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LYMPHOPROLIFERATIVE DISEASE AFTER INTESTINAL TRANSPLANTATION UNDER PRIMARY FK506 IMMUNOSUPPRESSION

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INTRODUCTION

Post-transplant lymphoproliferative disorder (PTLD) is a well recognized complication after transplantation, and has been reported to occur in approximately 2% of organ transplant recipients both with Cyclosporine and FK506 immunosuppression (1-6). The use of FK506 in clinical small bowel transplantation has resulted in improved patient and graft survival (7). This report describes the clinical and pathologic features of (PTLD) arising in intestinal transplant recipients treated primarily with FK506. This complication has been known to be a special risk of intestinal transplantation since the first reports of long survival of multivisceral recipients who were treated with cyclosporine (8,9).

MATERIAL AND METHODS

Case Material: Between May 2, 1990 and August 7, 1993 a total of 54 patients received intestinal transplants with or without other abdominal organs using FK506 as their primary immunosuppressive therapy. This group comprised 18 isolated

intestine recipients (I), 26 liver/intestine recipients (L/I), and 10 multivisceral recipients (MV) (1 MV without the liver or modified multivisceral). Within this population 29 pediatric patients were transplanted, including 5 I, 20 L/I, and 4 MV recipients.

Immunosuppressive therapy (induction, and treatment of rejection) was as previously described and based on FK506 as primary drug (7).

Pathologic Studies: All available surgical and autopsy specimens as well as EBV serologic data were reviewed. The evaluation of PTLD lesions included histopathology, analysis of clonal status, and demonstration of EBV (by in-situ hybridization for EBER).

RESULTS

Patient Population and Tumor Incidence: A total of 8 cases of PTLD were identified. Four occurred in males and 4 occurred in females (M:F ratio, 1/1). The age of these recipients at the time of transplantation ranged from 1.7 to 44 years. Six patients were children, with a mean age of 4.1 years. The time between the date of organ transplant and the date of disease presentation ranged between 24 days and 2.3 years, however, 6 patients presented after 10 months post-transplant (mean of 1.2 years). These 8 cases represent 14.8% of the total study population. The overall incidence in adult recipients was 8%, and the overall incidence in pediatric recipients was 20.6%. The distribution of cases relative to the graft type revealed 5 cases in L/I grafts, and 3 cases in MV

grafts. Interestingly, the 2 adult patients were recipients of MV grafts.

Clinical Presentation and Location of PTLD: Symptoms of fever, weight loss and malaise were common (4 patients), however, nonspecific, initiating a work-up and a search for infection and/or rejection. One patient presented with hemolysis and diarrhea. A lymphadenopathic presentation was noted in 2 patients (22%) and localized to the head and neck region in one patient and generalized in the other. Six patients (66.6%) had involvement of the gastrointestinal tract presenting as nodular ulcerated tumors. The intestinal graft was involved with disease in 5 patients (55.5%) and generally presented with vomiting, diarrhea and gastrointestinal bleeding. Of these, 2 patients developed complications related to their graft which included bleeding and intestinal perforation. One patient presented isolated right lung involvement. After resolution of this tumor she later presented spindle cell tumors in the native colon which was positive for EBV at in-situ hybridization studies. One patient presented fulminant disseminated disease, a recipient of an MV graft who received intensive therapy for early exfoliative type rejection of the intestine. He developed early onset disease (involving all thoracic and abdominal organs) and died of fulminant PTLD and multisystem organ failure at 2 months post-transplant. Of note, PTLD was identified on routine endoscopy without associated symptoms in 2 patients.

Pathologic Features of PTLD: The evaluation of PTLD in this

series was hindered by sample size and necrosis (when ulcers were present). The range of histology was that of activated lymphocytes with a polymorphic appearance, which was seen in all patients. Clonal analysis was feasible in only 4 cases; the lesions were monoclonal in all cases studied. Evidence of EBV DNA was found in all specimens.

Serologic evidence of EBV infection was found in all patients, 7 were non primary infections, and 1 was primary.

Treatment: Treatment consisted of reduction in immunosuppression combined with intravenous acyclovir or gancyclovir for as long as there were lesions present. Alpha-interferon and/or Foscarnet were used in selected cases where there seemed to be rapid progression of disease, extensive disease, recurrent disease, or there had been a history of severe rejection and immunosuppression could not be reduced. In 2 cases the immunosuppression being utilized was stopped entirely while there was evidence of clinical disease. In 1 patient immunosuppression was not reduced because of previous repetitive rejections. This patient had resolution of lesions on gancyclovir and alpha-interferon. Lesions were followed by a combination of endoscopy, and radiologic studies (CT scans, plain and contrast films, etc.).

