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OTHER HEPATITIS VIRUSES

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Abbreviations

anti-S	soluble complement-fixing antigens	HBV	hepatitis B virus	HSV	herpes simplex virus
CDC	Centers for Disease Control and Prevention	HCC	hepatocellular carcinoma	PCR	polymerase chain reaction
CMV	cytomegalovirus	HGV	hepatitis G virus	SARS-CoV	SARS-associated coronavirus
EBV	Epstein-Barr virus	HHV-6	human herpes virus-6	SEN-V	SEN-virus
EBVNA	EBV nuclear antigen	HHV-7	human herpes virus-7	TTV	TT virus
FHF	fulminant hepatic failure	HHV-8	human herpes virus-8	VCA	viral capsid antigens
HBsAg	hepatitis B surface antigen	HPV-B19	human parvovirus B19	VZV	varicella zoster virus

INTRODUCTION

There are viral agents apart from hepatitis viruses that may affect the liver as part of systemic involvement. This may include acute hepatitis or, in some instances, acute liver failure. They may lead to fulminant hepatitis. These agents' ability to cause chronic liver disease has not been proven unequivocally, although it seems unlikely. As the cause of acute liver failure remains unknown in a significant proportion of cases, these viral agents have been evaluated as etiological factors. These agents include cytomegalovirus, Epstein–Barr virus, herpes simplex virus, varicella zoster virus, human herpesviruses 6, 7, and 8, human parvovirus B19, adenoviruses, occult hepatitis B virus, and more recently, SARS-associated coronavirus.

CYTOMEGALOVIRUS (CMV)

Human cytomegalovirus (CMV) is the largest member of the β herpesviridae family of viruses. Cytomegaly (giant cell) and prominent intranuclear inclusion bodies characterize the cellular response to CMV infection. CMV infections are quite common, reaching 60–70% in urban populations, and play a significant role as an opportunistic pathogen in immunocompromised hosts. Early recognition of infection, institution of therapy, and prevention of infection are critical in altering the outcome in these patients.[1,2]

Several factors determine the manifestations and severity of CMV infection. Infection is acquired either in the perinatal period and infancy or in adulthood through sexual contact, blood transfusions, or organ transplantation. Most primary CMV infections in immunocompetent adults are either asymptomatic or associated with a mild mononucleosis-like syndrome. As with other herpes viruses, all primary infections resolve and enter into lifelong latency, in which live virus is sequestered in a non-replicative state. Persons with latent infection and an intact immune system have no symptoms but exhibit antibodies to CMV. Circulating lymphocytes, monocytes, and polymorphonuclear leukocytes may serve as the predominant site of viral latency. The risk for intermittent reactivation is increased with diminished host immune status. In immunocompromised patients, CMV disease can result from either a primary infection in a previously uninfected (seronegative) host, or more commonly from reactivation of latent infection. Although adequate anti-CMV antibodies are detected during episodes of reactivation of infection, cell-mediated immunity (characterized by decreased numbers of cytotoxic T lymphocytes and natural killer cells) is defective. The incidence and severity of CMV disease closely parallel the degree of cellular immune dysfunction.[3,4]

A wide spectrum of clinical syndromes associated with CMV disease ranges from asymptomatic infection, life-threatening congenital CMV syndrome in neonates, infectious mononucleosis syndrome in young adults, to severe pulmonary, retinal, neurological, gastrointestinal, and hepatic diseases in immunocompromised hosts, in whom CMV is a very common opportunistic pathogen.[5]

Congenital CMV infection is associated with substantial morbidity and mortality and is manifest shortly after birth by jaundice, hepatosplenomegaly, thrombocytopenic purpura, and severe neurological symptoms. Multifocal hepatic necrosis with cytomegalic cells, intranuclear inclusion bodies, inflammatory response, and marked bile stasis may be detected on liver biopsy. If the child survives the jaundice and hepatosplenomegaly may subside, but the neurological sequelae and mental retardation persist.[6–8]

A different form of neonatal CMV infection occurs as a result of perinatal (from the mother's cervix during delivery) or postnatal (from breastfeeding) transmission of the virus, resulting in a clinical picture resembling mild infectious mononucleosis syndrome without neurological involvement. A mild self-limiting hepatitis may occur, but usually resolves during the first year of life.[9–11]

