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Investigation into bacteremia and spontaneous bacterial peritonitis in patients with liver cirrhosis in Japan

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Background/aims: *Liver cirrhosis patients tend to develop bacteremia, but relatively little has been reported about the situation in Japan. Therefore, we investigated the microorganisms involved and the outcome among liver cirrhosis patients with bacteremia, including spontaneous bacterial peritonitis.* ***Methods:*** *The subjects were 236 patients who underwent a total of 377 blood cultures and 30 patients diagnosed with spontaneous bacterial peritonitis, among 6,096 inpatients with liver cirrhosis admitted to several hospitals during the period 1991-2009.* ***Results:*** *The rate of positive blood culture was 37.1% (140/377), and the isolated microorganisms were predominantly Gram-negative bacteria. In patients with confirmed bacteremia, the Child-Pugh score and serum blood urea nitrogen and creatinine levels were significantly higher than in non-bacteremia cases. Moreover, short-term mortality (within 1 month) was 48.2% (53/110), being significantly higher than that among non-bacteremia cases (18.8%; 22/117). Among spontaneous bacterial peritonitis cases, mortality within one month was 33.3% (10/30). Again, the Child-Pugh score and serum blood urea nitrogen and creatinine levels were significantly higher among the fatalities than among survivors.* ***Conclusions:*** *These results indicate that severity of liver dysfunction and severity of renal dysfunction are both important determinants of short-term mortality among liver cirrhosis patients with bacteremia and spontaneous bacterial peritonitis in Japan.*

Key words: Bacteremia, spontaneous bacterial peritonitis, liver cirrhosis, hepatorenal syndrome, microorganisms

Japonya'daki karaciğer sirozlu hastalarda bakteremi ve spontan bakteriyel peritonit araştırması

Amaç: *Karaciğer sirozlu hastalar bakteremiye meyillidir, ancak bu durumla ilgili Japonya'dan nispeten az bildirim yapılmıştır. Bu nedenle, spontan bakteriyel peritonitli hastalar da dahil olmak üzere, karaciğer sirozlu hastalarda görülen bakteremi vakalarında saptanan mikroorganizmalar ve tedavi sonuçları araştırılmıştır.* ***Yöntem:*** *1991–2009 yılları arasında çeşitli hastanelere başvuran 6096 yatan hasta arasında saptanan, 236 vakadaki toplam 377 kan kültürü ve 30 spontan bakteriyel peritonit epizotu değerlendirilmiştir.* ***Bulgular:*** *Kan kültüründe pozitiflik oranı %37.1 (140/377)'dir ve izole edilen mikroorganizmalar ağırlıklı olarak Gram–negatif bakterilerdir. Bakteremisi kesinleşmiş hastaların Child–Pugh skoru, kan üre azotu ve kreatinin seviyeleri, bakteremisiz hastalarla karşılaştırıldığında anlamlı şekilde fazladır. Dahası, kısa dönem mortalite (1 ay içinde) %48.2 (53/110), non–bakteremik hastalara (%18.8; 22/117) göre anlamlı şekilde fazladır. Spontan bakteriyel peritonitli olguların 1 aylık mortalitesi %33.3 (10/30)'dur. Yine, ölen hastaların Child–Pugh skoru, kan üre azotu ve kreatinin seviyeleri yaşayanlardan daha fazlaydı.* ***Sonuçlar:*** *Bu bulgulara göre, Japonya'da bakteremi ve spontan bakteriyel peritonitli karaciğer sirozu hastalarında, karaciğer ve böbrek disfonksiyonunun ciddiyeti kısa dönem mortalitenin önemli belirleyicileridir.*

Anahtar kelimeler: Bakteremi, spontan bakteriyel peritonit, karaciğer sirozu, hepatorenal sendrom, mikroorganizmalar

INTRODUCTION

Liver cirrhosis patients tend to develop bacteremia due to hypoactivity of neutrophils and the hepatic reticuloendothelial system, as well as influx of bacteria into the general circulation due to portal-caval shunts (1-3). It is thought that 30% to 60% (1,4,5) of patients with liver cirrhosis develop bac-

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terial infection, and such infection is involved in one-fourth of deaths among liver cirrhosis patients (6,7). In addition, spontaneous bacterial peritonitis (SBP) is a disease that is peculiar to decompensated cirrhosis. However, relatively little has been published about the ratio of development of bacteremia among patients with liver cirrhosis, or about the prognosis. Therefore, we have investigated retrospectively bacteremia and SBP in Japanese inpatients with liver cirrhosis.

