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Liver Disease Associated with Viral Infections

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ABBREVIATIONS

AIDS acquired immunodeficiency syndrome
ALT alanine aminotransferase
AST aspartate aminotransferase
CCHF Crimean-Congo hemorrhagic fever
CMV cytomegalovirus
DEN1 to DEN4 dengue virus serotypes 1 through 4
DHF dengue hemorrhagic fever
DSS dengue shock syndrome
EBV Epstein-Barr virus
ELISA enzyme-linked immunosorbent assay
HAART highly active antiretroviral therapy
HHV human herpesvirus
HIV human immunodeficiency virus
HSV herpes simplex virus
IgG immunoglobulin G
IgM immunoglobulin M
PTLD posttransplant lymphoproliferative disease
RT-PCR reverse transcription polymerase chain reaction
SARS severe acute respiratory syndrome
TTV torquetenovirus
VZV varicella-zoster virus

The liver is a major blood-filtering organ and consequently is predisposed to blood-borne infections causing infectious hepatitis. Viral infections tend to affect the liver in particular, and because of their high affinity for the liver, a subgroup of viruses is termed hepatitis viruses. This group is covered in separate chapters of this book. Here, we summarize other viral infections that do not primarily target the liver but can cause viral hepatitis as part of a systemic infection or lead to hepatic complications under certain conditions, such as immunodeficiency. Of course, this chapter cannot replace a clinical textbook on viral infections but instead focuses on the hepatic aspects of viral infections.

Infections caused by viruses other than the hepatitis viruses can roughly be classified into three major categories: liver disease in patients with fever returning from tropical and subtropical areas, which is frequently caused by exotic agents; severe liver damage in patients with immunodeficiency as a result of de novo infection or exacerbations of common agents such as herpesviruses or adenoviruses; and liver involvement in patients with respiratory and systemic infections, frequently mediated via immunologic mechanisms.

Viral Hemorrhagic Fevers

Approximately 8% of travelers to the developing world require medical care during or after travel, and fever is the underlying problem in 28% of them.[1,2] Physicians evaluating returned travelers with fever frequently suspect rare or exotic diagnoses. Travel-associated liver disease caused by exotic infections such as Ebola virus, Rift Valley fever, or Lassa fever has been reported sporadically in the literature but currently does not represent a frequent health problem. Of the identified causes, dengue is among the top three etiologic agents, and it accounts for approximately 6% of febrile illnesses in travelers.[2] Of note, although malaria is the leading cause of systemic febrile illness worldwide, travelers from every tropical or subtropical region except sub-Saharan Africa and Central America have confirmed or suspected dengue more frequently than malaria. Chikungunya is an emerging novel viral infection that has recently been reported in Asia and Africa to cause fever with prominent myalgia, arthralgia, and rash in increasing numbers of patients.[3]

Viral hemorrhagic fevers share some epidemiologic and clinical features and cause rather similar liver pathology. Most viruses are transmitted via arthropod vectors. The various viruses cause damage to small vessels in multiple organs, which frequently leads to overt hemorrhage. The spectrum of diseases and their geographic distribution are listed in **Table 34-1**. Much attention has been paid to abnormal liver function and altered hepatic pathology. Nevertheless, clinically significant liver disease and death from liver failure are rare complications except in patients with yellow fever.

Dengue Fever

The dengue virus complex consists of four antigenically related but distinct flaviviruses termed dengue virus serotypes 1 through 4 (DEN1 to DEN4).[4] Dengue viruses are transmitted by *Aedes aegypti* mosquitos in epidemic and endemic

Table 34-1 Viral Hemorrhagic Fevers Affecting the Liver

DISEASE	VIRUS GROUP	GEOGRAPHIC REGION
Dengue	Flaviviridae	Africa, Asia, tropical America
Yellow fever	Flaviviridae	Africa, South America
Lassa fever	Arenaviridae	West Africa
Argentine hemorrhagic fever (Junin virus)	Arenaviridae	Argentina
Ebola fever	Filoviridae	Central and western Africa
Marburg fever	Filoviridae	Central and southern Africa
Rift Valley fever	Bunyaviridae	East and central Africa
Congo-Crimea hemorrhagic fever	Bunyaviridae	Former Soviet Union, central-western Asia, Africa
Hemorrhagic fever with renal syndrome	Bunyaviridae	Northern Eurasia
Chikungunya	Togaviridae	West Africa, Asia, Oceania, southern Europe

outbreaks and cause acute infections. Three to 6 days after a mosquito bite the virus spreads via the bloodstream, and among the various organs it can be isolated frequently from liver samples,[5] where dengue viral antigens have been detected in Kupffer cells, sinusoidal endothelial cells, and hepatocytes.[6,7] Dengue virus infection usually causes a flulike illness with a rash—dengue fever. Hepatomegaly and elevated serum aminotransferases, which are usually mild, are common in dengue virus infections.[8,9] Clinically more severe diseases, such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), can follow secondary infection with dengue virus of a different serotype, thus suggesting that immune responses generated during previous exposure to dengue viruses may enhance the damage triggered by secondary dengue infection. In DHF there are widespread petechial hemorrhages together with multiple organ damage; in DSS, which mostly affects children younger than 15 years, there is extensive capillary leakage and severe fluid depletion leading to hypovolemic shock. If untreated, mortality approaches 50%. In fatal cases of DHF the liver is enlarged, is pale as a result of steatosis, and shows multifocal hemorrhages. Microscopically, focal hepatocellular necrotic areas are seen, as well as coalescent perivenular and midzonal necrosis with Councilman bodies, but relatively little inflammatory cell infiltration.[10,11] It is supposed that liver injury is mediated by dengue virus infection of hepatocytes and Kupffer cells, as in vitro infection of a human hepatoma cell line with dengue virus has been shown to induce apoptotic cell death.[12]

Currently, a vaccine against dengue virus is not available, and treatment is supportive, with DSS requiring intensive care.

Yellow Fever

Yellow fever is the prototype member of the Flaviviridae family, a group of plus-strand, single-stranded RNA viruses. The yellow fever virus has a single conserved serotype and seven major genotypes reflecting distinct regions in western Africa, central-east Africa, and South America.[13,14] Yellow fever virus is transmitted by a variety of different *Aedes* vectors and causes endemic and epidemic outbreaks in Africa and South America. Approximately 200,000 cases of yellow fever are currently still reported per year, with 90% occurring in Africa. Yellow fever in travelers to Africa and South America has become rare since the introduction of routine vaccination.

The spectrum of infection with yellow fever virus ranges from subclinical infection to a life-threatening disease with fever, jaundice, renal failure, and hemorrhage. Usually, yellow fever initially appears as an acute, flulike illness of sudden onset with fever, myalgia, and headache that cannot easily be distinguished from other acute infections.[15] Between 48 and 72 hours after onset, serum aminotransferases start to rise, thus heralding the development of jaundice. The degree of liver abnormalities at this stage predicts the severity of liver disease later during the course of the illness.[16] Next, a period of remission lasting up to 48 hours may follow the initial infection. Patients with abortive infection recover at this stage, but approximately 15% of patients will enter the third stage of intoxication, which is characterized by the return of fever, prostration, and organ dysfunction leading to nausea, vomiting, epigastric pain, jaundice, oliguria, and a hemorrhagic diathesis. Yellow fever differs from all other viral causes of hepatitis by the fact that serum aspartate aminotransferase (AST) levels exceed those of alanine aminotransferase (ALT). Aminotransferase levels are proportional to the severity of disease.[16] Direct bilirubin levels range between 5 and 10 mg/dl, with levels being higher in those with fatal infection than in recovering patients. The diagnosis of yellow fever is confirmed by the serologic demonstration of specific IgM by enzyme-linked immunosorbent assay (ELISA), by polymerase chain reaction (PCR), or by isolation of the virus from blood. Liver biopsy is not recommended because of a high risk for hemorrhage.

The outcome of infection with yellow fever virus is determined during the second week after onset, when many patients recover rapidly, but between 20% and 50% of the patients who have progressed to the stage of intoxication will ultimately die of circulatory shock. Convalescence may be associated with fatigue for several weeks, and in some cases jaundice and elevated aminotransferase levels may persist for months.

Liver pathology varies according to the stage of the disease. In fatal cases, approximately 80% of hepatocytes undergo coagulative necrosis. The midzone of the liver lobule is affected, with sparing of cells neighboring the central vein and portal tracts.[17] Very high viral loads have been detected in liver samples from patients who died, and viral antigen is located at the midzone of the hepatic lobule, thus indicating that this is the site of direct viral injury.[18] Liver injury is characterized by eosinophilic degeneration and the presence of Councilman bodies. Rarely, intranuclear inclusion bodies (Torres bodies) are present. Fatty changes may be prominent. In specimens from surviving patients, the liver shows ballooned hepatocytes and regenerative hyperplasia with multiple multinucleated hepatocytes and some portal inflammation consisting mainly

of $CD4^+$ T cells and smaller numbers of natural killer and $CD8^+$ T cells.[19,20] Biopsy specimens from survivors during the recovery phase may show a nonspecific acinar hepatitis.[21] However, the hepatic reticular architecture is not disrupted, and in nonfatal cases healing is complete without any residual postnecrotic fibrosis.

