In the name of allah

Other viral infections

(Nonpolio Enteroviruses & Epstein-Barr Virus)

Nelson Textbook of Pediatrics 2020

CHAPTER 2 7 7- Nonpolio Enteroviruses

The genus Enterovirus contains a large number of viruses spread via the gastrointestinal and respiratory routes that produce a broad range of illnesses in patients of all ages. Many of the manifestations predominantly affect infants and young children.

Etiology

Enteroviruses are nonenveloped, single-stranded viruses in the Picornaviridae (“small RNA virus”) family, which also includes the rhinoviruses, hepatitis A virus, and parechoviruses. The original human enterovirus subgroups —polioviruses , coxsackieviruses, and echoviruses—were differentiated by their replication patterns in tissue culture and animals. Enteroviruses have been reclassified on the basis of genetic similarity into 4 species, human enteroviruses A-D. Although more than 100 types have been described, 10-15

account for the majority of disease. No disease is uniquely associated with any specific serotype, although certain manifestations are preferentially associated with specific serotypes. The closely related human parechoviruses can cause clinical presentations similar to those associated with enteroviruses.

Epidemiology

Enterovirus infections are common, with a worldwide distribution. In temperate climates, annual epidemic peaks occur in summer/fall, although some transmission occurs year-round. Enteroviruses are responsible for 33–65% of acute febrile illnesses and 55–65% of hospitalizations for suspected sepsis in infants during the summer and fall in the United States. In tropical and semitropical areas, enteroviruses typically circulate year-round.

In general, only a few serotypes circulate simultaneously. Infections by different serotypes can occur within the same season. Factors associated with increased incidence and/or severity include young age, male sex, exposure to children, poor hygiene, overcrowding, and low socioeconomic status. More than 25% of symptomatic infections occur in children younger than 1 yr of age. Breastfeeding reduces the risk for infection, likely via enterovirus-specific antibodies. Humans are the only known natural reservoir for human enteroviruses. Virus is primarily spread person to person, by the

fecal-oral and respiratory routes, although types causing acute hemorrhagic conjunctivitis may be spread via airborne transmission.

Enteroviruses can survive on environmental surfaces, permitting transmission via fomites. Enteroviruses also can frequently be isolated from water sources, sewage, and wet soil. Although contamination of drinking water, swimming pools and ponds, and hospital water reservoirs may occasionally be responsible for transmission, such contamination is often considered the result rather than the cause of human infection.

Transmission is common within families (≥50% risk of spread to nonimmune household contacts), daycare centers, playgrounds, summer camps, orphanages, and hospital nurseries; severe secondary infections may occur in nursery outbreaks. Transmission risk is increased by diaper changing and decreased by handwashing.

The incubation period is typically 3-6 days, except for a 1-3 day incubation period for acute hemorrhagic conjunctivitis. Infected children, both symptomatic and asymptomatic, frequently shed cultivable enteroviruses from the respiratory tract for 1 wk. White blood cell (WBC) count and results of routine laboratory tests are generally normal, although transient neutropenia can be seen. Concomitant enterovirus and bacterial infection is rare but has been observed in a small number of infants.

Clinical Manifestations

Manifestations are protean, ranging from asymptomatic infection to undifferentiated febrile or respiratory illnesses in the majority, to, less frequently, severe diseases such as meningoencephalitis, myocarditis, and neonatal sepsis. A majority of individuals are asymptomatic or have very mild illness, yet may serve as important sources for spread of infection. Symptomatic disease is generally more common in young children.

Nonspecific Febrile Illness

Nonspecific febrile illnesses are the most common symptomatic manifestations, especially in infants and young children. These are difficult to clinically differentiate from serious infections such as urinary tract infection, bacteremia, and bacterial meningitis, often necessitating hospitalization with diagnostic testing and presumptive antibiotic therapy for suspected bacterial infection in young infants. Illness usually begins abruptly with fever of 38.5-40°C (101-104°F), malaise, and irritability. Associated symptoms may include lethargy, anorexia, diarrhea, nausea, vomiting, abdominal discomfort, rash, sore throat, and respiratory symptoms. Older children may have headaches and myalgias. Findings are generally nonspecific and may include mild conjunctivitis, pharyngeal injection, and cervical lymphadenopathy. Meningitis may be present, but specific clinical features such as meningeal findings or bulging anterior fontanelle

distinguishing those with meningitis are often lacking in infants. Fever lasts a mean of 3 days and occasionally is biphasic. Duration of illness is usually 4-7 days but can range from 1 day to >1 wk. White blood cell (WBC) count and results of routine laboratory tests are generally normal, although transient neutropenia can be seen. Concomitant enterovirus and bacterial infection is rare but has been observed in a small number of infants.

