Original Paper

A series of fungal infections with rare presentation in critically ill patients: diagnostic and treatment challenges

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ABSTRACT. Invasive fungal infections are alarmingly common in ICU patients, associated with increased morbidity and mortality. Risk factors are the increased use of indwelling central venous catheters, the use of broad spectrum antibiotics, parenteral nutrition, renal replacement therapy and immunosuppression. Diagnosis of these infections might be complicated, requiring tissue cultures. Additionally, therapy of invasive fungal infections might be difficult, given the rising resistance of fungi to antifungal agents. We present three rare cases of fungal infections in critically ill patients: a *Candida albicans* pyelonephritis, a *Candida albicans* thrombophlebitis of central veins and an orofacial mucormycosis. Difficult to treat fungal infections may complicate the clinical course of critically ill patients and render their prognosis unfavorable. *Pneumon 2015, 28(2):167-172.*

Key Words:
- Emerging fungal infections
- ICU patients
- Treatment

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INTRODUCTION

Invasive fungal infections are increasingly common in ICU patients and are associated with prolonged hospitalization duration and increased mortality[1,2]. The worldwide EPIC II study showed that almost 20% of all isolated pathogens in ICU patients were fungi, with *Candida* spp. ranking fourth after *Staphylococcus* spp., *Pseudomonas* spp. and *Escherichia coli*. *Candida* spp. were the most frequently isolated yeasts, responsible for almost 88% of fungal infections. The cited attributable mortality for *Candida* infections varies from 5% to 71%[3]. Increased incidence of fungal infections in ICU patients may be attributed to a variety of reasons such as the increasing incidence of immunocompromised patients requiring ICU admission, the ageing population of ICU patients, and the large number of invasive medical practices required in ICUs[4]. This report presents three difficult to treat cases in a Medical-Surgical Intensive Care Unit (MSICU)of a tertiary hospital recorded between 2008 and 2013 (Case 1-3 respectively).

CASE 1: CANDIDA ALBICANS PYELONEPHRITIS

A 47-year old woman with stage IV cervical cancer, after seven cycles of chemotherapy and radiotherapy, underwent pelvic exenteration, ileocystoplasty and implantation of both ureters in anisolated intestinal segment. Fifteen days later she developed fever (>39^{0}C), respiratory, renal and hepatic failure, leading to tracheal intubation and admission to ICU. The ultrasound study of the kidneys revealed bilateral pyelocalicic dilatation and hypoattenuated lesions in the left papillary region, consistent with necrotizing papillitis. Percutaneous nephrostomy catheters were placed while *Candida albicans* was isolated from urine and blood cultures. Digital nephrostomogram of the left (Figure 1a) and right (Figure 1b) nephrostomy catheter depicted moderate dilatation and multiple fillings defects indicative of fungus balls located in the pelvicalyceal systems. The patient was managed with Liposomal amphotericin B (4 mg/kg daily) and fluconazole (400 mg×2 daily) intravenously according to the recorded MIC (μg/mL) 0.06 amphotericin B; 2 fluconazole by the EUCAST method. Seven days later blood cultures were negative but *Candida albicans* was stillisolated from samples drawn from the nephrostomy catheters while the patient remained febrile. Irrigation of urinary tract with Amphotericin B-deoxychoalate at 50 μg/ml was applied by nephrostomy catheters once per day. Seven days later the clinical status and the renal function of the patient gradually improved while urine cultures became sterile.

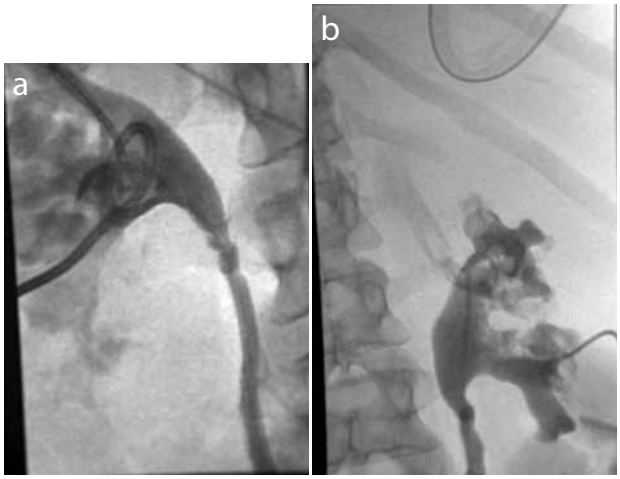

FIGURE 1. Digital nephrostomogram from the left (a) and right (b) nephrostomy catheter depicts moderate dilatation and multiple fillings defects which are caused by the fungus balls located in the pelvicalyceals systems.

