JOURNAL OF PURE AND APPLIED MICROBIOLOGY, May 2014. Vol. **8**(Spl. Edn. 1), p. 667-670

Fungemias Following Liver or Kidney Transplantation: A Clinical Analysis of 17 Patients

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(Received: 12 April 2014; accepted: 09 May 2014)

The present study is to investigate the clinical manifestations, distribution and characteristics of drug susceptibility of pathogens among liver or kidney transplant recipients with fungemias. Seventeen patients developed 21 episodes of fungemias between January 2003 and December 2013. Retrospective analysis to the pathogens and their drug susceptibility characteristics was carried out. The clinical and laboratory data on patients were obtained by hospital record review. *Candida spp.* accounted for 90.5% of all pathogens (18/21). The most common fungus was *Candida albicans* (7/21), followed by *candida parapsilosis* (6/21). Death occurred in 52.9% (9/17) of patients with fungemias. The fungi were relatively sensitive to amphotericin B, flucytosine, voriconazole and caspofungin. The clinical manifestations of fungemias included high body temperature, onset in the early period after liver transplantation as well as high mortality. The antibiotic resistant rate of pathogens causing fungemias was low among liver or kidney transplantation.

Key words: Liver transplant; Kidney transplant; Fungemia; Drug resistance.

Blood stream infections (BSIs) represent a serious complication after solid organ transplantation (SOT). Fungemias were responsible for 3.7%-19.5% of all BSIs in SOT [1-12]. *Candida spp.* [1-5,13,14], *Candida albicans* [6-8] or *Candida glabrata* [9,10] was the most common fungus pathogen causing fungemias after SOT. Kim S *et al* [11] revealed that 50% of fungi causing BSIs among liver transplantation were resistant to fluconazole. Van Hal SJ [15] *et al* found that fluconazole resistance of *Candida* species was 25% among SOT recipients with candidemia. It is very important to investigate the clinical manifestations, distribution and characteristics of drug susceptibility of pathogens causing fungemias among liver or kidney transplant recipients. The fungemias in SOT are well documented, but only few works [11,15] concern the study of antibiotic resistance of fungi isolates. In the present study, we summarize these aspects mentioned above to make antibiotics be used reasonably and improve the success of liver or kidney transplantation.

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MATERIALS AND METHODS

Study population and clinical isolates

This study was conducted at the Third Xiangya Hospital, Central South University, Changsha and Zhongnan Hospital, Wuhan University, Wuhan, China, between January 1, 2003

and December 31, 2013. Twenty-one isolates of fungi were obtained. Seventeen recipients had fungemia including fourteen liver and three kidney transplant recipients. The range of these 17 recipients ages at the onset of fungemias was 12 to 67 years (mean, 41.4 years). All recipients with fungemias enrolled were administrated with triple drug immunosuppression including mycophenolate mofetil, cyclosporine/tacrolimus, and corticosteroids. Recipients were rapidly tapered to 20 mg of prednisone per day by 7 days after surgery. We defined fungemias as the isolation of fungi from at least one blood culture. The present study was approved by the ethics committees of the two hospitals.

Microbiologic studies

A 10-mL blood sample drawn under sterile conditions was injected into a BACTEC Myco/F Lytic bottle. Blood samples were processed by the BACTEC 9120 blood culture system (Becton Dickinson, Cockeysville, MD, USA). Species identification for the bacteria was performed using the Vitek-2 system (bioMérieux, Marcyl'Etoile, France). Isolates of fungi were identified through standard microbiological tests [16]. Nystatin, flucytosine, amphotericin B, fluconazole, voriconazole, itraconazole and caspofungin were tested using the ATB FUNGUS 3 system (1000723260; BioMérieux, France). Quality control was performed by testing *Candida albicans* ATCC 60193 simultaneously with each batch of isolates. The results were evaluated according to the NCCLs manual [16]. Intermediate susceptibility to the antibiotics was considered as resistance.

RESULTS AND DISCUSSIONS

Clinical manifestation

The clinical manifestation of liver or kidney transplant recipients with fungemias included: I. Fever and abnormal blood pressure. Most of the recipients with fungemias (13/17) had a fever, and there were 10 recipients with temperature of 39°C or greater. Nine recipients had septic shock at the onset of fungemias. II. Onset in the early period after liver transplantation while in the later period after kidney transplantation. The incidence and timing of fungemias post transplant was influenced by the transplanted organ type, with all episodes (n=3, 100%) occurring 4 years after renal transplantation and the majority of episodes (n=12, 85.7%) occurring within one month after liver transplantation. III. Poor status of nutrition and immune function. About 53% of patients (9/17) had the serum albumin level of < 35 g/L, and about 65% of patients (11/17) had the lymphocyte count of $< 0.5 \times 10^9$ / L. IV. Most of the fungemias were secondary to other fungemias or bacteremias. Ten fungemias were secondary to bacteremias and 3 fungemias were secondary to fungemias. V. High mortality. There were 9 cases of 17 patients with fungemias died with a mortality rate of 52.9%.