Enterovirus illnesses may be associated with a wide variety of skin manifestations, including macular, maculopapular, urticarial, vesicular, and petechial eruptions. Rare cases of idiopathic thrombocytopenic purpura have been reported. Enteroviruses have also been implicated in cases of pityriasis rosea. In general, the frequency of cutaneous manifestations is inversely related to age. Virus can occasionally be recovered from vesicular skin lesions.

Hand-Foot-and-Mouth Disease

Hand-foot-and-mouth disease, one of the more distinctive rash syndromes, is most frequently caused by coxsackievirus A16, sometimes in large outbreaks, and can also be caused by other enteroviruses. It is usually a mild illness, with or without low-grade fever. When the mouth is involved, the oropharynx is inflamed and often contains scattered, painful vesicles on the tongue, buccal mucosa, posterior pharynx, palate, gingiva, and/or lips. These may ulcerate, leaving 4-8 mm shallow lesions with surrounding erythema.

Maculopapular, vesicular, and/or pustular lesions may occur on the hands and fingers, feet, and buttocks and groin.

Skin lesions occur more commonly on the hands than feet and are more common on dorsal surfaces, but frequently also affect palms and soles. Hand and feet lesions are usually tender, 3-7 mm vesicles that resolve in about 1 wk. Buttock lesions do not usually progress to vesiculation. Disseminated vesicular rashes described as eczema coxsackium may complicate preexisting eczema. Coxsackievirus A6, in particular, is responsible for relatively severe, atypical hand-foot-and-mouth disease (and herpangina) affecting adults and children that is characterized by fever, generalized rash (face, proximal extremities, and trunk, in addition to hands, feet, and buttocks), pain, dehydration, and desquamation of palms and soles. Onychomadesis (nail shedding) has been observed following coxsackievirus A6 and other coxsackievirus infections. Hand-foot-and-mouth disease caused by enterovirus A71 can be associated with neurologic and cardiopulmonary involvement, especially in young children (see Neurologic Manifestations below). Hand-foot-and-mouth disease caused by coxsackievirus A16 also can occasionally be associated with complications such as encephalitis, acute flaccid paralysis, myocarditis, pericarditis, and shock.

Herpangina

Herpangina is characterized by sudden onset of fever, sore throat, dysphagia, and painful lesions in the posterior pharynx. Temperatures range from normal to 41°C (106°F); fever tends to be higher in younger patients. Headache and backache may occur in older children, and vomiting and abdominal pain occur in 25% of cases. Characteristic lesions, present on the anterior tonsillar pillars, soft palate, uvula, tonsils, posterior pharyngeal wall, and, occasionally, the posterior buccal surfaces, are discrete 1-2 mm vesicles and ulcers that enlarge over 2-3 days to 3-4 mm and are surrounded by erythematous rings that vary in size up to 10 mm. The number of lesions can range from 1 to >15, but is most commonly around 5. The remainder of the pharynx appears normal or minimally erythematous. Most cases are mild and have no complications. However, dehydration due to decreased oral intake may occur and some cases are associated with meningitis or more severe illness. Fever generally lasts 1-4 days, and resolution of symptoms occurs in 3-7 days. Respiratory Manifestations Symptoms such as sore throat and coryza frequently accompany and sometimes dominate enterovirus illnesses. Other respiratory findings may include wheezing, exacerbation of asthma, apnea, respiratory distress, pneumonia, otitis media, bronchiolitis, croup, parotitis, and pharyngotonsillitis, which may occasionally be exudative. Lower respiratory tract infection may be significant in immunocompromised patients.

Respiratory Manifestations

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Pleurodynia (Bornholm disease), is an epidemic or sporadic illness characterized by paroxysmal thoracic pain, due to myositis involving chest and abdominal wall muscles and, possibly, pleural inflammation. In epidemics, which occur every 10-20 yr, children and adults are affected, but most cases occur in persons younger than age 30 yr. Malaise, myalgias, and headache are followed by sudden onset of fever and spasmodic, pleuritic pain in the chest or upper abdomen aggravated by coughing, sneezing, deep breathing, or other movement. During spasms, which last from a few minutes to several hours, pain may be severe and respirations are usually rapid, shallow, and grunting, suggesting pneumonia or pleural inflammation. A pleural friction rub is noted during pain episodes in 70%) but is more rare with coxsackievirus infections.

