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SPONTANEOUS BACTERIAL PLEURITIS IN PATIENTS WITH LIVER CIRRHOSIS: PREVALENCE AND RISK FACTORS

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ABSTRACT

Background: Spontaneous bacterial pleuritis or spontaneous bacterial empyema (SBEM) is the natural infection of a hepatic hydrothorax. SBEM is often under diagnosed although it`s associated with a bad outcome, mortality reaching 38%. **Objectives:** This study was designed to study the prevalence of SBEM in patients with liver cirrhosis and hepatic hydrothorax and to determine the possible risk factors contributing to the development of SBEM. **Patients and Methods:** The present study included patients with liver cirrhosis and hepatic hydrothorax admitted to the Chest, Tropical medicine & Gastroenterology departments, Sohag University Hospitals during the period between October 2017 to October 2018. Sonographic guided aspiration of the pleural and ascitic fluid was done, then the aspirate was subjected to chemical, bacteriological and cytological examination. **Results:** 105 patients (53.3% males) were included with a mean age of 59.7 years old, 13.3% of patients had SBEM, and 22.8% had SBP. 57.14% of cases with SBEM showed positive pleural fluid culture. E. Coli was the most common organism in culture positive patients (50%). Most patients with SBEM were presented with fever, chest pain, abdominal pain and septic shock. Presence of SBP, low serum albumin level, low pleural fluid protein level and advanced liver disease as expressed by high Child Pugh score and class C Child Pugh class together with prolonged INR were found to be independent risk factors for the development of SBEM. The mortality rate in patients with SBEM was 35.7%. **Conclusion:** This study confirmed that SBEM is a common complication in patients with liver cirrhosis and hepatic hydrothorax with increased risk of mortality. Many risk factors are associated with increased incidence of SBEM as presence of SBP, low serum albumin level, low pleural fluid protein level and advanced liver disease as expressed by high Child Pugh score and class C Child Pugh class together with prolonged INR.

KEYWORDS: SBEM, SBP, liver cirrhosis, hepatic hydrothorax.

ABBREVIATIONS

SBP: Spontaneous bacterial peritonitis, SBEM: Spontaneous bacterial empyema, BMI: Body Mass Index, DM: Diabetes Mellitus, HTN: Hypertension, COPD: Chronic Obstructive Pulmonary Disease, ILD: Interstitial Lung Disease, AST: Aspartate Transaminase INR: International Normalization Ratio, ALT: Alanine Transaminase, WBCs: White Blood Cells, HGB: Hemoglobin, PLTs: Platelets, SBP: Spontaneous Bacterial Peritonitis, PMNL: Plymorph Nuclear Leucocytes, LDH: Lactate Dehydrogenase, PH: Power of Hydrogen, AFB: Acid Fast Bacilli.

INTRODUCTION

Hepatic hydrothorax is defined as a significant pleural effusion, usually greater than 500 mL, in a cirrhotic patient without any underlying pulmonary or cardiac diseases. It appears to be a relatively uncommon complication of portal hypertension with an estimated prevalence of 5–12% in patients with cirrhosis of the liver. Hepatic hydrothorax is usually right sided (65–87% of reported cases), but may be left sided or bilateral,[2,1] Spontaneous bacterial pleuritis or spontaneous bacterial empyema (SBEM) is the natural infection of a hepatic hydrothorax. 2 -2.4% of patients with cirrhosis and 13 -16% of patients with hepatic hydrothorax are estimated to have SBEM.[3] Spontaneous bacterial empyema is defined by pleural fluid polymorphonuclear (PMN) count > 250 cells/mL with a positive culture or a pleural fluid PMN count > 500 cells/mL with a negative culture - following exclusion of parapneumonic infections. Excluded parapneumonic infections by documenting: absence of radiological

