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Mini Review

Spontaneous Fungal Peritonitis in Patients with Liver Cirrhosis

Toru Shizuma*

Department of Physiology, School of Medicine, Tokai University, Japan

ABSTRACT

Although spontaneous peritonitis is a common infection in liver cirrhosis patients, little is known about the clinical characteristics and treatments of spontaneous fungal peritonitis (SFP) or fungiascites. Although diagnosis of SFP or fungiascites is made according to the cell counts and culture in ascitic fluid, delayed diagnosis has been associated with poor prognosis of SFP. Risk factors for SFP include severe underlying liver dysfunction, hospitalization and nosocomial infections. SFP mortality rates have been estimated as higher than those of spontaneous bacterial peritonitis. Although early administration of appropriate antifungal agents may be necessary, it remains uncertain whether antifungal therapies would decrease SFP's mortality rate.

Keywords: Spontaneous fungal peritonitis; Fungiascites; Spontaneous bacterial peritonitis; Liver cirrhosis

Abbreviations: Cr: Creatinine; LC: Liver Cirrhosis; MELD: Model for End-Stage Liver Disease; PCR: Polymerase Chain Reaction; PMNs: Polymorphonuclear Leukocytes; PT: Prothrombin Time; SBP: Spontaneous Bacterial Peritonitis; SFP: Spontaneous Fungal Peritonitis; spp.: species

INTRODUCTION

Patients with liver cirrhosis (LC) are susceptible to bacterial and fungal infections, which are often life-threatening complications for them [1,2]. Patients with ascites are at risk of spontaneous peritonitis due to bacterial infections (spontaneous bacterial peritonitis (SBP) and bacterascites), fungal infections (spontaneous fungal peritonitis (SFP), and fungiascites (or fungal ascites)) [3-5]. Although the clinical characteristics and prognosis of SBP have been well documented [5], the clinical characteristics of SFP and fungiascites in patients with LC are less well known. However, some clinical studies of SFP and fungiascites have been reported in recent years, including those that have evaluated and compared SFP and SBP [6-10] or spontaneous peritonitis with a fungus-positive ascitic culture (SFP or fungiascites) and spontaneous peritonitis with a bacteria-positive ascitic culture (culture-positive SBP or bacterascites) [11,12]. In the present article, we review and summarize spontaneous peritonitis due to fungal infections (SFP and fungiascites).

Diagnosis of SFP and fungiascites

Spontaneous peritonitis is a peritoneal cavity infection with no surgically treatable intra-abdominal source of infection or malignancy [13]. Spontaneous peritonitis with culture-positive ascites is defined as culture-positive SBP and bacterascites or SFP and fungiascites. SFP is diagnosed if ≥ 250 polymorphonuclear leukocytes (PMNs)/mm^3 are present in the ascitic fluid and the ascites are fungal-culture-positive regardless of bacterial co-colonization [5,10]. Fungiascites are defined as a fungus-positive ascitic culture regardless of bacterial co-colonization and <250 PMNs/mm^3 in the ascitic fluid [5,10].

Early diagnosis of SFP and fungiascites is challenging, partly because of the time required for diagnostic fungal cultures [14] and partly because of lack of suspicion of SFP or fungiascites by the clinician. Diagnostic methods for SFP or fungiascites include polymerase chain reaction (PCR), 1,3-beta-D-glucan assay and galactomannan of the ascitic fluid [9,14-18].

Recent review article supports the usefulness of testing ascitic fluid using methods such as pan-fungal PCR and 1,3-beta-D-glucan assay for early diagnosis of SFP [19]. Therefore, these tests may also be performed at the first paracentesis in cases of suspected spontaneous peritonitis. Biomarkers, such as procalcitonin level and leukocyte esterase reagent strips, can help diagnose SBP [20] but may not distinguish between SFP and SBP.

Fungal infections in patients with LC

A recent multicenter study reported that of 1052 patients with LC and concomitant infections, 134 (12.7%) involved fungal agents [3]. Prophylactic use of antibiotics and nosocomial infection both affect the incidence of fungal infection in LC [3,21]. Zhao et al. [22] reported that, of 232 episodes of bloodstream infections in

Correspondence to: Toru Shizuma, Department of Physiology, School of Medicine, Tokai University, 143, Shimokasuya, Isehara, Kanagawa 259-1193, Japan, Tel: +81-0463-93-1121; E-mail: shizuma@is.icc.u-tokai.ac.jp

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patients with LC, 12 (5.2%) involved fungal agents (nine were *Candida albicans* and three were *Cryptococcus neoformans*).

Underlying liver dysfunction, renal dysfunction and low ascites protein concentration reportedly increase the risk of mortality in patients with LC and fungal infections [3]. Alexopoulou et al. [8] reported that fungal infections had a significantly higher mortality rate than bacterial infections in those with LC.

