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REVIEW

Liver involvement in systemic infection

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Abstract

The liver is often involved in systemic infections, resulting in various types of abnormal liver function test results. In particular, hyperbilirubinemia in the range of 2-10 mg/dL is often seen in patients with sepsis, and several mechanisms for this phenomenon have been proposed. In this review, we summarize how the liver is involved in various systemic infections that are not considered to be primarily hepatotropic. In most patients with systemic infections, treatment for the invading microbes is enough to normalize the liver function tests. However, some patients may show severe liver injury or fulminant hepatic failure, requiring intensive treatment of the liver.

Key words: Liver dysfunction; Liver function test; Systemic infection; Immunology; Liver failure

Core tip: The liver is frequently involved in systemic infections, resulting in various types of abnormal liver function test results. It is very important to know the frequency and the patterns of abnormal liver function test results in each infection for the appropriate management of the patients. However, there have been few reports focusing on this issue. Here, we gather information from previous reports on this topic to provide a comprehensive summary that will help clinicians interpret abnormal liver function test results according to the associated infection.

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INTRODUCTION

It is well known that the classical hepatotropic viruses, hepatitis A through E, can infect the liver and cause hepatic injury. Other systemic infections by non-hepatotropic viruses or bacteria can also cause hepatic injury, either by direct invasion or indirectly through toxins and cytokines, but there are few reports of the correlations between liver function abnormalities and these infections. This review will describe features of liver injury caused by various systemic infections. It will discuss, in order, bacterial infections, infection by specific pathogens, non-hepatitis viral infections, fungal infections, and liver involvement of parasitic diseases.

BACTERIAL INFECTIONS

Sepsis

Sepsis is a clinical syndrome that complicates severe infection and accompanies systemic abnormalities such as tachycardia, tachypnea and/or hypotension. It is thought to be associated with vasodilation and increased microvascular permeability caused by bacterial products and cytokines. Liver function test abnormalities and jaundice frequently accompany a variety of bacterial infections, especially sepsis[1]. Various sites of infection can cause jaundice, which include intra-abdominal infection, urinary

Table 1 Mechanism of Jaundice in Sepsis

Increased bilirubin load
Hemolysis
Red blood cells lysed by bacterial products (*e.g.*, exotoxin)
Red blood cells lysed by immunological mechanisms
Hepatic dysfunction
Hepatocellular injury (hepatitis and/or necrosis)
Hepatic ischemia
Decreased bilirubin uptake; dysfunction of basolateral transport (*e.g.*, NTCP)
Decreased transport of conjugated bilirubin; dysfunction of canalicular transport (*e.g.*, BSEP, MRP2)
Decreased bile flow

NTCP: Na^+/taurocholate cotransporting polypeptide; BSEP: Bile salt export pump; MRP2: Multidrug-resistance-associated protein 2.

tract infection, pneumonia, endocarditis, and meningitis. Although several retrospective studies have reported incidences of jaundice ranging from 0.6% to 54% in adults with sepsis[2,3], the precise incidence remains unclear because of the absence of a large-scale prospective study. In patients with sepsis, jaundice can be caused by several organisms including aerobic and anaerobic gram-negative (*Escherichia coli* and *Klebsiella*) and gram-positive bacteria (*Staphylococcus aureus*). Kanai *et al*[4] isolated microorganism species in patients with bacteremia and reported *S. aureus*, *E. coli*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa* as comprising 29.3%, 14.4%, 6.0%, and 6.0% of all isolates, respectively. Uslan *et al*[5] also reported that the most common organisms identified in the blood of patients with bacteremia were *E. coli* (25.1%) and *S. aureus* (16.6%). Of the bloodstream infections, 44.5% were community acquired, 36.5% were health care associated, and 19.1% were nosocomial[5].

Hyperbilirubinemia in the range of 2-10 mg/dL is often seen in patients with sepsis, but on rare occasions, much higher levels (30 to 50 mg/dL) have been reported[6]. Serum alkaline phosphatase (ALP) is usually elevated in range of 1 to 3 times the upper limit of normal (ULN), but serum ALT is only modestly elevated. Infected patients with bacteremia had significantly higher serum levels of gamma-glutamyl transpeptidase (γ-GTP) and ALP and significantly lower serum concentrations of albumin, cholesterol and cholinesterase as compared with those without bacteremia. If septic shock and hypoperfusion complicate, a striking elevation of aminotransferases may occur.

