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Chapter 33

# Diseases of the central nervous system caused by lymphocytic choriomeningitis virus and other arenaviruses

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## INTRODUCTION

While investigating a presumed outbreak of St. Louis encephalitis virus in 1933, Armstrong and Lillie first isolated lymphocytic choriomeningitis virus (LCMV) from pathologic studies of a dying patient (Armstrong, 1941). At least 22 genetically and serologically related lipid-enveloped RNA viral species have since been identified within the genus *Arenavirus* in the family Arenaviridae. The term *arenosus* (Latin: sand) describes the sandy appearance of the *Arenavirus* virions as a result of the ribosomes that they frequently incorporate (Rowe et al., 1970) (Fig. 33.1). This group of viruses is maintained in nature by chronic infection of rodents or, possibly in the case of Tacaribe virus, fruit-eating bats. Although humans are incidental hosts, LCMV is a common cause of aseptic meningitis in humans, and a number of other arenaviruses cause hemorrhagic fever, many times with accompanying neurologic disease (Traub, 1935; Meyer et al., 1960; Fields et al., 2007).

In addition to the notable human diseases caused by a number of arenaviruses, research on this group of pathogens has had an outsized impact on our understanding of immunology and immunopathology. Concepts of immunologic tolerance were first developed studying mice chronically infected with LCMV. This led to a Nobel Prize for Burnet and Medawar in 1960 that built upon initial observations by Traub in the 1930s (Burnet, 1957). After CD8+ T lymphocytes were found to be the specific cell population responsible for acute choriomeningitis in LCMV-infected mice, Zinkernagel and Doherty (1974) used the LCMV model to show that cytotoxic T cells are restricted by class I major histocompatibility complex (MHC) antigens. They were awarded a Nobel Prize for this work in 1996. More recently, it was shown with the LCMV mouse model of viral persistence that blockade of the programmed cell death 1 ligand restored T-cell function lost during viral persistence (Barber et al., 2006). This may very well have implications for other chronic viral infections like human immunodeficiency virus (HIV) and hepatitis C. The humoral side of immunity was further explicated by exploring the role that LCMV immune complexes play in the nephritis of chronically infected mice (Oldstone and Dixon, 1969). This has provided an important model for systemic lupus erythematosus and other immune complex diseases.

Arenaviruses are classified according to their antigenic properties into two major groups, the Lassa-lymphocytic choriomeningitis (LCM) serocomplex and the Tacaribe serocomplex. The LCM serocomplex (i.e., Old World arenaviruses) includes LCMV, Lassa, Lujo, Mobala, Mopeia, and Ippy viruses. The Tacaribe serocomplex (i.e., New World arenaviruses) includes the hemorrhagic fever agents Junin, Flexal, Machupo, Guanarito, and Chapare viruses. Several arenaviruses are found in North America, including Tamiami, Bear Canyon, and Whitewater Arroyo viruses, although only the latter is suspected of causing human disease (Milazzo et al., 2011). Of note, a new group of highly divergent arenaviruses were recently discovered in snakes, expanding the host range of arenaviruses beyond mammals (Stenglein et al., 2012) (Fig. 33.2).

## MORPHOLOGY

Arenaviruses are enveloped, pleomorphic particles that range in diameter from 50 to 300 nm. They mature by

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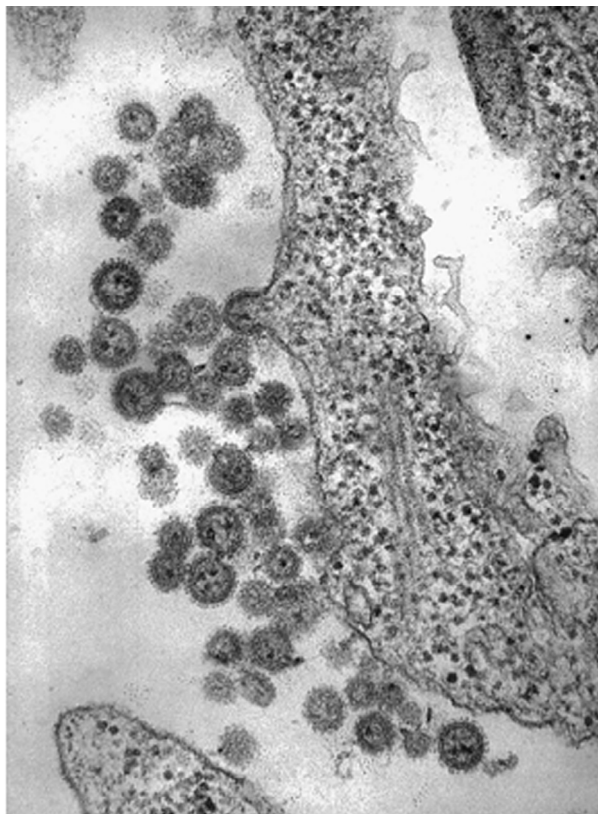
**Fig. 33.1.** Electron photomicrograph of budding Machupovirus. (From the Centers for Disease Control Public Health Image Library. Image identification number 1869. Courtesy of Fred Murphy and Sylvia Whitfield.)

