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REVIEW

Diagnostic Evaluation of Mononucleosis-Like Illnesses

Christopher Hurt, MD,[a] Dominick Tammaro, MD[b]

[a]Department of Medicine, Division of Infectious Diseases, University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC; [b]Department of Medicine, Division of General Internal Medicine, Brown Medical School, Providence, RI.

ABSTRACT

Clinicians face a diagnostic challenge when a patient with the classic fever, pharyngitis, and lymphadenopathy triad of infectious mononucleosis has a negative "spot" heterophile antibody test. This screening test, although commonly considered sensitive for the presence of Epstein-Barr virus (EBV) infection, may be negative early after infection. A growing number of pathogens have been reported to cause heterophile-negative mononucleosis-like illnesses, including cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), human immunodeficiency virus (HIV), adenovirus, herpes simplex virus (HSV), *Streptococcus pyogenes*, and *Toxoplasma gondii*. Other infectious and noninfectious disorders also may present in ways that mimic mononucleosis, but fail to generate EBV's archetypal triad of clinical findings. A systematic approach to the diagnosis of mononucleosis-like illnesses ensures that conditions warranting specific therapy are distinguished from others requiring only supportive care.

KEYWORDS: Acute retroviral syndrome; Cytomegalovirus; Epstein-Barr virus; Human herpesvirus 6; Human immunodeficiency virus; Infectious mononucleosis; Mononucleosis-like illness; Toxoplasmosis

A 26-year-old graduate student presents with a 2-day history of fever, headache, and sore throat. She denies any rhinorrhea, cough, or sick contacts. Physical examination reveals slight tachycardia with normal temperature and blood pressure. Diffuse erythema of the pharynx is noted without tonsillar exudates. Her lungs are clear bilaterally. Rapid pharyngeal testing for group A streptococcal antigen is negative, and supportive care is advised. She returns several days later with a fever of 38.9°C, persistent pharyngeal erythema, and scattered tender anterior cervical lymph nodes. The tip of the spleen is palpable. A heterophile antibody test for Epstein-Barr virus-induced infectious mononucleosis is negative. How should you proceed?

INFECTIOUS MONONUCLEOSIS

Although the clinical triad of pharyngitis, fever, and lymphadenopathy was first described in 1889 as "glandular fever," it was not until 1920 that the first formal definition of infectious mononucleosis (IM) was made.[1] Examination of the peripheral blood smears of 6 college students presenting with glandular fever revealed striking similarities: an absolute lymphocytosis, with atypically abundant cytoplasm in many mononuclear cells. In 1932, Paul and Bunnell discovered that serum from patients with IM caused sheep erythrocytes to agglutinate, and their so-called "heterophile" antibody test became the basis for serologic diagnosis of infectious mononucleosis.[2]

When a laboratory worker infected with the newly discovered Epstein-Barr virus (EBV) in 1968 developed clinical symptoms of IM and heterophile antibodies,[3] the cause of the disease was finally identified. EBV accounts for approximately 9 of every 10 clinical presentations suggestive of IM, and 25% to 30% of adolescents and adults up to age 30 years with primary EBV infection will fall ill.[4] In contrast, childhood infection is generally subclinical. Within industrialized societies, lower socioeconomic status groups are infected with EBV at younger ages than affluent groups;[5] whites in the United States are 30 times more likely than blacks to develop IM.[6] More than 90% of adults worldwide who are seropositive for EBV have lifetime latent viral infection of their B lymphocytes and persistent viral shedding into saliva—the most probable source for transmission.[7] The diagnosis of "infectious mononucleosis" is reserved

Requests for reprints should be addressed to Dominick Tammaro, MD, Rhode Island Hospital, Jane Brown Ground, Suite 0100, 593 Eddy Street, Providence, RI 02903.

E-mail address: dtammaro@lifespan.org

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for the syndrome caused by EBV, and similar presentations caused by other processes should be referred to as "mononucleosis-like illnesses" (MLI).

