Fungal peritonitis and cancer near the abdominal regions

Seyed Reza Aghili[1], Tahereh Shokohi[1*], Ghasem Jan Babaei[2], Samaneh Afshar[1], Bahar Salmanian[3]

1. Department of Medical Parasitology and Mycology, Faculty of Medicine, Mazandaran University of Medical Sciences Sari, Iran
2. Department of Internal Medicine, Molecular Cell-Biology Research Center, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
3. Faculty Member of Farhangian University, Sari, Iran

***Corresponding author:** Tell: +98 151 3543087; fax +98 1513543088
Address: Department of Medical Parasitology and Mycology, Faculty of Medicine, Mazandaran University of Medical Sciences Sari, Iran
Email: shokohi.tahereh@gmail.com
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Abstract

Introduction: Guidelines have recommended that structured programs should be introduced to support fungal peritonitis in cancer patients. The role of fungi is rare in causing peritonitis, but fungal peritonitis has high morbidity and mortality. The abdominal fullness may be secondary to the fungi accumulation of peritoneal fluid. The isolation of fungi, particularly *Candida*, from peritoneal fluid samples is an increasingly common occurrence in patients with cancer near abdominal region which creates a hypothesis on the role of fungi as a pathogen or an innocent bystander in the disease process.
Materials and methods: In this paper, all the relevant papers about the analysis of clinical signs, diagnosis and management fungal peritonitis in cancer patients particularly those near abdominal region were reviewed. An extensive search was undertaken of texts published during 1950-2012 using identified keywords and index terms.
Results: It seems that tumor-related local factors permit fungi to cross the gut wall and enter the peritoneum, resulting in the growth of fungi, inflammation, and weakening of the immune system in peritonitis. In this regard, treatment is very difficult due to lack of specific clinical signs and difficulty in isolating pathogenic organisms from clinical specimen.
Conclusion: Examination of peritoneal fluid for the fungal element (direct microscopic exam and culture) is necessary in malignant patients with inflammation of peritoneum.

Keywords: Fungal peritonitis, malignancy, cancer, abdominal region cancer, management

Introduction

Peritonitis is viewed as the inflammation of the peritoneum and dependence on the underlying pathology which might be infectious or sterile pathogenic.

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Microorganisms such as gram positive and gram-negative bacteria are the main causes of peritonitis (1). The role of fungi in causing peritonitis is rare, but fungal peritonitis (FP) has high morbidity and mortality (between 20% -70%) (2-4). According to what researches have reported, fungi represent about 2% – 23.8% of infectious peritonitis (5–8). *Candida* species are the most common cause of FP (2,5,8). Other yeasts and filamentous fungi such as *Aspergillus, Paecilomyces, Penicillium*, and *Zygomycetes* are found, but much less frequently. *Albicans* is the most common candida species causing intra-abdominal infections, but a shift toward non-albicans species such as *C. parapsilosis, C. glabrata, C. tropicalis, C. krusei*, and *C. lusitaniae* has been recently observed (9-11). Penetration of fungi in peritonea needs underlying conditions. The strongest risk factors for FP include peritoneal dialysis (PD) and certain co-morbidities such as diabetes or neoplastic diseases (12, 13). Malignant conditions, particularly near abdominal region, such as hepatocellular carcinoma ("liver cancer"), cancer metastasized to the liver, and pelvises in ~~of~~ gynecologic dissemination cases are the risk factors for FP (14, 15). Among women, an infected fallopian tube or a ruptured ovarian cyst also spreads to peritonea and creates localized peritonitis (16).

Virtually, any tumor can cause body fluid accumulation, but carcinomas of the lung, breast, ovary, and gastrointestinal tract (GI) are the most common. Candida species are endogenous commensal organisms as part of the normal flora of the human mucus membranes, gastrointestinal tract, respiratory tract, and vagina. According to the American Cancer Society, ovarian cancer ranks fifth in cancer incidence among women by site, superseded by breast, colon, rectum, lung, and uterine cancers (17). The abdominal fullness may be secondary to the fungi accumulation of peritoneal fluid. The isolation of fungi, particularly *Candida* from peritoneal fluid samples is an increasingly common occurrence in patients with cancer near abdominal region that creates a hypothesis on the role of fungi as a pathogen or an innocent bystander in the disease process. Despite this, there still is some debate over the importance of positive peritoneal fungal cultures and initiation of antifungal therapy (18). Furthermore, very little research has been published on this topic. Therefore, it is important to address the role of fungi in peritonitis in patients with cancer near abdominal region. The purpose of this review was to present the latest researches on fungal peritonitis in patients with cancer near abdominal region and the latest methods of diagnosis and treatment to guide clinicians in the management of such infections. Candida peritonitis associated with peritoneal dialysis is not within the scope of this article.

