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Liver Disease Associated with Non-Hepatitis Viruses

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Introduction

The liver is a highly perfused organ and the first filter for blood coming from the intestines. Thus, the liver is particular prone to become involved in blood-borne infections. Apart from the so-called hepatitis viruses, many other viruses, primarily targeting other extrahepatic tissues, also lead to liver damage and hepatitis. Damage can range from asymptomatic elevations of aminotransferases to fulminant hepatic failure depending on the virus and the host's immune response. When the immune system controls infection poorly, direct infection of hepatocytes and liver necrosis may occur. This situation applies to patients under severe immunosuppression or infections with particularly virulent agents such as the viruses that cause hemorrhagic fevers.

Alternatively, liver cells may become victims of collateral damage without direct infection when cytolytic CD8+ T effector lymphocytes are expanded outside the liver and then recruited via liver-resident macrophages such as Kupffer cells presenting viral antigens (Polakos et al., 2006; Schumann et al., 2000). This type of liver damage is particularly associated with respiratory viruses such as influenza virus. However, since many viral infections expand CD8+ T lymphocytes, this by-stander mechanism may affect the liver more often (Murali-Krishna et al., 1998).

Here, we provide a brief overview over viral infections primarily not designated as hepatitis viruses which may lead to liver disease and hepatic complications. This overview will largely focus on the hepatic aspects of viral infections. Thus, readers interested in more detailed information should consult a comprehensive textbook in microbiology or clinical infectious diseases.

Virus-Induced Liver Necrosis and Viral Hemorrhagic Fevers

General Comments

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 (Wilson et al., 2007). Physicians evaluating returned travelers frequently suspect rare or exotic diagnoses. Although exotic diseases, in particular viral hemorrhagic fevers are a severe threat in certain regions of the world, liver disease due to exotic infections such as Ebola virus, Rift valley fever or Lassa fever have been reported only sporadically but do not represent a frequent health problem in returning travelers.

Viral hemorrhagic fevers share some epidemiological and clinical features and cause rather similar liver pathology. Most viruses are transmitted via arthropod vectors. The viruses cause small vessel damage in multiple organs resulting in overt hemorrhage. The spectrum of diseases and their geographical distribution are listed in Table 1. Much attention has been paid to abnormal liver function and altered hepatic pathology. Nevertheless, clinically significant liver disease or death from liver failure are rare complications except in yellow fever.

Dengue fever is among the top three etiological agents, accounting for approximately 6% of febrile illnesses in the traveler (Wilson et al., 2007). Of note, although malaria is the leading cause of systemic febrile illness worldwide, apart from Sub-Saharan Africa and Central America travelers returning from tropical or sub-tropical regions had Dengue fever more frequently than malaria. Chikungunya fever is an emerging novel virus infection recently expanding in Asia and Africa, which also causes fever, myalgia, arthralgia and skin rash in increasing numbers of patients.

Table 1 Viral hemorrhagic fevers affecting the liver

Disease	*Virus family*	*Geographical regions*
Dengue fever	Flaviviridae	Africa, Asian, tropical America
Yellow fever	Flaviviridae	Africa, Southern America
Lassa fever	Arenaviridae	Western Africa
Argentinian hemorrhagic fever	Arenaviridae (Junin virus)	Argentina
Ebola Fever	Filoviridae	Central and Western Africa
Marburg fever	Filoviridae	Central and South Africa
Rift Valley fever	Bunyaviridae	Eastern and Central Africa
Kongo-Krim Hemorrhagic fever	Bunyaviridae	Former Soviet union, Central and Western Asia Africa
Hemorrhagic fever with renal failure	Bunyaviridae	Northern Europe and Asia
Chikungunya fever	Togaviridae	Western Africa, Southeast Asia, Oceania, Southern, Europe

Dengue-Fever

Risk factors and epidemiology

The dengue virus complex comprises four antigenically related but distinct Flaviviruses termed dengue virus serotypes 1 through 4 (DEN-1 to DEN-4). Dengue viruses are transmitted by *Aedes aegypti* mosquitos in epidemic and endemic outbreaks and cause acute infections. Three to six days after a mosquito bite the virus spreads via the blood-stream, and among the various organs it can be isolated frequently from liver samples (Rosen and Khin, 1989).

Clinical presentation

Dengue virus infection usually causes a flu-like illness with a rash—dengue fever (Fig. 1). Hepatomegaly and elevated serum aminotransferases, which are usually mild, are common in dengue virus infections (Wahid et al., 2000). Clinically more severe diseases, for example, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) can follow from secondary infection with dengue virus of different serotype. In 2009, the World Health Organization issued new guidelines and introduced a revised classification scheme consisting of the following categories: dengue without warning signs, dengue with warning signs, and severe dengue (World Health Organization, 2009). However, there are no reliable warning signs for severe dengue.

In DHF there are widespread petechial hemorrhages together with multiple organ damage; in DSS, which mostly affects children below the age of 15, 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, pale from steatosis and shows multifocal hemorrhages.

Diagnosis

Laboratory diagnosis of dengue virus infection is done by detection of viral components, for example, PCR in serum or indirectly by serology. The sensitivity of each approach depends on the duration and course of the patient's illness when the patient presents for evaluation.

Therapy

Currently vaccines against dengue virus are being developed but have not become licensed, yet. There is no direct antiviral therapy available against the dengue viruses. Thus, treatment is supportive, requiring meticulous fluid management and intensive care in DSS. Details for treatment are summarized in recent WHO guidelines (World Health Organization, 2012).

Chikungunya-Fever

Risk factors and epidemiology

Chikungunya is an arthropod-borne Toga virus initially endemic to West Africa, which next spread to the Indian Ocean islands and Southeast Asia (Charrel et al., 2007). Chikungunya fever was originally considered a disease of tropical and subtropical regions, until an outbreak in Northern Italy was recorded in 2007 (Rezza et al., 2007). Since then chikungunya infections have become

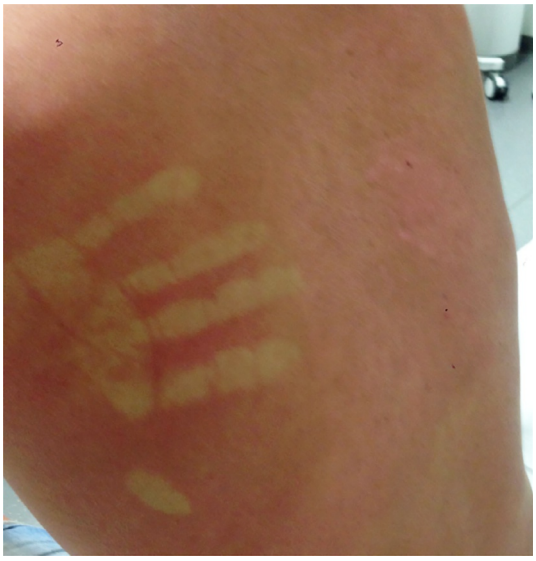

Fig. 1 Dengue virus infection. Hyperemic rash in a patient with dengue fever.

exported to other Western countries, the Americas and Caribbean region via international travel. Of note, dengue and Zika viruses are transmitted by the same mosquito vectors as chikungunya. Thus, the viruses can co-circulate in the same geographic region, and coinfections have been documented. Transmission of chikungunya via blood products has been reported in France, where a nurse was infected by exposure to blood from an infected patient. Chikungunya, might also be transmitted inadvertently by organ transplantation since viremia can exceed high levels prior to onset of symptoms.