In immunocompetent children and adults CMV infection is usually subclinical, but can sometimes cause a disease that resembles EBV infectious mononucleosis syndrome. Unlike in EBV mononucleosis, pharyngitis and cervical lymphadenopathy are absent and the heterophil response is negative (negative monospot).[12,13] The mode of transmission for these patients is through sexual contact, kissing, intrafamilial transmission (sharing objects with contaminated saliva among family members), and blood transfusion. In surgical patients requiring massive blood transfusions CMV infection should be considered as a source of postoperative fever (sometimes called postperfusion syndrome).[14]

Liver dysfunction is commonly associated with CMV mononucleosis. It is usually mild and rarely symptomatic in the immunocompetent patient. Hepatosplenomegaly and laboratory evidence of mild to moderate hepatic dysfunction are the predominant features, with increased transaminases and alkaline phosphatase values in 88% and 64% of cases, respectively, but lower than commonly encountered in active viral hepatitis.[15,16] Rare manifestations of CMV hepatitis include tender hepatomegaly, granulomatous hepatitis (with scattered microscopic granulomas found on liver biopsy), anicteric or icteric cholestatic form of hepatitis, and acute hepatitis with massive hepatic necrosis.[17–24]

In patients with impaired cell-mediated immunity, disseminated CMV infection results in serious life threatening diseases. CMV is the most common opportunistic viral infection in AIDS patients, causing retinitis, central nervous system infections, esophagitis, and colitis. CMV may also invade the hepatobiliary tract in AIDS patients, causing hepatitis, pancreatitis, and acute acalculous gangrenous cholecystitis.[25–27] The presence of cytomegalovirus retinitis, gastrointestinal disease, or viremia in AIDS patients increases the risk for the development of a cholestatic syndrome caused by papillary stenosis and sclerosing cholangitis, which does not usually respond to antiviral therapy.[28] Other immunocompromised patients at risk are organ transplant recipients, including liver transplantation.

The diagnosis of CMV hepatitis always requires confirmatory laboratory tests, as the clinical presentation alone is not sufficient to establish the diagnosis. Serologic studies of CMV IgM antibodies may be helpful in primary infections.[29] Viral culture technique could be greatly enhanced with the use of 'shell vial' assays, using CMV early antigens.[30,31] Using molecular techniques to detect CMV early antigen or the CMV DNA polymerase increased the sensitivity of detection of CMV infection in the blood or tissue.[32,33]

Liver biopsy with distinct pathologic findings is important in establishing the diagnosis in CMV hepatitis, especially in the immunocompromised host. Giant multinucleated cell reaction with an inflammatory response, multifocal necrosis, and biliary stasis are commonly found. Large nuclear inclusion-bearing cells, sometimes called 'owl's eye' inclusions, can be found in hepatocytes or bile duct epithelium.[34,35]

Treatment of CMV with antiviral agents is not always indicated, especially in self-limited disease in immunocompetent adults. For severe and worrisome cases, particularly in patients with impaired cell-mediated immunity, therapy can be life-saving. Aciclovir is ineffective.[36] Ganciclovir is a nucleoside analog of guanosine and a homolog of aciclovir that has a longer intracellular half-life. It is considered the antiviral agent of choice against CMV. The duration of therapy should be guided by repeated measurement of CMV in blood samples. Emerging resistant strains to ganciclovir pose a therapeutic challenge, where foscarnet or cidofovir may become alternative antiviral agents.[37]

EPSTEIN–BARR VIRUS (EBV)

Epstein–Barr virus (EBV) shares the characteristic morphologic features of the herpesviridae family. The EBV genome consists of a linear DNA molecule that encodes nearly 100 viral proteins. After infecting B lymphocytes the linear EBV genome becomes circular, forming an episome, which usually remains latent in these B cells. Viral replication is spontaneously activated in only a small percentage of latently infected B cells.[38]

Transmission of EBV usually occurs via contact with oral secretions (saliva droplets, or possibly cells in saliva). Transmission by blood transfusion has been reported but is very unusual.[39] The virus replicates in the nasopharyngeal epithelial cells, and nearly all seropositive persons actively shed virus in the saliva. B cells in the oropharynx may be the primary site of infection.[40] Resting memory B cells are thought to be the site of persistence of EBV in the body. Researchers were able to identify various clinical conditions associated with EBV, such as infectious mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease, peripheral T-cell lymphoma, and post-transplant lymphoproliferative disease.[41]

EBV infection is very common, infecting over 90% of humans worldwide and persisting for the lifetime of the person. Hepatosplenomegaly and palatal petechiae may be present in more than 10% of symptomatic patients.

