Risk Factors for Spontaneous Bacterial Empyema in Cirrhotic Patients with Hydrothorax

Background. Spontaneous bacterial empyema (SBEM) is a rare complication of portal hypertension. The characteristics and risk factors for SBEM are not well known. This study was performed to investigate the risk factors for SBEM in cirrhotic patients with hydrothorax.

Methods. From July 1996 to December 1998, 862 cirrhotic patients were studied. All patients underwent chest radiography, abdominal sonography or computed tomography after admission to detect the existence of pleural effusion. Pleural fluid was obtained after thoracentesis and sent for analysis. The clinical and laboratory data from patients with sterile hydrothorax and from SBEM at the time of first episode were compared.

Results. Seventeen patients had 26 episodes of SBEM during the study period, 56% (14 of 26) of these SBEM episodes were associated with spontaneous bacterial peritonitis (SBP) and 31% (8 of 26) were associated with bacteremia. The incidence of SBEM was 2% (17 of 862) in cirrhotic patients and 13% (17 of 132) in cirrhotics with hydrothorax. Patients with SBEM had a higher Child-Pugh score, lower serum albumin, prolonged prothrombin time, lower pleural fluid protein, and higher rate of associated SBP than patients with sterile hydrothorax. Multivariate analysis revealed that pleural fluid protein level ($p = 0.0035$) and presence of SBP ($p = 0.0062$) were predictive factors of SBEM. The hospitalization mortality rate of SBEM was 38%.

Conclusions. Patients with advanced liver disease, low pleural fluid protein level, or SBP are predisposed to SBEM. A diagnostic thoracentesis should be performed in cirrhotic patients with pleural effusion when infection is suspected or clinical deterioration occurs.

Original Article

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Sponaneous bacterial peritonitis (SBP) is a well-known complication in cirrhotic patients with ascites. Patients who have low protein content in ascites, low C3 concentrations, low ascitic fluid opsonic activity, and hepatic insufficiency are at higher risk for the development of SBP, as well as its recurrence. 7,8

Like SBP, spontaneous bacterial empyema (SBEM) is a complication of cirrhotic patients in which preexisting pleural effusion becomes infected. To date, studies focusing on SBEM are rare. 9-11 Characteristics and risk factors for SBEM have not yet been well investigated. The aim of this study was to identify possible factors for SBEM in cirrhotic patients with hydrothorax.

METHODS

From July 1996 to December 1998, all cirrhotic patients admitted to the Division of Gastroenterology at the Kaohsiung Veterans General Hospital were enrolled in this study. The diagnosis of liver cirrhosis was based on liver biopsy or typical clinical findings (splenomegaly, ascites, and/or esophageal varices), imaging studies (abdominal sonography and/or computerized tomography) and laboratory findings.

All patients underwent chest radiography, abdominal sonography or computed tomography after admission to detect the existence of pleural effusion and/or ascites. A

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Key Words

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Thoracentesis was performed on patients with pleural effusion when pleural effusion was detected for the first time or when an infection was suspected during admission. If ascites was present, a paracentesis was also performed at the same time. Pleural fluid and ascites analysis included RBC count, polymorphonuclear (PMN) leukocyte count, glucose, protein, lactic dehydrogenase (LDH), cytology, bacterial culture, and mycobacterial culture. The bacterial culture was performed using a conventional method (on chocolate agar, blood agar, Mac Conkay agar, and thioglycolate broth): 10 mL of fluid was collected in an empty sterile container and sent to the laboratory immediately. Serum tests were also performed immediately after admission or with thoracentesis. The clinical and laboratory data from patients with sterile hydrothorax and with SBEM were compared by statistical methods to identify possible factors for SBEM.

The diagnosis of SBEM was made according to previously reported criteria.10,11
1. Positive pleural fluid culture and a PMN count ≤ 250 cells/mm³ or, if a negative culture, pleural fluid PMN count ≤ 500 cells/mm³.
2. No image of pneumonia on a chest radiograph or computed tomography scan.
3. Evidence of pleural effusion before the infected episode or pleural fluid transudate characteristics during infection.

The separation of transudates or exudates was according to Light’s criteria.12 Sterile hydrothorax was defined as transudative characteristics of pleural fluid with PMN count < 250 cells/mm³ and sterile pleural fluid bacterial cultures with cirrhosis as the only cause of pleural effusion.

