Egyptian Journal of Medical Microbiology Volume 28 / No.1 / January 2019 81-86 Online ISSN: 2537-0979

ORIGINAL ARTICLE

Spontaneous Fungal Peritonitis in Egyptian Patients with Cirrhotic Ascites

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Key words:
Spontaneous fungal peritonitis; spontaneous bacterial peritonitis, ascites, liver cirrhosis

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ABSTRACT

Background: *Spontaneous fungal peritonitis in liver cirrhotic patients is considered a serious complication with a grave prognosis. The available data describing this entity are still deficient, however they all stress that early diagnosis and proper management is essential to decrease mortality.* ***Objectives:*** *This study was conducted to assess the incidence, characteristics and predisposing factors of fungal peritonitis in patients with cirrhotic ascites.* ***Methodology:*** *Ascitic fluid samples were collected from 141 Egyptian patients with cirrhotic ascites. Ascetic fluid specimens were subjected to direct microscopic examination, bacterial and fungal culture.* ***Results:*** *Sixty one patients were diagnosed to have spontaneous bacterial peritonitis (SBP), eight of them were culture positive SBP and E. coli was the commonest organism to be isolated. A single case of spontaneous fungal peritonitis (SFP) was detected caused by Candida albicans. Child-Pugh C, high MELD score and high bilirubin level might be among the risk factors of development of SFP.*

INTRODUCTION

Different causes of chronic liver disease end in cirrhosis. Liver cirrhosis is accompanied by dysfunction of the immune system,[1] consequently, cirrhotic patients are more vulnerable to different types of infections, especially caused by bacterial agents[2]. Spontaneous bacterial peritonitis (SBP) is one of the most common bacterial infections in cirrhotic patients. It has been associated with significant morbidity and mortality.[3, 4] Early diagnosis and proper treatment of this serious infection will result in decrease mortality. Third generation cephalosporins have been widely used as the standard empirical therapy for SBP[5], however, many cases reported unresponsiveness and/or deterioration of the general conditions despite early initiation of proper antibacterial agents[6]. Many studies addressed the causes of failure of management in many of these cases, and few of them could prove that fungal rather than bacterial infection may be the cause of peritonitis in patients with cirrhosis, a condition named spontaneous fungal peritonitis (SFP). The most common isolated fungus was *Candida albicans*.[7] The corner stone in the diagnosis of SFP is the high clinical suspicion of certain susceptible cirrhotic population especially those with clinical deterioration on proper antibacterial agents.[7]

The aim of the present study was to assess the incidence, predisposing factors, causative fungi and prognosis of SFP in cirrhotic patients compared with SBP.

METHODOLOGY

The study was approved by the ethical committee of Endemic Medicine Department, Faculty of Medicine, Cairo University. Informed consent was taken from all patients included in the study.

This study was conducted on 141 patients with liver cirrhosis and ascites who presented to Endemic Department at Kasr Al-Ainy Hospital during the period from January 2016 to January 2017. Patients with recent abdominal surgeries, sero-positive patients for human immunodeficiency virus (HIV), Patients with non-portal hypertension related ascites and patients undergoing continuous ambulatory peritoneal dialysis were excluded from this study.

History taking and Clinical evaluation:

- **Detailed history taking** including (the etiology of liver cirrhosis; abdominal surgery, biliary tract infection, duration of hospitalization, prior antibiotic treatment within 3 months, recent history of SBP successfully treated by antibiotics within 1 month, and gastrointestinal bleeding).
- **Complete clinical examination** with special stress on the presence of ascites, hepatic encephalopathy and other manifestations of chronic liver disease.
- **Evaluation of the severity of liver disease according to Modified Child-Pugh and MELD score** which were calculated to assess the degree of hepatic decompensation. Patients were classified to Child A, B and C; with child A score (5-6), child B score (7-9), child C score (10-15).[8]

Abdominal ultrasonography

Upper endoscopy: for presence of varices or any evidence of fungal infection

Laboratory evaluation:

Blood and ascitic fluid (10 ml was collected by abdominal paracentesis at the bedside) samples were collected from all patients.