MATERIALS AND METHODS

Subjects

We examined the records of 6,096 inpatients with liver cirrhosis admitted from 1991 through 2009 to the Department of Gastroenterology, Tokyo Women's Medical College, Tokyo (1991~2002), Nagashio Hospital, Tokyo (1996~2004), Kikuna Memorial Hospital, Kanagawa (2007~2008), or the Department of Gastroenterology, International University of Health and Welfare Hospital, Tochigi (2008~2009), all located in the Kanto district of Japan. The main purposes of hospitalization were examination for or treatment of hepatocellular carcinoma (HCC), 2,935 cases (48.1%); treatment of gastroesophageal varices or gastrointestinal bleeding, 729 cases (12.0%); treatment of ascites, 611 cases (10.0%); hepatic coma, 322 cases (5.3%); fever, 190 cases (3.1%); and others, 1,309 cases (21.5%).

Bacteremia Cases

Among the above patients, we identified 236 (age range: 29-87 years; male-to-female ratio, 160:76) who had undergone a total of 377 blood cultures. We excluded cases where contamination was doubtful. As regards the blood culture procedure, one to two samples of venous or arterial blood had been aseptically collected and inoculated into aerobic (ACTEC Plus Aerobic/F Culture Vial) and anaerobic (BACTEC Plus Anaerobic/F Culture Vial) culture bottles. Shaken culture was conducted for seven days using a dedicated blood culture system (Becton, Dickinson Co., USA). Although the borderline by which to determine whether bacteremia is due to nosocomial or non-nosocomial infection has been suggested to be 72 hours after hospital admission, we defined cases that were positive in a blood culture procedure conducted within 48 hours after hospital admission as non-nosocomial infection cases, and those that were positive as a result of blood culture conducted later than 48 hours after admission as nosocomial infection cases, in order to allow comparison with other available data (8,9). In the bacteremia cases, we studied the distribution of pathogenic bacteria and the ratio of nosocomial/non-nosocomial infections, and compared short-term survival with that of blood culture-negative cases.

SBP Cases

In diagnosing SBP, infectious pleural effusion, peritonitis carcinomatosa and hemorrhagic ascites, such as HCC rupture, were excluded. SBP was diagnosed regardless of the presence of bacteria in the ascitic fluid in cases where the neutrophil count in ascitic fluid was ≥500/mm^3. In cases having subjective and objective symptoms of SBP, a neutrophil count of 250/mm^3 - 500/mm^3 was considered sufficient (10).

We selected 30 SBP patients (age range: 37-86 years; male-to-female ratio: 21:9) who met our diagnostic criteria. We studied the pathogenic bacteria and clinical manifestations, examined the short-term outcome for each case (up to 1 month after diagnosis), and compared the survivors with the fatalities. According to the criteria set forth by the International Ascites Club (11), we diagnosed cases with serum creatinine (Cr) levels of ≥1.5 mg/dl and with no evident disease associated with renal failure as hepatorenal syndrome. Such cases were then classified into two types: type I (in which the Cr level increased 2-fold or reached 2.5 mg/dl within 2 weeks, and renal failure progressed rapidly) and type II (in which the Cr level was ≥1.5 mg/dl, but rapid deterioration of renal function was not seen).

Statistical Analysis

Contingency tables were used for the comparison of positive rates. The unpaired t-test was conducted for comparison of levels between two groups. The criterion of significance was taken to be $p<0.05$. Values are given as mean and standard deviation.

RESULTS

Bacteremia

The positive rate of the 377 blood culture procedures was 37.1% (140/377). A comparison of the bacteremia and blood culture-negative cases revealed that complications of ascites, history of upper gastrointestinal hemorrhage within two weeks and catheterization were significantly more frequent

in the bacteremia cases (Table 1). Moreover, the white blood cell (WBC) level, Child-Pugh score and blood urea nitrogen (BUN) and Cr levels were significantly higher in the bacteremia cases than in the blood culture-negative cases (Table 2).

Among the bacteremia cases, excluding two unknown cases, nosocomial infection accounted for 70.2% (97/138) and non-nosocomial infection accounted for 29.8% (41/138). Among them, Gram-positive bacteria accounted for 39.3% (57/145), Gram-negative bacteria for 56.6% (82/145) and other bacteria for 4.1% (6/145). The bacterial strain most frequently detected was *Escherichia coli,* followed by *Klebsiella sp.* Among the Gram-positive bacteria, *Staphylococcus Rosenbach* accounted for more than 80% (Table 3).