Epidemiology and risk factors

FP is classified as primary, secondary or tertiary. Primary FP is spontaneous peritonitis with no apparent breach in the gastrointestinal (GI) tract and usually occurs in immune-compromise patients from hematogenous dissemination after chronic liver disease (19). Secondary FP is related to a pathologic process in a visceral organ, such as perforation or trauma, including iatrogenic trauma or local infectious process within the abdominal cavity. However, tertiary FP often develops in the absence of the original visceral organ pathology and persistent or recurrent infection after adequate initial therapy. It's prognosis is worse than a bacterial peritonitis. The overall incidence of FP is difficult to establish and varies with the underlying abdominal disease processes. The disease

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occurs in both children and adults. According to the data, FP makes up 4-10% of the peritonitis cases in children and 1-23% of those in adults in peritoneal dialysis (20, 21). Fungi are widely found in human environments, being part of the normal flora of the skin and mucosa, but in certain conditions they can become pathogenic as a risk factor. Table 1 shows the major risk factors for FP considered in researches.

Table 1. Risk factors associated with Candida peritonitis in cancer patients

➢ Hollow viscus perforation ➢ Abdominal surgery ➢ Thoracic surgery ➢ Surgical drains in situ ➢ Prolonged time with the intravenous catheter inserted ➢ Prolonged time with the urinary catheter inserted ➢ Advanced age ➢ Presence of an extraperitoneal fungal infection ➢ Severe sepsis ➢ Previous bacterial peritonitis episodes	➢ Wide-spectrum antibiotic treatment in previous months ➢ Administration of immunosuppressants or corticosteroids ➢ Prolonged time in the continuous ambulatory peritoneal dialysis (CAPD) ➢ Intra-abdominal malignancy ➢ Presence of immunocompromising or debilitating diseases ➢ Malnutrition ➢ Diabetes ➢ Hospitalization ➢ Neoplastic diseases

Colonization by fungi such as Candida species may occur in patients who have received prolonged antibiotic therapy and those with an extended hospital stay. This flora may be responsible following penetrating and causing intra-abdominal abscesses. Some fungi can penetrate into the peritoneal cavity through intra-luminal or peri-luminal pathways and cross the intestinal mucosa, or enter through the haematogenic pathway due to a distant fungal infection. In patients with malignancy, receiving cytotoxic or corticosteroid drugs and chemotherapy cause underlying conditions to ease penetration or invade opportunisms fungi in tissues. Knowledge of the relation of FP and malignancy are essential in understanding its medical and public health impact, though few studies have been carried out on the case. In recent years, many reports have stressed the increasing frequency of infection caused by fungal organisms in patients with acute malignancy (22, 23). Although few reports have indicated the relationship of intra-abdominal malignancy to bacterial peritonitis (24, 25), patients with malignancy have an unclear and ower rate of FP incidence. In spite of the low incidence of FP associated with the malignancy underlying condition rather than bacterial peritonitis, it has a worse prognosis and can be life threatening if not treated properly (mortality rate >50%) (1). Malignancy and intra-abdominal abscess act as risk factors in 40-50% of FP patients (26).

Source and etiological agents

Table 2 shows the major sources of Candida peritonitis in cancer patients. Because of tenderness of tissues, swelling, fever, and abscesses, FP may occur after the penetration or invasion of fungi to the abdominal cavity in patients with cancer near abdominal regions. Both yeasts and filamentous fungi may cause FP.

