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CLINICAL REVIEW

Management of hepatitis B virus-related acute liver failure

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Abstract Hepatitis B virus (HBV) is the most important cause of acute liver failure (ALF) in Eastern countries. HBV-related ALF may occur after acute HBV infection (A-ALF) or during acute exacerbation (flare) of chronic HBV infection (C-ALF). C-ALF may occur spontaneously or as a result of the effect of immunosuppression due to chemotherapeutic or immunosuppressive agents. The definition of HBV-related ALF is uncertain, because different diagnostic criteria are used in C-ALF, which may present as acute-on-chronic liver failure. Although the pathogenesis differs in the two subgroups of ALF, the symptoms and biochemical parameters can be similar. High titers of immunoglobulin M hepatitis B core antibody and lower viral loads are frequent in A-ALF as compared with C-ALF. The prognosis of C-ALF is significantly poor as compared with that of A-ALF. In C-ALF, most immunosuppression-mediated reactivation of hepatitis B results in fatality. Many case series or case-control studies have not demonstrated the survival benefit of nucleos(t)ide treatment. This treatment failure is probably related to delayed initiation of nucleos(t)ide treatment and viral suppression. Treatment with nucleos(t)ide analogs should be started immediately and should be continued regardless of subgroups of HBV-related ALF. Liver transplantation is the only treatment option that improves the prognosis of HBV-related ALF. Patients under consideration for transplantation should be given nucleos(t)ide analogs as prophylaxis to reduce the likelihood of post-transplant HBV recurrence.

Keywords Acute liver failure · Fulminant hepatitis · Hepatitis B virus reactivation · Antiviral drugs · Liver transplantation

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Introduction

Hepatitis B virus (HBV) is the most important cause of acute liver failure (ALF) in Eastern countries [1–3]. HBV-related ALF may occur after acute HBV infection (A-ALF) or during an acute exacerbation (flare) of chronic HBV infection (C-ALF). Differentiation between these clinical entities is sometimes difficult without historical or histological evidence of chronicity. C-ALF may occur spontaneously or as a result of the effect of immunosuppression due to chemotherapeutic or immunosuppressive agents.

Recently, as a result of strict testing for HBV and universal precautions including vaccination, chronicity rates have been decreasing in patients with acute HBV infection. In contrast, with the increasing use of potent immunosuppressive therapy, immunosuppression-mediated reactivation of hepatitis B in endemic regions is becoming a clinical problem [4]. A recent annual nationwide survey in Japan clarified that ALF due to immunosuppression-mediated reactivation has been increasing in patients with malignant lymphoma and other hematological malignancies [2]. Furthermore, rituximab plus steroid-containing

chemotherapy was identified as a risk factor for reactivation in hepatitis B surface antigen (HBsAg)-negative patients with malignant lymphoma.

The immunopathogenesis and clinical characteristics differ between A-ALF and C-ALF and clinicians need to manage HBV-related ALF by taking this dissimilarity into account. Here, we summarize the clinical management of two subgroups of HBV-related ALF.

Definition

The definition of HBV-related ALF is uncertain because different diagnostic criteria are used and patients with C-ALF might be included. The definition accepted by the American Association for the Study of Liver Disease (AASLD) position paper stated that patients with Wilson's disease, vertically acquired HBV infection, or autoimmune hepatitis may be included if their disease has only been recognized for <26 weeks [5]. However, it is not clearly defined for chronic HBV infection. Chronic HBV infection can generally be divided into four distinct phases—immune tolerance phase (asymptomatic carrier), immune active phase (active hepatitis), low-replication phase (inactive carrier) and resolved phase (past infection). When HBV-related chronic liver diseases have been recognized before the onset of ALF, the disease entity of acute-on-chronic liver failure (ACLF) may be appropriate [6]. The problem is that the diagnostic criteria of ACLF are different in individual regions [7]. Diagnostic criteria for ALF in Japan state that HBV carriers and autoimmune hepatitis patients showing acute exacerbation of hepatitis in the normal liver are included under the disease entity of ALF [8]. In the case of indeterminate previous liver function, the patients who are HBV carriers and those with autoimmune hepatitis are diagnosed as having ALF with no liver function impairment. This means that chronic liver diseases (chronic hepatitis or cirrhosis) are excluded.

