[CANCER RESEARCH 56, 4378–4381, October 1, 1996]

Advances in Brief

Microsatellite Analysis of Posttransplant Lymphoproliferative Disorders: Determination of Donor/Recipient Origin and Identification of Putative Lymphomagenic Mechanism[1]

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Abstract

The genetic mechanisms that give rise to posttransplant lymphoproliferative disorders (PTLDs) are not well established, yet previous studies have focused on the role of immunosuppression and EBV infection. We investigated whether microsatellite analysis could: (*a*) determine the recipient/donor origin of the tumor; and (*b*) document novel genetic alterations in PTLDs, *i.e.*, microsatellite instability. We characterized seven cases of PTLD (five B-cell and two T-cell non-Hodgkin's lymphomas) in which donor allograft tissue, normal recipient tissue, and tissue from the PTLDs were available. In each case, six microsatellite loci were analyzed. Five cases were of host origin (three B-cell and two T-cell lymphomas). The two cases of donor origin were B-cell lymphomas. Multiple loci showed microsatellite instability in two cases of host-derived T-cell non-Hodgkin's lymphomas (28% of PTLDs). These findings show that microsatellite analysis may be used to determine the host or donor origin of PTLDs and suggest for the first time that defective DNA mismatch repair may be an underlying genetic mechanism of lymphomagenesis in some cases of PTLD.

Introduction

PTLDs[3] are a clinically and pathologically complex group of disorders (1–8). In solid organ transplant recipients, the reported incidence varies considerably (1–10%; Refs. 2–5) and is influenced by the immmunosuppressive regimen (2, 4, 5). Defective immunosurveillance is therefore cited as providing the environment in which lymphoproliferations can arise. Other studies have also suggested a role for EBV infection (3, 6–8). However, it seems unlikely that immunosuppression and EBV infection alone account for PTLDs because many cases of PTLD occur years after transplant when immunosuppression is minimal, and not all patients or tumors have evidence of EBV infection. Furthermore, because allograft recipients harbor both donor and host tissue, PTLDs potentially arise from either host or donor lymphocytes, adding further complexity to the pathogenesis of this process (9).

Alteration in the integrity of the DNA mismatch repair mechanism can be measured by documenting MSI (10). Microsatellites are small nucleotide repeats scattered throughout the genome. They are stably inherited and heterogeneous among individuals, and although they have a low mutation rate in normal cells, they may be hot spots for alterations in cells with defective DNA repair. Microsatellite alterations may not affect the phenotype of the cell, but they are a sensitive measure of defective DNA mismatch repair, a likely precursor event to neoplastic transformation in some cells (10). Specific genetic alterations have been documented in relatively few cases of PTLD (6–8), and previous authors have reported that MSI is rare in hematopoietic neoplasms in nonimmunocompromised hosts (<4%; Refs. 11–13). However, MSI has been recently described in AIDS-related lymphomas (14), and mice deficient in DNA mismatch repair genes have a high incidence of lymphomas (15). Therefore, we investigated whether microsatellite analysis may: (*a*) determine the recipient/donor origin of the tumor; and (*b*) document novel genetic alterations in PTLDs (*i.e.*, MSI).

Materials and Methods

Case Selection. Seven cases of PTLD from four kidney, two heart, and one liver allograft recipients were identified from the files of the hematopathology division at Vanderbilt University between 1984 and 1995. Their inclusion was based on the availability of paraffin-embedded tissue from normal tissue of the recipient/host, donor allograft tissue, and tissue from the PTLDs. All relevant clinical information was collected by reviewing the medical records of each patient. Five of the seven patients had received one allograft. Patients 6 and 7, both kidney transplant recipients, received four and two different allografts, respectively, and the PTLDs arose subsequent to the last allograft. Histological sections, immunophenotyping studies (flow cytometric analysis or paraffin immunoperoxidase studies), and Southern blot analysis for immunoglobulin heavy chain rearrangement were performed by standard techniques, and the classification of the PTLDs was agreed upon by two hematopathologists (R. S. L. and T. L. M.).

