Epstein-Barr Virus Infection and Infectious Mononucleosis

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Contents

General Principles

Background

The Epstein-Barr virus (EBV) is a double-stranded linear DNA virus. Its DNA core is enclosed by an icosahedral nucleocapsid and by a viral envelope. As a member of the Herpesviridae family, EBV is specifically a gamma herpesvirus [1]. There are two subtypes of EBV, EBV-1 and EBV-2, sometimes referred to as EBV types A and B. These are genetically very similar and are not often distinguished from each other in clinical practice [2].

One of the defining characteristics of the gamma herpesvirus class is its infection of and latency within lymphoid tissue. EBV primarily infects B lymphocytes, integrating itself into the genome and remaining latent. It can also infect natural killer (NK) cells and T lymphocytes, though with less efficiency [1–3]. It is the cause of heterophile-positive infectious mononucleosis, often referred to simply as "infectious mononucleosis" (IM). Colloquial names for it include "mono" and "the kissing disease," due to its primary method of transmission. EBV was the first virus discovered to contribute to the development of several types of malignancies in humans [4].

Epidemiology

Although greater than 90 % of the world's population has antibodies to EBV, the clinical course

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and significance of EBV varies significantly between developing and industrialized countries. In developing countries, as well as members of lower socioeconomic status living in industrialized countries, there is extensive transmission of the virus in infancy and early childhood; the majority of children develop antibodies by the age of three and do not typically experience symptomatic infection. In the industrialized world, EBV typically causes IM primarily among adolescents and young adults, with estimates of yearly incidence ranging from 100 to 500 per 100,000 adolescents in the United States [2, 5]. Worldwide the incidence is 20–70 per 100,000 annually. Adults over the age of 30–40 are less frequently symptomatic; when symptoms in this age group occur, it is often among those suffering from immune deficiency states such as AIDS.

Clinical Presentation

EBV has an incubation period of approximately 30–50 days. The prodromal phase is characterized by the insidious onset of symptoms that include fatigue, malaise, and myalgia, typically lasting 1–2 weeks. Fever may or may not occur during this time and may last more than a month [2]. Sore throat, lymphadenopathy, and the typical prodromal symptoms form the classic triad of IM, occurring in over 80 % of patients [3]. The pattern of lymphadenopathy is generalized, present in 90 % of patients, and may include epitrochlear adenopathy.

Additional signs include splenomegaly in over 50 %, petechiae present at the junction of the hard and soft palate, tonsillar exudates, hepatomegaly, and a maculopapular rash which may last anywhere from 15 to 50 days. Also typical of IM is the eruption of a copper-colored maculopapular rash specifically in response to amoxicillin, which may have been given for presumptive strep throat. In adults, signs such as fever, transaminitis, hepatomegaly, or pneumonitis may be more common than the lymphadenopathy and pharyngitis typical of adolescent cases [6]. Table 1 summarizes the symptoms whose presence increases the likelihood of a diagnosis of IM.

Table 1 Factors increasing likelihood of IM

Pharyngitis with abnormal liver enzymes
Atypical lymphocytosis >10 % (specificity 92 %)
Lymphocytosis >50 % (specificity 85 %)
Palatal petechiae
Splenomegaly
Posterior cervical lymphadenopathy

Symptoms, particularly malaise and fatigue, may last for months. Rarely, patients may develop chronic active EBV infection (CAEBV). This condition is defined by the presence of symptoms accompanied by markedly elevated titers of EBV antibody, indicating active replication that persists for more than 6 months. Guidelines were proposed in 2005 for the diagnosis of CAEBV, including (1) persistent or recurrent IM-like symptoms; (2) unusual pattern of anti-EBV antibodies, specifically IgG against EBV VCA (greater than 1:640) and early antigen (greater than 1:160), and/or detection of EBV DNA in affected tissues, including blood; and (3) no other known disease process present to explain chronic illness at diagnosis [7].

