California Association for Medical Laboratory Technology

Distance Learning Program

The Bug Everyone Has
Epstein-Barr Virus:
A Case Study

Course # DL-905

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CSU – Sacramento

Approved for 2.0 CE
CAMLT is approved by the California Department of Public Health as a CA CLS Accrediting Agency (#21)

Level of Difficulty: Basic

Notification of Distance Learning Deadline
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This is a reminder that all the continuing education units required to renew your license/certificate must be earned no later than the expiration date printed on your license/certificate. If some of your units are made up of Distance Learning courses, please allow yourself enough time to retake the test in the event you do not pass on the first attempt. CAMLT urges you to earn your CE units early!
DISTANCE LEARNING ANSWER SHEET
Please circle the one best answer for each question.

COURSE NAME: THE BUG EVERYONE HAS ~ EPSTEIN-BARR VIRUS: A CASE STUDY   COURSE # DL-905

NAME ____________________________________ LIC. # ____________________ DATE ____________

SIGNATURE (REQUIRED) ___________________________________________________________________

EMAIL _____________________________________________________________________________________

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STREET      CITY    STATE/ZIP

2.0 CE – FEE: $24.00 (MEMBER) | $44.00 (NON-MEMBER)

PAYMENT METHOD: [  ] CHECK or [  ] CREDIT CARD # _____________________________________ TYPE – VISA or MC

EXP. DATE ________  |  SECURITY CODE: ___  -  ___  - ___

1.  a  b  c  d  11.  a  b  c  d
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3.  a  b  c  d  13.  a  b  c  d
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8.  a  b  c  d  18.  a  b  c  d
9.  a  b  c  d  19.  a  b  c  d
10. a  b  c  d  20. a  b  c  d

DISTANCE LEARNING EVALUATION FORM
According to state regulations, this form must be completed and returned in order to receive CE hours. Your comments help us to provide you with better continuing education materials in the distance learning format. Please circle the number that agrees with your assessment with, with 5 meaning you strongly agree and 1 meaning you strongly disagree.

1. Overall, I was satisfied with the quality of this Distance Learning course.
   5  4  3  2  1

2. The objectives of this Distance Learning course were met.
   5  4  3  2  1

3. The difficulty of this Distance Learning course was consistent with the number of CE hours.
   5  4  3  2  1

4. I will use what I learned from this Distance Learning course.
   5  4  3  2  1

5. The time to complete this Distance Learning course was: ________ hours

6. Please comment on this Distance Learning course on the back of this sheet. What did you like or dislike?
The Bug Everyone Has – Epstein-Barr Virus: A Case Study

By: Jane Bruner, Ph.D., CLS, MT(ASCP)
Associate Dean, College of Natural Sciences and Mathematics
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OBJECTIVES
At the end of this course the participant will be able to:
1. define the endemic role of Epstein-Barr virus.
2. describe Epstein-Barr virus basic structure.
3. identify the pathogenesis of Epstein-Barr virus.
4. relate laboratory tests necessary to differentiate among the various types of Epstein-Barr virus infection.

INTRODUCTION
One of the most common human viruses is the Epstein-Barr virus (EBV). Viral particles, identified by Epstein and Barr in 1964, in continuous cell lines of Burkitt’s lymphoma cells were the first evidence of this virus’ presence. Burkitt’s lymphoma had been described in 1958. In 1968, a casual relationship was established between Epstein-Barr virus and infectious mononucleosis. EBV’s ability to immortalize lymphocytes in cell culture was validated in 1969.

EBV has worldwide prevalence and most people will be infected at some time in their lives. In the United States, most of these people will be infected by their fortieth year. Infants become susceptible to EBV as soon as protective maternal antibody disappears and many children are infected with no evidence of symptoms. If symptoms do manifest, they are generally indistinguishable from other early childhood ailments. People who do not contract EBV during their early childhood, but rather during adolescence or young adulthood, commonly develop infectious mononucleosis.