Liver involvement is well recognized in EBV infections. Manifestations of liver involvement range from the most commonly encountered mild self-limiting acute hepatitis to occasional reports of fatal acute fulminant hepatitis.

Mild elevation of aminotransferase two to three times the upper limit of normal, and elevated lactic dehydrogenase levels are seen in up to 90% of cases of infectious mononucleosis. Typically, the rise in aminotransferases is gradual, reaching a peak that is lower than that commonly encountered in acute viral hepatitis. The rise occurs over a 1–2-week period, then aminotransferases decline gradually over 3–4 weeks.[15,42–46] Patients older than 30 years generally have a more severe disease than do children. Mild elevation of alkaline phosphatase levels is also seen in 60% and mild hyperbilirubinemia in about 45%.[42]

Severe cholestatic jaundice and right upper quadrant abdominal pain may occur in elderly patients. Jaundice may occasionally be the initial clinical presentation, in combination with fever and abdominal pain, and can be mistaken for extrahepatic biliary obstruction. Jaundice occurs predominantly when EBV infection is complicated with autoimmune hemolytic anemia, and occasionally as a direct result of virus-induced cholestasis.[47–51]

Other occasional clinical settings for EBV liver involvement include post-transfusion hepatitis, granulomatous hepatitis, and fatal fulminant hepatitis. In some cases of granulomatous hepatitis serologic evidence of chronic EBV infection was found.[52,53] A detailed clinicopathologic analysis of 30 patients with sporadic fatal infectious mononucleosis was described by Markin et al.[54] Cases of fatal fulminant hepatitis with massive hepatic necrosis and disseminated intravascular coagulation were reported in both immunocompromised and immunocompetent hosts.[55–59]

The diagnosis of infectious mononucleosis is established on the basis of the clinical features, laboratory and serological findings indicative of a recent EBV infection. The most common hematological findings include leukocytosis in 70% of cases, with predominantly lymphocytosis and monocytosis, and mild thrombocytopenia in up to 50%. The 'monospot' test that detects heterophile antibodies, although sensitive, is not very specific. EBV-specific IgG and IgM antibodies, directed against the viral capsid antigens (VCA), early antigens (EBV anti-D and anti-R), nuclear antigen (EBVNA),

and soluble complement-fixing antigens (anti-S), improve sensitivity and specificity in detecting the infection.[60–62] With liver involvement, abdominal ultrasound may show a fatty liver appearance or gallbladder wall thickening.[63,64] In the vast majority of cases there is no indication for liver biopsy. There may be portal and sinusoidal mononuclear cell infiltration with focal hepatic necrosis or fatty infiltration. Multinucleated giant cells are not seen.[39] Of particular utility as diagnostic methods are in situ hybridization, Southern blot analysis, and polymerase chain reaction to identify specific RNA or DNA sequences in the organs involved.[65,66]

The differential diagnosis of EBV hepatitis includes other viral hepatitis A–E, cytomegalovirus hepatitis, and drug-induced hepatitis. Cervical lymphadenopathy is less common and peripheral monocytosis is encountered as observed with CMV hepatitis.[12]

There is no specific drug or treatment for EBV infection. Aciclovir inhibits EBV in vitro replication and reduces viral shedding in the oropharynx, but has no effect on the symptoms of infectious mononucleosis (which are primarily due to immune response to the virus) and is therefore not recommended.[67] In EBV hepatitis no antiviral agent has proved to be effective. There is one single report of fulminant hepatic failure in an immunocompetent young girl caused by primary EBV infection that was treated by orthotopic liver transplantation.[68]

HERPES SIMPLEX VIRUS (HSV)

Herpes simplex virus (HSV-1 and HSV-2) is a common infection in humans and produces a wide variety of illnesses, including mucocutaneous infection, infections of the central nervous system, and an occasional infection of the visceral organs. The clinical manifestations and course of HSV infections depend mainly on the site involved and the host's age and immune status.