It is important that HBV-related ALF can develop in any distinct phase of chronic HBV infection, as a result of acute exacerbation of chronic hepatitis, or spontaneous or immunosuppression-mediated reactivation (Fig. 1). However, concerning the diagnosis there are many complicated issues not yet determined. The symptoms and biochemical parameters in A-ALF and C-ALF can be similar [9]. Diagnosis of chronic HBV infection is difficult when the past status of hepatitis B markers or the past history of hepatitis is unknown. A possibility exists that a proportion of patients with suspected acute hepatitis B might actually be suffering from chronic hepatitis B and manifesting clinically for the first time an episode of reactivation. Furthermore, not only patients with active hepatitis, but some patients with inactive carrier status or past infection also show histological cirrhosis. Clinical, laboratory, and radiological findings cannot reliably predict the presence of underlying liver cirrhosis in patients with HBV-related ALF.

Pathogenesis

Upon exposure to HBV, individuals with a vigorous immune response to the virus develop an acute self-limited

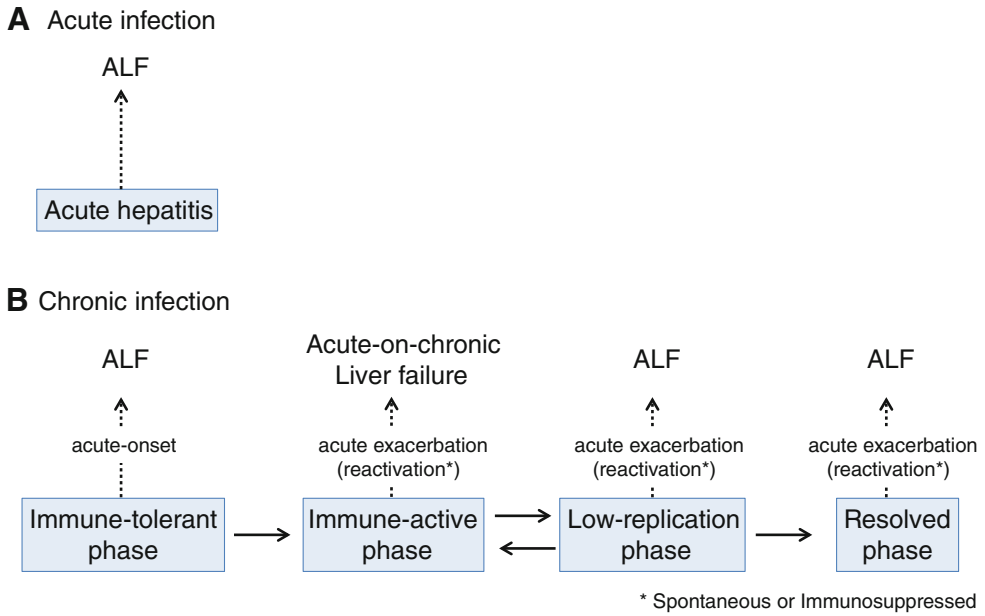

Fig. 1 Two subgroups of HBV-related acute liver failure

infection, which may result in acute hepatitis. Fulminant hepatitis (i.e., ALF) is a severe form of acute hepatitis B infection. In the early phase of infection, HBV does not stimulate the innate immune system, which recognizes pathogen-associated molecular patterns [10]. In contrast to these observations, recent in vitro studies have indicated that the innate immune response of hepatocytes may sense the infection and inhibit the spread of HBV [11]. In the later phase of infection, an adaptive cellular immune response is induced. A T cell-dependent noncytolytic mechanism and cytolytic immune response generate acute hepatitis. CD8 cytotoxic T lymphocytes attack the infected hepatocytes by recognizing epitopes of HBV proteins, especially hepatitis B core antigen (HBcAg), presented on the cell surface. CD8 T cells also have a noncytolytic effect through the production of interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α), which are known to elicit antiviral effects via multiple mechanisms. A vigorous immune response against HBV-infected hepatocytes usually leads to viral eradication. HBsAg antibody (anti-HBs) forms during convalescence, and at the later stage, can neutralize HBsAg and block serial infection of hepatocytes by released HBV. At the cost of liver damage, acute hepatitis results in viral clearance. Typically in A-ALF, HBV DNA and hepatitis B e antigen (HBeAg) become undetectable as liver failure supervenes.