A new digital nephrostomogram performed fifteen days later depicted resolution of the filling defects of both kidneys (Figure 2a and 2c) while a good patency of the distal anastomosis was observed (Figure 2b). Local irrigation with amphotericin B-deoxychoalate was discontinued a week later (total duration of irrigation: 15 days). Intravenous administration of liposomal amphotericin B was continued for 15 days after sterilization of blood cultures while fluconazole (400mg x 2 pos) was administered for six weeks in total. The patient's clinical condition progressively improved, all cultures were negative, and she was discharged from the ICU a week after completing the fluconazole course of therapy.

CASE 2: CANDIDA ALBICANS THROMBOPHLEBITIS OF CENTRAL VEINS

A 18-year old man with ventriculoperitoneal shunting, was admitted to the internal medicine department of a tertiary hospital due to fever, dyspnea and respiratory failure, attributed to aspiration pneumonia. During the present hospitalization the patient was initially treated with cefuroxime and metronidazole. A central venous catheter (CVC) was inserted to the left subclavian vein. Ten days later the patient presented with a new episode of fever and progressive clinical deterioration, leading to tracheal intubation and mechanical ventilation, due to respiratory failure and septic shock. *Candida albicans* was isolated from the CVC tip and in blood cultures, and *Pseudomonas aeruginosa* in bronchial secretions cultures (10^6cfu/mm^3). Antimicrobial therapy was changed empirically to fluconazole 200mg q12h, meropenem 2g q8h and linezolid 600mg q12h. The relatively low dose of fluconazole is due to the issue that the patient was hospitalized during 2005, and the reported data were poor. The following days the patient remained febrile,candidemia persisted as seven successive blood cultures (drawn on sequencing days) yielded *Candida albicans*, while the new CVC tip was sterile. Transthoracic and transesohpageal echocardiography did not reveal any vegetative endocardiac lesions and fundoscopic examination did not show evidence of endophthalmitis. A whole body computer tomography was performed, revealing thrombophlebitis of the left internal jugular vein, left subclavian vein and left brachiocephalic vein, without embolic phenomena (Figure 3). Liposomal amphotericin B, 5mg/kg body weight was added to the antimicrobial treatment. Fifteen days later the patient became a febrile and the blood cultures were