Spontaneous peritonitis due to fungi

The breakdown of the intestinal mucosa barrier, dysbiosis (changes in the composition of the intestinal bacterial flora), translocation of pathogens, in addition to deficiencies in local host immune defenses may be involved in the onset of ascitic infections that reach the systemic circulation from the gut in patients with LC [23-25]. Fungi in the ascitic fluid in SFP or fungiascites may also be the result of a fundamental pathogenic mechanism of fungal translocation from the gut to systemic circulation [5,19]. Antibiotic treatment of SBP may increase the risk of fungal peritonitis by allowing excessive fungal growth in the intestinal flora [19]. Subsequent translocation of fungi into the peritoneal cavity could induce SFP or fungiascites [19,26], even though their size may make fungal translocation across the gut mucosa more difficult than bacterial translocation [10,14,19]. Fungal translocation may be facilitated by upper gastrointestinal bleeding, which is also common in patients with advanced LC [21]. Direct percutaneous inoculation of fungi has been proposed as a route of fungal infection in patients with refractory ascites and a history of paracentesis [19,21]. Bajaj et al. [3] reported that 6.0% (8/134) of fungal infections in patients with LC involved spontaneous peritonitis.

Fungiascites

A few studies have characterized fungiascites. In a series of nine fungiascites cases, reported by Bucsics et al. [11], seven were Child–Pugh class B and two were class C. The in-hospital mortality was 33% (3/9). Park et al. [27] evaluated 16 cases of spontaneous peritonitis in which Cryptococcus was identified in the ascitic fluid, among which 13 cases (81%) were reported to involve fungiascites. They also reported that 69% (11/16) of patients with spontaneous peritonitis involving Cryptococcus died within one week after paracenteses [27]. Choi et al. [28] evaluated 21 patients with spontaneous peritonitis in which *Candida* species (spp.) was identified in the ascitic fluid, among which ten (48%) were reported to involve fungiascites. Three patients were Child–Pugh class B and seven were class C and the one-month fungiascites mortality rate was 20% (2/10) [28].

Spontaneous fungal peritonitis

SFP has mainly been described in patients with end-stage liver disease, such as LC. However, a rare case of SFP due to cardiac origin has been reported [29].

The reported frequencies of culture-positive ascites accompanying SFP have ranged from 0% to 10% [6,10,11,19,23,26]. It may be difficult to discuss the geographical differences of frequencies of SFP partly because there are limitations in number of clinical studies or number of SFP patients. The review article indicated that frequencies of SFP among culture-positive spontaneous peritonitis ranged 1%–7% in studies reported from Asia and Europe [26].

Several previous studies identified *Candida albicans* as the most frequent SFP isolate [6,7,9,10,11,14,19,26,30-32] and the review article indicated that it is the most frequently isolated pathogen regardless of the geographic differences worldwide [26]. Other isolated fungi included non-albicans *Candida* (*Candida glabrata*, *Candida krusei*, *Candida tropicalis*, *Candida parapsilosis*, etc.) [6,26,33], Cryptococcus spp. [10,34,35], *Aspergillus* spp. [11,21,36], *Penicillium* spp. [11] and *Fusarium solani* [37]. In SFP cases, 32% to 74% included polymicrobial infections (e.g., bacterial co-colonization) [6,7,10,11,14,30].

The few available SFP studies have identified high Child–Pugh scores (most patients with LC and SFP were Child–Pugh class C [6,9,10,28]), high model for end-stage liver disease (MELD) scores [10,26,38], invasive procedures [6], length of hospital stay [6,30] and nosocomial infection as risk factors for SFP occurrence [4,10,30]. In previous studies of ascitic culture-positive spontaneous peritonitis diagnosed between 2003 and 2016, nosocomial SFP was confirmed in 7.7% (53/689) of nosocomial spontaneous peritonitis and non-nosocomial SFP was confirmed in 1.7% (17/1018) of non-nosocomial spontaneous peritonitis [30]. However, further studies may be necessary to identify well-defined risk factors for SFP [4] partly because diagnosis of SFP is often delayed.

Comparative studies between spontaneous peritonitis due to fungus and those due to bacteria

Lahmer et al. [38] reported no significant differences in prothrombin time (PT) or albumin or creatinine (Cr) levels in patients with LC with SFP and those without peritonitis. They also found that serum bilirubin levels were significantly higher in patients with LC with SFP than in those without peritonitis [38].