Acute exacerbation of chronic HBV infection can also be manifested as a form of ALF. Rapid increase in HBV replication from a low-replicative state (i.e., HBV reactivation) is the main cause of this episode. Reactivation of chronic HBV infection can occur spontaneously. Increased T-cell responses against HBeAg and HBcAg occur in the early phase of acute flares and subside after recovery from acute exacerbation in HBsAg response [12]. T-cell responses do not diminish if the patient does not enter clinical remission and low-level responses to S gene products are noted throughout all phases of the flare. These indicate that HBcAg/HBeAg-specific T cells play an important role in acute exacerbation. Clinically, HBV DNA level is extraordinarily high in the hepatitis phase and tends to be continuous unless treated. Pathogenesis of immunosuppression-mediated reactivation is more complicated; it mostly depends on the immunosuppressive and immune restoration effects influenced by chemotherapy or immunosuppressive therapy [13]. The clinical presentation of the disease can vary, from a subclinical, asymptomatic course to severe acute hepatitis, ALF, fibrosing cholestatic hepatitis and even death [14].

Viral factors

Several studies have indicated that HBV genotypes may play a role in the outcome of acute infection. In a study by the US Acute Liver Failure Study Group, a higher prevalence of HBV genotype D persisted in patients with ALF compared with chronic HBV infection, even after matching for race and HBeAg status (32 vs 16 %, $p = 0.007$) [15]. In studies from Asia and the Middle East, precore (G1896A) and core promoter mutations (A1762T/G1764A) are frequent in patients with ALF [16, 17]. However, these mutations were not detected in the USA and Europe. A large cross-sectional study in Japan revealed an association between genotype Bj/B1, A1762T/G1764A, G1896A, G1899A and A2339G mutations and development of fulminant hepatitis [18]. The report revealed marked enhancement of viral replication by introducing either G1896A or core A1762T/G1764A mutation into the Bj clone in an in vitro transfection study. Recently, T1961V/C1962D, which led to S21 substitution in the core protein, was detected in fulminant hepatitis [19]. Surface gene mutations, which are pre-S2 defective or HBV defective in secretion, have been reported in patients with fulminant hepatitis. These mutants showed a feature of virus retention in hepatocytes and misassembly with high replication capacity [20–22].

Spontaneous reactivation of chronic HBV infection can occur in the immune-clearance phase, affecting 40–50 % of HBeAg-positive patients and in 15–30 % of HBeAg-negative patients [23, 24]. Genotype B was found to be predominant among patients with severe acute exacerbation compared with control patients [24–26]. HBV mutant strains, including mutations in precore, core promoter, and deletion in mutation in pre-S/S genes have been reported [27]. Mutations at the basal core promoter region are associated with decreased HBeAg synthesis and increased viral replication [28]. On the contrary, the risk of immunosuppression-mediated reactivation is mainly influenced by the underlying disease and the immunosuppressive or chemotherapeutic agent used [29, 30]. Virological factors responsive for ALF due to immunosuppression-mediated reactivation have not been determined. Genotype B and mutations in the precore and core promoter regions of the HBV genome are also frequent in reactivation in patients with past infection [31, 32]. Cytotoxic chemotherapy does not appear to put wild-type or mutant HBV under preferential selection pressure [33]. Intrahepatic covalently closed circular DNA, a key intermediate in HBV replication, has clinical significance in reactivation in patients with past infection [34].