budding at the surface of an infected cell, and their envelopes are derived from the cell's plasma membrane (Fig. 33.1). The virion surface is densely covered with 8–10-nm-long, club-shaped projections (Rowe et al., 1970; Murphy and Whitfield, 1975; Muller et al., 1983). The life cycle of the virus is restricted to the cell cytoplasm. The recent development of a reverse genetics system to allow for genetic manipulation of LCMV is already yielding additional insights into the molecular biology and pathogenesis of arenaviruses (Flatz et al., 2006; Sanchez and de la Torre, 2006).

## VIRAL GENOME ORGANIZATION

Arenaviruses have a bisegmented, linear, single-stranded, negative-sense RNA genome. Thus, each virion contains two nucleocapsids, one containing the large (L) RNA (7200 basepairs) while the other nucleocapsid contains the small (S) RNA (3400 basepairs). The two nucleocapsids are beaded, loosely helical structures (9–15 nm in diameter). They each form a closed smaller (400–600 nm) or larger (1000–1300 nm) circle depending on whether they contain the S or

L RNA, respectively (Young and Howard, 1983). Virions are frequently genetically diploid. The viral L RNA codes for the viral polymerase (RdRp or L polymerase) and the small RING finger protein (Z). The S species codes for the viral nucleoprotein (NP) and the glycoprotein precursor (GPC) (Buchmeier et al., 2007). Arenaviruses have a unique ambisense or bidirectional genomic organization, meaning that a single RNA can direct the synthesis of two polypeptides in opposite orientation. Intergenic non-coding regions separate the genes on both the L and S RNAs, and these non-coding regions form hairpin structures that serve as transcription termination signals (Fields et al., 2007).

## VIRAL PROTEINS

NP and the L polymerase are the minimum proteins required for viral RNA replication and transcription while the Z protein has a dose-dependent inhibitory effect on viral RNA transcription and replication. The GPC and Z proteins are required to generate infectious virus-like particles (Lee et al., 2002). The Z protein is also instrumental in arenavirus budding (Perez et al., 2003; Strecker et al., 2003; Urata et al., 2006).

GPC is transcribed as a single protein and then is post-translationally cleaved by a host protease S1P to form GP1 and GP2, the virion surface glycoproteins (Beyer et al., 2003; Pinschewer et al., 2003). GP1 mediates attachment of the virus to its cellular target and subsequent receptor-mediated endocytosis (Pasqual et al., 2011). Alpha-dystroglycan has been identified as a cell receptor for LCMV and Lassa fever (LF) virus while human transferrin receptor 1 is the cell receptor for Junin and several other New World viruses (Cao et al., 1998; Smelt et al., 2001; Rojek and Kunz, 2008).

