Severe Cutaneous Candidiasis in a Liver Transplant Patient

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ABSTRACT

Candida infections are common diseases in immunocompromised patients. A 19-year-old boy with liver transplantation, necrotic skin lesion, jaundice, dyspnea, and ascites was admitted to Namazi Hospital, Shiraz, southern Iran. The mycological examination for the skin lesion was requested. The skin sample was cultured on Sabouraud dextrose agar and evaluated by direct microscopic smear. Identification of isolated yeast was performed with RFLP-PCR. In direct smear, pseudohyphae, blastopores and yeasts were observed. *Candida* species was isolated from the media and identified as *Candida albicans* by molecular method. He died before starting any treatments. A skin lesion may present as the only sign of a systemic fungal infection in immunocompromised people. Careful attention and follow up are therefore recommended.

KEYWORDS: *Candida albicans*; Liver transplantation; Fungal infection

INTRODUCTION

Fungal infections in liver transplant recipients are a frequent cause of morbidity and mortality. Invasive candidiasis and cutaneous *Candida* infections are the common fungal infections during both the early and late post-transplantation periods [1, 2]. *Candida* species are normal flora of human body and may be isolated from the oral cavity, gastrointestinal tract, female genital tract, and the skin [3]. In some patients, "skin lesions may be the only sign of a systemic fungal infection" [4]. A case of Candida albicans subcutaneous abscess in a heart transplant recipient was reported, which was successfully treated with aspiration and fluconazole therapy [5]. Skin infections due to fungal species have been reported in the literature including *Alternaria* species in kidney allograft recipients, *Scedosporium apiospermum* sternal wound infection in a heart transplant recipient, and *Fusarium proliferatum* soft tissue infection at the site of a puncture [6-8]. Herein, we report on a case of cutaneous candidiasis diagnosed in the latest days of life of a liver transplant recipients.

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CASE REPORT

Nine months after liver transplantation of a 19-year-old boy due to Wilson's disease, he was admitted to the emergency ward with jaundice, dyspnea, ascites and a necrotic skin lesion. He had low fat diet and received various broad-spectrum antibiotics for liver damage. He was on myfortic (mycophenolic acid) 720 mg tid, sirolimus 2 mg qd, methylprednisolone 500 mg and hydrocortisone 100 mg q8h, and meropenem 500 mg and targocil 200 mg qd for three days. No antifungal therapy was started for him. For the skin lesion, MEBO ointment, mupirocin cream, and hydroderm repair cream were used bid. According to the