Clinical Presentation

In IM, the subacute onset of pharyngitis is accompanied by moderate-to-high fevers (≥37.5°C) and generalized lymphadenopathy.[8] Up to 25% of patients have petechiae of the palate at least transiently, and the majority have pharyngeal erythema noted on examination.[8,9] An evaluation of 70 different clinical signs and symptoms of IM showed that only 4 occurred statistically more often in patients with a positive heterophile antibody test: petechiae of the palate, and adenopathy in the inguinal, axillary, and posterior auricular lymph node groups.[9] Among patients over age 40 years presenting with IM, cervical lymphadenopathy is observed with a much lower incidence, whereas hepatomegaly and jaundice are more common.[10]

Lymphadenopathy in IM is typically symmetric, moderately tender, and tends to peak during the first week of symptoms. Mild-to-moderate tonsillar enlargement is common, frequently with grayish exudates. In general, urticarial and maculopapular rashes are rare except among those patients given beta-lactam antibacterials erroneously, 90% of whom go on to develop a rash.[11]

A palpably enlarged spleen may be present in as many as 63% of patients.[12] In a study of 29 patients hospitalized on an otolaryngological service for severe IM, all were found to have splenomegaly ultrasonographically, but only 17% had a palpable spleen on physical examination.[13] Spontaneous atraumatic splenic rupture is an exceedingly rare complication of IM.[14]

Diagnosis of IM: The Heterophile Antibody Test

The Paul-Bunnell heterophile antibody (HetAb) is actually a heterogeneous *group* of mostly IgM-class immunoglobulins generated in response to acute EBV infection. Immunologic studies suggest that the Paul-Bunnell *antigen* is actually a complex glycoprotein structure on the surface of EBV-infected cells.[15] Structurally similar epitopes on nonhuman erythrocytes cross-react with HetAb, forming the basis of the red cell agglutination test. Absorbing other nonheterophile antibodies from patient serum with guinea pig kidney cells improves the specificity of these assays,[2] with even greater gains seen when horse erythrocytes are used instead of those of sheep.[16] Development of a slide-based test using equine erythrocytes resulted in the "spot" test.[17]

Of the adolescents and adults who develop clinical IM, up to 85% have detectable HetAb.[18] The antibodies develop within the first 7 days after the onset of symptoms, peak between 2 and 5 weeks into illness, and can be detected at low levels up to 12 months later. The heterophile test may be falsely negative in up to 25% of patients in the first week of symptoms, when antibody levels are below the limit of detection of the assay.[19] Although heterophile testing in the pediatric population may miss 50% to 75% of acute EBV infections, it remains an excellent test for adolescents and adults, with the capability to detect between 71% and 90% of cases.[20] Nearly 1 in 10 adults with true IM will be persistently heterophile-negative, but can be diagnosed by detection of IgM antibodies against the viral capsid antigen (VCA) of EBV.[21] Many of these patients are at the extremes of age.

Because of the excellent specificity of current heterophile tests for IM, a positive result is generally considered definitive for the diagnosis of acute EBV infection. However, reports of EBV-negative, heterophile-*positive* patients presenting with symptomatic, acute infection from human immunodeficiency virus, type 1 (HIV-1) are important to bear in mind.[22]

CLINICAL SIGNIFICANCE

- The diagnosis of "infectious mononucleosis" describes the syndrome of fever, pharyngitis, and lymphadenopathy, and is specific for illness caused by Epstein-Barr virus (EBV).
- Of patients with EBV infection, 10% will be persistently heterophile-negative.
- Cytomegalovirus and human herpesvirus 6 are the most common non-EBV causes of mononucleosis-like illness.
- Acute HIV infection is important to consider also because conventional diagnostic methods will be negative until detectable antibodies develop.

