ve syndrome appears to be nonmal-
d reversible when immunosuppres-
py is withdrawn. Production of olig-
develops at this phase. Whether the
tion intervenes early or after this
nt of restricted B-cell clones is spec-

, it may be noted that the T4+
te subset is dramatically decreased
ipheral blood of these patients dur-
to a degree comparable to findings
patients, and that correction of this
ity is slow (over 2 months) in the
patients.

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Histiocytic Lymphoma in Renal Transplant Patients Receiving Cyclosporine

J. T. Rosenthal, S. Iwatsuki, T. E. Starzl, R. J. Taylor, and T. R. Hakala

THE higher incidence of cancer in immunosuppressed patients over the general population has long been recognized. A high percentage of these cancers have been called lymphomas. The first clinical trial of cyclosporine for renal transplantation reported by Calne et al.[1] included almost a 10% incidence of lymphoma (3/32). Concern was expressed for the ultimate utility of cyclosporine based on this experience. We now have experience in over 300 cases of cadaveric renal transplantation over a 3.5-year period. In this article we present the experience with lymphoma in these patients, documenting incidence, clinical presentation, treatment, and outcome following cadaveric renal transplantation.

From December 1979 to September 1980, 66 patients underwent cadaveric renal transplantation in Denver in the first trials with cyclosporine and steroid combination. The results of that trial have been reported in detail by Starzl et al.[2,3] From March 1981 to 1983 an additional 244 patients have undergone cadaveric renal transplantation in Pittsburgh, using the same immunosuppression regimen. The results of this experience have been reported.[4,5] Immunosuppression consisted of cyclosporine, 17.5 mg/kg/day, begun by mouth pretransplant and daily thereafter. Tapering occurred from 2 weeks to 6 months posttransplant. The average cyclosporine dose at 1 year posttransplant was 6 mg/kg/day. Methylprednisolone, 1 g, was given i.v. pretransplant. Prednisone was begun by mouth on day 1 posttransplant and tapered over 5 days to 20 mg/day. By 1 year, the average prednisone dose was 10 mg/day.

Six patients of the 310 (1.9%) developed "lymphoma" during the course of these trials. Two of these have been reported in detail.[2,6] Four additional cases will be discussed here in addition to these two. The clinical features of the patients are shown in Table 1. These were 5 males and 1 female; age ranged from 16 years to 57 years. Five patients developed bowel lesions, which were manifested by perforation and peritonitis. One patient developed a painless neck swelling. The time of development of the lesion was 3–6 months posttransplant. The first patient from the Denver series was receiving 16 mg/kg/day of cyclosporine at the time of development of lymphoma at 6 months posttransplant. The other 5 patients were receiving 6–11 mg/kg/day cyclosporine 3–5 months posttransplant at the time of development of lymphoma. Only one patient had been treated for rejection; this consisted of recycling of oral steroid to 200 mg/day, with a 5-day taper again to 20 mg/day. Three patients had oral herpes within 1–2 months of transplantation, while 2 patients had elevated serum creatinine indicative of cyclosporine nephrotoxicity.

The five patients with bowel lesions underwent resection of the affected segment and prompt reduction in the dose of cyclosporine. Two of these patients received small doses of cytotoxic drugs before the lesions were adequately characterized. One patient received small doses of acyclovir. The others had the cyclosporine dose reduced, but received no other treatment. The patient with the neck mass received local radiation, primarily because most of the lesion was necrotic and could not adequately be characterized. No systemic therapy was undertaken in this patient, except to lower the cyclosporine dose. Dose adjustment was in the range of 1–3 mg/kg/day cyclosporine.

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Table 1. Clinical Features

Patient	Age/Sex	Cyclosporine Dose (mg/kg/Day)	Site	Time After Transplant
L.P.	25F	16	Bowel	6 Months
S.C.	21M	10	Bowel	5 Months
A.L.	49M	6	Neck	3 Months
P.L.	57M	8	Bowel, prostate	4 Months
E.F.	30M	10	Bowel	4 Months
L.S.	16M	8	Bowel	3 Months

All 6 patients so treated are alive and well 3 months to 4 years after treatment (Table 2). Two patients suffered irreversible rejection of the graft when immunosuppression was decreased. The other 4 patients have normal renal function.