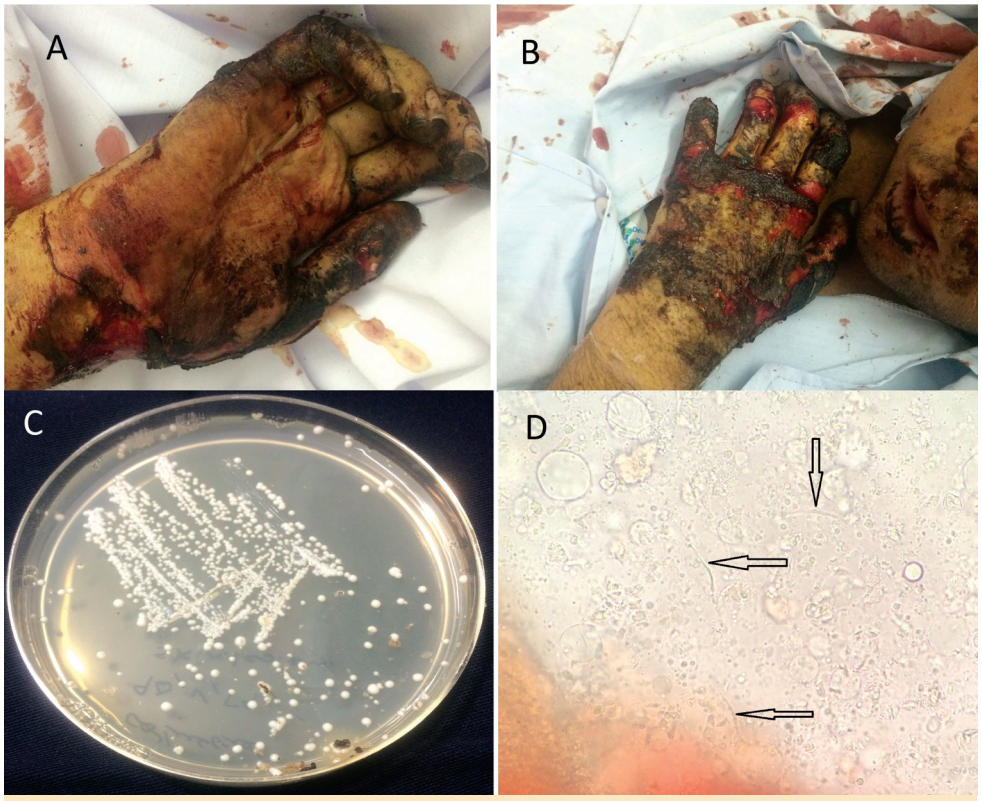

Figure 1: Cutaneous bloody lesion from the hand (A) and face (B); C) Candida colonies in fungal culture on SDA (40× magnification); D) microscopic observation of pseudohyphae in KOH smear

pathology report, moderate biliary type fibrosis but no evidence of rejection was observed. The latest results of blood biochemistry included a sugar level of 59 mg/dL, blood urea nitrogen of 66 mg/dL, creatinine of 3 mg/dL, Na of 146 mmol/L, K of 6 mEq/L, aspartate aminotransferase of 543 U/L, alanine aminotransferase of 286 U/L, alkaline phosphatase of 226 U/L, total bilirubin of 32.2 mg/dL, direct bilirubin of 14 mg/dL, and total protein of 5.5 g/dL. Blood cultures (by BACTEC medium, BD, USA) and urine cultures were negative. The results for other laboratory examinations including hepatitis B virus antigen, hepatitis C virus antibody, HIV antigen/antibody, hepatitis A virus antibody (IgM), hepatitis B viral protein, Epstein-Barr virus, and cytomegalovirus were negative. White blood cell count was 7400/mm^3 on the first day of admission but increased to 33,900/mm^3 in last days. Platelet count ranged between 44,000 and 98,000/mm^3. The international normalized ratio (INR) was 2.77. The patient had a mild normochromic normocytic anemia. Severe lesions were apparent on his hands, neck and face (Fig 1A and 1B). Ten days after hospital admission, fungal laboratory tests including potassium hydroxide (KOH) smear and fungal culture of the skin sample were requested by a consultant dermatologist. The skin sample was evaluated by direct microscopic smear and cultured on Sabouroad dextrose agar (Merck, Germany). Yeast colonies were grown on the culture medium (Fig 1C). Pseudohyphae, blastopores and yeasts were observed in KOH smear (Fig 1D). The yeast was identified with RFLP PCR method (Fig 2), using ITS region, ITS1 5'-TCC GTA GGT GAA CCT GCG G-3' and ITS4 5'-TCC TCC GCT TAT TGA TAT GC-3' [9]. The restricted enzyme used in the present study was MspI (Thermo scientific, USA). Antifungal susceptibility test was performed by broth microdilution method to determine the minimum inhibitory concentrations (MICs) of amphotericin B, caspofungin, voriconazole, fluconazole, posaconazole, and itraconazole, based on the CLSI document M27-A3 and CLSI M27-S4 [10, 11]. The MIC values of isolated species to antifungal agents were shown in Table 1. The patient had bleeding from the

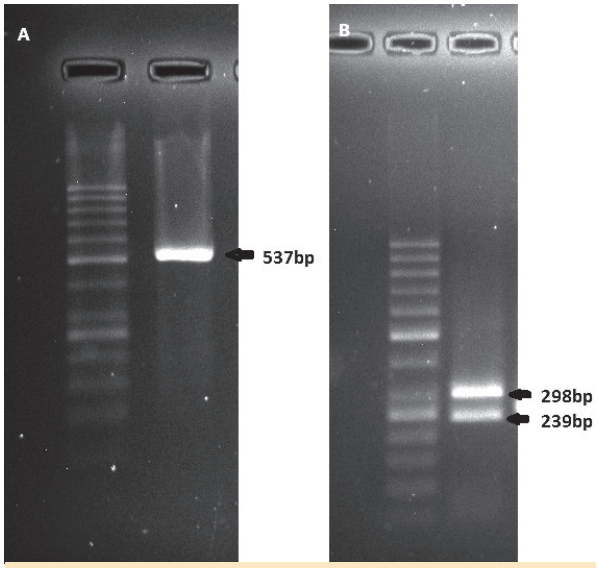

Figure 2: The results of RFLP-PCR. A) The first round of PCR with 537-bp product, and B) the second round with 289- and 239-bp products