Clinical presentation

The infection begins abruptly with high fever, symmetric polyarthralgia and macular or maculopapular skin rash (Taubitz et al., 2007). Pruritus and bullous skin lesions have also been described. Previously chikungunya fever has been considered a self-limited disease. However, severe complications also comprising acute viral hepatitis and deaths have been reported in the recent outbreaks; particularly in elderly patients (>65 years) and people with pre-existing chronic medical problems. Some patients have persisting symptoms for a variable length of time after the acute illness. Manifestations include arthritis/arthralgia, edematous polyarthritis of fingers and toes, morning pain and stiffness, and severe tendosynovitis.

Diagnosis

Clinically chikungunya fever must be differentiated from dengue fever, which shares many symptoms and features. The diagnosis of chikungunya virus infection should be suspected in a patient with acute onset of fever and polyarthralgia who had possible exposure by travel to or residency in an epidemiological risk area. The diagnosis of chikungunya is established by detection of Chikungunya viral RNA via real-time reverse-transcription polymerase chain reaction (RT-PCR) or Chikungunya virus serology (Pan-American Health Organisation, 2017). Chikungunya IgM antibodies become detectable by ELISA 5 days after the onset of symptoms. For certain regions simultaneous testing for dengue and Zika virus infection is recommended.

Therapy

There exists no specific antiviral therapy for acute chikungunya virus infection. Treatment consists of supportive care and includes rest, fluid replacement, and eventually the use of nonsteroidal antiinflammatory drugs (NSAIDs) or acetaminophen to relieve pain and fever. In patients suspected to have dengue virus coinfection NSAIDs should be avoided before the patient becomes afebrile for >2 days, in order to avoid bleeding complications associated with severe dengue virus infection. Chikungunya infection cannot be prevented by vaccination.

Hanta-Viruses

Risk factors and epidemiology

Hanta viruses are examples of emerging viruses, which belong to the genus Hantavirus within the Bunyaviridae family. They are negative-sense single-stranded RNA viruses, primarily harbored in rodents and shed in rodent urine, saliva and feces. The virus is inhaled by man as aerosols from dried rodent excreta, or in unusual circumstances, transmitted by bites (Nichol et al., 2000). Hantaviruses exist in multiple serotypes worldwide, which differ in their virulence. Some are considered apathogenic, while certain isolates can produce two distinct severe syndromes in humans: the Hanta virus cardiopulmonary syndrome, mostly due to isolates in the Americas; and the hemorrhagic fever with renal syndrome caused by isolates (Seoul virus, Dobrava virus, Puumala virus, Hantaan virus) in Europe and Asia (Plyusnin et al., 2001).

Clinical presentation

In some instances, patients with Hanta virus hemorrhagic fever suffered from severe acute hepatitis, whereas renal damage was rather mild (Wong et al., 1987; Chan et al., 1987; Lledó et al., 2003). Hanta virus has also been incriminated as a potential cause of cryptogenic hepatitis in Southwestern China. However, this hypothesis has not been confirmed by antibody studies in Japan. Hanta viruses, however, may still play some role, because Hanta virus infection has been observed to trigger autoimmune liver disease (Yotsuyanagi et al., 1998). Thus, this mechanism may contribute to community-acquired hepatitis (Martin et al., 2008). Nevertheless, the precise role of Hanta virus infections for human liver disease still awaits clarification.

Diagnosis

By the time symptoms are evident, patients uniformly have antiviral IgM antibodies and most have IgG antibodies. Diagnostic assays to detect Hanta virus antibodies include enzyme-linked immunosorbent assay (ELISA), immunoblot test (SIA), Western blot, indirect immunofluorescence (IFA), complement fixation, and hemagglutinin inhibition as well as neutralization assays.

Therapy

Hanta virus strains associated with hemorrhagic fever and hepatorenal syndrome are sensitive to ribavirin in vitro. A prospective, randomized, double-blind, placebo-controlled trial in the People's Republic of China reported a sevenfold decrease in mortality among ribavirin-treated patients with serologically confirmed Hanta virus disease (Huggins et al., 1991). However, ribavirin appeared to be less effective in Hanta virus cardiopulmonary syndrome. Thus, it has not yet been approved, but nevertheless may be tried as rescue treatment in emergency situations (Sidwell and Smee, 2003).

Yellow Fever Virus

Risk factors and epidemiology

Yellow fever is a member of the Flaviviridae family and constitutes a single-stranded plus strand RNA virus. It comprises a single conserved serotype and seven major genotypes reflecting distinct regions in West Africa, Central-East Africa and South America (Vasconcelos et al., 2004; Barnett, 2007). Yellow fever virus is transmitted by a variety of different Aedes vectors and causes endemic and epidemic outbreaks in Africa and South America. Yellow fever can be prevented by vaccination, and thus, has become rare in travelers.

Clinical presentation

The spectrum of yellow fever virus infection ranges from subclinical infection to a life-threatening disease with fever, jaundice, renal failure and hemorrhage. Usually yellow fever initially presents as an acute, flu-like illness of sudden onset with fever, myalgia and headache, which cannot be distinguished easily from other acute infections such as severe malaria, leptospirosis, fulminant viral hepatitis or Dengue hemorrhagic fever.

Between 48 and 72 h after onset, aminotransferases start to rise in blood heralding the development of jaundice. The degree of liver abnormalities at this stage predicts the severity of liver disease during the course of the illness later on. Next, a period of apparent remission lasting up to 48 h may follow the initial infection. Patients with abortive infection recover at this stage. About 15% of patients will enter the third stage of intoxication characterized by the return of fever, prostration and organ dysfunction. Patients suffer from nausea, vomiting, or epigastric pain, and develop jaundice and oliguria. Bleeding can occur from the mouth, nose, eyes or stomach. Serum aspartate transferase (AST) levels usually exceed those of alanine transferase (ALT).

The outcome of yellow fever infection is determined during the second week after onset, when many patients either rapidly recover, while between 20% and 50% of the patients, who have progressed to the stage of intoxication, will ultimately die from circulatory shock. Convalescence may be associated with fatigue over several weeks, and occasionally jaundice and elevated aminotransferases may persist for months.