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Table 2. Source of Candida peritonitis in cancer patients

➢ Per-cutaneously implanted ➢ Hepatic artery catheters ➢ Gastrointestinal perforation ➢ Anastomotic leakage ➢ Bladder perforation ➢ Peritoneal dialysis ➢ More localized abscesses with association of fungi in pelvic inflammatory disease	➢ Pancreatitis ➢ Peptic ulcer disease ➢ Appendicitis ➢ Flora of Skin, mucous membrane of the gastrointestinal and genital tracts ➢ Cancer near abdominal regions

Among the yeasts, strains of the genus Candida have the greatest incidence rate in FP and are responsible for about 70-90% of all cases. Candida albicans has classically been considered in predominant species. In recent years, other non albicans candida sp. such as C. parapsilosis (27), C. krusei (28), C. guilermondii (29) and C. glabrata (30) were distinguished in FP. Some studies reported that other yeasts such as Cryptococcus neoformans (31), Trichosporon sp. (32), Rhodotorula sp. (33) and Pichia ohmeri (34) may be the agents of FP. Despite the fact that the filamentous fungi are widely found in nature, FP caused by molds is a rare clinical problem and they often cause problems in patients on continuous ambulatory peritoneal dialysis (CAPD). They cause FP less than yeasts (about 10-30%). They involve peritonea or abdominal region tissues after penetration into the abdominal cavity. Peritonitis caused by Aspergillus (35), Fusarium (36), Acremonium (37), Paecilomyces (38), Penicillium (39), Cladosporium (40), Exophiala (41), Curvularia (42), and Zygomycetes (35) is described in the literature.

Symptoms of disease

Disease symptoms vary from limited and mild disease to systemic and severe disease with septic shock. The signs and symptoms of FP are similar to those seen in bacterial or malignant peritonitis. It is usually suspected on clinical grounds with symptoms and signs such as swelling and tenderness in the abdomen, loss of appetite, cloudy peritoneal effluent, abdominal pain, bloating in abdomen, fever, low urine output, inability to pass stool or gas, nausea and vomiting. In some patients, the number of leukocytes was below 500/mm3 in peritoneal effluent. The number of leukocytes was above 500/mm3 in only a few numbers of patients (1). FP often appears with marked edema or ascites in the peritoneal cavity (43). Ascites occurs because of problems such as disease in the peritoneal cavity which produces excessive fluid (infections or cancer).

Diagnosis

Fungal peritonitis can be difficult to diagnose in patients with cancer. Clinical signs and symptoms are nonspecific and similar to those seen with bacterial infection. The diagnosis of FP can be made by visualization of free air or fluid in the abdomen on plain radiographs, by cytology, and by diagnostic peritoneal lavage. Cytological evaluation of abdominal fluid can reveal the hallmarks of septic peritonitis. Bowel obstruction, bloody effluent, and in rare cases a visible fungal colonization of the peritoneal catheter may be present (mostly with filamentous molds). Peritoneal fluid's gram stain of can help to establish an early diagnosis in up to 30% of cases. However, the only fungi diagnosis that is usually gram-positive on a smear are Candida species. Growth rates are generally slow in fungal cultures, varying from several

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days to several weeks, and therefore the diagnosis can be considerably delayed. In secondary and tertiary FP, Candida species are often isolated as leading pathogen fungi (44-48). When purulent drainage occurs, an exit-site infection with or without erythema of the skin is defined. In addition to the culture of the peritoneal fluid, any purulent discharge from the exit site should be swabbed for culture and Gram-stain. FP should always be included in the differential diagnosis of any other peritonitis, such as peritoneal dialysis with cloudy effluent, renal or biliary colic, peptic ulcer disease, pancreatitis, and acute intestinal perforation. A cloudy effluent may be caused by chemical inflammation, haemoperitoneum, or peritoneal malignancy (49, 50).

Correct mycological culturing of peritoneal effluent is the most important chllenge in establishing fungi responsible for FP. Identification of organism's type and subsequent antifungal sensitivities will not only help selection of antifungal but can also indicate the possible source of infection (51).

Aspirate cultures should be carried out for any patients with symptoms of peritonitis particularly patients with cancer near abdominal region, even if the aspirate is clear and abdominal pain is absent or without an obvious cause (52). Rapid blood-culture techniques (e.g., BACTEC, Septi-Chek, BacT/Alert; Becton Dickinson) may further speed up isolation and identification.

The results of serologic tests for systemic fungal pathogens are often difficult to interpret and may be unreliable. Recent diagnostic advances include detection of fungal cell-wall components such as galactomannan, β-d-glucan, or genomic DNA amplified by polymerase chain reaction (43, 53 and 54). Those tests may improve the diagnostic ability in the future, but they are still under investigation. Other imaging techniques like positron emission tomography scanning may be useful for diagnosing and managing FP infection (55).