HETEROPHILE-NEGATIVE MONONUCLEOSIS-LIKE ILLNESSES

Heterophile-negative conditions with a clinical presentation similar to IM (Table 1) can be grouped into 3 principal categories: non-EBV viral etiologies, bacterial infections, and protozoal causes. Although some literature discusses systemic disorders such as sarcoidosis and malignancies like Hodgkin's disease as causes of MLI (Table 2), their inclusion is based mostly on the presence of a particular finding, such as atypical lymphocytosis or adenopathy, rather than the classic triad of IM's physical findings—and they thus fall outside the scope of this review.

Viral Causes

Cytomegalovirus. Cytomegalovirus (CMV) causes an estimated 7% of MLI cases.[23] A herpesvirus relative of EBV, CMV establishes latent infection in a substantial portion of the general population and may reactivate with immune compromise.[24] Adolescents and adults in close contact with children under age 2 years, including daycare workers and

Table 1 Characteristics of Infectious Mononucleosis and Mononucleosis-Like Illnesses

Agent	Associated Condition(s)	Estimated Proportion of MLI Presentations*	Distinguishing Features	Diagnostic Test(s) for Acute Infection
Epstein-Barr Virus (EBV)	Infectious mononucleosis	50%-90%	Tender inguinal, axillary, or posterior auricular LAD Petechiae of palate Tonsillar enlargement Splenomegaly Adolescents and adults up to age 30 Higher socioeconomic status in childhood	Heterophile ("spot") test EBV anti-VCA IgM, IgG
Human Herpesvirus 6 (HHV-6)	Roseola infantum (Exanthem subitum)	9%	Bilateral, nontender, anterior and posterior LAD lasting up to 3 months	Anti-HHV-6 IgM and IgG HHV-6 PCR
Cytomegalovirus (CMV)	Mononucleosis-like illness	5%-7%	Anicteric hepatitis Prolonged fevers Mild cervical LAD Contact with children, especially younger than age 2 years	Anti-CMV IgM Spin amplified urine culture for CMV, with pp65 antigen detection CMV PCR
Herpes Simplex Virus, Type 1 (HSV-1)	Herpes labialis	6%	Gingivostomatitis, tonsillar exudates Profound odynophagia	Slide-based DFA Viral throat culture
Group A, β-hemolytic *Streptococcus pyogenes* (GABHS)	Pharyngitis Rheumatic fever	3%-4%	Abrupt onset of sore throat Tonsillopharyngeal erythema Tender, enlarged anterior cervical LAD Absence of hepatomegaly or splenomegaly Winter and early spring peak incidence	RADT Bacterial throat culture
Toxoplasma gondii	Toxoplasmosis	$\leq$3%	Small, symmetric, nontender LAD History of ingesting undercooked meat Exposure to cats or cat droppings	Anti-Toxoplasma IgM Anti-Toxoplasma IgG ELISA and/or avidity assay
Human Immunodeficiency Virus, Type 1 (HIV-1)	Acute retroviral syndrome (ARS) AIDS	$\leq$2%	Abrupt onset of symptoms, lasting up to 2 weeks Painful mucocutaneous ulcerations on oral mucosa, penis, or anus Nontender axillary, cervical, and occipital LAD between 7 and 14 days Nonpruritic, macular or maculopapular exanthem generalizing from face, chest to extremities—including palms and soles Intravenous drug use, unprotected sexual intercourse, or other HIV exposure risks	ELISA with Western blot HIV-1 PVL
Adenovirus	Nonspecific upper respiratory symptoms Pharyngo-conjunctival fever Pneumonia	$\leq$1%	Clinically similar to GABHS Conjunctivitis may accompany pharyngitis	EIA Viral culture of conjunctivae or throat Shell vial culture of throat or nasopharyngeal secretions

AIDS = acquired immune deficiency syndrome; DFA = direct fluorescent antibody; EIA = enzyme immunoassay; ELISA = enzyme-linked immunosorbent assay; LAD = lymphadenopathy; PCR = polymerase chain reaction; PVL = plasma viral load; RADT = rapid antigen detection test; VCA = viral capsid antigen.

