Fungal infections in liver transplant recipients

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Abstract. A retrospective analysis of 462 consecutive orthotopic liver transplantations was undertaken to evaluate incidence, risk factors, clinical course, and outcome of fungal infections. Infections involving Aspergillus (6 cases), Candida (5 cases), Mucor (1 case), and Cryptococcus (1 case) were observed in 2.8% (13/462) of our patients. Twelve of the 13 episodes developed during the first 2 postoperative months. None of the potential risk factors for fungal infections described by other authors (i.e., age, rejection treatment, dialysis, mechanical ventilation, graft failure, long operation time, second transplant, serious non-fungal infection) correlated significantly with the episodes in our patients. However, in patients who exhibited three or more of these potential risk factors the incidence of fungal infections was elevated (P<0.001). Six of seven exogenous infections (Aspergillus, Mucor) began before July 1991 when our department moved from Charlottenburg to Wedding, thus indicating that the incidence of these infections is highly influenced by exposure (P=0.01). Exposure prophylaxis should therefore be meticulously followed, particularly when severely compromised patients are involved, in order to prevent exogenous infections (i.e., Aspergillus/Mucor). Infections involving such patients are combined with a very high mortality (57%). We observed Candida infection as a pathological overgrowth of physiological oropharynx flora into the esophagus and/or trachea in five patients. In each case treatment led to full recovery.

Infection remains the most common cause of morbidity and mortality after organ transplantation. Opportunistic infections by fungi are well-known problems in transplantation programs [2–5, 11]. Accordingly, we retrospectively analyzed these episodes in our liver transplant recipients in order to evaluate incidence, course, and outcome and to recognize possible risk factors.

Patients and methods

A retrospective review was performed on the records of 462 consecutive liver transplantations conducted in 420 recipients from the in-
Fig. 1. The first location of the liver transplantation program at Rudolf Virchow University, Berlin: 172 liver transplantations were performed in this old ivy-clad building between October 1988 and June 1991. The ICU was located on the ground floor.

Fig. 2. The second location of the liver transplantation program: 290 procedures were performed in this new facility between July 1991 and February 1994. The ICU is located on the 7th floor.

ception of the transplantation program at the Rudolf Virchow University Berlin in October 1988 until February 1994. Thirty-nine were second and three were third transplantations. Ages ranged from 3 to 66 years (median: 45 years) with only 3 patients being younger than 18 years old. In July 1991 our surgical department was relocated from the first floor of an old ivy-clad building on the university campus (Fig. 1) to the seventh floor of a newly constructed hospital (Fig. 2). One hundred seventy-two transplantations were performed over a 33-month period in the old hospital whereas 290 operations were performed over a 31-month period in the new one.

Most patients received triple immunosuppression (cyclosporine A, prednisolone, azathioprine, along with an initial induction of antithymocyte-globulin (ATG Fresenius, Homburg)) during the first 7 days. One hundred twelve patients were administered a new monoclonal anti-IL-2 receptor antibody (BT 563) for 12 days instead of ATG [9]. Eighty-nine patients received FK 506 and prednisolone as part of a prospective randomized multicenter trial. Rejection episodes were treated by steroid bolus and/or cytolytic therapy (OKT 3, Raritan Pharmaceuticals, New Jersey). Selective bowel decontamination was performed by administering non-absorbable antibiotics preoperatively and during the first 3 weeks after transplantation [8, 10]. Postoperative infection prophylaxis was provided through perioperative antibiotics (cefotaxim, metronidazole, tobramycin), acyclovir, and an oral amphotericin suspension, which was administered for 3 weeks postoperatively.

Fungal infection was diagnosed only after clinical symptoms were observed and a positive specimen culture obtained from the corresponding organ. Antimycotic therapy consisted of fluconazole (400 mg/day for 3 weeks) for *Candida* infections and a combination of flucytosin (150 mg/kg/day for 1 week) and amphotericin B (0.5–1 mg/kg/day for 3 weeks) for *Aspergillus/Mucor* infections. All dosages were adapted to renal function.

For statistical analysis chi-square test or Fischer’s exact test were used to compare proportions. Differences were considered significant if the P value was less than 0.05.

Results

Fungal complications were diagnosed in 13 of 462 liver transplant recipients (2.8%). Twelve of the 13 events occurred within the first 2 postoperative months. No significant difference between the incidence of fungal infection in patients older or younger than the median age (45 years) was noted, although it tended to be higher in the older patients ($P=0.07$). When compared to first transplant recipients or patients whose operation time was shorter than the median of 395 min, neither second and third transplant recipients ($P=0.99$) nor patients with an operation time longer than 395 min ($P=0.18$) seemed to have an elevated risk for fungal complications.

Nine of the 13 fungal infections were preceded by a rejection episode that was treated with high immunosuppression (steroid boli and/or OKT). However, the incidence of these infections was not significantly higher than in patients with maintenance immunosuppression ($P=0.21$). Furthermore, no significant differences in incidence were found between steroid boli and OKT for rejection treatment ($P=0.27$), or between ATG and BT 563 for induction therapy ($P=0.57$), or between CyA and FK 506 for maintenance immunosuppression ($P=0.12$). None of the other potential risk factors for fungal infections described by other authors (dialysis, mechanical ventilation, graft failure, serious non-fungal infection) correlated significantly with the episodes observed in our patients ($P > 0.6$). However, the incidence was significantly elevated ($P<0.001$; Table 1) in patients having three or more of these potential risk factors (age, dialysis, mechanical ventilation, graft failure, long operation time, second transplant, rejection treatment, serious non-fungal infection).

In all six episodes involving *Aspergillus* the lungs were affected first (Fig. 3). Despite receiving aggressive antimycotic therapy, only the patients with local infections (i.e., pneumonia) survived (2/6). If fungemia (3×), cerebral involvement (1×), or multiple organ failure syndrome was diagnosed, the course was fatal (4/6). One *Mucor* in-