The pathogenesis of jaundice in systemic infections is multifactorial. Jaundice is mainly associated with cholestasis in patients with sepsis[1], but isolated jaundice without cholestasis can occur through increased bilirubin load from hemolysis in some cases[7,8]. Several bacterial infections, especially *Clostridium perfringens*, may cause hemolysis. Phospholipase C produced by *C. perfringens* may be associated with the release of lysolecithin and the lysing of red blood cell membranes. It also can produce proteolytic exotoxins, which may lead to hemolysis[9,10].

Cholestasis is mainly thought to be caused through the inhibition of the canalicular excretion of conjugated bilirubin by proinflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-1,6 (IL-1,6), which are mainly released by macrophages in response to endotoxins[11]. Interestingly the serum concentrations of ALP and bilirubin are often discordant, because jaundice in sepsis is associated with various factors including increased bilirubin load, decreased bilirubin uptake, intrahepatic processing, and canalicular excretion (Table 1)[12,13].

The major histological finding in sepsis is bland intrahepatic cholestasis with bile in the bile canaliculi and hepatocytes. Minimal degenerated changes of hepatocytes with Kupffer cell hyperplasia and lymphocyte infiltration may also be seen.

Pneumonia

Lobar pneumonia is a common disease usually caused by any one of a variety of bacteria (*e.g.*, *S. pneumonia, Haemophilus influenza*, *S. aureus*, or *P. aeruginosa*). Patients with pneumococcal pneumonia sometimes show elevated concentrations of serum aminotransferases and bilirubin. Jaundice was reportedly observed in 3%-25% of such patients[14]. Pneumonia-associated jaundice is mostly thought to be a result of hepatocellular damage, because hepatic necrosis is often seen in liver biopsies of patients with pneumonia[15]. In *Mycoplasma pneumonia* infection, an adult case with acute hepatitis without pulmonary manifestations was also reported by Lee *et al*[16]. They also summarized five other cases (5 to 22 years of age) with similar clinical characteristics to those of *M. pneumonia* infection. *Legionella* is an important species of bacteria which causes pneumonia, often accompanied by laboratory abnormalities indicating hepatic dysfunction, renal dysfunction, thrombocytopenia, and hyponatremia[17].

Microbial foodborne disease

Microbial foodborne illness is very common and mainly causes gastrointestinal symptoms including nausea, vomiting, abdominal pain, diarrhea, and fever. These patients may have other complications such as hepatitis, renal failure, and neurogenic symptoms (Table 2).

***Salmonella typhi* infection:** *Salmonella typhi* can cause an acute systemic illness known as typhoid fever, while being nontyphoidal *Salmonella* (most commonly *S. enteritidis* and *S. typhimurium*) primarily induces gastroenteritis. The majority of patients with typhoid fever present with fever, malaise, abdominal discomfort, and hepatosplenomegaly. Typhoid fever may also cause liver injury with elevated aminotransferases and jaundice[18]. Hepatomegaly and jaundice were reportedly observed in 44% and in 33% of patients with typhoid fever, respectively. Although severe elevation of aminotransferases is rare in patients with typhoid fever, typhoid fever and viral hepatitis A sometimes need to be discriminated because clinical features of typhoid fever are similar to those of acute viral hepatitis A infection (Table 3). The ALT/LDH ratio may be useful to distinguish these diseases; the ALT/LDH ratio has been shown to be significantly lower (< 4.0) in typhoid fever compared with the ratio (> 5.0) in acute viral hepatitis A[19]. The hepatic histology shows

Table 2 Foodbrone pathogens and manifestations

Pathogens	Manifestations
Bacteria	
Staphylococcus aureus	Vomiting (exotoxin), toxic shock syndrome
Clostridium spp	
C. botulinum	Neurogenic finding (paralysis)
C. perfringens	Diarrhea, gas gangrene, intravascular hemolysis, jaundice, liver abscess, gas in the portal vein
Campylobacter spp	
C. jejuni	Inflammatory diarrhea, liver injury (possible)
C. fetus	Systemic, liver injury (possible)
Escherichia coli	
Enterotoxigenic E. coli	Inflammatory diarrhea
Enterohemorrhagic E coli	Inflammatory diarrhea, hemolytic uremic syndrome
Listeria monocytogens	Systemic (Listeriosis), elevated aminotransferases
Salmonella spp	
Non-typhoidal	Inflammatory diarrhea
S.typhi	Systemic (Typhoid fever), acute hepatitis (Salmonella hepatitis)
S.paratyphi	
Shigella spp	Inflammatory diarrhea, cholestatic hepatitis
Vibrios spp	
V. cholera	Watery diarrhea
V. parahemolyticus	Inflammatory diarrhea
V. vulnificus	Systemic (sepsis, DIC)
Yersina entrrocolitica	Inflammatory diarrhea, multiple liver abscesses
Virus	
Hepatitis A	Acute hepatitis, jaundice
Hepatitis E	Acute hepatitis, jaundice
Norovirus	Vomiting, watery diarrhea
Rotavirus	Vomiting, watery diarrhea

minimal parenchymal changes with focal infiltration of mononuclear cells or focal hepatocyte necrosis known as "typhoid nodules"[20,21].