## SMALL-ANIMAL MODEL SYSTEMS

The mouse model of LCMV has proven quite versatile. Depending on the viral strain, dose and route of infection, the clinical phenotype varies from viral clearance, immune suppression, viral persistence, or fatal central nervous system (CNS) disease (Kang and McGavern, 2008). There are two primary types of LCMV-mediated pathologies. The first is antibody-mediated (immune complex disease) and is associated with viral persistence. This occurs when animals are infected before or immediately after birth. Mice develop diffuse viral infection both systemically as well as in the CNS, including productive and widespread neuronal infection (Rodriguez et al., 1983). The infection is not cytopathic, but mice nevertheless develop deficits in behavior and learning ability (Hotchin and Seegal, 1977; Kunz et al., 2006). Infection of the thymus results in the development of T-cell tolerance to LCMV and inability to clear the virus (Pircher
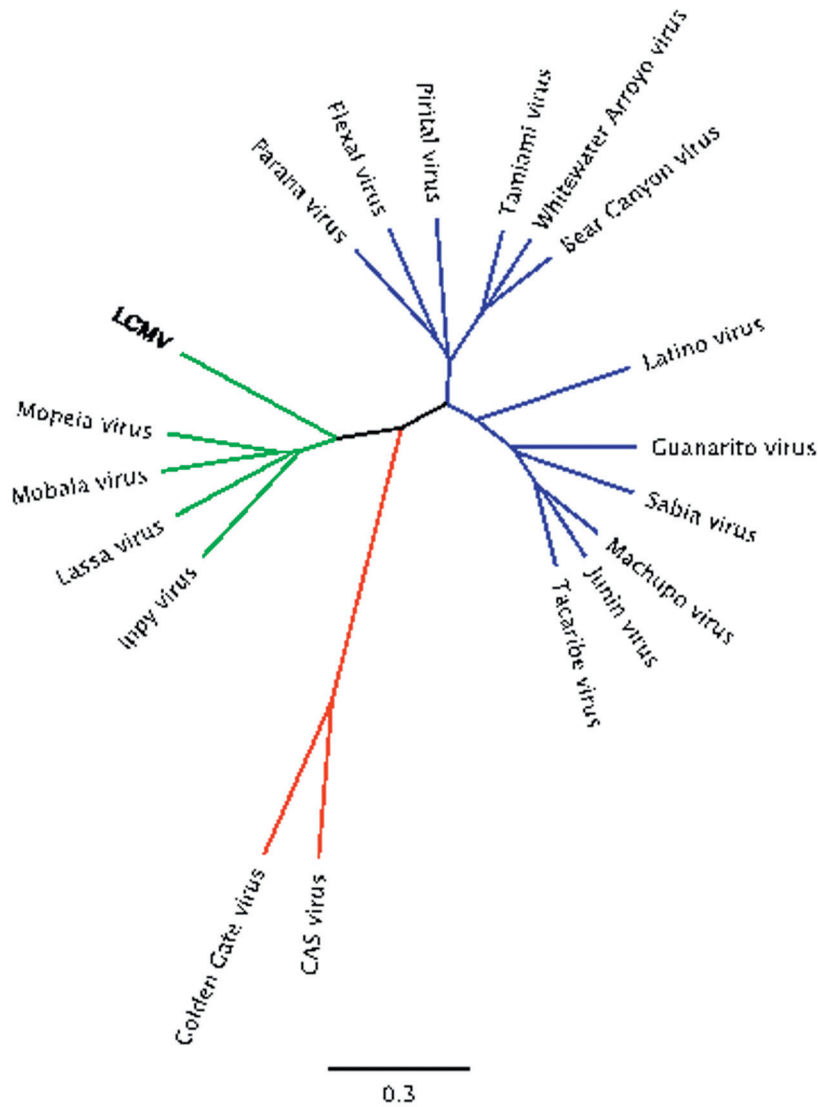
**Fig. 33.2.** Neighbor joining arenavirus phylogenetic tree based on amino acid alignment of the L protein produced using Geneious 5.5. Scale bar is substitutions per site. LCMV, lymphocytic choriomeningitis virus. Key: blue, Old World arenaviruses; green, New World arenaviruses; red: Snake arenaviruses. (Courtesy of Joseph L. DeRisi.)

et al., 1989). While the cytotoxic T-lymphocyte arm of the immune response is disabled, antiviral antibodies are produced and circulate in the serum as infectious immune complexes (Hotchin and Cinits, 1958; Volkert and Larsen, 1965; Oldstone and Dixon, 1969; King et al., 1992). These large-molecular-weight complexes accumulate in the kidneys and are able to fix complement, resulting in a chronic fatal glomerulonephritis. The quantity of the antibody is determined by the MHC and can be large or small, with the former resulting in earlier and more extensive disease (Oldstone and Dixon, 1969).

The second immunopathology is T-cell-mediated and is seen with intracerebral inoculation of the adult mouse, resulting in a rapidly (i.e., 5–7 days) fatal choriomeningitis involving the ependyma, choroid plexus, and meninges but sparing the cerebral parenchyma (Rivers and Scott, 1936; McGavern et al., 2002). Before death, mice appear dirty, and have ruffled fur, half-closed eyes, and hunchbacks. They move little except when disturbed, which can cause them to leap up and fall over backwards. The mice typically have seizures that terminate in a tonic extension of the hind legs. They either die 1–3 days after onset of symptoms (symptoms usually start 6–9 days after inoculation) or recover after 5–6 days (Rivers and Scott, 1936). In fatal infections, massive leukocytic infiltrates are found throughout the meninges and even in the parenchyma, suggesting that the immune response

is the primary driver of the disease phenotype (Kang and McGavern, 2008). Choriomeningitis can be blocked by ablating the CD8+ T-cell response through radiation, cyclophosphamide treatment, or prior thymectomy, any of which can result in chronic viremia. Transfer of LCMV-sensitized CD8+ T cells usually results in acute CNS disease and/or clearance of virus.

