1948

Epstein Barr Virus Associated Posttransplant Lymphoproliferative Disease After Intestinal Transplantation

J. Reyes, M. Green, J. Bueno, N. Jabbour, M. Nalesnik, E. Yunis, S. Kocoshis, M. Kauffman, S. Todo, and T.E. Starzl

PREVIOUS reports of posttransplant lymphoproliferative disease (PTLD) after intestinal transplantation described a high incidence with consequent significant morbidity and mortality.[1] We present the clinical/pathological spectrum of PTLD occurring after intestinal transplantation with particular emphasis on risk factors and effect on patient and graft survival.

MATERIALS AND METHODS

Case Material

Between May 1990 and June 1995, 73 patients received 78 intestinal transplants under tacrolimus and steroid immunosuppression. These included the following grafts: small bowel (SB) (n = 28), liver/small bowel (LSB) (n = 35), and multivisceral (MV) (n = 15) recipients. There were 41 children and 32 adults transplanted; their ages ranged between 0.5 and 58.1 years. Immunosuppression, donor, and recipient surgical procedures, and nutritional management have been described elsewhere.[2]

Pathological Studies

All available surgical and autopsy specimens were reviewed. The evaluation of PTLD lesions included histopathology, analysis of clonal status, and demonstration of EBV (by in-situ hybridization [EBER]). PTLD was defined as the presence of lymphoid growths from any site after transplantation. These lymphoid growths may present as tumor, destructive infiltrates, with or without clonal proliferations, and show EBER positivity. Recipient EBV serology was obtained preoperatively.

RESULTS

Patient Population and Tumor Incidence

Fourteen cases (19%) of PTLD were identified. The overall incidence in the adult and pediatric recipients was 9.3% and 26.8%, respectively. Seven occurred in males and 7 occurred in females (male/female ratio 1/1). Eleven patients were children with a median age of 2.8 years. The time between the date of organ transplant and the date of disease presentation ranged between 24 days to 5 years (median time of 9 months).

The recurrence of PTLD at retransplantation produced 16 cases which were distributed relative to graft type as follows: three cases after SB (10.7%), seven cases after LSB graft (20%), and 6 cases after MV grafts (40%). There were a total of 18 episodes of PTLD among these 14 recipients (recurrence rate of 28.5%). Persistent, intractable disease was seen in four patients, with eventual death in three.

Pathological Features of PTLD

The range of histology was that of lymphocytic infiltrates with a monomorphic and/or polymorphic appearance. Plasmacytoid features were seen in the chronic cases. Depending on the stage of the PTLD, there was some admixture of immunoblastic cells as well as eosinophils and polymorphonuclear cells. Reed-Sternberg-like cells were seen in only three cases in a setting of very atypical lymphocytes and immunoblastic cells, with necrosis. Two patients presented a unique spindle cell tumor (of smooth muscle origin) in the native and allograft intestine as previously reported.[3] Clonal analysis was performed in nine patients: the lesions were monoclonal in seven patients and polyclonal in two. Evidence of EBER positivity was seen in all cases. Serologic evidence of prior EBV infection was found in 10 patients.

The most common region of involvement was the gastrointestinal tract, principally allograft but also native. A lymphadenopathic presentation was seen in only one patient and was amenable to rapid and complete remission of disease with preservation of graft function. Seven of 14 patients received OKT3. A history of splenectomy was noted in 12 of 14 recipients.

Treatment of PTLD

Therapy consisted of reduction of immunosuppression combined with intravenous acyclovir or ganciclovir for as long as the lesions were present. Alpha interferon and foscarnet were used in selected cases. Two of the patients who were placed on interferon suffered significant rejection episodes post-interferon therapy. In two cases the immunosuppression was stopped completely while there was evidence of clinical disease; however, one patient suffered severe rejection post-withdrawal of immunosuppression which required augmentation of immunosuppression. Hyperimmuneglobulin therapy was used in four patients. Chemotherapy was used in one patient with fulminant disease.

OUTCOME

Seven of the 14 patients diagnosed with PTLD have survived (mortality of 50%). Only five of the surviving patients have had complete remission of their disease, whereas two

From the Pittsburgh Transplantation Institute, University of Pittsburgh, Pittsburgh Medical Center and Children's Hospital of Pittsburgh, Departments of Infectious Disease (M.G.), Pathology (E.Y.), and Gastroenterology (S.K., T.E.S.).

Address reprint requests to Jorge Reyes, MD, Associate Professor of Surgery, Pittsburgh Transplantation Institute, 3601 Fifth Avenue, 4C, Falk Clinic, Pittsburgh, PA 15213.

0041-1345/96/$3.00/+0

patients continue to have lesions and are under therapy. Four of the surviving patients have retained their original grafts and are TPN free. Retransplantation was performed in two cases, with one death. A SB recipient was retransplanted after complete resolution of disease and has survived. He is presently off TPN. Of the seven patients who died, all were identified to have residual PTLD. Causes of death included: PTLD (n = 4), intestinal allograft rejection (n = 2), and iatrogenic hypernatremia (n = 1).

DISCUSSION

The mainstay of therapy continues to be judicious reduction of immunosuppression with antiviral therapy. However, though this has been generally successful for the treatment of PTLD in recipients of other organs, this has not been so in the intestinal transplant population. Rebound intestinal allograft rejection has occurred early, without complete resolution of the PTLD disease. This has percipiated significant morbidity as well as patient and graft loss not only from PTLD, but also as a result of rejection.

The addition of hyperimmuneglobulin therapy in this patient population was stimulated by the use of EBV PCR, and its consequent decrease in one patient. However, the role of this type of therapy as well as the use of alpha interferon or foscarnet remains to be determined.

In light of the experience reported with EBV PCR in this issue,[5] it is likely that both early diagnosis added to immunemodulation and antiviral therapy may be successful in the future. PTLD was treated successfully in three surviving patients, who presently maintain a base line immunosuppression using tacrolimus and steroids.

REFERENCES

1. Reyes J, Tzakis AG, Bonet H, et al: Transplant Proc 26(3): 1426, 1994

2. Todo S, Tzakis AG, Abu-Elamgd K, et al: Ann of Surgery 216(3):223, 1992

3. Lee ES, Locker J, Nalesnik M, et al: N Eng J of Med 332:19, 1995

4. Nalesnik MA and Starzl TE: Transplantation Science 4(1):61, 1994

5. Green M, Reyes J, Jabbour N: Transplant Proc 28:(this issue), 1996