*Data from: 23, 47, 52, 60.

Table 2 Diseases with Presentations Suggestive of Infectious Mononucleosis

Connective tissue disorders
Sarcoidosis
Systemic lupus erythematosus
Malignancies
Hodgkin's disease
Non-Hodgkin lymphoma
Infections
Bartonella henselae (cat-scratch disease)
Corynebacterium diphtheriae (diphtheria)
Enteroviruses (coxsackieviruses, ECHO viruses)
Francisella tularensis (oropharyngeal tularemia)
Hepatitis A virus
Hepatitis B virus
Mycobacterium tuberculosis (tuberculous adenitis)
Rubella virus (German measles)
Drug reactions
Carbamazepine
Minocycline
Phenytoin

schoolteachers, are at higher risk of acute CMV infection. Although primary infection is usually asymptomatic, CMV can produce a MLI difficult to distinguish clinically from IM. Sore throat, fatigue, and malaise are prominent in both, although the degree of lymphadenopathy, pharyngeal erythema, and splenomegaly is generally less with CMV.[25] Nonspecific rashes also may be seen.

Unlike IM, elevated transaminases are frequent in CMV-induced MLI, occurring in up to 92% of cases.[26] Although this sometimes causes confusion with more typical forms of viral hepatitis, the increase in transaminase levels rarely exceeds 5-fold above normal—in sharp contrast to the increases as high as 100-fold seen with classic hepatitis viruses. Assays for anti-CMV IgM antibodies, generally positive during acute infection, have been replaced as the diagnostic test of choice by antigen detection assays. In the most useful of these, monoclonal antibodies are used to detect pp65, a component of the shell surrounding the virus' nucleoprotein core—either directly from clinical specimens or in shell vial cultures of CMV.[27] Antigenemia assays and commercially available polymerase chain reaction (PCR)-based techniques have proven their utility in diagnosing CMV disease among post-transplant, immunocompromised patients,[28] and may have a role for immunocompetent ones as well.[29]

Human Herpesvirus 6. Lesser known than EBV or CMV, human herpesvirus 6 (HHV-6) causes a generally mild but prolonged febrile MLI among adults, characterized primarily by nontender cervical lymphadenopathy.[30] HHV-6 is responsible for a classic childhood exanthem: roseola infantum (also called exanthem subitum or "sixth disease"). Similar to its herpesvirus cousins, HHV-6 usually produces latent infection early in life, with the highest seroconversion rates between 6 and 8 months of age.[31] IgM titers increase to detectable levels within days after infection, but because 5% of healthy adults have circulating anti-HHV-6 IgM at any time,[32] detection is not always diagnostic for acute infection. Comparison of acute and convalescent sera demonstrating an increase in titers is compelling evidence, but unhelpful during the acute illness. Culture remains the reference standard for diagnosis, although PCR-assisted detection of viral DNA in whole blood in the absence of detectable anti-HHV-6 antibodies is both highly sensitive and specific for primary infection.[33]

Human Immunodeficiency Virus, Type 1. The acute retroviral syndrome (ARS) of symptomatic early HIV-1 infection was first described as a MLI in 1985.[34] Approximately 90% of patients develop ARS within 6 months of acquiring HIV,[35] and many are ill enough to seek medical attention.[35] Symptoms develop abruptly after an average incubation time of 2 to 4 weeks and may include sore throat, myalgias, arthralgias, headache, malaise, and nausea.[36] Fever may be as high as 40°C and accompanies pharyngitis and nontender lymphadenopathy of the axillary, cervical, and occipital nodes.[37] Mucocutaneous ulceration may be seen in primary HIV-1 infection, with well-demarcated, painful, shallow ulcers of the oral mucosa, penis, or anus.[38] A nonpruritic, maculopapular rash is common in ARS. Developing 48 to 72 hours after the onset of fever and lasting up to a week, the exanthem erupts on the face and upper chest before spreading to the extremities, including the palms and soles.[38]