evidence of pneumonia, history of a pleural effusion and transudate characteristics during current infection.[3] The infection of the pleural fluid is frequently associated with few localizing signs. Therefore, a high index of suspicion is essential for the diagnosis of SBEM. Any patient with hydrothorax who develops fever, pleuritic pain, encephalopathy, or unexplained deterioration in renal function should undergo diagnostic thoracentesis,[2,4] The actual incidence of SBEM may be higher than reported due to under-diagnosis. The diagnosis of SBEM is overlooked by the immediate initiation of empiric antibiotics in patients with cirrhosis and fever or hepatic encephalopathy for suspicion of spontaneous bacterial peritonitis (SBP).[3,5] The common pathogens isolated from pleural fluid in patients with SBEM are similar to those ordinarily grown in ascitic fluid cultures in patients with SBP namely E.coli and K. pneumonia. The proposed mechanism for the development of SBEM is the transmigration of infected fluid from the peritoneal cavity to the pleural space, commonly the right side, through the defects in the diaphragm which are weakened as a result of hypoalbuminemia, malnutrition, and hypercatabolic state. The evidence supporting this mechanism is that 54 - 58% of SBEM patients have concomitant SBP. Studies have reported 34% - 38% patients with SBEM and concurrent ascites did not have SBP.[3,6,8,7] Hematogenous spread of gut bacteria to the pleural cavity was proposed to explain SBEM in patients without SBP. A combination of bacterial overgrowth and translocation, depressed hepatic reticuloendothelial system and low concentrations of C3, C4 and opsonic activity levels in the pleural fluid was thought to explain this theory.[3,9,10] Patients with advanced liver disease (higher Child-Pugh score, lower serum albumin, prolonged prothrombin time), low pleural fluid protein level, or SBP are predisposed to SBEM.[7] SBEM does not conform to the classical definition of empyema or its management; although SBEM can rarely turn into an empyema, pus in the pleural cavity, if neglected. Chest tube insertion, the least aggressive management for empyema, is relatively contra-indicated in SBEM. Studies have uniformly proven that SBEM can be successfully treated with antibiotics alone. The term spontaneous bacterial pleuritis, which was intermittently used in the past, would more aptly describe this condition and help prevent improper management.[3] The mortality and recurrence rates of patients with SBEM were notably 38% and 25%, respectively.[3,8]

PATIENTS AND METHODS

This prospective study was carried out on 105 patients (56 males and 49 females) with liver cirrhosis admitted to chest, tropical medicine and gastroenterology departments, Sohag university hospitals during the period from October 2017 to October 2018. All patients were informed and a written consent was obtained from all patients to participate to the study.

Patients Inclusion criteria

All patients with liver cirrhosis presented with pleural effusion.

Patients Exclusion criteria

- Patients with exudative pleural effusion.
- Patients showing radiological evidence of pneumonia together with the pleural effusion.
- Patients already diagnosed lung cancer.
- Patients under chemotherapy due to extrapulmonary malignancy.

Methods

All patients were subjected to the following

1. Through clinical history.
2. Through clinical examination:
3. Abdominal ultrasound and/or computerized tomography: To confirm the presence of liver cirrhosis and to detect ascites.
4. Chest radiographs:

- Chest X-Rays.
- Chest ultrasound if needed.
- Chest C.T. scan if needed.
- CT pulmonary angiography if needed.

5. ECG and echocardiography if needed.

6. Laboratory investigations:

- Complete blood count including differential count.
- Complete metabolic profile (serum urea, serum creatinine, liver enzymes, serum albumin, serum total proteins, serum bilirubin, serum alkaline phosphatase, serum glucose, serum electrolytes (NA+, K+, Ca++).
- Arterial blood gases.

7. Sonographic guided aspiration of the pleural and ascitic fluid were done.

- Chemical analysis of pleural and ascitic fluid were done (pH, white blood cells both total and differential count, proteins, glucose, LDH).
- Pleural and ascitic fluid direct film for acid fast bacilli AFB.
- Pleural and ascitic fluid cytology for malignant cells.
- Pleural and ascitic fluid bacterial culture were performed using a conventional method: 10 mL of fluid was collected in an empty sterile container and sent to the laboratory immediately and cultured on chocolate agar, blood agar, MacConkay agar, and thioglycolate broth under aerobic and anaerobic conditions at 37°C for 5 days

8. Child Pugh score was calculated for each patient.

Statistical methods used for data analysis

Data was analyzed using STATA version 14.2 (Stata Statistical Software: Release 14.2 College Station, TX: StataCorp LP.). Quantitative data was represented as mean, standard deviation, median and range. Data was analyzed using student t-test to compare means of two

groups. When Mann-Whitney test was used. Qualitative data was presented as number and percentage and compared using either Chi square test or fisher exact test. Odds ratios were obtained from logistic regression analysis. Graphs were produced by using Excel or STATA program. P value was considered significant if it was less than 0.05.

RESULTS

The study was conducted on patients with liver cirrhosis admitted to chest & tropical medicine and gastroenterology departments, Sohag university hospitals during the period from October 2017 to October 2018. After application of inclusion and exclusion criteria, 105 patients (56 males and 49 females) were included in this study.

Table (1): Comparison between patients with uncomplicated hepatic hydrothorax and patients with SBEM according to personal characteristics.