SBP was defined as a positive ascitic fluid culture plus an ascitic fluid PMN count ≥ 250 cells/mm³ or a negative culture with PMN count ≥ 500 cells/mm³, with an absence of findings suggesting secondary peritonitis.6

In all patients suffering from SBEM, antibiotic treatment was initiated with cefazolin and gentamicin or a third-generation cephalosporin if the serum creatinine level was higher than 2 mg/dL at the time of diagnosis, then the antibiotic was changed according to susceptibility testing. No chest tube was placed in any episode and chest tapping was performed if patient suffered from dyspnea due to massive pleural effusion. SBEM was considered successfully treated when the pleural fluid culture became negative showing PMN count < 250 cells/mm³.

To demonstrate the communication between the peritoneal and pleural spaces, a nuclear scan by intraperitoneal injection of Tc⁹⁹m-labeled sulfur colloid was used in selective cases.13

An independent t test was used to compare quantitative data. The χ² test was used for other statistical analysis of the results for qualitative variables. Fisher’s exact test was used for correction if necessary. To identify independent factors, variables that achieved statistical significance (p < 0.05) in the univariate analysis were subsequently included in a multivariate analysis using a logistic regression procedure. For quantitative variables, the cut-off level chosen was according to clinical significance. A p value of < 0.05 was considered significant. All p values were two-tailed. Data were presented as mean ± SD.

RESULTS

During the study period, 862 cirrhotic patients were admitted to our unit. The etiologies of cirrhosis were as follows: chronic hepatitis B virus infection in 371 (43%) cases, chronic hepatitis C virus infection in 285 (33%) cases, chronic hepatitis B and C virus infection in 9 (1%) cases, alcoholism in 129 (15%) cases, and other or unknown etiologies in 68 (8%) cases. Among these 862 patients (Fig. 1), 451 (52%) had ascites and 132 (15%) had detectable pleural effusion. There were 93 (11%) patients who had ascites in addition to pleural effusion. In the patients with ascites, 23% (104 of 451) had ascites and 132 (15%) had detectable pleural effusion. There were 93 (11%) patients who had ascites in addition to pleural effusion. In the patients with ascites, 23% (104 of 451) had SBP at least one time during this period. Only 56 patients’ pleural fluids were obtained after thoracentesis because 53 patients had only minimal pleural effusion which was detectable but impractical or technically not feasible for thoracentesis, and 23 patients refused to undergo thoracentesis because they thought the procedure was not necessary or the hydrothorax was not troublesome. Among the 56 patients, 7 had hepatoma with lung metastasis, 3 had pneumonia with lung abscess, 2 had heart...
failure, 17 met the criteria of SBEM, and the remaining 27 were considered sterile hydrothorax. Thus, only 17 of the 132 (13%) patients had confirmed SBEM, all with right-sided pleural effusion.

The 17 patients had 26 episodes of SBEM during the study period. One had four episodes, 1 had three episodes, 4 had two episodes, and 11 had one episode. Ascites was present in 22 (85%) of the 26 episodes of SBEM, and 14 (56%) were associated with SBP. Eight (31%) were associated with bacteremia (4 E. coli, 1 Klebsiella pneumoniae, 2 Streptococcus, 1 Gemella morbillorum). Only 5 episodes (19%) had positive bacterial culture of pleural fluid (4 E. coli, 1 Enterococcus). Only 1 episode had the same bacterial organism (E. coli) in the blood, pleural fluid, and ascites culture. Another had the same bacterial organism (E. coli) in the blood and pleural fluid culture but a negative culture for SBP, while the other had the same bacteria (E. coli) in SBEM and SBP but a negative blood culture. The signs and symptoms of SBEM at time of diagnosis are shown in Table 1.

The clinical and laboratory data from patients with sterile hydrothorax and from SBEM at the time of the first episode are compared in Table 2. Patients with SBEM had a significantly higher Child-Pugh score (p = 0.002), lower serum albumin level (p = 0.016), prolonged prothrombin time (p = 0.02), lower pleural fluid protein level (p = 0.001), and a higher rate to associated SBP than patients with sterile hydrothorax (p = 0.007). Multivariate analysis revealed that the pleural fluid protein level (p = 0.0035) and presence of SBP (p = 0.0062) were independent risk factors (Table 3). In cirrhotics with hydrothorax, patients with a pleural fluid protein level less than 1.2 g/dL had a 14-fold higher risk for having of SBEM compared with those with a protein level

Table 1. Symptoms and signs of SBEM at time of diagnosis

<table>
<thead>
<tr>
<th>No. of episodes</th>
<th>Total 26 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Fever/Chills</td>
<td>16 (62%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>8 (31%)</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Shock (&lt; 90/60 mmHg)</td>
<td>2 (8%)</td>
</tr>
</tbody>
</table>

NOTE. Data are presented as number and percentage of total episodes; SBEM = Spontaneous bacterial empyema.
more than 1.2 g/dL. In addition, patients with SBP had a 18-fold higher risk for having SBEM compared with those without SBP. The mortality rate during treatment was 38% (10 of 26 episodes).