The EBV is a member of the herpes family of viruses. It has a limited target cell population (tropism). EBV infects B-lymphocytes and epithelial cells. EBV may be divided into subtypes based on its ability to transform B-cells. Human infection with EBV initiates in the oropharynx (throat). B cells are infected as they migrate through the throat. EBV remains dormant in the infected cells of the throat and blood for the remainder of the person’s life. The dormant infection can initiate a rare late event in viral carriers. EBV plays an important role in the presence of Burkitt’s lymphoma and nasopharyngeal carcinoma. These cancers are unusual in the United States. EBV does, however, present a significant problem in initiating lymphocyte disorders in persons who are immunocompromised.

The most frequently manifested disease state in Epstein Barr viral infections is infectious mononucleosis. Most people beyond childhood who are subjected to contact with persons with infectious mononucleosis are at no risk of developing infectious mononucleosis because they have protective antibodies to EBV. Transmission also requires contact with the saliva of the infected person (hence, the name “kissing disease”). Infection is rarely acquired through airborne or blood borne routes. The common source of transmission is actually the saliva of healthy
persons who can carry and spread the virus throughout their lives. The incubation period for acute illness is four to six weeks. The symptoms of infectious mononucleosis usually resolve in a few months. Cases lasting longer than six months have been called chronic EBV infections, however, few of these chronic infections have substantiated evidence of continuous active EBV viral presence.

OVERVIEW

Epstein-Barr virus, now designated Human Herpesvirus 4 (HHV4), (family Herpesviridae, subfamily Gammaherpesvirinae, genus Lymphocryptovirus) is structurally similar to other herpes viruses. The virus is composed of a protein core wrapped with DNA. This protein/DNA arrangement is enclosed in a nucleocapsid surrounded by a protein covering. The entire virus is cloaked in an envelope with external glycoprotein spikes. The chromosome of the Epstein-Barr virus is linear and double-stranded. EBV was the first herpes virus to have its complete genetic sequence determined. There have been two EBV types designated, initially called EBV type A and type B. In keeping with the Herpes simplex virus types designation, HSV 1 and HSV 2, the nomenclature has been modified to EBV 1 and EBV 2.

The oropharyngeal epithelium is permissive for Epstein-Barr virus replication. EBV infection usually begins at this site in humans. During the early phase of the infection, B-lymphocytes traveling through the oropharynx are infected with EBV also. The virus does not usually replicate in B cells but rather lingers inside them causing a latent infection. The states of EBV infection are:

1. **Adsorption** – During this phase the virus attaches to a cell-surface protein which functions as a viral receptor.
2. **Penetration and Uncoating** – The virus is endocytosed and moves into the cell. The viral envelope then fuses with the vesicle membrane and releases the viral contents into the cell’s cytoplasm.
3. **Initiation of Virus Replication or Establishment of Latent Infection** – The mechanisms of viral infection once inside the cell have not been clearly detailed. Infection of oropharyngeal epithelial cells results in viral replication and release generally. Infection of B-cells results in a latent infection that can persist without symptoms in those cells for years.

PATHOGENESIS:

In healthy, infected individuals who are asymptomatic, the primary viral infectious process is fairly straightforward. The virus enters through the oropharynx, establishes in epithelial cells and replicates. Submucosal B lymphoid cells are then infected by virus proliferating in the epithelial cells. Even in the absence of clinical symptoms, Epstein-Barr virus can be demonstrated in the B-lymphocytes of most EBV seropositive individuals. There is also a distinct immune response to the virus residing in the epithelial and B cells. Antibodies are produced against EBV viral proteins which include the viral capsid antigen (VCA), the early antigens (EA), and the nuclear antigens (EBNA).

In addition to the so-called “silent” infection of asymptomatic individuals, primary infection can include symptomatic conditions such as infectious mononucleosis. As in asymptomatic carriers, the route of infection is usually close contact. There is little evidence for airborne or bloodborne infection. The virus is secreted in saliva and active infections usually occur in situations where saliva is shared; such as on the surface of toys shared among small
children or on the surface of lips shared by adolescents. The incubation period for the disease is four to six weeks. The disease is generally self-limiting although the convalescence may take up to three or four months in severe cases.