Blood samples were subjected to:

- *Complete blood count* (RBC, WBC, platelet count and hemoglobin)
- *Biochemical test* (ESR, CRP, Serum bilirubin, Serum amino-transaminases, Total serum proteins & serum albumin, Prothrombin time, concentration and international normalized ratio (INR), Urea and Creatinine, Fasting blood sugar, Hemoglobin A1c, HIV Ab types 1 and 2, Alpha fetoprotein).

Ascitic fluid samples were subjected to:

Macroscopic examination: to report the color and aspect whether clear, cloudy or purulent.

Microscopic examination**:**

- Total leucocytes were counted using well mixed un-centrifuged sample.
- Leishmann stained smear: It was done to differentiate PMN & lymphocytes.
  - Values of WBCs/ml <250/cmm with Lymphocyte predominance is normal,
  - WBCs/ml ≥ 250/cmm with predominance of neutrophils was diagnosed as bacterial peritonitis.
- Gram stained smear: it was done to detect bacterial morphology and Candida.
- India ink: for detection of Cryptococcus *neoformans*.
- Lactophenol cotton blue stain for detection of fungal hyphae, spores or yeast cells.

Culture:

Centrifuged specimens were subjected to inoculation on Blood agar (Oxoid, UK), Chocolate agar (Oxoid, UK) and MacConky's agar (Oxoid, UK) incubated at 37 ◦C for 24-48 hours. All specimens were inoculated also on Sabouraud Dextrose agar (SDA) with antibiotics (Oxoid, UK) incubated at 37◦C and 25 ◦C for 4 weeks. Plates were inspected daily for growth.

Identification:

- Colonies grown on blood, chocolate and MacConkey's agar were identified by colony morphology, Gram staining and biochemical reactions.
- Isolates on SDA can be identified as Candida by colony morphology and Gram staining. *Candida albicanus* is identified by germ tube test, and culture on CHROMagar Candida medium (CHROMagar, France).
- Filamentous fungi (molds) can be identified on SDA by their colony morphology and microscopic morphology using lactophenol cotton blue stain.

Response to treatment:

It was assessed by ascitic fluid follow up paracentesis in some cases along with improvement in the clinical symptoms and signs in other cases.[9]

RESULTS

The mean age of the studied population was 58.03 years with male predominance (70.9%). The most common presenting symptoms in the studied population were abdominal pain (40.4%), fever (36.2%) and hepatic encephalopathy (33.3%). 56% of the studied patients were Child-Pugh class B, 44% were Child-Pugh class C, while none was Child-Pugh class A and MELD score ranging from (6-35).

Abdominal ultrasonography: Sonograghic findings revealed different grades of ascites, splenomegaly (88.7%) and HCC (22%).

The endoscopic findings: Range from portal hypertension gastropathy (PHG) in (58.9%) of cases, duodenal ulcer (1.4%), small varices (31.2%), large varices (27.7%), residual varices (17.7%) and moniliasis (15.6%)

Laboratory data:

Patients had chronic liver disease with thrombocytopenia (mean=100), elevated bilirubin (mean=3.15 mg/dl), hypoalbuminemia (mean=3.3 g/dl) and elevated INR (mean=1.64).

According to the microbiological findings of the ascitic fluid (neutrophil count ≥ 250/mm^3); patients were classified into SBP group (n=61) and non-SBP group (n=80).

The mean age of both SBP and non-SBP population was (58) with male predominance in the SBP group. Clinical symptoms of abdominal pain, fever, deterioration of ascites and hepatic encephalopathy were significantly more common among patients with SBP with *p-values* of (<0.001), (<0.001), (0.02) and (0.02) respectively. Other data did not show a statistically significant difference among the studied groups.

