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150 Orthoreoviruses and Orbiviruses

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SHORT VIEW SUMMARY

Definition
- Reoviruses are linear double-stranded RNA viruses with broad host ranges.
- The term *reovirus* is an acronym for respiratory enteric orphan virus, which emphasizes the anatomic site from which these viruses were initially isolated.

Epidemiology
- Infection of humans is common but is rarely associated with significant disease.
- Asymptomatic infection is common; symptomatic infection usually consists of mild, self-limited upper respiratory tract and gastrointestinal illness.
- Reoviruses have been identified as the causative agent in rare human cases of meningitis, encephalitis, pneumonia, and myocarditis and are potentially associated with biliary atresia and choledochal cysts.

Microbiology
- Five genera of the Reoviridae have been etiologically linked with diseases of humans: *Orthoreovirus, Orbivirus, Rotavirus, Coltivirus,* and *Seadornavirus.*
- Double-stranded RNA is organized into 10 to 12 segments, which are capable of reassortment and resultant generation of novel viruses.

Diagnosis
- Laboratory diagnosis can be made serologically by a fourfold rise in acute and convalescent serum antibody response or by virus isolation from serum, stool, respiratory secretions, or cerebrospinal fluid.

Therapy
- No specific therapy is available.

Prevention
- No specific preventative measures are recommended—reoviruses are ubiquitous.

The Reoviridae family of viruses consists of nine genera, whose members have a widely varied host range, including plants and invertebrate (insects, crustaceans) and vertebrate (mammalian, reptilian, avian) animals. Five genera have been etiologically linked with diseases of humans: *Orthoreovirus, Orbivirus, Rotavirus, Coltivirus,* and *Seadornavirus.* The genome of all Reoviridae consists of linear double-stranded RNA surrounded by a nonenveloped icosahedral capsid 60 to 80 nm in diameter. Genomic material is organized into 10 to 12 segments, which are capable of reassortment and resultant generation of novel viruses.[1] In this chapter clinically relevant information is presented pertaining to human infection due to orthoreoviruses and orbiviruses. Rotaviruses, coltiviruses, and seadornaviruses are discussed in Chapters 151 and 152.

ORTHOREOVIRUSES

Background and Epidemiology

Reoviruses were first discovered in the 1950s after isolation from human enteric specimens, and they were subsequently documented to infect a wide range of hosts. Reovirus serotypes 1, 2, and 3 are found ubiquitously in the environment, and their sources include stagnant and river water and untreated sewage. The term *reovirus* is an acronym for respiratory enteric orphan virus, which emphasizes the anatomic site from which these viruses were initially isolated as well as the fact that infection of humans, although common, is only rarely associated with significant disease. Human infection primarily results in either asymptomatic infection or mild, self-limited symptoms such as upper respiratory tract illness and gastroenteritis.[2,3] Rarely, reoviruses have been identified as the causative agent in human cases of meningitis, encephalitis, pneumonia, and myocarditis and are potentially associated with biliary atresia and choledochal cysts (discussed later).[2-4] Serologic studies of reovirus prevalence have documented steady increases from infancy (5% to 10% seropositivity at 1 year of age; 30% at 2 years of age; 50% at 5 years of age) through adulthood (50% at 20 to 30 years of age; >80% by 60 years of age),[4,5] reflecting immunity acquired as a consequence of natural infection. Despite this, it has been difficult to provide convincing evidence linking reoviruses to specific human diseases. Transmission occurs by the fecal-oral and airborne routes in humans. Reovirus infection serves as an important experimental animal model of viral encephalitis and myocarditis, a presentation of which is beyond the scope of this discussion but is reviewed in Chapters 86 and 91.[6]

Clinical Disease

Respiratory Tract Manifestations

Mild upper respiratory tract illness consisting primarily of rhinorrhea and pharyngitis accompanied by low-grade fever, headache, and malaise (35% to 80%), with or without mild diarrhea (15% to 65%), has been described in children during outbreaks and was produced in experimental reovirus infections of adult volunteers.[7,8] In children, a maculopapular (and, in one case, vesicular) exanthem has been described,[4] as has otitis media. Rarer reports of lower respiratory tract disease have included interstitial or confluent pneumonia, one of which was fatal.[9,10] A novel reassortant reovirus designated as BYD1 strain was isolated in 2003 from five patients with severe acute respiratory syndrome (SARS) who were coinfected with SARS-associated coronavirus. Subsequent characterization in animal experimental models has suggested a possible copathogenic role for this virus in SARS.[11,12] More recently, two new and closely related reoviruses (Melaka and Kampar viruses) have been identified and characterized from six adult and pediatric Malaysian patients with acute respiratory tract infection.[13,14] Both viruses are presumably of bat origin with transmission to humans by bat droppings or contaminated fruits. Index adult cases suffered from high fever, chills and rigors, sore throat, headache, and myalgia. Human-to-human transmission has been substantiated by serologic analysis of secondary cases, including children.

