

Chapter Outline

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Nonhepatotropic viruses may infect many organs, including the liver. The liver, however, is not the primary target organ, but becomes involved within the context of a generalized viral infection. Clinically and histologically, liver involvement may remain in the background or assume paramount prognostic importance when extended parenchymal necrosis leads to fulminant hepatic failure [24]. Nonhepatotropic viruses that may affect the liver are listed in [Table 64.1](#).

The multifaceted clinical manifestations of various diseases caused by nonhepatotropic viruses is beyond the scope of this chapter. Rather, the hepatic involvement of various viral diseases will be highlighted in the following paragraphs.

Herpes Viruses

Herpes Simplex Virus 1 and 2

Primary herpes simplex virus (HSV) infection is characterized by vesicular lesions on skin and mucous membranes. Reactivation of latent infection can cause disease in many organs, including the liver [8]. Neonates, immunocompromised patients, patients with cancer or myelodysplastic syndromes, and pregnant women are at particular risk of developing HSV hepatitis, which may be caused by HSV type 1 and 2 [15, 30]. HSV hepatitis in immunocompetent persons, however, has also been reported [9, 12].

Macroscopically the liver is enlarged, appears mottled with multiple, partly confluent yellowish necrotic foci that are surrounded by a red rim.

Microscopically randomly distributed patchy areas of coagulative necrosis surrounded by dilated and blood filled sinusoids, hemorrhages, and hepatocytes

Table 64.1 Nonhepatotropic viruses that may infect and injure the liver

<i>Herpesviruses</i>
<ul style="list-style-type: none"> • Herpes simplex virus 1 and 2 • Human herpesvirus 6 and 7 • Human herpesvirus 8 • Varicella-zoster virus • Cytomegalovirus • Epstein-Barr Virus
<i>Adenoviruses</i>
<i>Enteroviruses</i>
<ul style="list-style-type: none"> • Coxsackie B virus • Echovirus
<i>Paramyxoviruses</i>
<ul style="list-style-type: none"> • Measles virus
<i>Togaviruses</i>
<ul style="list-style-type: none"> • Rubella virus
<i>Flaviviruses^a</i>
<ul style="list-style-type: none"> • Yellow fever virus • Dengue virus • Kayasanur forest fever virus • Omsk hemorrhagic fever
<i>Bunyaviruses^a</i>
<ul style="list-style-type: none"> • Phlebovirus (Rift valley fever) • Nairovirus (Krim Kongo fever) • Hantavirus
<i>Arenaviruses^a</i>
<ul style="list-style-type: none"> • Lassavirus • Junin- and Machupovirus (South America)
<i>Filoviruses^a</i>
<ul style="list-style-type: none"> • Marburg virus • Ebola virus
<i>Parvoviruses</i>
<ul style="list-style-type: none"> • Parvovirus B19
<i>Coronaviruses</i>
<ul style="list-style-type: none"> • SARS Corona virus (SCoV)

SARS Severe acute respiratory syndrome

^aCause hemorrhagic fevers

containing intranuclear viral inclusions (Cowdry A: inclusion surrounded by a clear halo; Cowdry B: homogeneous, ground glass like inclusion) are seen [12]. Typically there is only a minimal inflammatory response. In neonatal HSV hepatitis multinucleated giant cells (giant cell hepatitis) occur. The viruses may be demonstrated by electron microscopy, immunocytochemistry, and by DNA-in situ hybridisation. However, the light microscopic appearance is so characteristic that these sophisticated techniques are not required to diagnose HSV hepatitis.

Hepatitis is a rare complication of HSV infection, but when it occurs it usually presents as a fulminant disease with a high mortality rate of up to approximately 80% [15, 21].

HSV hepatitis in *pregnant women* (usually caused by HSV type 2) occurs in the late second and in the third trimester. The disease is heralded by nonspecific influenza-like symptoms, right upper quadrant pain, and eventually signs of hepatic encephalopathy. Indeed, the first case of HSV infection associated fulminant liver necrosis in adults was described in a pregnant woman.

