

Bacterial infections in cirrhotic patients with hepatocellular carcinoma

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Abstract

AIM: To establish the prevalence of bacterial infection in cirrhotic patients with hepatocellular carcinoma (HCC).

METHODS: All 719 cirrhotic patients with HCC were investigated retrospectively for occurrence of bacterial infections.

RESULTS: The incidence of bacterial infection was 15.4% (111/719). According to Child-Pugh classification, the incidences of bacterial infection in Class A, B and C were 2.3%, 8.0%, and 26.4%, respectively. The bacterial infection incidence increased with the severity of cirrhosis, and severe bacterial infections usually occurred in Child-Pugh class B and C patients.

CONCLUSION: The susceptibility of HCC patients to bacterial infection is mainly due to the underlying cirrhosis and not to the HCC itself.

Key words: Liver cirrhosis; Liver neoplasms; Bacterial infection; Hepatocellular carcinoma (HCC)

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INTRODUCTION

The predisposition of cirrhotic patients to bacterial infections is well documented^[1-5]. However, the susceptibility to bacterial infections according to the severity of liver disease has not yet been evaluated. There has been no published report of bacterial infections in patients with hepatocellular carcinoma (HCC), except for cases of

spontaneous bacterial peritonitis (SBP)^[6]. In China, the majority of HCC reportedly occurs in patients with cirrhosis.

We undertook the present study with three aims: (1) to establish the prevalence of bacterial infections in HCC patients; (2) to evaluate the susceptibility of HCC patients to bacterial infections, according to the severity of the liver disease; and (3) to assess the clinical and bacteriological features of bacterial infection in cirrhosis with HCC.

MATERIALS AND METHODS

We retrospectively investigated 719 cirrhotic patients with HCC admitted to our hospital from September 1985 to July 1995. Altogether, 543 males and 176 females participated in the study, aged between 50 years to 68 years. The diagnosis of cirrhosis with HCC was verified by liver biopsy, ultrasonography, computerized tomography, and/or angiography. All patients were confirmed to have underlying cirrhosis. The grading of the severity of the liver cirrhosis was made according to the Child-Pugh classification. Hepatitis B and C sera were examined, and 78% of the cases tested were found to have hepatitis C antibody but the rest remained untested. The schistosomal circumoval precipitin test (COP), indirect hemagglutination test (IHT) and enzyme linked immunoassay (ELISA) were performed. Diagnosis of primary biliary cirrhosis was made based on the histopathology and the positive result for anti-mitochondrial antibody (AMA). Complete physical examinations, standard laboratory tests, chest X-ray, and cultures of blood, urine, and other body fluids were performed whenever signs of infection became apparent. A diagnosis of bacteremia, urinary tract infection, or bacterial enteritis was made according to positive culture. SBP was diagnosed as ascitic PMN $> 250 \times 10^6$ cells/L or by positive culture.

RESULTS

Incidence of bacterial infection relevant to Child-Pugh classification

To investigate the effect of hepatic functional reserves on the incidence of bacterial infection, we divided the patients into three groups: 173 patients were in class A, 201 in class B, and 345 in class C. Differences were not significant among the three groups. Table 1 shows that the rate of bacterial infection increased with the severity of cirrhosis.

Etiology of cirrhosis and bacterial infection

Susceptibility to bacterial infection was compared in patients with varied etiologies of cirrhosis. Differences were not significant among the five groups as to average age and to distribution of patients according to Child-Pugh classification. The incidence of bacterial infection in patients with HCC was 18.7% (38/203) for schistosomiasis cirrhosis, 14.0% (26/186) for hepatitis B cirrhosis, 14.2% (41/289) for non-A, non-B hepatitis, and 13.3% (2/15) for primary biliary cirrhosis (Table 2). The difference in rates of bacterial infec-

Table 1 Child-Pugh classification and incidence of bacterial infections in patients with hepatocellular carcinoma

Child-Pugh class	<i>n</i>	No. of bacterial infections	%
A	173	4	2.3
B	201	16	8.0 ^a
C	345	91	26.4 ^b
Total	710	111	15.4

^a*P* < 0.05 vs class B; ^b*P* < 0.01 vs class A or B.**Table 2** Etiology of cirrhosis and incidence of bacterial infections

Etiology of cirrhosis	<i>n</i>	Bacterial infection	
		Rate ¹	%
Schistosomiasis	203	38	18.7
Hepatitis B	186	26	14.0
Non-A, non-B hepatitis	289	41	14.2
Primary biliary cirrhosis	15	2	13.3
Other causes	26	4	15.4

¹No significant differences, as analyzed by χ^2 test.**Table 3** Organisms isolated from infectious ascites in cirrhotic patients with hepatocellular carcinoma