Variable	Uncomplicated hepatic hydrothorax N=91	SBEM N=14	P value
Age (year)			
Mean ± SD	60.15±18.10	57.07±15.78	0.44
Median (range)	61.5 (17-90)	60 (27-84)	
Gender			
Female	45 (49.45%)	4 (28.57%)	0.14
Male	46 (50.55%)	10 (71.43%)	
Residence			
Rural	49 (53.85%)	8 (57.14%)	0.86
Urban	42 (46.15%)	6 (42.86%)	
BMI			
Mean ± SD	24.44±1.49	23.81±0.86	0.13
Median (range)	24.91 (20.91-27.21)	23.81 (22.02-24.8)	
Smoking			
Non-smoker	64 (70.33%)	7 (50.00%)	0.31
Current smoker	15 (16.48%)	3 (21.43%)	
Former smoker	12 (13.19%)	4 (28.57%)	
Smoking index	N=27	N=7	
Mild	1 (3.70%)	0	0.26
Moderate	19 (70.37%)	7 (100%)	
Heavy	7 (25.93%)	0	

BMI: Body Mass Index
SBEM: Spontaneous Bacterial Empyema

There was no significant statistical relationship between incidence of SBEM and age, sex, residence, BMI, smoking status or smoking index (P value 0.44, 0.14, 0.86, 0.13, 0.31 and 0.26 respectively).

Table (2): Comparison between patients with uncomplicated hepatic hydrothorax and with SBEM according to clinical picture.

Variable	Uncomplicated hepatic hydrothorax N=91	SBEM N=14	P value
Dyspnea			
No	26 (28.57%)	1 (7.14%)	0.18
Yes	65 (71.43%)	13 (92.86%)	
Chest pain			
No	81 (89.01%)	8 (57.14%)	0.003
Yes	10 (10.99%)	6 (42.86%)	
Fever			
No	59 (64.84%)	5 (35.71%)	0.03
Yes	32 (35.16%)	9 (64.29%)	
Cough			
No	53 (58.24%)	3 (21.43%)	0.008
Yes	38 (41.76%)	11 (78.57%)	
Abdominal pain			
No	72 (79.12%)	7 (50.00%)	0.02

Yes	19 (20.88%)	7 (50.00%)	
Hepatic encephalopathy			
No	31 (34.07%)	3 (21.43%)	0.54
Yes	60 (65.93%)	11 (78.57%)	
Grade of hepatic encephalopathy	N=60	N=11	
II	21 (35.00%)	6 (54.55%)	0.47
III	21 (35.00%)	3 (27.27%)	
IV	18 (30.00%)	2 (18.18%)	
Septic shock			
No	91 (100%)	10 (71.43%)	<0.0001
Yes	0	4 (28.57%)	

SBEM: Spontaneous Bacterial Empyema

Regarding the clinical presentation, there was a highly statistically significant relationship between the presence of chest pain, cough and septic shock and the incidence of SBEM (P value 0.003, 0.008 and <0.0001 respectively). There was a statistically significant relationship between the presence of fever and abdominal pain and the incidence of SBEM (P value 0.03 and 0.02 respectively). There was no statistically significant relationship between presence of dyspnea, presence of hepatic encephalopathy or its grade and the incidence of SBEM (P value and 0.18, 0.54 and 0.47 respectively).

Table (3): Comparison between patients with uncomplicated hepatic hydrothorax and patients with SBEM according to clinical and radiological chest characteristics.

Variable	Uncomplicated hepatic hydrothorax N=91	SBEM N=14	P value
Chronic chest problem			
No	78 (85.71%)	14 (100%)	
Bronchial asthma	3 (3.30%)	0	0.66
Bronchiectasis	2 (2.20%)	0	
COPD	5 (5.49%)	0	
ILD	3 (3.30%)	0	
DM			
No	78 (85.71%)	10 (71.43%)	0.11
Yes	13 (14.29%)	4 (28.57%)	
Hypertension			
No	82 (90.11%)	13 (92.86%)	1.00
Yes	9 (9.89%)	1 (7.14%)	
Laterality of pleural effusion			
Right	82 (90.11%)	11 (78.57%)	0.50
Left	6 (6.59%)	2 (14.29%)	
Bilateral	3 (3.30%)	1 (7.14%)	
Amount of pleural effusion			
Mild	75 (82.42%)	9 (64.29%)	
Moderate	9 (9.89%)	5 (35.71%)	0.07
Marked	5 (5.49%)	0	
Massive	2 (2.20%)	0	

SBEM: Spontaneous Bacterial Empyema
DM: Diabetes Mellitus
COPD: Chronic Obstructive Pulmonary Disease
ILD: Interstitial Lung Disease

There was no significant statistical relationship between incidence of SBEM and presence of any chronic chest problem, laterality or amount of pleural effusion, presence of DM or HTN (P value 0.66, 0.50, 0.07, 0.11 and 1.00 respectively).

Table (4): Comparison between patients with uncomplicated hepatic hydrothorax and with SBEM according to laboratory characteristics.