***Campylobacter* infection:** *Campylobacter* enteritis is an important cause of acute diarrhea, and several complications are known in patients with *Campylobacter* infection, which include cholecystitis, reactive arthritis and Guillain-Barré syndrome. Mild to severe hepatocellular dysfunction is rarely observed in these patients, and liver biopsy shows nonspecific reactive hepatitis[22]. The symptoms and liver dysfunction are commonly improved after antimicrobial therapy.

***Clostridum perfringens* infection:** *Clostridum perfringens* is an important cause of watery diarrhea and also a toxin-mediated disease including hemolysis, jaundice, hypotension, and renal failure. *C. perfringens* is well known to cause clostridium myonecrosis (gas gangrene), which is a life-threatening muscle infection spreading directly from the area of trauma or hematogenously from gastrointestinal tract infection[23]. Jaundice may develop in up to 20% of patients with gas gangrene. On rare occasions, it can cause necrotizing massive gas gangrene in the liver leading to fulminant hepatic failure[24].

Pelvic inflammatory disease

Pelvic inflammatory disease (PID) refers to infection of the uterus, fallopian tubes, and adjacent pelvic structures, and the most important causative organisms are *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Occasionally, patients with these infections develop perihepatitis (Fitz-Hugh-Curtis syndrome), an inflammation of the liver capsule and adjacent peritoneal surfaces[25,26]. The clinical presentations include right-upper quadrant (RUQ) pain or pleuritic pain, and it may be confused with acute cholecystitis or pleurisy. The levels of aminotransferases are usually normal because of the minimal stromal hepatic involvement.

It has been reported the use of intrauterine devices (IUDs) causes a slight increase in the risk for PID[27-29]. Gelfand *et al*[30] reported a case of *Streptococcus milleri* bacteremia and multiple hepatic abscesses secondary to a tuboovarian abscess associated with IUD. Long-term indwelling IUDs was also reported to cause pelvic actinomycosis, which is a slowly progressive infection of *Actinomyces* species[31]. Moreover, a case of hepatic actinomycotic abscess associated with IUD was reported[32].

Toxic shock syndrome

Toxic shock syndrome is caused by the staphylococcal toxic shock syndrome toxin (TSST-1) and is commonly associated with *S. aureus* infections[33]. The clinical findings include fever, a scarlatiniform rash, mucosal hyperemia, vomiting, and diarrhea. It may cause liver dysfunction with severe jaundice and high levels of aminotransferases by hypoperfusion and circulating toxins.

Moreover, it should be noted that *Aeromonas* bacteremia, mostly *Aeromonas hydrophila*, causes significantly severe soft tissue infection such as necrotizing fascilitis with high mortality in patients with liver cirrhosis in contrast to self-limiting recovery in healthy subjects[34].

Hepatic encephalopathy and systemic infection

Systemic infection such as sepsis has been associated with the development of hepatic encephalopathy (HE). In patients with acute liver failure, rapidly progressing and severe HE is found more frequently in those with infection and inflammation[35,36]. It has also been reported that infection and inflammation exacerbate HE in patients with cirrhosis[37]. Systemic inflammation might have synergistic effects with HE. In a bile duct-ligated rat model, lipopolysaccharide (LPS)-treated rats showed severe HE with cytotoxic brain edema and increased nitrotyrosine in the frontal cortex despite preservation of the blood-brain barrier, whereas those without LPS developed pre-coma status only[38]. In systemic inflammation, increased cerebral blood flow, activated neutrophils or produced cytokines such as TNF-α, IL-1β or IL-6 contribute to the pathogenesis of HE[39,40].