Organism	Blood	Fluid	Sputum	Urine	Other	Total	%
Gram-positive						68	33.3
<i>S. aureus</i> (MRSA)	5 (2)	3 (1)	6 (3)	2	7	23 (6)	11.3
<i>Enterococcus</i>	2	3	3	4	4	16	7.8
<i>S. epidermidis</i>	3	1	2	1	2	9	4.4
<i>S. pneumoniae</i>			4		3	7	3.4
Others	1	2	8	1	1	13	13
Gram-negative						122	59.8
<i>E. coli</i>	4		5	8	6	27	13.2
<i>Pneumoniae</i>	6	4	6	2	3	20	9.8
<i>P. aeruginosa</i>	3	3	7	2	3	20	9.8
<i>Enterobacter</i>	1	5	2	6	1	10	4.9
<i>Serratia</i>	2		2	1	2	9	4.4
<i>Cepacia</i>	4			2	3	9	4.4
Others	3	2	8	9	5	27	13.2
<i>Candida</i> sp.	3	1	5	2	3	14	6.9

tion was not significant among the five groups (by χ^2 test).

Bacteriology

There were 260 cases of bacterial infections among 111 patients, and 204 yielded isolates of bacteria. The isolates consisted of 59.8% (122/204) of Gram-negative bacilli, *Escherichia coli* and *Klebsiella pneumoniae*, with *Pseudomonas aeruginosa* being the most frequent. The most common Gram-positive isolate was *Staphylococcus aureus*, with 26.1% (6/23) of the *S. aureus* isolates being methicillin-resistant (MRSA). Blood cultures yielded one organism in all bacteremic patients. Cases of mixed *S. aureus* and *K. pneumoniae* were also seen. Among 32 cases of bacteremia, 16 were spontaneous, 8 were associated with SBP, 3 were associated with urinary tract infection, 3 were associated with infections from intravenous cannulation, and 2 were associated with pneumonia. Positive cultures were obtained in 15 (68.2%) of the 22 total SBP cases. A single bacterium was often recovered in patients with SBP (66.7%, 10/15). *E. coli* and *P. aeruginosa* were the two most common organisms. The remaining 7 SBP patients had culture-negative neutrocytic ascites (CNNA). In the 42 cases of pneumonia, 57 bacteria were isolated, among which *K. pneumoniae*, *P. aeruginosa*, and *S. aureus* were most frequent. Seventy-five percent (30/40) of the organisms isolated from urine were Gram-negative bacteria, usually of enteric origin (Table 3).

DISCUSSION

The high susceptibility of cirrhotic patients to bacterial infections is due to decreased function of the hepatic reticuloendothelial system, diminished opsonic activities, low levels of serum complement, and impaired monocytic and neutrophil phagocytic functions. Rimda *et al.*^[4] reported that the elimination rate constant of technetium^{99m}sulfur colloid (k-Tc) is a good index for risk evaluation, as it shows a direct correlation with the plasma elimination rate constant of indocyanine green (k-ICG). In our patient series, the rate of bac-

terial infection in cirrhotic patients increased with severity of cirrhosis, according to the Child-Pugh classification; a similar pattern was also observed in HCC patients. The susceptibility of HCC patients to bacterial infection is related mainly to the underlying cirrhosis rather than to HCC itself.

The occurrence of bacterial infection in patients with liver diseases is difficult to ascertain from the literature^[1]. The high susceptibility to bacterial infection of patients with cirrhosis may be related to the severity of the liver disease rather than to the causes of cirrhosis. Severe bacterial infections, in particular bacteremia, pneumonia and SBP, were more commonly seen in Child-Pugh class B and C patients, who tended to have a high mortality rate.

Infection of the urinary tract, bacteremia and pneumonia are the most common sources of bacterial infection, although patients with ascites are particularly prone to SBP^[4]. Pneumonia was the most common bacterial infection in our patient series and was associated with a mortality of 26%. One study reported that infections in soft tissue were the most common source of bacteremia, and Gram-positive organisms were isolated in 69%^[2]. Half of the bacteremic episodes of our patients were spontaneous and were caused by bacteria normally present in the intestinal flora, as previously reported by others^[4-6]. These spontaneous infections in patients with cirrhosis may be due to the passage of the intestinal bacteria from the bowel into the portal circulation. Clinically apparent foci of infection were found in half of the bacteremic cases. SBP was the most common source of bacteremia, followed by urinary tract infection and then by infection from intravenous cannulation. Half of the urinary tract infections were catheter-related.

Our study indicated that bacterial infection was a major problem in HCC. Despite the rapid initiation of appropriate antibiotic therapy, a high mortality rate was observed. The observed high incidence of and high mortality from bacterial infection in patients with advanced chronic liver disease emphasized the need to consider prophylactic parenteral antibiotics therapy as gut sterilization with oral antibiotics in these high-risk patients. Most of the microorganisms isolated in

our study were highly sensitive *in vitro* to imipenem and ofloxacin, either of which may represent an effective first-line therapy or prophylactic therapy for bacterial infection in cirrhosis with HCC.

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