Chest radiographs are generally normal but can demonstrate pulmonary infiltrates or pleural effusions. Pain localized to the

abdomen may suggest colic, intestinal obstruction, appendicitis, or peritonitis. Pain usually subsides within 3-6 days but can persist for up to weeks. Symptoms may occur in a biphasic or, rarely, recurrent pattern, with less prominent fever during recurrences. Pleurodynia may be associated with meningitis, orchitis, myocarditis, or pericarditis. Life-threatening noncardiogenic pulmonary edema, hemorrhage, and/or interstitial pneumonitis may occur in patients with enterovirus A71 brainstem encephalitis.

Ocular Manifestations

Epidemics of acute hemorrhagic conjunctivitis, are explosive and marked by high contagiousness, with spread mainly via eye-hand-fomite-eye transmission. School-age children, teenagers, and adults 20-50 yr of age have the highest attack rates. Sudden onset of severe eye pain is associated with photophobia, blurred vision, lacrimation, conjunctival erythema and congestion, lid edema, preauricular lymphadenopathy, and, in some cases, subconjunctival hemorrhages and superficial punctate keratitis. Subconjunctival hemorrhage is the hallmark of enterovirus D70 cases (>70%) but is more rare with coxsackievirus infections. Eye discharge is initially serous but becomes mucopurulent with secondary bacterial infection. Systemic symptoms including fever and headache occur in up to 20% of cases; manifestations suggestive of pharyngoconjunctival fever occasionally occur. Recovery is usually complete within 1-2 wk.

Polyradiculoneuropathy or acute flaccid paralysis following enterovirus D70 infection occurs occasionally.

Other enteroviruses have occasionally been implicated as causes of keratoconjunctivitis. Epidemic and sporadic uveitis in infants can be associated with severe complications, including destruction of the iris, cataracts, and glaucoma. Enteroviruses have been implicated in cases of chorioretinitis, uveoretinitis, optic neuritis, and unilateral acute idiopathic maculopathy.

Myocarditis and Pericarditis

Enteroviruses account for approximately 25–35% of cases of myocarditis and pericarditis of proven etiology. Coxsackie B viruses are most commonly implicated, although coxsackie A viruses and echoviruses also may be causative. Adolescents and young adults (especially physically active males) are disproportionately affected. Myopericarditis may be the dominant feature or it may be 1 manifestation of disseminated disease, as in neonates. Disease ranges from relatively mild to severe. Upper respiratory symptoms frequently precede fatigue, dyspnea, chest pain, congestive heart failure, and dysrhythmias. Presentations may mimic myocardial infarction; sudden death may also occur (including apparent sudden infant death syndrome). A pericardial friction rub indicates pericardial involvement. Chest radiography often demonstrates cardiac enlargement and echocardiography may confirm ventricular

dilation, reduced contractility, and/or pericardial effusion. Electrocardiography frequently reveals ST segment, T wave, and/or rhythm abnormalities, and serum myocardial enzyme concentrations are often elevated. The acute mortality of enterovirus myocarditis is 0–4%. Recovery is complete without residual disability in the majority of patients. Occasionally, chronic cardiomyopathy, inflammatory ventricular microaneurysms, or constrictive pericarditis may result.

Gastrointestinal and Genitourinary Manifestations

Gastrointestinal symptoms such as emesis (especially with meningitis), diarrhea (rarely severe), and abdominal pain are frequent but generally not dominant. Diarrhea, hematochezia, pneumatosis intestinalis, and necrotizing enterocolitis have occurred in premature infants during nursery outbreaks. Enterovirus infection has been implicated in acute and chronic gastritis, intussusception, chronic intestinal inflammation in hypogammaglobulinemic patients, sporadic hepatitis in normal children, severe hepatitis in neonates, and pancreatitis, which may result in transient exocrine pancreatic insufficiency.

Coxsackie B viruses are second only to mumps as causes of orchitis, most commonly presenting in adolescents. The illness is frequently biphasic; fever and pleurodynia or meningitis are followed approximately 2 wk later by orchitis, often with epididymitis.

Enteroviruses have also been implicated in cases of nephritis and IgA nephropathy.

