



Infectious Mononucleosis

Introduction

Infectious mononucleosis (IM) is the name given to an etiologically heterogeneous syndrome characterized by the presence of fever, sore throat, lymphadenopathy, and a predominance of atypical lymphocytes on peripheral blood smear. The majority of cases of IM are caused by the Epstein Barr Virus (EBV) or Cytomegalovirus (CMV). The number of cases attributed to each virus depends somewhat on local factors; one report from 1970 found that 79% of cases were due to EBV while the other 21% were due to CMV (1). Acute infection with the human immunodeficiency virus (HIV) can also produce an IM-like illness. One retrospective survey from the late 1990s showed that approximately 1% of patients who had laboratory investigations ordered to rule out EBV showed evidence of acute HIV infection (2).

Epidemiology

IM occurs most commonly in persons between the ages of 10 and 19 (6-8 cases/1000 persons/year)(3,4). Infectious mononucleosis is commonly associated with populations where young people live in close contact, such as military bases and universities. A prospective cohort study in university students followed individuals who were seronegative for EBV at the start of their studies; forty-six per cent (46%) experienced seroconversion during their stay at university and one in four of these students developed symptomatic IM (5). Transmission is thought to be through exposure to saliva. A recent study showed that after infection with EBV, virus was detectable in blood for an average of three days, but in saliva for an average of 32 weeks (6).

Clinical Features

Primary infection with EBV, CMV, or HIV can range from a clinically unapparent course to a severe illness with multiple manifestations. Patients with typical IM complain of sore throat (82%) and present with a combination of lymphadenopathy (94%) and fever (76%). Other commonly encountered

symptoms include malaise (57%), anorexia (21%), myalgia (20%), nausea (12%), and abdominal pain (9%) (7). Clinical pharyngitis with erythema and pharyngeal exudates is seen in a majority of patients (8). Lymphadenopathy may be local or diffuse. Nodes are typically freely mobile and only mildly tender to palpation. Splenomegaly is present in as many as 63% of patients and is usually maximal at the end of the second week of illness (7). Hepatomegaly is encountered less frequently, and jaundice is present in ~ 5% of cases (9).

Most cases of IM resolve with no long-term sequelae, with the obvious exception of acute HIV infection. However, in a minority of cases the syndrome of IM can be associated with serious and occasionally life-threatening complications. Death from IM is rare and is most commonly found in patients presenting with neurologic complications, splenic rupture, or upper airway obstruction.

in some instances; they can be severe and rapidly progressive, but full recovery usually follows (7). Other nervous system complications, such as seizure, Guillain-Barre syndrome, and transverse myelitis have been described (12). Clinically apparent complications of the renal, cardiac, and pulmonary systems are rare but have been reported.

Diagnosis

The hallmark of IM in the laboratory is a relative lymphocytosis with a predominance of atypical lymphocytes. Hoagland (13) proposed a set of diagnostic criteria based on this finding under which IM is diagnosed in patients with a compatible clinical presentation with a lymphocytosis of greater than or equal to 50% of the white blood cell (WBC) differential, and atypical lymphocytes accounting for greater than or equal to 10% of the total WBC count. Atypical lymphocytes

The classic heterophile antibody test involves finding the highest serum dilution that is able to agglutinate sheep erythrocytes after absorption of the test serum by guinea pig kidney.

Infectious mononucleosis can present with abnormalities of the hematologic system beyond the atypical lymphocytosis, which in part defines the syndrome. Autoimmune hemolytic anemia, thrombocytopenia, and neutropenia occur occasionally. The thrombocytopenia is usually mild, but severe platelet deficiency resulting in fatal intracerebral hemorrhage has been reported (10).

Splenic rupture is a rare but potentially catastrophic complication of IM. Rupture is most common in the second or third week of illness and is the basis for the suggestion that patients avoid contact sports for at least the first month after diagnosis (11).

Neurologic complications are rare in the setting of IM, occurring in less than 1% of clinical cases. Encephalitis and aseptic meningitis can both be the initial presentation

are generally larger than typical mature lymphocytes and often have basophilic and vacuolated cytoplasm and lobulated, eccentric nuclei. They are a non-specific finding and can be observed in a number of conditions, including CMV infection, acute HIV, roseola, toxoplasmosis, acute viral hepatitis, rubella, mumps, and some drug reactions. In order to overcome the low specificity of atypical lymphocytosis, a number of tests can be employed. The most important of these include the heterophile antibody tests and the specific EBV antibody tests.