LCMV infection is not always limited to the meninges. In fact, cerebellar hypoplasia and retinal damage have been observed in rats infected soon after birth via the intracerebral route (Monjan et al., 1974; Bonthius et al., 2007a). These abnormalities have been observed in neonatal humans as well. Administration of antilymphoid serum to rats prevented these complications (Monjan et al., 1974).

# HUMAN ILLNESSES

## LCMV

Human LCMV infections are rarely lethal. While asymptomatic infection with LCMV almost certainly occurs in nature, asymptomatic infections after known exposures to infected animals have been documented (Biggar et al., 1975; Lehmann-Grube et al., 1979). The most frequent manifestation of LCMV infection is viral or aseptic meningitis, eponymously known as Wallgren's syndrome. Almost from its initial description by Rivers and Scott (1936), who first isolated LCMV from the cerebrospinal fluid (CSF) of two meningitic patients in 1935, the syndrome of aseptic meningitis has been associated with LCMV infection. However, soon thereafter it became apparent that viral meningitis has a multitude of causes.

While there can be an abrupt onset of symptoms, infection with LCMV typically starts with an asymptomatic incubation period of 6–13 days, followed by fever, chills, malaise, and myalgias (Armstrong, 1941; Blanc et al., 1951; Baum et al., 1966; Hirsch et al., 1974; Vanzee et al., 1975). Common symptoms also include sore throat, gastrointestinal upset, and cough. More rarely, orchitis, pancreatitis, pericarditis, or cutaneous rash can be present. Acute hydrocephalus may occur, reflecting the tropism of LCMV for the ependyma, both in mice and in humans. Early characteristic laboratory findings include leukopenia and thrombocytopenia. After defervescence, the patient can have a recurrent fever and headache indicative of CNS disease that varies widely in phenotype from aseptic meningitis to severe meningoencephalitis (Adair et al., 1953; Meyer et al., 1960; Asnis et al., 2010; Folk et al., 2011).

The clinical meningitis caused by LCMV does not have features that easily distinguish it from other typical viral meningitides (Fig. 33.3). The CSF shows a moderate to marked lymphocytic pleocytosis (often exceeding 1000 cells/μL) as well as a moderate increase in total protein (Farmer and Janeway, 1942). Unlike many viral meningitides, the pleocytosis can persist for more than 1 month (Chesney et al., 1979). Oligoclonal CSF bands have been reported (Jamieson et al., 1986) and hypoglycorrhachia is common (Adair et al., 1953).

LCMV not uncommonly affects the brain parenchyma and spinal cord in addition to the meninges, resulting in cases of altered level of consciousness and paralysis. In a series of 57 LCMV-infected patients with CNS involvement, 20 had meningoencephalitis, resulting in a number of neurologic sequelae in this and other patient cohorts (Meyer et al., 1960). As with CNS infection with mumps virus, LCMV has been associated with acute hydrocephalus requiring ventricular drainage (Hirsch et al., 1974; Larsen et al., 1993), myelitis (Ackermann et al., 1972; Park et al., 1997b), ascending paralysis (Adair et al., 1953), and sensorineural deafness (Hirsch, 1976; Ormay and Kovacs, 1989). While mortality is less than 1%, there have been deaths as a result of LCMV encephalitis in immunocompetent individuals (Warkel et al., 1973).

### LCMV INFECTION IN PREGNANCY

LCMV infection in a pregnant woman can spread to the fetus, resulting in abortion early in pregnancy (Deibel et al., 1975) or malformations, including hydrocephalus, intracranial calcifications, and chorioretinitis if the infection occurs later in pregnancy (Ackermann et al., 1974; Sheinbergas, 1975; Barton et al., 1993, 1996; Wright et al., 1997; Marrie and Saron, 1998; Barton and Hyndman, 2000; Jamieson et al., 2006; Bonthius et al., 2007b). A study by Bonthius and colleagues (2007b) reports on 20 children with serologically confirmed congenital LCMV infection who were followed for up to 11 years. Imaging abnormalities included microencephaly, ventriculomegaly, periventricular calcification, pachygyria, cerebellar hypoplasia, porencephalic and periventricular cysts, and hydrocephalus. The children suffered from mental retardation, epilepsy, blindness, and motor disorders. The authors hypothesize that the wide variability in their cohort's clinical phenotype reflected LCMV infection occurring at different stages of gestation. In a companion paper, they supported this supposition by inoculating rat pups with LCMV at varying gestational ages and observing the same wide variety in clinical pathology as well as differences in cellular targets and immune response (Bonthius et al., 2007a).

