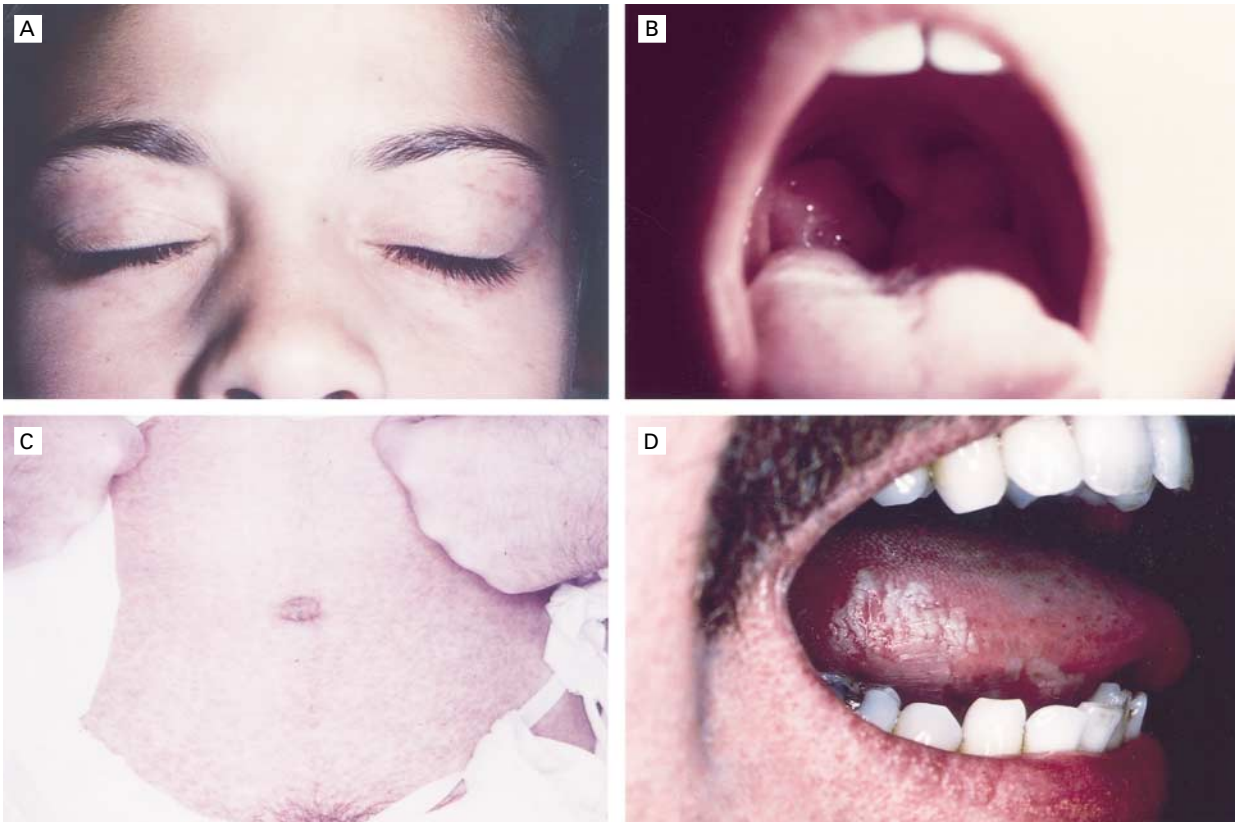

Figure 3. Clinical Findings in Epstein–Barr Virus (EBV) Infection.
Panel A shows petechiae of the eyelids with periorbital edema, and Panel B shows tonsillar enlargement in a patient with infectious mononucleosis. Panel C shows macular rash after ampicillin therapy in a patient with infectious mononucleosis. Panel D shows oral hairy leukoplakia in a patient with AIDS. Photographs courtesy of Maria Turner, M.D.

fectious mononucleosis are attributed to the proliferation and activation of T cells in response to infection. Up to a few percent of the peripheral B cells may be infected with EBV in infectious mononucleosis. Activation of B cells by EBV, with resultant production of polyclonal antibodies, causes elevated titers of heterophile antibodies and occasionally causes increases in cold agglutinins, cryoglobulins, antinuclear antibodies, or rheumatoid factor.