Occasionally, HSV viremia results in visceral involvement, affecting mainly three organs: the esophagus, lungs, and liver. Liver involvement occurs in the following settings: neonatal infections, pregnancy, immunocompromised hosts, and rarely immunocompetent adults.

In neonates, hepatitis occurs with multiorgan involvement and usually carries a high mortality rate. Fulminant hepatitis caused by HSV was first described by Hass in 1935 in a neonate with liver and adrenal necrosis associated with distinctive intranuclear inclusions.[69] Several subsequent reports have shown that acute fulminant hepatitis and adrenal insufficiency remain the most common causes of death in neonates with disseminated HSV infection.[70] The delay in instituting antiviral therapy against HSV, while awaiting confirmation of the diagnosis, results in a catastrophic outcome.[71]

HSV hepatitis in pregnant women was first reported in 1969 and was seen in the context of disseminated primary infection, usually late in gestation – 65% in the third trimester – and usually manifests as acute fulminant hepatitis.[72–74] Mucocutaneous lesions are present in only half of cases; therefore, the clinical suspicion for diagnosis of this condition must be high. Twenty-five percent of cases were not diagnosed until autopsy. Early recognition, with initiation of antiviral therapy, may reverse an otherwise fatal process.[75–79]

HSV is an uncommon cause of hepatitis in immunocompetent patients. A mild asymptomatic elevation of transaminase levels can be detected in 14% of healthy adults with acute genital herpes infection.[80] Fulminant hepatitis with more than a 100-fold rise in transaminases was reported and associated with a favorable outcome after antiviral therapy.[81–83] In immunocompromised hosts HSV hepatitis has occurred during primary and rarely during recurrent infection, with a triad of fever, leukopenia, and markedly elevated aminotransferases being suggestive of the diagnosis.

Liver biopsy is essential to establish the diagnosis of HSV hepatitis, especially in pregnancy. It usually shows focal, sometimes extensive, hemorrhagic or coagulative necrosis of the hepatocytes, with limited inflammatory response (usually mononuclear and scattered lymphocytes). Typical intranuclear inclusions (Cowdry A type) are often identified at the margins of the foci of necrosis. The diagnosis is confirmed by the detection of HSV DNA sequences by PCR, which is more sensitive than tissue culture methods.[75,81,84,85]

HSV hepatitis is one of the infectious disease emergencies associated with a rapid and lethal course and requires early recognition and the institution of antiviral therapy while awaiting confirmation of the diagnosis, in order to improve outcome.[86,87] At the Mayo Clinic the incidence of HSV hepatitis was reported to be 6% among all fulminant hepatitis patients reviewed from 1974 to 1982.[88] High-dose aciclovir is the antiviral drug of choice (at least 10 mg/kg/day every 8 hours) and has been successfully used.[75,89–91] Shanley[92] reported a case of a healthy female who developed disseminated HSV-2 infection and fulminant hepatitis during the third trimester of pregnancy requiring high-dose antiviral therapy, which resulted in eradication of HSV mucocutaneous lesions. However, the patient's condition continued to deteriorate, leading to orthotopic liver transplantation. Recurrence was not observed, suggesting that disseminated HSV infection should not be an absolute contraindication for transplantation in certain clinical settings. A more recently published series demonstrated the utility of liver transplantation in this setting.[93]

VARICELLA ZOSTER VIRUS (VZV)

Varicella zoster virus causes two distinct clinical diseases. Varicella (commonly called chickenpox) is the primary infection, which is characterized as a benign generalized exanthematous rash. Recurrence of infection results in a more localized phenomenon known as herpes zoster (often called shingles).[94] Rare non-cutaneous manifestations, such as encephalitis, pneumonitis, myocarditis, and hepatitis, may accompany the skin rash, especially in immunocompromised patients, and may be life-threatening.[95]