### LCMV IN THE IMMUNOSUPPRESSED

LCMV given to a normal mouse with certain transplanted lymphomas results in regression of the tumor because of infection of the malignant cells and a
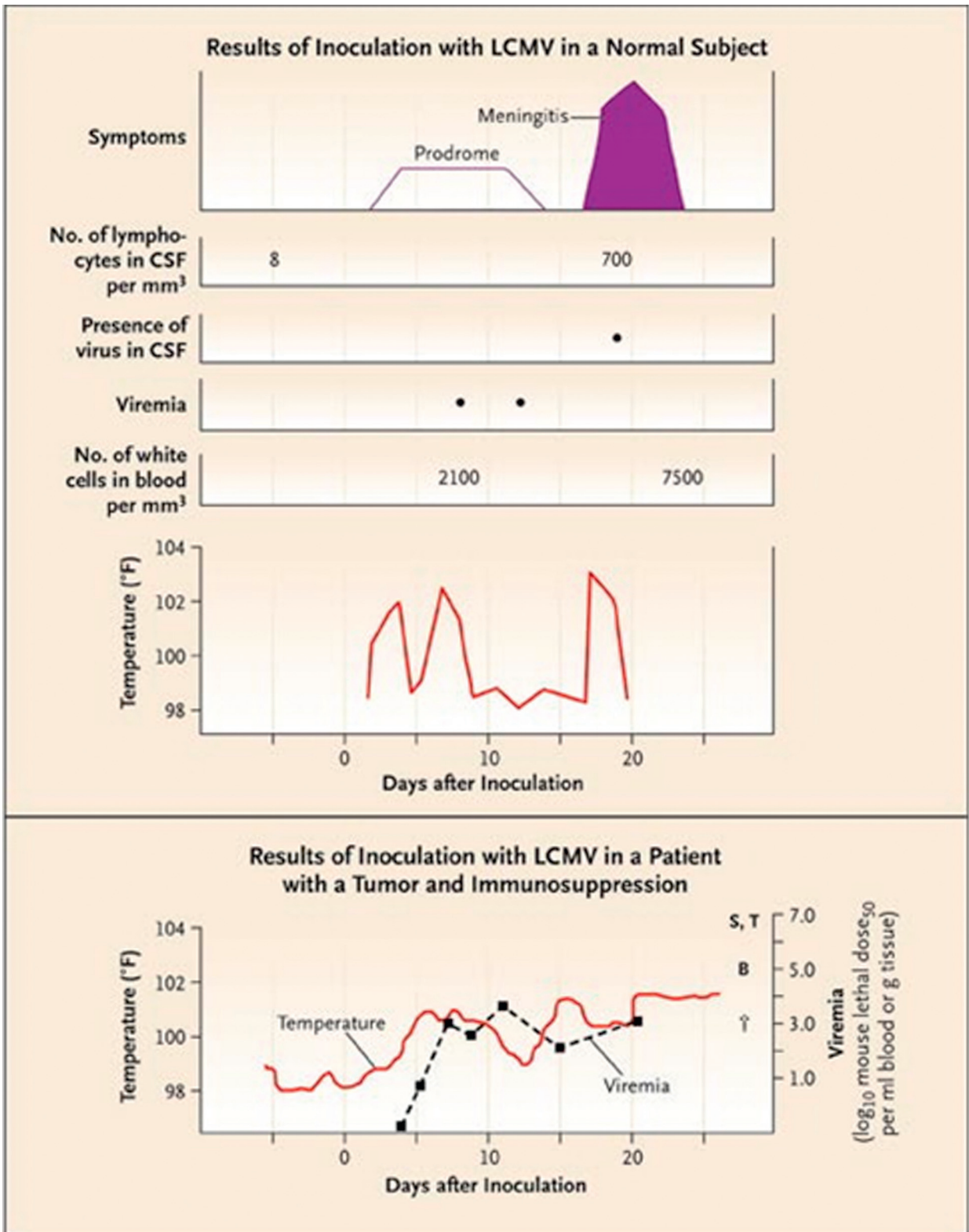
## Results of Inoculation with LCMV in a Normal Subject