INFECTION BY SPECIFIC PATHOGENS

Mycobacterium infection

Although the lungs are the major site for *Mycobacterium*

Table 3 Frequency of symptoms and signs in salmonella and acute viral hepatitis A

	Nausea/ vomiting	Abdominal discomfort	Jaundice[b]	Diarrhea	Relative bradycardia[d]	Fever > 104° F[b]	Hepatomegaly	Splenomegaly
Salmonella hepatitis	70%	33%	33%	48%	37%	41%	44%	7%
Acute viral hepatitis A	89%	63%	89%	30%	4%	0%	66%	11%

Modified from El-Newihi *et al*[19]. Salmonella hepatitis *vs* acute viral hepatitis A: [b]$P < 0.0001$; [d]$P < 0.002$.

tuberculosis infection, liver involvement has been also reported in patients with mycobacterial infection[41]. Miliary tuberculosis is defined as hematogenous dissemination of *Mycobacterium tuberculosis*, and the liver is frequently involved. Hepatic tuberculosis can be classified into various types such as military, granulomatous, and localized hepatic tuberculosis. The clinical presentations include fever, abdominal pain, and hepatomegaly. Liver function abnormalities have been observed in patients with hepatic tuberculosis, including elevated ALP and aminotransferases in 83% and 42% of these patients, respectively[42]. Cholestatic jaundice has also been reported in miliary tuberculosis, and fulminant hepatic failure can occur, if only rarely[43]. Importantly, hepatic tuberculosis can occur in the absence of apparent pulmonary tuberculosis, and tuberculous liver abscess without lung involvement has also been reported[44]. Histologically, the presence of caseating granulomas is suggestive of hepatic tuberculosis, but the yields of acid-fast bacillus smears and cultures are low. Detection using tissue PCR for *Mycobacterium tuberculosis* has a higher sensitivity and specificity.

Atypical mycobacteremia caused by *M. avium intracellulare* or *M. genavense*, can also cause granulomatous hepatitis with an elevation of ALP and low-grade fever in immunocompromised hosts such as those with AIDS syndrome[45].

Syphilis

Hepatic involvement in patients with syphilis is not uncommon. Schlossberg *et al*[46] reported that 39% of early syphilis patients had liver enzyme abnormalities at the time of diagnosis and that 2.7% of syphilis patients were diagnosed with syphilitic hepatitis. Other reports also show that liver enzyme abnormalities have been observed in about 10% to 50% of patients with secondary syphilis[46,47]. Syphilitic hepatitis is characterized by a high serum ALP level and normal to mild elevation of aminotransferases. Clinical hepatitis is rare, but acute cholestatic syphilitic hepatitis has been reported[48]. Hepatic gummas consisting of a caseous mass with a fibrous capsule may present in patients with tertiary syphilis. After starting therapy using penicillin, jaundice may occur with chills, fever, and a rash (erythema of Milan), as part of the Jarisch-Herxheimer reaction.

It is well known that syphilis continues to occur at high rates among human immunodeficiency virus (HIV) -infected patients. Crum-Cianflone *et al*[49] reported that syphilitic hepatitis is common, occurring in 38% of HIV-positive patients with early stages of syphilis infection, and that syphilis should be included in the differential diagnosis of HIV patients with liver dysfunction.

Leptospirosis

Leptospirosis caused by *Leptospira interrogans* is one of the most common zoonoses, and it may occur as one of two different clinical courses: anicteric leptospirosis (> 90% of cases) or icterohemorrhagic (Weil's) disease (5%-10% of cases)[50]. The former is characterized by self-limited viral infection-like symptoms with fever and conjunctival suffusion. The latter presents severe jaundice (approaching 30 mg/dL of total bilirubin) and several complications such as renal failure. Mild elevation of serum aminotransferases and thrombocytopenia can be seen[51]. Importantly, it is difficult to distinguish leptospirosis from other febrile infectious diseases such as *Salmonella typhi* or influenza because of similar clinical manifestations in the early phase.

In spite of severe functional impairment of the liver and kidneys, histopathological changes are usually slight, consisting of minimal focal hepatocyte necrosis. In severely jaundiced cases, leukocyte infiltration and bile thrombi can be observed.

Lyme disease

Lyme disease is a spirochetal infection by *Borrelia burgdorferi*, and it can involve multiple organs including skin, muscle, liver, heart, and nervous system. Hepatic involvement can be seen in 20% of patients with Lyme disease; elevations of aminotransferases and γ-GTP are commonly observed[52,53].

Q fever

Q fever is one of the zoonotic infections caused by *Coxiella burnetii*; it is characterized by relapsing fevers, headache, and myalgias, and can involve several organs including the lungs, heart and liver. Nearly 50% of patients with Q fever may have liver function abnormalities, and the clinical features may mimic anicteric viral hepatitis[54].

Rocky Mountain spotted fever

Rocky Mountain spotted fever (RMSF) is the most common manifestation of *Rickettsia rickettsii* infection in the United States. The clinical spectrum of human infection ranges from mild to fulminant, and hepatic involvement is frequent, predominantly in the form of jaundice[55,56]. RMSF is commonly mistaken for other viral or bacterial infection, because the symptoms are commonly nonspecific during the first few days of illness.