Diagnosis

The diagnosis of yellow fever is confirmed by demonstration of specific IgM by ELISA, by PCR or by isolating the virus from the blood. Polymerase chain reaction (PCR) testing in blood and urine can detect the virus in early stages of the disease. In later stages, testing to identify antibodies is recommended. Liver biopsies should be avoided due to a high risk of bleeding complications.

Therapy

There is currently no specific anti-viral drug to treat yellow fever but specific care to manage dehydration, liver and kidney failure as well as fever improves outcomes. Ribavirin inhibits yellow fever virus in vitro. However, the extremely high concentrations of the drug needed cannot be achieved in vivo. Recently there have been attempts to treat liver failure resulting from yellow fever infection by high urgency liver transplantation (Song et al., 2019). However, outcomes after liver transplantation were mixed and the few survivors had frequent postoperative bacterial and cytomegalovirus infections.

A highly active attenuated live-vaccine is available, which induces seroconversion rates >95% and provides a high level of protection. Due to potential risks associated with a live virus vaccine children below the age of 9 months, pregnant women and immunosuppressed individuals should not receive the vaccine, nor should subjects be vaccinated who are allergic to egg proteins. Infrequently two serious vaccine-related complications may occur: a form of encephalitis termed yellow fever-associated neurotropic disease and a syndrome resembling natural infection designated as yellow fever vaccine-associated viscerotropic disease.

Adenoviruses

Risk factors and epidemiology

Adenoviruses have a worldwide distribution and cause febrile diseases. Over 50 serotypes can be distinguished which are further subdivided into the six subgoups A through F. Typical syndromes comprise 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 (Garnett et al., 2009), and can cause a variety of clinical syndromes in immunocompromised individuals including severe hepatitis (Kojaoghlanian et al., 2003). In particular, transmission of latent adenovirus with the donated organ is a risk factor for adenoviral hepatitis in pediatric liver transplantation (Michaels et al., 1992).

Clinical presentation

Adenoviral hepatitis occurs in congenital and acquired immunodeficiency syndromes and resembles severe necrotizing hepatitis associated with Herpes simplex virus infection. Patients develop extensive areas of liver cell necrosis (Fig. 2), massively elevated aminotransferases, and a severe coagulopathy (South et al., 1982; Janner et al., 1990; Krilov et al., 1990). Ultimately, outcomes may be fatal.

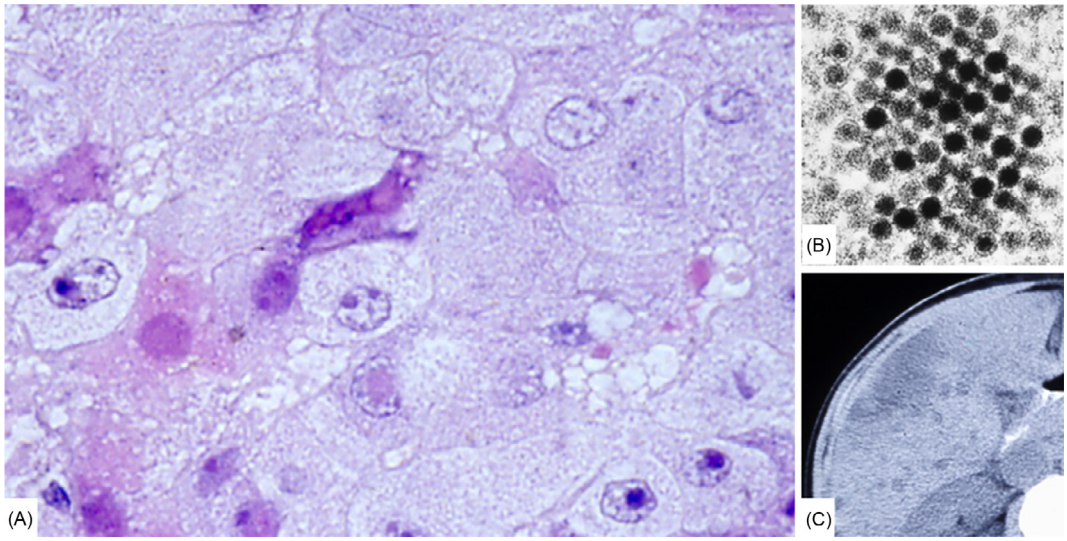

Fig. 2 Adenoviral hepatitis. (A) Areactive necrosis of liver tissue in a HIV-positive patient with hepatitis. Hämatoxylin-Eosin (HE) stain. (B) Detection of adenovirus particles in the liver tissue by electron microscopy. (C) Necrotic tissue was visualized by computerized tomography in this patient.

Diagnosis

Liver biopsy specimens may reveal typical intranuclear inclusion bodies in necrotic areas of the liver, but biopsies carry an extremely high bleeding risk. Viral isolation and PCR techniques help to identify the causative viral strain.

Therapy

To date a proven therapy or vaccine to prevent adenoviral hepatitis does not exist, but ribavirin may be helpful in selected cases (Wulffraat et al., 1995).

Liver Damage Associated With Respiratory Viruses

General Comments

Liver damage in fatal influenza has been considered immune-mediated, because high cytokine levels were detected (Murali-Krishna et al., 1998; Peiris et al., 2004). Moreover, volunteers infected experimentally with intranasal influenza A/Kawasaki/86 (H1N1) transiently developed elevated aminotransferases (Polakos et al., 2006). Since the rise in liver enzymes occurred after pyrexia had settled, it was concluded that the host's immune responses rather than viral infection caused damage to the liver. Immune mediated liver damage may also be the cause for elevated aminotransferases in other viral respiratory infections such as respiratory syncytial virus (Peiris et al., 2004). However, cardiovascular failure and hepatic ischemia must be considered in as alternative factors in patients with severe respiratory infections (Fig. 3) (Eisenhut et al., 2004).

Influenza Viruses

Risk factors and epidemiology

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

Clinical presentation

Influenza viruses commonly cause a self-limited acute respiratory infection with fever, rhinorrhea, sore throat and occasionally gastrointestinal symptoms. Therefore, aminotransferases are not monitored routinely. In the 2004 H1N5 influenza outbreak, however, about 60% of patients with pneumonia had deranged liver function tests with gastrointestinal symptoms such as vomiting, abdominal pain and diarrhea on initial presentation (Yuen and Wong, 2005). Although molecular evidence for viral liver disease was not found, autopsy revealed hepatic centro-lobular necrosis in some cases (To et al., 2001).

Diagnosis

In influenza virus infection the clinical presentation is dominated by fever and respiratory symptoms. The diagnosis be established by detecting viral antigen or antibodies, but nowadays the gold standard has become detection of viral RNA in throat washings by PCR.