Laboratory data

I. Platelet dropped markedly. The amount of platelet in 57.9% of patients with fungemia was less than 50×10^9/L. II. Procalcitonin (PCT) elevated slightly. The highest serum level of PCT was less than 5 ng/mL. III. Causative organisms were mainly *Candida spp.* (85.7%).

Classification of pathogens

Twenty-one microorganisms were responsible for fungemias in our present study. The causative organisms were mainly *Candida spp.* (18/21), among which there were 11 *non-Candida albicans* (52.4%). As far as pathogen was concerned, *Candida albicans* predominated (33.3%), followed by *Candida parapsilosis* (28.6%), C*andida krusei* (19.0%), and *Trichosporon cutaneum* (9.5%) (Table 1).

Drug resistance of fungi

The drug resistance of fungi from the highest to the lowest were fluconazole, itraconazole, nystatin, amphotericin B, flucytosine, voriconazole and caspofungin. Total drug

Table 1. Classification and constituent ratio of fungi

Fungi	Strain (n=21)	Constituent ratio(%)
Candida spp.	19	90.5
Candida albicans	7	33.3
Non-Candida albicans	12	66.7
Candida parapsilosis	6	28.6
Candida krusei	4	19.0
Candida tropicalis	1	4.8
Saccharomyces	2	9.5
Trichosporon cutaneum	2	9.5
Torulopsis	1	4.8
Torulopsis glabrata	1	4.8

resistance of fungi to fluconazole and itraconazole was 38.1%, and the drug resistance of fungi to the other five antifungal agents was less than 10% (Table 2).

Table 2. In vitro susceptibilities of 21 fungi isolates to seven antifungal agents [n,(%)]

Anti-microbial	*Candida albicans* (7)	*Non-Candida albicans*(11)	*Trichosporon cutaneum* (2)	*Torulopsis glabrata*(1)	Total drug resistance rate (%)
Nystatin	0(0.0)	1(9.1)	0 (0.0)	1(100.0)	9.5
Amphotericin B	0(0.0)	0(0.0)	0(0.0)	1(100.0)	4.8
Flucytosine	0(0.0)	0(0.0)	0(0.0)	1(100.0)	4.8
Fluconazole	2(28.6)	5(45.5)	0(0.0)	1(100.0)	38.1
Itraconazole	2(28.6)	5(45.5)	0(0.0)	1(100.0)	38.1
Voriconazole	0(0.0)	0(0.0)	0(0.0)	1(100.0)	4.8
Caspofungin	0(0.0)	0(0.0)	0(0.0)	1(100.0)	4.8

DISCUSSION

BSIs, especially fungemias, are still an important factor threatening the success of SOT so far. In the present study, the main pathogens causing fungemias after liver or transplantation were *Candida spp.* (59.1%) in the both hospitals investigated over ten years.

The drug susceptibility test showed that the sensitivity of fungi to nystatin, amphotericin B, flucytosine, voriconazole and caspofungin was high (drug resistance rate < 10%). In the present study, *non-Candida albicans* accounted for 63.2% of all *Candida spp.* (12/19) and 57.1% of all fungi, indicating that *non-Candida albicans* had become a difficult clinical problem.

Although the sensitivity of fungi to antifungal agents was high, we found that death occurred in 52.9% (9/17) of patients with fungemias among liver or kidney transplantation, which was concordant with other studies [1,3-6,13,15] reporting that the mortality of SOT recipients with fungemias ranged from 10% to 71%.

It is very important to prevent transplant recipients from developing fungemias to improve the outcome. According to the clinical and laboratory features of fungemias after liver or kidney transplantation and the distribution of pathogens, we can choose effective antifungal agents in suspected patients with fungemias when awaiting the results of blood cultures.

Some solutions such as limiting the use of broad-spectrum antibiotic strictly, improving nutrition status and immune function and preventing the cross-infection can effectively reduce the occurrence of fungemias.

CONCLUSIONS

The clinical manifestations of fungemias included high body temperature, onset in the early period after liver transplantation while in the later period after kidney transplantation as well as poor status of nutrition and immune function. Although the sensitivity of fungi to antifungal agents was high, liver or kidney transplant recipients with fungemias had high mortality.

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