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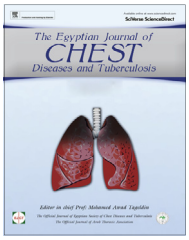

ORIGINAL ARTICLE

Prevalence and risk factors for spontaneous bacterial pleuritis in cirrhotic patients with hydrothorax

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Abstract *Background:* Spontaneous bacterial pleuritis is a high mortality complication in cirrhotic patients with hydrothorax.

Aim: To investigate the prevalence and risk factors for spontaneous bacterial pleuritis in cirrhotic patients with hydrothorax.

Methods: Adult inpatients with liver cirrhosis and hydrothorax were enrolled. The severity of liver disease was assessed by the Model for End-Stage Liver Disease (MELD) score. Pleural fluid was analyzed [pH, polymorphonuclear (PMN) leucocyte count, total protein level, lactate dehydrogenase (LDH) level, glucose level, bacterial culture and cytology]. Spontaneous bacterial pleuritis was diagnosed by positive pleural fluid culture or, if negative, a pleural fluid PMN count >500 cells/μL without radiographic evidence of pneumonia.

Results: Out of 98 cirrhotic patients with hydrothorax enrolled in the study; 14 (14.3%) fullfilled the criteria for the diagnosis of spontaneous bacterial pleuritis. Of those 14 patients; 9 were culture positive and 5 were culture negative. The other 84 did not have evidence of spontaneous bacterial pleuritis and were considered to have uncomplicated hydrothorax. Patients with spontaneous bacterial pleuritis had more severe liver diseases (MELD score), and higher rate of associated spontaneous bacterial peritonitis (SBP) and bacteraemia than patients with uncomplicated hydrothorax.

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Patients with spontaneous bacterial pleuritis had a significantly higher PMN count and a lower protein level in the pleural fluid.

Conclusion: The prevalence of spontaneous bacterial pleuritis in the studied group of patients with hepatic hydrothorax was 14.3%. Patients with advanced liver disease, low pleural fluid protein, or SBP are at risk for spontaneous bacterial pleuritis.

Introduction

Spontaneous bacterial peritonitis (SBP) is a frequent complication in cirrhotic patients with ascites. The current proposed pathogenic mechanism for SBP suggests the passage of intestinal bacteria to the mesenteric lymph nodes and from there into the general circulation because of impaired reticuloendothelial phagocytic activity [1]. These pathogens reach the ascitic fluid after an episode of bacteremia.

According to previous reports, approximately 5–15% of cirrhotic patients may develop pleural effusion [2]. Hepatic hydrothorax results from pathologic transdiaphragmatic migration of ascitic fluid in patients with liver cirrhosis. It is diagnosed clinically after excluding primary pulmonary or cardiac causes of the pleural effusion in a cirrhotic patient with transudative pleural fluid. Hepatic hydrothorax most commonly presents as a right-sided pleural effusion but can result in a unilateral left effusion or bilateral pleural effusions [3]. Although ascites is usually evident at presentation, hepatic hydrothorax can present without clinically detectable ascites [4]. Patients are prone to recurrent bouts of spontaneous bacterial pleuritis with or without concurrent spontaneous bacterial peritonitis [5]. The initial evaluation of this effusion should be pleural fluid analysis. Complete pleural fluid analysis will establish the transudative nature of the fluid and identify the presence or absence of spontaneous bacterial pleuritis. It is also helpful in excluding other causes of pleural effusion such as malignancy [6].

Although the transudative nature of hepatic hydrothorax is well established, the characteristics and risk factors for spontaneous bacterial pleuritis have not been well investigated. Therefore, the aim of this study was to identify the prevalence and possible risk factors for spontaneous bacterial pleuritis in cirrhotic patients with hydrothorax.

Patients and methods

Patients

Adult inpatients with liver cirrhosis and hydrothorax were selected from the ward of Tropical Medicine, Mansoura University Hospitals. The diagnosis of cirrhosis was based on liver biopsy or typical clinical findings, imaging studies and laboratory findings. Patients with cirrhosis and pleural effusion who had a concurrent cause of the pleural effusion as determined by the clinical evaluation and subsequent laboratory and radiographic tests were excluded e.g. pneumonia and heart failure.