Diagnosis

The clinical diagnosis of IM most commonly relies on the presence of typical symptoms in the presence of a positive heterophile antibody test ("monospot") [8, 9]. The complete blood count (CBC) often reveals 20 % or greater atypical lymphocytes; the white count may be normal or mildly elevated [2]. Lymphocytosis is more likely to be seen in older patients [6].

In certain instances, the heterophile antibody test can be falsely negative. In children under the age of 12, the test may be positive in only 25–50 % of patients. The test is particularly insensitive in those below 2 years of age. It may also be negative in up to 25 % of patients during the first week of infection, as well as 5–10 % of patients in or after the second week [2]. Infections such as toxoplasmosis and cytomegalovirus may cause false-positive heterophile antibody tests. Furthermore, antibodies may persist for 1 year or more.

Table 2 Differential diagnosis for infectious mononucleosis

Diagnosis	Differentiating characteristics
Cytomegalovirus, toxoplasmosis	Can be clinically indistinguishable
	Usually heterophile antibody negative
	Clinical suspicion requires further testing in pregnant women due to risk of congenital infection
HIV	Weight loss, mucocutaneous ulceration, rash 48–72 h following fever
	Concurrent symptomatic infection from EBV more likely in adults with HIV/AIDS
	Presence of oral hairy leukoplakia (OHL) is specific for HIV
Streptococcal pharyngitis	Exudative pharyngitis, positive rapid strep or throat culture
	More typically anterior cervical lymphadenopathy than posterior
Adenovirus	Heterophile negative
	Less systemic lymphadenopathy
Viral hepatitis	Jaundice is more common, particularly in hepatitis B
	More common among middle-aged adults than EBV
Rubella	Presence of pink maculopapular rash that begins on the face then spreads to the body
	Clinical suspicion requires further testing in pregnant women due to risk of congenital infection
Leukemia	Very high or very low white blood cell count
	Hemolytic anemia
	Moderate to severe thrombocytopenia
Drug effect	Phenytoin, carbamazepine, isoniazid, minocycline

However, when positive in the presence of IM symptoms, test sensitivity is approximately 85 % and specificity approaches 94 % [3]. If EBV is strongly suspected but heterophile antibody testing is negative, EBV-specific antibodies can be obtained for confirmation of infection.

Differential Diagnosis

Table 2 summarizes the differential diagnosis of IM caused by EBV. It can be difficult to distinguish between disease entities clinically, particularly toxoplasmosis and cytomegalovirus (CMV). In high-risk populations, such as pregnant patients, it is prudent to pursue confirmatory testing due to the risk of TORCH infections to the fetus.

Streptococcal pharyngitis can usually be distinguished by the presence of exudative pharyngitis, as this is more common in strep pharyngitis than in IM; it can, however, still occur in IM. Cervical adenopathy commonly involves the posterior cervical chain and may be generalized, as opposed to streptococcal pharyngitis, which tends to cause anterior cervical adenopathy [2, 4]. These two are best distinguished from each other by a rapid test for streptococcal antigen and/or throat culture.

Laboratory findings more suggestive of EBV include atypical lymphocytosis greater than 20 % and lymphocytosis of greater than 50 %. Not uncommonly, EBV infection may result in hematologic abnormalities such as hemolytic anemias or cytopenias. Similar findings may be seen in leukemia.

Complications

During the acute infection, the most worrisome complications include hemolytic anemia, encephalitis, meningitis, Guillain-Barré syndrome, myocarditis, pneumonitis, and acute interstitial nephritis. Airway compromise from pharyngitis or tonsillitis is rare but may be life threatening [2, 3, 5]. Finally, although rare, the risk of splenic rupture is greatest in the first 21 days after infection. This becomes an important consideration for return-to-play guidelines for athletes as well as

military trainees, who often fall within the age range for EBV infection (see "Community and Family Considerations").