Neurologic Manifestations

Enteroviruses are the most common cause of viral meningitis in mumps immunized populations, accounting for up to 90% or more of cases in which a cause is identified. Meningitis is particularly common in infants, especially in those younger than 3 mo of age, often during community epidemics. Most cases in infants and young children are mild and lack specific meningeal signs, whereas nuchal rigidity is apparent in more than half of children older than 1-2 yr of age. Fever is present in 50–100% and may be accompanied by irritability, malaise, headache, photophobia, nausea, emesis, anorexia, lethargy, hypotonia, rash, cough, rhinorrhea, pharyngitis, diarrhea, and/or myalgia. Some cases are biphasic, with fever and nonspecific symptoms lasting a few days and followed by return of fever with meningeal signs several days later. Fever usually resolves in 3-5 days, and other symptoms in infants and young children usually resolve within 1 wk. In adults, symptoms tend to be more severe and of longer duration. CSF findings include pleocytosis (generally <500 but occasionally as high as 1,000-8,000 WBCs/µL; often predominantly polymorphonuclear cells in the first 48 hr before becoming mostly mononuclear); normal or slightly low glucose content (10% < 40mg/dL); and normal or mildly increased

protein content (generally <100 mg/dL). CSF parameters are normal in up to half of young infants despite detection of enterovirus in CSF and may also be normal in older children early after illness onset. Acute complications occur in approximately 10% of young children, including simple and complex seizures, obtundation, increased intracranial pressure, syndrome of inappropriate antidiuretic hormone secretion, ventriculitis, transient cerebral arteriopathy, and coma. The long-term prognosis for most children, even in those with acute complications, is good.

Enteroviruses are also responsible for ≥10–20% of cases of encephalitis with an identified cause. After initial nonspecific symptoms, there is progression to encephalopathy characterized by confusion, weakness, lethargy, and/or irritability. Symptoms are most commonly generalized, although focal findings, including focal motor seizures, hemichorea, acute cerebellar ataxia, aphasia, extrapyramidal symptoms, and/or focal imaging abnormalities, may occur. Meningeal signs and CSF indices similar to enteroviral meningitis are commonly present, leading to characterization of most cases as meningoencephalitis . Severity ranges from mild alteration in mental status to coma and decerebrate status. Long-term sequelae, including epilepsy, weakness, cranial nerve palsy, spasticity, psychomotor retardation, and hearing loss, or death may follow severe disease. Persistent or recurrent cases have been

observed rarely. Many affected children have had hand-foot-and-mouth disease, some have had herpangina, and others have had no mucocutaneous manifestations. Neurologic syndromes in a fraction of children have included meningitis, meningoencephalomyelitis, acute flaccid paralysis , Guillain-Barré syndrome, transverse myelitis, acute disseminated encephalomyelitis, cerebellar ataxia, opsoclonus-myoclonus syndrome, benign intracranial hypertension, and brainstem encephalitis (rhombencephalitis involving the midbrain, pons, and medulla).

Patients with antibody or combined immunodeficiencies (including human immunodeficiency virus infection, acute lymphocytic leukemia, and transplantation) and patients receiving anti-CD20 antibody therapy are at risk for acute or, more commonly, chronic enterovirus meningoencephalitis. Chronic enterovirus meningoencephalitis has become less common with prophylactic high-dose intravenous immunoglobulin replacement in agammaglobulinemic patients. Other neurologic syndromes include cerebellar ataxia; transverse myelitis; Guillain-Barré syndrome (including Miller-Fisher variant) and axonal polyneuropathy; acute disseminated encephalomyelitis; peripheral neuritis; optic neuritis; sudden hearing loss, tinnitus, and inner ear disorders such as vestibular neuritis; and other cranial neuropathies.

Myositis and Arthritis

Although myalgia is common, direct evidence of muscle involvement, including rhabdomyolysis, muscle swelling, focal myositis, and polymyositis, has uncommonly been reported. A dermatomyositis-like syndrome and arthritis can be seen in enterovirus-infected hypogammaglobulinemic patients. Enteroviruses are a rare cause of arthritis in normal hosts.

Diagnosis

Clues to enterovirus infection include characteristic findings such as hand-foot and-mouth disease or herpangina lesions, consistent seasonality, known community outbreak, and exposure to enterovirus-compatible disease. In the neonate, history of maternal fever, malaise, and/or abdominal pain near delivery during enterovirus season is suggestive. Traditionally, enterovirus infection has been confirmed with viral culture using a combination of cell lines. Sensitivity of culture ranges from 50% to 75% and can be increased by sampling of multiple sites. Direct testing for nucleic acid has replaced culture due to increased sensitivity and more rapid turnaround. RT-PCR detection of highly conserved areas of the enterovirus genome can detect the majority of enteroviruses in CSF; serum; urine; conjunctival, nasopharyngeal, oropharyngeal, tracheal, rectal, and stool specimens; dried blood spots; and tissues such as myocardium, liver, and brain. Sensitivity and specificity of RT-PCR are high, with results available in as short as 1 hr. PCR testing of CSF from

children with meningitis and from hypogammaglobulinemic patients with chronic meningoencephalitis is frequently positive despite negative cultures. Sequence analysis of amplified nucleic acid can be used for serotype identification and phylogenetic analysis and to establish a transmission link among cases.