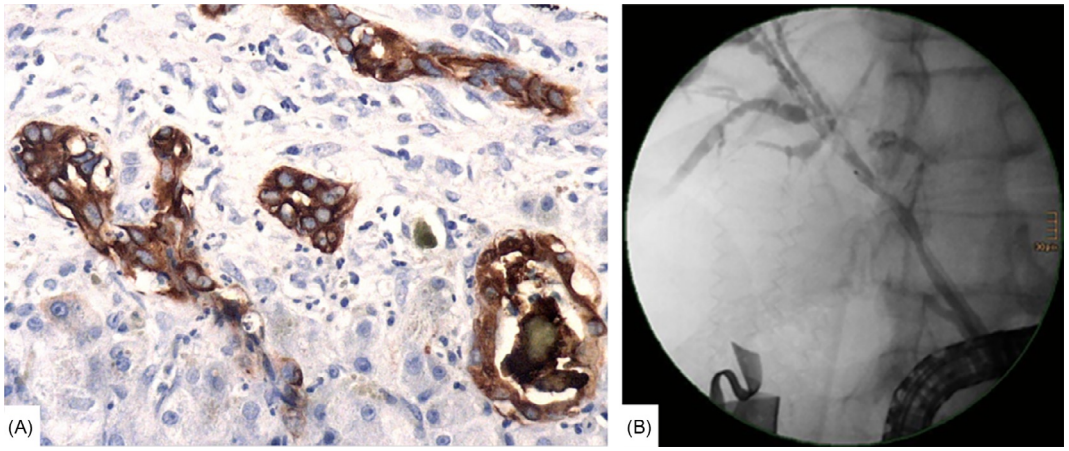

Fig. 3 Ischemic damage of the biliary system resulting from hypoxia in severe influenza virus pneumonia. (A) Cytokeratin 7 staining reveals damaged intrahepatic bile ducts in patient who developed progressive intrahepatic cholestasis after severe influenza virus pneumonia requiring respiratory support. (B) Several weeks later ischemic type biliary damage (biliary strictures and sludge) becomes apparent in ERCP.

Therapy

Influenza virus infection can be treated and prevented by neuraminidase inhibitors such as oseltamivir and zanamivir, which have been recommended especially for treatment in influenza H1N5 infection by the WHO in 2010 (Schünemann et al., 2007). However, their benefit is limited due to the appearance of resistant isolates in recent outbreaks. A preventive vaccine is adapted annually to the circulating strains.

Coronaviruses

Risk factors and epidemiology

Severe acute respiratory syndrome (SARS) is caused by a novel coronavirus (SARS-coronavirus, SARS-CoV), which caused outbreaks of severe infections of the lung and gastrointestinal tract in the Far East and Canada (Ksiazek et al., 2003; Drosten et al., 2003; Lee et al., 2003; Poutanen et al., 2003). There was also other organ involvement. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) first appeared in the Arabian peninsula and meanwhile has occasionally been observed also in few travelers returning from risk areas. Apart from viral pneumonia other internal organs may become affected including hepatitis (Alsaad et al., 2018), particularly when MERS-CoV hits patients with concomitant diseases, for example, diabetes mellitus. Sars-CoV and MERS-CoV have been detected in masked palm civets, dogs and cats as well as camel and thus represent zoonotic infections in man.

Clinical presentation

Approximately 25% of patients with SARS had elevated liver enzymes at the onset of infection, and further 45% of patients with normal liver enzymes at initial presentation developed elevated aminotransferases later on, so that overall up to 70% of patients showed elevated liver enzymes during their illness (Booth et al., 2003; Choi et al., 2003; Wong et al., 2003; Chan et al., 2005). Jaundice was observed in $<10\%$ of cases. In most patients aminotransferases 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 >5 times the upper limit of normal) was observed more frequently in male patients, and those with significant other comorbidities or elevated serum creatinine levels (Chan et al., 2005).

Diagnosis

Diagnosis of SARS-CoV and MERS-CoV infection is suspected in persons with typical symptoms who had contact to risk areas. The diagnosis is confirmed in certified specialized microbiology labs by PCR from respiratory fluids. Hygienic prevention measures have to be respected when handling samples and caring for patients with suspected coronavirus pneumonia.

Therapy

During SARS outbreaks both ribavirin and Kaletra (baby dose ritonavir/lopinavir) were tested as experimental therapy but showed limited success.

Infections by Herpesviruses

General Comments

Herpesviruses form a large family of DNA viruses, which comprises eight members that can cause disease in man (Table 2). Herpes simplex virus (HSV), varizella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV) and Human

Table 2 Human herpesviruses

Systematic name	*Common name*	*Herpesvirus subfamily*	*Estimated prevalence*	*Route of transmission*
Human herpesvirus 1	Herpes simplex virus (HSV)-1	Alphaherpesvirinae	75%–>95%	Oral secretions, close contact
Human herpesvirus 2	HSV-2	Alphaherpesvirinae	4%–95%	Genital secretions, close contact
Human herpesvirus 3	Varicella zoster virus (VZV)	Alphaherpesvirinae	>90%	Aerosole, close contact
Human herpesvirus 4	Epstein-Barr virus (EBV)	Gammaherpesvirinae	70%–95%	Oral secretions
Human herpesvirus 5	Human Cytomegalovirus (CMV)	Betaherpesvirinae	40%–95%	Oral secretions, genital secretions
Human herpesvirus 6	Human Herpes virus 6 (HHV6)	Betaherpesvirinae	>85%	Oral secretions
Human herpesvirus 7	Human Herpes virus 7 (HHV7)	Betaherpesvirinae	>85%	Oral secretions
Human herpesvirus 8	Kaposi Sarcoma associated Herpesvirus	Gammaherpesvirinae	10%–25%	Oral secretions, genital secretions

Herpesvirus type 6 or 7 (HHV6, HHV7) can directly affect the liver and are infections in the human population usually acquired during childhood or adolescence. HHV8 can be transmitted sexually and presumeably also vertically from mother to child but has a more limited prevalence. In severely immunosuppressed patients HHV8 can cause Kaposi sarcoma and body cavity lymphoma. Herpesviruses persist life-long and can reactivate liver disease in immunosuppressed patients later on.

Herpesviruses Types 1–3 (Herpes simplex Virus, Varicella-Zoster Virus)

Risk factors and epidemiology

Primary herpes simplex infection produces characteristic oral (HSV-1) or genital (HSV-2) vesicular lesions. Symptoms can be severe with fever and malaise but primary infections are frequently asymptomatic. Fulminant hepatitis is a complication both of HSV-1 and HSV-2 infection (Pinna et al., 2002). Organ transplantation and treatment for hematological malignancies are the most frequent underlying predispositions (Johnson et al., 1992). Further individuals at risk include neonates, patients on steroids, HIV-infected patients, and patients with cancer or myelodysplastic syndromes (Pinna et al., 2002; Johnson et al., 1992; Kusne et al., 1991; Zimmerli et al., 1988; Frederick et al., 2002). Rarely fatal HSV-hepatitis has also been reported in immunocompetent adults (Goodman et al., 1986).