The apparent foci of bacteremia were as follows: Unknown cases 53.0% (70/132), catheterization 15.9% (21/132), urinary tract infection 8.3% (11/132), respiratory tract infection 7.6% (10/132), colitis 5.3% (7/132), infection of skin or soft tissues 3.8% (5/132), and others 6.1% (8/132). Four cases of SBP were detected (3.0%). The short-term mortality was 48.2% (53/110) and 18.8% (22/117) in the bacteremia cases and blood culture-negative cases, respectively, being significantly higher in the bacteremia cases ($p<0.001$). Moreover, in the fatal bacteremia cases, the Child-Pugh score and ammonia, BUN and Cr levels were significantly higher than those in the surviving bacteremia cases (Table 4).

Table 1. Comparison of backgrounds between liver cirrhosis patients with and without bacteremia

	Bacteremia case	Non-bacteremia cases	p-value
Ages	61.9±10.7	62.8±11.7	p>0.05
Hepatocellular	52.6%(60/114)	59.5%(72/121)	p>0.05
Diabetes	25.9%(29/112)	23.5%(28/119)	p>0.05
Ascites	86.2%(94/109)	57.1%(68/119)	p<0.001
Gastro-intestinal bleeding within 2 weeks	23.9%(26/109)	9.2%(11/119)	p<0.01
Intravenous catheter	24.3%(26/107)	7.8%(9/115)	p<0.01

Table 2. Comparison of laboratory findings between liver cirrhosis patients with and without bacteremia

	Bacteremia cases	Non-bacteremia cases	p-value
WBC (/ μ L)	9820±5190	7560±4510	p<0.01
PT (%)	42.1±20.9	52.7±23.2	p<0.01
Albumin (g/dL)	2.42±0.42	2.77±0.49	p>0.05
T-bil. (mg/dL)	9.0±3.5	4.1±7.7	p<0.001
NH3 (μ g/dL)	83±37	89±60	p>0.05
BUN (mg/dL)	27.1±8.9	11.9±16.3	p<0.001
Creatinine (mg/dL)	1.32±0.35	1.11±0.50	p<0.001
Child-Pugh score	11.8±1.9	10.6±2.3	p<0.001

WBC: White blood cells. PT: Prothrombin time. T-bil: Total bilirubin. NH3: Ammonia. BUN: Blood urea nitrogen.

SBP

Among the SBP cases, 36.7% (11/30) were ascites culture-positive. The pathogenic bacteria were *E. coli* in four cases, *Klebsiella* sp. in four cases, and *Streptococcus, Listeria* and *Bacteroides* in one case each.

The following clinical symptoms were observed: fever of ≥37.5°C in 80.0% (24 cases), abdominal pain in 20.0% (6 cases), diarrhea in 16.7% (5 cases) and reduction in blood pressure in 6.7% (2 cases). As for the short-term outcome, 10 out of 30 patients (33.3%) died. Each of them had developed

Table 3. Microorganisms isolated from blood cultures in patients with liver cirrhosis

Microorganisms	Number	%
Gram-positive bacteria	57	39.3%
MRSA	24	16.6%
MSSA	15	10.3%
Staphylococcus epidermidis	8	5.5%
Enterococcus sp.	4	2.8%
Streptococcus sp.	3	2.1%
Others	3	2.1%
Gram-negative bacteria	82	56.6%
Escherichia coli	28	19.3%
Klebsiella sp.	26	17.9%
Pseudomonas sp.	11	7.6%
Aeromonas sp.	7	4.8
Enterobacter sp.	3	2.1%
Others	7	4.8
Anaerobic bacteria	3	2.1%
Fungi	3	2.1%
Total	145	100%

MRSA: Methicillin resistant *Staphylococcus aureus*.
MSSA: Methicillin sensitive *Staphylococcus aureus*.

Table 4. Comparison of laboratory findings between survivors and fatalities with bacteremia

	Survivors	Fatalities	p-value
PT (%)	48.9±20.9	33.7±19.0	p<0.01
Albumin (g/dL)	2.51±0.42	2.35±0.45	p>0.05
T-bil. (mg/dL)	4.0±3.5	14.1±12.7	p<0.001
NH3 (μ g/dL)	70±37	106±56	p>0.05
BUN (mg/dL)	16.1±8.9	41.9±20.3	p<0.001
Creatinine (mg/dL)	0.99±0.35	1.72±0.87	p<0.001
Child-Pugh score	10.6±1.9	12.9±1.7	p<0.001

PT: Prothrombin time. T-bil: Total bilirubin. NH3: Ammonia. BUN: Blood urea nitrogen.