Mild and transient liver enzyme abnormalities are not uncommon in varicella infection in children and can occur in up to 25%.[96–98]

Primary infection in immunocompetent adults may cause severe acute hepatitis with a more than 10-fold increase in transaminases,[8] and sometimes fulminant hepatic failure with evidence of VZV in liver and other organs is only revealed on autopsy.[99]

In contrast to the rather benign course of zoster (reactivation of infection) in the setting of organ transplantation, primary varicella infection can be quite aggressive.[100] Visceral involvement, including the liver, may occur in the immediate postoperative period or may be delayed several months after transplantation. Usually it is associated with rapid onset and fatal fulminant hepatitis.[101–105]

Serologic testing is of little use, especially in immunocompromised patients. Confirmation of diagnosis is possible through the isolation of VZV from the skin lesions or other affected organ. Liver biopsy often shows foci of coagulative necrosis and intranuclear inclusions with an inflammatory response. PCR and immunoperoxidase techniques may be needed to distinguish VZV from HSV hepatitis.

CDC guidelines for the prevention and control of nosocomial infections must be instituted for infection control in hospital personnel.[106] Early administration of antiviral therapy is critical in the setting of VZV hepatitis, especially in immunocompromised patients. The drug of choice is intravenous aciclovir 30 mg/kg/day in three divided doses for 7–10 days.[107,108]

HUMAN HERPES VIRUS-6 (HHV-6)

HHV-6 infects nearly all humans by the age of 2 years and usually causes exanthema subitum (roseola infantum; sixth disease), infantile fever without rash, febrile seizures, and occasionally encephalitis.[109,110] Liver involvement with HHV-6 infection has been investigated, but attempts to prove an etiologic association have been inconclusive. Elevated aminotransferase levels were not appreciated as a common feature of roseola in a large case series.[111] PCR techniques and in situ hybridization led to the isolation of HHV-6 from the liver tissue of infants with chronic hepatitis, suggesting HHV-6 as a causative agent.[112,113] Reactivation of infection may occur after solid organ transplantation, with questionable clinical significance.[114] Foscarnet has a better in vitro virus sensitivity than aciclovir and ganciclovir against HHV-6.[115]

A recent study[116] reported the involvement of HHV-6 in 15 patients with non-A, non-E hepatitis who underwent liver transplantation for acute liver failure. HHV-6-specific antigens were analyzed in the explanted livers by immunohistochemistry, and the possible presence of the virus in peripheral blood mononuclear cells was demonstrated by the HHV-6 antigenemia test. The involvement of hepatitis viruses and other viral agents, such as CMV and HHV-7, was excluded. Of the 15 patients with acute liver failure of unknown cause, 12 (80%) demonstrated HHV-6 antigens in the liver. Most of these patients (10/12) also demonstrated HHV-6 antigenemia. No other viruses were found in the livers of the patients with acute liver failure (ALF). These observations led the authors to speculate that HHV-6 may be a cause of ALF.

Although HHV-6 has been reported to cause acute hepatitis and fatal fulminant hepatic failure (FHF),[116–119] and demonstrated to be in the blood or liver samples of patients, these reports did not necessarily establish causality.

HUMAN HERPES VIRUSES-7 AND -8 (HHV-7, AND HHV-8)

HHV-7 also infects all humans by the age of 5 years, causing febrile syndromes. Hepatitis in association with HHV-7 has been infrequently reported.[120]

HHV-8 (also called Kaposi's sarcoma-associated human herpes virus-8) has been detected consistently in Kaposi's sarcoma, lymphoma, and multicentric Castleman's disease, in HIV-positive patients, and occasionally in HIV-negative patients. Liver involvement may occur in the visceral type of Kaposi's sarcoma.