In terms of long-term complications, lymphoproliferative disorders and other malignancies are of concern, particularly among immunocompromised individuals. Impaired immunity presumably allows increased viral replication over time, enhancing the ability of EBV to transform cells. While the complications of infection tend to affect the B-cell line, they remain varied and have the potential to affect almost every system. For example, nasopharyngeal carcinoma, particularly the undifferentiated type, is prevalent in Southern China, among Caucasians in North Africa, and the Inuit of North America [2]. EBV-related thymic cancer has been identified in the United States, as well as leiomyosarcoma, Burkitt lymphoma, and other B-cell lymphomas. Oral hairy leukoplakia is a manifestation of EBV replication and can be seen in adults with HIV/AIDS. Children with AIDS can develop lymphoid interstitial pneumonitis, leading to dyspnea and respiratory distress [2, 3, 6, 10].

Evidence exists that suggests an association between EBV and the development of multiple sclerosis [11–13]. However, the exact relationship remains to be elucidated. It is likely multifactorial, to include age at infection and genetic susceptibility or predisposition. Lingering fatigue can also be a complication of IM, creating implications for the patient's subsequent ability to participate in school, work, and play. Females are particularly affected [14, 15]. It is important to note that to date no evidence exists to link infectious mononucleosis with chronic fatigue syndrome. Chronic active EBV infection is distinct from chronic fatigue syndrome.

Additionally, there exists evidence linking psychologically stressful events within the 6 months prior to infection with the severity of EBV infection symptoms and subsequent time to recovery [14]. A systematic review of the literature showed that while premorbid psychological diagnoses did not seem to correlate with length of illness or failure to recover, female sex and older age both appeared to contribute to prolonged time to recovery and distress following the active phase of illness. Furthermore, poor physical conditioning, lower physical functioning, and longer absence from work or school were consistently associated with prolonged illness [16].

Management

Supportive care is the mainstay of treatment for infectious mononucleosis. Acyclovir, while effective in reducing replication rate of the virus and oral shedding, does not alter the disease length or severity of symptoms [17]. NSAIDs, oral hydration, and salt water gargles may help provide symptomatic relief. Bed rest can be offered to those with especially severe fatigue, though evidence suggests that this may hinder recovery.

Tonsillar enlargement causing difficulty breathing may be treated by hydration, humidified air, a short course of corticosteroids, and elevation of the head of the bed. Suggested dosing of steroids is prednisolone one milligram per kilogram orally for 7 days with subsequent tapering over 7 days [2]. Significant swelling with respiratory compromise may necessitate intubation and/or tonsillectomy. Corticosteroids can also be considered in cases of thrombocytopenia with bleeding, autoimmune hemolytic anemia, seizures, and meningitis. Corticosteroids should not be used in uncomplicated cases of EBV [2, 3, 6].

Prevention

Symptoms may not present until weeks after the initial inoculation. Thus, prevention of transmission can be difficult. Advice against kissing children on the mouth due to the intermittent asymptomatic oral shedding of the virus would seem to be a sensible intervention. Toys, particularly in daycare settings, should be kept clean to prevent transmission by fomites.

Furthermore, although transmission through sexual contact has been reported, it has not been associated with development of clinically significant disease. Studies have demonstrated the coexistence of EBV with the human papilloma virus

(HPV) in cervical neoplasms [18]. There has not been, however, an established link to the development of cervical cancer.

Vaccines against EBV are currently being studied. However its clinical application is likely to be for the prevention of complications, specifically malignancies, rather than reducing rates of primary infection [2].

Family and Community Issues

For active patients, including athletes and those serving in the military, activity restriction can help protect against splenic injury or rupture, given the prevalence of splenomegaly in IM. There are no conclusive studies that establish firm guidelines regarding return to play for athletes recovering from IM. Recommendations vary, but include restriction from contact sports and high-risk activities for four weeks from symptom onset. Light activity may be resumed if the patient is afebrile and hydrated and has no spleen or liver enlargement. Complete return to play should be considered only if the patient feels well, as malaise and fatigue can persist for months after the infection resolves [2, 3, 5, 19, 20].

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