Table 5. Comparison of laboratory findings between survivors and fatalities with spontaneous bacterial peritonitis

	Survivors	Fatalities	p-value
WBC (/ μ L)	7760±3210	11890±7650	p>0.05
PT (%)	48.1±18.9	39.9±23.0	p>0.05
Albumin (g/dL)	2.56±0.46	2.41±0.44	p>0.05
T-bil. (mg/dL)	4.1±3.5	8.0±9.7	p>0.05
NH3 (μ g/dL)	101±47	89±39	p>0.05
BUN (mg/dL)	19.1±8.9	46.9±21.9	p<0.001
Creatinine (mg/dL)	0.98±0.29	1.68±0.89	p<0.01
Child-Pugh score	11.0±1.8	12.9±2.0	p<0.01

MRSA: Methicillin resistant *Staphylococcus aureus*.
MSSA: Methicillin sensitive *Staphylococcus aureus*.

type I hepatorenal syndrome. Table 5 compares the surviving and fatal SBP cases. The fatal cases showed significantly higher Child-Pugh scores, as well as higher BUN and Cr levels, than the survivors.

DISCUSSION

Patients with liver cirrhosis are prone to opportunistic infection, and it has been reported that the blood culture-positive rate of inpatients with liver cirrhosis ranges from 3.5% to 8.8% (1,2,8,12). In our study, the rate was low, at 2.3% (140/6096). However, only approximately 6% of the patients with liver cirrhosis had undergone blood culture. Additionally, it has been suggested that bacteremia develops more frequently in patients with catheterization and gastrointestinal bleeding (6), and that the presence of concomitant HCC is irrelevant (13). Our results are consistent with that view. It seems possible that changes to the intestinal bacterial flora and the rupture of the intestinal mucosa barrier caused by gastrointestinal bleeding, as well as bacterial translocation (BT) from the intestine to the mesenteric lymph node (14,15), may be involved in the onset of bacteremia and SBP. Moreover, it has been reported in animal experiments that BT occurs in 37%-83% of animals in liver cirrhosis models, while it occurs in 30%-40% of patients with ascites complications, though more frequently in patients with Child C (16).

In addition, the reported percentage of nosocomial infections in liver cirrhosis patients varies widely (24%-63%) (8,9). In our study, the percentage was high, at 70.2%. The value is likely to be affected by catheterization and the extent of gastrointestinal tract treatment after hospital admission.

In Japan, the percentage of Gram-positive bacteria in inpatients has been increasing since the first half of the 1980s due to the increased general use of cephem antibiotics and catheterization. However, we found that Gram-negative bacteria were predominant among bacterial strains involved in bacteremia, and this is consistent with the fact that BT is known to be strongly correlated with the presence of aerobic Gram-negative bacteria. In agreement with previous reports (8,9,12), we found that the pathogenic bacteria most frequently detected in bacteremia were *E. coli*, followed by *Klebsiella sp*. These bacteria were also detected most frequently in the ascitic culture of SBP patients.

It has been reported that susceptibility to bacteremia is correlated with severity of liver cirrhosis (17,18). We previously investigated *Aeromonas* bacteremia in patients with liver cirrhosis, and found that all patients with *Aeromonas* bacteremia had severe liver cirrhosis with a Child-Pugh score of 13 or greater (19). In our present study as well, the severity of liver cirrhosis was significantly greater in the bacteremia cases than in the blood culture-negative cases. Renal impairment was also significantly greater in the bacteremia cases than in the blood culture-negative cases.

Although slightly different definitions of short-term mortality have been used, it has been reported that the short-term mortality in liver cirrhosis accompanied with bacteremia ranges from 30%-60% (12,20). In our study, the mortality within a month of the initial diagnosis was 48.2%, being significantly higher than in the blood culture-negative cases. In addition to the severity of liver dysfunction, renal function was an important factor in determining the prognosis. In the case of SBP, old age (1), gastrointestinal bleeding (21) and severity of liver dysfunction and renal impairment (1,21-23) are reported to be predictive factors. We also found that severity of liver cirrhosis and renal dysfunction was important. In particular, type I hepatorenal syndrome was associated with all 10 cases of short-term SBP fatality. The prognosis of type I hepatorenal syndrome is extremely poor; the average survival is reported to be only about two weeks (24), whereas that of patients with SBP is reported to be approximately nine months (25).

It has been suggested that combined use of an antibiotic and albumin injection may prevent the aggravation of renal function in patients with liver

cirrhosis accompanied with SBP (26). However, based on the finding that renal dysfunction is also a predictive factor for the prognosis of bacteremia or SBP in patients with liver cirrhosis, we question whether this approach would be very effective, in particular, in type I hepatorenal syndrome.

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