Extended parenchymal necrosis in HSV hepatitis leads to marked elevation of aminotransferase levels up to several thousand U/L (AST > ALT) and to a coagulopathy demonstrated by a prolongation of prothrombin time. In contrast to aminotransferases, serum bilirubin concentration usually is only slightly (≤ 5 mg/dL) elevated. Pregnancy specific liver diseases, such as acute fatty liver, HELLP-syndrome and cholestasis of pregnancy should be considered in the differential diagnosis (see Section XXI). The fatality rate of HSV hepatitis in pregnancy is high, approximately 40–50% for mother and child. Therefore, *in pregnant women, HSV infection must be excluded in every case of acute hepatitis*. Liver biopsy is the definitive diagnostic test (often a transvenous approach is necessary). Additionally, vaginal, cervical and pharyngeal smears should be obtained [18].

Opportunistic HSV hepatitis in *patients after solid organ transplantation* is not as frequent as CMV and EBV infection, but usually occurs earlier after the transplant than CMV and EBV hepatitis [21]. HSV infection in these patients is mostly due to reactivation of latent virus rather than to a *de novo* infection.

HSV hepatitis requires *immediate treatment*. Acyclovir (30 mg/kg body weight i.v. daily) is life saving in many patients.

Human Herpesvirus 6 and 7

Infections with the human herpesviruses 6 and 7 are ubiquitous in childhood. Rarely, especially in children, both viruses may cause a fulminant hepatitis during a primary infection. Viral reactivation in immunosuppressed patients after organ transplantation may also be responsible for hepatitis [4]. The laboratory findings are nonspecific, and are characterized by elevation of aminotransferases, cholestatic enzymes, leuko- and thrombocytopenia. The viruses may be isolated from peripheral blood lymphocytes, and may be identified by negative contrast and thin-section electron microscopy, DNA-hybridization, and immunofluorescence [38].

Human Herpesvirus 8

Human herpesvirus 8 causes Kaposi's sarcoma (KS), and is linked with two other neoplasms, a B cell non-Hodgkin's lymphoma (body cavity based lymphoma) and multicentric Castleman's disease (MCD). The liver is frequently involved in visceral KS, predominantly in HIV infected persons with advanced immunodeficiency, and more rarely after organ transplantation.

Peliosis hepatis, perisinusoidal fibrosis and nodular regenerative hyperplasia have been described in few cases of MCD.

Varicella-Zoster Virus

A disseminated varicella-zoster virus (VZV) infection is rare. It may occur in children within the context of chickenpox, while in adults immunosuppression with reactivation of VZV is the usual cause. Hepatic involvement with varicella (varicella hepatitis) is uncommon and predominantly affects immunosuppressed hosts, such as transplant recipients, cancer and AIDS patients, but also normal hosts.

Histologically, focal liver cell necrosis as well as massive widespread hepatic necrosis with intranuclear hepatocellular inclusions and multinucleated giant cells at the periphery of necrotic parenchyma is seen. The lesions resemble those of HSV hepatitis.

Clinically varicella hepatitis may manifest as a symptomatic or subclinical aminotransferase elevation coincident with the onset of varicella, or, especially in the immunocompromised host, as fulminant hepatic failure leading to death [20, 31]. The varicella skin rash may precede, appear coincident with, or follow the onset of hepatitis, but varicella hepatitis with fulminant failure with widespread visceral dissemination in the absence of a rash has also been documented in bone marrow transplant recipients [32].

In fulminant hepatic failure aminotransferase levels reach several thousand U/L, with levels of AST being generally higher than ALT.

Reye's syndrome has been reported to be preceded by a VZV infection in approximately 10% of patients. A diffuse microvesicular steatosis, vomiting and signs of a hepatic encephalopathy are characteristic of Reye's syndrome [23].