Varicella zoster virus (Herpesvirus type 3) causes chicken pox; and shingles when latent infection is reactivated. After primary infection there is replication of varicella zoster virus in the epithelia of gut, respiratory tract, liver and endocrine glands. Secondary viraemia then leads to infection of the skin and causes the typical rash. Liver disease is rare and limited to patients with severe immunodeficiency.

Clinical presentation

HSV-related hepatitis has a high (>80%) mortality and resembles septic endotoxic shock; jaundice is not always present (Kusne et al., 1991). Patients suffer from fever, anorexia, nausea, vomiting, abdominal pain, leucopenia, and coagulopathy. Typical oral or genital vesicular lesions may be present in only about 30% of patients (Pinna et al., 2002). Some patients have disseminated further extrahepatic involvement, for example, lung, lymphnodes, spleen, and adrenal glands.

In severe varicella zoster virus infection hepatic lesions are similar to herpes simplex hepatitis. Varicella zoster virus has also been reported to trigger severe autoimmune type hepatitis (Al-Hoamoudi, 2009).

Diagnosis

The diagnosis of HSV-related hepatitis must be rapidly established. Serologic assays are of little use. Herpes simplex and varicella zoster viruses are detected preferentially by the polymerase chain reaction (Finström et al., 2009), or occasionally by viral isolation or immunofluorescence staining.

Therapy

Prompt systemic treatment with acyclovir reduces HSV-associated morbidity and serious complications in HIV-infected patients. Antiviral acyclovir prophylaxis has markedly reduced HSV re-activation after organ transplantation (Seale et al., 1985; Pettersson et al., 1985). Acyclovir resistance occurs in about 5% of immunocompromised patients and is negligible (<0.5%) in immunocompetent subjects (Tyring et al., 2002). Valacyclovir is a prodrug of acyclovir, and famciclovir a prodrug of penciclovir, which have similar antiviral mechanisms as acyclovir. Thus HSV isolates resistant to acyclovir are also resistant to these drugs (Levin et al., 2004). Cidofovir and foscarnet are alternative choices to treat acyclovir-resistant HSV but are less well tolerated (Safrin et al., 1991). Treatment and prophylaxis of varicella zoster hepatitis is similar to herpes simplex viruses because acyclovir also inhibits replication of varicella zoster virus.

Cytomegalovirus (CMV)

Risk factors and epidemiology

In immunocompetent hosts cytomegalovirus (CMV) infection may be rather asymptomatic but occasionally causes transient minimally symptomatic acute disease. Congenital cytomegalovirus infection occurs in <2% of newborns and is encountered in

mothers with primary CMV infection or CMV re-activation during pregnancy. Approximately 10% of neonates with congenital CMV-infection show hepatosplenomegaly and jaundice at birth (Kylat et al., 2006). When newborns or immunocompromised patients, for example, HIV infection, cancer, solid organ or bone marrow transplantation become CMV-infected, they may develop serious disease. CMV-related liver disease represents the commonest cause of viral hepatitis after organ transplantation. Infection may result from re-activation of endogenous virus under immunosuppression, infection from the transplanted organ or blood transfusion of a CMV-positive donor. In liver transplantation, most CMV disease occurs at 1–4 months after transplantation. CMV infection is also a potential factor triggering acute and chronic rejection. Vice versa, rejection therapy with corticosteroid boluses may induce endogenous CMV reactivation.

Although CMV re-activation is a frequent complication also in HIV-positive patients with advanced immunodeficiency (CD4 counts <200/μL), involvement of the liver seems to be rather rare (Palmer et al., 1987), but CMV occasionally causes bile-duct necrosis and a so-called HIV-cholangiopathy, a sclerosing cholangitis encountered in patients with terminal HIV-immunodeficiency (Bonacini, 1992).

Clinical presentation

In about 10% of immunocompetent subjects primary cytomegalovirus infection produces an infectious mononucleosis-like syndrome, which is associated with elevated aminotransferases and a mild hepatitis (Fig. 4). Liver histology may show focal hepatocyte and bile duct damage with lymphocytic infiltration into the sinusoids and occasionally epithelioid granulomas without necrosis, while CMV inclusion bodies or CMV immunostaining are only rarely seen (Snover and Horwitz, 1984). Fetal CMV infection has also been associated with obstructive biliary disease and neonatal hepatitis with giant cell transformation, cholestasis and viral inclusion bodies (Finegold and Carpenter, 1982).

Diagnosis

In liver biopsies hepatocytes are swollen and may contain basophilic granules in the cytoplasm. A typical intranuclear amphophilic inclusion body can be present, resembling an "owl's eye" (Fig. 3C). Both nuclear and cytoplasmic inclusions are full of virions (Desmet, 1983). However, in posttransplantation CMV hepatitis cytomegalovirus inclusion bodies are scanty. Instead small foci of necrosis and inflammation (microabscesses) may be present (Fig. 3B).

De novo appearance of CMV IgM antibodies or a fourfold rise in IgG antibodies herald CMV infection in immunocompetent individuals. However, serology is unreliable in immunocompromised patients and is replaced by quantitative molecular DNA amplification assays (Humar et al., 1999; Caliendo et al., 2003). Meanwhile most transplant centers perform CMV surveillance by weekly quantitative determination of CMV DNA.

Therapy

In most transplant units organ recipients at high risk for acquiring CMV disease receive immune prophylaxis with CMV-hyperimmune antibodies and antiviral drugs (Paya, 2001). However, CMV infection and disease may still develop. CMV hepatitis