Special considerations and literature review

Although most cases cancer may remain silent and invasion of organ wall is usually limited to the superficial epithelium, extensive tissue necrosis and ulceration resulting in cancer tissue perforation is possible. Peritonitis is usually caused by the spread of an infection into the sterile peritoneal environment through organ perforation. So, perforation should be considered in patients with cancer near abdominal region. They have symptoms such as unexplained fever, abdominal pain, bloating in abdomen, nausea, vomiting, pleuritic chest pain, and inability to pass stool or gas. Fungal infection of fallopian tube or a ruptured ovarian cyst also creates localized FP in women (56). Ascites are at risk for developing spontaneous fungal peritonitis in patients with cancer near abdominal region. It is possible that irradiation and chemotherapy might have led to mucosal disruption, thereby it facilitates deeper invasion of the organ by fungi. FP has emerged as a relatively common infection in patients who receive peritoneal dialysis, ventriculoperitoneal shunt or intra-peritoneal delivery of chemotherapy. Also, FP has been reported among malignant patients, particularly those with cancer near abdominal region or those receiving chemotherapy medications in the setting of disseminated disease.

Among the fungal pathogens, *Candida* sp is frequently isolated from the ascitic fluid of patients with perforated ulcers. On the other hand, fungi (yeast or mold) can aggravate ulcer perforation where they exist as a commensally opportunistic organism (57). FP has also been rarely associated with patients who have recently had oral or upper

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gastrointestinal tract bleeding (58). Many of these patients do not show clear signs of peritonitis or some of these patients might have been previously diagnosed with other kinds of sites. There have been some previous reported cases of FP in patients with cancer. Most of these occur predominantly in patients with solid tumors, such as gastrointestinal tract or genitourinary tract cancer.

Gerald P. Bodey (1966) recorded 189 fungal infections in 161 patients with acute leukemia during a 10.5-year period. Severe Candidiasis occurred in 71 patients and 62 patients had only focal gastrointestinal lesions. *Candida* spp. was the major agent of infections. Approximately, one-half of the Candida infections were localized to the gastrointestinal tract. He explained two cases, which resulted in perforation of *Candida* and *Rhizopus* from abdominal infection. He reported increased incidence of fungal disease in patients with acute leukemia related to the use of anti-leukemia agents, adrenal corticosteroids and antibiotics (59).

Singer C. et al (1977) studied 364 episodes of bacteremia and fungemia in patients with neoplastic disease (leukemia or lymphoma) at Memorial Sloan-Kettering Cancer Center during a 14 month period. They found 13 episodes candidemia. The patients had underling condition or signs such as abdominal infection, catheter-related infections and symptoms of peritoneal inflammation (60).

Kopelson G. et al (1979) reported two patients with intra-abdominal malignancy that developed isolated *Candida albicans* peritonitis. They postulated tumor-related local factors permitting fungi to cross the gut wall and enter the peritoneum. Also, they concluded that patients who develop fungal peritonitis may have a primary or metastatic intra-abdominal malignancy and fungi should be considered as a cause of peritonitis in cancer patients (61).

Martino R. et al (1997) in their study, titled "reactivation of invasive fungal infection in patients with hematologic malignancy" studied 17 patients with a previous invasive fungal infection (IFI) due to Aspergillus during 4 years, Pseudallescheria boydii or Candida Spp. 18 had an underlying hematologic malignancy and received further intensive chemotherapy. Eight patients died. They concluded that these patients might have risked for reactivation of IFI (62).

C. Viscoli et al (1999) recorded 249 episodes in a surveillance study of candidemia in cancer patients. Candida albicans was isolated in 70% of cases involving patients with solid tumors and in 36% of hematologic disease. Solid tumors were mainly located in the genitourinary tract (29%) and the gastrointestinal tract (29%). Clinically or microbiologically documented organ involvement was present in only 24 patients (10%) and 3 patients (12.5%) had shown peritonitis (63).

M. O. Almoujahed et al (2003) reported 33 cases of fungal peritonitis during a 4-year period (5.3% of all microbiology reports). Neoplastic conditions and human immunodeficiency virus infection were present in some patients as underlying conditions (16% and 3.2%). They explained percutaneously implanted catheters in 15 cases, gastrointestinal perforation or anastomotic leakage in 15 cases and bladder perforation in one case where the source of peritonitis involved. *Candida* spp. (93.8%), *Trichosporon pullulans* (3.1%) and unidentified yeast (3.1%) were isolated from them (64).