Treatment

In the absence of a proven antiviral agent for enterovirus infections, supportive care is the mainstay of treatment. Newborns and young infants with nonspecific febrile illnesses and children with meningitis frequently require diagnostic evaluation and hospitalization for presumptive treatment of bacterial and herpes simplex virus infection. Immunoglobulin has been utilized to treat enterovirus infections based on the importance of the humoral immune response to enterovirus infection and the observation that absence of neutralizing antibody is a risk factor for symptomatic infection. Immunoglobulin products contain neutralizing antibodies to many commonly circulating serotypes, although titers vary with serotype and among products and lots. Anecdotal and retrospective, uncontrolled use of intravenous immunoglobulin or infusion of maternal convalescent plasma to treat newborns with severe disease has been associated with varying outcomes. Immunoglobulin has been administered intravenously and intraventricularly to treat hypogammaglobulinemic patients with chronic enterovirus

meningoencephalitis and intravenously in transplant and oncology patients with severe infections, with variable success. Intravenous immunoglobulin and corticosteroids have been used for patients with neurologic disease caused by enteroviruses. Successful treatment of enterovirus myocarditis with interferon-α has been reported anecdotally, and interferon-β treatment was associated with viral clearance, improved cardiac function, and survival in chronic cardiomyopathy associated with persistence of enterovirus (or adenovirus) genome. Pleconaril, an inhibitor of attachment and uncoating, was associated with benefit in some controlled studies of enterovirus meningitis and picornavirus upper respiratory tract infections, and uncontrolled experience suggested possible benefits in high-risk infections. Pocapavir, an agent with a similar mechanism of action that is in development for treatment of poliovirus infections, has been used in a small number of cases of severe neonatal enterovirus sepsis.

Complications and Prognosis

The prognosis in the majority of enterovirus infections is excellent. Morbidity and mortality are associated primarily with myocarditis, neurologic disease, severe neonatal infections, and infections in immune compromised hosts.

Prevention

The first line of defense is prevention of transmission through good hygiene, such as handwashing, avoidance of sharing utensils and drinking containers and other potential fomites, disinfection of contaminated surfaces, and avoiding community settings where exposures are likely to occur. Chlorination of drinking water and swimming pools may be important. Contact precautions should be used for all patients with enterovirus infections in the hospital setting; droplet precautions should also be included for patients with respiratory syndromes. Infection control techniques such as cohorting have proven effective in limiting nursery outbreaks. Prophylactic administration of immunoglobulin or convalescent plasma has been used in nursery epidemics; simultaneous use of infection control interventions makes it difficult to determine efficacy. Pregnant women near term should avoid contact with individuals ill with possible enterovirus infections. Maintenance antibody replacement with high-dose intravenous immunoglobulin for patients with hypogammaglobulinemia has reduced the incidence of chronic enterovirus meningoencephalitis, although breakthrough infections occur. Inactivated vaccines to prevent enterovirus A71 infections have been demonstrated to be safe and effective (>90% against enterovirus A71 handfoot-and-mouth disease and >80% against enterovirus A71 serious disease) in phase 3 clinical trials.

CHAPTER 2 8 1 – Nelson Textbook of Pediatrics

Epstein-Barr Virus

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Infectious mononucleosis is the best-known clinical syndrome caused by Epstein-Barr virus (EBV). It is characterized by systemic somatic complaints consisting primarily of fatigue, malaise, fever, sore throat, and generalized lymphadenopathy. Originally described as glandular fever, it derives its name from the mononuclear lymphocytosis with atypical-appearing lymphocytes that accompany the illness.

Etiology

EBV is a double-stranded DNA virus that is a member of the gammaherpesviruses and causes >90% of cases of infectious mononucleosis. The virus lead to persistent, lifelong, latent infection. As many as 5–10% of infectious mononucleosis–like illnesses are caused by other types of primary infections, particularly cytomegalovirus but also pathogens such as Toxoplasma gondii, adenovirus, hepatitis viruses and HIV. In the majority of EBV-negative cases of infectious mononucleosis, the exact cause remains unknown.