Antiviral activity against yellow fever has been demonstrated for several nucleosides and plant alkaloids.[22] Ribavirin inhibits yellow fever virus in vitro, but only at extremely high concentrations that cannot be achieved in vivo. Thus treatment is supportive. A highly active attenuated live vaccine is available that induces seroconversion rates of greater than 95% and provides a high level of protection. This vaccine should not be given to pregnant women and immunosuppressed individuals because of concern about the risk associated with live attenuated virus vaccines. Infrequently, two serious vaccine-related complications may also occur in immunocompetent persons: a form of encephalitis termed yellow fever–associated neurotropic disease and a syndrome resembling natural infection that is designated yellow fever vaccine–associated viscerotropic disease.

Lassa Fever

Lassa virus is an enveloped, single-stranded, bisegmented RNA virus that belongs to the Arenaviridae family. Its natural reservoir is the multimammated rat, *Mastomys natalensis*, which excretes the virus through urine, saliva, and other secretions.[23] Humans presumably become infected directly via contact with infected rodent excreta through the fecal–oral route or inhalation of contaminated air.[24] The risk of human–human transmission is low.[25,26] Serologic evidence demonstrates that the infection is widespread in western Africa, but clinically overt disease occurs in fewer than 10% and overall mortality is 1%. Increasing international travel has sporadically resulted in importation of Lassa fever to Western countries, which challenges the diagnostic skills of physicians.[27]

At onset, the infection is insidious, with fever, myalgia, headache, and malaise.[28] More specific features include ulcerations in the oral cavity, bleeding from the gums, sore throat, cough, pleurisy, and watery diarrhea. There is lymphadenopathy and swelling of the liver and kidney, which become painful on palpation.[29] Serum aminotransferase levels rise, but jaundice is not present. In Lassa fever the liver has a mottled appearance, and liver histology shows necrosis without inflammation. Single hepatocytes or groups of cells stain acidophilic and are found to harbor abundant arenaviruses under electron microscopy. There is no steatosis or cholestasis, whereas lipofuscin deposits are conspicuous.

ELISAs for Lassa virus antigen and immunoglobulins M and G (lgM and IgG)antibodies are sensitive and specific and in Africa have largely replaced indirect fluorescent antibody testing.[30] In Western countries, the diagnosis can be established reliably by reverse transcription PCR (RT-PCR).[31]

Supportive therapy is often necessary. In addition, the antiviral drug ribavirin is effective against Lassa virus infection, but only if administered early in the course of illness.[32] A study from Sierra Leone in patients at high risk for mortality confirmed the efficacy of ribavirin in the treatment of Lassa fever: only 1 of 20 patients died if intravenous ribavirin administered over a period of 10 days had been started within the first 6 days after the onset of fever, whereas mortality was 26% in the 43 patients whose treatment had begun later.[33] However, because of its toxicity and teratogenicity, the need for intravenous application, and its expense, empiric therapy with ribavirin is not advised.[33]

Junin virus is another arenavirus that in Argentina can cause a viral hemorrhagic fever similar to Lassa fever.[34] Ribavirin, as well as ribavirin-interferon combination therapy, has been attempted with some success in this disease.[35]

Ebola and Marburg Hemorrhagic Fever

Marburg and Ebola viruses are nonsegmented, negative-sense, single-stranded RNA viruses that belong to the Filoviridae virus family.[36] They are among the most virulent pathogens and cause severe hemorrhagic fever and fulminant septic shock. No approved therapy is currently available to treat the devastating infections with Ebola and Marburg viruses.

All isolates of Marburg virus represent members of a single family, whereas Ebola isolates can be divided into different species (Zaire, Sudan, Ivory Coast, Reston, and probably Uganda 2007) that differ in their virulence.[37,38] The natural reservoirs of these viruses still remain a mystery, although it is suspected that both viruses are maintained in small animals, with bats heading the list of suspects.[39-43] Retrospective analyses of African epidemics suggest that person–person transmission can occur through contact with virus-contaminated fluids (e.g., blood, vomitus, feces, urine).

Marburg virus fever was first detected in 1967, when people had come in contact with African green monkeys imported from Uganda. Mortality in this first outbreak was 25%. Meanwhile, natural outbreaks of Marburg virus and Ebola fever have been reported repeatedly from several western and central African regions (**Fig. 34-1**). Ebola and Marburg virus

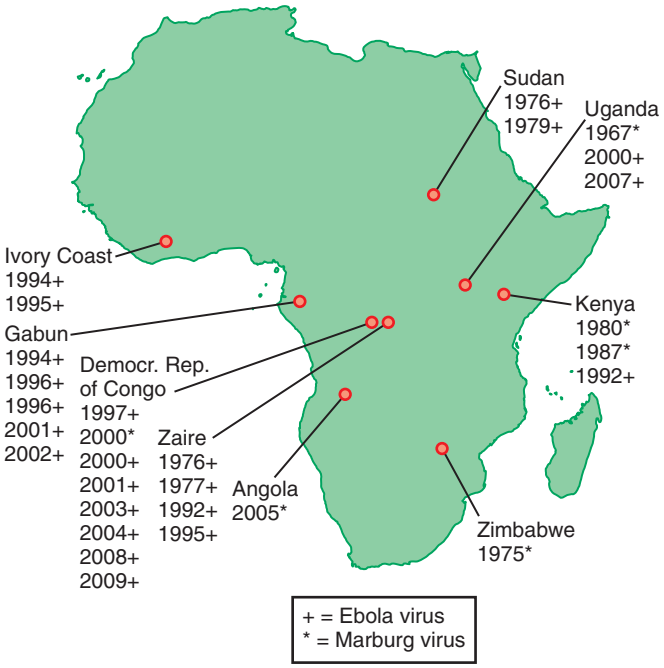

Fig. 34-1 Localization of recent Ebola and Marburg virus outbreaks in Africa.

infections are still relevant. In 1989, monkeys imported into the United States from the Philippines died of Ebola virus infection. Outbreaks still occur in western Africa, and the risk of undiagnosed patients arriving in industrialized countries remains real. Information on current outbreaks is available on the World Health Organization website (www.who.int/topics/haemorrhagic_fevers_viral/en).

The disease caused by the various Marburg and Ebola virus isolates results in similar syndromes that differ only in severity and case fatality rates. The incubation period is 5 to 10 days but may exceed 20 days. Symptomatic persons have high levels of virus in their blood and must be considered contagious, so appropriate safety precautions should be taken.[44] Marburg and Ebola infections typically begin with an abrupt onset of fever, chills, and general malaise. Other features include weakness, severe headache, pain in the muscles of the trunk and lower part of the back, nausea, vomiting, diarrhea, and abdominal pain.[37,45,46] A nonproductive cough, pharyngitis, and a maculopapular rash on the upper half of the body are also frequent findings. Symptoms persist with worsening of prostration, stupor, and hypotension; disseminated intravascular coagulation eventually leads to conjunctival hemorrhages, easy bruising, and bleeding from venipuncture sites. Marked laboratory abnormalities include a striking leukopenia with immature granulocytes and abnormal lymphocytes, as well as thrombocytopenia. Filoviruses cause multifocal hepatic necrosis. Thus AST and ALT levels rise rapidly in the first days. Hypoproteinemia and proteinuria may also be present. The hepatic pathology is similar to that seen with Lassa virus infection: spotty to widespread necrosis of hepatocytes and minimal hepatic inflammation, but no cholestasis.[47-49] Abundant filovirus particles are found in blood, phagocytes, endothelial cells, and hepatocytes. In lymph nodes, the reticular network is damaged.