Variable	Uncomplicated hepatic hydrothorax N=91	SBEM N=14	P value
WBCs			
Mean ± SD	7.40±1.82	8.82±0.74	0.005
Median (range)	7.05 (4.3-12)	8.9 (7.5-9.9)	
HGB			
Mean ± SD	7.46±1.85	8.20±1.38	0.15
Median (range)	7.2 (4.3-12)	8.25 (5.8-10.7)	
PLTs			
Mean ± SD	161155±103795	126000±38723	0.51
Median (range)	143500 (20000-478000)	130000 (56000-180000)	
AST			
Mean ± SD	63.17±17.06	64.21±17.90	0.83
Median (range)	62 (36-90)	64 (36-90)	
ALT			
Mean ± SD	62.90±15.70	61.21±17.41	0.71
Median (range)	60 (36-90)	59 (36-90)	
Serum albumin			
Mean ± SD	2.33±0.37	1.84±0.40	<0.0001
Median (range)	2.25 (1.9-2.9)	1.75 (1.3-2.5)	
Serum total protein			
Mean ± SD	5.98±0.41	4.98±0.43	0.003
Median (range)	6 (5.1-6.8)	5 (4.1-5.8)	
Total bilirubin			
Mean ± SD	3.02±0.87	3.06±0.94	0.93
Median (range)	2.8 (1.6-4.5)	3.0 (1.6-4.5)	
Direct bilirubin			
Mean ± SD	1.92±0.64	2.02±0.77	0.63
Median (range)	1.85 (1-3.7)	2 (1-3.5)	
Indirect bilirubin			
Mean ± SD	1.13±0.40	1.04±0.48	0.41
Median (range)	1.1 (0.4-1.9)	1.0 (0.4-1.9)	
INR			
Mean ± SD	1.46±0.27	1.94±0.19	<0.0001
Median (range)	1.4 (1.0-1.9)	1.9 (1.7-2.3)	
Creatinine			
Mean ± SD	1.52±0.61	1.57±0.62	0.78
Median (range)	1.4 (0.8-2.7)	1.45 (0.8-2.7)	
Na^+			
Mean ± SD	135.22±6.76	134.93±7.61	0.88
Median (range)	135.5 (120-147)	136.5 (120-147)	
K^+			
Mean ± SD	3.68±0.84	3.4±0.78	0.24
Median (range)	3.7 (1.9-5.1)	3.45 (2.4-5.1)	
Ca^{++}			
Mean ± SD	1.0±0.11	1.0±0.12	0.97
Median (range)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	

SBEM: Spontaneous Bacterial Empyema
AST: Aspartate Transaminase INR: International Normalization Ratio
ALT: Alanine Transaminase WBCs: White Blood Cells
HGB: Hemoglobin
PLTs: Platelets

The WBCs count was significantly elevated in patients with SBEM compared with patients with uncomplicated sterile hepatic hydrothorax (P value 0.005). There was no significant relationship between blood hemoglobin or platelet count and the incidence of SBEM (P value 0.15 and 0.51 respectively). There was a highly significant statistical relationship between prolonged INR, serum albumin level and total serum protein level and the incidence of SBEM (P value <0.0001, <0.0001 and 0.003 respectively). There was no significant statistical

relationship between AST, ALT, total, direct and indirect bilirubin and the incidence of SBEM (P value 0.83, 0.71,0.93, 0.63 and 0.41 respectively).There was no statistically significant relationship between serum creatinine, serum Na^+, serum K^+ and serum Ca^{++} and the incidence of SBEM (P value 0.78, 0.88, 0.24 and 0.97 respectively).

Table (5): Comparison between patients with uncomplicated hepatic hydrothorax and patients with SBEM according to SBP, child Pugh score and child Pugh classification.

Variable	Uncomplicated hepatic hydrothorax N=91	SBEM N=14	P value
SBP			
No	75 (82.42%)	6 (42.86%)	0.002
Yes	16 (17.58%)	8 (57.14%)	
Child Pugh score			
Mean ± SD	9.66±1.41	11.57±1.16	<0.0001
Median (range)	10 (7-12)	12 (9-13)	
Child Pugh classification			
B	31 (34.07%)	1 (7.14%)	0.006
C	60 (65.93%)	13 (92.86%)	

SBEM: Spontaneous Bacterial Empyema
SBP: Spontaneous Bacterial Peritonitis

There was a highly significant statistical relationship between presence of SBP, high Child Pugh score and Child Pugh class and the incidence of SBEM (P value 0.002, <0.0001 and 0.006 respectively).

Table (6): Comparison between patients with uncomplicated hepatic hydrothorax and with SBEM according to pleural fluid characteristics.