When illness lingers for more than six months the term “chronic EBV infection” has been applied. There has been little valid evidence to support such a long period of activity for Epstein-Barr virus and these cases are probably more appropriately described as incidences of chronic fatigue syndrome. During the mid-1980s, several studies described a prolonged illness that was associated with chronic EBV infection. This condition was characterized by extreme fatigue and a group of other related symptoms, including headache, sore throat, low grade fever, muscle and joint aches, memory loss, and difficulty in concentrating. However, further studies were unable to clearly establish a causative link between Epstein-Barr virus and the illness. Data gathered in these studies found affected individuals were no more likely to have antibodies to EBV than healthy individuals. Since 1988, investigators have used the term chronic fatigue syndrome to describe this illness.

There is a rare inherited disorder – X-linked Lymphoproliferative Syndrome – in which affected individuals develop a fatal primary infection. Although rare in any case, it should be noted that about half the fatal cases of infectious mononucleosis are sporadic.

There is no vaccine or antiviral drug available for specific treatment of infectious mononucleosis. The normal course of therapy is to treat the symptoms. There has been some anecdotal evidence that steroid treatment decreases the overall length and severity of the illness.

**DIAGNOSIS**

Clinical indications for infectious mononucleosis are sore throat, fatigue, fever, generalized lymphadenopathy, and occasional splenomegaly and hepatomegaly. However, laboratory tests are required for confirmation of EBV infection. Although atypical or reactive lymphocytosis in the peripheral blood and abnormal liver function tests are indicative of EBV infection, they are neither particular to nor diagnostic in and of themselves for infectious mononucleosis. Interpretation of the laboratory results is complex and a complete evaluation of a patient is best performed in view of the laboratory data and a complete clinical picture of the patient.

**LABORATORY TESTS**

Laboratory tests are critical to the diagnosis of many disease states. Unfortunately, tests are not always guaranteed to accurately reflect patient condition. Two of the ways test results can fail to indicate an accurate diagnosis are:

1. false positive results which indicate a condition exists when it does not; and
2. false negative results which miss the presence of an existing condition.

Inaccurate test assessment for Epstein-Barr virus may include some of the following sources of error:

1. inadequate sensitivity levels to detect viral or antibody presence;
2. non-specific results caused by infection with another microorganism;
3. problems in specimen handling or incorrect test performance; and
4. misinterpretation of results.
In most cases of infectious mononucleosis, the clinical diagnosis can be made from the characteristic presentation of fever, lymphadenopathy, and pharyngitis lasting for one to four weeks. Peripheral blood findings in infectious mononucleosis include a normal to moderately elevated white count with an increased number of total lymphocytes and greater than ten-percent reactive or atypical lymphocytes. These reactive lymphocytes are not the infected B lymphocytes but are the activated lymphocytes responding to the infection. Serological analysis may yield a positive Paul-Bunnell heterophile antibody test. A positive “mono spot” test result is diagnostic in a patient with appropriate clinical symptoms. Moderate to high levels of heterophile antibodies are seen during the first month of illness but antibody levels decrease rapidly after that time period. False positive results may be found in three percent of cases. False negative results are found in ten to fifteen percent of cases, particularly in children younger than ten years of age.

When the heterophile tests are negative, additional laboratory testing is necessary to distinguish EBV viral infection from other similarly presenting diseases such as infection with Cytomegalovirus, Adenovirus, or *Toxoplasma gondii*. Direct detection of EBV in lymphocytes or epithelial cells is possible by techniques such as microscopic analysis using fluorescent antibody detection (FA or IFA) or viral nucleic acid amplification using polymerase chain reaction (PCR) analysis. However, although these direct methods are coming into more common usage every day, they still are not part of the routine diagnostic scheme in most situations.