Survivors of Marburg and Ebola hemorrhagic fever require prolonged convalescence and suffer from marked weakness, fatigue, and failure to regain weight. Marked sloughing of the skin and hair loss are commonly observed.[50]

Rift Valley Fever

Rift Valley fever is an acute vector-borne zoonotic disease caused by the Rift Valley fever virus, which belongs to the Bunyaviridae family and genus Phlebovirus. The virus was initially described in sheep and was first isolated from humans in Kenya.[51] The disease is widespread in sub-Saharan Africa and also occurs in Egypt, Mauretania, Senegal, Saudi Arabia, and Yemen. Rift Valley virus is transmitted by several mosquito species or by direct contamination from infected animals. Patients with Rift Valley fever have symptoms and signs of an influenza-like illness. Fewer than 8% of patients progress to severe disease, including hepatitis, encephalitis, retinitis, and a generalized hemorrhagic syndrome.[52]

Crimean-Congo Hemorrhagic Fever

Crimean-Congo hemorrhagic fever (CCHF) is a tick-borne viral infection that occurs in parts of Africa, Asia, eastern Europe, and the Middle East.[53] The virus belongs to the genus Nairovirus in the Bunyaviridae family. Isolates from different regions show considerable genetic diversity. Farmers and healthcare workers are particular at risk for this infection, but fortunately, CCHF develops in only one of five people infected. The disease has four stages: incubation, prehemorrhagic, hemorrhagic, and convalescence. Incubation takes 3 to 7 days, and then fever, headache, myalgia, and dizziness develop suddenly. Facial hyperemia, conjunctivitis, and occasionally diarrhea are also noted. This stage lasts 4 to 5 days. The hemorrhagic period is short (2 to 3 days). The most common bleeding sites are in the nose, the gastrointestinal tract, the genitourinary tract, and the respiratory tract. In survivors, the convalescence phase begins about 10 to 20 days after the onset of disease. RT-PCR is the method of choice for rapid laboratory confirmation of CCHF viral infection.[54] Leukopenia and thrombocytopenia are consistent laboratory features, and raised levels of AST, ALT, and lactate dehydrogenase and prolonged coagulation tests are other common findings. Aminotransferase levels seem to correlate with the severity of disease.[55,56] Microscopic examination of liver tissue reveals variable degrees of hepatocellular necrosis with hemorrhage and Councilman bodies, fatty changes, Kupffer cell hyperplasia, and mild mononuclear portal inflammatory infiltrates.[57]

Treatment options are limited, but ribavirin has demonstrated antiviral activity against CCHF virus in vitro and in an animal model.[58,59] However, thus far, clinical effectiveness of ribavirin has been demonstrated only in observational studies.[55,60-62] In a recent outbreak, patients with severe disease were treated successfully with ribavirin for 10 days (30 mg/kg body weight as an initial loading dose, then 15 mg/kg every 6 hours for 4 days, and then 7.5 mg/kg every 8 hours for 6 days).[53]

Hantaviruses

Hantaviruses are prime examples of emerging viruses and are members of the genus Hantavirus within the Bunyaviridae family. They are negative-sense single-stranded RNA viruses that are carried primarily in rodents, which shed the virus in their urine, saliva, and feces. The virus is inhaled by humans as aerosols from dried rodent excreta or, in unusual circumstances, is transmitted via rodent bites.[63] Hantaviruses exist in multiple serotypes worldwide, which differ in their virulence. Some are considered nonpathogenic, whereas certain isolates can produce two distinct severe syndromes in humans: Hantavirus cardiopulmonary syndrome, mostly caused by isolates in the Americas, and hemorrhagic fever with renal syndrome, caused by isolates (Seoul virus, Dobrava virus, Puumala virus, Hantaan virus) in Europe and Asia.[64] In some instances, patients with Hantavirus hemorrhagic fever have suffered from severe acute hepatitis, whereas renal damage was rather mild.[65,66] Furthermore, a significantly increased prevalence of Hantavirus antibodies has been reported in patients with acute hepatitis of unknown cause from southwestern China[67] and in patients with chronic hepatitis from Japan.[68] However, the latter study failed to detect any Hantavirus antibodies in patients with acute hepatitis, thus implying a rather indirect pathogenetic role of Hantaviruses. Of note, Hantavirus infection has been observed to trigger acute exacerbations of autoimmune liver disease, and this mechanism has been proposed to contribute to community-acquired hepatitis.[69] Nevertheless, the precise role of Hantavirus infections in human liver disease still awaits clarification. Analogous to other bunyaviruses, Hantavirus is sensitive to ribavirin, which, although not approved by the Food and Drug Administration, can be used as emergency treatment.[70]

Chikungunya Fever

Chikungunya is an arthropod-borne togavirus initially endemic to western Africa that in recent years has spread to the Indian Ocean islands and Southeast Asia.[71] Although traditionally considered a disease of tropical and subtropical regions, in 2007 a local outbreak of chikungunya was even recorded in northern Italy.[72] Because of international travel, chikungunya infections have also been exported from Southeast Asia and Indian Ocean islands to other Western countries. The infection begins abruptly with high fever, symmetric polyarthralgia, and macular or maculopapular rash.[73] Pruritus and bullous skin lesions have also been described. Previously, chikungunya fever has been considered a self-limited disease. However, severe complications, including acute viral hepatitis and death, have been reported in recent outbreaks, particularly in elderly patients (>65 years) and people with chronic medical problems. Clinically, chikungunya fever must be differentiated from dengue fever, which shares many symptoms and features. Serology is the primary diagnostic tool in clinical practice, and chikungunya IgM antibodies become detectable by ELISA 5 days after the onset of symptoms. Viral culture and molecular techniques are valuable tools in a research setting. Although interferon alfa and ribavirin exhibit in vitro activity against chikungunya virus,[74] an effective specific antiviral therapy does not exist. Thus treatment is primarily supportive. Chikungunya infection cannot currently be prevented by vaccination.

Viral Liver Disease Associated with Immunodeficiency

The establishment of organ transplantation as a routine therapeutic procedure, the growing use of anticancer chemotherapy, and the recent pandemics of human immunodeficiency virus (HIV) infection have resulted in increasing awareness of unusual manifestations of viral infections as complications of immunosuppression. Such infections occur either as acute disease during primary infection or as severe exacerbation of a latent viral persistence. Cytomegalovirus is the most common opportunistic pathogen that causes hepatitis in both patients with drug-induced immunosuppression and HIV-infected patients with advanced immunodeficiency, but the other members of the herpes family, as well as common community-acquired agents such as adenovirus, are also important causes in this setting.

Liver Disease Attributable to HIV

In approximately half of patients, a faint rash and an infectious mononucleosis–like syndrome develop 3 weeks to 6 months after a primary HIV infection. Several case reports have described a hepatitis-like syndrome in such patients that could not be explained by other concomitant infections.[75,76] Patients complained of vomiting, upper abdominal pain, and hepatomegaly. There was a rise in aminotransferases, but jaundice or elevated serum alkaline phosphatase was not present. The liver disease resolved spontaneously, and no histologic reports are available for this condition.

At autopsy, hepatomegaly was found in approximately two thirds of patients with acquired immunodeficiency syndrome (AIDS).[77] In liver biopsy specimens, macrovesicular steatosis has been a common finding, which in rare instances could become excessive.[78] HIV has repeatedly been detected in the liver, particularly in Kupffer cells and endothelial cells, both by in situ hybridization and by p24 immunohistochemical staining,[79-81] thus suggesting that the liver might be an important site of HIV replication. A moderate chronic lymphocytic portal inflammation can be encountered in liver specimens and is thought to reflect HIV-associated reactive hepatitis. These nonspecific changes associated with HIV infection can then become superseded by further liver pathology caused by opportunistic infections and tumors (**Fig. 34-2**), illicit drug

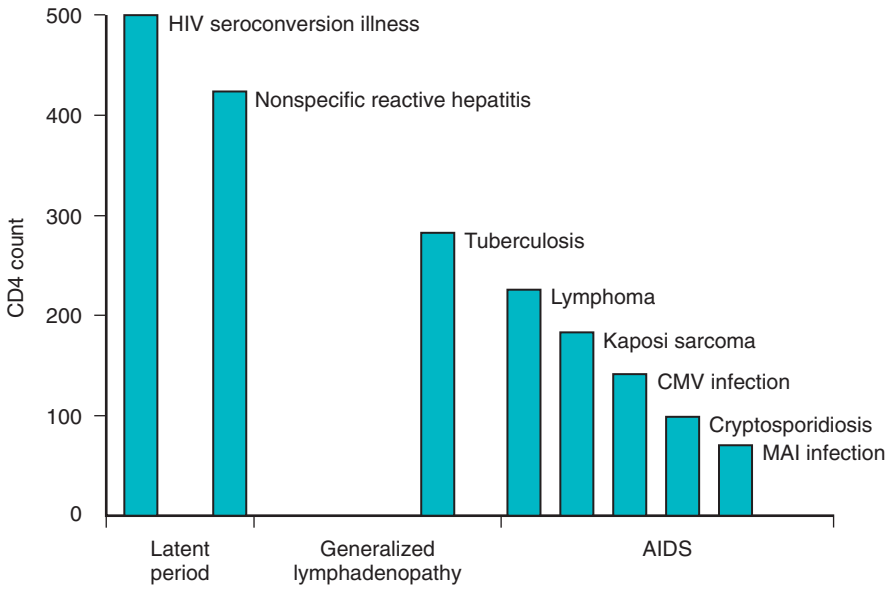

Fig. 34-2 Overview of opportunistic diseases associated with human immunodeficiency virus (HIV) infection and their relationship to progressing immunodeficiency. AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus; MAI, *Mycobacterium avium-intracellulare* complex.