Epidemiology

EBV infects more than 95% of the world's population. It is transmitted primarily via oral secretions. Among children, transmission may occur by exchange of saliva from child to child, such as occurs between children in out-of-home childcare. EBV is shed in oral secretions consistently for more than 6 mo after acute infection and then intermittently for life. As many as 20–30% of healthy EBV-infected persons shed virus at any particular time. EBV is also found in male and female genital secretions, and some studies suggest the possibility of spread through sexual contact. Nonintimate contact, environmental sources, and fomites do not contribute to transmission of EBV.

Infection with EBV in developing countries and among socioeconomically disadvantaged populations in developed countries usually occurs during infancy and early childhood. In central Africa, almost all children are infected by 3 yr of age. Among more affluent populations in industrialized countries, half of the population is infected by 6-8 yr of age with approximately 30% of infections occurring during adolescence and young adulthood. Large differences are seen by family income, with highest seroprevalence in children of families with lowest income. The epidemiology of the disease manifestations of infectious mononucleosis is related to the age of acquisition of EBV infection. Primary infection with EBV during childhood is usually asymptomatic or mild and indistinguishable from

other childhood infections. Primary EBV infection in adolescents and adults manifests in 30–50% of cases as the classic triad of fatigue, pharyngitis, and generalized lymphadenopathy , which constitute the major clinical manifestations of infectious mononucleosis. This syndrome may be seen at all ages but is rarely apparent in children younger than 4 yr of age, when most EBV infections are asymptomatic, or in adults older than 40 yr of age, when most individuals have already been infected by EBV. The prevalence of serologic evidence of past EBV infection increases with age; almost all adults in the United States are seropositive.

Pathogenesis

After transmission by saliva to the oral cavity, EBV infects both oral epithelial cells and tonsillar B lymphocytes, although it is unclear which cells are the primary initial targets. Ongoing viral replication leads to viremia and dissemination of infected B lymphocytes into peripheral blood and the lymphoreticular system, including the liver and spleen. Clinical manifestations of infectious mononucleosis, which are due to the host immune response to EBV infection, occur after a 6-wk incubation period following acute infection. The atypical lymphocytes that are frequently detected in patients with infectious mononucleosis are primarily CD8 T lymphocytes. Polyclonal CD8 T lymphocyte activation occurs early during the incubation period following infection, while expansion of EBV-specific CD8 T

lymphocytes is detected closer to the time of symptom onset. The host immune response is effective in rapidly reducing the EBV viral load, although persistent shedding of high levels of virus can be detected in the oropharynx for up to 6 mo. Intermittent shedding from the oropharynx occurs for many years following primary infection. EBV, like the other herpesviruses, establishes lifelong latent infection after the primary infection. Latent virus persists primarily in memory B lymphocytes. Reactivation and new viral replication occurs at a low rate in populations of latently infected cells and is responsible for intermittent viral shedding in oropharyngeal secretions of infected individuals. Reactivation is unlikely to be accompanied by distinctive clinical symptoms.

Clinical Manifestations

The incubation period of infectious mononucleosis in adolescents is 30-50 days. In children, it may be shorter. The majority of cases of primary EBV infection in infants and young children are clinically silent. In older patients, the onset of illness is usually insidious and vague. Patients may complain of malaise, fatigue, acute or prolonged (>1 wk) fever, headache, sore throat, nausea, abdominal pain, and myalgia. This prodromal period may last 1-2 wk. The complaints of sore throat and fever gradually increase until patients seek medical care. Splenic enlargement may be rapid enough to cause left upper

quadrant abdominal discomfort and tenderness, which may be the presenting complaint.

The classic physical examination findings are generalized lymphadenopathy (90% of cases), splenomegaly (50% of cases), and hepatomegaly (10% of cases). Lymphadenopathy occurs most commonly in the anterior and posterior cervical nodes and the submandibular lymph nodes and less commonly in the axillary and inguinal lymph nodes. Epitrochlear lymphadenopathy is particularly suggestive of infectious mononucleosis. Although liver enzymes are often elevated, symptomatic hepatitis or jaundice is uncommon. Splenomegaly to 2-3 cm below the costal margin is typical (15–65% of cases); massive enlargement is uncommon. The sore throat is often accompanied by moderate to severe pharyngitis with marked tonsillar enlargement, occasionally with exudates (Fig 1). Palatal petechiae at the junction of the hard and soft palate are frequently seen. The pharyngitis is similar to that caused by streptococcal infection. Other clinical findings may include rashes and edema of the eyelids. Rashes are usually maculopapular and have been reported in 3–15% of patients. Patients with infectious mononucleosis who are treated with ampicillin or amoxicillin may experience an ampicillin rash, which may also occur with other β-lactam antibiotics (Fig. 2). This morbilliform, vasculitic rash is probably immune mediated and resolves without specific treatment.