Table 4 Comparison of clinical features of hepatitis caused by various viruses

	n	Median age (range)	ALT (U/L)	ALP (U/L)	Bilirubin (μmol/L)	Lymphocyte count (× 10^9/L)	Lymphocytosis *n* (%)
EBV	17	40 (18-68)	395 (87-1362)	345 (160-756)	74 (13-165)	6.91 (3.77-24.82)	17 (100)
HAV	11	44 (20-61)	1056 (595-4122)	231 (91-342)	154 (42-214)	2.16 (1.23-4.1)	1 (9)
HBV	16	39 (20-60)	1858 (499-3856)	230 (93-406)	122 (36-355)	2.00 (1.26-3.52)	2 (12.5)
HEV	20	63 (54-81)	1387 (318-6357)	192 (139-464)	61 (8-297)	1.89 (0.96-10.25)	5 (25)

Modified from Vine *et al*[60]. EBV: Epstein-Barr virus; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HEV: Hepatitis E virus.

Hepatic actinomycosis

Actinomycosis is a chronic granulomatous disease caused by filamentous, gram-positive, anaerobic bacteria, mainly *Actinomyces Israelii*. Hepatic involvement may occur through intestinal actinomycosis in the appendix and ileocecal region. The clinical presentation includes fever, anemia, body weight loss, and hepatosplenomegaly, which is not characteristic as actinomycosis; therefore, it is difficult to diagnose as actinomycosis preoperatively[57]. Percutaneous liver biopsy is useful, as sulfur granules can typically be observed.

NON-HEPATITIS VIRAL INFECTION

Although the hepatotropic viruses, hepatitis A though E, are the most common viral cause of acute liver injury (acute hepatitis), other viruses such as Epstein-Barr virus (EBV) or cytomegalovirus (CMV) can also cause acute liver injury. Serological tests and direct-detection by PCR/ISH/IHC are useful to diagnose these viruses, but it is not easy to distinguish between hepatitis viral infections and these non-hepatotropic viral infections at the time of the first medical examination.

EBV

EBV is a member of the herpes virus family. Infection commonly occurs in childhood and is asymptomatic. On the other hand, symptomatic disease develops mostly in young adults with high fever, sore throat and lymphadenopathy, known as infectious mononucleosis. Liver injury with a mild elevation of aminotransferases often occurs in patients with infectious mononucleosis, but acute hepatitis and jaundice has been observed in some patients with EBV infection without clinical features of infectious mononucleosis[58]. Manifestations of liver involvement range from mild hepatitis to hepatosplenomegaly with jaundice, and on rare occasion, acute fulminant hepatitis[59]. Vine *et al*[60] reported the clinical features of EBV hepatitis compared with those of acute viral hepatitis caused by hepatitis A, B, and E viruses (Table 4). Patients with EBV hepatitis rarely present with more than 1000 IU/L of serum ALT, and usually have lymphocytosis (> 5×10^9/L). Splenomegaly has been shown to be present in 88% of these patients. In this context, EBV hepatitis may be suggested by the presence of lymphocytosis and splenomegaly. Interestingly, the median age of patients with EBV hepatitis is older than that of patients with typical infectious mononucleosis, with nearly half the patients more than 60 years old[60].

It is well known that EBV primarily replicates nasopharyngeal epithelial cells and B lymphocytes, and expression of EBV-encoded small RNA is also observed in liver specimens from transplant recipients. Histologically, various findings can be seen, including sinusoidal infiltration of mononuclear cells and mildly ballooning hepatocytes with vacuolization.

Chronic active EBV infection (CAEBV) is well known as a rare disorder occurring in immunocompetent as well as immunocompromised hosts, and may cause EBV-associated lymphoproliferative diseases (LPDs). It has been reported that a third of the patients with EBV-driven LPDs have liver involvement[61]. The incidence of post-transplant lymphoproliferative diseases has been reported to range from 0.5% to 30% depending on the EBV status and the transplanted organs[62,63].

There are also several reports on chronic hepatitis by EBV infection in immunocompetent adults, which might be caused by the reactivation of EBV and increased viral-specific CTL responses[64,65]. The criteria for establishing this diagnosis have been proposed by Drebber *et al*[66]: namely, the presence of suggestive histopathological features, a specific serological profile, and detection of EBV genome in the liver tissue. When chronic hepatitis with unknown etiology is diagnosed, EBV infection could be the cause.

