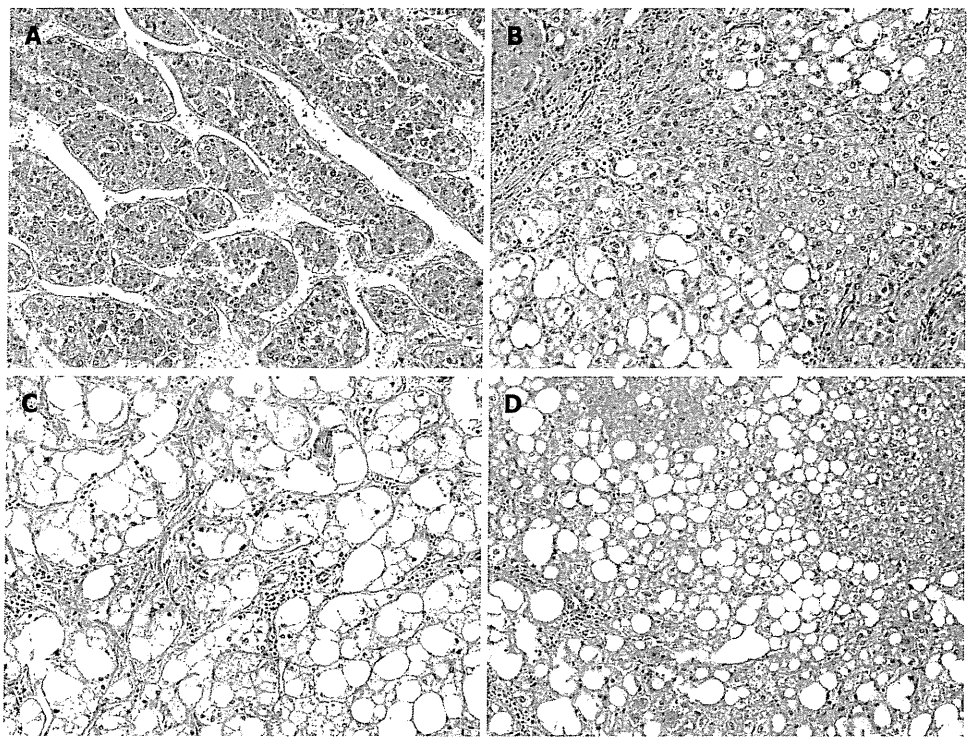

Figure 1 Histological examination of resected specimen in Case 1 showing four liver tumors of multicentric origin (HE stain, × 200). A: A moderately differentiated hepatocellular carcinoma (HCC); B: A well-differentiated HCC; C: A well-differentiated HCC; D: A dysplastic nodule.

Case 1

A 73 year old female had been diagnosed with hypertension at age 40 and T2DM at age 70. After the diagnoses, she was treated with an angiotensin II receptor blocker and an oral anti-hyperglycemic agent at our affiliated hospital. A liver tumor measuring 35 mm in diameter in segment 6 was found with a nodule-in-nodule appearance on a surveillance dynamic CT in January 2003. The finding was consistently shown on dynamic MR imaging, CTAP and CTHA. Near the tumor, another nodule 8 mm in diameter was depicted as a hyperechoic nodule on ultrasonography (US) and as a perfusion defect on CTAP without early enhancement on CTHA. A well-differentiated HCC or a dysplastic nodule was suspected. The patient was referred to our hospital and underwent surgical resection of segment 6. During the operation, multiple hyperechoic nodules measuring less than 10 mm in diameter in addition to the main tumor were detected in segment 6 and segment 8 by intraoperative US which led to an additional resection of segment 8. The largest tumor in segment 6 was histologically diagnosed with a moderately differentiated HCC (Figure 1A). In addition, two well-differentiated HCCs and one dysplastic nodule were observed among the other small nodules (Figure 1B, C and D). All of these tumors were considered to occur in a multicentric manner.

In October 2008, recurrence of HCC was found in segment 8 on dynamic CT with early enhancement and the patient underwent transcatheter arterial chemoembolization. In March 2009, one and two nodules were detected in segments 8 and 3, respectively, as hypovascular tumors measuring less than 15 mm in diameter on dyna mic MR imaging that were suspicious for well-differentiated HCCs or dysplastic nodules. The tumors subsequently increased in diameter and were compatible with well-differentiated HCCs on imaging studies which suggested metachronous MO. The patient was treated with percutaneous ablation therapy and has had no recurrence of HCC after the therapy.

Case 2

An 81 year old male had been diagnosed with hypertension at age 40 and T2DM at age 75. After the diagnoses, he was treated with a calcium channel blocker and an oral anti-hyperglycemic agent. When he was admitted to the Division of Dermatology at our hospital for the treatment of psoriasis vulgaris, dynamic CT and MR imaging depicted multiple tumors in the bilateral lobes of the liver. The classical pattern of contrast enhancement that indicated advanced HCCs was observed in those tumors with the exception of a nodule measuring 10 mm in diameter in segment 3. This distinct nodule was recognized as hypoattenuation in the arterial and equilibrium phases on dynamic CT. Dynamic MR imaging demonstrated hypointensity only in the equilibrium phase but isointensity in the arterial phase and other sequences. The nodule was also shown as isoattenuation on CTAP and CTHA. We regarded this nodule as an equivocal lesion and decided to follow it closely. The combination therapy with transcatheter arterial infusion chemotherapy and percutaneous radiofrequency ablation was repeated four times for the advanced HCCs. Approximately 1 year later, the follow-up study with dynamic MR imaging showed an altered appearance of the nodule in segment 3; it was hypointense in the arterial and equilibrium phases and on T1- and T2-weighed images (WIs) and was slightly

enlarged, 18 mm in diameter. This nodule was finally diagnosed with a well-differentiated HCC by tumor biopsy and the surrounding nontumorous parenchyma was histologically defined as cirrhosis derived from NASH. Thus, the development of this well-differentiated HCC was considered MO and the tumor was treated with local ablation therapy. Afterward, multiple HCCs recurred *via* intrahepatic metastases and transcatheter arterial chemoembolization therapies were repeated. Unfortunately, the patient died of hepatic failure with marked extension of HCCs at age 86.

Case 3

A 78 year old male was referred to our hospital for further workup and treatment of liver tumors detected on CT. Abnormal liver function tests had been found for 8 years. The patient had a 2 year history of treatment for hypertension and T2DM with oral drugs. Two tumors, 40 mm in diameter in the posterior segment and 20 mm in diameter in segment 8, respectively, were discovered on US, performed as part of the regular screening. Other imaging studies, including dynamic CT, MR imaging, CTAP and CTHA, indicated advanced HCCs. Other than those tumors, a nodule measuring 8 mm in diameter with different characteristics was detected in segment 5. The nodule was slightly hypointense in the arterial and equilibrium phases and isointense on T1- and T2-WIs of dynamic MR imaging. It was exhibited as isoattenuation on CTAP and hypoattenuation in both phases of CTHA. On the basis of these results, the tumor was suspicious for a well-differentiated HCC or a dysplastic nodule. The patient underwent surgical resection of the right hepatic lobe. The histological examination revealed cirrhosis of a nontumorous liver caused by NASH. The advanced tumors in the posterior segment and segment 8 were diagnosed with moderately differentiated HCCs and the distinct nodule in segment 5 was confirmed as a well-differentiated HCC which implied MO. After the surgery, the patient suffered from pneumonia, renal insufficiency and subsequent hepatic failure and he finally died of multiple organ failure approximately 2 mo later.