Outcome: Five of the 8 patients diagnosed with PTLD have survived (mortality of 37.5%) with a mean follow-up of 20 months. Four of these surviving patients have had complete remission of their disease, whereas 1 patient continues to have lesions and is under therapy. Four surviving patients have retained their grafts.

All of these patients are presently on maintenance immunosuppression using FK506. Four patients developed rejection after resolution of there PTLD and required aggressive therapy. Three patients were treated successfully with resumption of maintenance FK506 therapy and steroids; 1 patient was retransplanted.

The deaths in this series of PTLD occurred in recipients of L/I (n=2) and MV (n=1) grafts. The median time from transplant to death as a result of PTLD was 15 months. Of these 3 patients who died all were identified as having residual PTLD at autopsy. Both fatalities (66%) presented severe bacterial and fungal infection as well as multi system organ failure. One of these patients presented perforation and bleeding of the PTLD lesions. Two of these patients who died had received OKT3 sometime during there course. One patient died of iatrogenic administration of an excessive amount of enteral sodium after successful treatment of PTLD. He was found to have recurrent PTLD at autopsy.

DISCUSSION

Three identifiable factors could contribute to the higher incidence of PTLD (14.8%) in these intestinal transplant recipients: the lymphoid content of the graft, the aggressive immunotherapy required in these cases, and earlier diagnosis in 2 patients in whom the EBV was identified by in-situ hybridization. One patient who was at the lower end of the EBV infection spectrum before clonal expansion and tumor development was diagnosed after

presentation with minimal enlargement of cervical lymph node and Flu-like symptoms. Hopefully, early diagnosis will improve treatment response.

The time of PTLD onset in these intestinal recipients was later (>10 months) than in recipients of other kinds of organ transplants (1,5). However, there were 3 examples of early aggressive disease, from which 2 patients died. The spectrum of lesions was peculiar in that histologically the PTLD's were all within the range of a polymorphic pattern. Also, monoclonality was found in the 4 patients studied, 2 patients with severe disease and 2 patients with a mononucleosis like picture. The occurrence of spindle cell lesions in 2 patients reflects a significant, as of yet unexplained, deviation from the expected pattern. Complications of PTLD (infections, bleeding, perforation) and late diagnosis have been responsible for death in 2 patients.

Gastrointestinal involvement, of both native and transplanted gut, was the most common site of presentation. A lymphodenopathic presentation is amenable to a rapid and complete remission of their disease, with preservation of graft function.

The mainstay of therapy is above all reduction of immunosuppression to which intravenous acyclovir or gancyclovir is an adjuvant measure. The risk of complete discontinuation of treatment is rejection which led to retransplantation in 1 patient and left another child with a marginal graft. PTLD was treated successfully in 1 child while maintaining base line immunosuppression.

The role of alpha-interferon and Foscarnet for the treatment of any PTLD in organ transplant recipients remains to be determined. These agents may be regarded as adjuvant to reduction of immunosuppression in patients with severe disease, or as primary treatment in selected patients for whom reduction of immunosuppression would carry a high risk of rejection.

REFERENCES

1. Starzl TE, Nalesnik MA, Porter KA, Ho M, Iwatsuki S, Griffith BP, Rosenthal JT, Hakala TR, Shaw BW Jr, Hardesty RL, Atchison RW, Jaffe R, Bahnson HT: Lancet 1:583-587, 1984.

2. Henle G, Henle W, Diehl V: Proc Natl Acad Sci USA 59:94-101, 1968.

3. Purtilo DT: Arch Pathol Lab Med 111:1123-1129, 1987.

4. Penn I, Hammond W, Brettschneider L, et al.: Transplant Proc 1:106, 1969.

5. Nalesnik MA, Makowka L, Starzl TE: In: Current Problems In Surgery (M Ravitch, ed) Year Book Medical Publishers, Inc, 1988, 25:367-472.

6. Reyes J, Tzakis A, Green M, et al.: Transplant Proc 23:3044-3046, 1991.

7. Todo S, Tzakis AG, Abu-Elmagd K, et al.: Annals of Surg 216:223-234, 1992.

8. Starzl TE, Rowe M, Todo S, Jaffe R, Tzakis A, Hoffman A, Esquivel C, Porter K, Venkataramanan R, Makowka L, Duquesnoy R: JAMA 261:1449-1457, 1989.

9. Williams JW, Sankary HN, Foster PF, Lowe J, Goldman GM: JAMA 261:1458-1462, 1989.