Table 34-2 **Human Herpesviruses**

SYSTEMATIC NAME	COMMON NAME	HERPESVIRUS SUBFAMILY	ESTIMATED PREVALENCE	ROUTE OF TRANSMISSION
Human herpesvirus 1	Herpes simplex virus 1 (HSV1)	α-Herpesvirinae	75% to >95%	Oral secretions Close contact
Human herpesvirus 2	HSV2	α-Herpesvirinae	4% to 95%	Genital secretions Close contact
Human herpesvirus 3	Varicella-zoster virus (VZV)	α-Herpesvirinae	>90%	Aerosol Close contact
Human herpesvirus 4	Epstein-Barr virus (EBV)	γ-Herpesvirinae	70% to 95%	Oral secretions
Human herpesvirus 5	Human cytomegalovirus (CMV)	β-Herpesvirinae	40% to 95%	Oral secretions Genital secretions
Human herpesvirus 6	Human herpesvirus 6 (HHV6)	β-Herpesvirinae	>85%	Oral secretions
Human herpesvirus 7	Human herpesvirus 7 (HHV7)	β-Herpesvirinae	>85%	Oral secretions
Human herpesvirus 8	Kaposi sarcoma–associated herpesvirus	γ-Herpesvirinae	10% to 25%	Oral secretions Genital secretions

abuse, and currently, also the side effects of HIV antiretroviral therapy.[82]

The Herpesvirus Group

The herpesviruses form a large family of DNA viruses, and eight members cause disease in humans (Table 34-2). Herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus type 6 (HHV6) can directly affect the liver and are infections that in humans are usually acquired during childhood or adolescence. Herpesviruses persist lifelong and can reactivate and induce aggressive liver disease in immunosuppressed patients. Unlike the other herpesviruses, the prevalence of Kaposi sarcoma–associated virus, or HHV8, is more limited. HHV8 is found in saliva, which may serve as a source for transmission both sexually and probably also vertically from mother to child. Apart from Kaposi sarcoma, HHV8 can cause Castleman disease and body cavity lymphoma in severely immunosuppressed patients.

Herpes Simplex Virus

Primary herpes simplex infection produces characteristic oral (HSV1) or genital (HSV2) vesicular lesions on an erythematous base. The symptoms can be severe, with fever and malaise, but many primary infections are asymptomatic. Once primary infection has been established, the virus adopts a latent state and persists in the nerve cell bodies of the dorsal ganglia, from where it can reactivate under immunosuppression.

Fulminant hepatitis is a complication of both HSV1 and HSV2 infection.[83] Organ transplantation and treatment of hematologic malignancies are the most frequent underlying predispositions.[84-86] Other individuals at risk include neonates, patients taking steroids, HIV-infected patients, and patients with cancer or myelodysplastic syndromes.[83,85-90] Fatal HSV-related hepatitis has also rarely been reported in immunocompetent adults.[91] HSV-related hepatitis has high mortality (>80%) and resembles septic endotoxic shock; jaundice is not always present.[85,87] Clinical features include fever, anorexia with nausea and vomiting, abdominal pain, leukopenia, and coagulopathy. Typical oral or genital vesicular lesions occur in only about a third of patients.[83] Some patients also have disseminated extrahepatic involvement of the lung, lymph nodes, spleen, and adrenal glands. The diagnosis of HSV-related hepatitis must be established rapidly via detection of HSV by either viral isolation,[92] immunofluorescence staining, or preferentially, PCR[92,93]; serologic assays have rather limited application.

In fatal cases the liver is enlarged and congested at autopsy and has a mottled appearance with multiple white and yellow foci. Microscopy reveals irregular parenchymal necrosis with little inflammation. At the margins of necrotic areas multinucleated hepatocytes may be found, and hepatocytes may contain purple nuclear inclusion bodies with a surrounding halo.[88]

After organ transplantation, none of the patients survived once the liver was diffusely involved, whereas three of seven patients with more focal disease had survived with acyclovir therapy.[85] Prompt systemic treatment with acyclovir has also been shown to reduce HSV-associated morbidity and the risk for serious complications in HIV-infected patients.[94] In addition, anti-HSV prophylaxis with acyclovir at organ transplantation has markedly reduced HSV reactivation after surgery.[95,96] Acyclovir resistance occurs in about 5% of immunocompromised patients and is negligible (<0.5%) in immunocompetent subjects.[97] Valacyclovir, a prodrug of acyclovir, and famciclovir, a prodrug of penciclovir, have similar antiviral mechanisms as acyclovir, and thus HSV isolates resistant to acyclovir are also resistant to these drugs.[98] Cidofovir and foscarnet are alternative choices to treat acyclovir-resistant HSV, but side effects are greater with these drugs than with acyclovir.[99]

Varicella-Zoster Virus

Varicella-zoster virus causes chickenpox, as well as shingles when latent infection is reactivated. In a first viremic phase after infection, VZV replicates in the epithelia of the gut, respiratory tract, liver, and endocrine glands. A secondary viremia leads to infection of the skin, which results in the usual rash. Liver disease is rare and limited to patients with severe immunodeficiency. Anticancer chemotherapy and corticosteroid

treatment are risk factors for this complication.[100] In severe VZV infection, hepatic lesions are similar to herpes simplex hepatitis, with massive liver necrosis and inclusion bodies but little inflammation. Electron microscopy and immunohistochemistry reveal abundant VZV. The diagnosis is best made by PCR,[93] and treatment and prophylaxis are similar to that for HSV, with acyclovir also being effective against VZV. In addition, VZV has been reported to trigger severe autoimmune hepatitis.[101]

Epstein-Barr Virus

Epstein-Barr virus is the agent that accounts for 90% of acute infectious mononucleosis syndromes. It persists lifelong in a latent state, which results from a dynamic interplay between viral evasion strategies and the host's immune responses. However, unlike other herpesviruses, reactivation-associated disease is not a prominent feature in chronic EBV disease. Still, EBV is a potent cause in a variety of malignancies, such B- and T-cell lymphomas, Hodgkin lymphoma, and nasopharyngeal carcinoma. In transplant patients, EBV has been associated with an aggressive lymphoproliferative disease.

EBV is shed in oral secretions, and most primary EBV infections originate in the oropharynx. Based on genetic differences in the EBV nuclear antigen-3 genes, two types of EBV have been identified[102] that show divergent prevalence throughout the world: in Western countries, EBV1 is 10 times more prevalent than EBV2, whereas in Africa, the two EBV genomes are distributed equally.[103]

Because few pregnant women are susceptible, intrauterine EBV infection is rare but in isolated cases may lead to diverse congenital anomalies, including biliary atresia.[104] In infants and young children, primary infection is common and frequently asymptomatic, whereas in adults, it results in the infectious mononucleosis syndrome, which begins with malaise, headache, and low-grade fever before more specific symptoms such as pharyngitis/tonsillitis, swelling of the cervical lymph nodes, and moderate to high-grade fever develop.[105] Patients have peripheral blood lymphocytosis with characteristic large abnormal lymphocytes in their blood smears. Nausea, vomiting, and anorexia are common findings and probably reflect the mild hepatitis that accompanies infectious mononucleosis fever in approximately 90% of patients. Liver histology shows diffuse lymphocytic infiltrates in the sinusoids, and focal apoptotic hepatocytes can occasionally be seen (**Fig. 34-3, *A***).[106,107] These infiltrates may be atypical and must then be carefully differentiated from leukemia/lymphoma. Nonnecrotic hepatic granulomas are occasionally detected in