Clinical features

Our study has shown that several clinical features differ between A-ALF and C-ALF (Table 1) [35]. The mean age of patients was significantly higher for the immunosuppression-mediated reactivation than for transient infection and acute exacerbation in inactive carriers. Days of onset

Table 1 Clinical characteristics of ALF patients with transient HBV infection compared with those with acute exacerbation in HBV carriers

		Acute exacerbation in HBV carrier	
	Transient infection ($n = 91$)	Nonimmunosuppressed ($n = 35$)	Reactivation immunosuppressed ($n = 37$)
Age (years)	46 (17–72)	53 (15–89)	64 (29–86)**††
Male/female	58/33	23/12	22/15
Disease types (F-A/F-SA/LOHF)	80/10/1	14/20/1**	4/27/6**††
O–C duration	6 (2–106)	18 (0–160)**	23 (6–160)**††
ALT (IU/L)	3,413 (20–10,168)	781 (28–6,500)**	344 (28–5,480)**
Total bilirubin (mg/dL)	8.4 (2.5–44.3)	12.7 (2.0–40.9)*	15.6 (3.3–35.8)**
Prothrombin time (%)	18.4 (3.1–58.6)	24.9 (2.2–58.1)**	29.8 (8.0–48.0)**
INR	3.8 (1.5–14.8)	2.7 (1.6–17.3)	2.5 (1.7–19.5)*
HBsAg negativity	13 (12/90)	0 (0/35)*	0 (0/37)*
IgM anti-HBc positivity	99 (90/91)	47 (15/32)**	31 (10/32)**
IgM anti-HBc (CLIA) >10	88 (45/51)	0 (0/9)**	13 (2/16)**
HBV DNA level (log copies/mL)	5.6 (2.8–8.6)	7.3 (4.1–8.8)	8.0 (5.3–9.1)**
Nucleos(t)ide analog use	92 (84/91)	94 (32/34)	97 (36/37)
Interferon use	31 (28/91)	31 (11/35)	30 (11/37)
Corticosteroid use	74 (67/91)	74 (26/35)	68 (25/37)
LT	16 (15/91)	29 (10/35)	5 (2/37)†
Spontaneous survival	53 (40/76)	28 (7/25)*	6 (2/35)**†
Overall short-term survival	58 (53/91)	40 (14/35)	8 (3/37)**††

Continuous data are shown as median (range) and categorical data are percentages (numerator/denominator)

Laboratory data are at the onset of hepatic encephalopathy of coma grade >II. HBV DNA levels are at the onset of hepatitis

The significant difference among groups was assessed by the Student's *t*-test, the Mann–Whitney *U* test and the chi-squared test

* Values significantly different from patients with transient infection; $p < 0.05$, ** $p < 0.01$

† Values significantly different from patients with nonimmunosuppressed carrier status; $p < 0.05$, †† $p < 0.01$

ALF acute liver failure, *ALT* alanine aminotransferase, *INR* international normalized ratio, *CLIA* chemiluminescent immunoassay, *HBV* hepatitis B virus, *F-A* acute type fulminant hepatitis, *F-SA* subacute type fulminant hepatitis, *LOHF* late-onset hepatic failure, *LT* liver transplantation, *O–C duration* days from onset of symptoms to onset of hepatic coma

of symptoms to onset of hepatic coma were significantly longer for acute exacerbation in HBV carriers than for those with transient infection. Patients with transient infection have higher alanine aminotransferase (ALT) levels, lower bilirubin levels, and higher international normalized ratio (INR) levels than acute exacerbation in HBV carriers. Spontaneous survival rate was significantly higher for transient infection patients than for those with acute exacerbation in HBV carriers. The prognosis of patients with immunosuppression-mediated reactivation was poor. Forty-six percent (17/37) of patients had reactivation of past HBV infection (i.e., de novo hepatitis B). Thirteen of these patients had received rituximab plus steroid-containing chemotherapy for malignant lymphoma. In this setting, HBV reactivation resulted in fatality. The possibility of liver transplantation for these patients is low because of the presence of underlying malignant diseases.