EBV can also be associated with Gianotti-Crosti syndrome, a symmetric rash on the cheeks with multiple erythematous papules, which may coalesce into plaques and persist for 15-50 days. The rash has the appearance of atopic dermatitis and may appear on the extremities and buttocks.

Diagnosis

A presumptive diagnosis of infectious mononucleosis may be made by the presence of classical clinical symptoms with atypical lymphocytosis in the peripheral blood. The diagnosis is usually confirmed by serologic testing, either for heterophile antibody or specific EBV antibodies.

Differential Diagnosis

EBV is the most common cause of infectious mononucleosis. Infectious mononucleosis–like illnesses may also be caused by primary infection with other pathogens, such as cytomegalovirus, T. gondii, adenovirus, and HIV. Streptococcal pharyngitis may cause sore throat and cervical lymphadenopathy indistinguishable from that of infectious mononucleosis, but it is not typically associated with hepatosplenomegaly. Approximately 5% of cases of EBV associated infectious mononucleosis have positive throat cultures for group A streptococcus, representing pharyngeal streptococcal carriage. Failure of a patient with presumed streptococcal

pharyngitis to improve within 48-72 hr should evoke suspicion of infectious mononucleosis. Hematologic malignancies should also be considered in a patient with an infectious mononucleosis–like illness, particularly when lymphadenopathy and hepatosplenomegaly are appreciated and the results of an initial laboratory evaluation are not consistent with an infectious etiology.

Laboratory Diagnosis

The majority of patients (>90%) have a leukocytosis of 10,000-20,000 cells/µL, of which at least two thirds are lymphocytes; atypical lymphocytes usually account for 20–40% of the total number. The atypical cells are mature T lymphocytes that have been antigenically activated. Compared with regular lymphocytes microscopically, atypical lymphocytes are larger overall, with larger, eccentrically placed indented and folded nuclei with a lower nuclear-to cytoplasm ratio. Although atypical lymphocytosis may be seen with many other infections associated with lymphocytosis, the highest degree of atypical lymphocytes is classically seen with EBV infection. Mild thrombocytopenia to 50,000-200,000 platelets/µL occurs in more than 50% of patients but only rarely is associated with purpura. Mild elevation of hepatic transaminases occurs in approximately 75% of uncomplicated cases, but it is usually asymptomatic and without jaundice.

Detection of Heterophile Antibodies

Heterophile antibodies are cross-reactive immunoglobulin M (IgM) antibodies that agglutinate mammalian erythrocytes but are not EBV-specific. Heterophile antibody tests, such as the monospot test, are positive in 90% of cases of EBV associated infectious mononucleosis in adolescents and adults during the second week of illness, but in only up to 50% of cases in children younger than 4 yr of age. Test results can remain positive for up to 12 mo. The false-positive rate is low, generally < 10%. A positive heterophile antibody test in a patient with classic clinical manifestations of mononucleosis strongly supports that diagnosis. However, because of the nonspecific nature of heterophile antibody testing, EBV-specific antibody testing should be performed when a precise diagnosis is necessary.

Detection of Epstein-Barr Virus–Specific Antibodies

If the heterophile test result is negative and an EBV infection is suspected, EBV specific antibody testing is indicated. Measurement of antibodies to EBV proteins including viral capsid antigen (VCA), Epstein-Barr nuclear antigen (EBNA), and early antigen (EA) are used most frequently (Fig. 281.3 and Table 281.1). The acute phase of infectious mononucleosis is characterized by rapid IgM and IgG antibody responses to VCA in all cases and an IgG response to EA in most cases. The IgM response to VCA is transient but can be detected for at least 4 wk and occasionally up to 3 mo. The IgG

response to VCA usually peaks late in the acute phase, declines slightly over the next several weeks to months, and then persists at a relatively stable level for life.

Anti-EBNA IgG antibodies are the last to develop in infectious mononucleosis and gradually appear 3-4 mo after the onset of illness and remain at low levels for life. Absence of anti-EBNA when other antibodies are present implies recent infection, whereas the presence of anti-EBNA implies infection occurring more than 3-4 mo previously.