HUMAN PARVOVIRUS B19 (HPV-B19)

Human parvovirus B19 is a small DNA virus. It was discovered incidentally in 1974 when parvovirus-like particles were noted in serum specimens from asymptomatic blood donors being tested for hepatitis B surface antigen. Sample number 19 in panel B (hence B19) gave an anomalous 'false positive' result that was later recognized as a member of the Parvoviridae family.[121,122]

Human parvovirus B19 infection produces a spectrum of clinical manifestations including: erythema infectiosum – 'fifth disease' – in children; hydrops fetalis and fetal death; an arthritis syndrome associated with acute infections in adults; hematological disorders such as leukopenia, thrombocytopenia, transient aplastic crisis in patients with chronic hemolytic anemia, and chronic anemia in immunocompromised patients including AIDS; other rare organ involvement, including neurologic, cardiac, liver, and vasculitis.[122]

Hepatic manifestations range from a transient elevation of serum aminotransferases[123,124] sometimes seen during the course of erythema infectiosum[125,126] to fulminant hepatic failure (FHF).[127] HPV-B19 DNA has been found in liver samples from 67% of patients with non-A, non-E FHF and aplastic anemia, and in 50% of patients with cryptogenic FHF without aplastic anemia, compared to 15% of control subjects with chronic liver failure. This led some investigators to suggest that HPV-B19 is a possible causative agent of fulminant liver failure.[128,129]

Definitive diagnosis of acute HPV-B19 infection relies on the detection of HPV-B19 IgM or viral DNA. PCR is much more sensitive for detecting viral DNA in the serum, other body fluids, and fresh and paraffin-embedded tissue.

In most cases HPV-B19 infection is benign and self-limited and requires no treatment other than symptomatic relief.[122] At the Mayo Clinic we reported two cases of a less severe form of hepatitis-associated aplastic anemia.[130]

ADENOVIRUSES

There are close to 50 serotypes of adenovirus causing acute infections of the respiratory system, conjunctivae, and gastrointestinal tract, and occasionally hemorrhagic cystitis, infantile diarrhea, intussusception, and central nervous system infections.[131] Disseminated disease with multiorgan involvement has been reported in immunocompromised patients and associated with an increased mortality.[132]

The role of adenovirus as an etiologic agent of hepatic damage has been controversial. Fatal cases of adenovirus infection with fulminant hepatitis were reported in these immunosuppressed adult patients. Postmortem liver pathology has revealed widespread hepatic necrosis with intranuclear inclusions within viable hepatocytes. Electron microscopy may show crystalline arrays of virions within hepatocytes.[133,134] No specific therapy for adenovirus hepatitis is currently available.

OCCULT HEPATITIS B VIRUS INFECTION

Occult or cryptic hepatitis B virus (HBV) infection is defined as the detection of HBV DNA in the serum or liver tissue of patients who are negative for hepatitis B surface antigen (HBsAg).[135] It has been suggested that occult HBV infection maintains pro-oncogenic properties leading to hepatocellular carcinoma (HCC) in HBsAg-seronegative patients.[135,136] Occult HBV infection was first reported in the mid-1980s when hybridization techniques for the detection of HBV DNA became available. These studies showed that HBV DNA could be detected in HBsAg-negative patients with hepatocellular carcinoma (HCC).[137] Recent studies using more sensitive techniques have confirmed these observations.[136] Usually, patients with occult HBV infection have low HBV DNA levels: 10^{2-3} copies/ml in the serum and 0.01–0.1 copy per liver cell.[138] Therefore, detection of occult HBV infection most often requires ultrasensitive polymerase chain reaction (PCR) assays.

Pollicino et al.[136] investigated the prevalence and molecular status of occult HBV infection among Italian patients with HCC. They tested tumor tissues from 107 patients with HCC and the corresponding non-tumor liver tissue from 72 of these patients for HBV DNA, utilizing ultrasensitive PCR assays. All cases were hepatitis B surface antigen negative. Viral DNA was detected in 63.5% cases of tumorous tissue with HCC and in 72% of adjacent benign tissue, suggesting that occult HBV is a risk factor for development of HCC. These observations suggest that the same mechanism of oncognesis described for patients with overt HBV infection (HBsAg positive) are operative in patients with occult HBV infection (see Chapter 10). Future studies are needed to determine the exact role of occult HBV infection in the development of HCC.

SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

SARS is a newly recognized, severe febrile respiratory illness caused by a previously unknown coronavirus, SARS-associated coronavirus (SARS-CoV). It was responsible for the first epidemic of the 21st century, emerging in the southern Chinese province of Guangdong in November 2002.[139] The worldwide epidemic was triggered in late February 2003 when an ill physician from Guangdong infected several other guests at a hotel in Hong Kong.[140,141] These people subsequently became the index patients for large outbreaks of SARS in many areas of the world. On 12 March 2003, the World Health Organization (WHO) issued a historic global alert for SARS, a deadly new infectious disease with the potential for rapid spread from person to person and via international air travel. WHO and its partners, including the Centers for Disease Control and Prevention (CDC), promptly initiated a rapid, intense and coordinated investigative and control effort that led within 2 weeks to the identification of the etiologic agent, SARS-CoV, and to a series of decisive and effective containment efforts. By the time SARS-CoV transmission was brought to an end in July 2003, more than 8000 cases and 780 deaths had been reported to WHO. The CDC published guidelines in order for localities and healthcare facilities to develop operational preparedness and response plans.[140]

Lymphocytopenia, thrombocytopenia, and elevated levels of D-dimers and activated partial thromboplastin time are common laboratory findings in SARS. The levels of alanine aminotransferase, creatine kinase, and lactate dehydrogenase may be increased. However, these laboratory findings do not allow reliable discrimination between SARS and other causes of community-acquired pneumonia.[142] One-third of patients with SARS improve and the other two-thirds develop persistent fever, worsening pulmonary symptoms, and radiographic findings. Some patients develop multiorgan failure and die. Age and coexisting illness, especially diabetes mellitus and heart disease, are consistently found to be independent prognostic factors for the need for intensive care and the risk of death.

Liver involvement in SARS is common and has been reported in up to 60% of patients.[142–144] The majority of these have been treated with antibiotics, antiviral medications, and steroids, which are potentially hepatotoxic. Hence, whether or not SARS-CoV infection can lead to liver damage per se remains unknown. The most common abnormality is elevated aminotransferases, or the less common ischemic injury in cases of multiorgan failure. However, Chua et al.[145] reported the clinical course and liver pathology in three SARS patients with liver impairment. All three had moderate to marked elevation of their liver aminotransferases and common causes of hepatitis were excluded by serologic tests. Histologic examination of the liver specimens revealed prominent mitoses, acidophilic bodies, Kupffer cells, ballooning of hepatocytes, and mild to moderate lobular inflammation as the common histologic features. All of the patients showed positive RT-PCR for SARS-CoV in liver tissue but not in the sera, suggesting that the virus was localized in liver. The investigators concluded that SARS-CoV may infect the liver, leading to mild to moderate lobular inflammation and apoptosis.

ADDITIONAL HEPATITIS AGENTS

Additional hepatitis agents have been suggested from transfusion-associated hepatitis studies, CDC Sentinel Counties studies, and cases of fulminant hepatitis in whom no agent have been identified in the majority of them. In all these conditions, a viral agent is suspected to exist but no specific virus has been identified.

The GB agent and the hepatitis G virus (HGV) are RNA viruses that belong to the Flaviviridae family.[146] Extensive investigations have failed to show that these agents play any etiologic role in acute or chronic liver disease.[147,148]

The TT virus (TTV) has been shown to be a small, non-enveloped single-stranded circular DNA virus in the family of Circoviridae.[149,150] It is now clear that TTV is a heterogeneous agent that can be transmitted to humans by both parenteral and non-parenteral routes. The agent is of particularly high prevalence in Japan, where TTV has been detected in healthy persons. Although initially implicated in fulminant hepatitis and cryptogenic chronic liver disease, these associations have not been confirmed and there are currently no proven hepatic diseases associated with this agent.[151,152]

The newly described viruses in this family have been designated SANBAN and YONBAN.[153–156] These agents have similar properties

to TTV but sufficient nucleotide differences to make them distinct members of the Circoviridae family.

SEN virus (SEN-V) was discovered independently using amplification strategies with highly degenerate TTV primers.[153] Two SEN-V variants (SEN-D and SEN-C/H) have been studied and have been found as acute infections in 11 of 12 (93%) transfusion-transmitted non-A, non-E hepatitis cases. There is no current evidence that SEN-V is truly a hepatitis virus, and further work is needed.

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