Thomas D W. et al (2005) reported *Candida albicans* peritonitis in a patient with Felty's syndrome (a syndrome consists of

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rheumatoid arthritis, splenomegaly, and neutropenia) who had skipped ulcers with fungal hyphae. They presumed that when host defenses are compromised, fungal invasive disease might associatively occur with other predisposing factors such as corticosteroids and antibiotic treatments (65).

P. Montravers et al (2006) in study of mortality in peritonitis recorded that among 164 patients with signs of nosocomial peritonitis (NP), 84 (51%) had malignancy and immunosuppression as an underlying disease. Also they explained the significantly increased mortality and morbidity observed in the group of NP with Candida isolation in the peritoneal fluid. It shows the pathogenic role of Candida (66).

Afridi SP. et al (2008) studied 300 perforation peritonitis in patients who had pain in abdomen, abdominal distention, altered bowel habit, nausea vomiting, fever and shock due to septicemia. The most common cause of perforation peritonitis noticed in their series was acid peptic disease (45%) and the mortality was 10.6%. Among the patients, 33 (11%) cases had a malignancy as underlying diseases and 2.6% showed peritonitis. They recorded that the perforation is a rare complication of gastric carcinoma (less than 1%), but perforated gastric ulcer has a high malignancy incidence of. As seen in their study, out of 7 gastric perforations 2 were malignant (67).

P. Montravers et al (2010) studied detailed prospective of 271 ICU patients with proved to have invasive Candida infection. They reported that, 26 (9.6%) of these patients had candidemia and 93 (34.3%) had Candida peritonitis. Mortality was 38% in ICU. Among patients with peritonitis, 36% had solid tumor, 4% hematological malignancy, 11% immunosuppression and 12% Chronic renal failure, while 90% used central venous catheter and 89% urinary catheter (68).

Prophylaxis

In order to find a probable relationship between FP and cancer near abdominal region, the use of antifungal prophylaxis such as oral nystatin or fluconazole seems to be a logical approach. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology for prevention and treatment of infections in Patients with Cancer which highlights the importance of antifungal prophylaxis as a key therapeutic strategy in the management of high risk patients for invasive fungal infections. Risk factors can be undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes, or stem cell transplantation (69) since these infections are major causes of death in these seriously ill patients. However, some studies show that the prophylaxis given during other therapies in patients with cancer has yielded conflicting results (70-72). So, until the results of larger randomized trials is available, the guidelines from the International Society for Peritoneal Dialysis (ISPD) recommend antifungal prophylaxis only in centers with high FP rates. For programs with lower rates, there is no clear message, and decisions have to be made on an individual basis (1). Management Despite improved diagnostic techniques, potent pharmaceutical antifungal, modern intensive care, and aggressive surgical treatment, up to one third of patients still die of severe secondary FP. As FP's clinical signs and symptoms are nonspecific and similar to other kind of peritonitis, immediate medical management should include correction of metabolic and acid-base imbalances. Fluid, colloid, and electrolyte replacement with an isotonic solution are the major focus of medical management. Analgesics and

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antiemetic are administered for pain, nausea and vomiting. Patients' blood pressure and urine output should be monitored frequently and the character of drainage should be observed and recorded. Mortality of FP correlates with the severity of disease and it's underlying conditions, so that improving the underlying conditions are necessary. Broad-spectrum antibiotic therapy usually is initiated immediately. Drainage of the abdomen may be accomplished by placement of peritoneal drains or by open abdominal management. Commercial peritoneal catheters seem a preferable method of providing continuous drainage; omentectomy must be performed to allow any drains to function. If culture results showed fungal growth and drug sensitivity was determined to fungi, antifungal therapy should be initiated immediately. Antifungal drug is administered intravenously, but they may also be infused directly into the peritoneum. If one or more agents are actually isolated, therapy will indeed be targeted at them. The selection or doses and combinations of antifungal therapy are not the same and vary based on case series and opinions. Prescription of antimycotics can be intraperitoneal, intravenous, or oral. If the catheter is removed, the switch to systemic therapy will be necessary.