Gastrointestinal and Hepatobiliary Manifestations

A long-term study of children with diarrhea implicated reoviruses in only 0.1% of cases, and those occurred mainly in infants younger than

KEYWORDS

biliary atresia; coltivirus; gastroenteritis; meningitis; orbivirus; orthoreovirus; Reoviridae; RNA virus; seadornavirus; upper respiratory tract infection

1 year.[2] A role for reovirus infection in the pathogenesis of extrahepatic biliary atresia and choledochal cysts has long been proposed based on similarities between pathologic changes observed in pediatric patients suffering from these diseases and reovirus-infected mice.[15] However, results from serology-based, as well as more recent molecular-based, studies are conflicting.[15,16] In one study, reovirus RNA was detected in hepatic or biliary tissues from 55% of patients with extrahepatic biliary atresia and 78% of patients with choledochal cysts, compared with 21% of patients with other hepatobiliary diseases and 12% of autopsy cases.[15] However, a subsequent study failed to detect reovirus genome in hepatobiliary tissues taken from 26 patients with extrahepatic biliary atresia and 28 patients with congenital dilation of the bile duct.[16] No convincing data exist to support an etiologic role for reovirus infection in the setting of idiopathic cholestatic liver diseases in adults.

Central Nervous System Manifestations

Reovirus types 1, 2, and 3 have been isolated from cerebrospinal fluid of infants with meningitis, systemic illness, or both. Reovirus type 1 was isolated from a previously healthy 3-month old with symptoms of meningitis, diarrhea, vomiting, and fever.[17] Reovirus type 2 (subsequently identified as a new mammalian reovirus type 2 Winnipeg) was isolated from the cerebrospinal fluid of an 8-week-old presenting with active varicella-zoster virus infection, *Escherichia coli* sepsis, intermittent fever, diarrhea, and feeding intolerance.[18,19] A novel serotype 3 reovirus (T3C/96) was isolated from a 6-week-old child with meningitis and was subsequently shown to be capable of producing lethal encephalitis in neonatal mice.[20] A novel reovirus strain (serotype 2), MRV2Tou05, was implicated in two cases of acute necrotizing encephalopathy in children from the same family.[21] These reports illustrate the rare but possible neuroinvasive potential of reoviruses in the human host.

Reovirus as an Oncolytic Agent

Reoviruses induce apoptosis in multiple cell types.[6] They replicate preferentially in cells with activated *ras* genes or ras signaling pathways, which is the case in as many as 60% to 80% of human malignancies and 90% of metastatic disease.[22] A wide range of preclinical studies have demonstrated the potential application of reoviruses as an anticancer oncolytic agent.[23] Multiple tumor types have been shown to be susceptible to reovirus infection in vitro as a novel antitumor agent, including breast, ovarian, brain (glioma, medulloblastoma), colon, melanoma, bladder, pancreatic, prostate, and lung cancers; childhood sarcoma; and head and neck tumors.[24,25] Human clinical trials with mammalian reovirus serotype 3 Dearing (Reolysin, Oncolytics Biotech Inc., Calgary, Alberta, Canada) began in 2002. To date, hundreds of patients have been treated in phase I, II, and III trials (in the United States, Canada, and the United Kingdom), using Reolysin intratumorally or intravenously, alone or in combination with other chemotherapeutic agents or radiation therapy.[26,27] More than 17 clinical trials are currently recruiting and/or actively evaluating Reolysin as monotherapy or in combination with other agents for treatment of metastatic melanoma, squamous cell carcinoma of the lung, head and neck cancer, multiple myeloma, relapsed or refractory childhood solid tumors, ovarian epithelial, fallopian tube, primary peritoneal, and pancreatic cancers.

Although reovirus-based oncotherapy primarily targets cancer cells through direct killing by apoptosis (oncolysis), additional immune-based mechanisms aiding in tumor elimination have been proposed.[28] Synergistic antitumor effects of reovirus in combination with radiation or chemotherapy have been demonstrated.[29] Characterization of immune responses to intravenous Reolysin have been reported[30]; in most clinical trials to date, the anti-reovirus immune response has been observed to correlate with decreased efficacy. Investigation into the use of reovirus as an immune adjuvant is underway with the goal of redirecting immune responses to target tumors.[29]

ORBIVIRUSES

Background and Epidemiology

The genus *Orbivirus* contains more than 100 subspecies classified within 14 serogroups, infecting a broad range of arthropod and vertebrate hosts. Orbiviruses are named based on their characteristic doughnut-shaped capsomers. The bulk of disease due to orbiviruses occurs in nonhuman vertebrates; the most frequently identified are bluetongue virus (sheep, cattle, goats, and wild ungulates), African horse sickness virus (horses, donkeys, and dogs), and epizootic hemorrhagic disease virus (deer). Disease in humans has been reported infrequently (fewer than 100 cases reported in the literature worldwide). However, infection can occur in humans who serve as an incidental host during the maintenance cycle of vector-borne transmission between nonhuman vertebrate hosts. Vectors for disease include mosquitoes, midges, gnats, sand flies, and ticks.[31,32]