Therapy of varicella hepatitis is early high dose acyclovir (30mg/kg body weight i.v. daily) or liver transplantation in fulminant cases with organ failure [27, 37].

Cytomegalovirus

Congenital cytomegalovirus (CMV) infection may be due to intrauterine or peripartal contagion. Histologically steatosis, focal liver cell necrosis, mononuclear inflammatory infiltrates, and occasionally multinucleated giant cells (neonatal hepatitis) are seen. The typical intranuclear inclusions surrounded by a clear halo impart the cells an "owl's eye" appearance. They are found in hepatocytes, bile duct epithelia and in endothelial cells. The affected cells are enlarged. Intrauterine CMV infection may result in biliary atresia.

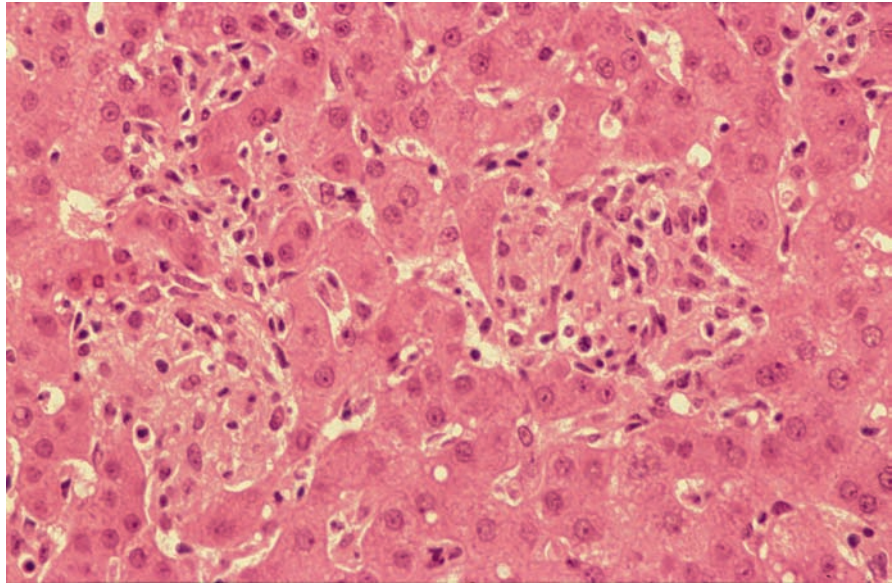
CMV hepatitis in the immunocompetent host clinically resembles hepatitis of infectious mononucleosis [14]. The liver and spleen are enlarged and the clinical manifestations are mild, with mild increases of aminotransferase and bilirubin levels. Often hepatitis is anicteric. Occasionally alkaline phosphatase and γ GT may be markedly elevated (up to >1,000 U/L), which, however, does not portend a serious prognosis. The course of CMV hepatitis is self-limited, and chronic hepatitis does not ensue. Isolated cases of Budd-Chiari syndrome and portal vein thrombosis associated with CMV hepatitis have been reported [34, 35]. Compared to viral hepatitis A, B and C, CMV hepatitis is characterized by prolonged fever, splenomegaly, atypical lymphocytosis, milder elevations of aminotransferases and milder histopathological alterations.

Histologically, focal liver and bile duct injury, lymphocytic sinusoidal infiltrates, and occasionally non-caseating histiocytic granulomas are seen (Fig. 64.1). Thus, CMV hepatitis should be included in the differential diagnosis of granulomatous hepatitis [3]. Viral inclusions or immunocytochemically detectable viral antigens usually cannot be demonstrated.

In *CMV hepatitis in the immunocompromised host* viral inclusions may be found in the absence of an inflammatory reaction. If such inclusions are accompanied by hepatocellular injury and by lymphocytic infiltration, hepatitis may be attributed to CMV infection.

