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Original article

Epidemiology of invasive fungal infections after liver transplantation and the risk factors of late-onset invasive aspergillosis

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ABSTRACT

Invasive fungal infection (IFI) in liver transplant recipients is associated with poor outcomes. Targeted antifungal prophylaxis is recommended for high-risk populations; however, the epidemiology of IFI has changed, and the risk criteria remain unclear. In addition, the risk factors for late-onset invasive aspergillosis (IA) have not been fully characterized. We examined 279 recipients over 16 years of age to uncover their IFI epidemiology, clinical characteristics and outcomes. In addition, a case–control study was performed to identify the risk factors of late-onset IA. Of the 279 recipients, 96.1% underwent living donor liver transplantation. Antifungal prophylaxis was administered to 80.6% of the recipients. IFI occurred in 15 patients, among which 8 cases were early-onset (≤90 days after liver transplantation) and 7 cases were late-onset (>90 days after liver transplantation). Five of the late-onset cases were invasive pulmonary aspergillosis, and 2 were fungemia cases. The mortality rate of late-onset IA was 80.0%. According to a multivariate analysis, steroid use before liver transplantation, bloodstream infection within 90 days after liver transplantation and reoperation within 90 days after liver transplantation were significant risk factors for late-onset IA after liver transplantation. The prevalence of IFI was low in our population given that over 80% of liver recipients received antifungal prophylaxis. The prognosis of late-onset IA remains poor, and predictors associated with late-onset IA, such as steroid use before liver transplantation, bloodstream infection and reoperation after liver transplantation, may help clinicians to optimize prevention measures for these devastating infections.

1. Introduction

Invasive fungal infection (IFI) is an important cause of morbidity and mortality among liver transplant recipients [1–7]. Recent studies have revealed that the incidence of IFI after liver transplantation has declined since the mid-1990s; however, the reported incidence of IFI in liver transplant recipients varies, and infections still develop in approximately 5–20% of recipients [4–8]. Previously, we reported that preoperative steroid administration for fulminant hepatitis could predispose patients to develop invasive aspergillosis (IA) in living-donor liver transplant recipients; however, guidelines for the selection of antifungal prophylaxis have changed, and many studies regarding the risk factors for IFI have been published since our earlier report [9].

In addition, because of improvements in surgical techniques and immunosuppression therapy, the liver function prognosis of transplant patients has improved; however, a delayed occurrence of IFI has been observed and still represents a significant burden [10–12]. An understanding of the specific risk factors for IFI, especially for IA is essential for guiding effective empiric and preventive antifungal strategies. However, studies on risk factors for IA have primarily focused on early-onset infection, and few studies have revealed the risk factors for late-onset infection [13–15].

This study was performed to assess the current epidemiology of IFI after liver transplantation during the era of newer antifungal

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agents. In addition, we performed a case–control study to reveal the risk factors for late-onset IA after liver transplantation.

2. Material and methods

2.1. Study population

This study was a retrospective analysis of patients who received liver transplantations at Kyoto University Hospital, Japan, from 2007 to 2013. Follow-up continued until December 2014. All transplant recipients over 16 years of age were included in the analysis, irrespective of whether they had received a graft from a deceased or living donor or if they had undergone a primary transplant or re-transplantation. Only one transplantation event (the most recent) per person was included. All medical records were reviewed to obtain data on demographics, underlying diseases, transplant types, clinical characteristics, microbiological screening results, potential risk factors, types and sites of infections and medical and surgical complications during the study period.

To reveal the risk factors for late-onset IA in our population, we performed a case–control study. The controls included 5 recipients without IA or other fungal infections who had undergone liver transplantation within a month before or after each IA patient so that the surgical techniques and choices of immunosuppressive regimens might not affect the results, because attending doctors periodically rotate through the hospitals affiliated with our institution.

2.2. Clinical definitions

IFI was suspected on the basis of clinical or radiological signs. A diagnosis of proven or probable IFI was based on histopathological findings or blood/tissue cultures according to EORTC/MSG criteria [16]. Early-onset IFI was defined as an infection that occurred within 90 days after transplantation and late onset IFI was defined as an infection that occurred at least 90 days after transplantation. The day of diagnosis was defined as the day of the first microbiological documentation of infection or the day of death in the case of postmortem diagnosis.