**Symptoms**

Meningitis

Prodrome

**No. of lympho-cytes in CSF per mm³**

8      700

**Presence of virus in CSF**

**Viremia**

**No. of white cells in blood per mm³**

2100      7500

Temperature (°F)

104
102
100
98

0    10    20

**Days after Inoculation**

## Results of Inoculation with LCMV in a Patient with a Tumor and Immunosuppression

Temperature (°F)

104
102
100
98

Temperature

Viremia

0    10    20

**Days after Inoculation**

S, T   7.0
B   5.0

3.0

1.0

Viremia

(log₁₀ mouse lethal dose₅₀ per ml blood or g tissue)

**Fig. 33.3.** Pathogenesis of human lymphocytic choriomeningitis virus (LCMV) infection. A normal human volunteer shows an initial period of viremia associated with fever, leukopenia, and systemic symptoms (top panel). This period is followed by the onset of the cellular immune response, with meningeal inflammation that results in mild, transient disease of the central nervous system. The virus was isolated from the cerebrospinal fluid (CSF). The course of infection in a patient with immunosuppression caused by

*(Continued)*

T-cell response directed to the LCMV antigens in the cell membranes of transplanted, infected tumor cells. This observation resulted in a trial of LCMV in humans with lymphoid tumors, but the patients were far advanced and receiving chemotherapy (Horton et al., 1971) (Fig. 33.3). Presumably because of this, there was no aseptic meningitis or tumor regression. There was, however, a serious systemic disease resembling that caused by another arenavirus, LF virus.

Four transplant donors who were apparently infected with LCMV at the time of organ harvest have transmitted an often fatal LCMV infection to the organ recipients (Fischer et al., 2006; Anonymous, 2008; Palacios et al., 2008; Macneil et al., 2012). The 14 solid-organ recipients (but not cornea recipients) were all infected with LCMV and suffered a difficult Lassa-like clinical course, resulting in 11 deaths. There was no evidence of isolated encephalitis or aseptic meningitis, although virus was present in the brain when sought. The clinical setting was one of multiorgan failure. One of the three survivors was treated with ribavirin, and his immunosuppressive drugs were decreased. This may have contributed to his survival (Fischer et al., 2006). Recipients can be diagnosed with a combination of virus isolation, reverse transcriptase polymerase chain reaction, immunohistochemistry, and/or serology.

## EPIDEMIOLOGY

The natural reservoir for LCMV is the house mouse *Mus musculus*, with 3.9–13.4% of wild mice infected in the United States (Childs et al., 1992). Laboratory animals and pets including hamsters have also become asymptomatic carriers capable of vertical transmission and have served as sources of human disease outbreaks (Traub, 1935; Bowen et al., 1975; Gregg, 1975; Brouqui et al., 1995). Mice maintain high concentrations of virus in many organs. Virus is excreted in saliva, nasal secretions, and urine. Humans become infected through the inhalation or ingestion of dust or food contaminated by the urine, feces, blood, or secretions of infected animals. Incidence peaks in winter when cold weather drives mice indoors.

Current epidemiology with regard to human LCMV infection is difficult to assess as LCMV diagnostic testing is not widely available, making any numbers likely underestimates (Jahrling and Peters, 1992; Anonymous, 2006). In older cohorts, like a 1960 study of 713 Veterans Affairs and military patients with aseptic meningitis, 58 patients (8%) were diagnosed with LCMV (Meyer et al., 1960). A similar incidence was found in a Hungarian study in 1978 (143/1630) (Miklos, 1978). The overall prevalence of serum immunoglobulin G (IgG) antibody to LCMV was 5% in two adult urban populations in the United States (Childs et al., 1991; Stephensen et al., 1992). However, in people under 30, the prevalence of antibodies drops to 0.3%.

Overall, LCMV is probably responsible for less than 0.5% of viral meningitis cases currently in the United States (Knust et al., 2011). It should be noted that, in a 2011 US study looking at the prevalence of IgG antibodies against arenaviruses, there was an indication that, in addition to LCMV, a recently identified arenavirus, Whitewater Arroyo virus (WWAV), was responsible for human infections. Antibodies were found in 3.5% of 1185 people with either acute CNS disease or nonspecific febrile illnesses. WWAV likely accounted for illness in two people and LCMV in three others. However, it is not clear whether the WWAV-infected patients had actual CNS disease (Milazzo et al., 2011).

