Acute Infectious Mononucleosis: A Review for Urgent Care Physicians

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Abstract

Acute infectious mononucleosis (IM) is a common illness that presents to urgent care facilities. The presenting symptoms of acute IM can range from the obvious, such as persistent exudative tonsillitis and marked cervical lymphadenopathy, to the more vague symptoms of fatigue and malaise. Although most cases of acute IM are either subclinical or require only supportive care, some cases can have severe and life-threatening complications. Arrival at the correct diagnosis can be complicated by the timing of the patient's presentation, since the sensitivities and specificities of the various laboratory and diagnostic tests change as the illness evolves. Even those patients without any complications can have prolonged symptoms and difficulty returning to school, work, or physical activities.

Introduction

Sore throat and fever are among the most common complaints presenting to an urgent care facility. One common cause of a sore throat, Group A *Streptococcus*, can often be reliably diagnosed with rapid antigen testing and/or culture. On the contrary, acute infectious mononucleosis (IM) is not always considered early in the course of a sore throat and can often be diagnostically challenging. However, a better understanding of the pathophysiology, clinical course, and limits of laboratory testing of acute IM can help the urgent care clinician to become proficient with the diagnosis, treatment, and prognosis of this illness.

History and Pathophysiology

Infectious mononucleosis was first described in the 19th century as *Drüsenfieber*, or "glandular fever," owing to its clinical presentation of fever with lymphadenopathy and splenomegaly. Later, in the 1920s it was found to be associated with a "mononuclear leukocytosis" by Sprunt and Evans. However, it was not until the 1960s that the link between infectious mononucleosis (IM) and Epstein-Barr virus (EBV), a human herpes type 4 virus, was established.[1,2]

Spread of the virus occurs from oral secretions. Shedding of EBV has also been detected from the cervix and seminal fluid, which raises concern for the possibility of transmission through sexual contact.[3] The incubation period between exposure and presentation of symptoms can range between 30 to 60 days, making identification of the initial exposure difficult.

Human exposure and infection with EBV is ubiquitous, with 50% of children by the age of five having detectable EBV antibodies. This increases to 90% by the age of 25, with the majority of these adults having had asymptomatic or subclinical infection. The most common age group presenting with acute infectious mononucleosis is between the ages of 15 to 24.[4]

Clinical Presentation

Fatigue and malaise are the most frequent complaints, followed by sore throat and fever. Exam often reveals enlarged, erythematous, and exudative tonsils, but these findings are not always present later in the course of the illness. A thin, grey

membrane covering the tonsils can sometimes be seen and is associated with acute infectious mononucleosis. Posterior cervical lymphadenopathy can be suggestive of acute infectious mononucleosis but is not always seen. On the contrary, anterior cervical lymphadenopathy can be quite marked and is usually found more easily than the posterior chain enlargement.

Enlarged cervical lymph nodes should also prompt the clinician to check for other areas of lymphadenopathy (axillary, inguinal) that can be associated with IM as well as other infections and malignancies. Also, findings of splenomegaly or hepatomegaly can be suggestive of acute IM. In fact, the initial presenting symptom could be abdominal pain from hepatitis or spontaneous rupture of the spleen, requiring rapid recognition. The clinician should also perform a thorough examination of the skin and sclera checking for jaundice or a diffuse, erythematous, maculopapular rash. These skin manifestations may also be the presenting complaint, especially the latter in a patient who may have been prescribed amoxicillin for presumed Group A streptococcal pharyngitis.

