GENOTYPIC ANALYSES OF CYCLOSPORINE-ASSOCIATED LYMPHOPROLIFERATIONS

We recently reported a series of 17 allograft recipients who developed lymphoproliferative disorders while on a cyclosporine-steroid-containing regimen (1). The results indicated good patient survival with conservative therapy, (i.e., control of local complications and reduction of immunosuppression), regardless of whether the lesions were monoclonal or polyclonal. Clonal designation in that report was based on immunoperoxidase staining of formalin-fixed, paraffin-embedded tissues. Appropriate caution was recommended regarding noncritical acceptance of clonal status, due to the known shortcomings of the immunoperoxidase technique (J -3).

Tissue from several cases has been analyzed for immunoglobulin gene rearrangements (J. S. and M. L. C.), using published techniques (+) (Table 1). Four of five cases so studied have shown evidence of monoclonality, supporting our original interpretation. Indeed, one case phenotypically categorized by us as polyclonal (No.9) on the basis of a kappa:lambda ratio of 1.5:1 was shown to be monoclonal by gene analysis. Because the majority of cells were unstained by immunoperoxidase methods, the gene rearrangement results are consistent with a true monoclonal tumor or a monoclonal proliferation arising in a polyclonal background.

Three separate synchronous tumors from patient 12 showed different monoclonal patterns of rearrangements, suggesting either independent primary tumors or possible subclones derived from one original clone (5). Tissue from patient 16 exhibited clonal rearrangements only of kappa light chains. This verifies the monoclonal nature of the lesion and agrees with the original kappa designation of the tumor. Multiple bands in patient 17, originally designated as polyclonal, may instead indicate the presence of a small number of proliferating clones in the lesions.

Patients 6 and 12 are alive and well at 39 and 28 months, respectively, following tumor diagnosis. Both underwent surgical intervention and a reduction of immunosuppression. Patient 12 received no chemotherapy, whereas patient 6, diagnosed in 1982, did. Patient 17 died 17 months following tumor diagnosis. Death was consequent to a second heart-lung transplant for pulmonary difficulties. No tumor was found at autopsy. Patients 9 and 16 died a short time after diagnosis, as previously reported.

The correlation between the clinical results and gene rearrangement studies encourages us to employ a conservative approach based on operation followed by reduced immunosuppression in the management of these tumors, even when monoclonality is demonstrated. However, at the same time, we recognize that significant differences of disease manifestation among different series may exist, as noted by Hanto et al. (3). These investigators pointed out the high frequency of gastrointestinal lymphomas in our series (3), This contrasts with the frequent central nervous system involvement seen in their cases (6). The reasons for these differences are not clear, but may reflect differences in the immunosuppressive regimens used. Only 1 of their 19 reported patients received cyclosporine (6), in contrast to all in our series (1). It thus appears prudent to apply our findings with this caveat in mind, until differences can be reconciled and generalizations established.

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*H: heavy chain region; K: kappa region; L: lambda region; R: rearranged; D: deleted; G: germline; M: multiple; (F, G, I) = different gastrointestinal nodules.
Hydergine is a partial \( \alpha_1 \) and \( \alpha_2 \) adrenergic agonist that also has a stimulating effect on dopamine and an antagonistic activity on the 5HT receptor. Considering these properties of Hydergine, it has been suggested that it might interfere with the proposed mechanism of CsA-induced nephrotoxicity (5). The present study, using a rat kidney allotransplant model, was undertaken to investigate whether Hydergine could prevent or offer partial protection from CsA-induced nephrotoxicity.

Male BN (RT1\(^a\)) and WAG (RT1\(^b\)) rats, weighing about 250 g were used as kidney graft donors and recipients, respectively. Kidney transplantations in the BN-to-WAG combination were performed using microsurgical techniques, as described earlier (16). Bilateral nephrectomy was done at the time of operation. CsA, diluted in olive oil, was administered i.m. in a volume of 0.2 ml. Hydergine (Sandoz) was administered i.p. in doses of 0.5 mg/kg/48 hr. Glomerular filtration Rates (GFR) were measured as clearances of \( ^{51} \text{Cr} \)-ethylenediaminetetraacetate using a method described in detail earlier (17). The relative glomerular filtration rate (RGFR; expressed as a percentage of normal GFR) was calculated by considering the GFR of WAG rats with both kidneys intact to possess an RGFR of 100% (17).

Serum creatinine (normal value 43±4 \( \mu \)mol/L), blood urea nitrogen (BUN, normal value 8.5±1.1 mmol/L), and serum Na and K values, were determined at regular intervals using standard analytical procedures.

The experimental design was as follows: Kidney transplantations in the BN-to-WAG combination were performed and the rats divided into two groups. One group was treated with CsA 15 mg/kg/48 hr from the day of transplantation for a period of 35 days (group 1, n=8). At the end of this period GFRs were determined. From day 42 onward these rats were treated with CsA 100 mg/kg/48 hr for a period of 21–28 days (group 1a). At the end of this period GFRs were determined again. A second group of kidney-allografted rats underwent the same treatment with CsA as the group above, except that they additionally received Hydergine, from the day of transplantation, 0.5 mg/kg/48 hr (groups 2 and 2a, n=8). All through this treatment period serum creatinine, BUN, Na, K, and body weight were determined regularly. The results were analyzed statistically by using the Student’s t test.

In Table 1 the RGFRs of the groups treated with CsA and CsA + Hydergine are given. At the end of the first 35 days of treatment with low doses of CsA, the mean RGFRs of the CsA (group 1) and CsA + Hydergine groups (group 2) were 34.4± 8.2 and 28.2±16.7, respectively. This difference is not statistically significant. After completion of the treatment with a dose