The predicted mortality as assessed by the MELD score was significantly higher in patients with SBP in comparison to those without SBP with a *p-value* of <0.001. However, both groups showed no significant difference in severity of liver disease as assessed by Child-Pugh score**.**

Patients with SBP showed a significantly more decompensated liver disease in the form of high bilirubin and low prothrombin concentration than those with non-SBP with *p-values* of (0.04) and (<0.001) respectively. Moreover, patients with SBP showed significantly higher markers of inflammation in the form of leucocytosis (mean=8.6) and CRP (mean=50 mg/dl) with a *p-value* of <0.001.

Risk factors for development of SBP in studied population include: previous antibiotic prophylaxis, high bilirubin level and high MELD score with high

statistically significant difference between SBP and non-SBP groups, *p-values* of (0.03), (0.04) and (<0.001) respectively (Table 1).

Table 1: Risk factors for development of SBP in studied population

	SBP (n=61) No. (%)	Non-SBP (n=80) No. (%)	*P-value*
Prior hospitalization	23(37.7%)	26 (32.5%)	0.6
Antibiotics prophylaxis	23(37.7%)	16 (20%)	0.03
Proteins in ascetic fluid Median (IQR)	1(0.8-1.3)	1(0.7-1.1)	0.5
Bilirubin Median (IQR)	2.6 (4-1.1)	1.8(2.5-1.2)	0.04
MELD Score	17.5(23-13)	11(16-9)	<0.001
Hematemesis	8(13.11%)	11 (13.75%)	0.9

The PMNL count in patients with SBP was significantly higher than that in patients with non-SBP with a *p-value* of (<0.001). There were 8 cases (13.12%) with positive bacterial cultures in SBP group versus a single case (1.25%) of positive fungal culture in those with non-SBP (Table 2).

Table 2: Isolated organisms from ascitic fluid cultures in the studied patients

	SBP (n=61) No. (%)	Non-SBP (n=80)No. (%)
E. coli	5 (8.2%)	0
Acinetobacter	1 (1.64%)	0
Pseudomonas	1 (1.64%)	0
Enterococcus	1 (1.64%)	0
Candida albicans	0	1 (1.25%)
Negative	53 (86.88%)	79 (98.75%)

In the present study, out of 61 patients of SBP group; 45 cases were treated with cefotaxime, 7 cases with ceftriaxone and 9 cases with imepenem. 51 (78.7%) cases responded to treatment and mortality was recorded in 16.4% of cases.

Our study showed a single case of proved fungal peritonitis:

A 58 year-old female patient presented with liver cirrhosis and moderate ascites, complaining of abdominal pain and tenderness. The patient reported history of antibiotic intake for 10 days without clinical improvement. No history of fever, bleeding, resistant ascites, hepatic encephalopathy or antibiotic prophylaxis. The patient is not known to be diabetic.

Laboratory findings were: thrombocytopenia ($87x10^3$), hypoalbuminemia (2.3g/dl), hyperbilirubinemia (3.2 mg/dl), elevated INR (1.8) and CRP (24 mg/dl).

Ascitic fluid findings were as following: Elevated TLC (260) with lymphocytic predominance, low total proteins (0.7 g/dl). *Candida albicans* was detected by SDA culture, microscopic examination, germ tube test and subculture on chromagar.

Antifungal therapy in the form of fluconazole was started and completed for 14 days with improvement of the clinical symptoms.

DISCUSSION

SFP is a less recognized entity in patients with liver cirrhosis, with few studies focusing on its magnitude and characteristics especially among cirrhotic population[7]. The incidence of such a serious complication is variable ranging from 0 to 13%[10]. Its diagnosis requires a high suspicion and awareness about the risk factors and based on ascitic fluid culture.[7]

The present study was conducted to assess the incidence, predisposing factors, causative fungi and prognosis of SFP in a group of 141 Egyptian patients with cirrhotic ascites compared with SBP.