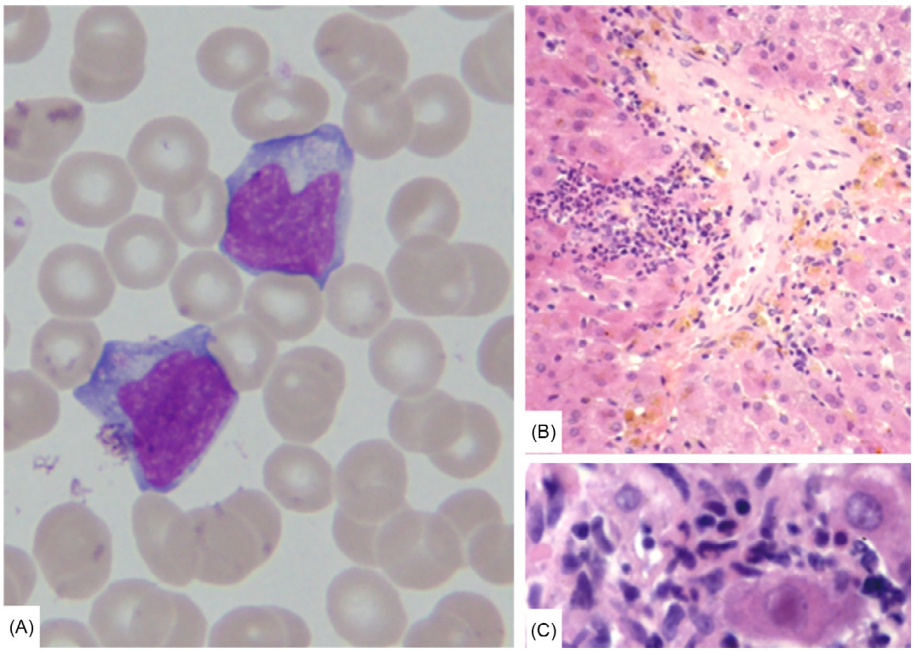

Fig. 4 Cytomegalovirus (CMV) hepatitis. (A) Activated monocyte-like lymphocytes in the blood in a 25-year-old patient with hepatitis. (B) Non-necrotic granuloma in the liver biopsy (HE-stain) from another patient with CMV hepatitis. (C) Detection of CMV inclusion bodies ("owl's eye") in CMV hepatitis.

should be treated promptly in patients with immunodeficiency. Intravenous ganciclovir or oral valganciclovir over 3 weeks is the treatment of choice. Drugs must be continued in reduced doses as chemoprophylaxis, if prolonged immunosuppression is anticipated (Crumpacker, 1996). Fortunately, ganciclovir resistance is still rare (Martin et al., 2008), so that the more toxic alternatives cidofovir and foscarnet are rarely needed.

Epstein-Barr Virus (EBV)

Risk factors and epidemiology

Epstein-Barr virus (EBV) is shedded in oral secretions, and most primary EBV infections occur in adolescents. EBV accounts for 90% acute infectious mononucleosis syndromes. It persists life-long in a latent state, which results from a dynamic interplay between viral evasion strategies and the host's immune responses. While—unlike other herpesviruses—EBV reactivation-associated liver disease is not a prominent feature of persistent EBV infection, this herpesvirus is a potent cause for various malignancies such B- and T cell lymphomas, Hodgkin lymphoma, and nasopharyngeal carcinoma. EBV has also been associated with an aggressive lymphoproliferative disease after liver transplantation. EBV intrauterine infection may lead to diverse congenital anomalies also comprising biliary atresia (Goldberg et al., 1981). However, only few pregnant women are susceptible, thus intrauterine EBV infection is rare.

Clinical presentation

In infants and young children primary infection is frequently asymptomatic, while in adults it results in the infectious mononucleosis syndrome. Patients develop malaise, headache, low-grade fever, before the more specific symptoms such as pharyngitis/tonsillitis, swelling of cervical lymphnodes and moderate to high-grade fever occur. Nausea, vomiting, and anorexia are frequent findings. A mild clinical hepatitis accompanies infectious mononucleosis in approximately 90% of patients (Fig. 5). Splenomegaly is found in about half of patients, but hepatomegaly and jaundice are infrequent findings. Patients show peripheral blood lymphocytosis with characteristic large abnormal lymphocytes in their blood smears. The vast majority of patients recover over 2–4 weeks, but fatigue may persist over several months after infection. EBV does not infect hepatocytes but lymphoid tissue. Thus, liver damage is due to immune-mediated pathology and—when exceptionally done—biopsy specimens show diffuse lymphocytic infiltrates in the sinusoids but only occasionally focal apoptotic hepatocytes (Fig. 3A) (Purtilo and Sakamoto, 1981). Moreover, EBV-related immune activation can lead to several complications:

Patients with X-linked lymphoproliferative disease (XLP) caused by a mutation in the SH2D1A gene on the X chromosome are particularly vulnerable to the Epstein-Barr virus and may suffer fatal infections with extensive liver necrosis (Seemayer et al., 1995).

In patients with severe immunodeficiency lymphomatoid granulomatosis is a further unusual complication of Epstein-Barr virus infection leading to granuloma formation in multiple organs including the liver, which may require interferon-alpha antiviral therapy (Wilson et al., 1996).

In patients with HIV infection an EBV-associated lymphoproliferative disorder with hepatic infiltration of immunoblasts (Beissner et al., 1987), and a hemophagocytic syndrome have been reported (Albrecht et al., 1997).

Epstein-Barr virus is also the major causative agent for 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 (Hanto, 1995). PTLD occurs more commonly in children than in adults, depending on the degree of immunosuppression. It is primarily a complication in EBV-negative organ recipients, who develop primary EBV infection under immunosuppression owing to a graft from an EBV-positive donor.

Finally, EBV is a potent risk factor to develop lymphoma in later life even in patients without overt immunosuppression (Fig. 6).

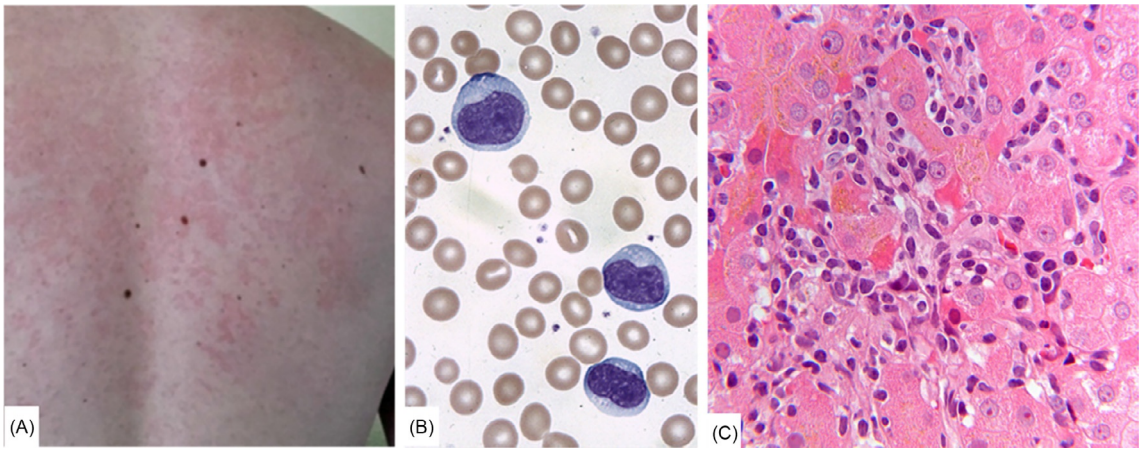

Fig. 5 Infectious mononucleosis (EBV-infection). (A) Rash in a patient with acute EBV infection. (B) "Hepatitis" in EBV infection. Note the lymphocytes are located in the sinusoids and do not seem to directly attack hepatocytes.