Chronic Active EBV Infection

Chronic active EBV infection is a very rare disorder that has been defined by the presence of the following three features: severe illness of more than six months' duration that begins as a primary EBV infection or that is associated with abnormal EBV antibody titers; histologic evidence of organ disease, such as pneumonitis, hepatitis, bone marrow hypoplasia, or uveitis; and demonstration of EBV antigens or EBV DNA in tissue.[48] There are often extreme elevations of virus-specific antibody titers. In contrast, chronic fatigue syndrome is a different disorder in which patients can have slightly elevated antibody titers to EBV and other viruses.

X-Linked Lymphoproliferative Disease

Patients with the X-linked lymphoproliferative disease, an inherited disease of males, are unable to control infection with EBV. Among 161 patients with X-linked lymphoproliferative disease who were listed in a registry, 57 percent died of infectious mononucleosis, 29 percent had acquired hypogammaglobulinemia, and 24 percent had malignant lymphomas.[49] EBV DNA and antigens were present in tissues from these patients. The gene on the X chromosome that is mutated in this disease has been identified as *SAP* (signaling lymphocyte activation molecule [SLAM]–associated protein),[50] also known as *SH2D1A* or *DSHP*. This gene encodes a protein located on the surface of T cells that interacts with two other proteins: SLAM, which is present on T and B cells, and 2B4, which is present on T cells and natural killer cells.[50,51] The absence of a functional SAP in patients with X-linked lymphoproliferative disease is thought

to impair the normal interaction of T and B cells, resulting in unregulated growth of EBV-infected B cells.

CANCERS ASSOCIATED WITH EBV

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma is prevalent in southern China, in northern Africa, and among Alaskan Eskimos. In southern China the incidence of nasopharyngeal carcinoma approaches 50 per 100,000 persons per year.[52] Nasopharyngeal carcinoma occurs sporadically in the United States and western Europe. Nearly 100 percent of anaplastic or poorly differentiated nasopharyngeal carcinomas contain EBV genomes and express EBV proteins (Table 1). The EBV genome is present in the transformed epithelial cells but not in the lymphocytes of the tumor. Clonal EBV genomes are found in the early preinvasive dysplastic lesions or carcinoma in situ, indicating that EBV infection precedes the development of malignant invasive tumors.[53]

Patients with nasopharyngeal carcinoma often have elevated titers of IgA antibody to EBV structural proteins. Measurement of EBV-specific IgA antibodies is useful in screening patients for early detection of nasopharyngeal carcinoma in southern China.[54] An increase in EBV-specific antibody titers after therapy for nasopharyngeal carcinoma is associated with a poor prognosis, whereas a declining or constant level of antibody is associated with a better prognosis.[55]

Burkitt's Lymphoma

Burkitt's lymphoma is a high-grade malignant lymphoma of small, noncleaved B cells. In equatorial Africa, Burkitt's lymphoma is associated with *Plasmodium falciparum* malaria, and tumors usually present in the jaw; over 90 percent of these cases are associated with EBV. Infection with malaria is thought to diminish the T-cell control of proliferating EBV-infected B cells and enhance their proliferation. In the United States, patients with Burkitt's lymphoma usually present with abdominal tumors, only 20 percent of which are associated with EBV.

Burkitt's lymphoma cells contain a chromosomal translocation involving chromosomes 8 and 14, 22, or 2. These translocations result in the positioning of the c-*myc* oncogene (chromosome 8) near the immunoglobulin heavy-chain (chromosome 14) or light-chain (chromosome 2 or 22) constant region, leading to abnormal regulation of the c-*myc* gene. Expression of c-*myc* in EBV-immortalized B cells results in increased tumorigenicity of the cells.[56]

Epidemiologic studies suggest that EBV may have a causal role in the development of Burkitt's lymphoma in Africa. Children in Uganda who have elevated titers of antibody to EBV structural proteins are at high risk for Burkitt's lymphoma.[57] Tissue from patients with Burkitt's lymphoma in Africa usually contains EBV DNA and expresses only one EBV protein, EBNA-1. As in nasopharyngeal carcinoma, clonal EBV genomes are found in Burkitt's lymphoma tissues, indicating that the tumor arises from a single EBV-infected cell.