Antibody tests for Epstein-Barr virus measure the presence and, in some formats, the concentration of specific EBV antibodies. The fact that a person has antibodies to EBV does not automatically indicate a recent infection. The body produces a number of specific antibodies to EBV that are present at different stages of infection. Some types of EBV antibodies are present only during active infection. Other specific EBV antibodies are present for years after active infection. Still other antibodies are present during reactivated infection with EBV. Most adults will show some type or types of antibodies to EBV since ninety-five percent of adults have been infected with Epstein-Barr virus. By measuring the type and amount of the specific antibodies present, laboratory tests can determine the presence of current or past infection or reactivated infection.

When the mono spot is negative, antibodies to several antigen complexes may be measured. These antigens are the viral capsid antigen (VCA), the early antigen (EA), and the EBV nuclear antigen (EBNA). In addition, differentiation of immunoglobulin G and M subclasses to the viral capsid antigen can often be helpful in determining acute or past infection. Because the humoral response in primary EBV infection appears to be quite rapid, effective laboratory diagnosis can be made on a single acute-phase serum sample. Four distinctive EBV antibodies are used to provide a comprehensive picture of EBV infection. These antibodies are IgM viral capsid antibody, IgG viral capsid antibody, IgG antibody to early antigen, and antibody to nuclear antigen. IgM antibody to the viral capsid antigen appears early in infection and disappears in four to six weeks. IgG viral capsid antigen antibody appears in the acute phase, peaking at two to four weeks after onset. Accurate interpretation of EBV infection will be based on the results from all these antibodies, not on any single antibody value.
Clinical Diagnosis of Epstein-Barr Viral Infection by Antibody Presence

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<th>IgG-VCA</th>
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INTERPRETATION SUMMARY

If no antibodies to EBV viral capsid antigen are detected, a person is susceptible to Epstein-Barr virus infection. Primary infection antibody presence is dynamic with IgM-VCA appearing first, accompanied by rising IgG-VCA antibody levels, and the appearance of antibody to early antigen (EA). EA antibodies are not detected in about twenty percent of primary EBV infections. If both IgG-VAC and EBNA antibodies are present, past infection is indicated. In the presence of antibodies to EBNA, an elevation of antibodies to early antigen suggests reactivation. Occasionally, a person will have a persistence of antibodies to EA with no clinical symptoms of EBV infection. Persistent levels of EA antibodies have also been found in persons with Burkitt’s lymphoma or nasopharyngeal carcinoma.

CASE STUDY:

A 12-year-old male complaining of fatigue, aching joints, and a sore throat was taken to his family physician by his father. These symptoms were apparent when the boy woke up that morning, although the patient related a history of feeling “flu-like” for the past week or so. Initial examination by the physician revealed swollen lymph nodes and an elevated temperature. A mono spot test was negative and other laboratory results were unremarkable. The patient was sent home.

The patient returned to the doctor’s office the next day with a further elevated temperature and increased pain from the sore throat and, now generalized, aching. The boy’s illness persisted with frequent trips to the physician. A summary of the laboratory results follows:

(SEE ATTACHED FOUR (4) CHARTS)

As often occurs in infectious mononucleosis, onset symptoms for this patient were vague and could have any of a number of etiologies. Lymphadenopathy, sore throat, and fever are common to infectious mononucleosis as they are to many other diseases. Eighty five to one hundred percent of acutely infected EBV patients have demonstratable abnormal liver function. Leukocyte counts generally are increased to a range of 12 to 25 K/MM3. During the first week of infection, there may be a shift to the left with decreased neutrophil counts. Toxic granulation can
be present. The increase is usually accompanied by a lymphocytosis (60 to 90%). Many of these are atypical or reactive lymphocytes with nuclear alterations and increased amounts of cytoplasm and basophilia. There is often a transient monocyte population increase. Additionally, young children often produce heterophile antibodies in limited amounts which may account for negative mono spot tests.

Although laboratory testing failed to show increased total leukocyte counts, this patient’s differential diagnosis is Epstein-Barr virus antibody positive, heterophile negative infectious mononucleosis.