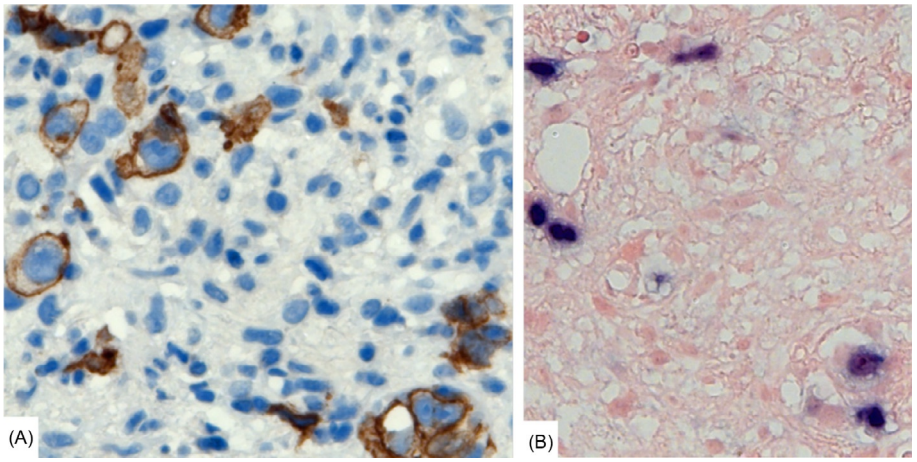

Fig. 6 EBV-associated lymphoma (Hodgkin's disease). (A) CD30 expression in the lymphoid tissue from a liver biopsy of a patient with Hodgkin's disease (Peroxidase stain). (B) In situ hybridization reveals expression of EBER—an EBV-associated marker—in the lymphoma tissue.

Diagnosis

The clinical suspicion of Epstein-Barr virus infection is confirmed by detection of heterophilic or EBV-specific antibodies in infectious mononucleosis and quantitative polymerase chain reaction assays in patients with lymphoproliferative disorders (Bruu et al., 2000; Weinberger et al., 2004). Liver biopsy is not recommended for routine diagnostics.

Therapy

Treatment of Epstein-Barr virus infection is primarily supportive. Corticosteroid therapy can ameliorate symptoms. However, this option should be only considered in individuals with immune-mediated life-threatening complications, for example, imminent liver failure. Because of theoretical concerns to suppress the immune system in an infection with a potentially oncogenic virus, corticosteroids are not recommended in general. Acyclovir inhibits the EBV DNA polymerase, and antiviral therapy with this drug has shortened virus shedding but failed to demonstrate a convincing clinical benefit even in severe acute Epstein-Barr virus infection (Torre and Tambini, 1999). Acyclovir antiviral therapy is not effective against latent EBV-infection. Thus, reduction in immunosuppression, anticancer chemotherapy, and B-cell depleting antibodies are needed to treat EBV-related lymphoproliferative disorders.

Human Herpesviruses Types 6 (HHV6) and 7 (HHV7)

Risk factors and epidemiology

HHV-6 exists in two variants, HHV6-A and HHV-6B, which infect T cells and various other cells types expressing the CD46 receptor (Santoro et al., 1999). Although genetically clearly distinct from HHV-6, HHV-7 is another β-herpesvirus that shares many features with HHV-6. Primary infection with either virus commonly occurs at young age and can lead to a febrile illness known as exanthema subitum or roseola infantum (Leach, 2000). *Pityriasis rosea* reflects primary infection with HHV-7. HVV-6 also integrates into the host's genome and is transmitted via the germline. HHV6 and HHV-7 can reactivate each other (Tanaka-Taya et al., 2000) as well as cytomegalovirus leading to symptomatic CMV-disease in liver transplantation (Humar et al., 2000).

Clinical presentation

The full spectrum of diseases caused by chronic HHV-6 and -7 infection is still unclear, but these viruses are putatively involved in a variety of different syndromes such as encephalitis, multiple sclerosis, pneumonitis, an infectious mononucleosis-like syndrome, postinfectious drug hypersensitivity as well as lymphoproliferative disorders and systemic disease in immunocompromised patients (Stoeckle, 2000). HHV-6 can cause severe and fatal hepatitis in neonates, children and adults (Mendel et al., 1995; Chevret et al., 2008; Härmä et al., 2003). Hepatitis due to infection and reactivation of HHV-6 and HHV-7 can also complicate organ transplantation (Dockrell and Paya, 2001; Härmä et al., 2006; Ohashi et al., 2008). In addition, HHV-6 has been associated with autoimmunity and giant-cell hepatitis and giant-cell transformation of bile duct cells (Potenza et al., 2008).

Diagnosis

HHV6-IgM antibodies develop within a week after infection but are an unreliable marker, because false-positive test results in about 5% of healthy controls. Beyond that serology does not distinguish between HHV-6A and HHV-6B variants and may cross-react with HHV7. The preferred method to diagnose HHV-6 and -7 infection is by quantitative DNA amplification assays (Deback et al., 2008). Detecting high viral loads in liver specimens or HHV-6 viremia is associated with approximately twofold increased mortality after liver transplantation (Pischke et al., 2012).

Therapy

In immunocompetent patients HHV-6 and -7 cause a benign self-limited infection, which does not require specific antiviral treatment. Unlike HHV-6B both HHV-6A and HHV-7 are relatively resistant against ganciclovir, while foscarnet acts against all three viruses (Yoshida et al., 1998; De Clercq et al., 2001). Cidofovir may be a therapeutic alternative, but some resistant HHV-6 isolates have been identified (Bonnafous et al., 2008).

Human Herpesvirus Type 8 (HHV8)

Risk factors and epidemiology

Human herpesvirus 8 is a γ-herpesvirus, which has potential for malignant transformation. Although primary HHV-8 infection can cause rash and fever in children and immunocompromised individuals, the onset of HHV-8-related diseases usually occurs several years after HHV-8 acquisition: Kaposi sarcoma, body cavity lymphoma, and multicentric Castleman's disease are the typical presentations of HHV-8 infection but bone marrow aplasia and multiple myeloma has also been described in association with HHV-8 infection (Lee and Henderson, 2001).

Clinical presentation

In autopsy studies Kaposi sarcoma involved the liver in approximately 20% of patients with AIDS and was usually part of a widespread cutaneous and visceral disease. Due to highly active antiretroviral combination therapy, Kaposi sarcoma has become a rare complication of HIV infection. However, fulminant hepatic Kaposi sarcoma may occur after organ transplantation (Cahoon et al., 2018, Fig. 7). Macroscopically there are dark-red tumors on the skin, the liver capsule and the parenchyma. Under the microscope the typical lesion is a mesh of spindle-cell-like tumor cells and dilated thin-walled vessels (Glasgow et al., 1985).