Human cytomegalovirus

Human cytomegalovirus (CMV) infection is commonly subclinical in immunocompetent adults, but it sometimes can cause a disease such as infectious mononucleosis or hepatic injury[67]. Liver dysfunction associated with CMV infection usually presents with mild to moderate elevation of serum aminotransferases and ALP, but jaundice is not common. CMV hepatitis rarely includes granulomatous hepatitis, cholestatic hepatitis, or acute hepatic failure with massive necrosis.

Watanabe *et al*[68] retrospectively analyzed the clinical features and laboratory data of patients with CMV hepatitis compared with EBV hepatitis. Although common signs and symptoms were similar, epigastralgia was more common in CMV hepatitis than EBV hepatitis ($P < 0.05$), and cervical lymphadenopathy was more frequently observed in EBV hepatitis than CMV hepatitis ($P < 0.01$). Also, the ratio of peripheral blood monocytes in the white blood cells was greater in CMV hepatitis ($P < 0.01$). On the other hand, CMV is one of the most important opportunistic pathogens and can cause severe pulmonary, retinal, gastrointestinal, and hepatic disease in im-

munocompromised hosts. About 10% of recipients of liver transplantation suffer from hepatitis associated with CMV, and the hepatitis may be caused by reactivation rather than primary infection[69].

The typical histological finding of CMV hepatitis is thought to be vital inclusion bodies in hepatocytes in recipients after liver transplantation, but this is not absolute. Microabscesses, lymphocytic infiltration, and parenchymal alterations are also common.

Other human herpes viruses

Other human herpes viruses besides EBV or CMV, including herpes simplex virus-1 and -2 (HSV-1, HSV-2), Varicella-Zoster virus (VZV), and human herpesvirus-6, -7 and -8 (HHV-6, -7, and -8), can occasionally cause liver injury[70]. Although HSV hepatitis is uncommon in immunocompetent patients, mild elevations of aminotransferases can be observed in 14% of patients with acute HSV infection. Severe hepatitis associated with HSV was reported in neonatal infection, pregnancy, and immunocompromised hosts. Rakela *et al*[71] reported that 6% of fulminant hepatitis cases at the Mayo Clinic were associated with HSV infection.

In primary infection by VZV, a typical manifestation is generalized exanthematous rash, which is known as varicella, and mild elevations of aminotransferases can be observed in up to 25% of children with varicella. After organ transplantations, the primary infection and reactivation of varicella can occasionally cause severe hepatitis including fatal fulminant hepatitis[72].

HHV-6 infection, known as Sixth Disease, typically occurs in infants under the age of 2. Härmä *et al*[73] reported HHV-6 was found in 80% of patients with acute liver failure (ALF) of unknown cause, which suggests that HHV-6 might be one of the causes of ALF. Reactivation of HHV-6 is also known to relate to the pathogenesis of drug-induced hypersensitivity syndrome (DIHS), which is characterized by fever, rash, lymphadenopathy, hepatitis, and leukocytosis with eosinophilia after administration of specific drugs. Shiohara *et al*[74] reported that an altered immune response, including changes of functional regulatory T cells, may influence the pathogenesis of DIHS. There are a few reports of hepatitis associated with HHV-7 infection[75]. Liver involvement of HHV-8 may occur in patients with HIV infection.

Other viruses

Parvovirus B19 infection commonly causes the erythema infectiosum in children, and causes liver dysfunction and hematologic disorder in adults. There are several case reports of parvovirus B19-infected patients with fulminant hepatitis and aplastic anemia[76].

It is well known that rubella infection during pregnancy may cause hepatocellular injury in the newborn as a part of the congenital rubella syndrome. Acquired rubella infection also may cause acute hepatitis with mild elevation of aminotransferases in adults[77,78]. In these cases, the most characteristic finding of the laboratory data is a marked increase of LDH level, whereas cholestasis is rarely observed. It has been reported that the increase of LDH consisted of both LDH isozyme-3 derived from lymphocytes/platelets and LDH isozyme-5 derived from the liver[79,80]. The reported hepatic histological findings were compatible with acute hepatitis, including the ballooning of hepatocytes, spotty necrosis, and infiltration of inflammatory cells[79,80].

Hepatic involvement in measles has also been reported[81], with the prevalence of hepatitis in measles patients ranging from 71% to 89%[82-85]. Therefore, hepatitis should be considered as a common finding in patients with measles. Although the liver enzymes are elevated to more than 5 times ULN in 22% of patients with measles, clinical jaundice is rare[86]. It should be noted that rubella or measles could be a cause of liver dysfunction in patients with skin rash or fever, which may be misdiagnosed as drug-induced liver injury under medication.

Moreover, adenovirus commonly causes acute infections of the respiratory system and gastrointestinal tracts, and a few cases of ALF associated with adenovirus have been reported[87].