Interpretation of the histopathology in each case was histiocytic lymphoma. Four lesions were subsequently characterized as polyclonal B-cell masses by immunoperoxidase staining. The neck mass tissue was mostly necrotic, precluding characterization. The tumor mass from one patient showed no immunoglobulin. Most of the tissue resected from the bowel was necrotic also, so that EBNA was identified in only one tumor. This also prevented DNA hybridization studies for Epstein-Barr virus (EBV) genome. Serology to EBV disclosed evidence of primary infection in one patient (L.P.) previously reported[2] and reinfection in another (E.F.), manifested by a threefold rise in antibody titer to viral capsid antigen (Table 3).

Table 2. Treatment and Outcome

Patient	Treatment	Patient Survival	Graft Survival
L.P.	Bowel resection	Yes	Yes
	Decrease cyclosporine		
S.C.	Bowel resection	Yes	Yes
	Decrease cyclosporine		
A.L.	Local radiation	Yes	Yes
	Decrease cyclosporine		
P.L.	Bowel resection	Yes	Yes
	Decrease cyclosporine		
	Chemo Rx		
E.F.	Bowel resection	Yes	No
	Decrease cyclosporine		
	Chemo Rx		
L.S.	Bowel resection	Yes	No
	Decrease cyclosporine		

DISCUSSION

Because of the high incidence of lymphoma in the early experience with cyclosporine, it was feared that the drug itself was more tumorogenic than conventional immunosuppression regimens and that its use would be severely limited by this fact. Two issues are of concern; one is the incidence, and the other is the clinical significance of these lesions. Overall incidence of lymphoma reported here is 1.9%, considerably less than the feared 10% and comparable to the 2.5% reported by Bird[7] in cyclosporine-treated cases and comparable to the incidence reported in cadaveric renal transplantation under conventional immunosuppression.[8] Evidence that the development of these lesions is related to the general level of immunosuppression comes from the higher incidence of tumors reported from cardiac transplantation,[9] where immunosuppression may be maintained at a higher level out of necessity.

The role of Epstein-Barr virus in the development of these lymphomas has been well described.[10] Epstein-Barr virus is implicated directly or indirectly in 3 of the 6 patients reported here. The majority of these lesions

Table 3. Immunologic Studies

L.P.	Polyclonal B cell	Primary EBV infection
S.C.	No immunoglobulin	EBNA positive
A.L.	—	—
P.L.	Polyclonal B cell	—
E.F.	Polyclonal B cell	Reactivation EBV infection
L.S.	Polyclonal B cell	Pending

Time After Transplant
6 Months
5 Months
3 Months
4 Months
4 Months
3 Months

viral capsid antigen (Table

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have been found to be polyclonal, as opposed to monoclonality of killing lymphoma. Whether or not they can be distinguished by morphology is not clear.[11] All the material in our six cases was interpreted as histiocytic lymphoma prior to immunologic examination. When polyclonality is determined, the term lymphoproliferative disorder is more appropriate, or perhaps pseudolymphoma, as described by Iwatsuki.[12] The issue is of more than academic interest, since there is great enthusiasm for the use of cytotoxic drugs when the clinical diagnosis of histiocytic lymphoma appears on the chart. Previously, there was a high mortality, two of three in Calne's first group,[1] and five of six in the cases reported by Hanto.[10] If this is a virally induced B-cell proliferation, maintenance of immunosuppression and the use of cytotoxic drugs would be counterproductive. Iwatsuki treated three patients by reduction of immunosuppression only, with good outcome in all three patients.[12] In our six patients, only two received small doses of cytotoxic drugs before the exact nature of their lesions could be discerned. In all six cases, significant reductions in immune suppression were carried out immediately. Prompt resolution occurred in all patients so treated. The effectiveness of this maneuver was vividly documented in one patient who required repeat laparotomy for persistent GI bleeding. This was found to be suture line bleeding and was corrected by repeat resection. At the time of this repeat resection, 1 month following his original operation, large bowel lesions that had been seen at the first operation and left in place were entirely resolved. The question of transformation from polyclonal to monoclonal cannot be answered from the clinical data presently available. It has been suggested that monoclonal lesions in transplant patients are killing cancer and associated with development of chromosomal abnormalities in the B cells so transformed by virus.[13]

CONCLUSION

Incidence of lymphoma using cyclosporine and steroid is no different than in transplantation under conventional immunosuppression. Most of these lesions are more appropriately called lymphoproliferative disorders despite their histologic appearance. When the masses are polyclonal, prompt reduction in immunosuppression should result in excellent survival. The role for additional antiviral agents for treatment is unclear, but played no role here. Cytotoxic drugs should be avoided.

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