The wide range of individual antibody responses and the various laboratory methods used can occasionally make interpretation of an antibody profile difficult. The detection of IgM antibody to VCA is the most valuable and specific serologic test for the diagnosis of acute EBV infection and is generally sufficient to confirm the diagnosis.

Complications

Severe complications are unusual in patients with infectious mononucleosis. Splenic rupture, either spontaneous or following mild trauma, may occur in approximately 0.1% of cases but is rarely fatal. Airway obstruction due to swelling of oropharyngeal lymphoid tissue occurs in 0.1% of cases but is rarely fatal. Airway obstruction due to swelling of oropharyngeal lymphoid tissue occurs in < 0.5% of cases.

A variety of neurologic conditions have been associated with EBV infectious mononucleosis. Headache is a common symptom, but symptomatic meningitis or encephalitis is uncommon. More severe neurologic manifestations, such as seizures and ataxia, may occur in 1–5% of cases. Perceptual distortions of sizes, shapes, and spatial relationships, known as the Alice in Wonderland syndrome (metamorphopsia), may be a presenting symptom. Some reports suggest an association between infectious mononucleosis and the possible development of multiple sclerosis.

Hematologic abnormalities such as mild hemolytic anemia, thrombocytopenia and neutropenia are relatively common, but aplastic anemia, severe thrombocytopenia, and severe neutropenia are rare. Other rare complications include myocarditis, interstitial pneumonia, pancreatitis, parotitis, and orchitis.

Patients with dysregulated immune responses to primary infection, such as individuals with primary or secondary hemophagocytic lymphohistiocytosis (HLH), can develop severe, life-threatening complications with primary EBV infection.

Patients with other primary immunodeficiencies that result in failure to control EBV infection and/or abnormal inflammatory responses to infection are at risk for severe manifestations of EBV infection, often with fulminant infectious mononucleosis, chronic viremia, dysgammaglobulinemia, and lymphoproliferation.

Immunodeficiencies most commonly linked to severe EBV infection tend to be those affecting aspects of NK cell, T lymphocyte, and NKT lymphocyte function.

Oncogenesis

Infection with EBV, the first human virus to be associated with malignancy, accounts for up to 2% of cancers worldwide. Manipulation of infected cells by EBV to establish and maintain latency can lead to transformation and oncogenesis. EBV is associated with lymphoid malignancies, such as Burkitt lymphoma, Hodgkin lymphoma, aggressive NK cell leukemia, T- and NK cell lymphoproliferative disorder, and epithelial cell malignancies such as nasopharyngeal carcinoma and gastric carcinoma.

Treatment

There is no specific treatment for infectious mononucleosis. The mainstays of management are rest, adequate fluid and nutrition intake, and symptomatic treatment to manage fever, throat discomfort, and malaise. Bed rest is necessary only when the patient has debilitating fatigue. As soon as there is definite symptomatic improvement, the patient should be encouraged to resume normal activities. Because blunt abdominal trauma may predispose patients to splenic rupture, it is customary and prudent to advise against participation in contact sports and strenuous athletic activities during

the first 2-3 wk of illness or while splenomegaly is present. Antiviral therapy is not recommended. Although nucleoside analogs such as acyclovir inhibit viral replication in vitro and decrease the duration of oropharyngeal viral shedding in patients with infectious mononucleosis, they have not been shown to not provide consistent clinical benefit for patients with infectious mononucleosis or EBV-associated malignancies. Short courses of corticosteroids may be helpful for selected complications of infectious mononucleosis, such as airway obstruction, but there are insufficient data to support the use of corticosteroids to control typical symptoms in patients with infectious mononucleosis.

Prognosis

The prognosis for complete recovery is excellent. The major symptoms typically last 2-4 wk, followed by gradual recovery within 2 mo of symptom onset. Cervical lymphadenopathy and fatigue may resolve more slowly. Prolonged and debilitating fatigue and malaise may wax and wane for several weeks to 6 mo and are common complaints even in otherwise unremarkable cases.

Prevention

Vaccination against EBV would be appealing strategy to prevent acute disease (infectious mononucleosis) and complications such as EBV-associated malignancies. Early clinical trials using strategies

targeting the EBV gp350 envelope glycoprotein demonstrated some protection against symptomatic infectious mononucleosis, although vaccination did not prevent EBV infection. No EBV vaccine is currently approved for clinical use.

The End