Hepatosplenomegaly, fever, and weight loss are typical features of multicentric Castleman's disease, a pre-malignant proliferation of B-lymphocytes (Fig. 8A). Lymphocytes in multicentric Castleman's disease and Kaposi sarcoma seem to cooperate with each other, and thus the two HHV-8-related lesions occasionally occur within the same lymphnode (Naresh et al., 2008).

Ascites and pleural effusions are the hallmark of HHV-8-related body cavity lymphoma possibly giving rise to a false initial diagnosis of decompensated liver cirrhosis. However, abundant lymphoma cells in the aspirated fluids provide a pivotal diagnostic hint (Fig. 8B). HHV-8 can also cause solid organ lymphoma involving the liver (Cesarman and Knowles, 1999).

Diagnosis

The diagnosis of HHV-8 associated malignancies is established from biopsies via their characteristic histopathological features. The virus itself is detected by various antibody assays or polymerase chain reaction (PCR) assays (Chiereghin et al., 2017).

Therapy

Reconstitution of immune function is the primary goal for treatment of HHV-8 associated diseases. This can be achieved by highly active antiretroviral therapy in HIV infection and alternatively by antiproliferate m-TOR (mammalian target of rapamycin) inhibitors for immune suppression in transplantation (Barozzi et al., 2009). Immune stimulation with imiquimod and interferon-alpha (Babel et al., 2008; Van der Ende et al., 2007) has been attempted. Oncological therapy with liposomal

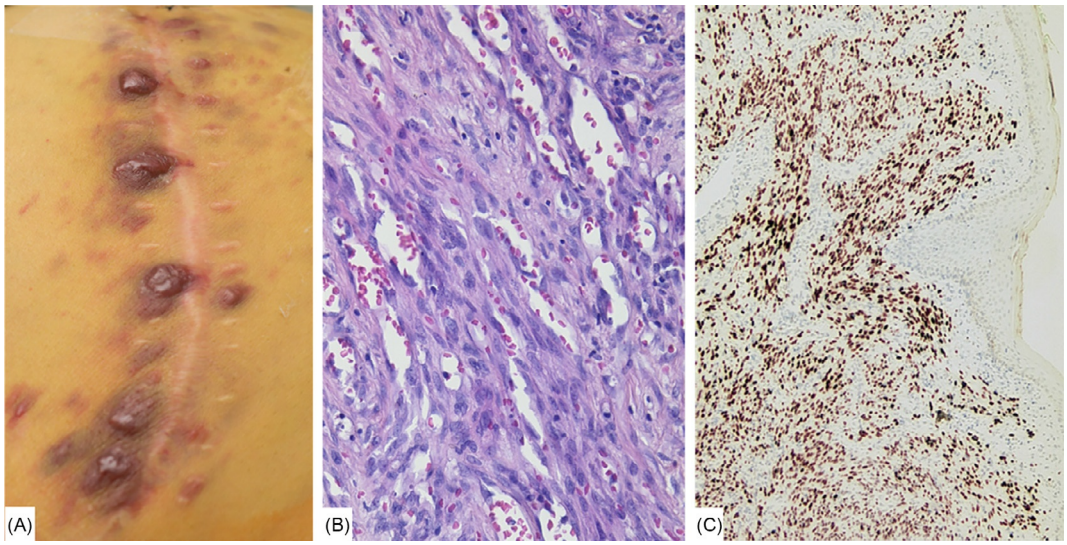

Fig. 7 Kaposi sarcoma after liver transplantation. (A) Brownish nodules appear in the abdominal scars 12 weeks after liver transplantation. (B) Histology reveals a spindle-cell rich tumor confirming the clinical diagnosis of Kaposi sarcoma. (C) In situ detection of human herpesvirus 8 (HHV) in the Kaposi tissue.

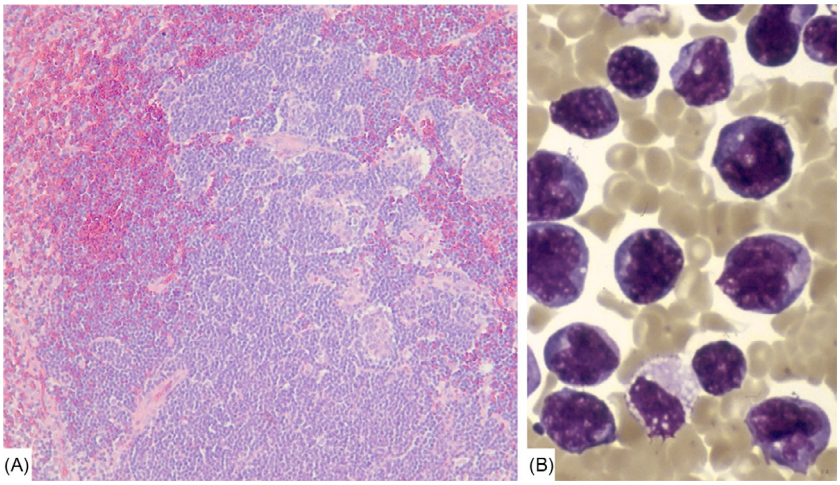

Fig. 8 Rare tumor entities associated with persistent HHV8 infection. (A) Castleman's disease in a lymphnode of HIV-positive patient who developed malaise, fever and cutaneous Kaposi sarcoma. Castleman's disease is a HHV8-associated pre-malignant lymphoproliferative disorder, which can progress to B-cell lymphoma. (B) Tumor cells of HHV8-associated body cavity lymphoma found in ascites from a HIV-positive patient.

anthracyclines or paclitaxel in Kaposi sarcoma (Di Trolio et al., 2006; Stebbing et al., 2003), or rituximab in the case of Castleman's disease and lymphoma are further potent treatment options (Bower et al., 2007). Ganciclovir, cidofovir, foscarnet, adefovir and lobucavir but not acyclovir can block HHV-8 replication in vitro, and in a controlled crossover trial valganciclovir reduced oropharyngeal shedding of HHV-8 by 80% (Casper et al., 2008).

Outlook

This overview addresses the currently most relevant viral infections involving the liver. However, it provides only an outline and is in far not exhaustive. In rare instances, hepatitis occurred in the context of infections with enteroviruses (Sun and Smith, 1966), measles (Khatib et al., 1993) and rubella viruses (McLellan and Gleiner, 1982) as well as Parvovirus B19 (Yoto et al., 1996; Hayakawa et al., 2007). The reader will find details of these rare infections in microbiology textbooks. Beyond that, international travel and global warming are likely to introduce new exotic infections, which must be considered in the differential diagnosis of severe hepatitis. This problem is illustrated by the recent autochthonous Crimean–Congo hemorrhagic fever (CCHF) virus infections in Spain (Negredo et al., 2017), which did not occur in this country before. Thus, hepatologists must be constantly prepared to face new challenges.

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