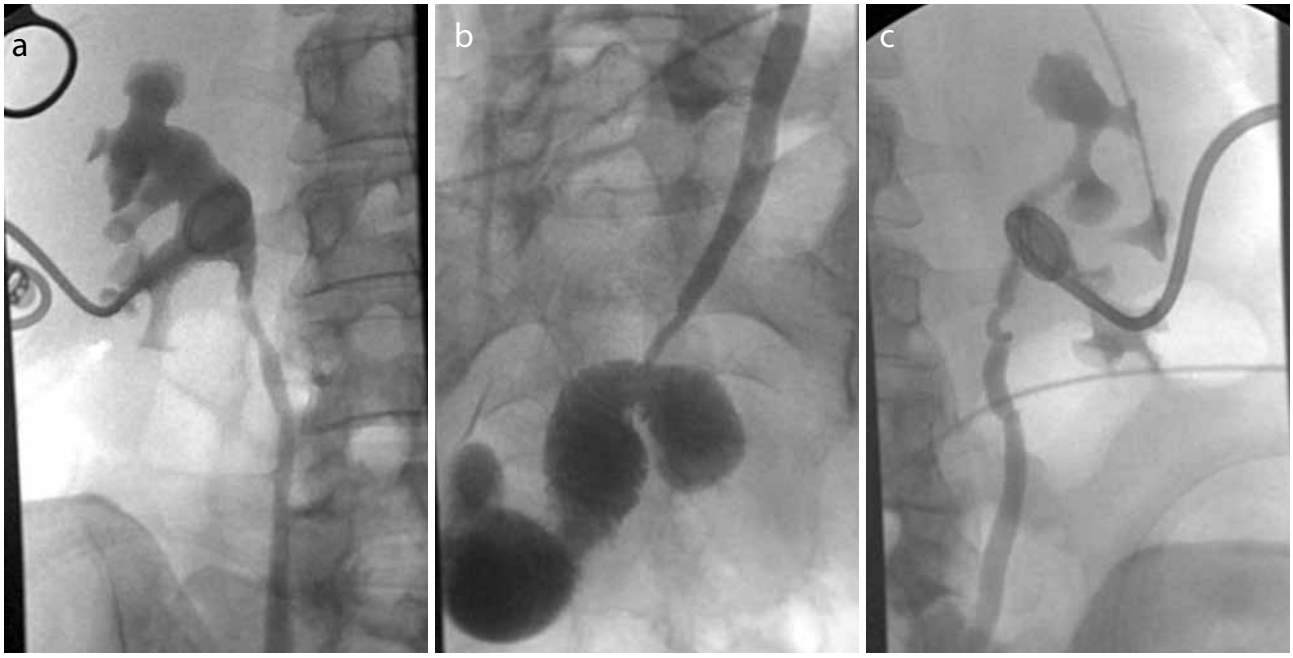

FIGURE 2. Digital nephrostomogram obtained fifteen days following the bilateral percutaneous nephrostomies depict resolution of the filling defects of the both the left (A), and the right (C) kidneys. Note good patency of the distal anastomosis (B).

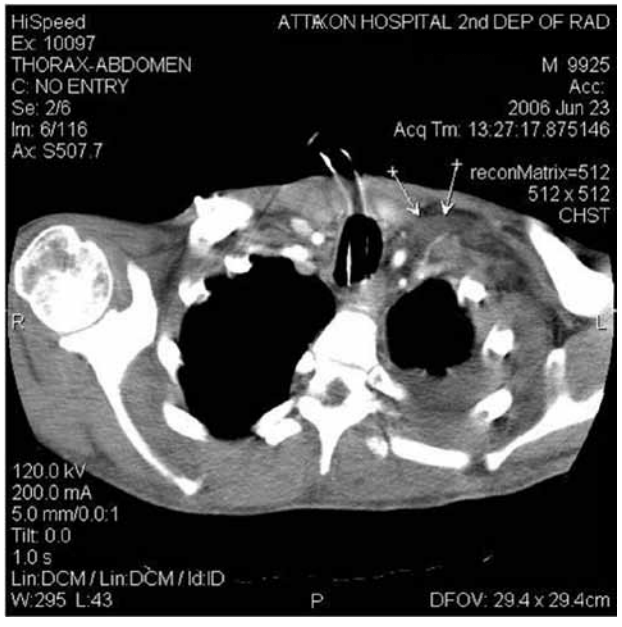

FIGURE 3. Chest computer tomography revealing thrombophlebitis of left internal jugular vein, left subclavian vein and left brachiocephalic vein.

negative for microbial growth. He was gradually weaned from mechanical ventilation and was transferred to the ward for rehabilitation, and he was discharge a week later. A Doppler ultrasound showed recanalization of the previously affected large vessels. The patient received antifungal therapy (LAMB and fluconazole) for seven weeks and stayed in the ICU for 50 days.