Case 4

A 71 year old female had received medical treatment for hypertension, dyslipidemia and T2DM at a clinic 7 years prior to presentation. At age 66, abnormal liver function tests were revealed on a routine examination and the patient was diagnosed with cryptogenic cirrhosis by liver biopsy at another hospital. Multiple liver tumors were detected on periodic US and the patient was referred to our hospital for further management. The definitive diagnosis of NASH was made as the cause of cirrhosis by a pathologist at our hospital with reevaluation of the previously obtained liver specimen. Two tumors in segment 8 and one tumor in segment 3, both less than 30 mm in diameter, were demonstrated as advanced HCCs on dynamic CT, MR imaging and CTHA. CTAP was not informative because of insufficient portal perfusion due to hepatofugal portal flow through a gastrorenal shunt. Meanwhile, a nodule in segment 1 with a diameter of 28 mm was shown as a nodule-in-nodule appearance on dynamic MR imaging. Therefore, this tumor was considered multicentric in origin. The patient was treated with transcatheter arterial chemoembolization and/or percutaneous ablation therapy. Furthermore, 18 mo after the treatment, another well-differentiated histologically confirmed HCC emerged in segment 7 and was treated with RFA. Thereafter, the patient remains alive without recurrence of HCC.

DISCUSSION

HCC occurs frequently through multicentric carcinogenesis in chronic liver diseases caused by HBV or HCV infection. In the present study, we found the prevalent occurrence of HCC with multicentric manner in patients with NASH as well. According to the previous studies based on pathological examinations, frequencies of synchronous MO in patients with HBV- or HCV-related HCC were 3.7%-16.5% and 11.9%-34.1%, respectively[10-12]. As for metachronous MO, it was reported that the 1 year, 3 year and 5 year MO rates were also as high as 5.3%, 28.9% and 50.8%, respectively, in HCC patients, most of whom were associated with HCV infection[9]. HCV infection that causes persistent active inflammation in the liver is believed to be one of the most important factors for MO of HCC[8-13]. Contrary to the abundant clinical data on MO in HBV- and HCV-related HCC, there is no epidemiological study addressing MO in NASH-related HCC. However, informative observations were reported by Oikawa *et al*[12]. They evaluated the liver specimens surgically obtained from 94 cases with nonB-nonC HCC and detected synchronous MO of HCC in 12 cases (12.8%). They speculated that these cases might have occult HBV infection or other undefined hepatitis virus infection. Although the etiology of the underlying chronic liver disease in this group could not be further estimated because of the lack of clinical profiles and histological findings of noncancerous liver tissues, it is not difficult to suppose a causal attribution to NASH in some cases. In addition, Tokushige *et al*[20] revealed a high recurrence rate of HCC with NASH after two years or more of curative treatment. Those recurrent tumors in the later follow-up years were found in 9 of 16 patients (56.3%) and some of them were presumed to be of multicentric origin. Therefore, even in our cases without synchronous MO of HCC, it is possible that HCC may develop metachronously in the future. MO may be a frequent manner of HCC development in NASH as well and it is crucial to clarify the exact prevalence of MO with further studies.

Clinical features of patients with MO of HCC related to NASH are also quite obscure. There are only two case reports that have documented MO of HCC in NASH with histological proof. Zen *et al*[6] reported a 72 year old female with HCC arising multicentrically from cirrhotic NASH. The patient was diagnosed with T2DM. Three tumors developed synchronously and metachronously and were histologically defined as a moderately differentiated HCC, a well-differentiated HCC and a

Table 2 Clinical characteristics of patients with nonalcoholic steatohepatitis-related hepatocellular carcinoma with multicentric occurrence in previous and present reports

Author	Cases	Age older than 70 yr	Gender		Metabolic diseases				Histological features	
			M	F	OB	DM	DL	HT	LC	Non-LC
Zen *et al*[6]	1	1	0	1	0	1	0	0	1	0
Sasaki *et al*[7]	1	1	0	1	1	1	0	0	1	0
Present authors	4	4	2	2	4	4	1	4	4	0
Total	6	6	2	4	5	6	1	4	6	0
(%)	-	(100)	(33.3)	(66.7)	(83.3)	(100)	(16.7)	(66.7)	(100)	(0)

M: male; F: female; OB: obesity; DM: type 2 diabetes mellitus; DL: dyslipidemia; HT: hypertension; LC: liver cirrhosis; Non-LC: non-liver cirrhosis. All values represent number of cases.

Table 3 Clinical characteristics of patients with solitary hepatocellular carcinoma related to nonalcoholic steatohepatitis in previous and present reports

Author	Cases	Age older than 70 yr	Gender		Metabolic diseases				Histological features	
			M	F	OB	DM	DL	HT	LC	Non-LC
Cotrim *et al*[21]	1	0	1	0	1	1	0	0	1	0
Orikasa *et al*[22]	1	0	0	1	0	1	0	0	1	0
Shimada *et al*[23]	4	1	2	2	3	2	1	2	4	0
Mori *et al*[24]	1	1	1	0	1	1	0	0	1	0
Bullock *et al*[25]	2	1	2	0	2	2	0	2	0	2
Cuadrado *et al*[26]	2	1	2	0	2	2	0	0	1	1
Sato *et al*[27]	1	0	1	0	1	0	1	0	0	1
Ichikawa *et al*[28]	2	0	1	1	1	0	1	1	0	2
Ikeda *et al*[29]	1	0	1	0	1	1	0	1	1	0
Hai *et al*[30]	2	1	2	0	2	2	0	1	1	1
Hashizume *et al*[31]	7	5	4	3	5	5	6	5	5	2
Maeda *et al*[32]	3	0	2	1	NA	NA	NA	NA	3	0
Kawada *et al*[33]	6	4	3	3	2	3	1	4	0	6
Malik *et al*[34]	8	2	6	2	5	6	NA	5	8	0
Chagas *et al*[35]	4	3	2	2	4	3	1	NA	4	0
Takuma *et al*[36]	8	5	4	4	4	6	3	6	3	5
Present authors	3	2	1	2	2	1	2	2	3	0
Total	56	26	35	21	36	36	16	29	36	20
(%)	-	(46.4)	(62.5)	(37.5)	(67.9)	(67.9)	(35.6)	(59.2)	(64.3)	(35.7)

M: male; F: female; OB: obesity; DM: type 2 diabetes mellitus; DL: dyslipidemia; HT: hypertension; NA: not available; LC: liver cirrhosis; Non-LC: non-liver cirrhosis. All values represent number of cases.

dysplastic nodule, respectively. Sasaki *et al*[7] described a 73 year old female with MO of HCC based on cirrhotic NASH. The patient was complicated by T2DM and obesity. Two liver tumors were detected metachronously and both were diagnosed with well-differentiated HCCs.

In the present report, the clinical profiles of old age, obesity, T2DM, hypertension and cirrhosis are identified as common characteristics of the 4 patients with MO of HCC (Table 1); these may be predisposing factors to MO of HCC. Moreover, of these characteristics, old age, T2DM and cirrhosis are recognized as common conditions among the 2 patients with MO of HCC in previous reports (Table 2). Although these conditions are also observed in some patients with solitary HCC which is unaccompanied by MO as described in the present report and previous literature (Table 3)[21-36], they do not always satisfy these conditions. A literature search shows that the proportion of patients with age older than 70 years, T2DM and cirrhosis with solitary HCC is 46.4% (26 of 56 cases), 67.9% (36 of 53 cases) and 64.3% (36 of 56 cases), respectively. Thus, it is appropriate to consider that those conditions (old age, T2DM and cirrhosis) are necessary preconditions of synchronous MO.

The role of each factor in the pathogenesis of MO of HCC is not understood. Old age and cirrhosis have been shown to be the strongest risk factors for the development of HCC in NASH with a prospective cohort study[37]. Obesity has been confirmed as an independent risk factor for the development of HCC in several studies[38-42], as has T2DM[43-45]. With regard to the association of T2DM, it was postulated that chronic hyperinsulinemia and insulin-like growth factor 1 might be involved in carcinogenesis[46]. Although MO of HCC may be attributable to independent factors, a concurrence of the factors of old age, metabolic abnormalities and cirrhosis perhaps significantly raises the malignant potential in the liver and probability of subsequent synchronous and multifocal development of HCCs. The exact mechanism of MO of HCC under those conditions needs to be elucidated.