Clinical Disease

Only four orbivirus serogroups have been linked to disease in humans; these are the viruses belonging to the Kemerovo antigenic complex, including Kemerovo, Lipovnik, and Tribec viruses (Russia and eastern Europe), Orungo virus (sub-Saharan Africa), Lebombo virus (South Africa and Nigeria), and Changuinola virus (Central America).[32] The spectrum of reported human disease includes neurologic infection (encephalitis, meningitis, meningoencephalitis, polyradiculitis) as well as acute febrile illnesses. Many orbiviruses preferentially infect vascular endothelial cells; thus, clinical and laboratory manifestations can mimic those seen in the setting of rickettsial illnesses. No deaths have been reported due to human orbivirus infection, and patients generally recover without long-term sequelae of infection. All age groups may be infected; however, the pediatric population is overrepresented in seroprevalence studies. In animals, orbivirus infection has been linked to congenital abnormalities such as hydranencephaly, arthrogryposis, and deafness, but this has not been reported in humans.[32]

Clinical Manifestations of Specific Agents

Kemerovo Virus Antigenic Complex

Viruses of the Kemerovo complex (Kemerovo, Tribec, and Lipovnik) are transmitted by *Ixodes* spp. ticks in Russian and Eastern Europe and were first isolated in 1963 from ticks and patients with meningitis and meningoencephalitis. Meningoencephalitis and polyradiculitis have been linked to Lipovnik virus in the present Czech Republic. Seroprevalence studies in healthy residents of the former Czech Republic indicate up to 18% seropositivity; additional serologic evaluation of patients from central Europe with tick-borne encephalitis virus infection and neurologic symptoms demonstrated the presence of concurrent Lipovnik virus antibodies in more than 50% of patients.[33]

Oklahoma Tick Fever

In the United States, cases of acute febrile illness, subsequently designated as Oklahoma tick fever, have been reported in Oklahoma and Texas and attributed to orbivirus infection, which is likely a Kemerovo-related virus. Clinical features of these reports included myalgia, vomiting, and severe abdominal pain. Laboratory features include transient leukopenia, thrombocytopenia, and anemia, suggesting possible rickettsial disease; however, serologic analysis for Rocky Mountain spotted fever, Colorado tick fever, and Powassan virus was negative.[31] Diagnosis was based on positive serology for Kemerovo group–related orbiviruses (Sixgun City and Lipovnik viruses). Viremia was not present in these patients; therefore, a specific viral etiology was not confirmed in these cases. Transmission of Kemerovo-related viruses in rabbit and large animal populations has been documented in states in the Midwest, but no human cases have been reported to date.

Orungo Virus

Orungo virus is transmitted primarily by *Aedes* spp. but also by *Culex* and *Anopheles* spp. mosquitoes in regions of sub-Saharan Africa. Seroprevalence studies in that region are as high as 24% to 34%.[34] Acute febrile illness, including fever, headache, and myalgia has been reported, as has one case of encephalitis in a child with convulsions and flaccid paralysis.[35,36] Coinfection with yellow fever virus has been documented.[37]

Lebombo Virus

Transmission of Lebombo virus occurs from *Aedes* and *Mansonia* spp. mosquitoes in South Africa and Nigeria. A case of nonspecific acute febrile illness has been reported in a Nigerian child.[35]

Changuinola Virus

Acute febrile illness due to Changuinola virus has been reported in a single human case from Panama. Seroprevalence studies indicate high rates of seropositivity in parts of South America, but the infection-to-disease ratio is unknown. Transmission has been proposed by phlebotomine flies.

African Horse Sickness Virus

Naturally occurring infection of humans with African horse sickness virus has not been reported. However, four workers in a South African veterinary office were infected in 1989 with accidentally aerosolized freeze-dried virus present in a vaccine containing attenuated viral strains. Illness was severe in all exposed workers: three developed frontotemporal encephalitis, and all four developed uveochorioretinitis. Diagnosis was confirmed serologically.[38]

Diagnosis

Laboratory diagnosis of orbivirus infection is made serologically by a fourfold rise in acute and convalescent serum antibody response as detected by complement fixation, enzyme immunoassay, or neutralization or by virus isolation from serum or cerebrospinal fluid by inoculation of suckling mice or cell cultures (Vero or BHK021). Virus-specific immunoglobulin M testing is available at reference laboratories, including the Centers for Disease Control and Prevention and the U.S. Army Medical Research Institute for Infectious Diseases. No specific therapy is available.

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The complete reference list is available online at Expert Consult.

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