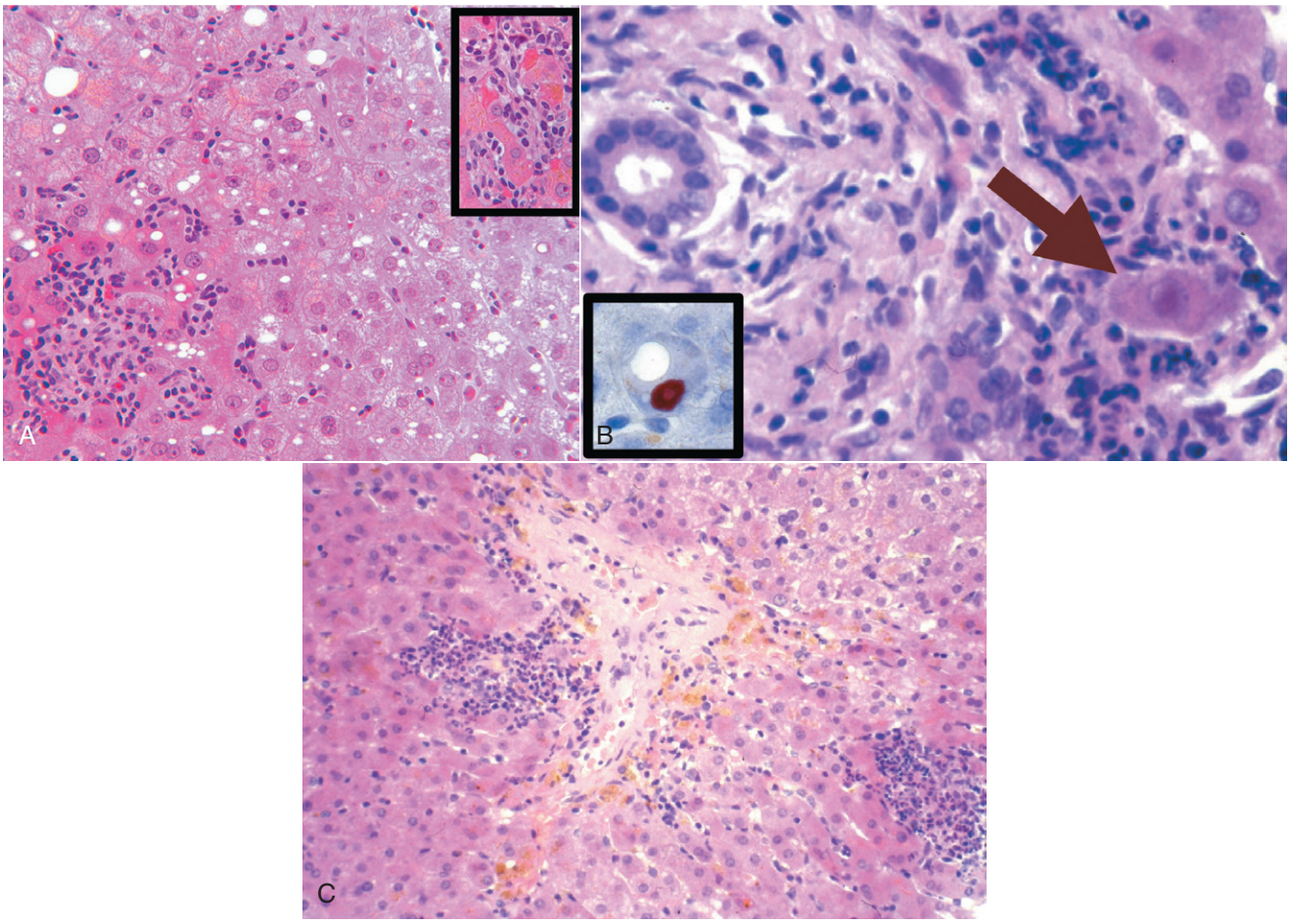

Fig. 34-3 Histologic changes in the liver associated with Epstein-Barr virus (A) and cytomegalovirus (B and C) infections. A, Prominent sinusoidal infiltration of lymphocytes into the sinusoidal space. **B,** Cytomegalovirus inclusion bodies *(arrow)* and immunohistochemical nuclear staining for cytomegalovirus antigen. **C,** Microabscesses in early cytomegalovirus infection.

patients with infectious mononucleosis. Splenomegaly is found in about half of patients, but hepatomegaly and jaundice are uncommon findings. The vast majority of patients recover over a period of 2 to 4 weeks, but fatigue may persist for several months after infection.

Patients with X-linked lymphoproliferative disease, which is caused by a mutation in the *SH2D1A* gene on the X chromosome, are particularly vulnerable to EBV[108] and may suffer fatal infections with extensive liver necrosis.[109] In patients with severe immunodeficiency, lymphomatoid granulomatosis is a further unusual complication of EBV infection that leads to granuloma formation in multiple organs, including the liver, and may require interferon alfa antiviral therapy.[110] An EBV-associated lymphoproliferative disorder with hepatic infiltration of immunoblasts[111] and a hemophagocytic syndrome[112] have also been reported in patients with HIV infection.

EBV is also the major causative agent of the so-called posttransplant lymphoproliferative disease (PTLD), which after organ transplantation may result in lymphocytic infiltration of the liver and other organs ranging from benign polyclonal B-cell proliferation to malignant B-cell lymphoma.[113] PTLD occurs more commonly in children than in adults and is related to the type and degree of immunosuppression. It is a particularly common complication in EBV-negative individuals who receive a graft from an EBV-positive donor, with primary EBV infection developing as a result of immunosuppression.[114] Clinical suspicion of EBV infection is confirmed by detection of heterophilic or EBV-specific antibodies in patients with infectious mononucleosis and quantitative PCR assays in those with lymphoproliferative disorders.[115,116]

Treatment of EBV infection is primarily supportive. Corticosteroid therapy can ameliorate the symptoms but is not generally recommended because EBV infection is usually a self-limited disease and there are theoretic concerns of suppression of immune responses with a viral infection, which can potentially cause malignant disease. Nevertheless, corticosteroids should be considered in individuals with life-threatening complications such as imminent liver failure. Acyclovir inhibits EBV DNA polymerase, and antiviral therapy with this drug has shortened viral shedding but failed to demonstrate a convincing clinical benefit even in patients with severe acute EBV infection.[117] Acyclovir does not affect latent EBV infection. Thus anticancer chemotherapy,[118,119] B-cell monoclonal antibodies,[120-122] and if possible, a reduction in immunosuppression[123] are needed to treat EBV-related lymphoproliferative disorders, but antiviral therapy in general is not effective.

Cytomegalovirus

In immunocompetent hosts, CMV infection is asymptomatic or causes only transient, minimally symptomatic acute disease. Newborns and immunocompromised patients, such as those with HIV infection, cancer, and solid organ or bone marrow transplantation, are commonly infected with CMV and may be susceptible to the development of serious disease.

In about 10% of immunocompetent subjects, primary CMV infection produces an infectious mononucleosis–like syndrome that is associated with elevated serum aminotransferase levels and a mild hepatitis. Liver histology may show focal hepatocyte and bile duct damage with lymphocytic infiltration into the sinusoids.[124] In other patients, epithelioid granulomas without necrosis were present, but CMV inclusion bodies or CMV immunostaining were rarely detectable.[124,125]

Congenital CMV infection is observed in fewer than 2% of newborns and commonly occurs when mothers have primary CMV infection or reactivation of CMV during pregnancy. Approximately 10% of such neonates have symptoms at birth, including hepatosplenomegaly and jaundice.[126] Fetal CMV infection has also been associated with obstructive biliary disease and neonatal hepatitis with giant cell transformation, cholestasis, and viral inclusion bodies.[127] In CMV infection of the liver, endothelial cells, Kupffer cells, and hepatocytes become swollen and may contain basophilic granules in their cytoplasm. A typical intranuclear amphophilic inclusion body surrounded by a clear halo resembling an owl's eye may also be present (see **Fig. 34-3, *B***). Both nuclear and cytoplasmic inclusions are full of virions.[128]

CMV-related liver disease is the most common cause of acute viral hepatitis in patients after organ transplantation. Infection may result from reactivation of endogenous virus because of immunosuppression, transmission from the transplanted organ of a CMV-positive donor, or transfusion of blood and blood products. In liver transplantation, most CMV disease occurs after 1 and 4 months, and CMV infection is also discussed as a potential risk factor for the subsequent development of acute and chronic rejection. On the other hand, rejection therapy with corticosteroid boluses may trigger reactivation of endogenous CMV. Liver biopsy specimens from patients with posttransplant CMV hepatitis usually show scanty CMV inclusion bodies, which may be associated with small foci of necrosis and inflammation (microabscesses) (see **Fig. 34-3, *C***).

Although reactivation of CMV is also a common severe complication in HIV-positive patients with advanced immunodeficiency (usually $CD4^+$ counts <50/μl), hepatic involvement seems to be rather minor.[129] Occasionally, CMV causes severe bile duct necrosis, and it is also a major cause of HIV cholangiopathy, a sclerosing cholangitis that is encountered rarely in patients with terminal HIV-related immunodeficiency.[130-132]

De novo appearance of CMV antibodies of the IgM class or a four-fold rise in IgG antibodies is considered indicative of active CMV infection in immunocompetent individuals. However, serology is unreliable in immunocompromised patients and is being replaced by quantitative molecular DNA amplification assays.[133-136] Currently, most transplant centers perform CMV surveillance by weekly quantitative determination of CMV DNA and also administer hyperimmune antibodies or antiviral drugs for CMV prophylaxis to transplant recipients at high risk for acquiring CMV disease.[137,138] However, CMV infection and disease may still develop. In patients with immunodeficiency, CMV hepatitis should be treated promptly. At present, intravenous ganciclovir or oral valganciclovir for 3 weeks is the treatment of choice. Treatment can be continued in reduced doses as chemoprophylaxis if prolonged immunosuppression is anticipated.[139] Fortunately, ganciclovir resistance seems to be a rather rare event,[140] so the toxic alternatives cidofovir and foscarnet can largely be avoided.

