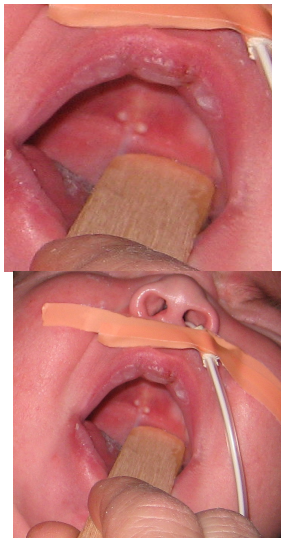

EPSTEIN-BARR VIRUS

Epidemiology

Epstein-Barr virus (EBV) is a worldwide pathogen with more than 90 percent of adults latently infected. In developed countries, most cases of primary infection occur during adolescence or

early adulthood, and clinically may present as infectious mononucleosis. Primary infection may occur during childhood; however, is often sub-clinical, probably because children are better able to clear the infection. In developing countries, most of the population is infected during childhood, thus infectious mononucleosis is much less common.

EBV is transmitted primarily by saliva through close contact. Viral replication occurs during primary infection, allowing infectious viral particles to be shed from the oropharynx. There are also reports of EBV acquired via blood transfusion.
It
is also thought that EBV may be transmitted through breast milk and genital secretions.

Etiology and Pathogenesis

EBV, also called human herpesvirus 4 (HHV-4), belongs to the Herpesviridae family and is approximately 180 to 200 nm in diameter. The double-stranded DNA genome encodes approximately 100 proteins and is enclosed within a
capsid
. The
capsid
is surrounded by an envelope, composed primarily of glycoprotein gp350. CD21 is present on the surface of B cells and binds with gp350, allowing entry of EBV into the cell.

EPSTEIN-BARR VIRUS AT A GLANCE

- Human herpesvirus 4.
- In developed countries, primary infection most often occurs during adolescence/early adulthood.
- Infectious mononucleosis characterized by the triad of fever, lymphadenopathy, and phary

ngitis
.

- Morbilliform exanthem with primary infection; most common after administration of ampicill in /amo xicillin.

- Oral hairy leukoplakia, nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin disease, Kikuchi histiocytic necrotizing lymphadenitis, and certain types of cutaneous T-cell lymphoma associated with Epstein-Barr virus infection.

EBV infects B lymphocytes directly within the oral mucosa or infects mucosal epithelial cells, which then infect the B lymphocytes. The infected B cells are activated, and their population is expanded. These B lymphocytes allow dissemination of the virus throughout the lymphoreticular system.
A clonal expansion of cytotoxic T lymphocytes allows recovery from primary infection and is the source of the atypical lymphocytes associated with EBV infection. Symptoms are likely a result of this immunologic response.

EBV establishes an indefinite latent infection within the B cells, during which time low levels of the latent proteins are produced. The previously linear DNA forms a circular structure, called an episome. Thereafter, B cells may re-activate and re-infect the oropharynx; replication and shedding of the viral DNA allows transmission of the virus to new hosts.

Clinical Findings

There is an incubation period of 30 to 50 days. Primary infection with EBV in adolescents and adults typically results in infectious mononucleosis, or the “kissing disease.” The classic triad of fever, lymphadenopathy, and pharyngitis are noted in more than 50 percent of patients. The fever may range from 37.5°C (99.5°F) to 40.5°C (104.9°F) and lasts 1 to 3 weeks. Lymphadenopathy
is tender and characteristically found in the posterior cervical chain. Examination of the posterior pharynx may vary from mild
erythema
to grossly enlarged tonsils with white exudates.
87

CUTANEOUS LESIONS

Seventy percent to 100 percent of patients with infectious mononucleosis develop an eruption when antibiotics, specifically ampicillin, are administered. Similar rashes have been reported with other antibiotics, such as amoxicillin,
cephalexin
, erythromycin, and
levofloxacin
. The rash typically begins 7 to 10 days after the initial administration of antibiotics. A
pruritic
,
erythematous
,
morbilliform
, or
scarlatiniform
eruption is noted on the trunk and extremities. The rash has been described as copper-colored. Coalescence may be observed on the extensor surfaces and dependent areas. . The palms, soles, or oral mucosa may be involved. Clearance, which is usually within 7 days, is accompanied by prominent desquamation.
90

The rash is thought to be a result of EBV-induced antibodies that are produced in response to the administered drug; these antibodies subsequently form immune complexes, which fix complement. This
exanthem
does not usually indicate a permanent allergy to the medication.

An exanthem due to EBV alone may also occur in a minority of cases (approximately 5 percent to 15 percent). This rash is also morbilliform and pruritic; however, usually it commences during the first few days of illness and resolves faster, typically in 1 to 6 days. Periorbital
and eyelid edema may be seen in up to 50 percent of those with infectious mononucleosis. In approximately 25 percent of cases, an
enanthem
is noted. Six to 20
petechiae
, measuring 0.5 to 1.0 mm, may be visualized at the junction of the hard and soft palate. Lesions may coalesce forming larger lesions.

Erythema multiforme, erythema nodosum, acrocyanosis, erythema annulare centrifugum, pityri asis
lichenoides
,
palmar
dermatitis, cold
urticaria
, and
granuloma
annulare
have all been reported

during infection with EBV. Genital ulcers have also been observed during primary infection with EBV (Fig. 192-8). Typically occurring after the onset of fever and lymphadenopathy, ulcers are painful, deep, and red-
violaceous
in color. The base of the ulcer can be clear,
seropurulent
, or with granulation tissue. The ulcers heal in approximately 2 weeks, and treatment is symptomatic.