CASE 3: OROFACIAL MUCORMYCOSIS

A 67-year-old woman with no history of diabetes mellitus or immunosuppression underwent sigmoidectomy and colostomy and peritoneal lavage, because of perforation of sigmoid diverticulitis and fecal peritonitis. Postoperatively she was admitted to the intensive care unit because of hemodynamic instability, acute kidney injury requiring continuous renal replacement therapy (CRRT)and respiratory distress. By the 7th hospital day a septic episode was noticed. An abdominal contrast tomography (CT) was clear. Blood cultures were negative. The following day a large red-purple lesion was noted over the patient's left cheek and upper lip which progressed rapidly within hours to necrotic lesion with a central blackish eschar, extending to the tongue and the hard and soft palate (Figure 4a and 4b). A brain CT was performed, showing blurred bony structures of the floor of the mouth and tongue, consolidation of left maxillary sinus and accompanying invasion of the maxillary bone

FIGURE 4A and 4b. Necrotic lesions with a blackish eschar to the left cheek and upper lip, extended rapidly to the tongue and the hard and soft palate.

(Figure 5a and 5b). Lingual and palatal tissue histological examination of tissue showed broad infarct-like necrosis of connective tissue, in and around vessels, and nonseptate

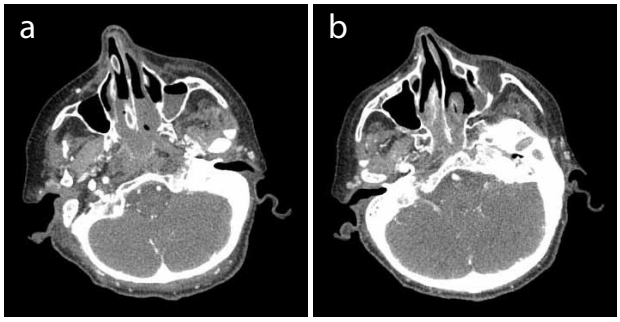

FIGURE 5A and 5b. A brain CT showing blurred bony structures of the floor of the mouth and the tongue, consolidation of left maxillary sinus and accompanying invasion of the maxillary bone.

hyphae compatible with mucormycosis (Figure 6). The patient was immediately started on liposomal amphotericin B (4mg/kg). Due to the patient's hemodynamic instability and bleeding diathesis, surgical debridement of the lesions could not be performed. Unfortunately, she deteriorated rapidly developing multi-organ dysfunction syndrome, and died 3 days later.

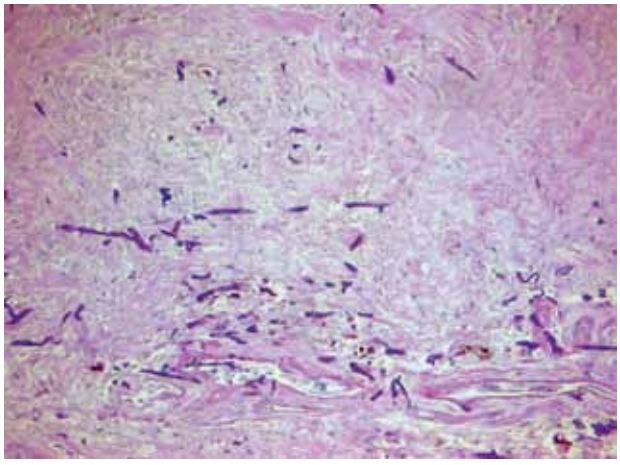

FIGURE 6. Histological examination of lingual tissue showing broad infarct-like necrosis of connective tissue, in and around vessels, and nonseptate hyphae compatible with mucormycosis.

DISCUSSION

The first case relates to a woman suffering from *C. albicans* pyelonephritis complicated by fungemia. According to recent publications, in cases of Candida urinary tract infections complicated by fungus balls formation, local irrigation of the renal pelvis through a nephrostomy tube with amphotericin B at a dosage of 50mg/L of sterile water can be useful in combination with systemic antifungal agents[5,21]. In our patient the diagnosis of *Candida* pyelonephritis with fungus balls was well established, while a bloodstream infection due to *C. albicans* was also identified. IDSA guidelines suggest the use of fluconazole at a dosage of 3-6 mg/kg as first line choices for susceptible strains involved in *Candida* pyelonephritis. Alternatively, guidelines suggest the use of Amphotericin B-deoxycholate with or without fluconazole and no Liposomal Amphotericin B (LAMB) because of its low observed concentration in urine[5]. Yet, according to the same guidelines, LAMB and the echinocandines constitute a stronger action against *Candida* biofilms while azoles are

not effective. Additionally, an echinocandine is preferred in case of candidemia in patients with severe illness, as was our patient. Taking into account these considerations, we used a combined therapeutic strategy including LAMB (targeted to candidemia and biofilm), fluconazole (targeted against pyelonephritis) and irrigation with Amphotericin B-deoxycholate (targeted against the fungus ball).

