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INTRODUCTION

Infectious mononucleosis (IM) is an acute infection caused by Epstein-Barr virus (EBV), characterized by fever, lymphadenopathy, sore throat and atypical lymphocytes. Various names of IM are Pfeiffer's disease, Kissing disease, Druesenfieber, Glandular fever and "acute leukemia with spontaneous cure". Apart from IM, EBV is known to cause various lymphoproliferative diseases and epithelial malignancies like virus associated hemophagocytic syndrome, oral hairy leukoplakia, lymphoid interstitial pneumonitis, Burkitt lymphoma, Hodgkin disease, nasopharyngeal carcinoma and post-transplant lymphoproliferative disease.

EPIDEMIOLOGY

Seroprevalence

Infectious mononucleosis is frequently acquired during early childhood and is often asymptomatic. Various studies in India suggest that it has relatively high prevalence (70–80%) in normal adults. Age at primary infection and manifestations associated with primary infection varies markedly in different cultural and socioeconomic status. In developing countries and lower socioeconomic conditions, primary EBV infection occurs at an early age with most children becoming seropositive by 6 years of age and their primary infection is clinically silent or manifests as mild disease. In developed countries or higher socioeconomic status, primary EBV infection occurs later in life (adolescents and young adults) and is more likely to induce clinical symptoms in the form of IM syndrome.

Incidence

Various population based studies have reported incidence of IM as 50–100 cases per 100,000 population. One study from Chandigarh, India, has reported percentage of Paul-Bunnell antibody positivity of 11.1% among clinically suspected IM patients.

Viral Shedding

Virus is shed mainly in oropharyngeal secretions, although it is shedding in urine, uterine cervix, male reproductive tract and breast milk is also reported. After the acute attack, virus is shed regularly in oropharyngeal secretions for 6 months or longer and intermittently thereafter. Sixty percent of immunosuppressed patients continue to shed the virus.

Modes of Transmission

Intimate sharing of oral secretions is the major mode of transmission, although transmission via blood transfusion, intrauterine and perinatal transmission and sexual transmission are reported occasionally.

Incubation Period

Typical EBV—associated IM has incubation period of 30–50 days.

ETIOPATHOGENESIS

Epstein Barr virus, the causative agent of IM, belongs to the family Herpesviridae and is a DNA virus. Its taxonomic name is human herpesvirus type 4, although it is popularly known by its historic name, i.e. EBV. Like any other herpesvirus, it has ability to remain in dormant or latent state after acute infection which allows for reactivation and recurrence of disease. Primary reservoir of EBV in body is latently infected B cells. Two genotypes of EBV, i.e. EBV-1 and EBV-2, were identified. Immunological effects of infected B cells are responsible for EBV associated disease manifestations. Detecting humoral antibodies against viral capsid [anti-viral capsid antigens (VCA)] and nuclear proteins [anti Epstein Barr nuclear antigens (EBNA)] establishes the diagnosis of acute infection while cellular immunity is important for effective control of EBV infection. During IM, there is generalized impairment in cell mediated and humoral immunity in spite of brisk immunological response to EBV. Sequential infection of oral epithelial cells, salivary gland, B lymphocytes and lymphoreticular system is seen after transmission of virus through saliva. The atypical lymphocytes are CD8+ T lymphocytes. The latent virus resides in oropharyngeal epithelial cells and memory B lymphocytes. Reactivation of EBV is asymptomatic.

More than 90% cases of IM are caused by EBV, while remaining 10% IM like illness are due to primary infection by cytomegalovirus, *Toxoplasma gondii*, HIV, adenovirus, rubella and hepatitis virus.

CLINICAL FEATURES

Clinical features of classic IM develops in mostly adolescents and adults after a primary EBV infection. Primary infection in younger children is silent or may result in mild clinical features, although classical IM is described rarely in young children. Clinical features of IM are described in three phases: (1) prodromal, (2) acute and (3) resolution.

Prodromal Phase

It lasts for around 1 week and like any other viral disease is accompanied by malaise, fatigue, fever, headache, myalgia and nausea.