Diagnostic Testing

Over the decades following the discovery of the Epstein-Barr virus's association with infectious mononucleosis, various diagnostic tests have been developed, beginning with the heterophile antibody agglutination (monospot) test. After infecting B-cell lymphocytes in the oral epithelium, the virus is then spread by these B-cells throughout the reticulo-endothelial system. This, in turn, induces the B-cells to produce IgM antibodies against EBV. In the presence of these antibodies, sheep and horse red blood cells will agglutinate, which indicates a positive test. The IgM antibodies peak within two to six weeks after the onset of symptoms, so testing in the first week of illness has a lower (50%) sensitivity. However, by the third week, the sensitivity increases to over 80%, and the specificity is nearly 100%.[5,6] Therefore, when clinical suspicion for IM is high, it is recommended to repeat the heterophile antibody testing every two weeks, for a period six weeks from the onset of symptoms. It should be noted that if the heterophile antibody test is positive, it can remain so for up to a year before the antibodies decline. Also, false positive tests are rare but can be caused by some malignancies (lymphoma and leukemia), infections (HIV, HSV, toxoplasmosis, rubella), and autoimmune disorders (rheumatoid arthritis and systemic lupus erythematosis).[6] In particular, in the adolescent and young adult age group that most frequently presents with acute mono-like symptoms, acute HIV/retroviral syndrome should also be considered as it can mimic acute IM.

Testing for more specific EBV antibody serologies has been developed and is also available to most practitioners. The drawbacks of these serologies compared to the heterophile antibody test are their higher cost and complexity, the latter often leading to frequent misinterpretation.

During the initial three to four weeks of acute IM, EBV early antigen (EA) antibodies will begin to rise but then will quickly decrease over the next three months or so. Also, early in the course of the illness, EBV viral capsid antigen (VCA) IgM antibody will begin to peak during the first two to six weeks of symptoms. It will then slowly decline over the following two to three months as well.[4] Therefore, if repeat VCA IgM and EA levels remain low during the course of the illness, the diagnosis of acute IM is unlikely.

After two to three months from the onset of symptoms, VCA IgG antibodies begin to appear and will remain elevated for life. Also, around this time EBV nuclear antigen (EBNA) antibodies will begin to be detected. EBNA will also remain elevated for the remainder of one's life, and the presence of these antibodies likely excludes acute IM within the last year.[5]

In summary, VCA IgM and EA antibodies appear in the first few months of symptoms and are indicative of acute IM, while VCA IgG and EBNA antibodies appear much later in the course and during convalescence (Table 1). If serologic results are equivocal or do not agree with the clinical picture, the serologies should be rechecked in two to four weeks.

Table 1: Progression of Epstein Barr Virus Serological Markers

Infection status	EA	VCA IgM	VCA IgG	EBNA
No prior infection	-	-	-	-
Early infection	+	+	+/-	-
Late infection	-	+/-	+	+/-
Past/latent infection	-	-	+	+/-

In ascending order of appearance (left to right): early antigen (EA) antibody, viral capsid antigen IgM antibody (VCA IgM), viral capsid antigen IgG antibody (VCA IgG), and Epstein Barr nuclear antigen antibody (EBNA).

Besides specific EBV antibody testing, there is other non-specific laboratory testing that may support the diagnosis of acute IM. During the initial two to six weeks of symptoms the patient will often have leukocytosis with an elevated number of atypical lymphocytes (greater than 10%) and may also have a mildly decreased platelet count. Up to 10% of patients may also have mildly elevated liver transaminases that usually normalize within three months.

Treatment and Complications

Treatment of acute IM is mostly supportive with analgesics, increased fluid intake, and rest. The vast majority of patients are treated as outpatients. Since EBV is spread by oral secretions or intimate contact, there is no risk of transmission when returning to work or school.

However, in cases of extreme tonsillar hypertrophy and dehydration, hospital admission or observation for intravenous fluid therapy may be required. Although corticosteroids (prednisone) have been shown to be effective in decreasing the pain

from acute tonsillitis, there is a concern that suppressing the body's cellular response could lead to further proliferation of EBV.[8] EBV complications can include other sites of infection (meningitis, encephalitis, Guillain-Barré Syndrome), and EBV is also involved with the development of some malignancies (lymphomas). Corticosteroids should, therefore, be used with some caution. In severe cases requiring corticosteroids, the recommended dosage is 0.5mg -1.0mg/kg per day of prednisone for seven days, followed by a taper.[9]

The fatigue and malaise from acute IM varies widely from mild symptoms lasting only a few weeks to more severe symptoms of fatigue that can persist for several months, or even up to a year or more in up to 10% of patients. The persistence of fatigue that is seen in some patients after acute IM would seem to implicate EBV as the causative agent of chronic fatigue syndrome (CFS). However, no convincing link has been found between EBV and CFS.