CMV hepatitis after liver transplantation usually manifests 1–4 months after the operation, either as a *de*

Fig. 64.1 Histiocytic granulomas in acute CMV hepatitis. Hematoxylin & Eosin (×400)



novo infection of the donor liver through blood transfusion or as reactivation of a latent CMV infection in the recipient due to postoperative immunosuppressive therapy. Clinically the disease may be asymptomatic or resemble infectious mononucleosis, with mild elevation of aminotransferases, leuko- and thrombocytopenia. It must be differentiated from a rejection reaction.

The *histological appearance* of CMV hepatitis in a transplanted liver is characteristic. Focal accumulations of neutrophils form so-called microabscesses or a necrotic hepatocyte is surrounded by a mixed inflammatory cell infiltrate (“microgranuloma”). Furthermore, the nuclear inclusions described above are present. Viral antigens may be demonstrated by immunocytochemistry. The portal inflammatory infiltrate varies in density. In contrast to cellular rejection, in CMV hepatitis neither an endothelitis nor a cholangitis are seen. Patients with CMV hepatitis after liver transplantation have an increased risk of developing a vanishing bile duct syndrome.

Therapy of CMV hepatitis with ganciclovir (5 mg/kg i.v. bid) is usually successful.

Epstein-Barr Virus

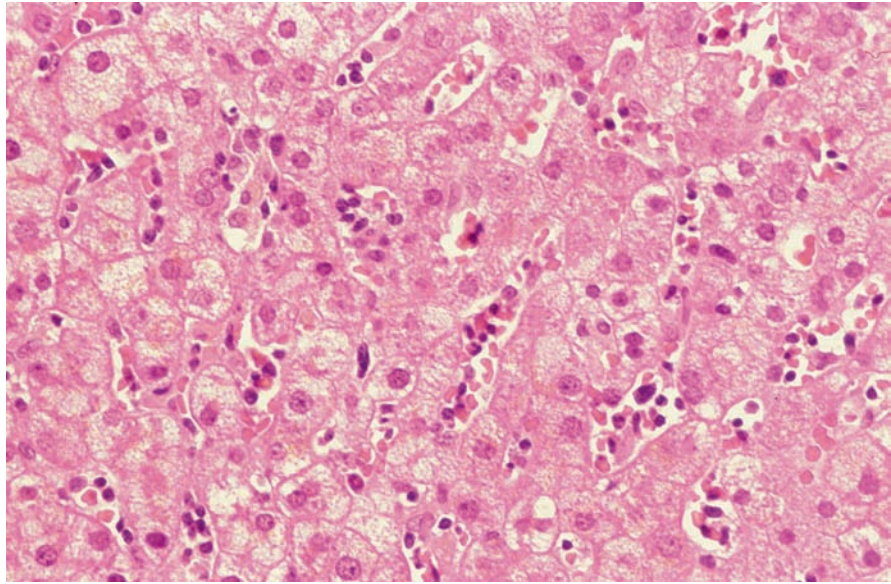
Epstein-Barr virus (EBV) causes infectious mononucleosis. It infects and transforms B lymphocytes, and is

associated with the development of hairy leukoplakia, certain lymphomas and nasopharyngeal carcinoma. Approximately 5% of patients with infectious mononucleosis develop jaundice and 15% have elevated serum aminotransferases.

EBV hepatitis generally is a mild hepatitis accompanying a generalized EBV infection [16]. Its clinical manifestations are overshadowed by systemic signs and symptoms of infectious mononucleosis. Jaundice in a patient with EBV infection mostly is due to autoimmune hemolytic anemia and not to hepatitis. In the vast majority of cases EBV hepatitis is self-limited. Fulminant courses with liver failure are extremely rare [17, 33]. They occur predominantly in X chromosomal inherited lymphoproliferative syndrome (Duncan’s syndrome) and in lymphoproliferative diseases after organ transplantation.