EBV is currently the most common cause of Gianotti-Crosti syndrome (GCS; see Chap. 106). In children, primary infection with EBV is often mild or asymptomatic; as a result, typical features of infectious mononucleosis may not be observed.

RELATED PHYSICAL FINDINGS

Associated symptoms and signs may include fatigue, rigors, headache, and hepatosplenomegaly.

Laboratory Tests

Most patients with infectious mononucleosis demonstrate a lymphocytosis, often with lymphocytes accounting for more than 50 percent of the absolute white blood cell count. Atypical lymphocytes are a hallmark, typically more than 10 percent atypical lymphocytes; most of these cells represent activated T cells responding to infected B cells. Mild, transient neutropenia and thrombocytopenia are common.
Transaminases
are elevated in more than 80 percent of patients with infectious mononucleosis.

The presence of heterophile antibodies confirms most cases of infectious mononucleosis. Heter ophile
antibodies recognize antigens on the erythrocytes from a number of different species including horses, sheep, bulls, and humans; however, they do not recognize EBV. They are thought to be a result of polyclonal stimulation during the viral infection
,
and can occasionally be detected (false positives) in other illnesses such as lymphoma, hepatitis, or autoimmune disease.
Heterophile
antibodies typically appear within 1 week of the onset of symptoms, peak within 2 to 5 weeks, and may persist for up to 1 year. They are not the ideal diagnostic test in children less than 4 years old, as sensitivity is quite low.
[95]
In the past, the Paul-
Bunnell
test had been used with sheep erythrocytes. Currently, the more sensitive
monospot
test is used, which is a latex agglutination assay with horse erythrocytes to look for
heterophile
antibodies. Up to 10 percent of patients with EBV mononucleosis never develop
heterophile
antibodies; this is referred to as
heterophile
-negative mononucleosis.

A number of antibodies specific to EBV develop in the course of disease as well. Measurement of these specific antibodies may be warranted if infectious mononucleosis is suspected and het erophile
antibodies are negative.
IgM
and
IgG
antibodies form to viral
capsid
antigen (VCA) and are both present at onset of disease.
IgM
VCA antibodies wane after approximately 3 months;
IgG
VCA antibodies persist for life and are a marker for previous infection.
IgG
antibodies to EBV nuclear antigen develop 6 to 12 weeks into the course of disease and also persist for life.

IgG
to early antigen develops at the onset of disease and is made up of two subsets of antibodies, anti-D and anti-R. The presence of anti-D antibodies suggests recent infection, although 30 percent of patients do not produce antibodies at all. Anti-R antibodies have no clinical significance. Thus, primary infection may be most easily diagnosed in the presence of
IgM
and
IgG
VCA antibodies as well as negative
IgG
EBV nuclear antigen antibodies.

Histopathology

The morbilliform exanthem associated with EBV demonstrates non-specific histopathologic findings.
There
is usually a mild
perivascular
infiltrate of inflammatory cells. Specific
cutaneous
manifestations may show their characteristic pathologies.

Differential Diagnosis

Complications

Complications of infectious mononucleosis occur in approximately 20 percent of patients and

include airway obstruction, autoimmune hemolytic anemia or thrombocytopenia, neutropenia,[87] myocarditis
, and hepatitis.
[80]

Neurologic
complications occur in approximately 5 percent

of patients. Examples include encephalitis, meningitis, and Guillain-Barré syndrome. The risk of splenic rupture is
estimated at 0.1 percent and is spontaneous in greater than one-half of cases. Between 3 percent and 30 percent of patients with infectious mononucleosis also have concomitant group A streptococcal pharyngitis.
[96]

Finally, in some patients, fatigue and
hypersomnia
can persist up to 6 months.

Differential Diagnosis of Infectious Mononucleosis

Most Likely

- Group A streptococcal infection
- Cytomegalovirus mononucleosis
- Toxoplasmosis

Consider

- Viral hepatitis
- Measles
- Rubella
- Enterovirus
- Adenovirus

Always Rule Out

- Primary exanthem of human immunodeficiency virus
- Drug rash with eosinophilia and systemic symptoms syndrome

Treatment for Epstein-Barr Virus Infectious Mononucleosis

First line

Fever, throat discomfort, myalgias , headache. Splenomegaly .

Acetaminophen/ nonsteroidal anti-inflammatory drugs Avoid contact sports until spleen

Second line

Impending airway obstruction, thrombocytopenia, hemolytic anemia.

Systemic corticosteroids.

Prognosis and Clinical Course

Recovery from infectious mononucleosis is typically gradual over 2 to 3 weeks without specific treatment. Disease may be more protracted in older adults. Chronic active EBV infection occurs rarely.[80] It begins as a primary EBV infection and persists for more than 6 months with severe illness and histologic evidence for organ disease. EBV DNA or antigens can be demonstrated from tissue, and usually EBV antibody titers are significantly elevated.

Treatment

Treatment for uncomplicated infectious mononucleosis is symptomatic Acetaminophen or nons teroidal
anti-inflammatory agents may be useful in treating the fever or throat discomfort. Because splenomegaly
is often an associated finding, contact sports should be avoided until the spleen has returned to its normal size to avoid
splenic
rupture.

Systemic corticosteroids may decrease the duration of fever or pharyngeal symptoms, but in general, are not recommended for uncomplicated disease.

Prevention

Because infectious mononucleosis is often mistaken for a bacterial infection, antibiotics may initially be used to treat. Antibiotics should be avoided in infectious mononucleosis as an exanth em is
much more likely to occur in this setting.

Vaccinations are currently being investigated and may prove to be helpful in preventing EBV infections in the future, particularly in high-risk patients.