The mechanism of liver injury associated with non-hepatitis viral infection

Although the mechanism of liver injury caused by non-hepatitis viral infection remains unclear, several factors may be concerned. Hepatocellular injury may be caused by both host immune responses with activated $CD8^+$ T cells and direct viral cytopathy. On the other hand, pro-inflammatory cytokines induced by virus infection may influence the function of sinusoidal and canalicular transporting systems, which may lead to cholestasis[88,89].

EBV-infected T or NK cells could cause chronic active EBV infection (CAEBV) in some cases; therefore, the possibility exists that EBV-infected T cells affect the pathogenesis of hepatitis.

An animal model study showed that activated $CD8^+$ T cells are recruited to and trapped in the liver through interaction with intracellular adhesion molecule 1, which is expressed on sinusoidal endothelial cells and Kupffer cells[90]. A number of experiments have shown that soluble factors of the immune responses, especially interferon-γ, the Fas ligand and TNF-α, induce hepatitis[91-93].

FUNGAL INFECTION

Deep fungal infections can usually occur in immunocompromised hosts, including patients with HIV infection, neutropenia after chemotherapy, and organ-transplanted recipients. The liver is often involved in deep fungal infections, together with other organs.

Hepatosplenic candidiasis

Hepatosplenic candidiasis may be caused by *Candida* species, including *C. albicans* and *C. tropicans*, through candidemia or the portal vasculature from the gut with degenerated barriers of gastrointestinal mucosa[94]. Dis-

Table 5 Parasitic infection of the liver

Disease (organism)	Organs/status	Clinical presentation
Malaria	Pre-erythrocytic phase	Asymptomatic
(*P. falciparum, malariae, vivax, ovale*)	Erythrocytic phase	Anemia, jaundice, mild elevation of aminotransferases, tender hepatomegaly, splenomegaly
Amebiasis	Intestine	Right upper quadrant pain, fever,
(*Entameba histolytica*)	Amebic liver abscess	hepatomegaly (50%), jaundice (< 10%)
Cystic echinococcosis	Single cyst (> 70%), < 10 cm	Asymptomatic
(*Echinococcus granulosus*)	and no complication	
	Size up (1-5 cm/year), > 10 cm	Abdominal pain, mass effect (possible)
	Rupture	Peritonitis, hypersensitivity reactions
Alveolar echinococcus		Malaise, tender hepatomegaly, eosinophilia,
(*E. multilocularis*)		obstructive jaundice, portal hypertension
Schitosomiasis	Acute phase	Eosinophilic infiltrate
(*S. mansoni, japonicum*)	Chronic phase	Presinusoidal portal hypertension, splenomegaly, gastroesophageal varices
Fascioliasis (*F. hepatica*)	Acute phase	Abdominal pain, fever, hemobilia, hepatomegaly
	Chronic phase	Biliary colic, cholangitis, cholelithiasis, obstructive jaundice
Ascariasis (*A.lumbricoides*)		Abdominal pain, fever, obstructive jaundice

seminated candidemia is usually seen among patients with hepatologic malignancies with prolonged severe neutropenia. The incidence of hepatosplenic candidiasis has been reported to be 3% to 7% in these high-risk patients, but it may have decreased recently due to the use of antifungal prophylaxis.

The clinical presentation of hepatosplenic candidiasis consists of persistent fever with spikes and right upper quadrant discomfort, nausea, and anorexia. Laboratory testing commonly shows elevated serum concentrations of ALP and γ-GTP, associated with small liver abscesses or granulomas[95]. Multiple hypoechoic lesions and non-enhanced low-attenuation lesions can be detected by ultrasound and CT scan, respectively[96].

Other fungal infections

Liver involvement in other fungal infections, including disseminated aspergillosis, cryptococcosis, mucormycosis, trichosporonosis, and histoplasma capsulanum occurs on rare occasion in immunocompromised hosts[97]. The incidence of liver involvement with other fungal infections is very low, because these are acquired exogenously. Park[97] reported that up to 90% of these patients could have liver involvement in spite of the very low incidence of disseminated histoplasmosis. Hepatic histological findings could be variable, including granulomatous changes and sinusoidal Kupffer cell hyperplasia.

LIVER INVOLVEMENT OF PARASITIC DISEASES

Parasitic liver involvement is common in highly endemic areas, and it should be considered in an individual who has visited such areas. Parasitic involvement is dominated by *Plasmodium spp.*, but *Entamoeba histolytica*, *Schistosoma spp.* and *Echinococcus spp.* infections are also important in clinical practice[98]. Hepatobiliary involvement is also caused by *Ascaris lumbricoides*, *Fasciola hepatica* and *Liver flukes* (Table 5).