2.3. Microbiological monitoring

Screening for IA was performed before and after transplantation using serum samples to test for *Aspergillus* galactomannan (GM) antigen (the Platelia *Aspergillus* test, SRL, Japan) and radiologic evaluations from head to abdomen by computed tomography (CT). The test was performed twice prior to transplantation (generally at 3 months and then within 1 month prior to surgery) and then weekly after surgery until discharge. A GM antigen index over 0.5 was designated as positive according to the manufacturer's recommendations. The beta-(1,3)-D glucan concentration was not determined as a monitoring tool but was instead used as a part of the diagnostic measures for IFI. Treatments for fungal infections were administered at the discretion of the physician if probable or proven IFI was present. Weekly monitoring for cytomegalovirus antigenemia was also performed during the hospital stay.

2.4. Prophylaxis strategy

Perioperative prophylaxis consisted of ampicillin and cefotaxime for 48 h. Trimethoprim and sulfamethoxazole were administered once daily as prophylaxis against *Pneumocystis jirovecii* infection. In addition, either fluconazole 400 mg or micafungin 100 mg was administered as an antifungal prophylaxis. The selection of recipients for antifungal prophylaxis was performed at the doctors' discretion if the recipients had at least one known risk factor for IFI including retransplantation, renal replacement therapy (RRT), repeat intra-abdominal surgery and transplantation for fulminant hepatic failure [7–9]. Enteral tube feeding was administered immediately after liver transplantation if there were no complications with the digestive organs. An antiviral agent for prophylaxis against cytomegalovirus infection was not routinely administered.

2.5. Statistical analysis

Data were compared between patients using the chi-square test for categorical data and the independent samples t-test for continuous data. The two-sided statistical significance was set at $P = 0.05$. Statistically significant variables ($P < 0.1$) in the univariate analysis were introduced within a multivariate model by using a forward stepwise logistic regression. The statistical analyses including an estimate for the c statistic for the logistic regression model were performed with PASW, version 18.0 (SPSS), for Microsoft Windows.

3. Results

3.1. Clinical characteristics of the entire cohort

A total of 279 patients underwent transplantation during the study period (Table 1). The overall incidence of IFI was 5.4%, which comprised 8 cases of early-onset IFI (5 IA cases and 3 cases of fungemia) and 7 cases of late-onset IFI (5 IA cases and 2 cases of fungemia). The most common indication for liver transplantation was cirrhosis from hepatitis B and/or C infection (47.5%), followed by primary biliary cirrhosis (15.1%) and post-Kasai biliary atresia (6.1%). Two hundred and fifty-five recipients (91.4%) underwent living-

Table 1
Patient characteristics, risk factors, and the incidence of invasive fungal infections.

	Total N = 279% (n)
Age, years, median (range)	54 (16–70)
Male gender, % (n)	47.3% (132)
Underlying liver disease, % (n)	
Hepatitis B and or C virus infection	47.3% (132)
Primary biliary cirrhosis	15.1% (42)
Post-Kasai biliary atresia	6.1% (17)
Alcoholic cirrhosis	5.7% (16)
Fulminant hepatitis	5.4% (15)
Primary sclerosing cholangitis	4.3% (12)
Autoimmune hepatitis	2.9% (8)
Nonalcoholic steatohepatitis	2.5% (7)
Others	10.8% (30)
Living donor	96.1% (268)
Deceased donor	3.9% (11)
Retransplantation	6.1% (17)
MELD score, median, (range)	18, (6–46)
MELD score ≧20	43.0% (120)
Steroid use before liver transplantation	9.0% (25)
ABO incompatible	25.1% (70)
Hepatocellular carcinoma	28.7% (80)
GM positive before transplantation	37.2% (90/242)[a]
Choledochojejunostomy	18.6% (52)
Rejection	33.3% (93)
Cytomegalovirus antigenemia	77.1% (168/218)[a]
Antifungal prophylaxis	80.6% (225)
Invasive fungal infection (total)	5.4% (15)
Early-onset invasive fungal infection	2.9% (8)
In-hospital mortality for first admission	20.4%

GM, Aspergillus galactomannan antigen.
MELD, Model for end-stage liver disease.
[a] Number of patients with positive results/number of patients tested.