872

Fungal Infections After Liver Transplantation

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A STUDY DONE at our institution between 1981 and 1983 showed that 42% of liver recipients developed invasive fungal infections, mostly due to *Candida* and *Aspergillus*.[1] Between July 1984 and September 1985 we studied 101 consecutive adult liver transplant recipients at Presbyterian University Hospital for the incidence and risk factors associated with invasive fungal infection. The risk factors that were analyzed included age, sex, underlying liver diagnosis, clinical status and laboratory values before transplantation, antibiotic use before and after surgery, total surgical time and number of laparotomies, immunosuppression, and the amount of blood products used.

METHODS

The patients included in this study were 39 men and 62 women who were followed prospectively for fungal infections after orthotopic liver transplantation using either a choledochocholedochostomy or a choledochojejunostomy. Venovenous bypass was used routinely.[2]

All patients received antibiotic prophylaxis with ampicillin and cefotaxime at 4 g/d each for five consecutive days after surgery. Nystatin (Mycostatin) (400,000 units four times daily) was used orally for candida prophylaxis. The immunosupressive agents used were cyclosporine (CsA) and corticosteroids. Azathioprine was used to allow the use of a lower dose of CyA. A high dose of oral or intravenous (IV) steroids and OKT3 were used for the treatment of acute rejection.

Criteria for the diagnosis of invasive fungal infections were any of the following: (1) a positive blood culture, (2) a positive culture from an ordinarily sterile site (peritoneum, pleural cavity, etc), or (3) demonstration of tissue invasion by biopsy or at autopsy. Simple candida cystitis and oral thrush were excluded.

Proportions were analyzed by chi-square, and means were compared with Student's t test.

RESULTS

The patients were followed for a mean of 394 days. There were 14 episodes of invasive candida infections in 13 patients and 4 cases of invasive aspergillosis in four patients. Overall, 16 (16%) patients developed an invasive fungal infection. Ten (77%) of 13 patients with candida infection and all four patients with aspergillosis died. Five (31%) of 16 patients were diagnosed at postmortem examination. These had not been treated with amphotericin B. All cases occurred within 2 months of liver transplantation, and 67% of the cases occurred in the first month after a transplant operation. No significant difference was found between sex, age, underlying diagnosis, and the frequency of invasive fungal infections. Other variables that did not correlate with an increased rate of invasive fungal infection were: the use of steroids and intravenous antibiotics in the month before transplantation, presence of ascites, gastrointestinal bleeding or encephalopathy, positivity for hepatitis B surface antigen, and presence of a thrombosed portal vein or a biliary drain.

All patients with invasive fungal infections spent more than the median number of hours (12 hours) of cumulative time in the operating room ($P < .001$, t test). A similar correlation was found between invasive fungal infections and number of laparotomies performed. Patients who had only one transplant operation and no subsequent abdominal operations had a significantly lower rate of invasive fungal infections than other patients in terms of episodes per patient (E/P) (0.04 E/P v 0.45 E/P, $P < .001$).

There was a trend toward a higher rate of invasive fungal infection in patients receiving OKT3 monoclonal antibody for rejection (0.24 E/P v 0.08 E/P, $.05 < P < .1$). Invasive

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fungal infections were significantly more frequent in the patients who received nonprophylactic IV antibiotics for more than the median (5) number of days (2.02 E/P *v* 0.68 E/P; $P < .001$). A correlation was found also between the use of a greater number of units of RBCs and fresh-frozen plasma, during the transplant admission (both comparisons, 0.29 E/P *v* 0.06 E/P; $P < .01$).

The following pretransplant laboratory findings were significantly correlated with fungus infections. All patients with fungal infections had thrombocytopenia (platelet count less than 150,000/μL). More fungal infections were diagnosed in patients with laboratory values below the following medians for the group: a T lymphocyte count less than 536, a CD4 helper cell count less than 390, a T helper/T suppressor cell ratio less than 2.8, and a serum IgA level less than 360 mg/dL.

DISCUSSION AND CONCLUSIONS

The rate of invasive fungal infections in this series (16%) was significantly decreased compared with the 42% of our 1981 to 1983 study,[1] probably because of better CsA monitoring, better surgical techniques, and the institution of venous bypass during surgery.[2] Fungal infections, however, were still an important cause of morbidity and mortality after liver transplantation. The risk factors for development of invasive fungal infections after liver transplantation were (1) longer duration of treatment with nonprophylactic IV antibiotics, (2) longer cumulative surgical time and a higher number of laparotomies, (3) an increased number of units of RBCs and fresh-frozen plasma, and (4) a series of pretransplant laboratory findings: thrombocytopenia, low T lymphocyte levels, low CD4 helper cell and lower helper/suppressor cell ratios and IgA serum levels. The significance of some of these findings is still unclear. Attention to the risk factors outlined earlier may aid both in preventing and in the early detection of invasive fungal infections after liver transplantation.

REFERENCES

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