Methods

(1) *Thorough clinical history and physical examination.*
(2) *Blood tests:* Complete blood picture, urea and creatinine, liver function tests, viral markers for hepatitis B and C, blood culture.
(3) *The Model for End-Stage Liver Disease (MELD) score:* The MELD score ranges from 6 to 40, with higher values indicating more severe disease. The score was calculated using the original formula without including the cause of liver disease; MELD score $= 0.957 \times \log(\text{creatinine mg/dL}) + 0.378 \times \log(\text{bilirubin mg/dL}) + 1.120 \times \log(\text{INR}) + 6.43$.
(4) *Abdominal ultrasound and/or computerized tomography:* To confirm the presence of liver cirrhosis and to detect ascites.
(5) *Chest X-ray:* Chest radiograph was reviewed for laterality of the effusion and exclude pneumonia.
(6) *Thoracentesis:* Pleural fluid analysis included pH, polymorphonuclear (PMN) leucocyte count, total protein level, lactate dehydrogenase (LDH) level, glucose level, bacterial culture and cytology. 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. A pleural fluid was considered a hydrothorax if it showed transudate characteristics according to Light's criteria [7]. Spontaneous bacterial pleuritis was diagnosed by positive pleural fluid culture or, if negative, a pleural fluid PMN count > 500 cells/μL without radiographic evidence of pneumonia [8].
(7) *Abdomenocentesis:* In patients with ascites, a paracentesis was performed at the same time, and the ascitic fluid was analyzed in the same way as the pleural fluid. The diagnosis of SBP was established by positive ascitic fluid culture or, if negative, an ascitic fluid PMN count > 500 cells/μL [9].

Statistical analysis

Quantitative data were expressed as means ± standard deviations while qualitative data were expressed as numbers (percentage). To test the difference between patients with and without spontaneous bacterial pleuritis; Student's *t*-test was used for quantitative data and Pearson's chi-square test for qualitative data. A p value < 0.05 was considered significant.

Data were analyzed using the Statistical Package for Social Sciences (SPSS, Chicago, IL).

Results

Prevalence of spontaneous bacterial pleuritis

Out of 98 cirrhotic patients with hydrothorax enrolled in the study; 14 (14.3%) fullfilled the criteria for diagnosis of spontaneous bacterial pleuritis. Of those 14 patients; 9 were culture positive and 5 were culture negative. The other 84 did not have evidence of spontaneous bacterial pleuritis and were considered to have uncomplicated hydrothorax.

Characteristics of patients with spontaneous bacterial pleuritis:

Table 1 shows the demographic and clinical data from patients with uncomplicated hydrothorax versus those with spontaneous bacterial pleuritis. Hepatitis C was the most frequent cause of cirrhosis, followed by hepatitis B. There were no significant differences between both groups regarding the laterality of effusion, age, gender and causes of liver disease. However; patients with spontaneous bacterial pleuritis had more severe liver diseases (higher MELD score), and higher rate of associated SBP and bacteraemia than patients with uncomplicated hydrothorax.

Table 2 shows the serum albumin levels and pleural fluid characteristics in patients with uncomplicated hydrothorax versus those with spontaneous bacterial pleuritis. There was no significant difference between both groups regarding the pleural fluid pH, glucose, LDH and serum albumin. However, patients with spontaneous bacterial pleuritis had a significantly higher PMN count and a lower protein level in their pleural fluid.

Discussion

The prevalence of spontaneous bacterial pleuritis among cirrhotic patients with hydrothorax in the studied group was 14.3% which is comparable to previous reports (ranging from 13% to 19%) [2,6,8].

As in previous reports, our data confirmed that hepatic hydrothorax is typically a right-sided pleural effusion [10]. In patients with bilateral pleural effusions, the right-sided effusion tended to be larger than the left. Our results showed that hepatic hydrothorax almost always presents with ascites. Hepatic hydrothorax in the absence of ascites has been reported previously [4]. The MELD score was used to assess the severity of liver disease in this study.

The MELD score was shown to be a more reliable measure of short and intermediate-term mortality risk in patients with end-stage liver disease of diverse aetiologies in comparison with the Child–Pugh score [11]. Patients with spontaneous bacterial pleuritis had a worse hepatic function, as determined by the MELD score, than did those with uncomplicated hydrothorax. The role of poor hepatic function in the development of SBP has been well documented [9].

The pleural fluid analysis of uncomplicated hydrothorax showed a paucicellular transudate with an alkaline pH and normal glucose value. Patients with uncomplicated hydrothorax had a significantly higher pleural total protein than patients with spontaneous bacterial pleuritis. Previous studies have reported a higher incidence of SBP with a lower ascitic fluid protein concentration and improved outcome with norfloxacin prophylaxis in advanced liver failure from cirrhosis with an ascitic protein < 1.5 g/dL [12]. To our knowledge, no studies have explored the benefits of antibiotic prophylaxis for those with a pleural fluid total protein < 1.5 g/dL in patients with hepatic hydrothorax. This finding suggests that a low pleural fluid protein is a risk factor for spontaneous bacterial pleuritis similar to previous findings on SBP [9]. Low pleural fluid protein implies a low complement level, which impairs the opsonic activity of the pleural fluid as in ascites [9], thus enhancing bacterial translocation. In this situation, pleural fluid will become easily infected. These data are further supported by the findings of other authors that a high Child–Pugh score, low pleural fluid protein and low levels of C3 component in pleural fluid were risk factors for spontaneous bacterial empyema [13]. Because there was a very good correlation

Table 1 Comparison of demographic and clinical data in uncomplicated hydrothorax and spontaneous bacterial pleuritis.