Acute Phase

It consists of classical features of IM like fever, fatigue, sore throat, rashes, tonsillopharyngitis, hepatosplenomegaly and lymphadenopathy and lasts for 3–4 weeks. Fever begins abruptly, ranges between 38°C and 40°C, lasting usually for 2 weeks and rarely up to a month. Tonsillopharyngitis develops in 1st week of illness, resolves spontaneously in the second, usually symptomatic and consists of exudative inflammation similar to one seen in streptococcal infection. Although *Streptococcus pyogenes* is seen in 5% of cases of IM in pharynx, it represents carriage rather than concomitant streptococcal tonsillopharyngitis. Maculopapular rashes are seen in 3–15% of cases. Vasculitic, immune mediated, maculopapular, pruritic rashes are seen in 95–100% of adolescents treated with ampicillin or amoxicillin. These rashes develop 5–10 days after initiation of treatment and resolve spontaneously within few days once the offending drug is discontinued. Such “ampicillin rash” is less common in children with IM. Gianotti-Crosti syndrome (papular acrodermatitis of childhood) consisting of symmetric erythematous papules developing into plaques, involving cheeks, extremities and buttocks and lasting for 15–50 days is sometimes seen with primary EBV infection. Hepatosplenomegaly is seen in almost half of the patients, more common in younger children, develops in 2nd week and resolves by 4th week. Lymphadenopathy, commonly involving cervical lymph nodes (and sometimes generalized lymphadenopathy), is seen in almost 90% cases of IM and like hepatosplenomegaly most prominent from 2nd to 4th week of illness. Palatal enanthem and eyelid edema are sometimes seen in children with IM.

Resolution Phase

Gradual and uneventful resolution of all clinical features usually occurs although sometimes biphasic course is seen. Organomegaly and severe fatigue may take months to resolve.

DIAGNOSIS

Leukocytosis, absolute lymphocytosis and atypical lymphocytes (bigger lymphocytes with large, indented, folded and eccentrically placed nucleus) are common findings. Atypical lymphocytes are also seen with other infectious agents enumerated above leading to IM like illness. Thrombocytopenia and elevated hepatic enzymes are also commonly observed. For a typical uncomplicated case of IM, blood counts and heterophile antibody test are sufficient for presumptive diagnosis. Diagnosis can be confirmed further by specific EBV antibodies in cases which lack positive heterophile antibodies have atypical or severe manifestations of IM, develop chronic, lymphoproliferative or oncogenic features or in cases where one needs to confirm past infection or determine susceptibility to future infection.

Heterophile Antibody Test

These antibodies agglutinate cells from different species. These IgM antibodies are known as Paul-Bunnell antibodies and are detected by Paul-Bunnell-Davidson test. These antibodies agglutinate sheep or horse RBCs but not guinea pig kidney cells. This test may be negative early in the course of disease and in children less than 4 years of age.

Specific EBV Antibodies

Antibodies to EBNA, Epstein-Barr virus early antigens (EBVEA) and VCA are specific EBV antibodies used for diagnosing EBV infections. Acute IM is characterized by immunoglobulin M (IgM) and immunoglobulin G (IgG) VCA and IgG EA. Anti-EBNA antibodies appear 3–4 months after the onset of infection, hence its presence indicates infection more than 3 months old and its absence (in presence of other antibodies) implies recent infection. IgM VCA is the most dependable antibody to confirm the diagnosis, although Rheumatoid factor may give false positive results.

Detection of EBV DNA by southern blot, *in situ* hybridization and PCR may be useful for diagnostic, epidemiological and pathogenetic purposes. Isolation of virus from body secretions and semiquantitative and quantitative viral load assay are available for research purposes.

DIFFERENTIAL DIAGNOSIS

Infectious mononucleosis like illnesses: Heterophile negative IM is caused by various agents like CMV, toxoplasma, adenovirus, rubella virus and hepatitis virus.

Acute HIV syndrome: This IM like syndrome is usually seen in adolescents at the time of initial burst of viremia, about 3–6 weeks after primary infection. It is of varying severity, most of the patients recovering spontaneously and followed by prolonged clinical latency.

Streptococcal pharyngitis: Presence of hepatosplenomegaly and failure to respond in 3 days to appropriate antibiotics favors IM.

Leukemia: Bone marrow examination may be necessary to differentiate from IM.

Scarlet fever: Diffuse erythema, strawberry tongue, sandpaper feel and response to antistreptococcal antibodies favors the diagnosis of scarlet fever.

Rickettsial infections: Evolving rash (from macular to popular to hemorrhagic), normal to low TLC, exposure to ticks and response to doxycycline are suggestive of Rickettsial infection.

SOJIA (systemic onset juvenile idiopathic arthritis): In absence of joint infection, SOJIA may be confused with IM. Evanescent rash at the height of fever, daily two spikes of fever, temperature dipping below baseline and thrombocytosis are in favor of SOJIA.