Hodgkin's Disease

EBV DNA has been detected in tumors from about 40 to 60 percent of patients with Hodgkin's disease in the United States. The EBV genome is present in the Hodgkin's and Reed–Sternberg cells, and the viral genomes are monoclonal.[7] EBV is present in Hodgkin's disease tumors of the mixed-cellularity or lymphocyte-depletion subtypes more often than in tumors of other subtypes, in tumors from children from underdeveloped countries more often than in tumors from children from developed countries, in tumors from Hispanic patients more often than in tumors from whites, in tumors from young men more often than in tumors from young women, and in tumors from patients with immunodeficiency (including those with human immunodeficiency virus [HIV] infection) more often than in tumors from healthy persons.[58,59] Patients with Hodgkin's disease often have higher titers of antibody to EBV structural proteins before the onset of lymphoma or with the development of lymphoma than the general population.[60]

Lymphoproliferative Disease

EBV is associated with lymphoproliferative disease in patients with congenital or acquired immunodeficiency. These include patients with severe combined immunodeficiency, recipients of organ or bone marrow transplants, and patients with AIDS. These patients have impaired T-cell immunity and are unable to control the proliferation of EBV-infected B cells. They present with symptoms of infectious mononucleosis or with fever and localized or disseminated lymphoproliferation involving the lymph nodes, liver, lung, kidney, bone marrow, central nervous system, or small intestine[61,62] (Fig. 4). Patients who receive T-cell–depleted or HLA-mismatched bone marrow, receive antilymphocyte antibodies, have cytomegalovirus disease, or acquire primary EBV infection after receiving a transplant are at higher risk for lymphoproliferative disease. Increases in EBV viral load in peripheral blood have been detected in patients before the development of disease, and these levels decrease with effective therapy.[63,64] Similarly, EBV RNA was detected in liver-biopsy specimens from 71 percent of patients before the development of lymphoproliferative disease, but in only 10 percent of those in whom the disease did not develop.[65] Patients with EBV lymphoproliferative disease often have elevated serum levels of interleukin-6, a B-cell growth factor that may increase the proliferation of EBV-infected B cells.[66]

Tissues from patients with EBV lymphoproliferative disease show plasmacytic hyperplasia, B-cell hy-