Standard enzyme-linked immunosorbent assays (ELISAs) detect the presence of HIV-specific antibodies from clinical specimens. Serum is incubated in wells of a microtiter plate containing immobilized HIV antigens, allowing any antibodies present in the serum to bind to their corresponding antigens. A second, assay-specific, enzyme-conjugated immunoglobulin is then added, which attaches to any plate-bound patient antibodies. The enzyme's activity is measured, serving as a proxy for the amount of original anti-HIV antibody present in the patient's serum. Typically, anti-HIV antibodies do not reach a detectable level for about 2 weeks after infection, so ELISAs therefore cannot be relied upon to diagnose ARS.[39]

Because initial, unchecked replication of HIV-1 in a new host leads to high levels of viremia, HIV antigen assays were used to detect acute infection before the advent of widespread plasma viral load (PVL) testing.[40] One antigen in particular, a structural protein of the viral capsid named p24, proved particularly useful. However, with inferior sensitivity to PVL and false-negative results in almost 25% of patients with ARS,[41] p24 antigen testing has fallen out of favor. Although not yet licensed by the Food and Drug Administration (FDA) for the diagnosis of ARS, reverse transcriptase polymerase chain reaction (RT-PCR) PVL testing appears to be highly sensitive and specific for this purpose.[41] False-positive RT-PCR results have been reported at a rate of about 2% to 3%,[41] and are suggested in those patients with less than 2000 copies of HIV-1 RNA per cubic centimeter of blood (copies/cc). If ARS is strongly

suspected and the PVL result is <10,000 copies/cc, the test should be repeated.[42]

Adenovirus. A common cause of self-limited childhood respiratory tract infections, adenovirus is often more aggressive among adults. Spread by aerosols or fecal-oral transmission, the virus is hearty and can survive for long periods outside of the host. Pharyngitis and coryza are common presentations of infection, often accompanied by fever and cervical lymphadenopathy.[43] When conjunctivitis is present as well, the findings mark one of the classic syndromes of adenoviral infection, pharyngoconjunctival fever—large outbreaks of which have been associated with public swimming pools. Adults may develop tracheobronchitis or a mild atypical pneumonia, although manifestations are often more severe among immunosuppressed patients.[44] Enzyme immunoassay (EIA) and PCR-based rapid diagnostic methods are available,[45] but the reference standard remains isolation of the virus in culture from nasopharyngeal or oropharyngeal secretions.

Herpes Simplex Virus, Type 1. Although the "cold sore" of herpes simplex virus, type 1 (HSV-1) is thought to be its major clinical manifestation, herpes labialis actually represents reactivation disease. Pharyngitis, tonsillar exudates, and gingivostomatitis are the most frequent manifestations of primary herpetic infection.[46] A study of over 600 college students demonstrated HSV-1 to be the cause of pharyngitis in almost 6% of cases.[47] Although fever and odynophagia are present for 3 to 8 days, cervical lymphadenopathy may continue for several weeks. Serologic techniques require comparison of acute and convalescent sera, and have a limited role in diagnosing acute infection. Rapid detection of HSV is possible with various ELISA and PCR-based methods.[48] From studies of genital ulcerative disease, PCR has proven to be both faster and more sensitive than traditional viral culture.[49]

Bacterial Causes

Streptococcus pyogenes. Group A β-hemolytic *Streptococcus pyogenes* (GABHS) is the most frequent bacterial cause of acute pharyngitis.[50] Most cases of "strep throat" occur in the winter or early spring months in temperate climates. Among all adults presenting with sore throat, GABHS accounts for up to 10% of cases.[51] Streptococcal illness is more likely among patients who have significant contact with school-aged children, especially those between 5 and 15 years of age. In 2 large studies of patients evaluated for MLI, rates of GABHS-associated pharyngitis were <5%.[52,53]