In the current study, the mean age of the studied population was 58 years with male predominance, which is approved since male gender and age > 50 years have been stated as risk factors of cirrhosis especially in chronic hepatitis C[11]. These findings may also reflect the increased incidence of hepatic decompensation in cirrhotic patients with advanced age, especially with development of ascites[12]. A male predominance in a country with a cultural background like Egypt, may also be attributed to the assumption that male patients tend to seek medical advice more than do female patients with the same clinical complaints.

SFP is an underestimated disease, especially in critically ill patients. Little is known about the clinical course, causative organisms and prognosis of SFP in critically ill patients[7]. The underestimation of SFP may be attributed to being under-investigated as many patients deteriorate and die before clinical suspicion and proper diagnostic approach take place provided that this entity was associated with grave prognosis in most of the studies especially when treatment is delayed[13].

In the current study, the incidence of SFP was very low, one case (0.7%) out of 141 patients with cirrhotic ascites hospitalized for different indications with isolation of *Candida albicans*. Due to very low incidence of SFP demonstrated in our study population, characteristics and predisposing factors could not be statistically analyzed.

Other studies from Korea and India have reported almost similar results of 1.05% and 1.1%, respectively, with isolation of Candida species in the first study, Candida and Aspergillus species in the second study[14,15]. Higher rates of 6%, and 3.6 %, 10.9% were recorded by other studies.[16,7,17] Candida species were the

commonest fungus isolated from cases of SFP in other studies.[13, 16, 7]

Low incidence of SFP in our study population may be attributed to lack of more sensitive diagnostic methods that were utilized in other studies such as PCR, Beta-Glucan and Galacto Mannan assays.

Unlike another study which included patients from the intensive care unit, with multiple co-morbidities and variety of invasive procedures known to predispose to fungal infection, our study included patients admitted to ward with less critical clinical condition.[17]

Our case of SFP was represented in a 58 year old female patient, not known to be diabetic, diagnosed to have HCV related chronic liver disease of five year duration, with abdominal pain and tenderness, no other manifestations were reported. The patient reported history of antibiotic intake during the last ten days before admission without clinical improvement.

SFP presents with a picture clinically similar to SBP, so usually empirical antibiotic is started and clinical suspicion should be raised when the patient deteriorates in spite of initiation of proper antibiotic regimens.[7, 17, 18] Clinical suspicion should also be raised in cirrhotic patients with nosocomial SBP and immunosuppressed or malnourished, all of which were not encountered in our.[10]

Other studies concluded that Child-Pugh C, high MELD score and high bilirubin level were among the risk factors of development of SFP, all of which were encountered in our case.[7, 19] Another study has reported that results of CRP along with leucocytosis and procalcitonin were variable among cases of SBP and SFP and that they were not specific for diagnosis of SFP.[19]

Although there are lacking data addressing the increased SFP in patients with HCC, it is conceivable that development of HCC may accelerate hepatic decompensation and so help in pathogenesis of several infections including fungal infections.

Endoscopic findings of our case demonstrated small esophageal varices, PHG and esophageal moniliasis which may constitute a portal of entry and dissemination of fungal pathogen. The patient reported history of endoscopic band ligation a month ago, an invasive procedure that may facilitate entry of fungal pathogens, however this seems to be a long period for this procedure to be incriminated in the pathogenesis.

In our case, ascitic fluid paracentesis was performed yielding total leucocytic count of 260 with lymphocyte predominance and growth of *Candida albicans* was noted in ascitic fluid culture. Other studies also demonstrated increased ascitic fluid lymphocytes among patients with fungal infections.[17, 20]

In our case, low ascitic fluid total proteins was described (0.7 g/dl), and this agrees with another study which demonstrated that low ascitic fluid proteins <1 g/dl is considered to be a risk factor for development of SFP.[7] On the other hand, our findings do not match another study which concluded that total protein, albumin, neutrophil and white cell count in ascitic fluid did not differ between patients with fungal and those with bacterial peritonitis.[16]