Diagnosis

The diagnosis of acute hepatitis B is based on the detection of HBsAg, immunoglobulin (Ig)M anti-HBc and HBV DNA. Quantification of IgM anti-HBc is necessary because ~30 % of ALF cases with severe acute exacerbation of chronic HBV infection have positive IgM. High IgM anti-HBc (>10 cut-off value by chemiluminescent immuno assay [CLIA]) suggests acute HBV infection [36]. Anti-HBc may also be useful to differentiate the two subgroups of ALF. Most patients with chronic HBV infection have high anti-HBc levels. Resolution of infection is accompanied by the disappearance of HBV DNA, HBeAg to anti-HBe seroconversion and then HBsAg to anti-HBs seroconversion. During the window period, patients present as HBsAg negative, but anti-HBs is not yet positive; this setting is common in patients with fulminant hepatitis B. A vigorous immune reaction against HBV reflects the

decrease in HBsAg concentrations and HBV DNA levels [37]. In contrast, reactivation of HBV is accompanied by high HBsAg and HBV DNA levels. Several studies have suggested that a low titer of IgM anti-HBc and high HBV DNA level is useful to identify C-ALF from A-ALF [9, 38].

Treatment

The efficacy of antiviral drugs against HBV-related ALF is not directly comparable among studies, because different diagnostic criteria of ALF were used. As acute hepatitis is a self-limiting disease, antiviral therapy is not indicated in most patients with acute hepatitis B. Patients with fulminant and severe acute hepatitis B are indicated for antiviral therapy. One retrospective uncontrolled study reported that lamivudine improved patient survival from 20 % in historic controls to 82.4 % in patients with severe acute or fulminant hepatitis B, which was defined as an INR >2.0 [39]. Similar to this report, good survival rates in patients receiving lamivudine have been reported by others [40–42].

In severe reactivation of chronic HBV infection, immune activity is already excessive and accompanied with a high level of HBV replication. Thus, oral nucleos(t)ide analogs should be the treatment option. However, many case series or case–control studies for patients with severe reactivation of chronic hepatitis B have not demonstrated the survival benefit of lamivudine treatment [43–45]. This treatment failure was probably related to the delayed beginning of lamivudine and viral suppression. In a group of consecutive chronic hepatitis B patients with severe reactivation treated with lamivudine, lamivudine treatment definitely improved survival compared with historic controls who did not receive lamivudine [46]. However, this effect was observed only in patients with low (<20 mg/dL) baseline serum levels. In a matched retrospective cohort study of patients with fulminant hepatitis, lamivudine therapy improved the mortality rates (63.2 % in the lamivudine group vs 84.6 % in the control group, $p = 0.029$) [42]. However, this benefit was not observed in patients with advanced stages of disease course accompanied with systemic inflammatory response. These studies suggest that the beneficial effect of lamivudine on short-term survival depends on the timing of treatment. Several studies have compared the efficacy of nucleos(t)ide analogs in A-ALF and C-ALF [38, 47]. In these studies nucleos(t)ide analogs did not show a survival benefit in any subgroups of HBV-related ALF. One study reported that duration of nucleos(t)ide treatment was only 6 days (range 1–21 days) [47]. Oral nucleos(t)ide analogs require a certain amount of time to decrease serum HBV DNA level. The lack of beneficial effect of nucleos(t)ide analogs for HBV-related ALF was perhaps because of rapid disease progression and short-term duration of therapy.