## DIAGNOSIS

There are no pathognomonic clinical features of LCMV infection. While a history of exposure to rodents certainly raises suspicion, the extensively investigated transplant cases illustrate that known rodent exposure is frequently not available in the history. LCMV can be confirmed by virus isolation. Viremia can persist for approximately 15 days. Virus titers in the CSF are lower and present for a shorter period of time. Indirect fluorescent or complement fixation antibodies appear 2–3 weeks after the onset of the illness and reach their maximum titers 5–6 weeks after the onset of illness before becoming undetectable after a few months. Neutralizing antibodies appear 2–6 weeks after onset of symptoms and persist for 6 months to 5 years. Acute and convalescent sera can be tested for increases in antibody titers, and an increase in the specific IgM in blood and CSF is diagnostic. A nested reverse transcriptase polymerase chain reaction assay has been developed for the detection of LCMV (Park et al., 1997a). The highly sensitive assay targets the GPC and N genes. Lastly, as the most recent transplant-

**Fig. 33.3, cont'd** Hodgkin's disease and chemotherapy is shown in the bottom panel. The patient was inoculated with LCMV in hopes of causing remission of the lymphoma. Viremia developed and was sustained; no indirect fluorescent, complement-fixing, or neutralizing antibodies developed; and there was no overt disease of the central nervous system. At the time of death, possibly caused by bacterial pneumonia and LCMV infection, there were high titers of the virus present in brain (B), spleen (S), and tumor (T) tissue. The dagger symbol denotes death. (Reproduced with permission from Peters CJ (2006) Lymphocytic choriomeningitis virus – an old enemy up to new tricks. N Engl J Med 354: 2210, Copyright © 2006 Massachusetts Medical Society.)

associated cases illustrate, newer unbiased diagnostic methods are becoming available that will not only facilitate improved detection of known viruses but also allow for the identification of wholly new viral pathogens (Palacios et al., 2008; Briese et al., 2009).

## Viral hemorrhagic fevers

The arenaviruses that cause hemorrhagic fever in humans include LF virus in West Africa, Junin virus in Argentina, Machupo virus in Bolivia, Guanarito virus in Venezuela, and Sabia virus in Brazil. In addition, a new hemorrhagic fever-associated arenavirus was described in South Africa (Briese et al., 2009). Lujo virus was isolated during a human disease outbreak as a result of nosocomial transmission. There was an 80% fatality rate (4/5 patients). As with the LCMV strain that caused fatal disease in a group of solid-organ transplant patients, Lujo virus was rapidly identified using the unbiased pyrosequencing of RNA extracts from serum and tissues of outbreak victims.

As their name suggests, these hemorrhagic fever viruses primarily induce a disease phenotype characterized by systemic symptoms including fever, myalgias, gastrointestinal dysfunction including varying degrees of liver failure and hematologic disarray (e.g., thrombocytopenia), resulting in diffuse hemorrhage and shock after an incubation period of 1–3 weeks. To varying degrees, these viruses can also be neurovirulent in humans.

## Lassa fever

Since 1969, LF virus has been recognized as a cause of hemorrhagic fever in West Africa (Buckley and Casals, 1970). Its natural host is the rodent *Mastomys* species complex. Infection occurs via either rodent exposure or exposure to grain stores frequently contaminated with virus. LF kills approximately 5000 people per year and likely infects several hundred thousand annually (Holmes et al., 1990). LF has also been imported from Africa to cities around the globe, including the United Kingdom, the United States, Japan, and Canada (Isaacson, 2001). Neurologic symptoms can be present in up to one-third of patients. About 20% have acute, transient sensorineural deafness at the time of systemic clinical improvement. Complications include meningitis, encephalitis, seizures, and transient or permanent sensorineural deafness (Cummins et al., 1990; Solbrig and McCormick, 1991; Liao et al., 1992). Survivors can have persistent cerebellar ataxia as well as unilateral or bilateral deafness. LF differs from the New World hemorrhagic fevers in that it less often has bleeding or leucopenia. Bleeding is associated with dysfunctional platelets rather than thrombocytopenia.