Human Herpesvirus 6 and Human Herpesvirus 7

There are two variants of HHV6, HHV6A and HHV6B, which infect not only T cells but also other cells types expressing the

CD46 receptor.[141] Though genetically clearly distinct from HHV6, HHV7 is another β-herpesvirus that shares many features with HHV6. Primary infection with either virus commonly occurs at a young age and can lead to a febrile illness known as exanthema subitum or roseola infantum.[142] Pityriasis rosea reflects primary infection with HHV7. Although the spectrum of diseases caused by HHV6 and HHV7 later on is not fully known, these viruses have been linked to a variety of different syndromes such as encephalitis, multiple sclerosis, pneumonitis, an infectious mononucleosis–like condition, and postinfectious drug hypersensitivity, as well as lymphoproliferative disorders and systemic disease in immunocompromised patients.[143]

HHV6 can also cause hepatitis, which has occasionally resulted in liver failure in neonates and young infants.[144-145] Moreover, HHV6 DNA and antigens have been detected in a significant proportion of children and adults who underwent transplantation for acute liver failure of unknown cause.[146-149] Of note, in two patients with HHV6 infection and imminent liver failure, HHV6 infection was controlled successfully with valganciclovir and with liver transplantation plus ganciclovir, respectively.[150] Hepatitis caused by HHV6 and HHV7 also complicates organ transplantation.[151-153] HHV6-induced acute liver failure and co-infection with hepatitis B and C viruses have been identified as risk factors for reactivation of HHV6 in patients after liver transplantation.[154,155] Of note, HHV6 reactivation seems to significantly increase mortality in living related liver transplant recipients.[155] HHV6 and HHV7 can reactivate each other[156,157] and can also reactivate CMV infection and lead to symptomatic disease in liver transplant patients.[158] In addition, HHV6 has been associated with autoimmunity and postinfantile giant cell hepatitis,[159,160] as well as giant cell transformation of bile duct cells.[161]

Seroconversion with at least a four-fold rise in IgG antibody titer between paired samples is considered diagnostic of HHV6 infection, but serology does not distinguish between HHV6A and HHV6B variants and may also be cross-reactive with HHV7. HHV6 IgM antibodies develop within a week after infection but are an unreliable marker because approximately 5% of healthy subjects may have a positive IgM test at any given time.[162] HHV6 can be detected in tissue samples by virus-specific monoclonal antibodies, but the preferred method for diagnosing HHV6 and HHV7 infection is by quantitative DNA amplification assays.[163-165]

In most immunocompetent patients, HHV6 and HHV7 cause a benign self-limited infection that does not require specific antiviral treatment. Nevertheless, foscarnet is active against HHV6A, HHV6B, and HHV7 in vitro, whereas unlike HHV6B, both HHV6A and HHV7 may be relatively resistant to ganciclovir.[166-169] Cidofovir may be a therapeutic alternative, but some resistant HHV6 isolates have been identified.[170] Although in vitro studies and anecdotal reports in the transplant setting seem to suggest some beneficial effects in human infections,[150,169] antiviral therapy against HHV6 or HHV7 has not yet been evaluated in controlled trials.

Human Herpesvirus 8

HHV8 is a γ-herpesvirus that has the potential for malignant transformation. Although primary HHV8 infection can cause rash and fever in children and immunocompromised individuals, the onset of HHV8-related diseases usually occurs several years after the acquisition of HHV8. Kaposi sarcoma, body cavity lymphoma, and multicentric Castleman disease are the typical manifestation of HHV8 infection, but bone marrow aplasia and multiple myeloma have also been described in association with this infection.[171] T lymphocytes play an important role in the control of HHV8 infection, which explains why the incidence of HHV8-related diseases is increased in patients with a transplant or AIDS. This concept is also supported by the observation that regression of Kaposi sarcoma is achieved when immunosuppression is reduced in patients with a transplant[172,173] and when highly active antiretroviral therapy (HAART) has improved immune function in subjects with AIDS.[174] Other risk factors for Kaposi sarcoma, the predominant manifestation of HHV8-associated disease, are multiple homosexual contacts in HIV-infected men[175] and, in the transplant setting, male sex, old age, and lung transplantation.[176]

In autopsy studies, Kaposi sarcoma has involved the liver in approximately 20% of subjects with AIDS, but its prevalence is declining with HAART. Hepatic Kaposi sarcoma is usually part of widespread cutaneous and visceral disease but may rarely be the primary manifestation.[177] Fulminant hepatic Kaposi sarcoma has also been observed in the first few weeks after liver transplantation (**Fig. 34-4, *A* to *E***). Macroscopically, dark red tumors 0.5 to 2 cm in diameter may be seen on the skin, the liver capsule, and the parenchyma. At the microscopic level, the typical lesion is a mesh of spindle cell–like tumour cells and dilated thin-walled vessels.[178] Diffuse plasma cells, infrequent mitosis, and clusters of intracytoplasmic eosinophilic inclusions resembling small erythrocytes are further characteristic features. Hepatosplenomegaly, fever, and weight loss are typical features of multicentric Castleman disease, a noncancerous proliferation of B lymphocytes (see **Fig. 34-4, *F***). Lymphocytes in patients with multicentric Castleman disease and Kaposi sarcoma seem to cooperate with each other, and thus the two HHV8-related lesions can occasionally be found within the same lymph node.[179,180]

Ascites and pleural effusions may initially raise suspicion of some underlying liver disease in patients with HHV8-related body cavity lymphoma, but they can be differentiated by the presence of abundant lymphoma cells in aspirated fluid (see **Fig. 34-4, *G***). HHV8 can also cause solid organ lymphoma, which in the liver leads to diffuse sinusoidal accumulation of HHV8-infected B lymphocytes.[181]

Reconstitution of immune function is a primary goal in the treatment of HHV8-associated diseases and, apart from HAART in HIV infection, may be achieved with the use of antiproliferative m-TOR (mammalian target of rapamycin) inhibitors for immune suppression in transplantation[182,183] or immune stimulation with imiquimod and interferon alfa.[184,185] Chemotherapy with liposomal anthracyclines or paclitaxel for Kaposi sarcoma[186,187] and rituximab for Castleman disease and lymphoma are further potent treatment options.[188] Ganciclovir, cidofovir, foscarnet, adefovir, and lobucavir, but not acyclovir, show some in vitro activity in blocking replication of HHV8-infected cell lines, and in a double-blind, placebo-controlled crossover trial, valganciclovir reduced oropharyngeal shedding of HHV8 by 80%.[189]