Streptococcal pharyngitis presents with the abrupt onset of fever and intense odynophagia. Physical examination generally reveals hyperemia of the pharynx, with or without exudates. Erythema and edema of the uvula and soft palate may be seen, occasionally with petechiae. Anterior cervical lymph nodes may become enlarged and tender. Throat culture remains the diagnostic standard, with a sensitivity of 90% to 95% if properly collected.[54] Although rapid antigen detection tests (RADTs) are not as sensitive as throat culture, their specificity for GABHS significantly increases the number of patients treated appropriately with antibiotics.[55] Because of the low incidence of GABHS pharyngitis among adults, current recommendations suggest that a confirmatory throat culture is not necessary if the RADT is negative.[56]

Protozoal Causes

Toxoplasma gondii. Toxoplasmosis is the main protozoal cause of MLI. The life cycle of *Toxoplasma gondii* can only be completed through sexual replication in the feline intestinal tract; the host cat sheds oocysts in its feces.[57] Shortly after ingestion by other animals, oocysts transform into freely motile tachyzoites that invade gut epithelium and disseminate. Tachyzoites tend to localize in brain and muscle tissue, encyst, and lay dormant for the life of the host. In most of the world, ingestion of undercooked meat containing *T. gondii* cysts appears to be the major vector for transmission.[57]

Immunocompetent patients with primary *T. gondii* infection are often asymptomatic, but nontender cervical or occipital lymphadenopathy is sometimes seen.[58] Constitutional symptoms are mild. Maculopapular rashes, pharyngitis, and hepatosplenomegaly also occur, but much less frequently. Toxoplasmosis is generally self-limited, resolving spontaneously over several months. Diagnosis of acute infection in pregnancy is particularly important, as toxoplasmosis may cause damage to the developing fetal nervous system.[58]

Because anti-toxoplasma IgM antibodies can persist for years after infection, their presence alone cannot be used to diagnose primary infection. The same is true for anti-toxoplasma IgG antibodies, which appear within 2 weeks of primary infection and remain detectable for life.[58] Acute versus chronic infection may be distinguished by IgG "avidity" testing, based on the finding that prolonged immunologic exposure to the organism results in the production of anti-toxoplasma IgG antibodies with progressively stronger binding to (or *avidity* for) toxoplasmal antigens. Thus, in a patient with a positive IgM, *weaker* binding of IgG in an avidity assay is suggestive of more recent infection.[59]

APPROACH TO DIAGNOSIS

Given the array of conditions mimicking infectious mononucleosis (Table 1), a systematic approach to heterophile-negative mononucleosis-like illness is essential. Before embarking on any laboratory assessment, a comprehensive history should be obtained from the patient, including past medical problems, family history, contact with pets or with any sick persons, sexual history, and any recent travel. Although physical examination may reveal only nonspecific findings, the discovery of characteristic features of some diseases—such as mucocutaneous ulceration in acute HIV-1 infection—can prove invaluable.