## Argentine hemorrhagic fever

An Argentine physician named Arribalzaga first recognized Argentine hemorrhagic fever (AHF) in the early 1950s (Arribalzaga, 1955). The initial cases occurred in agricultural workers near the town of Junin; they presented with hemorrhage and thrombocytopenia (Pirosky et al., 1959). Systematic studies have shown that the best predictors of AHF in the endemic area are a combination of fever, leucopenia, and thrombocytopenia. Bleeding is quite common, as are neurologic manifestations. The virus is carried by *Calomys musculinus*, which particularly inhabits fence lines and other linear habitats in rural zones. This results in a predominantly rural disease with a male preponderance. At its peak in the 1980s, hundreds of cases occurred annually, but a highly efficacious vaccine was ultimately developed and is currently licensed as an investigational drug (Maiztegui et al., 1998; Enria and Barrera Oro, 2002). Mortality is typically 15–30%. Headache can occur in the initial insidious symptoms of AHF. Within days, patients are typically bedbound with nausea, vomiting, dizziness, and diffuse flushing. Tongue and hand tremors are often present at this point and are thought to indicate cerebellar dysfunction. In the later stages, when diffuse hemorrhage resulting in shock can occur, patients may also develop an encephalitic syndrome characterized by coma and seizures (Ruggiero et al., 1960). A late neurologic syndrome can follow treatment with immune plasma, the usual treatment in endemic areas (Maiztegui et al., 1979). Occurring 2–3 weeks after the acute illness has resolved, patients can present with new-onset cerebellar and oculomotor symptoms and can progress to a more diffuse encephalitic syndrome that is rarely fatal.

## Bolivian hemorrhagic fever

Bolivian hemorrhagic fever (BHF) appeared from 1959 to 1962 near the Amazon River in Bolivia in the context of a government settlement program. Machupo virus was ultimately identified after multiple outbreaks with high mortality rates that led to the abandonment of some towns. The rodent reservoir is the species *Calomys callosus*. *C. callosus* is a field rodent and makes farming a dangerous occupation but it also enters houses, resulting in urban disease. Rodent-to-human transmission was demonstrated by a study in which the rodents in half the affected area were trapped and removed (Johnson et al., 1967). The dramatic difference in rates of infection between the two groups led to control of BHF by eliminating rodents that invaded towns (Peters, 2006). Subsequent cases have provided evidence for human-to-human transmission (Douglas and Couch,

1965; Peters et al., 1974; Kilgore et al., 1995). BHF patients resemble AHF patients in most manifestations. There have not been enough patients treated with adequate immune plasma to judge whether the late neurologic syndrome occurs. However, a similar syndrome has been seen in monkeys pretreated with immune plasma which were protected from the severe complications of the acute illness but developed neurologic deficits 4–6 weeks thereafter (Eddy et al., 1975). Whether these late neurologic complications of AHF and BHF are due to persistent virus infection in the CNS or an immunopathologic phenomenon remains unclear.

## Venezuelan hemorrhagic fever

Initially thought to be an outbreak of dengue hemorrhagic fever when first observed in 1989, a new arenavirus, Guanarito virus, was identified as a cause of hemorrhagic fever in the towns of Guanarito and Guanare in central Venezuela (Salas et al., 1991). Seizures occurred in 16% of a cohort of 165 patients. Overall mortality was 33% during the outbreak, but in the subset of patients who seized, mortality was 73% (de Manzione et al., 1998).

## TREATMENT

In addition to the live attenuated vaccine utilizing the Candid 1 Junin virus strain, work is ongoing to develop more broadly acting vaccines to protect against arenavirus infection (Kotturi et al., 2009; Botten et al., 2010). With regard to antiviral treatments, the nucleoside analogue ribavirin does have efficacy against multiple arenaviruses and has reduced mortality from LF virus when administered early in infection (Stephen et al., 1977; McCormick et al., 1986; Kilgore et al., 1997). It likely interferes with viral replication and may also induce mutations lethal to the virus (Moreno et al., 2011). However, its administration often leads to anemia and sometimes to other side-effects. Congenital disorders occur in laboratory species and the potential for these in humans limits its use in pregnant women. Fortunately, there are a number of promising avenues of research that hold out the hope of providing targeted therapy. These include attempts to target the arenavirus promoter, inhibiting the cleavage of the GPC protein into viral surface glycoproteins GP1 and GP2 and attempts to interfere with arenavirus budding (de la Torre, 2009). In addition, there has been promising recent small-animal model work using immunotherapies to modulate the neuroinflammatory response to arenavirus infection of the CNS (Pedras-Vasconcelos et al., 2008).

## CONCLUSION

While much remains to be explored regarding the neuropathogenesis of different arenaviruses, this group of pathogens has already played an important role in fundamental studies of virology and host immune response to infection. The neurologist's frequent conundrum of how much to balance treatment alternatives (if they exist) against the direct effects of the neurovirulent virus on the one hand or against the frequently deleterious immune reaction to the infection on the other hand is typified by the complicated and variable neuropathogenesis of the arenaviruses.

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