It is unclear whether the same conditions can be

adapted to cases with metachronous MO because it may not be long enough to observe metachronous MO of HCC in the present study. Even in patients without MO of HCC at diagnosis, HCC of multicentric origin might occur metachronously after longer periods of follow up. Moreover, the number of subjects is too small to draw a clear conclusion. These are limitations of this study and warrant further exploration with a larger scale and longer duration.

Discrimination of MO from IM is critical for selecting an appropriate method of treatment for HCC caused by HCV infection. The prognosis of HCV-related HCC patients with MO is thought to be better than that with IM because of the low rate of recurrence by IM in the MO group[13]. Therefore, it is reasonable to adopt locoregional therapy such as surgical removal or radiofrequency ablation which is more effective than transcatheter arterial chemoembolization or systemic chemotherapy, even in cases with multiple HCCs when they are considered of multicentric origin. However, whether the same strategy can be adapted to NASH-related HCC remains unclear because outcomes of HCC with or without MO in NASH have not been clarified. To establish an adequate strategy against HCC with NASH, their outcomes should be analyzed with stratification on the basis of not only tumor staging, hepatic reserve and kinds of treatment but also the manner of HCC development.

Furthermore, it is important to prevent MO of HCC. In patients with HCV-related HCC, eradication of HCV by interferon therapy after curative treatment for HCC provided promising effects on the prevention of HCC recurrence in several reports[47-49]. Adjuvant therapy using interferon reduced late recurrence of HCC after two or more years of curative treatment. This fact may be attributable to the suppression of multicentric carcinogenesis through the inhibition of chronic inflammation. Even in NASH, it would be possible that anti-inflammation or anti-fibrosis therapy for the liver leads to the prevention of HCC development with multicentric manner. Based on this, it may be worth attempting to intensely treat underlying liver disease as well as HCC to produce consequent improvement in the prognosis of NASH.

In summary, synchronous and/or metachronous MO was recognized in 4 of 12 patients with NASH-related HCC. MO may be frequently provoked in NASH-related HCC as well as in chronic liver diseases caused by HBV or HCV infection. The clinical status of age older than 70 years, obesity, T2DM, hypertension and cirrhosis was identified as common characteristics of the patients with MO of HCC and they might be predisposing factors to at least synchronous MO. Of these characteristics, old age, T2DM and cirrhosis are also common features of the other 2 patients from the previous case reports so these confined conditions may be necessary preconditions for synchronous MO. Adequate methods of treatment and prevention for MO of HCC are necessary and may lead to a consequent improvement in the prognosis of NASH.

COMMENTS

Background

Hepatocellular carcinoma (HCC) is an often fatal event of nonalcoholic steatohepatitis (NASH). Although multicentric occurrence (MO) is frequently observed characteristics in the development of HCC caused by HBV or HCV infection, the manner of HCC development in NASH remains unclear.

Research frontiers

Although many clinicopathological and epidemiological studies on NASH have been conducted to define the incidence of HCC and the predisposing factors to HCC, there has been no study that focuses on MO of HCC with NASH.

Innovations and breakthroughs

The authors demonstrated that MO of HCC was found in 4 of 12 patients with NASH-related HCC. The common characteristics among the patients with MO of HCC were old age, obesity, type 2 diabetes mellitus (T2DM), hypertension and cirrhosis, suggesting putative predisposing factors to synchronous MO of HCC with NASH. Of these characteristics, old age, T2DM and cirrhosis are also common features of the other 2 patients from previous case reports so these confined conditions may be necessary preconditions for synchronous MO.

Applications

Understanding the manner of HCC development in NASH may be helpful for developing an adequate treatment strategy for HCC.

Terminology

MO of HCC means development of multiple HCCs with independent origins. When multiple HCCs include an early HCC with a dysplastic nodule or a moderately and/or poorly differentiated HCC with a margin of well-differentiated HCC, they are referred to as multicentric in origin.

Peer review

The present manuscript reports four cases of NASH patients that developed HCC with multicentric occurrence. The results showed are potentially interesting, and the conclusions are, in general, adequately supported by the experimental findings. All these considerations plus the interest of the data reported make the paper to be considered worth publishing.

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Original Article

Fulminant hepatitis: Who survives without liver transplantation?

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Aim: In order to rescue more patients with fulminant hepatitis (FH) in a setting of the shortage of liver grafts, it is important not only to determine the suitable timing for liver transplantation (LT) but also to reduce avoidable operations for patients surviving without LT. This study aimed to identify prognostic parameters for survival without LT in FH patients.

Methods: In 96 FH patients who did not receive LT, we examined prognostic parameters at the time of the diagnosis of FH, which were associated with patient's survival.

Results: Fifty-three patients (55%) were female. The median age was 48 years. At the time of the diagnosis of FH, hepatic coma grade was II in 63 patients (66%), III in 22 (23%) and IV in 11 (11%). Forty-six patients (48%) were in a state of systemic inflammatory response syndrome (SIRS). Four parameters of age (<45 years), SIRS (no), direct bilirubin/total bilirubin ratio (>0.65), and total bilirubin (<12.0 mg/dL) were associated with patient's survival. Overall survival rate of eight patients ulfilling all four parameters were 88%. In 17 patients fulfilling any three parameters, 2-week, 4-week and overall survival rates were 82%, 77% and 71%, respectively. On the other hand, overall survival rate of 38 patients fulfilling any one parameter or none was less than 10%.

Conclusions: Patients fulfilling all four parameters will be successfully treated without LT. In patients fulfilling any three parameters, intensive care including artificial liver support in expectation of hepatic regeneration during a few weeks may be possible.

Key words: fulminant hepatitis, liver transplantation, prognostic factor, survival, systemic inflammatory response syndrome

INTRODUCTION

LIVER CELL DEATH of a critical degree with insufficient hepatocellular regeneration leads to the development of acute liver failure (ALF) characterized by hepatic encephalopathy and coagulopathy. The survival rate without liver transplantation (LT) is over 60% in patients with acetaminophen-induced ALF but 20–30% in those with non-acetaminophen-related ALF.[1]

Recently, the prognosis of ALF patients has been improved due to the advances in supportive intensive care: however, LT is the only effective intervention for those with fatal outcomes.[2] In the United States, patients in a state of UNOS status 1 including ALF has received LT with a median waiting time of 7 days,[3] and the 5-year survival has been reported 70%.[4]

On the other hand, in Asian countries, the donation from deceased donors is severely limited because of various cultural and social reasons.[5] Approximately 50% of patients listed for emergency LT have died while awaiting a graft because of the lack of a timely suitable donor.[6,7] Thus, in these regions, living donor LT rather than deceased donor LT has been mainly performed. The most reliable advantage of living donor LT is the speedy availability of a high-quality liver graft. However, a mortality of 0.15% of living donors and complications including bile leaks in approximately 30% have been reported.[8] Furthermore, psychologically, urgent LT frequently leads to anxiety and depression in donors.[9] Thus, in order to rescue more patients in a setting of the shortage of liver grafts, it is important to accurately identify not only patients with fatal outcomes but also those surviving without LT.