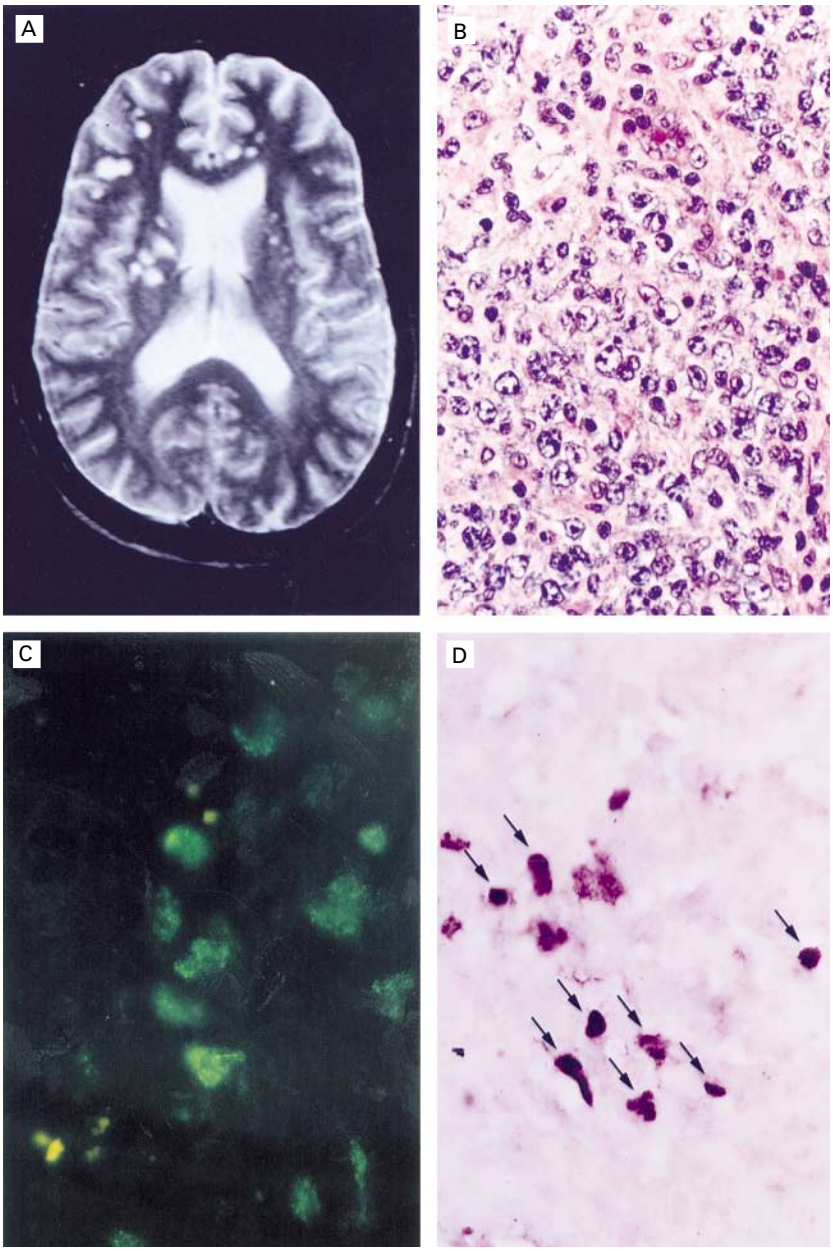

Figure 4. Pathological Features in a Patient with Epstein–Barr Virus (EBV) Lymphoproliferative Disease.
A magnetic resonance image (Panel A, courtesy of Dr. Steven Holland) shows multiple tumor nodules in the brain. Biopsy of a perirenal mass from the same patient shows immunoblastic lymphoma (Panel B). Staining of tumor tissue from the patient with monoclonal antibody to EBV nuclear antigen (EBNA) 2 (Panel C) shows that most cells express the protein. In situ hybridization using an EBV-encoded RNA (EBER) probe shows EBER expression (arrows) in tumor cells (Panel D, courtesy of Dr. Douglas Kingma).

perplasia, B-cell lymphoma, or immunoblastic lymphoma. The lesions may be monoclonal, oligoclonal, or polyclonal; patients with polyclonal lesions have the best prognosis. Lymphoproliferative lesions usually do not have the chromosomal translocations typical of Burkitt's lymphoma. The diagnosis of EBV lymphoproliferative disease requires the demonstration of EBV DNA, RNA, or protein in biopsy tissue.

Other Cancers

EBV DNA or proteins may have a pathogenic role in several other tumors in which they have been de-

tected, including nasal T-cell/natural-killer-cell lymphomas, lymphomatoid granulomatosis, angioimmunoblastic lymphadenopathy, central nervous system lymphomas in nonimmunocompromised patients,[67] smooth-muscle tumors in transplant recipients,[68] and gastric carcinomas.[69] Viral DNA or proteins have also been found in peripheral T-cell lymphomas, which can be accompanied by virus-associated hemophagocytic syndrome.[58]

EBV AND HIV

Patients with AIDS have 10 to 20 times as many circulating EBV-infected B cells as healthy persons. T cells from patients with AIDS suppress EBV-infected B cells less effectively than do cells from normal controls.[23] Patients with HIV have increased amounts of EBV in their oropharyngeal secretions[70] and have higher EBV antibody titers than HIV-seronegative persons. A decline in EBV-specific cytotoxic T cells and an elevated and increasing EBV viral load preceded the development of EBV-associated non-Hodgkin's lymphomas in patients with HIV infection; however, these changes were not seen in patients with HIV before the development of opportunistic infections.[71] HIV viral load and the progression of HIV disease were not affected by primary infection with EBV.[70,72]

Oral Hairy Leukoplakia

Oral hairy leukoplakia occurs in HIV-infected patients as well as in some immunosuppressed transplant recipients. It presents as raised, white, corrugated lesions of the oral mucosa, especially on the lateral aspect of the tongue (Fig. 3D). It is a nonmalignant hyperplastic lesion of epithelial cells. EBV DNA and herpesvirus particles are present in the upper, keratinized epithelial cells of the lesions. Multiple EBV strains are often present in the same lesion. Unlike EBV-associated cancers, oral hairy leukoplakia lesions show active viral replication and expression of lytic viral proteins.[5,73]