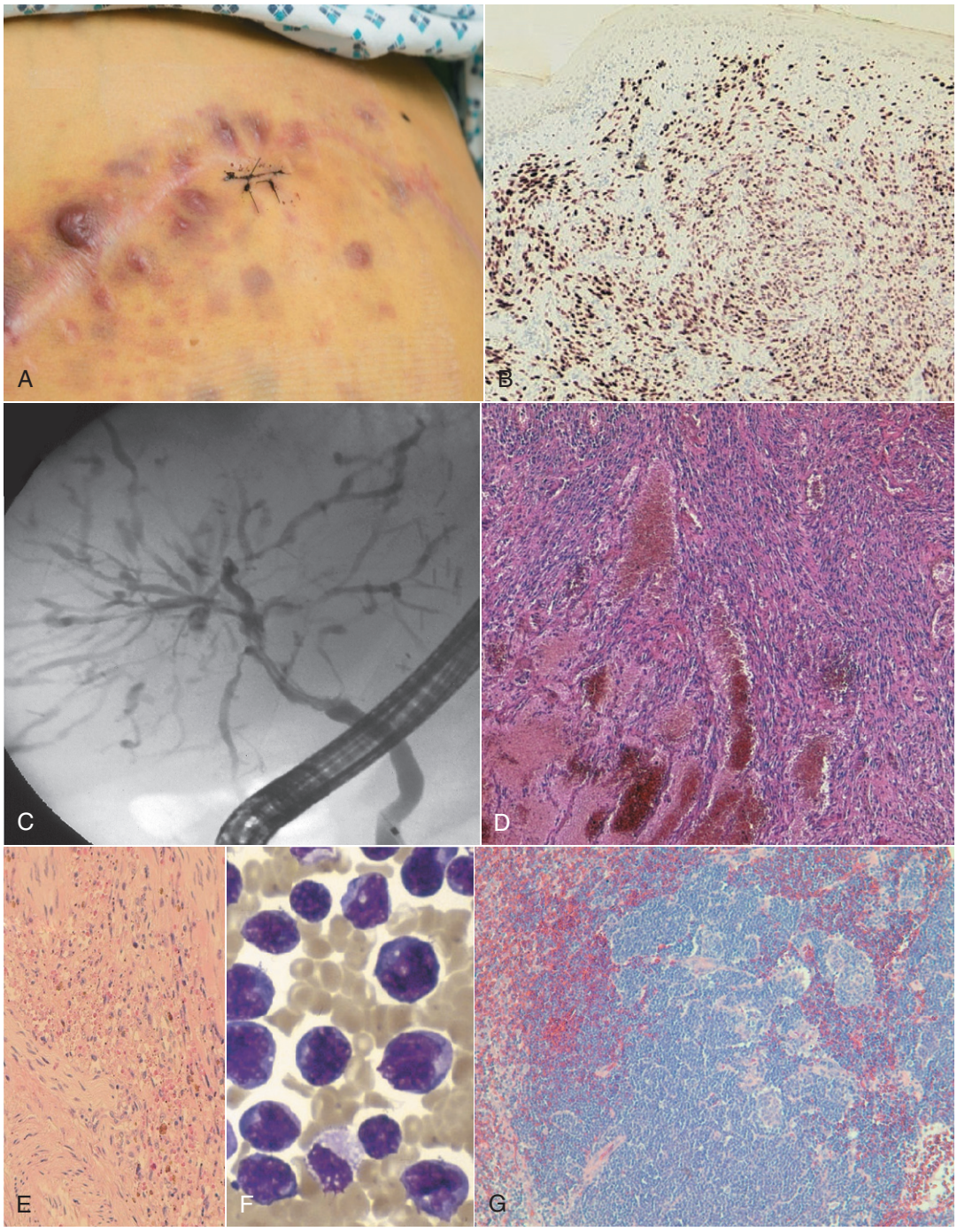

Fig. 34-4 Human herpesvirus 8 (HHV8)-associated manifestations. A, Cutaneous Kaposi sarcoma developing in a surgical scar 4 weeks after liver transplantation. **B,** Detection of HHV8 latency-associated nuclear antigen-1 in a skin section from the patient in **A. C,** Endoscopic retrograde cholangiopancreatography demonstrates compressed and partially blocked biliary ducts as a result of multifocal hepatic tumor infiltration (same patient as in **A**). **D,** Liver histology illustrating typical Kaposi sarcoma with abundant spindle cells and dilated vascular spaces (same patient as in **A**). **E,** High-power field of hepatic Kaposi sarcoma. **F,** Multicentric Castleman disease in a perihepatic lymph node. Histology shows many atypical follicle-like structures and abnormal vessels. **G,** Plasma cell–like lymphoma cells in an HIV-infected patient with HHV8-associated body cavity lymphoma.

Adenoviruses

Adenoviruses have a worldwide distribution and cause febrile diseases in infants and young children. More than 50 serotypes can be distinguished and are further subdivided into six subgroups, A through F. Typical syndromes include conjunctivitis, upper respiratory tract infections such as pharyngitis and coryza, pneumonia, and otitis media. In young children, an acute diarrheal illness is caused by subgroup F type 40 and 41 adenoviruses. Adenoviruses can persist in human tissue over prolonged periods[190,191] and can cause a variety of clinical syndromes in immunocompromised individuals, including serious hepatitis.[192] Adenoviral hepatitis occurs in congenital and acquired immunodeficiency syndromes and may be fatal

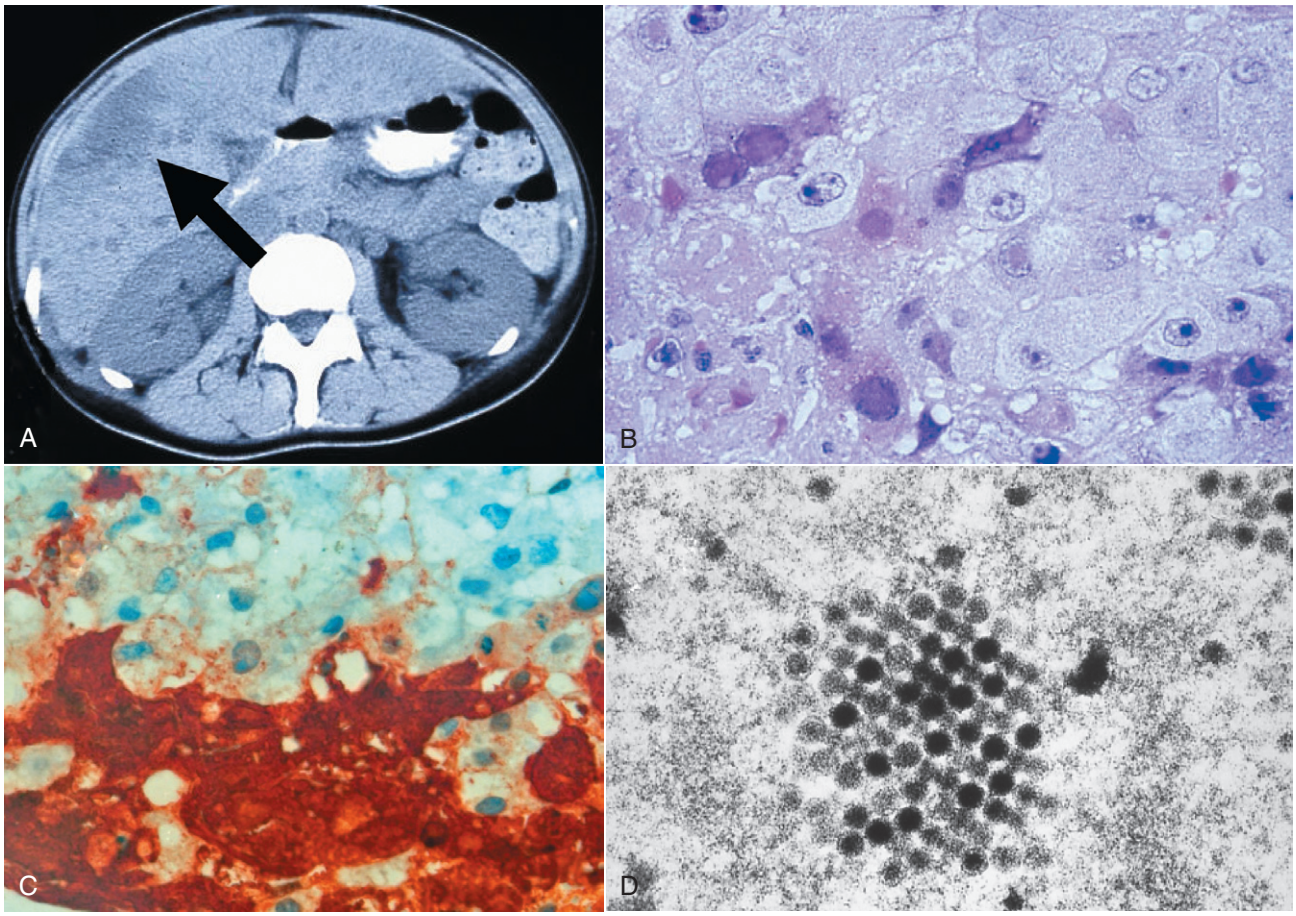

Fig. 34-5 **Fulminant adenoviral hepatitis in an HIV-infected woman. A,** Computed tomographic scan illustrating extensive focal necroses in the liver *(arrow)*. **B,** Necrosis and enlarged hepatocytes with adenoviral inclusions (same patient as in **A**). **C,** Immunohistochemistry demonstrates the presence of abundant adenoviral antigens (same patient as in **A**). **D,** Intracellular adenoviral virions seen on electron microscopy (same patient as in **A**).

in these individuals.[193-196] Adenoviral hepatitis is a particular problem in pediatric liver transplantation and was identified in 14 (3%) of 484 pediatric liver transplant recipients[197]; 6 of the 14 patients died, 4 required retransplantation, and only 4 patients recovered with a decrease in immunosuppressive therapy. Transmission of latent adenovirus with the donated organ seems to be a potential risk factor for this complication.[198] The signs and symptoms of adenoviral hepatitis resemble those of HSV infection and consist of massively elevated aminotransferase levels and severe coagulopathy. There are extensive areas of liver cell necrosis with little inflammation and intranuclear inclusion bodies (**Fig. 34-5, *A* to *D***). To date, a proven therapy for adenoviral hepatitis does not exist, but ribavirin may be helpful in selected cases.[199]

Liver Disease Associated with Systemic Viral Infections

The liver can be affected as part of a generalized infection with viruses that primarily target tissues other than liver, such as adenovirus and influenza. Liver involvement can range from asymptomatic deranged biochemistry to fulminant hepatic failure. Loss of immune control is considered responsible for hepatitis associated with opportunistic viral infections, and rather similar mechanisms may operate in severe acute respiratory syndrome (SARS)-associated hepatitis, which is characterized by focal lobular lymphocytic infiltrates. Finally, "collateral damage" has been proposed in influenza infection and reflects expansion of virus-specific $CD8^+$ T cells generated outside the liver that may trigger T-cell–dependent hepatitis even when viral antigens are apparently absent in the liver.[200] Kupffer cells play a pivotal role in this process because they can take up and present viral antigens, coordinate lymphocyte recruitment, or possibly become activated by lymphocytes to induce hepatocellular apoptosis.[201] Because T-cell expansion occurs with many viral infections,[202] this bystander mechanism may contribute to hepatitis in many extrahepatic infections, with important implications for liver pathobiology.