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Previous studies have focused argument on the prediction of fatal outcomes.[10–12] This study aimed to investigate prognostic parameters associated with patient's survivals without LT in fulminant hepatitis (FH), which has accounted for the major part of ALF in Japan and has been classified into five etiological categories; hepatitis due to viral infections, autoimmune hepatitis, drug allergy-induced liver injury, hepatitis of indeterminate cause despite sufficient examinations (unknown etiology), and hepatitis due to indeterminate cause due to insufficient examination.[13,14]

METHODS

Patients

ONE HUNDRED AND twenty patients with non-acetaminophen-related ALF, who showed hepatic encephalopathy of grade II or more within 8 weeks of the onset of the disease symptoms and a prothrombin activity (PT) of 40% or less of the standardized value,[14] admitted to the Okayama University Hospital and eight tertiary care centers between January 1990 and December 2009 were considered for this study. Of these patients, 21 received living donor LT based on the Guideline of the Acute Liver Failure Study Group of Japan.[15] However, recently, the predictive accuracy of this guideline was reported to decrease to 73%.[15] Especially, the positive predictive value of this guideline was shown to be low. So, including these 21 patients receiving LT into this study was considered inappropriate. Furthermore, from the remaining 99 patients who did not receive liver transplantation, one patient diagnosed with acute fatty liver of pregnancy and two patients with ischemic hepatitis were excluded. Thus, 96 FH patients who did not receive LT were included in the present analysis.[14]

Etiology of FHF

A diagnosis of hepatitis A, B and C was made based on the presence of immunoglobulin M antibody to hepatitis A virus, immunoglobulin M antibody to hepatitis B core antigen or hepatitis B surface antigen, and hepatitis C virus RNA identifiable by nested reverse transcription-polymerase chain reaction (RT-PCR), respectively.[13] A diagnosis of autoimmune hepatitis was made according to the criteria revised by the International Autoimmune Hepatitis Group in 1999.[16] A diagnosis of Epstein-Barr virus infection was made based on measurement of Epstein-Barr virus load in whole blood by quantitative PCR (qPCR) amplification assays.[17] A diagnosis of drug-induced liver injury, acute fatty liver of pregnancy, and ischemic hepatitis was made based on their distinctive clinical courses. A diagnosis of unknown FH was established when all of IgM anti-hepatitis A virus antibody, IgM anti-hepatitis B virus core antibody, hepatitis B surface antigen, hepatitis C virus-RNA, anti-nuclear antibody and anti-smooth muscle antibody were negative with no obvious cause such as drug, acute fatty liver of pregnancy, ischemic hepatitis, Wilson's disease, malignant infiltration, cytomegalovirus infection, Epstein-Barr virus infection and herpes simplex virus infection.

Systemic inflammatory response syndrome

Systemic inflammatory response syndrome is diagnosed by the presence of two or more of the following components: (i) temperature > 38°C or <36°C; (ii) tachycardia > 90/min; (iii) respiratory rate > 20/min or arterial PaCO2 <32 mmHg; and (iv) white blood cell (WBC) count > 12 000/mm^3 or <4000/mm^3 or immature forms >10%.[18]

Treatment

All patients were admitted to the Intensive Care Unit to receive supportive care through the monitoring of clinical, biochemical and hemodynamic parameters. Some patients received plasma exchange and/or hemodiafiltration. Plasma exchange and hemodiafiltration were performed according to the following indications: (i) patients with coagulopathy were indicated for plasma exchange; (ii) patients with the central nerve disorder including hepatic coma were indicated for plasma exchange only or plasma exchange combined with hemodiafiltration; and (iii) patients with renal failure were indicated for hemodiafiltration.[12]

Statistical analysis

SPSS statistical program (release 11.0.1 J, SPSS, Chicago, IL, USA) was used for the statistical analysis.

Continuous parameters were expressed as median and range. Dichotomous parameters were compared by the χ^2 test. The Mann–Whitney *U*-test was used to evaluate the significance of differences in the continuous parameters. Cumulative survival curves were analyzed using the Kaplan–Meier method, and differences in the curves were tested using the log-rank test. A *P*-value of <0.05 was considered significant.

To identify the prognostic parameters independently associated with FH patient's survivals, we tested the following parameters at the time of the diagnosis of FH when hepatic encephalopathy of grade II or more

developed with PT activity of 40% or less of the standardized value (age, gender, etiology, period from initial symptoms to the diagnosis of FH, hepatic coma grade, SIRS, platelet count, total bilirubin [T.Bil], direct bilirubin [D.Bil]/T.Bil ratio, alanine aminotransferase [ALT], creatinine [Cr] and PT activity) and treatment (plasma exchange and hemodiafiltration) in univariate and multivariate logistic regression analyses. We entered potential prognostic parameters, which were associated with patient's survival in the univariate analyses at the $P < 0.20$ level, in a multivariate analysis. In a multivariate logistic regression analysis, P-values <0.05 were considered significant. The cut-off value of each continuous parameter was determined using receiver operating characteristic (ROC) curve analysis.

Furthermore, concerning the prediction of patient's survival, we evaluated the Guideline of the Acute Liver Failure Study Group of Japan[15] and the Guideline of the Intractable Hepato-Biliary Diseases Study Group of Japan.[19]

RESULTS

Patient's characteristics

OF 96 PATIENTS, 53 (55%) were female. The median age was 48 (14–81) years. Seven patients (7%) were diagnosed with FH-A, 32 patients (33%) with FH-B, two patients (2%) with FH-C, nine patients (10%) with autoimmune hepatitis, 14 patients (15%) with drug-induced liver injury, and one patient (1%) with Epstein-Barr virus infection, while the remaining 31 patients (32%) exhibited unknown etiology. A median period from initial symptoms to the diagnosis of FH was 11.5 (1–54) days. At the time of the diagnosis of FH, hepatic coma grade was II in 63 patients (66%), III in 22 patients (23%) and IV in 11 patients (11%). Forty-six patients (48%) were in a state of SIRS.

Plasma exchange and hemodiafiltration were performed in 76 patients (79%) and 38 patients (40%), respectively. In 37 patients (39%), plasma exchange combined with hemodiafiltration was performed. As prognoses, 34 patients (35%) survived without LT, and the other 62 died without LT (Fig. 1).

Clinical characteristics and laboratory data at the time of the diagnosis of FH in survivors and deaths are shown in Table 1. The survivors were younger (29 [14–81] years versus 53 [16–79] years; $P = 0.0020$) and less frequently in a state of SIRS (18% versus 65%; $P < 0.0001$) than the subjects who died. The survivors showed higher D.Bil/T.Bil ratio (0.66 [0.43–0.92] versus 0.60 [0.27–0.81]; $P = 0.0031$). Differences in etiology of FH, hepatic coma grade, platelet count, serum T.Bil level, and PT activity between the survivors and the deaths were borderline. There is no difference in gender and treatment between the two groups.

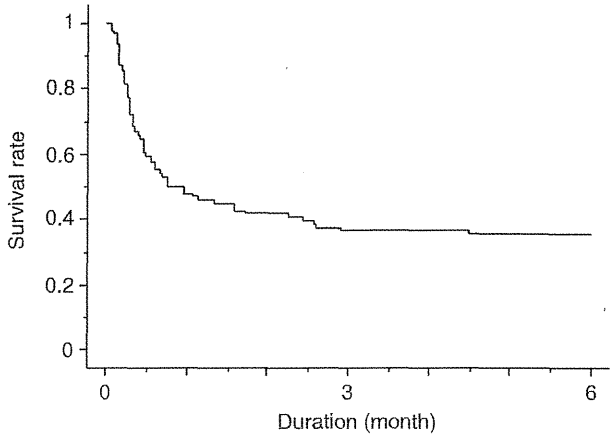

Figure 1 Kaplan–Meier curves depicting survival rate in 96 fulminant hepatitis (FH) patients.

Prognostic parameters

With the univariate logistic regression model, age (per onw year) (odds ratio [OR] 0.96, 95% confidence interval [CI] 0.94–0.99); $P = 0.0029$}, SIRS (yes) (OR 0.12, 95% CI 0.04–0.33; $P < 0.0001$), platelet count (per $1 \times 10^4/mm^3$) (OR 1.06, 95% CI 1.00–1.13; $P = 0.049$), and D.Bil/T.Bil ratio (per 0.10) (OR 1.92, 95% CI 1.20–3.07; $P = 0.0064$) were significantly associated with patient's survival. The association of etiology (viral hepatitis) (OR 2.15, 95% CI 0.92–5.03; $P = 0.078$), hepatic coma grade (II) (OR 2.20, 95% CI 0.86–5.63; $P = 0.10$), T.Bil level (per 1.0 mg/dL) (OR 0.96, 95% CI 0.92–1.01; $P = 0.11$) and PT activity (per 1%) (OR 1.04, 95% CI 0.99–1.08; $P = 0.078$) with patient's survival was borderline (Table 2).