The patient who had 4 episodes of SBEM underwent nuclear scan by intraperitoneal injection of Tc 99m-labeled sulfur colloid during the fourth episode of SBEM. No communication between peritoneal and pleural spaces was demonstrated, even when the ascites and pleural effusion had the same bacterial growth (E. coli) at that time. Other patients did not undergo nuclear scan.

**DISCUSSION**

According to previous reports, approximately 5-10% of patients with cirrhosis may develop pleural effusion. This is usually right-sided. In the absence of cardiac or lung disease, the presence of a pleural effusion in a cirrhotic patient is known as hepatic hydrothorax. In our study, 15% of our patients had pleural effusion. All of our patients had undergone abdominal sonography in addition to chest radiography or computed tomography. It is our experience that sonography is superior to chest radiography and computed tomography in detecting minimal pleural effusion, especially when the fluid is behind the liver. This may explain why our patients had a higher incidence of pleural effusion. Real-time image detection by sonography also helped us in tapping for minimal pleural effusion and avoiding traumatic tapping.

The incidence of SBEM in cirrhotic patients was
about 2% (17 of 862) in this study. In patients with hydrothorax, the incidence of SBEM was 13% (17 of 132), similar to a previous report. However, the incidence in this study should be considered underestimated because only 42% (56 of 132) of patients’ pleural fluids were available for analysis.

As in Table 1, 19% of the patients with SBEM had dyspnea and 8% had chest pain; thus less than 20% of symptoms and signs may arouse clinicians to check the chest condition. But when the chest pain especially arises from the right side, it may be meaningful to cirrhotic patients with right-side hydrothorax and to clinicians for early diagnosis of SBEM. It should be emphasized that diagnostic thoracentesis should be performed in cirrhotic patients with hydrothorax when infection is suspected or when clinical deterioration happens.

Similar to others’ findings on SBP, this study showed that a low serum albumin level, prolonged prothrombin time, low pleural fluid protein level, and advanced liver disease as expressed by high Child-Pugh scores were risk factors for the occurrence of SBEM. Advanced liver disease and a low pleural fluid protein level may imply low complement levels and poor opsonic activity in pleural fluid as in ascites. The pleural fluid will become easily infected.

Some studies suggested that the development of hepatic hydrothorax is secondary to passage of ascites from the abdomen to the pleural space via defects in the diaphragm, and that it may have occurred in patients with no demonstrable ascites. The ascites may be drawn into the chest preferentially through the defects because of the negative intrathoracic pressure. In this study, 4% (39 of 862) of cirrhotic patients had hydrothorax without ascites, but 88% (15 of 17) of patients with SBEM had ascites at the same time.

There are 2 hypotheses about the development of SBEM: through spontaneous bacteremia as in SBP, or through the flow of infected ascites from the peritoneal to the pleural cavity via defects in the diaphragm, i.e., SBEM is secondary to SBP. In cirrhotic patients, portal hypertension is responsible for the development of ascites and portosystemic collateral circulation. Normally bacteria are filtered from the blood stream by the liver, but in patients with portosystemic shunting, blood is diverted around the liver and bacteremia become more frequent and prolonged. Pleural effusion, as ascites, can be considered an innocent target of the prolonged bacteremia in patients with porto-systemic shunting and become infected in a similar manner as in SBP. If the pathogenesis of SBEM occurs this way, the bacterial organism in the blood culture and pleural fluid should be the same. If the pathogenesis of SBEM was secondary to SBP via the defects in the diaphragm, the bacterial organism in the ascites culture should be the same as in the pleural fluid culture.

In the present study, only 31% of SBEM were associated with bacteremia but 56% with SBP, which is one of the significant variables during the multivariate analysis. It seems most of the SBEM may be secondary to SBP via defects in the diaphragm; however, we did not have enough evidence to prove that due to the low positive culture rate. For the patient who had his fourth episode of SBEM when the ascites and pleural effusion showed the same bacterial growth (E. coli) but was with a negative blood culture, we were unable to demonstrate the communication between peritoneal and pleural spaces by nuclear scan. Due to this disappointing experience and the cost factor, the other patients did not undergo nuclear scan examination.

