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Posttransplant Lymphoproliferative Disorders Occurring Under Primary FK 506 Immunosuppression

J. Reyes, A. Tzakis, M. Green, B. Nour, M. Nalesnik, D. Van Thiel, M. Martin, M.K. Breinig, J.J. Fung, M. Cooper, and T.E. Starzl

POSTTRANSPLANT lymphoproliferative disease (PTLD) is a well-recognized complication of immunosuppression.[1] Previous reports of patients immunosuppressed with cyclosporine (CyA) revealed a 1.7% incidence of PTLD in solid-organ transplant recipients and a strong association with the Epstein-Barr virus (EBV).[2] The use of FK 506 in clinical trials has resulted in improved patient and graft survival, as well as a reduction in the prevalence of infectious complications and as a result infection-related mortality.[3,4] PTLD has also been seen among the complications observed in patients treated with FK 506, having a reported incidence of 0.7% to 1.5%.[5,6] This report describes the clinical and pathologic features of PTLD arising in the solid-organ transplant recipients treated primarily with FK 506.

MATERIALS AND METHODS

Case Material

Between March 1, 1989 and June 1, 1991, a total of 936 patients received FK 506 as the primary immunosuppressive therapy for their first organ transplant at the University of Pittsburgh. This group comprised 555 liver recipients, 217 kidney recipients, 67 heart recipients, 41 recipients of liver plus other organs, 1 heart/lung recipient, and 2 lung recipients. In addition, 53 patients are included who received FK 506 for diverse transplant indications including pancreatic islets, small intestine, bone marrow, and kidney plus one or more organs, as well as various putative autoimmune diseases. Within this population, 141 pediatric patients were transplanted, including 106 liver recipients, 16 kidney recipients, and 19 heart recipients.

The primary immunosuppression used in each case consisted of FK 506 combined with low-dose prednisone as described previously. Supplemental immunosuppression for episodes of acute cellular rejection included pulse doses of methylprednisolone, and/or prednisone recycles, with OKT3 reserved for cases of steroid-resistant rejection.

Pathologic Studies

The pathologic diagnosis of a posttransplant lymphoproliferative disorder (PTLD) included the entire spectrum of atypical lymphoproliferation arising in a transplant population. Both the histologic appearance and the phenotypic analysis of clonal status was assessed in each case. All available surgical and autopsy specimens as well as available EBV serologic data from these patients were reviewed.

RESULTS

Patient Population and Tumor Incidence

During the study period, a total of 15 PTLDs were identified. Seven occurred in males, and 8 occurred in females (M:F ratio, 0.87/1). The age of the recipients at the time of transplantation ranged from 4 months to 65 years, with a median age of 19 years. Six patients were under 18 years of age. One patient was over 55 years of age. The time between the date of the organ transplant and the date of tumor identification in this group of 15 organ graft recipients having a PTLD ranged between 30 and 351 days, with a median of 70 days. The mean follow-up time was 10 months.

These 15 cases represent 1.6% of the total study population. The distribution of cases relative to the organ transplanted revealed a total of 13 cases in liver graft recipients and 2 in kidney graft recipients, resulting in a corresponding prevalence of 2.3% for liver transplantation and 0.9% for kidney transplantation. Interestingly, no case of PTLD occurred in a patient in whom the liver was transplanted in association with another organ, or in any recipients of a heart, heart/lung, isolated lung, or patient receiving FK 506 for the indications included in the "miscellaneous" category. When the pediatric population was analyzed as a separate group, a PTLD incidence of 4.7% for liver recipients and 6.2% for kidney recipients was noted.

Clinical Presentation and Location of the PTLD

Symptoms of fever, malaise, and weight loss were present in most patients and were nonspecific. The predominant site of involvement for each PTLD dictated the manner in which the disease presented. Lymphadenopathy was noted in eight patients (53%), five (28%) of which were located in the head and neck region, and usually associated with other symptoms. However, one patient presented with an asymptomatic mass in the left groin. Eight patients (53%) had involvement of their gastrointestinal tract characterized predominantly by the presence of an ulcerated bleeding tumor. Isolated stomach, small bowel, and colon

From the Department of Surgery, Pathology and Infectious Disease, University Health Center of Pittsburgh, University of Pittsburgh, and the Veterans Administration Medical Center, Pittsburgh, Pennsylvania.

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Address reprint requests to Jorge Reyes, MD, University of Pittsburgh, 3601 Fifth Avenue, 5W Falk Clinic, Pittsburgh, PA 15213.