A multivariate logistic regression analysis indicated that four parameters of age (per one year) (OR 0.97, 95% CI 0.94–0.99; $P = 0.037$), SIRS (yes) (OR 0.12, 95% CI 0.03–0.42; $P = 0.0009$), T.Bil level (per 1.0 mg/dL) (OR 0.93, 95% CI 0.86–0.99; $P = 0.043$) and D.Bil/T.Bil ratio (per 0.10) (OR 1.95, 95% CI 1.03–3.69; $P = 0.040$) were significantly associated with patient's survival. Etiology, hepatic coma grade, platelet count, and PT activity was not associated with patient's survival (Table 2).

Table 1 Clinical characteristics of survivors and deaths at the time of the diagnosis of fulminant hepatitis

Parameter	Survivor	Death	*P*-value
Patients, *n*	34	62	
Age (years)	29 (14–81)	53 (16–79)	0.0020
Gender, female (%)	18 (53)	35 (56)	0.74
Etiology (%)			
Viral hepatitis	19 (55)	23 (37)	0.076
Hepatitis A virus	4 (11)	3 (5)	
Hepatitis B virus	12 (35)	20 (32)	
Hepatitis C virus	2 (6)	0 (0)	
Epstein-Barr virus	1 (3)	0 (0)	
Autoimmune hepatitis	5 (15)	4 (6)	
Drug-induced	5 (15)	9 (15)	
Unknown	5 (15)	26 (42)	
Period from initial symptoms to the diagnosis of fulminant hepatitis, day			
	13.5 (2–49)	10.5 (1–54)	0.65
Hepatic coma grade, *n* (%)			
II	26 (76)	37 (60)	0.098
III or IV	8 (24)	25 (40)	
Temperature >38°C or <36°C, *n* (%)			
	7 (21)	18 (29)	0.37
Heart rate >90 beats per min, *n* (%)			
	5 (15)	43 (69)	<0.0001
Tachypnea >20 breaths per min or PaCO2 <32 mmHg, *n* (%)			
	5 (15)	28 (45)	0.0027
SIRS, *n* (%)	6 (18)	40 (87)	<0.0001
Laboratory data			
WBC, $\times 10^3/mm^3$	8.8 (2.4–28.0)	8.8 (2.2–36.5)	0.98
Hemoglobin, g/dL	12.6 (7.3–18.0)	12.0 (5.9–19.0)	0.20
Platelet, $\times 10^4/mm^3$	14.1 (6.8–39.3)	11.7 (1.4–28.8)	0.067
T.Bil, mg/dL	10.4 (3.5–50.5)	15.1 (2.3–45.9)	0.083
D.Bil/T.Bil ratio	0.66 (0.43–0.92)	0.60 (0.27–0.81)	0.0031
ALT, IU/L	1546 (60–8610)	1 031 (40–10 159)	0.46
Cr, mg/dL	0.7 (0.2–6.4)	0.9 (0.1–5.1)	0.48
PT activity, %	24 (7–40)	20 (5–38)	0.092
Treatment			
Plasma exchange, *n* (%)	26 (76)	50 (81)	0.63
Hemodiafiltration, *n* (%)	16 (47)	22 (35)	0.27

ALT, alanine aminotransferase; Cr, creatinine; D.Bil, direct birilubin; PT, prothrombin; SIRS, systemic inflammatory response syndrome; T.Bil, total bilirubin; WBC, white blood cell count.

By using the ROC curve analysis, each cut-off value of age, T.Bil and D.Bil/T.Bil ratio was shown to be 45 years, 0.65 and 12.0 mg/dL, respectively (Table 3).

Survival

Overall survival rates of patients aged <45 years and those aged ≥45 years were 54% and 22%, respectively. These rates of patients in a state of SIRS and those not showing SIRS were 13% and 56%, respectively. These rates of patients showing T.Bil <12.0 mg/dL and those showing T.Bil ≥12.0 mg/dL were 45% and 27%, respectively. These rates of patients showing D.Bil/T.Bil ratio >0.65 and those showing D.Bil/T.Bil ratio ≤0.65 were 54% and 23%, respectively.

Cumulative 2-week, 4-week and overall survival rates of eight patients fulfilling all of these four parameters (age [<45 years], SIRS [no], D.Bil/T.Bil ratio [>0.65], and T.Bil [<12.0 mg/dL]) were 88%, 88% and 88%, respectively. These survival rates of 17 patients fulfilling any three parameters were 82%, 77% and 71%, respectively. In 33 patients fulfilling any two parameters, these survival rates of were 64%, 52% and 39%, respectively.

Table 2 Prognostic parameters predicting patient's survival by univariate and multivariate logistic regression analyses

Parameter	Univariate		Multivariate	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Age, per 1 year	0.96 (0.94–0.99)	0.0029	0.97 (0.94–0.99)	0.037
Gender, female	0.87 (0.37–2.01)	0.74	–	–
Etiology, viral hepatitis	2.15 (0.92–5.03)	0.078	1.57 (0.43–5.71)	0.49
Period from initial symptoms to the diagnosis of fulminant hepatitis, per 1 day				
	1.00 (0.97–1.04)	0.84	–	–
Hepatic coma grade, II	2.20 (0.86–5.63)	0.10	1.80 (0.47–6.80)	0.39
SIRS, yes	0.12 (0.04–0.33)	<0.0001	0.12 (0.03–0.42)	0.0009
Platelet count, per $1 \times 10^4/mm^3$	1.06 (1.00–1.13)	0.049	1.08 (0.99–1.18)	0.078
T.Bil, per 1.0 mg/dL	0.96 (0.92–1.01)	0.11	0.93 (0.86–0.99)	0.043
D.Bil/T.Bil ratio, per 0.10	1.92 (1.20–3.07)	0.0064	1.95 (1.03–3.69)	0.040
ALT, per 1 IU/L	1.00 (1.00–1.00)	0.38	–	–
Cr, per 1.0 mg/dL	1.14 (0.86–1.51)	0.37	–	–
PT activity, per 1%	1.04 (0.99–1.08)	0.078	1.05 (0.98–1.13)	0.16
Plasma exchange, yes	0.78 (0.28–2.15)	0.63	–	–
Hemodiafiltration, yes	1.62 (0.69–3.79)	0.27	–	–

ALT, alanine aminotransferase; CI, confidence interval; Cr, creatinine; D.Bil, direct birilubin; PT, prothrombin; SIRS, systemic inflammatory response syndrome; T.Bil, total bilirubin.

On the other hand, cumulative 2-week, 4-week and overall survival rates of 28 patients fulfilling any one parameter were 43%, 29% and 7%, respectively. These survival rates of 10 patients fulfilling none were 40%, 30% and 0%, respectively (Fig. 2).

Prediction of survival by the Guideline of the Acute Liver Failure Study Group of Japan[15]

Among the 96 patients, the estimated prognosis was alive in 25 patients, of whom 15 (60%) survived without LT. On the other hand, the estimated prognosis was death in the remaining 71 patients, of whom 19 (27%) survived without LT. The sensitivity, specificity, positive predictive value, negative predictive value and predictive accuracy were 44%, 84%, 60%, 73% and 70%, respectively.

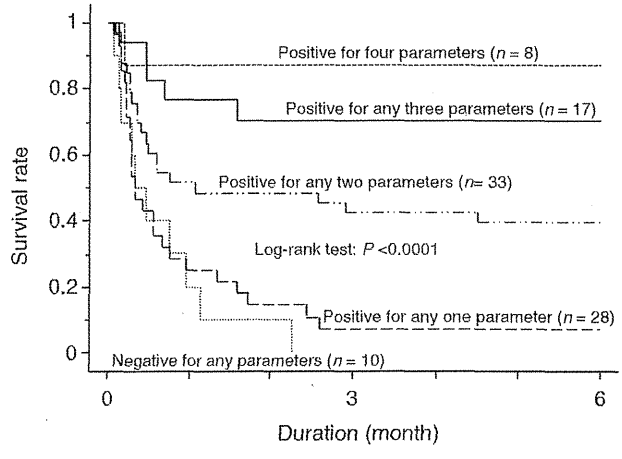

Figure 2 Kaplan–Meier curves depicting survival rate according to the number of prognostic parameters fulfilled at the time of the diagnosis of fulminant hepatitis (FH).