The second patient developed *Candida* thrombophlebitis of central veins (CTCV), a rare life-threatening complication of catheterization. According to a recent review, there are 24 reports of CTCV over the last 30 years[6]. Since diagnosis might be difficult, the persistence of fever and candidemia, despite proper antifungal therapy and removal of CVC, should raise the suspicion of presence of intravascular site of infection. Serious complications are endophthalmitis, endocarditis and osteomyelitis, and reported mortality rate is 16%[7]. Drainage or resection of the affected vein in combination with antifungal therapy is the recommended appropriate treatment of peripheral suppurative thrombophlebitis[8]. Nevertheless, radical excision of central veins is controversial because of possible inaccessibility and no clear effect on mortality[9]. Recommended antifungal therapy includes preparations of amphotericin B (LAMB 3-5mg/kg daily), fluconazole (6-12mg/kg daily) or an echinocandin for at least 2 weeks after the first negative blood culture, resulting in clinical success in the majority of reported cases[6,10]. Since our patient's clinical condition improved on combined antifungal therapy (fluconazole and LAMB), we did not perform surgical resection of the thrombus. Therefore there is no histological confirmation of CTVC. However, the clinical finding of persistent fever, septic shock and candidemia, despite the proper antifungal therapy, in combination with the imaging findings, is consistent with probable diagnosis of *Candida* thrombophlebitis. Prolonged antifungal therapy resulted in clinical cure of our patient without signs of relapse in follow-up cultures.

Our third case involves a critically ill patient who developed fatal orofacial mucormycosis. Mucormycosis is the third most common invasive fungal infection following aspergillosis and candidiasis[11]. Mucorales constitutes the largest order of Zygomycete fungi, but the genus *Rhizopus* accounts for 43% of cases of health care associated mucormycosis[12]. Mucorales can cause five forms of infection: rhino-orbito-cerebral (the most common form), pulmonary, disseminated, cutaneous and gastrointestinal[13]. Oral mucormycosis related to dental extraction, has been documented[13]. Nevertheless, there are only few cases of lingual mucormycosis described in the literature, most of them associated with the use of infected wooden tongue depressors[14,15]. Though more commonly affecting immunocompromised patients, rhinocerebralmucormycosis in normal hosts accounts for 9% of all cases of this form of infection[16,17]. Diagnosis requires tissue cultures and histopathological examination of biopsied tissue, with the characteristic finding of invasion of vessels and subepithelium tissue[18]. The cornerstone therapy of mucormycoses is antifungal treatment and surgical debridement of necrotic lesions. Antifungal treatment includes amphotericin B[19,22], while posaconazole constitutes an alternative effective agent[19,22]. Mortality rates are equally high in immunocompetent and immunosuppressed patients[17,18], reaching 60%, while with early surgical debridement the mortality can be reduced to 11%[18,20]. Our patient was a rare case of lingual mucormycosis not associated with the use of tongue depressors. As the infection predominantly affected the patient's face and the maxillary sinus, we characterize our case as rhinofacial mucormycosis involving the tongue. Because the CT showed invasion of maxillary bone, the infection might disseminate to the orbit and the cerebral region (rhino-orbito-cerebral form). Interestingly our patient lacked any of the known predisposing factors for mucormycosis. However, she was a critically ill septic patient who had recently undergone abdominal operation with possible depressed immune activity.

CONCLUSION

A multidisciplinary approach of patients with invasive fungal infections is frequently required, involving both combination of antifungal agents as well as surgical management where indicated. However, the mortality of invasive fungal infections in the ICU remains high in spite of efforts for prompt diagnosis and treatment.

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