TREATMENT

Symptomatic treatment with rest, fluids and antipyretics is the mainstay of therapy as there is no specific treatment for IM. Although high doses of acyclovir reduced viral replication and oropharyngeal shedding, this therapy is of no

use for resolution of signs and symptoms or reducing the rates of complications. Bed rest is important till there is debilitating fatigue. Avoiding contact sports and strenuous athletic activities in first 2–3 weeks of illness and till there is palpable spleen is of utmost importance in view of predisposition to splenic rupture. Imaging studies, like USG and CT abdomen, are neither accurate nor cost effective for predicting return to normal physical activities. A 2-week course of prednisone (1 mg/kg/day or equivalent for 1 week, followed by tapering doses over next 1 week) may be advocated with caution to some severely symptomatic patients (having high fever or severe pharyngitis). Corticosteroids are also used for complications of IM like stridor from massively enlarged tonsils or paratracheal lymphadenopathy, hematological complications like thrombocytopenia with bleeding or hemolytic anemia, neurologic complications like seizures or meningitis. Corticosteroids should not be used in uncomplicated cases of IM.

COMPLICATIONS

Most complications of IM are rare and transient. Significant hematologic, neurologic and pulmonary complications are seen in approximately 20% of IM cases.

Splenic subcapsular hemorrhage and rupture: It occurs during 1st to 3rd week of illness and related to physical trauma to palpably enlarged spleen. Clinical features of splenic rupture are abdominal pain, orthostatic hypotension, syncope, tachycardia and left shoulder pain. Apart from a small subset of patients who are hemodynamically stable having low transfusion requirements and with normal sensorium which may be managed by medical therapy or endovascular intervention, most need emergency splenectomy.

Respiratory complications like airway obstruction, neck abscesses or pulmonary infiltrates: Incidence of severe airway obstruction is 1–5% and can be due to enlargement of Waldeyer ring, edema of epiglottis or pharynx, pseudomembrane formation in airways or paratracheal lymphadenopathy. Drooling, stridor, dysphagia, odynophagia and dyspnea are the common manifestations. Various management options include head elevation, hydration, humidification, systemic corticosteroids, nasopharyngeal airway, tonsillectomy and tracheostomy.

Neurologic complications are seen in 1–5% of patients with IM, mostly at the height of typical manifestations of IM. Various neurologic complications are aseptic meningitis, meningoencephalitis, cerebritis, cranial nerve palsies, Guillain-Barré syndrome and transverse myelitis. In view of nonspecific symptomatology and absence of typical IM symptoms, EBV should be considered a possible etiology for any child presenting with acute encephalitis.

Psychiatric complications like Alice-in-Wonderland syndrome and chronic fatigue are described with IM. Alice-in-Wonderland syndrome or metamorphopsia is a visual illusion manifesting as a distortion in size, form, movement or color. This syndrome is also known to occur with migraine, epilepsy and hallucinogenic drugs apart from IM. It resolves in 4–6 weeks.

Hematologic complications like thrombocytopenia, aplastic anemia, hemolytic anemia and neutropenia are described with IM. Immune mediated thrombocytopenia is seen in 25–50% patients and resolves in 4–6 weeks. Corticosteroids and intravenous immunoglobulin (IVIg) are sometimes beneficial in severe, life-threatening cases.

Other complications like hepatic failure, tubulointerstitial nephritis, nephritic syndrome, Reye syndrome and electrocardiographic abnormalities are occasionally seen.

PROGNOSIS

Complete recovery is almost a rule for healthy individuals with IM, although symptoms usually persist for 2–4 weeks before gradual recovery. Immunocompromised persons can have infection with different types of EBV but these episodes are always asymptomatic. Prolonged fatigue and malaise may last for few weeks to 6 months. Mortality in IM is extremely rare and usually attributed to splenic rupture, Guillain-Barré syndrome, secondary infection or massive bleeding.

PREVENTION

Standard infection control policies are recommended for hospitalized patients with IM. As EBV is spread in saliva and ubiquitous in occurrence, it is quite difficult to prevent the infection. Three doses of recombinant EBV subunit glycoprotein 350 candidate vaccine may be useful for prevention or reducing symptoms of IM.

BIBLIOGRAPHY

1. Jenson HB. Epstein-Barr virus. In: Kliegman RM, Stanton BF, Schor NF, GemeJWS, Behrman RE (Eds). Nelson Textbook of Pediatrics, 19th edition. Elsevier Saunders; 2011. pp. 1110-5.
2. Leach CL, Sumaya CV. Epstein-Barr virus. In: Feigin RD, Cherry JD, Demmler Harrison GJ, Kaplan SL (Eds). Textbook of Pediatric Infectious Diseases, 6th edition. Saunders Elsevier; 2009. pp. 2043-71.
3. Mishra B, Mohan B, Ratho RK. Heterophile antibody positive infectious mononucleosis. *Ind Jour Ped.* 2004;71:15-8.