Epstein–Barr virus: Dermatologic associations and implications

Part I. Mucocutaneous manifestations of Epstein–Barr virus and nonmalignant disorders

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Learning Objectives

After completing this learning activity, participants should be able to describe the basic science underlying the EBV virus, select the appropriate laboratory tests to evaluate for EBV, and identify the cutaneous manifestations of diseases associated with EBV.

Disclosures

None declared.

Epstein–Barr virus (EBV) is a ubiquitous virus that has been implicated in a wide range of human diseases, many of which have mucocutaneous manifestations. As a member of the herpesviridae family, EBV causes lifelong infection by establishing latency in B lymphocytes. An intact immune response is critical in preventing progression of EBV disease, and the clinical manifestations of infection are dependent on the intricate relationship between virus and host immune system. This review provides a comprehensive overview of the epidemiology, pathophysiology, and diagnostic testing in EBV infection. In part I of this continuing medical education article, the mucocutaneous manifestations of EBV infection are reviewed with an emphasis on pathophysiology and management. (J Am Acad Dermatol 2015;72:1-19.)

Key words: Epstein-Barr virus; human herpes virus 4; latency; infectious mononucleosis; papular acrodermatitis of childhood; oral hairy leukoplakia; hydroa vacciniforme; nonsexually related acute genital ulcers; histiocytic necrotizing lymphadenitis; lymphoproliferative; heterophile antibodies.

BACKGROUND

The Epstein-Barr virus (EBV), or human herpesvirus-4, is a member of the gamma-herpesviridae family, and is one of the most ubiquitous viruses known to humankind, infecting >90% to 95% of the world's adult population.[1,2] The virus preferentially infects B lymphocytes and results in a wide spectrum of mucocutaneous and systemic diseases, ranging from self-limited illnesses to aggressive malignancies.

In 1964, EBV was discovered by electron microscopy of cells cultured from Burkitt lymphoma tissue,[3] making it the first identified human tumor virus. Four years later, it was shown to be the etiologic agent of heterophile-positive infectious mononucleosis (IM).[1] As medical technology advanced over the next several decades, EBV became the first human virus to have its genome fully sequenced.[4] Humans are the only known host of EBV, but the virus is genetically related to viruses found in the oropharynx and B cells of Old World nonhuman primates, suggesting that it likely evolved from a nonhuman primate virus.[5]

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Abbreviations used:

CAEBV:	chronic active Epstein–Barr virus
CMV:	cytomegalovirus
EA:	early antigen
EBV:	Epstein–Barr virus
EBER:	Epstein–Barr virus–encoded RNA
EBNA:	Epstein–Barr virus nuclear antigen
GCS:	Gianotti–Crosti syndrome
HMB:	hypersensitivity to mosquito bites
HV:	hydroa vacciniforme
IM:	infectious mononucleosis
ISH:	in situ hybridization
KFD:	Kikuchi–Fujimoto disease
LC:	Langerhans cell
LCL:	lymphoblastoid cell line
LMP:	latent membrane protein
NRAGU:	non–sexually related acute genital ulcer
NF-κB:	nuclear factor kappa light chain–enhancer of activated B cells
OHL:	oral hairy leukoplakia
PCR:	polymerase chain reaction
PTLD:	posttransplant lymphoproliferative disease
STAT1:	signal transducer and activator of transcription 1
VCA:	viral capsid antigen

EBV is an enveloped virus with an icosahedral nucleocapsid surrounding a double-stranded DNA genome of approximately 184-kb pairs in length, which encodes nearly 100 proteins.[6] Two distinct types of EBV have been identified: types 1 and 2 (also called types A and B). They share 70% to 85% sequence homology, and result in lifelong infection with no identified type-specific differences in disease.[6] In terms of geographic distribution, EBV-1 is prevalent worldwide, whereas EBV-2 is found more frequently in Africa. Dual infections of both types may occur, especially in immunosuppressed hosts.

EPIDEMIOLOGY

Key points

- **Epstein–Barr virus is one of the most successful viruses identified, resulting in lifelong infection in >95% of the earth's adult population**
- **The clinical presentation of primary Epstein–Barr virus infection varies based on age at time of infection and socioeconomic factors**

The prevalence of EBV infection increases with age, with >95% of the world's adult population being chronically infected.[1,2] The age at initial infection varies based on geography and socioeconomic position. In developing countries and among socioeconomically disadvantaged populations, transmission occurs almost universally during infancy and early childhood.[6] In developed countries, the prevalence approaches 60% to 80% in children, and increases to 95% between 35 and 45 years of age.[7]

EBV is transmitted primarily through exposure to infected saliva, and IM is commonly referred to as the "kissing disease." The virus is shed in oral secretions at high concentrations for >6 months after acute infection, followed by lifelong intermittent shedding at lower concentrations. Immunosuppression increases the probability of viral shedding in oral secretions.[6] EBV has been reported in breast milk[8] and male and female genital secretions,[9] which can result in transmission by sexual contact.

Primary infection with EBV before 4 years of age tends to be asymptomatic or resemble a nonspecific viral illness.[10] In contrast, primary infection in adolescents and adults results in the classic manifestations of IM in 30% to 50% of infected persons.[11] The incidence of IM in the United States is estimated at 20 to 70 per 100,000 persons annually.[12,13] In developing countries and patients of lower socioeconomic status, symptomatic IM is rare because 80% to 100% of children become seropositive by 6 years of age.[11] The transfer of maternal antibodies confers passive immunity in infancy, resulting in a low incidence of primary EBV infections in the first year of life in developed countries. No seasonal changes in incidence have been identified, and there is no apparent sexual predominance.

PATHOPHYSIOLOGY

Key points

- **Epstein–Barr virus has 2 life cycles within the body: a lytic cycle responsible for viral replication, and a latent cycle where the virus remains inactive within memory B cells until periods of reactivation**
- **In immunocompetent hosts, B lymphocytes infected with Epstein–Barr virus expressing a proliferative pattern of genes are rapidly removed by Epstein–Barr virus–specific T cell responses, resulting in a state of relatively harmless Epstein–Barr virus infection**
- **In immunocompromised hosts, Epstein–Barr virus is able to cause proliferation of lymphocytes, resulting in lymphoproliferative disease**

Primary EBV infection

After inoculation within the oral cavity, EBV infects nasopharyngeal epithelial cells, followed by intracellular viral replication, cell lysis, and the release of virions that disseminate to contiguous structures, including the salivary glands and oropharyngeal lymphoid tissues.[14] During an incubation period of 30 to 50 days, additional viral replication