Lymphoid Interstitial Pneumonitis

Lymphoid interstitial pneumonitis occurs primarily in children, but it also occurs in adults infected with HIV. It is characterized by diffuse interstitial pulmonary infiltrates. The pathological changes in the lesions include infiltration of the alveolar septa by lymphocytes, plasma cells, and immunoblasts. EBV DNA and proteins have been detected in pulmonary lesions from children with HIV and lymphoid interstitial pneumonitis.[74]

Non-Hodgkin's Lymphoma

EBV was detected more frequently in biopsy specimens from benign-appearing lymph nodes of HIV-infected patients who subsequently or concurrently had non-Hodgkin's lymphoma than in specimens from patients without lymphoma.[75] About 50 to 60 percent of these tumors contain EBV DNA or proteins.[76,77] Most of the tumors are classified as either immunoblastic lymphomas or Burkitt-type lymphomas, and a smaller number are large-cell lymphomas; most are monoclonal. Burkitt-type lymphomas in patients with AIDS often present before the development of severe immunodeficiency and usually have c-*myc* rearrangements. In contrast, immunoblastic lymphomas develop in the later stages of AIDS, lack c-*myc* rearrangements, and are more frequently EBV-positive.

Unlike other cancers in patients with AIDS, virtually all central nervous system lymphomas contain EBV DNA.[78] These tumors are usually immunoblastic lymphomas and occur in patients with very low CD4+ cell counts. A positive polymerase-chain-reaction test for EBV DNA in the cerebrospinal fluid is a useful predictor of lymphoma in patients with AIDS and focal brain lesions.[79]

Primary effusion lymphomas in patients with AIDS often contain genomes from both EBV and Kaposi's sarcoma–associated herpesvirus (human herpesvirus 8). EBV has also been detected in leiomyosarcomas from patients with AIDS.[80]

TREATMENT

Infectious Mononucleosis

No specific therapy is indicated for most patients with infectious mononucleosis. Although acyclovir inhibits EBV replication and reduces viral shedding, it has no significant effect on the symptoms of infectious mononucleosis (which are primarily due to the immune response to the virus) and is therefore not recommended.[81] Acyclovir is effective in the treatment of oral hairy leukoplakia,[82] in which lesions appear to be driven directly by the replication of linear viral genomes, but recurrences are frequent after therapy is stopped. Corticosteroids shorten the duration of fever and oropharyngeal symptoms associated with infectious mononucleosis; however, they are generally not recommended for the treatment of uncomplicated disease and have been associated with increases in certain complications.[47] Corticosteroid therapy should be considered for patients with severe complications of infectious mononucleosis, such as impending upper-airway obstruction, acute hemolytic anemia, severe cardiac involvement, or neurologic disease. A double-blind, placebo-controlled study of combined therapy with acyclovir and prednisolone in uncomplicated infectious mononucleosis showed that this treatment did not affect the duration of illness or of absence from work.[83]

EBV Lymphoproliferative Disease

Therapy for EBV lymphoproliferative disease should include reduction in the dose of immunosuppressive medication when possible. Reducing the dose may result in complete resolution of some lesions.[62,84] Surgical removal or irradiation of localized lymphopro-

liferative lesions, especially in the gastrointestinal tract, has been effective in selected patients. Acyclovir, which inhibits the replication of linear EBV DNA but does not affect EBV episomes in latently infected cells, is generally not effective.[61] Interferon alfa has been effective in some patients. In one study, 8 of 14 patients had total regression of lesions after therapy with interferon alfa.[85]

Monoclonal-antibody therapy has also been used in patients with EBV lymphoproliferative disease. Treatment of 58 patients with murine monoclonal antibodies to both CD21 (the EBV receptor) and CD24 (a pan-B-cell antibody) resulted in complete remission in 61 percent of patients.[86] Although these monoclonal antibodies are not approved for clinical use, rituximab, a monoclonal antibody directed against the CD20 B-cell antigen, was recently approved by the Food and Drug Administration for the treatment of low-grade B-cell non-Hodgkin's lymphoma. Two of three patients in whom EBV lymphoproliferative disease developed after lung transplantation had complete remissions after treatment with rituximab.[87] A preliminary study of 26 patients with lymphoproliferative disease found that 54 percent had a complete remission with rituximab therapy.[88] Cytotoxic chemotherapy has been effective for some patients who have had no response to a reduction in the dose of immunosuppressive drugs or to other therapies.[85,89]