In chronic hepatitis, entecavir and tenofovir are more recommendable than lamivudine because of their high potency and low rates of drug resistance [48]. Several studies revealed that entecavir also has a beneficial effect on the course of ALF similar to lamivudine [49–51]. Despite the use of entecavir, the prognosis of HBV-related ALF has not significantly improved when compared with that of lamivudine [51]. One study reported that entecavir was associated with increased short-term mortality compared with lamivudine, perhaps due to lactic acidosis [52]. A randomized trial revealed improved 3-month survival with tenofovir (57 %) compared with placebo (15 %) in patients with ACLF [53]. There is concern about which nucleos(t)ide analogs are favorable for HBV-related ALF. The major drawback of lamivudine is the development of resistance caused by mutations in the region of the reverse transcriptase gene. The most common mutations are located in the domain of C of HBV polymerase at the tyrosine–methionine–aspartate–asparate (YMDD) motif. Patients who develop lamivudine resistance always show a rebound in the HBV DNA load and rapid elevation of ALT. ALF has been described in association with emergence of YMDD mutations [54]. In one study, 34 patients with reactivation of chronic hepatitis B were consecutively treated with lamivudine or entecavir and all patients in both groups survived; however, 12 months after treatment, 42 % of 24 lamivudine patients developed lamivudine-resistant mutations [55]. On the contrary, it might be that lamivudine exhibits an immediate response benefit in patients with severe acute hepatitis B [39]. In that study, lamivudine improved prothrombin time after only 1 day, whereas 11/14 patients who did not require liver transplantation showed normalization of prothrombin time from <40 % within 1 week of lamivudine therapy. Thus, in severe acute hepatitis, the use of lamivudine may be logical because it has the advantage of rapid response, whereas the possibility of the emergence of YMDD mutants is low. However, in C-ALF, entecavir is recommended because the high viral load and long duration of nucleos(t)ide analog therapy have a high risk of causing emergence of drug resistance. In the case of immunosuppression-mediated reactivation, it is difficult to prevent development of liver failure, even when nucleos(t)ide analogs are administered after the onset of hepatitis. Most of the guidelines for preventing HBV reactivation recommend the administration of nucleoside analogs before the start of immunosuppressive therapy in inactive carriers, and at an early stage of reactivation during or after immunosuppressive therapy in patients with past infection [35, 56, 57].

IFN has been used for treating chronic hepatitis B since the 1980s; however, early studies of fulminant hepatitis B

and acute hepatitis B failed to demonstrate any significant benefit [58, 59]. Several studies stated that IFN was beneficial in patients with acute hepatitis [60, 61]. However, in severe reactivation of chronic hepatitis B when immune activity is already excessive, IFN-based treatment may aggravate the hepatic decompensation. Thus, IFN-based treatment for ALF is limited to specific conditions and at a low dose. Corticosteroids have been used mainly in patients with ACLF [62]. The efficacy of corticosteroids for HBV-related ALF has not been fully evaluated. Patients treated with high-dose corticosteroids show slightly higher survival rates and slightly more improved liver regeneration than controls do [63]. A recent study has reported that intravenous dexamethasone with continuous lamivudine improves the prognosis of ACLF [64]. In contrast, another study found that dexamethasone did not improve liver function and 12-week survival rates of patients with HBV-related ACLF [65].

The definitive treatment for HBV-related ALF is liver transplantation. Short- and long-term outcomes of living donor transplantation for ALF are good, irrespective of the etiology and disease types [66]. In a retrospective analysis, the 5-year survival rates exceeded 90 % in 149 patients with ACLF including 50 with severe exacerbation of chronic hepatitis B [67]. Although most studies have not revealed a significant survival benefit with nucleos(t)ide analog treatment, practice guidelines on treatment of HBV infection recommend nucleos(t)ide analogs for patients with HBV-related ALF [56, 68]. These patients are thought to be candidates for liver transplantation. After liver transplantation, long-term immunosuppressive therapy is necessary. Nucleos(t)ide analogs have also proven useful in preventing reactivation of HBV and decreasing HBV-related morbidity and mortality in patients with chronic HBV who are undergoing immunosuppressive therapy. Patients under consideration for transplantation should be given nucleos(t)ide analogs as prophylaxis to reduce the likelihood of post-transplant HBV recurrence [47, 69].

Conclusions

The presentation of C-ALF is common and is often difficult to differentiate clinically from A-ALF. The negativity of HBsAg and the high titer of IgM anti-HBc can differentiate A-ALF from C-ALF. The prognosis of C-ALF is poor, especially in patients with immunosuppression-mediated reactivation. Treatment with nucleos(t)ide analogs should be started immediately and continued regardless of subgroups of HBV-related ALF. Liver transplantation is the only treatment option that improves the prognosis of HBV-related ALF. Treatment with nucleos(t)ide analogs is indicated for patients who are listed to undergo liver transplantation for preventing post-transplant HBV recurrence.

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Disclosures

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Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5).

Informed Consent: This epidemiologic study does not apply to giving Informed Consent. The study was conducted with the approval of the ethical committee of Kagoshima University of Graduate School of Medical Dental Sciences.

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