Table 3 Accuracy and cut-off value of each prognostic parameter

Parameter	AUC (95% CI)	Cut-off value	Sensitivity	Specificity
Age (year)	0.69 (0.57–0.81)	45	68%	68%
D.Bil/T.Bil ratio	0.68 (0.57–0.79)	0.65	62%	68%
T.Bil, mg/dL	0.61 (0.49–0.72)	12.0	58%	62%
SIRS (yes)	–	–	65%	82%

AUC, area under the curve; CI, confidence interval; D.Bil, direct birilubin; T.Bil, total bilirubin; SIRS, systemic inflammatory response syndrome.

Prediction of survival by the Guideline of the Intractable Hepato-Biliary Diseases Study Group of Japan[19]

Of the 96 patients, the prognoses of 25 patients could not be estimated for lack of clinical data. Thus, the Guideline of the Intractable Hepato-Biliary Diseases Study Group of Japan[19] was evaluated in the remaining 71 patients. Among the 71 patients, the estimated prognosis was alive in 32 patients, of whom 13 (37%) survived without liver transplantation. On the other hand, the estimated prognosis was death in the other 39 patients, of whom nine (23%) survived without liver transplantation. The sensitivity, specificity, positive predictive value, negative predictive value and predictive accuracy were 59%, 61%, 41%, 77% and 61%, respectively.

DISCUSSION

WORLDWIDE, LT HAS become the treatment of choice for liver failure patients with fatal outcomes, especially for ALF patients. The 5-year graft survival rate in ALF patients has been shown to be 61%.[4] However, after LT, long-term immunosuppressive treatment is needed. Complications associated with immunosuppressive treatment cannot be by-passed. Recently, half of the deaths after LT have been reported to be associated with the complications attributable to immunosuppressive treatment including cardiovascular disease, renal failure, infection or malignancy.[20] Furthermore, ALF patients after LT show marked decline in quality of life for a long period, especially psychological health as well as social role functioning, compared with the general population.[21] Thus, it is important to reduce avoidable operations without the deterioration of the prognosis of ALF patients. Up to now, prognostic parameters for fatal outcomes and indication for liver transplantation in ALF patients have been mainly investigated. The King's college criteria and the end-stage liver disease (MELD) score have been widely accepted for the prediction of fatal outcomes; however, the negative predictive value (the prediction of patient's survival) in non-acetaminophen-related ALF is limited.[22] A model useful to predict patient's survival has yet to be proposed.

In Japan, the Guideline of the Acute Liver Failure Study Group of Japan[15] and the Guideline of the Intractable Hepato-Biliary Diseases Study Group of Japan[19] have been mainly used for the prediction of fatal outcomes in FH patients. However, this study suggests that the predictive accuracy of these guidelines for the prediction of patient's survival may be insufficient, although the sample size was limited and another validation study should be performed. In order to rescue more patients in a setting of the shortage of liver grafts, it is necessary to reduce avoidable operations in patients surviving without LT. For this purpose, we consider that another model useful to accurately identify not only patients with fatal outcomes but also those surviving without LT may need to be proposed as immediately as possible.

In this study, we analyzed various prognostic parameters such as age, etiology, hepatic coma grade, PT activity, SIRS, etc. which have been reported as prognostic parameters. As a result, four parameters (age [<45 years], SIRS [no], D.Bil/T.Bil ratio [>0.65], and T.Bil [<12.0 mg/dl]) were elicited as prognostic parameters associated with FH patient's survival. Overall survival rate of patients fulfilling all four parameters was 88%, and these patients may be successfully treated without LT. On the other hand, overall survival rate of patients fulfilling any one parameter or none was less than 10%, and these patients will need urgent LT. In patients fulfilling any three parameters, the 4-week and overall survival was 77% and 71%, respectively. So, for these patients, the intensive care including artificial liver support in expectation of hepatic regeneration during a few weeks from the diagnosis of FH may be possible. However, this study was retrospective, and the sample size was limited. In order to confirm these findings, a further prospective validation is required.

Systemic inflammatory response syndrome has been reported to affect the prognosis of acetaminophen-related ALF patients. The King's College Group[23] and the U.S. Acute Liver Failure Study Group[24] have revealed that SIRS worsened the hepatic coma grade and increased the mortality rate as the number of SIRS components fulfilled increased. On the other hand, in non-acetaminophen-related ALF, SIRS has been reported to be associated with increased probabilities of acute renal failure and mortality.[25] In this study, approximately 50% of FH patients were in a state of SIRS at the time of the diagnosis of FH, and SIRS extremely reduced survival rate. Thus, SIRS is considered to be an important prognostic parameter for ALF. Furthermore, patients in a state of SIRS frequently develop acute respiratory distress syndrome, disseminated intravascular coagulation, acute renal failure and multiple organ failure irrespective of positive or negative cultures.[26] In order to rescue ALF patients, LT before the development of these complications is required. Patients in a state of SIRS may need super-urgent LT.

In Japan, as artificial liver support, plasma exchange and hemodiafiltration have been performed in 92% and 76%, respectively, of FH patients.[27] In this study, most patients received plasma exchange and/or hemodiafiltration; however, the efficacy of these procedures on the prognosis was not shown. On the other hand, plasma exchange combined with high-volume hemodiafiltration using a high performance membrane has been revealed to be effective for recovery from hepatic coma and preventing brain edema and to be a reliable bridging procedure to LT.[28] Recently, from Japan, this combination procedure has been reported to provide a high survival rate of 76% without LT.[29] In a setting of the shortage of liver grafts, artificial liver support technologies have been developed remarkably although the efficacy of artificial liver support has yet to be evidenced. A prospective study with a larger number of patients is required to evaluate the role of artificial liver support in the treatment of ALF patients.

In this study, we excluded 21 patients receiving LT from the present analysis. Recently, the positive predictive value of the Guideline of the Acute Liver Failure Study Group of Japan is reported to be 73%.[15] Thus, approximately 30% of patients receiving LT based on this guideline may be unnecessary for LT. Thus, we consider that it is not be appropriate that the prognosis of patients receiving LT is classified into deaths.

In order to rescue more patients in a setting of the shortage of liver grafts, it is important not only to determine the suitable timing for LT but also to reduce avoidable operations in patients surviving without LT. For this purpose, we investigated prognostic parameters associated with FH patient's survival, and four parameters (age [<45 years], SIRS [no], D.Bil/T.Bil ratio [>0.65], and T.Bil [<12.0 mg/dL]) were elicited. Patients fulfilling all four parameters will be successfully treated without LT. In patients fulfilling any three parameters, short-term prognosis is relatively better, and the intensive care including artificial liver support in expectation of hepatic regeneration during a few weeks from the diagnosis of FH may be possible. On the other hand, patients fulfilling any one parameter or none will need urgent LT. A further prospective validation study is required.