REFERENCES
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- moderate reactive lymphs
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## CHART 4 - URINALYSIS

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REVIEW QUESTIONS
Course #DL-905
Choose the one best answer

1. Epstein-Barr virus will infect most persons in the United States by the age of:
   a. 25 years
   b. 2 years
   c. 40 years
   d. 10 years

2. Epstein-Barr virus infects what types of cells?
   a. B lymphocytes
   b. T lymphocytes
   c. epithelial cells
   d. a and c

3. Which of the following antibodies is not expressed in an acute EBV infection?
   a. IgM-VCA
   b. IgG-VCA
   c. EBNA
   d. EA

4. Epstein-Barr virus was discovered while working with continuous cell line propagated from tumors found in:
   a. Burkitt’s lymphoma
   b. leiomyosarcoma
   c. nasopharyngeal tumors
   d. acute lymphocytic leukemia

5. Latent Epstein-Barr viral infections persist for:
   a. 10 years
   b. a lifetime
   c. 4 to 6 months
   d. 2 to 4 weeks

6. The Epstein-Barr virus is a:
   a. naked (non-enveloped) double stranded DNA virus
   b. enveloped single stranded RNA virus
   c. enveloped double stranded DNA virus
   d. enveloped single stranded DNA virus

7. Peripheral smear finding in infectious mononucleosis would include:
   a. increased numbers of eosinophils
   b. decreased number of total white cells
   c. increased numbers of plasma cells
   d. increased numbers of reactive lymphocytes
8. EBV antibody studies in a patient yielded the following results: IgM-VCA absent; IgG-VCA present; EA absent; and EBNA present. These findings are consistent with:
   a. primary infection
   b. convalescence
   c. past infection
   d. reactivation

9. EBV antibody studies in a patient yielded the following results: IgM-VCA present; IgG-VCA present; EA present; and EBNA absent. These findings are consistent with:
   a. primary infections
   b. convalescence
   c. past infection
   d. reactivations

10. Polymerase chain reaction (PCR) analysis for EBV is a method for:
    a. amplifying antibody produced against viral antigen
    b. amplifying reactive lymphocyte nucleic acids
    c. amplifying viral nucleic acids
    d. distinguishing between IgM and IgG antibodies

11. Epstein-Barr virus begins its infectious process in the cell by:
    a. adsorption
    b. uncoating
    c. penetration
    d. celebration

12. The patient described in the case study had:
    a. chronic EBV infection
    b. chronic fatigue syndrome
    c. infectious mononucleosis
    d. chronic lymphocytic disorder

13. Epstein-Barr virus infections are usually acquired through:
    a. aerosolized droplets
    b. saliva exchange
    c. tears in mucous membranes
    d. blood transfusions

14. The incubation period for infectious mononucleosis is:
    a. 4 to 6 weeks
    b. 24 to 48 hours
    c. 21 days
    d. 3 to 4 months
15. The prescribed course of therapy for Epstein-Barr virus acute infections is:
   a. vaccine
   b. steroid therapy
   c. antiviral therapy
   d. supportive treatment

16. Initial infection with Epstein-Barr virus occurs:
   a. in the nasopharynx
   b. in the oropharynx
   c. in the intestinal tract
   d. through the skin

17. Inaccurate test assessment for infectious mononucleosis may include all but which of the following?
   a. misinterpretation of results
   b. inadequate sensitivity
   c. specific results indicating infection with another microorganism
   d. problems in specimen handling

18. In infectious mononucleosis, in addition to the presence of reactive lymphocytes on the blood smear, all but which of the following may be seen?
   a. increased basophils
   b. increased band neutrophils
   c. basophilic stippling of neutrophils
   d. increased monocytes

19. Initial symptoms of infectious mononucleosis frequently include all but which of the following?
   a. sore throat
   b. swollen lymph nodes
   c. fever
   d. diarrhea

20. Epstein-Barr virus belongs to which family of viruses?
   a. Retroviridae
   b. Adenoviridae
   c. Herpesviridae
   d. Paroviridae