Variable	Uncomplicated hepatic hydrothorax N=91	SBEM N=14	P value
Plural fluid WBCs			
Mean ± SD	448.60±73.31	1187.21±199.88	<0.0001
Median (range)	450 (250-600)	1105 (950-1650)	
Plural fluid PMNL			
Mean ± SD	45.06±7.85	1059.93±171.30	<0.0001
Median (range)	47 (20-60)	4022.5 (850-1482)	
Plural fluid protein			
Mean ± SD	2.45±0.23	1.24±0.16	<0.0001
Median (range)	2.5 (2-2.9)	1.2 (1.0-1.5)	
Plural fluid glucose			
Mean ± SD	130.99±24.15	104.57±30.80	0.0004
Median (range)	129 (59-185)	95 (69-151)	
Plural fluid LDH			
Mean ± SD	75.28±13.67	96.64±23.39	<0.0001
Median (range)	76 (50-100)	92.5 (65-129)	
Plural fluid PH			
Mean ± SD	7.42±0.05	7.41±0.04	0.42
Median (range)	7.42 (7.35-7.52)	7.42 (7.36-7.49)	

WBCs: White Blood Cells
PMNL: Plymorph Nuclear Leucocytes
LDH: Lactate Dehydrogenase
PH: Power of Hydrogen

There was a highly statistically significant relationship between pleural fluid protein, glucose and LDH and the incidence of SBEM (P value <0.0001, 0.0004 and <0.0001 respectively). There was no statistically significant relationship between pleural fluid PH and the incidence of SBEM (P value 0.42).

Table (7): Pleural fluid culture, causative organism and antibiotic sensitivity in SBEM patients (N=14).

Variable N=14	Summary statistics
Pleural fluid +ve culture	
No	6 (42.86%)
Yes	8 (57.14%)
Organism	**N=8**
E.coli	4 (50.00%)
Klebsiella	2 (25.00%)
Enterococcus	1 (12.50%)
Streptococcus spec.	1 (12.50%)
Antibiotic sensitivity	**N=8**
Meropenem	8 (100%)
Ceftriaxone	5 (62.50%)
Ciprofloxacin	5 (62.50%)
Levofloxacin	4 (50.00%)
Cefotaxime	4 (50.00%)

SBEM: Spontaneous Bacterial Empyema

14 patients were diagnosed as having SBEM, of them 8 patients had positive pleural fluid culture. Of these 8 patients, 8 cases showed positive culture for E.coli (50%), 2 cases were positive for Klebsiella (25%), 1 case was positive for Enterococcus (12.5%) and 1 case was positive for Streptococcus spec. (12.5%). All the 8 patients with positive pleural fluid culture showed sensitivity to Meropenem (100%), 5 patients showed sensitivity to Ceftriaxone (50%), 5 patients were sensitive to Ciprofloxacin (50%), while 4 patients were sensitive to Levofloxacin (50%) and 4 patients were sensitive to Cefotaxime (50%).

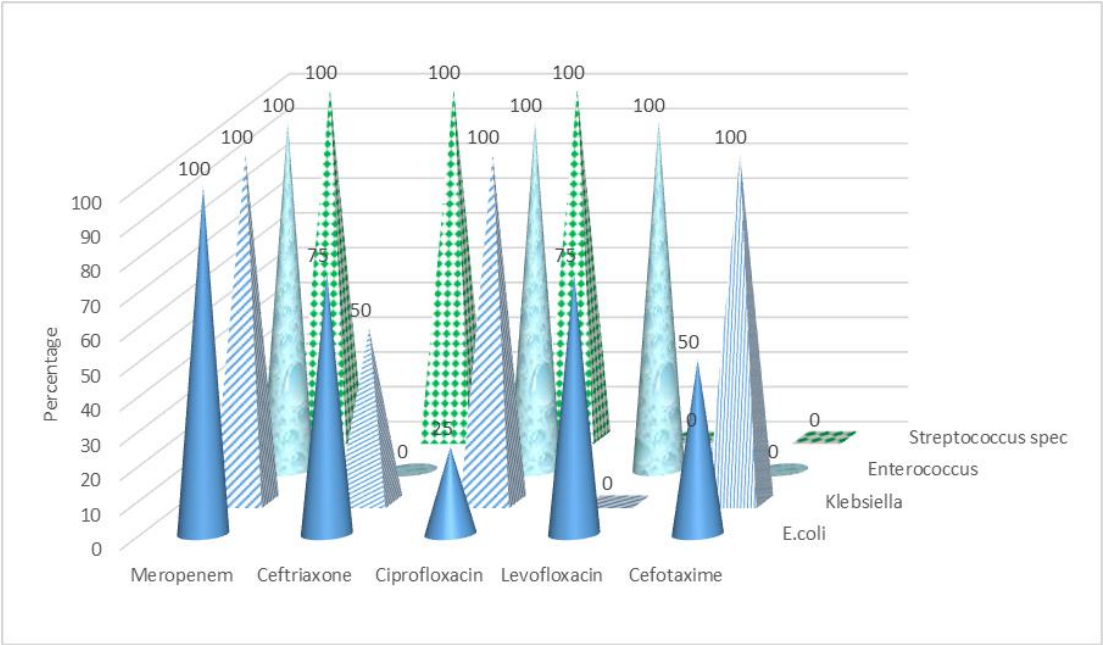

Figure (1): Antibiotic sensitivity by organism.