In this study, 17 patients had 26 episodes of SBEM during the follow-up period. This represents a high recurrence rate of 50%. Antibiotic prophylaxis was not administered in patients who had had a previous SBEM because resistant strains might be selected and side effects might develop due to the patient’s impaired liver function.

For hospital policy, we used conventional method for bacterial culture of pleural fluid. Only 21% of SBEM in this study had a positive bacterial culture. A previous report on SBP concluded that the inoculation of ascitic fluid into a tryptic-soy-broth blood culture bottle at the patient’s bedside is more sensitive than the conventional method. This should also be used for pleural fluid culture of cirrhotic patients with SBEM to improve culture yielding rate. However, it also raises the suspicion that many of the patients with pleural fluid PMN count 500 cells/mm³ with negative culture were not really developing SBEM but had other possible causes, such as reactive
leukocytosis or traumatic tap. As stated above, the diagnosis of SBEM in this study was according to previously reported criteria. The criteria are similar to the diagnosis of SBP except that pneumonia must be ruled out and there should be evidence of pre-existing pleural effusion before SBEM or with pleural fluid transudate characteristics during SBEM. The data of LDH and glucose level in pleural effusion were not included in the criteria. Transudate characteristics are the pleural effusion having predominance of mononuclear cells in the differential, glucose level in pleural effusion equal to that of serum, normal PH, and without neither of the following features as in exudates: (1) pleural effusion protein to serum protein ratio > 0.5; (2) pleural effusion LDH to serum LDH ratio > 0.6. But when we use the term “empyema” in pulmonary disease, it mean an exudative pleural effusion caused by direct infection of the pleural space. The resulting pleural effusion is purulent and exudative. The white blood cell count in pulmonary empyema is often > 25000 cells/mm³, with predominance of PMN leukocyte in the differential. According to the criteria of SBEM, this infection is a transudate but not an exudate. This may help distinguish SBEM from malignant effusion, parapneumonic effusion, tuberculosis, and real empyema. According to previous reports, placement of a chest tube is contraindicated in patients with hepatic hydrothorax and SBEM due to the risk of life-threatening fluid depletion and electrolyte imbalance. None of our patients underwent chest tube insertion, but 7 episodes underwent temporary pig-tail drainage for symptom relief without evident complication. About 1500 mL was drained daily until the amount was less than 150 mL/day. Two episodes had combined with ascites but only pleural effusion was drained. Transjugular intrahepatic portosystemic shunting (TIPS) procedure was suggested to patients with recurrent SBEM and intractable hydrothorax because some reports had recommended its benefits in such patients. In this study, our patients did not undergo TIPS.

The gross appearance of pleural effusion from hydrothorax and SBEM usually is transparent, yellowish, homogeneous and without clotting. In our experience, most bloody pleural effusion is the result of a slightly traumatic tap. Leakage of blood into the pleural cavity may lead to an elevated WBC count. Because neutrophils predominate in blood, the pleural effusion differential count may be altered by contamination of pleural effusion with blood. To correct this, 1 PMN is subtracted from the absolute pleural effusion PMN count for every 250 RBC, as we applied in the ascites cell counts. If the corrected PMN count in a bloody specimen is greater than 250 cells/mm³, the patient must be assumed infected. In this study, we usually performed thoracentesis under sonography-guidance to avoid traumatic tapping. Thus we had 53 patients with minimal pleural effusion not undergoing thoracentesis due to impractical or technical reason. None of these patients had been considered to have infection according to clinical characteristics. In this study, 7 patients had hepatoma with lung metastasis. The characteristics of their pleural effusion were bloody appearance and > 200,000 RBC/mm³. After correcting PMN count and culture of pleural effusion, these patients did not meet the criteria for diagnosis of SBEM. We also encountered 3 cirrhotic patients having pneumonia with lung abscess. Their pleural effusion had turbid appearance and > 25,000 WBC/mm³. These patients could be excluded from the diagnosis of SBEM by image studies and exudate characteristics in pleural effusion.

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The serum-ascites albumin gradient has been used to categorize ascites better than either the total protein concentration or other parameters do. Can serum-hydrothorax albumin gradient provide the same effect? We did not measure the albumin level of pleural effusion in this study. We hope further studies in the future can discuss this issue.

In summary, SBEM is a rare complication of cirrhotic patients. However, the mortality rate is as high as 38%. Patients with advanced liver disease, low pleural fluid protein level, or presence of SBP, are predisposed to SBEM. A diagnostic thoracentesis should be performed...
in cirrhotic patients with hydrothorax when infection is suspected or clinical deterioration occurs.

REFERENCES