For initial therapy, most clinicians prefer to start with fluconazole, intraperitoneally (200 mg in 1 exchange every 24 – 48 hours) intravenously or orally (100 – 200 mg daily) because it is well absorbed from the gastrointestinal tract and has a good intraperitoneal penetration. Fluconazole might be used either alone or in combination with other antifungal drugs such as flucytosine. But some species of mycotic agents such as *non-albicans Candida* species may be resistant to it (73). In these cases, a switch to amphotericin or a newer azole might be required. Since the fungi's resistance risk to Flucytosine is so high, it is recommended not to prescribe it alone. However, after oral dosage (500 mg twice daily), the peritoneal penetration is effective. On the other hand, it has toxic activity on bone marrow and liver. So, it should not be used in patients with bone marrow depression, hematologic, or hepatic disease. patients who are immunosuppressed or had significant prior exposure to azoles or if the pathogen agent is more resistant to fluconazole (e.g., *Candida glabrata*, *Candida krusei*), intravenous deoxycholate or lipid-associated amphotericin B is a chosen drug (0.5 mg/kg to 1 mg/kg daily depending on yeasts or mold pathogen). However, mortality is reported as high as 70% in patients who have undergone surgical intervention, though they had received amphotericin B (74, 75). Combination therapy with amphotericin B and either fluconazole or flucytosine has been used successfully (76, 77). There are very limited experiences with the newer antifungal agents such as newer triazole (e.g. voriconazole and posaconazole) and echinocandins (e.g. Caspofungin, micafungin, and anidulafungin).

Voriconazole can be used into oral and intravenous administration and its effects may yeast filamentous fungi except *Zygomycetes*. Oral posaconazole has proven effective in the case of FP due to *Zygomycetes* (78). As both agents carry a risk of hepatotoxicity, monitoring liver function is recommended in treated patients. The role of echinocandins in FP has not yet been defined. But their broad-spectrum activity and safety characteristics might make these agents as an important therapeutic alternative to amphotericin B in patients with peritonitis resulting from infection with moulds and some *non-albicans Candida* yeasts or in patients

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intolerant to other antifungal therapies. There is no consensus on the duration of FP treatment; however, most investigators advocate at least 2 weeks of therapy with the possibility of 4 or more weeks in certain clinical situations. Many investigators believe that the catheter has a role in the incidence of fungal peritonitis particularly in patients who have failed medical therapy alone (79- 81). If patients have a catheter, after an outbreak symptom of FP and fungi identified by microscopy or culture, NCCN guideline suggest that the catheter should be removed immediately in adults because fungi can be colonized. It forms biofilm and spreads on the catheter surface. Due to facility of vigorous peritoneal lavage with drugs, some recent pediatric reports were been promoted early but not immediately removed (82-84). The classical single operation for FP, which obliterates the source of infection and purges the peritoneal cavity, may be inadequate for severe forms of peritonitis. For the latter, more aggressive surgical techniques are necessary to decompress increased intra-abdominal pressure and prevent or treat persistent and recurrent infection. There is an increasing evidence that laparoscopy may play a definite role in patients with FP. As a result of perforated diverticular disease, treatment by laparoscopy and peritoneal lavage was successful in patients with generalized peritonitis. However, laparoscopic management of generalized peritonitis needs further assessment.

Summary

FP infection is increasingly important in clinical practice in patients with cancer near abdominal region. There was an association between perforation of the cancer tissues in patients and fungal peritonitis. Based on a limited number of published clinical experiences on the topic, it is estimated that less than 2% of patients with cancer near abdominal region involved FP. However, its importance resides in the disproportionately greater morbidity and mortality that has historically been associated with this infection. Several factors appear to predispose patients to the development of FP. The most consistently reported factor in these patients is the use of cytotoxic or corticosteroid drugs and chemotherapy or a catheter-related infection prior to the development of the fungal infection. Typically, *Candida* species account for the majority of fungal isolates, with *C. albicans* being the most common. Presumably, perforation of the cancer tissues helps in penetration of fungi from the gastrointestinal or genital tracts and overgrowth of them into the peritoneal cavity. The decision for empirical antifungal treatment in any patient with suspected FP has to be based on the exact knowledge regarding origin, severity of disease, knowledge of patient specific risk factors, and previous exposure to antifungal drugs. The optimal approach to the treatment of FP remains undetermined. Medical therapy of FP most often consists of a combination of antifungal medication, catheter removal and surgical techniques. The fact is that FP must be considered in all patients, especially malignant patients with symptoms of peritonitis and those unresponsive to the routine antibiotic therapy.

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