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特集 肝と免疫

3 原発性胆汁性肝硬変 (1) 診　断

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Key words: 原発性胆汁性肝硬変，抗ミトコンドリア抗体，オーバーラップ症候群，慢性非化膿性破壊性胆管炎

要 旨

原発性胆汁性肝硬変(PBC)は中年女性に好発する慢性胆汁うっ滞性の疾患で，発症に自己免疫的機序が想定されている．肝内の小型胆管が破壊され消失することにより慢性胆汁うっ滞を生じ，線維化の進行に伴い肝硬変へと移行する．PBCの診断には，①ALPやγ-GTPの上昇などの胆汁うっ滞を示す検査所見，②抗ミトコンドリア抗体(AMA)陽性，③慢性非化膿性破壊性胆管炎(CNSDC)を含む特徴的な病理組織所見，の三つが重要な所見である．臨床病期として，無症候性(aPBC)と症候性(sPBC)があり，症候性はさらに皮膚瘙痒感のみで黄疸のないs1-PBCと黄疸を有するs2-PBCに分類される．

はじめに

原発性胆汁性肝硬変(PBC)は中年女性に好発する慢性胆汁うっ滞性の疾患で，発症に自己免疫学的機序が想定されている．全国調査によると，年間の推定発生患者数は約500人で横ばいに推移し，推定患者総数は5〜6万人である[1]．

皮膚瘙痒感や黄疸などの症状を有する症例を症候性PBCと呼ぶが，近年では健診時や他疾患で受診時に肝機能異常を契機として診断される無症候性PBCが増加している．PBCの診断根拠の一つである抗ミトコンドリア抗体(AMA)が簡便になされるようになってから，診断される症例が増加している．AMAは感度・特異度ともに高い検査であり，その測定によりPBCの診断は比較的容易であるが，時に診断に苦慮する症例が存在する．ここでは，PBCの特徴的症候，診断および鑑別すべき病態につき概説する．

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Ⅰ．PBCの臨床症状

この項のポイント
- 多くのPBCは無症候性であるが，進行すると皮膚瘙痒感や黄疸が出現する．

無症候性PBCでは自覚症状に乏しい．初期に出現する自覚症状は皮膚瘙痒感であり，進行すると黄疸が出現する．さらに，肝機能の低下に伴い腹水や肝性脳症などの肝不全徴候が認められる．

1．疲労感・倦怠感

わが国ではあまり注目されていないが，欧米では疲労感・倦怠感はPBCの一般的な症状と考えられている．症状の程度はPBCの進行度や肝機能異常の程度とはあまり関連がないとさ

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れている.

2．皮膚瘙痒感

PBCにおいて最初に現れる症状である．特定の部位ではなく全身の瘙痒感を訴える．瘙痒感には末梢性と中枢性があるが，PBCにおける瘙痒感は中枢性でオピオイド受容体が関与していると考えられている[2]．

3．黄　　疸

肝内胆管の破壊と消失が進行するに伴い黄疸が出現する．黄疸が長期にわたると皮膚の色素沈着も伴う．

4．黄 色 腫

肝臓における脂質代謝の異常に基づく高コレステロール血症を合併し，しばしばHDL-コレステロールの上昇を伴う．長期に経過すると眼瞼に黄色腫が出現することがある．

5．Sjögren 症候群

PBCの20～30％にSjögren症候群を合併する．口腔内の乾燥，咳症状，う歯の増悪，眼の乾燥，などの症状を訴える．

6．食道胃静脈瘤

門脈圧の亢進に伴い食道胃静脈瘤が出現するが，肝硬変を伴わない比較的早期から静脈瘤を合併することがある．食道胃静脈瘤の破裂を初発症状とする症例が報告されている．

7．肝不全徴候

進行期PBCではほかの肝硬変と同様に，腹水や肝性脳症などの肝不全の徴候が出現する．

Ⅱ．PBCの検査所見

この項のポイント

- PBCの検査所見として胆道系酵素の上昇とAMA陽性が特徴的である．

1．血液生化学所見

症候性・無症候性を問わず，血清胆道系酵素(ALP，γ-GTP)の上昇を認める．早期ではALPは正常範囲でγ-GTPのみ上昇している場合がある．病状の進行に伴い胆道系酵素は上昇するが，末期ではかえって低下してくる．ALTは一般に100 IU/l以下の低値であるが，進行期のPBCや自己免疫性肝炎(AIH)とのオーバーラップ症候群では高値を示す．

2．自己抗体・免疫学的検査

1）抗ミトコンドリア抗体(AMA)

AMAはPBCにおける診断において，感度・特異度ともに高い自己抗体である．PBCにおける陽性率は90～95％で，他の疾患における陽性率は低い．

AMAは2-oxo acid dehydrogenase complex (2-OADC)に属する酵素のE2コンポーネントに対する抗体で，pyruvate dehydrogenase complex (PDC-E2)，branched chain 2-oxo acid dehydrogenase complex(BCOADC-E2)，2-oxoglutarate dehydrogenase complex (OGDC-E2)が含まれる[3]．なかでもPDC-E2に対する抗体がもっとも高頻度に検出される．AMAの測定には，間接蛍光抗体法による測定とELISAによる測定がある．間接蛍光抗体法は，ラット肝細胞や培養肝細胞に患者血清を反応させ自己抗体を発色させ検出する方法である．ELISAによる方法は，リコンビナントのPDC-E2，BCOADC-E2，OGDC-E2をプレートにのせ，患者血清との反応を定量的に判定する．ELISAによる測定が間接蛍光抗体法による測定より，感度・特異度ともに高い．

AMA は AIH の約 10%で陽性となる．当科における検討では，AMA 陽性 AIH における ELISA での抗体価は PBC に比べ低力価であり，陽性 cutoff 値を 7.0 から 10.0 に引き上げると PBC における陽性率を下げることなく AIH の陽性率を低下させることができる．

2）抗核抗体(ANA)

PBC の約 60%で ANA が陽性になる．とくにオーバーラップ症候群では ALT の高値と ANA 陽性を示す．また，核内の糖蛋白である gp 210 に対する抗体(抗 gp 210 抗体)は PBC の進行と強く関連することが報告されている[4]が，一般臨床での実用化はされていない．

3）抗セントロメア抗体(ACA)

PBC に CREST 症候群を伴う限局性強皮症を合併することがあるが，このような症例で高頻度に ACA が陽性となる．また，ACA 陽性の PBC では門脈圧亢進症を合併しやすいとの報告がある[4]．

4）免疫グロブリン M(IgM)

血清 IgM が高値を示す場合が多い．活動性と比較的よく相関し，治療により肝機能が改善すれば IgM も低下する．進行期では他の肝硬変と同様にγグロブリンが上昇する．

Ⅲ．PBC の病理所見

この項のポイント

- PBC の病理所見は，小型胆管の破壊と消失に伴う慢性胆汁うっ滞が特徴である．

PBC の病態の基本は，肝内の小型胆管が破壊され，消失することに伴う慢性の胆汁うっ滞である．胆汁うっ滞と interface hepatitis に伴う肝細胞障害および線維化が 2 次的に形成され肝硬変へと進展する．特徴的な病理所見は，慢性非化膿性破壊性胆管炎(chronic non-suppurative destructive cholangitis；CNSDC)，肉芽腫，胆管消失，細胆管増生，interface hepatitis など

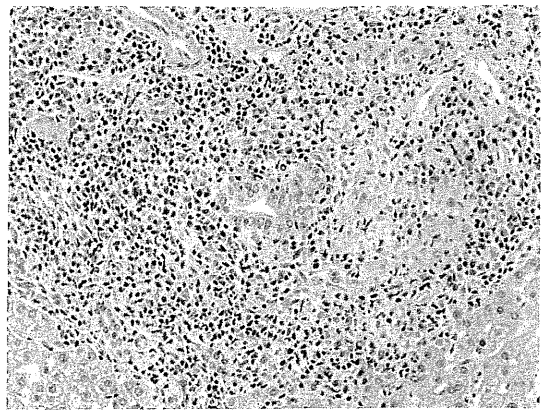

図　PBC の病理組織
慢性非化膿性破壊性胆管炎，肉芽腫，炎症細胞浸潤を認める．

である(**図**)．

PBC の病期分類として従来 Scheuer の分類や Ludwig の分類が用いられてきたが，Nakanuma ら[5]により新しい活動度(壊死炎症反応)と病期分類が提唱されている(**表 1**)．活動度については，胆管炎の活動度と肝炎の活動度をそれぞれ評価している．病期については，PBC の進行度を胆管消失の程度(0～3)，慢性進行性胆汁うっ滞の程度(0～3)，および肝線維化の程度(0～3)，の三つの因子で総合評価している．それらを総合評価し，Stage 1～Stage 4 までの 4 段階に分類している．今後，この病期分類の有用性や予後との関連性などについて，前向きに検討される必要がある．

Ⅳ．PBC の診断と臨床病期

この項のポイント

- PBC の診断には血液検査の胆汁うっ滞所見，AMA 陽性，肝組織像が重要である．

1．PBC の診断

PBC の診断は「難治性の肝・胆道疾患に関する調査研究」班の作成した「原発性胆汁性肝硬変の診断基準」にある診断に沿って行う(**表 2**)[6]．とくに，PBC の診断には以下の 3 項目が