lesions and nose due to thrombocytopenia, which was difficult to control. He passed away because of multiple organ failure one day after skin laboratory tests were requested for him.

DISCUSSION

Candida infections are the most frequent fungal infection in immunocompromised patients, especially transplant recipients, due to the use of immunosuppressive drugs and certain surgical procedures [1, 12]. These infections are associated with high morbidity and mortality, and early diagnosis and proper treatment are critical for the management of the respective patients. Cutaneous candidiasis involves the skin and may present as post-operative skin and soft tissue infections with *Candida* species and are difficult to manage [1, 2]. A wide spectrum of fungi including *Candida*, *Aspergillus*, *Dematiaceous* and *Dermatophyte* species can cause cutaneous diseases in immunocompromised patients [5-8]. The most common symptom of cutaneous candidiasis is rash with redness and itching under the breasts, armpits, groin, and between the fingers. Skin may become cracked and sore [3, 4]. In immunocompromised patients, symptoms of skin lesions may be atypical (specific or ambiguous). Outcomes of patients are depending upon early diagnosis and appropriate antifungal therapy. The cornerstones of management are effective antifungal therapy, improvement in host defenses and surgical resection of necrotic tissue generated by this angio-invasive fungus. Surgery is typically required if there is extensive necrosis or a threat to major vascular structures.

Diagnosis of fungal infection requires the isolation of etiologic agents from clinical samples, as a gold standard method. Direct microscopy examination is a suitable method for early diagnosis of fungal infection. Accordingly, the etiologic agents are diagnosed based on the shape of mycelium. *Candida* spp. and *Zygomycetes* fungi appear as pseudohyphae and blastopore, and broad non-septate and ribbon-like hyphae, respectively. Increasingly, molecular methods are being used for the detection of fungal agents [13].

In this study, infection was diagnosed by KOH smear immediately, after skin sampling. Identification of *Candida* isolates to the species level

Table 1: *In vitro* susceptibility of *Candid albicans* to six antifungal agents by CLSI methods

	MIC (µg/mL)	Drug breakpoints (µg/mL)			
		Susceptible	Susceptible dose dependent	Intermediate	Resistant
Amphotericin B	0.25	≤1	—	—	≥1
Caspofungin	0.032	≤0.25	—	0.5	≥1
Voriconazole	0.032	≤0.12	—	0.25–0.5	≥1
Fluconazole	0.125	≤2.0	4.0	—	≥8
Posaconazole	0.032	—	—	—	—
Itraconazole	0.032	≤0.12	—	—	≥1

and determining the susceptibility pattern are critically important in the patient's outcome. The sensitivity rates of *Candida* species to antifungal agents are different [14, 15]. Therefore, culture and identification of isolated species and corresponding sensitivity pattern can help the best antifungal therapy and treatment of the patients. In this study, isolated *C. albicans* was sensitive to all antifungal agents.

Candida infection of the skin may present as primary, inoculation by direct contact with *Candida* species, or secondary, through hematogenous spread. Also, cutaneous lesions may be a sign of a disseminated infection [16]. Therefore, early diagnosis may result in a better outcome. Diagnosis of systemic candidiasis is difficult. The overall sensitivity of blood cultures for the isolation of *Candida* species is estimated at 50% [17]. Non-cultural diagnostic methods like evaluation of mannan antigen and PCR can help early detection of systemic candidiasis [18]. Unfortunately, in our patient, blood culture was negative for *Candida* species and there was no request for non-cultural diagnostic tests for systemic fungal infections.

The patient died one day after skin sampling. In immunocompromised patients with many risk factors such as use of immunosuppressive drugs and broad-spectrum antibiotics treatment, follow up for early detection of fungal infection is suggested.

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