In the present study, antifungal treatment in the form of fluconazole according to the sensitivity testing was initiated with proper clinical and biochemical response documented by decrease in the ascitic fluid leucocytic count. The patient demonstrated clinical improvement and survived on follow up and this goes opposite to most of the studies which demonstrated poor survival in SFP[13, 17] and that mortality rates for SFP have been shown to be much higher than SBP.[7] However this outcome agreed with another study which reported that starting antifungal therapy as soon as possible improves prognosis in patients with invasive candidiasis.[21]

Among the 141 hospitalized patients with chronic liver disease and ascites included in our study, 61(43%) patients were diagnosed to have SBP based on clinical manifestations and ascitic fluid findings of total leucocytic count ≥ 250 with PMNLs predominance. A nearly similar rate was recorded by another study conducted on 70 cirrhotic patients, SBP was found in 26 patients (37.14%).[22] A higher rate was recorded by another study conducted in Egypt on 130 cirrhotic patients, SBP was diagnosed in 63.1% patients with neutrophil count ≥ 250/cmm.[33]

Our study demonstrated a high statistically significant difference of CRP, total blood leucocytic count, coagulopathy in the form of high INR and low prothrombin concentration in patients with SBP compared with non-SBP group. These findings go in agreement with another study which stated that CRP is a good indicator of SBP with a cut-off point of 10.5 mg/L at which SBP can be diagnosed with sensitivity and specificity of 91% and 97% respectively and that procalcitonin levels provide an early diagnostic accuracy in advanced liver cirrhotic patients with SBP.[23]

In the current study, patients with SBP had higher MELD score and bilirubin level than patients without SBP supporting that they were among the risk factors of development of SBP. Other studies have reported almost similar results.[24, 25] Different results recorded by another study which stated that MELD score is not associated with an increased risk of developing SBP.[26]

In our study, 8 patients (13.12%) only among SBP group had positive ascitic fluid culture for bacteria meeting the definition of culture positive SBP. In contrast, there were 53 patients (86.88%) with culture negative SBP known as CNNA (Culture Negative Neutrocytic Ascites). Another study conducted in Egypt on 130 cirrhotic patients; 35 (26.9%) ascitic fluid samples were positive for bacterial culture which represented a higher rate than recorded in our study.[33] The lack of culture positivity was described by another study which stated that classical culture techniques fail

to grow bacteria in up to 65% of neutrocytic ascites and that bedside inoculation of ascites into blood culture bottles has been shown to increase the sensitivity to nearly 80%.[27] CNNA variant of SBP may be attributed to poor culture technique, prior antibiotics or low opsonic activity in ascitic fluid or low microbial concentration.[6, 28]

In our study, the most common isolated bacteria were *E. coli* (62.5%), the remaining three isolates were Acinetobacter, Pseudomonas, Enterococcus. Other studies have recorded that Gram negative bacteria were among the most common isolated organisms in cases of SBP and *E. coli* was the commonest isolated bacteria among them.[29, 30, 33]

In this study, most of the patients with SBP received treatment in the form of third generation cephalosporins; (73.8%) receiving cefotaxime, (11.5%) receiving ceftriaxone and the rest (14.8%) were treated with imipenems due to presence of additional co-morbidities. Cefotaxime and other third-generation cephalosporin appears to be the treatment of choice for suspected SBP; it used to cover 95% of the flora including *E. coli*, *Klebsiella*. [31]

In this study, the mortality rate reached (16.4%), which was lower than that showed in another study, which detected that 30 day mortality reached up to (24%) in cases of SBP.[32]

CONCLUSION

Due to very low incidence of SFP in our study population, characteristics and predisposing factors could not be studied and statistically analyzed. Early detection of SFP and initiation of the proper anti-fungal therapy is essential in improving the prognosis and decreasing mortality.

Recommendations:

Further studies on a larger population scale with more recent diagnostic techniques are needed for better diagnosis of SFP.

Conflict of Interest: There is no conflict of interest

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