On *histologic examination* the portal tracts are heavily infiltrated by atypical lymphocytes and plasma cells. The inflammatory infiltrate spills over through the limiting plate to the lobular parenchyma. EBV antigens may be demonstrated in lymphocytes by immunocytochemistry and by *in situ* hybridization. The sinusoids are infiltrated either diffusely or in the form of small aggregates by mononuclear cells. Intrasinusoidal lymphocytosis often has a characteristic “Indian-file” appearance (Fig. 64.2). Liver cells are usually only mildly affected with scattered apoptotic bodies or foci of parenchymal necrosis filled with lymphocytes. Hepatocellular injury is clearly less pronounced than in acute viral hepatitis A

Fig. 64.2 EBV hepatitis. “Indian-file”-like intrasinusoidal lymphocytosis. Hematoxylin & Eosin (×400)



or B. Regenerative changes and mitoses may be prominent. A steatosis or non-caseating, fibrin-ring granulomas rarely occur. Cholestasis is not part of the typical microscopical picture of EBV hepatitis, and if present should prompt one to search for granulomas [6]. The main histological differential diagnosis of EBV hepatitis is from leukemia or lymphoma.

Adenoviruses

Adenovirus infection may cause severe hepatitis with liver failure in children and in immunosuppressed adults [1, 19]. Pathology and clinical manifestations resemble that of HSV hepatitis.

Enteroviruses

Liver involvement is seen in systemic infections with *Coxsackie B* and *echoviruses* [36]. Coxsackie virus, and more rarely echoviruses may cause a severe, hemorrhagic-necrotizing hepatitis in newborns. The clinical manifestations in adults are milder, generally reflecting an acute cholestatic hepatitis. *Histologically* centrilobular cholestasis and ballooned hepatocytes are seen. The

portal and sinusoidal inflammatory infiltrates are composed of mononuclear cells and neutrophil leukocytes.

Paramyxoviruses

Liver involvement in *measles virus infection* is mild and self-limited [25]. The histological alterations are nonspecific, showing “hepatocellular unrest,” nuclear vacuolization and a mild intrasinusoidal lymphocytosis. Isolated cases with clinically severe hepatitis and multinucleated giant cells have been documented, however, their paramyxovirus etiology has not been proven unequivocally [29].

Togaviruses

Rubella virus may cause hepatitis in the newborn within the context of the congenital rubella syndrome. Focal hepatocellular necrosis, signs of cholestasis and a mild chronic inflammatory portal infiltrate are seen. In isolated cases extensive parenchymal necrosis has been described.

Intrauterine infection with the rubella virus may cause biliary atresia.

Rubella infection in adults may be accompanied by a mild anicteric, subclinical or asymptomatic hepatitis with slightly elevated aminotransferases [28].

Arboviruses

Arthropode transmitted *Flavi-* and *Bunyaviruses* cause diseases that are characterized by disseminated intravascular coagulation with extended hemorrhages, and are therefore denominated *hemorrhagic fevers*. Liver injury in all arbovirus infections shows common features and is characterized by variably large areas of parenchymal necrosis and microvesicular steatosis, with a relatively mild inflammatory reaction. If the patient survives, scavenger and regenerative processes dominate the histological picture.

Yellow Fever Virus

The yellow fever virus belongs to the genus of flaviviruses. The disease is endemic in Africa and in South America. It manifests acutely with fever, myalgias and headaches that are followed by jaundice after a few days. Death is due to liver and renal failure. The *histopathological appearance* depends on the stage of the disease. Confluent, centrilobular parenchymal necrosis, scattered apoptotic bodies (classic *Councilman bodies*), and eosinophilic intranuclear inclusions that are arranged concentrically around the nucleolus (*Torres bodies*) characterize the acute stage. In contrast to the marked parenchymal injury the inflammatory response is scant. Surviving hepatocytes show microvesicular steatosis and ballooning. Regeneration is evidenced by hepatocellular hyperplasia and multinucleated hepatocytes [10].