Variables	Uncomplicated hydrothorax ($n = 84$)	Spontaneous bacterial pleuritis ($n = 14$)	P value
Laterality of pleural effusion			
Right unilateral	71 (84.5%)	12 (85.8%)	NS
Bilateral	7 (8.3%)	1 (7.1%)	
Left unilateral	6 (7.2%)	1 (7.1%)	
Age (years)	63.2 ± 11.4	69.7 ± 16.5	NS
Gender			
Male	51 (60.7%)	8 (57.1)	NS
Female	33 (39.3%)	6 (42.9)	
MELD score	19.1 ± 3.8	27.2 ± 5.7	< 0.05
Etiology of liver disease			
Hepatitis C virus	64 (76.1%)	11 (78.6%)	NS
Hepatitis B virus	15 (17.9%)	2 (14.3%)	
Auto-immune	5 (6%)	1 (7.1%)	
Ascites	81 (96.4%)	13 (92.9%)	NS
SBP	8 (9.5%)	8 (57.1%)	< 0.001
Bacteraemia	5 (6%)	5 (35.7%)	< 0.001

MELD, Model for End-Stage Liver Disease score; SBP, spontaneous bacterial peritonitis.

Table 2 Comparison of serum albumin and pleural fluid characteristics in uncomplicated hydrothorax and spontaneous bacterial pleuritis.

Variables	Uncomplicated hydrothorax (n = 84)	Spontaneous bacterial pleuritis (n = 14)	P value
Serum albumin (g/dL)	2.3 ± 0.5	2.1 ± 0.6	NS
Pleural fluid pH	7.48 ± 0.05	7.46 ± 0.09	NS
Pleural fluid glucose (mg/dL)	154 ± 49	132 ± 63	NS
Pleural fluid protein (g/dL)	2.3 ± 0.6	1.5 ± 0.5	<0.05
Pleural fluid LDH (IU/L)	76 ± 21	89 ± 34	NS
Pleural fluid PMN count (cells/mm^3)	87 ± 43	956 ± 123	<0.001

LDH, lactate dehydrogenase; PMN, polymorphonuclear leucocyte.

between pleural C3 and pleural fluid protein levels in the latter study, the authors suggested using the pleural fluid protein level to detect patients at risk of spontaneous bacterial empyema in clinical practice.

A high PMN count was documented in all cases of spontaneous bacterial pleuritis. The culture was positive in 9 patients (64.3%). This rate of positive cultures is slightly lower than previously reported (75%) [8]. We believe that our microbiological culture yield was lower secondary to delay in inoculation (conventional method) and use of prophylactic, as well as therapeutic dosage of antibiotics prior to thoracentesis. There was no significant difference between pleural fluid LDH in uncomplicated hydrothorax and spontaneous bacterial pleuritis. Additionally, the pH in spontaneous bacterial pleuritis was not lowered as would be expected in an infection of the pleural space. This likely reflects the earlier and widespread use of prophylactic as well as therapeutic antibiotics in such cases, limiting the inflammatory process in the pleural space. Also, the constant transdiaphragmatic influx of a large volume of transudative fluid may dilute the inflammatory milieu in these cases. Our findings suggest that PMN is the earliest and most reliable marker for spontaneous bacterial pleuritis.

Our results showed that patients with spontaneous bacterial pleuritis had a higher rate of concomitant SBP than patients with uncomplicated hydrothorax suggesting an association between spontaneous bacterial pleuritis and SBP. There are two hypotheses regarding the development of spontaneous bacterial pleuritis. One suggests that the infection is through spontaneous bacteraemia, as in SBP, and the other suggests that infection arises through the flow of infected ascites from the peritoneal to the pleural cavity via defects in the diaphragm because of the negative intrathoracic pressure [8,14]. In cirrhotic patients, portal hypertension is responsible for the development of ascites and porto-systemic collaterals. Normally bacteria are filtered from the blood stream by the liver, but in patients with porto-systemic shunting, blood is diverted around the liver and bacteremia become more frequent and prolonged [15]. Pleural effusion, as ascites may be infected in a similar manner as in SBP [14]. In the present study, only 35% of spontaneous bacterial pleuritis were associated with bacteremia but 57% with SBP suggesting that most of the spontaneous bacterial pleuritis may be secondary to SBP *via* defects in the diaphragm.

In summary, spontaneous bacterial pleuritis is a frequent but underdiagnosed complication of hepatic hydrothorax with a poor prognosis. Patients with advanced liver disease, low pleural fluid protein, or SBP are at risk for spontaneous bacterial pleuritis. A diagnostic thoracentesis with subsequent culture of pleural fluid should be performed in cirrhotic patients with hydrothorax when infection is suspected.

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