表1　PBCの組織学的病期分類(中沼安二ら，2006/厚労科研班会議，2010)

＜PBC組織病期評価のための組織病変とスコア＞

A. 線維化	Score	B. 胆管消失	Score
門脈域での線維化がないか，あるいは線維化が門脈域に限局	0	胆管消失がない	0
門脈域周囲の線維化，あるいは不完全な線維性隔壁を伴う門脈域線維化	1	1/3以下の門脈域で胆管消失をみる	1
種々の小葉構造の乱れを伴う架橋性線維化	2	1/3～2/3の門脈域で胆管消失をみる	2
再生結節と高度の線維化を伴う肝硬変	3	2/3以上の門脈域で胆管消失をみる	3

＜線維化(A)と胆管消失(B)スコアの合計による病期診断(Staging)＞

Stage	A. 線維化，B. 胆管消失 各スコアの合計
Stage 1 (no progression)	0
Stage 2 (mild progression)	1～2
Stage 3 (moderate progression)	3～4
Stage 4 (advanced progression)	5～6

＜オルセイン染色の評価を加えた病期分類(Staging)＞

C. オルセイン陽性顆粒沈着	Score
陽性顆粒の沈着なし	0
1/3以下の門脈域の周辺肝細胞(少数)に陽性顆粒の沈着をみる	1
1/3～2/3の門脈域の周辺肝細胞(種々の程度)に陽性顆粒の沈着をみる	2
2/3以上の門脈域の周辺肝細胞(多数)に陽性顆粒の沈着をみる	3

Stage	A. 線維化，B. 胆管消失 C．オルセイン陽性顆粒沈着 各スコアの合計
Stage 1 (no progression)	0
Stage 2 (mild progression)	1～3
Stage 3 (moderate progression)	4～6
Stage 4 (advanced progression)	7～9

〔Nakanuma, Y., et al.：Pathol. Int. 60；167-174, 2010[5]より引用〕

表2　PBCの診断

次のいずれか一つに該当するものをPBCと診断する 1）組織学的にCNSDCを認め，検査所見がPBCとして矛盾しないもの 2）AMAが陽性で，組織学的にはCNSDCの所見を認めないが，PBCに矛盾しない組織像を示すもの 3）組織学的検索の機会はないが，AMAが陽性で，しかも臨床像および経過からPBCと考えられるもの

〔文献6)より引用〕

表3　PBCの臨床病期分類

無症候性PBC (aPBC)	自覚症状を欠く
症候性PBC (sPBC)	皮膚瘙痒感，黄疸，食道胃静脈瘤，腹水，肝性脳症など肝障害に基づく自覚症状を有する
s1-PBC	黄疸がない時期(T. Bil<2.0 mg/dl)
s2-PBC	黄疸がある時期(T. Bil≥2.0 mg/dl)

重要である．

1．血液生化学所見で慢性の胆汁うっ滞所見

2．AMA陽性所見

3．肝組織像で特徴的所見

これらの所見を総合して，次のいずれか一つに該当するものをPBCと診断する．

1）組織学的にCNSDCを認め，検査所見がPBCとして矛盾しないもの

2）AMAが陽性で，組織学的にはCNSDCを認めないが，PBCに矛盾しない(compatible)組織像を示すもの

3）組織学的検索の機会はないが，AMAが陽性で，しかも臨床像および経過からPBCと考えられるもの

であり，PBCの診断には必ずしも肝組織学的所見は必要としない．しかし，PBCの病態や進行度を把握するためには肝病理所見は重要である．

2．PBCの臨床病期(表3)

PBCの臨床病期は症候性(symptomatic)と無症候性(asymptomatic)に分け，症候性は黄疸のない時期(s1-PBC)と黄疸のある時期(s2-PBC)に分ける．現在診断されるPBCの約80%は無症候性PBCであるが，そのなかには早期のPBCから完成した肝硬変まで含まれる．一方，症候性PBCは臨床症状の項目で記した種々の自他覚症状を呈する．s2-PBCでは内科的治療の限界であり，肝移植の適応である．

V．診断に苦慮する症例

この項のポイント

- AMA陰性PBCやオーバーラップ症候群では診断に苦慮することがある．

1．AMA陰性例

臨床病理学的にPBCと診断される症例のうち，5～10%にAMA陰性例が存在する．AMAの抗体価が検出感度以下の低力価の場合や，AMAは陰性であるが自己反応性T細胞はミトコンドリア抗原に反応している場合が考えられる[7]．胆汁うっ滞所見があり臨床的にPBCが疑われる場合は，肝生検を施行し組織学的所見を確認する必要がある．

AMA陰性でANA陽性，IgG高値でプレドニゾロンが有効である症例をautoimmune cholangitisとして独立した疾患として提唱されたことがあるが，現時点ではPBCの亜型とする考えが一般的である．

2．オーバーラップ症候群

PBCとAIHは代表的な自己免疫性肝疾患であり，その標的細胞はそれぞれ小型胆管と肝細胞と異なっており独立した疾患である．しかし，

表4　オーバーラップ症候群の診断

Ⅰ．Paris criteria〔Chazouillères[8]〕
PBC と AIH 診断基準それぞれの 2 項目以上を満たすもの
＜PBC の基準＞
1）ALP≧2×ULN or γ-GTP≧5×ULN
2）AMA（＋）
3）肝組織像で florid bile duct lesion
＜AIH の基準＞
1）ALT≧5×ULN
2）IgG≧2×ULN or ASMA（＋）
3）肝組織像で中等度以上の interface hepatitis

Ⅱ．PBC-AIH オーバーラップ症候群―ステロイド投与のための診断指針
（厚労省「難治性の肝・胆道疾患に関する調査研究」班）[6]
PBC-AIH オーバーラップ症候群と考えられる症例のうち，以下の 2 項目を同時に満たす症例に対しては，ウルソデオキシコール酸に加えて副腎ステロイドの投与を推奨する．
1）厚労省の診断基準（平成 22 年度版）[6]により PBC と診断される症例
2）IAIHG の simplified criteria（2008）[10]により probable/definite AIH と診断される症例

ULN：正常値上限

時に両者の性格をさまざまな程度で有する症例が存在する．すなわち，血液検査にて，AMA と ANA が両者陽性，ALT と ALP/γ-GTP の両者が高値，IgG と IgM の両方が高値などの所見を種々の程度に示す．オーバーラップ症候群を診断するために，Chazouillères らの基準（Paris criteria）[8]や厚生労働省「難治性の肝・胆道疾患に関する調査研究」班の診断指針[6]が示されている（**表 4**）．両者の合併を初発時に認める場合と，一方の疾患の経過中に他方の病状を合併してくる異時性の場合がある．このような場合にも，肝生検を施行し，組織学的所見を確認する必要がある．組織学的には，PBC に特徴的な所見に加え，interface hepatitis や小葉内の肝炎所見が強い所見を示す．PBC に AIH を合併した場合は，肝炎の沈静化に対してプレドニゾロンが有効である．

3．IgG4 関連硬化性胆管炎

自己免疫性膵炎では IgG4 の高値が特徴的で，ステロイド治療が有効である．この疾患に高率に胆管炎を合併することが報告されており，また膵炎の合併がなく胆管炎のみで発症する症例がある[9]．IgG4 陽性の形質細胞が多数浸潤することが特徴である．胆道系酵素の上昇を示す胆汁うっ滞を認めることで鑑別に上がる疾患であるが，IgG4 高値を認め AMA 陰性であり，むしろ原発性硬化性胆管炎との鑑別が重要である．

おわりに

PBC は人種差や地域差があり，当初はわが国においてまれな疾患とされていた．しかし，最近では診断基準が確立され，また慢性の胆汁うっ滞を示す疾患として健診などで無症候性の PBC が多く発見されるようになってきている．病因は未だ不明であるが，ウルソデオキシコール酸による治療は進行を遅らせ予後を改善することが明らかになっている．進行した PBC に