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involvement were seen in three patients respectively; five patients (63%) presented with disease involving more than one of these sites. One pediatric patient presented with small bowel perforation. Six patients (40%) presented with nonspecific signs and symptoms which included abdominal pain, vomiting, diarrhea, or gastrointestinal bleeding. Three patients (20%) required colectomies; two for control of bleeding and one for tumor management. Four patients (26%), all liver graft recipients, presented with disease in their graft. Three of these four patients developed graft failure, as a result of diffuse graft replacement with tumor and died having first been retransplanted. One liver recipient developed a tumor mass in the left hepatic lobe which was treated with a left hepatic lobectomy. Three patients (20%) had their PTLD occur in the thoracic cavity; the epicardium and lung were involved in one patient and the lung in two others. The patient with both epicardial and lung disease died from disseminated PTLD. Two patients (13%) had involvement of their central nervous system (CNS), which was identified only at autopsy. Two patients (13%) developed a hemolytic syndrome of uncertain etiology; each of these two cases had a splenectomy in an attempt to control the hemolysis. Moreover, each went on to develop graft failure and died.

Pathological Features of PTLD Under FK 506 Immunosuppression

The PTLD seen in this series had a similar range of histopathology (monomorphic/polymorphic), as described previously among patients treated with CyA. A polymorphic PTLD, in which a wide range of identifiable B lymphocyte forms could be recognized, was seen in nine patients. Seven of these were polyclonal and two were monoclonal in origin. A monomorphic PTLD having a uniform proliferation of cells at one stage of differentiation was seen in six cases; one of these was monoclonal and five were polyclonal.

Serologic evidence of EBV infection was found in all of the 15 patients; 12 were primary and 3 nonprimary infections. All of the pediatric patients presented evidence of primary infections. Eight of the patients had contemporaneous infections at the time of tumor diagnosis. Five patients had cytomegalovirus infections, 5 patients had severe bacterial infections, and 1 patient had an aspergillus lung abscess.

Treatment

Treatment of PTLD included reduction of immunosuppression combined with IV acyclovir (1500 mg/m^2 TID in children and 10 mg/kg TID in adults) and surgery (either for diagnosis or treatment of a symptomatic lesion). In each case, the immunosuppression being utilized was reduced or stopped entirely while there was evidence of clinical disease. Thirteen patients (86%) had at least one surgical procedure directed at the PTLD, which included a superficial lymph node biopsy (6 patients), resection of a portion of the gastrointestinal tract (4 patients), splenectomy (2 patients), and retransplantation (3 patients).

Outcome

Ten of the 15 patients diagnosed with PTLD have survived with a mean follow-up time of 10 months. At the time of this report, all surviving patients have had complete remission of their disease. Nine of the surviving patients had disease localized either to lymph nodes (usually one group, ie, head/neck, thorax, or abdominal) or single-organ involvement. One patient had both lymph node and solid-organ involvement. The histologic and clonal characteristics of the tumors present in the survivors were similar to those present in the five patients who died. All 10 surviving patients have retained their grafts. Eight of these patients are presently on maintenance immunosuppression using FK 506. Two pediatric patients have been completely off immunosuppression for 2 and 9 months, respectively. Two of the liver recipients and the two kidney recipients are on a maintenance dose of prednisone of between 2.5 and 12.5 mg/d. Three pediatric liver recipients and 1 pediatric kidney recipient developed rejection after resolution of the PTLD. These patients were treated successfully with resumption of maintenance FK 506 therapy and a single prednisone dose.

All five deaths in this series of PTLD occurred in recipients of a liver graft. The median time from transplant to death, as a result of PTLD, was 71 days. Patients in this group had both lymph node as well as solid-organ involvement, including the hepatic graft in three of the five (60%). Of the five patients who died, two were identified as having residual PTLD at autopsy. Four of the five patients (80%) had concomitant severe bacterial, fungal, or viral infections, which were major contributors to the death of these patients. Three of the five patients (60%) who died had received OKT3 sometime during their course. Four of these patients received more than one graft.

DISCUSSION

The overall incidence of PTLD for all patients receiving FK 506 as primary immunosuppression was 1.6%. The median time between transplant and tumor diagnosis was 4.4 months, which compares favorably with the transplant population treated with conventional immunosuppression.

Both monoclonal and polyclonal tumors occurred with a similar range of histology as seen in PTLDs occurring with CyA-based regimens.[5,7] Differences in the rate of PTLD frequency exist among the various organ allograft subpopulations, with liver recipients having the highest rate of PTLD in patients receiving FK 506.

A lymphadenopathic presentation, particularly that restricted to the head and neck region, or an isolated single-organ presentation, either thoracic or abdominal, has a good prognosis with reduced immunosuppression, IV acyclovir, and supportive surgery. Disseminated disease, particularly when involving the graft, regardless of

therapy, was associated with a poor overall survival. Associated infections were significant contributors to death in these patients.

In summary, FK 506 does not result in an increased incidence, morbidity, or mortality for PTLD.

REFERENCES

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

2. Nalesnik MA, Jaffe R, Starzl TE, et al: Am J Path 133:173, 1988

3. Fung J, Gordon R, Todo S, et al: Transplant Proc (in press)

4. Kusne S, Fung J, Alessiani M, et al: Transplant Proc (in press)

5. Nalesnik MA, Demetris AJ, Fung JJ, et al: Transplant Proc 23:1108, 1991

6. Nalesnik M, Locker J, Jaffe R, et al: Clin Transplant (in press)

7. Penn I: Transplantation 43:32, 1987