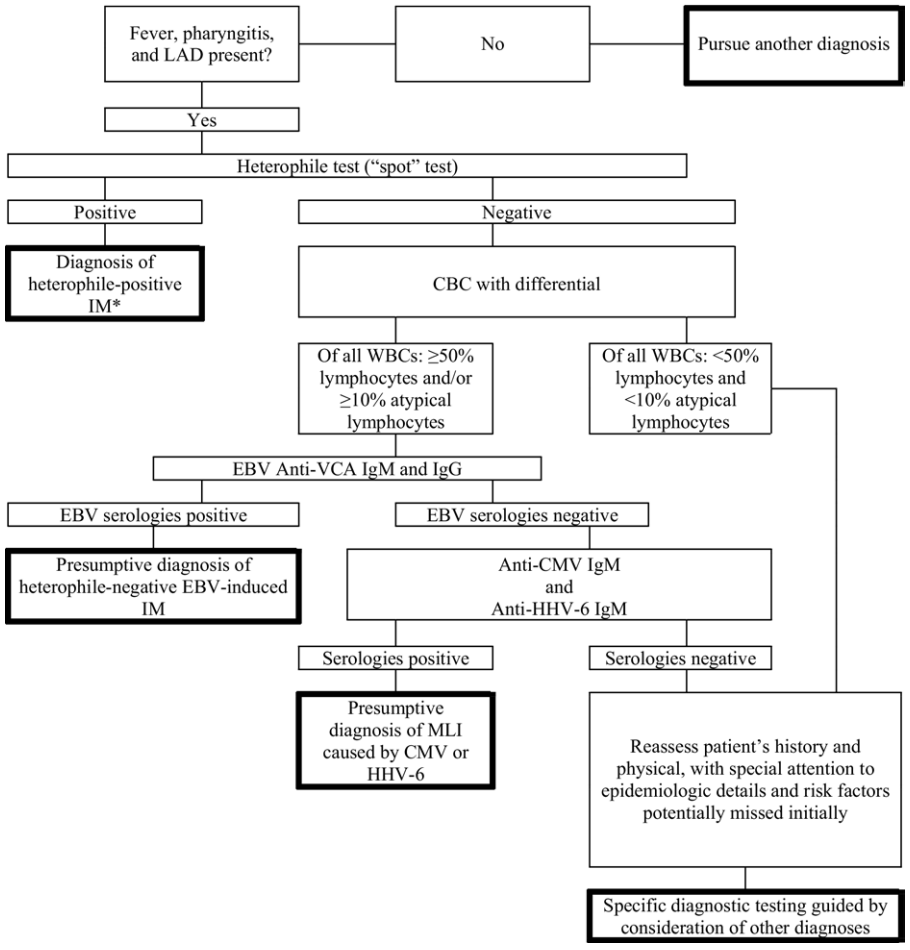

Figure Diagnostic algorithm for guidance in evaluation of MLI. CMV = cytomegalovirus; EBV = Epstein-Barr virus; HHV-6 = human herpesvirus 6; IM = infectious mononucleosis; LAD = lymphadenopathy; MLI = mononucleosis-like illness; VCA = viral capsid antigen; WBC = white blood cell. *Consider possibility of false-positive heterophile test due to HIV-1 before finalizing diagnosis. Adapted from Tsaparas YF et al, with permission from *Archives of Pathology & Laboratory Medicine*. Copyright 2006. College of American Pathologists.

An algorithm to guide the laboratory diagnosis of IM and heterophile-negative MLI is presented in the Figure, adapted from one published previously.[60] Initial screening for a clinical picture consistent with IM should include heterophile antibody testing. If positive, this is highly suggestive of EBV-induced IM, but does not rule out the possibility of other infections, including HIV-1.[22] If negative, a complete blood count (CBC) with automated differential may be helpful. Marked lymphocytosis (over 50% of all leukocytes) with atypical cells comprising at least 10% of all leukocytes constitutes Hoagland's criteria for atypical lymphocytosis,[8] suggesting heterophile-negative EBV-induced IM. Specific serologies for antibodies against EBV's capsid (VCA) should be sent for confirmation. If the anti-VCA IgM and IgG assays are negative, request serologic testing for the 2 other main viral etiologies of MLI: CMV and HHV-6. Negative results should prompt a reassessment of the patient's symptoms and history, with thought given to other less common diagnoses and appropriate testing.

SUMMARY

When a patient presenting with pharyngitis, lymphadenopathy, and fever has negative results on both HetAb and EBV-specific serologic tests, the clinician is faced with a diagnostic challenge. Consideration must be given to the many potential causes of heterophile-negative mononucleosis-like illness, with confirmatory testing driven by a careful appraisal of the patient's clinical course, history of exposures and risks factors, and physical examination.

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