Malaria

Malaria is one of the most important public health problems worldwide, as an estimated 300 to 500 million persons suffer from malaria annually. The malarial life cycle consists of the pre-eythrocytic and the erythrocytic phases. Usually malarial schizogony takes place in the liver without obvious liver injury in the pre-erythrocytic phase. In the erythrocytic phase, symptoms such as cyclical fever, malaise, nausea, vomiting, diarrhea, tender hepatomegaly and splenomegaly develop[99]. Jaundice associated with hemolysis can be observed in severe malarial infection, and hepatic failure can occasionally be seen in patients with severe *P. falciparum* infection[100]. Jaundice in malaria consists of both unconjugated and conjugated bilirubin, which could be caused by intravascular hemolysis of parasitized red blood cells, and hepatocellular dysfunction. Hepatic histological findings may show Kupffer cell hyperplasia with pigment deposition, hepatocyte necrosis, and cholestasis.

Schistosomiasis

Schistosomiasis is caused by trematodes of the genus Schistosoma, including *S. mansoni and S. japonicum*. Mesenteric infection may cause deposition of the eggs in the liver, which may lead to presinusoidal occlusion and periportal fibrosis associated with granulomatous response[101]. Chronic hepatic schistosomiasis presents with portal hypertension with splenomegaly and gastroesophageal varices. Laboratory test abnormalities include eosinophilia and increased serum IgE levels. Because hepatic schistosomiasis is one of the most common causes of noncirrhotic portal hypertension, it should be considered in differential diagnosis for that symptom.

Amebiasis

Amebiasis is caused by the *Entamoeba histolytica*, and about 40 to 50 million persons are infected annually. Amebiasis includes amebic dysentery and extraintestinal disease such as amebic liver abscess. Patients with amebic liver abscess

usually present with RUQ pain and fever. Although hepatomegaly can be seen in about 50% of cases, jaundice can be seen in less than 10%[102]. In the liver, *E. histolytica* lyses host's tissue and infiltrating neutrophils with its proteolytic enzymes[103]. Amebic liver abscess grows inexorably, and the retardation of making diagnosis leads to perforation in about 2% to 7% of these patients[104-106] with the mortality rate being 23% to 42% in the perforated patients[105,107]. Therefore, prompt diagnosis and treatment are very important for successful treatment in patients with hepatic amebiasis[108].

Hydatid disease

Hydatid disease is caused by infection with the metacestode stage of the tapeworm *Echinococcus*. Liver involvement may occur in about two-third of patients with *Echinococcus granulosu* infection, and commonly can form single cyst. Although a patient has no symptom when the cyst is small (< 10 cm in diameter) and without complication, intra-peritoneal rupture may be frequent and cause abdominal pain. Rupture into the biliary tract may cause biliary colic, obstructive jaundice, or cholangitis.

Echinococcus multilocularis can cause alveolar echinococcus, which commonly presents obvious complaints such as tender hepatomegaly, malaise, and weight loss. Because *E. multilocularis* can invade the biliary tract, hepatic vein, inferior vena cava, and/or diaphragm, a high mortality rate has been reported in untreated patients[109].

Liver flukes (Fascioliasis)

Fascioliasis is a trematode infection caused by *Fasciola hepatica* or *Fasciola gigantic*. Fascioliasis commonly consists of two phases, the acute/invasive and chronic obstructive phase. In the acute phase, symptoms usually include fever, RUQ pain, hepatomegaly and eosinophilia. The chronic phase usually begins about six months after infection and is characterized by bile duct obstruction associated with bile duct inflammation and hyperplasia due to the presence of adult flukes. Clinical presentations include recurrent biliary colic, cholangitis, cholelithiasis, and obstructive jaundice[110].

Ascariasis

Ascaris lumbricoides is an intestinal nematode, and arrives in the liver through the bile duct by a retrograde manner. Migration of adult worms into the biliary tree can cause biliary colic, cholecystitis, cholangitis, obstructive jaundice, and secondary liver abscess[111].

CONCLUSION

The liver is exposed to many systemic infectious pathogens including not only hepatotropic but also non-hepatotropic microorganisms through both the systemic and portal circulation. These pathogens may directly or indirectly cause liver injury presenting with various manifestations described in this review, but the mechanisms of these liver injuries have not been completely clarified. When making correct diagnosis of liver dysfunction in systemic infections, knowledge about non-hepatotropic pathogens and appropriate microbiological examinations are very important.

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