Dengue Virus

International travel to endemic areas is a major risk factor for both primary and secondary dengue infection. The primary infection manifests as an exanthematic, influenza-like illness. Hemorrhagic fever is caused by reinfection with different serotypes of dengue virus (DEN 1–4). Dengue remains a diagnostic challenge, given its protean nature, ranging from a mild febrile

illness to profound shock. Dengue shock syndrome has an estimated mortality rate close to 50%.

Liver involvement appears to occur more frequently when infections involve DEN-3 and DEN-4 serotypes. The liver is interspersed with extended, partly confluent areas of hemorrhagic parenchymal necrosis. The inflammatory reaction is mild. The surviving hepatocytes show a microvesicular steatosis. Fulminant liver failure is extremely rare in adults, but has been reported in single cases [11]. If the patient survives, diffuse parenchymal calcifications may be the only sign of previous liver involvement [7].

Hantavirus

Certain types of hantavirus cause hemorrhagic fever with a renal syndrome (HFRS), while others are responsible for the hantavirus pulmonary syndrome (HPS). Primary involvement of the liver does not occur in either syndrome. In Chinese patients with acute hepatitis of unknown etiology hantavirus infection has been discussed as a possible cause [26].

Arenaviruses

Arenaviruses cause Lassa fever and hemorrhagic fevers in Argentina and Bolivia.

Lassavirus

Lassavirus infection is endemic in Central and West Africa. Fever, pharyngitis, diarrhea and a hemorrhagic diathesis characterize the clinical picture. Pain in the right upper quadrant may supervene. There is a marked rise of serum aminotransferases, while jaundice is rare. The mortality rate is approximately 30%.

The liver has a mottled appearance caused by apoptotic hepatocytes (Councilman-like bodies) and hemorrhagic necrosis of groups of liver cells which may coalesce forming bridging necrosis. Liver injury is accompanied by a marked hyperplasia of Kupffer cells and by lipofuscin deposits in hepatocytes. Cholestasis and steatosis are lacking. The viral particles can easily be demonstrated by electron microscopy [5].

Junin- and Machupovirus

These viruses cause hemorrhagic fevers in South America. The clinical picture and pathological liver findings correspond to those of Lassa fever.

Filoviruses

Marburg Virus

Marburg virus disease is a highly contagious, febrile infection. It is associated with disseminated intravascular coagulation, hemorrhages, and shock. The mortality rate is 20–25%. The pathology of the liver corresponds to that of Lassa fever.

Ebola Virus

Ebola fever resembles clinically and pathologically Marburg virus infection. Mortality rate is close to 50%.

Parvoviruses

Parvovirus B19 is the only human pathogenic parvovirus, causing *erythema infectiosum* (fifth disease) in children. Epidemiologic data suggest that parvovirus B 19 may also cause an acute hepatitis in children [39]. Adults with parvovirus B 19 infection, especially patients with underlying hemoglobinopathies (e.g. sickle cell disease) or other erythrocytic disorders (e.g. hereditary spherocytosis) may develop transient aplastic crisis. Combined with aplastic anemia massive hepatic necrosis and acute liver failure may occur [22]. Parvovirus B 19 may be demonstrated by PCR in liver tissue.

Coronaviruses

Human coronaviruses have long been known to cause the common cold. In 2002 the *Severe Acute Respiratory Syndrome* (SARS) was described for the first time. It is

caused by SARS Coronavirus (SCoV) that is genetically dissimilar from known human or animal coronaviruses. The disease presents with fever, influenza-like symptoms, dry cough, atypical pneumonia, and diarrhea.

The liver is involved in up to 60% of cases and infection of the liver by SCoV was verified for the first time in 2004 by demonstrating SCoV-RNA in liver tissue. In approximately 25% of patients aminotransferases are elevated (ALT: 200–900 IU/L). Histological examination shows signs of hepatocyte injury, such as ballooning and apoptosis accompanied by mild to moderate lobular lymphocytic infiltrates. Numerous mitoses probably denote regenerative activity [2, 13].

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