Acyclovir has been used against other herpes viruses (herpes simplex and varicella zoster) with some success, and *in vitro* studies of acyclovir have shown it to be effective against EBV. However, to date, there are no convincing clinical studies to show that it improves the course in patients with acute IM. Nevertheless, acyclovir (along with IVIG) could be considered in those with serious complications or immunodeficiencies.[10]

Complications of EBV during the active infection can affect a variety of systems (Table 2). Localized spread of infection around the tonsils can lead to the development of peritonsillar cellulitis or abscess. This complication can occur in any patient with suppurative tonsillitis, including Group A streptococcal infections. Therefore, in patients presenting with a peritonsillar abscess, both acute IM and Group A *Streptococcus* should be considered. A peritonsillar abscess necessitates incision or aspiration with drainage as well as intravenous antibiotics and corticosteroids.

Table 2: Complications of Acute Infectious Mononucleosis

COMMON	RARE
Dehydration	Splenic rupture
Massive splenomegaly	Necrotic hepatitis
Hepatitis	CNS infections
Maculopapular rash	Hemolytic anemia
Prolonged fatigue/malaise*	Hemophagocytic Syndrome
Peritonsillar abscess	Myocarditis

*Post-infection fatigue and malaise can continue for one to two years in some patients with acute IM. This should not to be confused with chronic fatigue syndrome.

Acute IM is commonly associated with splenomegaly and mildly increased liver transaminases. Although a rare complication – splenic rupture – can occur. Splenic rupture is more often spontaneous rather than traumatic and is most likely to occur within the first three to four weeks of symptoms.[11] Therefore, it is recommended that all patients with acute IM be educated about this possibility as well as its associated symptoms. Since the majority of the cases of splenic rupture occur in the first three to four weeks of symptoms, this is often used as a guideline as to how long the patient should refrain from contact sports or vigorous activity. Determination of splenic size by ultrasound does not seem to be a very reliable prognostic indicator, since spleen sizes vary considerably among the population, and the patient's baseline spleen size was not likely to have been imaged prior to infection. Also, the degree of splenic enlargement does not necessarily correlate with the likelihood of rupturing.[12] Exam findings of splenomegaly and left upper quadrant tenderness are certainly more cost-effective than ultrasound but may not be reliable indicators themselves.[13]

Other, more rare complications can involve the central nervous system, such as aseptic meningitis, encephalitis, optic neuritis, cranial nerve palsies, transverse myelitis, and Guillain-Barré syndrome.[9] Additional rare complications include fulminant or necrotic hepatitis as well as hematologic emergencies, such as hemolytic anemia and hemophagocytic syndrome. The latter is a devastating syndrome that is highly associated with EBV. Clinical findings of hemophagocytic syndrome (also known as hemophagocytic lymphohistiocytosis, or HLH) are fever, jaundice, splenomegaly, and lymphadenopathy. Activated macrophages (histiocytes) consume leukocytes, red blood cells, and platelets in the bone marrow and spleen. This leads to a pancytopenia and can mimic T-cell lymphoma. The result is subsequent and profound immunodeficiency. HLH has a high rate of mortality, often from overwhelming secondary infections.[14]

Closing Remarks

Patients with acute infectious mononucleosis will frequently present to an urgent care facility. Therefore, urgent care providers must have acute IM in their differential when evaluating patients for fatigue, sore throat, lymphadenopathy, splenomegaly, and fever. In particular, in those patients with prolonged or vague symptoms (fatigue and malaise), the diagnosis of acute IM can be easily missed. Being on the lookout for acute IM and understanding the importance of the timing of laboratory testing as well as its limitations can assist the clinician in arriving at the correct diagnosis. Also, familiarizing oneself with the complications of acute IM can aid in arriving at the correct diagnosis in those patients with atypical presentations, such as hepatitis or splenic rupture. Lastly, urgent care clinicians should ensure that they are well-versed about the expected course, its potential complications, and prognosis, so that they can effectively educate their patients.

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