Infusion of unirradiated donor leukocytes into 18 patients with EBV lymphoproliferative disease after bone marrow transplantation resulted in the resolution of lymphomas in about 90 percent of them.[90] At follow-up 3 to 42 months later, 56 percent were still in remission; 11 patients had acute or chronic graft-versus-host disease.

EBV-specific cytotoxic T cells have been used in an effort to reduce the frequency of graft-versus-host disease associated with infusions of donor leukocytes. Two of three patients with lymphoproliferative disease at one center had complete regression of disease after treatment with EBV-specific cytotoxic T cells.[64,91] The patient for whom the therapy was unsuccessful had a tumor with a deletion in the EBV genome that allowed the malignant cells to escape killing by cytotoxic T cells. EBV-specific cytotoxic T cells have also been used to prevent lymphoproliferative disease in recipients of T-cell–depleted bone marrow.[64,91] None of 42 patients receiving prophylactic cytotoxic T cells had lymphoproliferative disease, and only 1 had graft-versus-host disease, whereas 15 percent of patients who did not receive prophylaxis had lymphoproliferative disease. Studies using gene-marked EBV-specific T cells have shown that they persist for up to three years in some patients.

Whereas EBV lymphoproliferative lesions in bone marrow–transplant recipients are nearly always derived from donor cells, lesions in patients who receive solid-organ transplants are usually from recipient cells, and therefore donor-derived T cells are not an option for therapy.[62] Infusions of HLA-matched allogeneic cells from a sibling,[92] autologous lymphokine-activated killer cells,[93] or autologous EBV-specific cytotoxic T cells[94] have resulted in regression of lymphoproliferative disease in organ-transplant recipients.

EBV-specific cytotoxic T cells obtained from patients with Hodgkin's disease have been used to treat patients during relapses. Infusion of these cells into three patients resulted in diminution of symptoms in two patients, and all three had reduced levels of EBV DNA in their blood.[95]

PREVENTION AND VACCINES

Since most cases of EBV lymphoproliferative disease associated with bone marrow transplantation are due to the proliferation of donor B cells, the frequency of disease may be reduced by the infusion of B-cell–depleted marrow. Removal of donor B cells along with T cells from bone marrow resulted in a lower incidence of lymphoproliferative disease in transplant recipients than did T-cell depletion alone.[96] Preemptive treatment with acyclovir or ganciclovir during therapy with antilymphocyte antibodies[97] or beginning at the time of transplantation[98] reduced the rate of lymphoproliferative disease in organ-transplant recipients relative to that in historical controls. However, another study found no difference in the development of EBV lymphoproliferative disease between patients receiving two weeks and those receiving one year of antiviral therapy after transplantation.[99]

Vaccination against EBV might be useful for several groups of people who are seronegative for EBV. These include patients undergoing organ or bone marrow transplantation, persons with X-linked lymphoproliferative disease, people in areas of the world with a high incidence of Burkitt's lymphoma (equatorial Africa) or nasopharyngeal carcinoma (southern China), and adolescents and adults at risk for infectious mononucleosis. Vaccination with purified EBV gp350 or vaccinia virus expressing gp350 protected cotton-top tamarin monkeys from the development of EBV-positive lymphomas after challenge with the virus.[100]

Preliminary studies in which nine EBV-seronegative children were vaccinated with vaccinia virus expressing gp350 found that neutralizing antibody responses to EBV developed in all nine and that six remained uninfected by EBV after 16 months, whereas all the unvaccinated controls became infected.[101] A phase 1 clinical trial using purified recombinant gp350 protein[102] was recently completed. In addition, immunization with EBV peptides corresponding to latent EBV antigens, which might boost cellular immunity and reduce morbidity from EBV-associated malignant diseases, is currently being tested in humans.[45]

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