Table (8): Comparison between patients with uncomplicated hepatic hydrothorax and with SBEM according to hospital outcome.

Outcome	Uncomplicated hepatic hydrothorax N=91	SBEM N=14	P value
Alive	83 (91.21%)	9 (64.29%)	0.02
Dead	8 (8.79%)	5 (35.71%)	

SBEM: Spontaneous Bacteria Empyema

SBEM was associated with increased risk of mortality compared to patients with uncomplicated hepatic hydrothorax (P value 0.02).

Table (9): Multivariate analysis of factors affecting occurrence of SBEM.

Variable	Odds ratio (95% confidence interval)	P value
SBP	2.67 (0.79-7.67)	0.03
Child Pugh score	2.75 (1.22-6.20)	0.02
WBCs	1.84 (1.02-3.30)	0.04
Serum albumin	0.06 (0.005-0.67)	0.02
Pleural fluid protein	0.04 (0.003-0.54)	0.02

SBEM: Spontaneous Bacterial Empyema
WBCs: White Blood Cells
SBP: Spontaneous Bacterial Peritonitis

There was a statistically significant relationship between presence of SBP, high Child Pugh score, leukocytosis, low serum albumin and low pleural fluid protein and the incidence of SBEM (P value was 0.03, 0.02, 0.04, 0.02 and 0.02 respectively).