Influenza

Influenza viruses represent three genera in the Orthomyxoviridae family. Generally, influenza A viruses are associated with more severe disease in humans than are influenza B and C viruses. Influenza A is further subdivided with respect to genetic variation in its hemagglutinin (H) and neuraminidase

(N) genes. Influenza viruses commonly cause a self-limited acute respiratory infection manifested as fever, rhinorrhea, sore throat, and occasionally, gastrointestinal symptoms. Therefore aminotransferase levels are not monitored routinely. In the 2004 H1N5 influenza outbreak, however, about 60% of patients with pneumonia had deranged liver function test values and gastrointestinal symptoms such as vomiting, abdominal pain, or diarrhea on initial evaluation.[203] Of note, among other extrahepatic abnormalities, autopsy revealed hepatic centrolobular necrosis, although neither viral antigen detection nor RT-PCR could provide evidence of viral liver disease.[204] Thus liver damage in patients dying of influenza has been considered immune mediated, in particular because high cytokine levels were detected.[205] Of note, in 4 of 15 volunteers infected intranasally with influenza A/Kawasaki/86 (H1N1), markedly elevated aminotransferase levels also transiently developed.[200] This experimental observation is remarkable because the rise in liver enzymes occurred after pyrexia had settled, thus suggesting that the liver damage was mediated by the host's immune response rather than viral infection of the liver. It has been proposed that immune-mediated liver damage may also be the cause of elevated aminotransferases in other viral respiratory infections such as respiratory syncytial virus,[206] although cardiovascular effects and hepatic ischemia must be considered in these severely ill patients as well.[207]

Coronavirus (Severe Acute Respiratory Syndrome)

A novel coronavirus (SARS-coronavirus [SARS-CoV]), causes SARs, and it resulted in an outbreak of severe infection of the lung and gastrointestinal tract in the Far East and Canada.[208,209] There was also involvement of other organs; approximately 25% of patients had elevated liver enzymes at the onset of infection, and elevated levels developed later in an additional 45% of patients with normal liver enzymes at initial evaluation, so overall, up to 70% of patients had elevated liver enzyme levels during their illness.[210-215] Jaundice was observed in less than 10% of patients. In most patients, aminotransferase levels started to rise toward the end of the first week and peaked at the end of the second week. With resolution of SARS, aminotransferases normalized spontaneously in the majority of patients. Severe liver damage (ALT more than five times the upper limit of normal) was observed more frequently in male patients and those with significant other co-morbid conditions or elevated serum creatinine levels.[215] The role of concomitant hepatitis B in disease severity is controversial.[214,215] However, there was a close relationship between the severity of hepatic dysfunction and degree of pulmonary damage and the outcome of SARS.[214] Thus high ALT levels appeared to be an independent predictor of more severe disease and a worse outcome.

Histopathologic studies revealed marked apoptosis of hepatocytes and conspicuous (presumably compensatory) mitotic activity.[216] Hepatocytes also showed some ballooning, and mild to moderate lymphocytic infiltrates were described in the portal tracts and liver lobules. Although SARS-CoV RT-PCR was consistently positive in liver specimens, immunohistochemistry and electron microscopy failed to detect viral antigens and viral particles in several biopsy and postmortem studies.[216-218] Thus only small amounts of SARS-CoV seem to be present in the liver, and analogous to influenza infection, the host's immune response may contribute to the liver damage.[219] In the recent SARS outbreak, both ribavirin and Kaletra (baby-dose ritonavir/lopinavir) were used as experimental therapy with limited success.

Measles (Rubeola)

Measles is caused by Morbillivirus of the Paramyxoviridae family. It is an acute febrile illness with a typical rash that is currently preventable by vaccination. Measles is associated with diverse complications such as pneumonitis or subacute sclerosing panencephalitis and causes significant mortality in third-world countries and in patients with immunodeficiency.[220] Liver dysfunction has increasingly been recognized as a complication of measles in children and adults[221-223] and may become a prominent feature in patients with atypical measles and partial immunity to the measles virus.[224,225] Hepatic abnormalities have been noted to occur more frequently in adult patients with primary infection (up to 66%) than in children.[226] Two patterns of hepatic dysfunction are encountered: asymptomatic elevations of aminotransferases, which resolve within a few days, and rarely, prolonged cholestasis and jaundice, which may appear when measles begins to recede.[227] In liver tissue, steatosis, portal inflammation, and focal necrosis have been reported.[228] Viral inclusions and giant cells are rarely seen but have been observed in a child with congenital immunodeficiency.[229] In addition, measles has been incriminated in triggering autoimmune hepatitis.[230] Paramyxovirus particles have also been reported in several patients with syncytial giant cell hepatitis.[231-234] However, the very nature of these particles has thus far remained elusive.

Rubella

Childhood rubella is apparently not associated with significant liver disease. Nonetheless, this virus has been proposed as a cause of neonatal giant cell hepatitis, which may also be accompanied by necrosis, cholestasis, and lymphocytic infiltrates on histologic examination.[235]

Enteroviruses

Group B coxsackievirus infection can cause liver disease as part of a serious multisystem infection in young children and also rarely in adults.[236-238] Liver histology shows hemorrhagic necrosis in neonates, whereas in adults, swollen hepatocytes, bile stasis, and a mixed infiltrate of mononuclear and polymorphic leukocytes in the portal tracts and sinusoids have been observed.

Parvovirus

Human parvovirus B19 is a nonenveloped, single-stranded DNA virus that belongs to the Erythrovirus genus of the Parvoviridae family. Humans are the only known host, in whom it can produce a wide range of different syndromes. Most immunocompetent people with B19 infection will be asymptomatic or suffer only nonspecific malaise, muscle pain, and fever, which in the second week may be followed by rash, arthralgia, pancytopenia, and edema in about a quarter of infected patients.[239-240] Erythema infectiosum occurs in

school-aged children and occasionally also in adults. Arthropathy and aplastic anemia are further complications in adults. Fetal infection during gestation is a cause of hydrops fetalis, which is associated with marked damage to the liver[241]; hepatocytes have ballooned, swollen nuclei that harbor eosinophilic nuclear inclusion bodies. In addition, erythroid-myeloid precursors are greatly expanded in the sinusoids. Parvovirus B19 has also been identified as a cause of acute hepatitis[242] and has been incriminated as the underlying cause in acute liver failure with anemia.[243] However, a subsequent study could not confirm parvovirus B19 as a cause of fulminant hepatic failure.[244]

Torquetenovirus and Other Anelloviruses

Torquetenovirus (TTV) was initially identified as a novel virus in three of five patients in whom posttransfusion hepatitis developed but were found to be negative for all known hepatitis viruses.[245] TTV is classified in the genus Anellovirus, which is not attached to any family. Torquetenominivirus and related viruses with smaller genomes, provisionally designated as small anelloviruses, are further members of this genus. TTV can be subdivided into five phylogenetic groups, 1 to 5, and co-infection with several genotypes is common. Some TTV variants have their own designation, such as SEN virus, named after the patient from whom it had been isolated.

Soon after its discovery, it became clear that TTV viremia occurs frequently in the healthy general population worldwide. Thus the clinical significance of TTV infections remains uncertain. Inoculation of chimpanzees with TTV led to viremia but did not cause hepatitis.[246] Moreover, several studies on TTV transmission failed to establish any consistent relationship between TTV viremia and elevated serum aminotransferase levels.[247-249] Nevertheless, it cannot be excluded that TTV is responsible for acute hepatitis in some subsets of patients,[247,250] and if so, TTV seems to cause a rather mild form of hepatitis.[251]

Likewise, most studies also could not confirm any consistent associations between persistence of TTV and the presence of biochemical and histologic hepatic abnormalities in a variety of different clinical settings.[248,252-254] TTV infection does not seem to trigger autoimmune hepatitis,[255] and a case-control study failed to establish TTV as an independent risk for factor hepatocellular carcinoma.[256]

Taken together, it seems most likely that the initial reports of an increased TTV prevalence in patients with chronic liver disease[257,258] reflect shared risk factors for infection and liver damage rather than TTV as the cause of the liver disease.

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