A few studies have compared the serum and ascitic fluid findings in SFP and SBP [6-10] or in spontaneous peritonitis with a fungus-positive ascitic culture (SFP and fungiascites) and spontaneous peritonitis with a bacteria-positive ascitic culture (culture-positive SBP and bacterascites) [11,12]. Some comparative studies reported no significant differences in PT or albumin or bilirubin levels between SFP and SBP patients [6,7,9] or between spontaneous peritonitis with a fungus-positive ascitic culture and those with a bacteria-positive ascitic culture [11,12]. The reports of serum Cr level are also inconsistent. As in this series, some comparative studies reported no significant differences in serum Cr between SFP and SBP [6,7,10] or between spontaneous peritonitis with a fungus-positive ascitic culture and spontaneous peritonitis with a bacteria-positive ascitic culture [11,12]. However, Elkhateeb et al. [9] found that serum Cr was significantly higher in SFP than in SBP (culture-negative neutrocytic ascites).

Regarding the severity of underlying disease, Gravito–Soares et al. [6] reported no significant differences in the Child–Pugh and MELD scores between patients with SFP and SBP. Our previous study [7] also reported no significant differences in the Child–Pugh scores between SFP and culture-positive SBP. Bucsics et al. [11] and our previous study [12] reported no significant differences in the Child–Pugh scores between spontaneous peritonitis with a fungus-positive ascitic culture and spontaneous peritonitis with a bacteria-positive ascitic culture. Hwang et al. [10] reported significantly higher Child–Pugh scores in SFP than in SBP.

Regarding the ascitic fluid findings in this series, many studies have observed no significant differences in total protein or albumin between SFP and SBP [6-9] and between spontaneous peritonitis with a fungus-positive ascitic culture and those with a bacteria-positive ascitic culture [12].

Prognosis of SFP

The severity of underlying liver disease [10], a high Child–Pugh [9] or MELD score [14], use of antibacterial prophylaxis [26], presence of hepatorenal syndrome [26], low ascitic fluid protein [26], high acute physiology and chronic health evaluation II score [14] and septic shock have been identified as risk factors associated with in-hospital SFP mortality [6].

The in-hospital mortality of SFP reportedly ranges from 33% to 100% [5-7,10,14,19,38]. Gravito–Soares et al. [6] indicated that 30-day mortality was 50% (four of eight patients) in SFP and 24.4% (29 of 119 patients) in SBP. Similarly, Hwang et al. [10] reported significantly higher one- and six-month mortality rates of 73.3% (11 of 15 patients) and 93.3% (14 of 15 patients) in SFP than in SBP (28.7%, 115 of 401 and 56.1%, 225 of 401 patients, respectively). Our previous study also showed that one- and six-month mortality rates were higher in SFP than in culture-positive SBP or bacterascites [7].

Hwang et al. [10] reported that a high SFP mortality rate was related to unresponsiveness to initial empirical treatment for suspected SBP. The condition of nearly all SFP patients has worsened after initial empirical treatment and they have died during the early stage of peritonitis regardless of undergoing antifungal treatment [10]. Some patients with SFP have improved after receiving the initial empirical treatment with no antifungal agents [10]. Those patients may have had SBP and colonization by innocent fungi because it was impossible to distinguish fungal colonization from true SFP in a clinical setting [10].

SFP is usually diagnosed after identifying fungi in cultures of ascitic fluid. The mortality rate is high partly because of delayed diagnosis, lack of clinical signs, lack of suspicion of SFP and delay in treatment with antifungal therapy [9,10,26,30,38]. Fungal resistance to empirical specific antifungal therapy together with delayed diagnosis and treatment is related to poor prognosis of SFP [6].

Treatments for SFP

Echinocandins are recommended as a first-line treatment for patients with LC and nosocomial SFP or critically ill patients with LC and community-acquired SFP [10]. Fluconazole is recommended for less severe infections [26,39]. De-escalation from echinocandins to fluconazole is advised in critically ill patients with LC and SFP when their condition is stable and sensitivity tests are available [26,39].

Although it remains uncertain whether antifungal therapies would decrease the mortality rate associated with spontaneous peritonitis by fungi [14,30,40], early initiation of antifungal therapies is necessary in SFP or suspected SFP cases. However, the question-when to start antifungal treatments—remains unanswered partly because of very low-quality of available evidence [4]. Although early differentiation between SFP and SBP may be difficult, clinicians should suspect SFP or SBP due to multidrug resistance bacteria if spontaneous peritonitis has not improved after 48 h of empirical antibiotic treatment [5]. Therefore, additional administration of antifungal agents (and alternation of antibiotics) may be considered for these patients [4,5,8]. Moreover, the recent review article suggests the rapid initiation of antifungal therapy in the presence of septic shock and failure to respond to broad spectrum antibiotic regimen [19]. However, the previous above-mentioned report by Hwang et al. [10] indicated that the condition of some patients with SFP have worsened after initial empirical antibiotic treatment for SBP, and they have died during the early stage of peritonitis despite undergoing antifungal treatment. Therefore, combination therapies of antibiotics and antifungal agents may be considered for patients with severe LC and nosocomial spontaneous peritonitis, although accumulations of further studies are necessary to justify this.

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