DISCUSSION

Progressive liver disease may finally lead to cirrhosis, which may be complicated by ascites, portal hypertension, varices, and hepatorenal syndrome.[11] Liver cirrhosis may be associated with various lung diseases such as hepatopulmonary syndrome, portopulmonary hypertension, and hepatic hydrothorax.[12] Hepatic hydrothorax is reported to occur in up to 10% of the patients with ascites, causing dyspnea and respiratory infection with bad prognosis.[13] It usually develops as a result of passage of the ascitic fluid through the diaphragmatic defects.[14] SBEM is a serious condition seen in patients with cirrhosis and is associated with high mortality.[15,2,7,8] However, few studies were conducted on SBEM, unlike SBP. The goal of this study is to determine the incidence and to identify the possible risk factors for developing SBEM among patients with liver cirrhosis and hepatic hydrothorax in the Sohag University Hospital. With regard to the laterality of hepatic hydrothorax, in the present study it was right sided in 88.6%, left sided in 7.6% and bilateral in 3.8% of the cases, agreeing with results by Makhlouf HA, et al., 2013.[2] that showed that it was right sided in 86.9% and left sided in 8.2% of the cases and with the results by Emam M., et al., 2015.[22] who found that right sided pleural effusion was present in 87.6%, left sided 9% and bilateral in 3.4%which coincides with earlier studies.[1,7,17] In our study the prevalence of SBP was 22.8% similar to the results by Chen T-A, et al., 2003.[7] who reported that the prevalence of SBP was 23% and Mohamed A, et al., 2017.[24] who reported that the incidence of SBP was 24.3%, while was lower than that reported by Emam M, et al., 2015.[22] (33.5%). In cirrhotic patients with hydrothorax, the prevalence of SBEM was 13.3% in the present study which was lower than that reported by Makhlouf HA, et al., 2013.[2] who reported that it was 26.2% and it was 30% in the results by Gur C., et al., 2004.[16] while agreeing with the results byXiol X., et al., 1996.[15] which was 13%, Chen T-A., et al., 2003.[7] which was 13% also, Chen C-H., et al., 2011.[8] which was 16%, Emam M, et al., 2015[22] and Mansour AE, et al., 2013[23] which was 14.3% and Mohamed A, et al., 2017[24] which was 51.4%.This study confirms that SBEM is a relatively common complication of cirrhotic patients with hydrothorax. SBEM is rarely diagnosed, not only because patients with hydrothorax are unusual, but also because thoracentesis is not performed routinely in cirrhotic patients with hydrothorax.[15] Any patient with hepatic hydrothorax who develops fever, pleuritic pain, encephalopathy, or unexplained deterioration in renal function should undergo diagnostic thoracentesis (4). In the present study, the most presenting manifestations of SBEM are dyspnea (92.7%), cough (78.6%), hepatic encephalopathy (78.6%), fever (64.3%), abdominal pain (50%), chest pain (42.9%) and septic shock (28.6%) agreeing with the results by Makhlouf HA, et al., 2013[2] who reported dyspnea was present in 93.8%, but the incidence of fever was higher than in our study (93.8%) followed by abdominal pain and encephalopathy (62.5% each) and septic shock (25%), while Chen T-A, et al., 2003[7] reported that 19% of patients with SBEM had dyspnea, 8% had chest pain, 62% had fever, 35% had chest pain. 12% presented with hepatic encephalopathy and 8% with septic shock. In this study, we found a statistically significant relationship between fever, abdominal pain and septic shock and the presence of SBEM rather than sterile hydrothorax agreeing with the results by Makhlouf HA, et al., 2013.[2] We also found a statistically significant relationship between cough and chest pain and SBEM in contrast to the results by Makhlouf HA, et al., 2013[2] who didn`t report such significant relationship. We also found no significant relationship between dyspnea and hepatic encephalopathy and SBEM while Makhlouf HA, et al., 2013[2] found that dyspnea was not statistically significant while hepatic encephalopathy had high statistically significant relationship with SBEM. In our study we found no statistically significant relationship between the laterality or the amount of pleural effusion and the incidence of SBEMagreeing with the results by Makhlouf HA, et al., 2013[2] and Emam M, et al., 2015[22] who found no significant relationship between laterality of pleural effusion and SBEM. There are two hypotheses about the development of SBEM: through spontaneous bacteremia as in SBP, or through the flow of infected ascites from peritoneal to pleural cavity via defects in the diaphragm, i.e., SBEM is secondary to SBP[15,19] 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 becomes more frequent and prolonged[20] Pleural effusion such as in ascites can be considered an innocent target of prolonged bacteremia in patients with portosystemic shunting and may become infected in a similar manner as in SBP,[19] In our study, 57.14% of patients diagnosed with SBEM had SBP versus only 17.58% of patients with sterile hydrothorax and that was statistically significant agreeing with the results by Makhlouf HA, et al., 2013[2] who found that 56.3% of patients with SBEM had SBP and 47% in the results by Mohamed A. et al., 2017[24] and 56% in the results by Chen T-A, et al., 2003,[7] and the results by Mansour AE., et al., 2013[23] who reported that 57.1% of patients with SBEM had SBP and Emam M, et al., 2015[22] who reported that 63% of patients with SBEM had concomitant SBP Vs only 9.5% of patients with sterile hepatic hydrothorax We also found that the mean Child Pugh score in patients with higher in patients with SBEM than in patients with sterile hepatic hydrothorax and that was statistically significant disagreeing with the results by Makhlouf HA, et al., 2013[2] who fund no statistically significant relationship between the Child Pugh score and the incidence of SBEM, while agreeing with the results by Chen T-A, et al., 2003.[7] In our study we found that high Child Pugh class was associated with increased risk of SBEM agreeing with the results by Emam M, et al., 2015.[22] Regarding CBC, we found a statistically significant relationship between increased WBCs count and the incidence of SBEM while there was no significant relationship between HGB level nor platelets count and SBEM in contrast to the results of Makhlouf HA, et al., 2013.[2] who reported no significant relationship between SBEM and WBCs, HGB or Platelets count.Regarding liver function tests, in our study we found a statistically significant relationship between the incidence of SBEM and low serum albumin, low serum total proteins and prolonged INR, in coincidence with the results by Makhlouf HA, et al., 2013[2] who reported that low serum albumin was associated with increased incidence of SBEM, while the same authors found no significant relationship between SBEM and prolonged INR, while Chen T-A, et al., 2003[7] reported that lower serum albumin level and prolonged INR were associated with increased incidence of SBEM. on the other hand, Mansour AE., et al., 2013[23] found no significant difference in serum albumin level between patients with sterile hepatic hydrothorax and patients with SBEM. There was no significant relationship in our study between SBEM and AST, ALT, serum bilirubin, serum creatinine and serum Na, K, Ca which is coincident with earlier studies as by Makhlouf HA, et al., 2013.[2] Regarding pleural fluid study, in our study we found a highly significant relationship between the incidence of SBEM and increased number of pleural fluid total leucocytic count, increased number of polymorph-nuclear leucocytes PMNL, increased level of pleural fluid LDH and low levels of pleural fluid glucose in agreement with the results by Makhlouf HA, et al., 2013 (2) who reported a statistically significant relationship between SBEM and increased pleural fluid PMNL, increased pleural fluid LDH and decreased pleural fluid glucose and Emam M, et al., 2015[22] who found a statistically significant relationship between increased pleural fluid polymorphs and increased incidence of SBEM and in contrast to Allam NAH, 2008,[18] who reported that LDH and glucose were not reported to differ significantly between the patients with SBEM and those with noninfected effusion, while Mansour AE., et al., 2013[23] who found a statistically significant relationship between increased pleural fluid PMNL count and increased incidence of SBEM while so significant relationship between pleural fluid glucose and pleural fluid LDH and the incidence of SBEM. We also found a statistically significant relationship between low pleural fluid protein level and SBEM agreeing with the results by Chen T-A, et al., 2003[7] who found that low pleural fluid protein was associated with increased incidence of SBEM and Mansour AE., et al., 2013[23] and in contrast to the results by Makhlouf HA, et al., 2013[2] who reported no significant relationship between SBEM and pleural fluid protein level, Allam NAH, 2008[18] who found no difference in pleural fluid protein between patients with SBEM and sterile hepatic hydrothorax. Our results supports the hypothesis that advanced liver disease as expressed by high Chile Pugh score and low ascitic/pleural fluid protein level imply low complement levels and poor opsonic activity in ascitic as well as pleural fluid, thus enhancing bacterial translocation.[21,26,28,27,29,30] The pleural fluid becomes easily infected. We also found no significant relationship between pleural fluid PH and SBEM agreeing with the results by Mansour AE., et al., 2013.[23] and in contrast to Makhlouf HA, et al., 2013.[2] who reported a statistically significant relationship between low pleural fluid PH and SBEM.In our study, 57.14% of cases with SBEM showed bacterial growth in pleural culture using the conventional method in contrast to 25% positive pleural culture in the study by Makhlouf HA, et al., 2013.[2] and 33% by Xiol X, et al., 1996.[15] and 19% by Chen T-A, et al., 2003.[7] and 64.3% by Mansour AE., et al., 2013.[23] and 67.4% in the results by Emam M, et al., 2015.[22] The bacteria responsible for SBEM are usually E. coli, Streptococcus, Enterococcus, and Klebsiella,[10] while In our study, of the cases who showed positive pleural culture, 50% showed E. Coli growth, 25% showed Klebsiella Pneumoniae, 12.5% showed Enterococcus and 12.5% showed Streptococcus spec. while Makhlouf HA, et al., 2013.[2] reported that 54.5% of cases with culture positive pleural fluid showed E. Coli. Xiol X, et al., 1996.[15] and Chen C-H et al., 2011.[8] reported that E. coli was the commonest organism for SBEM in culture positive cases (44.4 % and 20 %, respectively), while Chen T-A, et al., 2003.[7] reported that 80% of cases with positive culture showed E. Coli growth and 20% showed Enterococcus, while Emam M, et al., 2015.[22] found that E. Coli represented 54.8% of culture +ve SBEM patients, Klebsiella accounted for 29%, Streptococci 6.5%, Pseudomonas 6.5% and Clostridium 3.2%. Regarding antibiotic sensitivity in cases with culture +ve SBEM