Heterophile antibodies were originally described as sheep erythrocyte agglutinins in 1932 by Paul and Bunnell (14). The classic heterophile antibody test involves finding

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the highest serum dilution that is able to agglutinate sheep erythrocytes after absorption of the test serum by guinea pig kidney. Latex agglutination assays using horse red blood cells have been developed more recently and are the basis for the commercial spot tests currently available. Ninety per cent of patients with EBV IM will test positive for heterophile antibodies at some point in their illness. False negative tests occur as often as 25% during the first week after symptom onset, but these rates fall to less than 5% by the third week of illness (8). False positive results are rare, but have been reported in several conditions, including toxoplasmosis, rubella, lymphoma, and certain leukemias.

Heterophile antibodies, therefore, are extremely useful in narrowing the differential diagnosis in a patient presenting with a clinical picture consistent with IM. In addition to these non-specific antibodies, patients with EBV-associated disease will also develop EBV specific antibodies which can be detected by immunofluorescence. Antibody to viral capsid antigens (VCA) can be detected from the time of clinical presentation. IgG directed against VCA persist for life, while IgM are present for 4-8 weeks, giving them greater utility for diagnosis. Antibodies directed against EBV nuclear antigen and soluble complement fixing antigens (anti-S) appear three to four weeks after symptom onset and persist for life; their late appearance makes them useful for diagnosis of heterophile antibody negative IM (7).

Differential Diagnosis

In a patient with fever, pharyngitis, lymphadenopathy, malaise, and a positive heterophile antibody test, the diagnosis of infectious mononucleosis is fairly straightforward. Difficulties arise when patients present in an atypical manner, or in the case of heterophile negative IM. Infectious mononucleosis is often misdiagnosed as streptococcal pharyngitis. The distinction is difficult to make clinically as both conditions can present with an exudative pharyngitis, fever, and cervical lymphadenopathy. Furthermore, approximately 1/3 of patients with EBV IM have been shown to have nasopharyngeal colonization with group A streptococci (8). Infectious mononucleosis is more likely to present with systemic involvement, including diffuse lymphadenopathy, elevation in liver

transaminases, and splenomegaly. IM is often associated with a diffuse maculopapular rash early in the course of infection. This rash is distinct from the typical scarlatiniform rash which may accompany group A streptococcal infection, as well as from the maculopapular rash which may develop when patients with IM are misdiagnosed with strep throat and treated with amoxicillin or ampicillin. The latter rash is usually pruritic and prolonged.

Heterophile negative IM can be caused by a variety of infections. EBV may still be the cause of illness in heterophile negative patients, especially in the pediatric age group or in those early in the course of their illness (8). The most frequent etiologic agent in the absence of EBV infection is CMV (1). Clinical distinction between EBV and CMV IM is difficult and usually not clinically important. CMV is more frequently associated with blood transfusion and is more likely to present without pharyngitis and lymphadenopathy. Diagnosis can be made by demonstrating elevations in anti-CMV IgM levels.

Viral hepatitis and acute toxoplasmosis are also capable of producing a clinical syndrome similar to IM with atypical lymphocytosis. The diagnosis of viral hepatitis is suggested by marked elevation in liver transaminases early in the course of disease. Both viral hepatitis and toxoplasmosis tend to have a lower degree of atypical lymphocytes and serologic tests are available for confirmation of hepatitis A, B, C and toxoplasmosis.

Primary HIV-1 infection can present with fever, pharyngitis, and lymphadenopathy. Patients may also have a maculopapular rash and may present with aseptic meningitis. Diagnosis can be made through detection of HIV-1 p24 antigen or HIV-1 RNA in blood. Antibody based tests for diagnoses of HIV-1 are typically negative during acute HIV infection.

Conclusion

Infectious mononucleosis is a common syndrome most often associated with EBV, CMV, or HIV. Diagnosis depends on an appropriate level of suspicion coupled with appropriate laboratory diagnostics. Although infectious mononucleosis can lead to serious complications, in most individuals symptoms resolve with no long-term sequelae. ❖

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