cases, our study revealed that Meropenem sensitivity was 100%, Ceftriaxone and Ciprofloxacin was 62.5%, Levofloxacin and Cefotaxime was 50%, agreeing with the results by Emam M, et al., 2015[22] who reported that Meropenem sensitivity was 100%, Ceftriaxone was 64.5%, Ciprofloxacin was 58%, Levofloxacin was 51.6% and Cefotaxime was 58.4%. In our study, multivariate analysis revealed that presence of SBP, low pleural fluid protein, high Child Pugh score, low serum albumin level and the presence of leukocytosis were independent risk factors for the presence of SBEM agreeing with the results by Chen T-A, et al., 2003.[7] who found through multivariate analysis that low pleural fluid protein level and the presence of SBP were independent risk factors for SBEM. Spontaneous bacterial empyema is a serious complication of hepatic hydrothorax.[15,21] In our study, the mortality rate in cases with SBEM was 35.71%, which is higher than that reported by Makhlouf HA, et al., 2013[2] (25%) and Xiol X, et al., 1996.[15] who reported a mortality rate of 20% in patients with SBEM, and close to the results by Chen C-H, et al., 2011[8] and Chen TA, et al., 2003[7] who reported 38% mortality rate in SBEM patients. Also we found that SBEM is associated with increased mortality than that with sterile hydrothorax.

CONCLUSION

From this study we can conclude that SBEM is a serious complication in patients with liver cirrhosis and hepatic hydrothorax. SBEM is commonly right sided and associated with mild amount of pleural effusion. Patients with liver cirrhosis and SBEM are commonly presented with chest pain, fever, cough, abdominal pain and septic shock. SBEM is better diagnosed by cytological examination of pleural fluid. Positive pleural fluid culture is not usually present in all patients. Many risk factors can contribute to the development of SBEM such as presence of SBP, low serum albumin level, low pleural fluid protein level, advanced liver disease as expressed by high Child Pugh score and class C Child Pugh class and prolonged INR. SBEM is a risk factor for increased mortality in patients with liver cirrhosis and hepatic hydrothorax.

RECOMMENDATIONS

Pleural thoracentesis should be done routinely in cirrhotic patients presented with pleural effusion especially in patients who had one or more of the forementioned risk factors for development of SBEM. Early antibiotic therapy is advisable to guard against the complications caused by SBEM including mortality. Effort should be made to eliminate or decrease the risk factors for SBEM especially in patients with history of SBEM before to guard against future events. The incidence and mortality rate of SBEM are still high and increasing. Further studies should be done to assess more risk factors for the development of SBEM and discover new treatment modalities that lead to better outcome in SBEM patients.

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