Selection of Microsatellite Loci and Oligonucleotide Primers. Six microsatellite loci were arbitrarily chosen for study (Table 1). All loci were highly polymorphic (heterozygosity scores of 0.77–0.84) to maximize the number of informative loci in determining host *versus* donor origin. Three loci (*D1S464, D2S143,* and *D9S131*) were chosen because they were not known to be within or located near genes involved in oncogenesis (16), whereas the remaining three loci (*D5S107, D17S786,* and *D18S34*) were near genes involved in tumorigenesis (*FAP, p53,* and *DCC,* respectively; Refs. 16 and 17).

Microsatellite Analysis and Interpretation. Archival formalin-fixed paraffin-embedded tissues were sectioned, and DNA was extracted as described previously (18). The sites of the normal and neoplastic tissues used are summarized in Table 3. Microdisection of tumor cells was performed when both tumor and normal tissue were present within the same histological section to enrich for tumor DNA and prevent dilution of tumor DNA with flanking normal tissue.

For analysis, the forward primer was end-labeled with [γ-^{32}P]ATP (Amersham, Arlington Heights, IL) using T4 polynucleotide kinase (Life Technologies, Inc., Frederick, MD) and standard techniques. PCR reaction volumes were 100 μl, with amplification conditions specific for each oligonucleotide primer pair as described previously (17, 19–21). Each reaction (5–20 μl) was subjected to PAGE on a 6% denaturing gel. Autoradiography at −70°C was performed as necessary, with exposure times varying from 6 h to 1 week.

Determination of the origin of the lymphoma as host or donor was made by comparing the alleles of the recipient and donor with the tumor at informative

Received 7/17/96; accepted 8/23/96.

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[1] Supported in part by the Paul Techaun Grant, Incorporated as part of a collaborative study of posttransplant lymphoproliferative disorders in solid organ transplantation.

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[3] The abbreviations used are: PTLD, posttransplant lymphoproliferative disorder; MSI, microsatellite instability; NHL, non-Hodgkin's lymphoma; ALCL, anaplastic large cell lymphoma; PTCL, peripheral T-cell lymphoma.

Table 1 *Oligonucleotide primers of microsatellites*

Loci	Length (bp)[a]	Nucleotide repeat	Heterozygosity	Nucleotide sequence of primers
D1S464	101–121	CA	0.83	5′-GCCTAAATTTCTTACACATCCTAAC-3′ 5′-GCCTAAATTTCTTACACATCCTAAC-3′
D2S143	109–132	CA	0.84	5′-GGGNAAGTCTATAGGTATATAGGG-3′ 5′-ATTCTTTGTCACTCCTGCTA-3′
D5S107	133–155	CA	0.81	5′-GGCATCAACTTGAACAGCAT-3′ 5′-GATCCAATTTAACCCAAATAC-3′
D9S131	100–120	GT	0.83	5′-CCAGCGTGGCATGTCTCT-3′ 5′-TCATCTCATAACCCTCTGACC-3′
D17S786	135–157	CA	0.77	5′-GGATTTGGGCTCTTTTGTAA-3′ 5′-TACAGGGATAGGTAGCCGAG-3′
D18S34	103–119	CA	0.81	5′-CAGAAAATTCTCTCTGGCTA-3′ 5′-CTCATGTTCCTGGCAAGAAT-3′

[a] Length corresponds to the range of allele sizes.

loci in which instability was not present. The lymphoma was judged to have arisen from the source tissue with identical alleles as the tumor. This interpretation could then be confirmed at each locus in which instability was not present and for which the donor and recipient alleles could be distinguished.

MSI was documented in cases where a change in repeat length was identified between the normal and tumor tissue by gel electrophoresis in at least two of the six loci tested.

Results

Clinical Presentation. Clinical features of the seven PTLDs are summarized (Table 2). The patients ranged in age from 5–68 years and were recipients of liver (1 case), heart (2 cases) and kidney (4 cases) allografts. The interval from transplant to PTLD ranged from 1.5 months to 14 years. Two patients (cases 5 and 7) received multiple allografts; patient 7 received 4 kidney allografts ranging from 3–14 years before the PTLD, and patient 5 received 2 allografts 10 and 12 years before the PTLD.

Classification of PTLDs. The cell of origin and histological subtype of each case were determined by examining histological sections and either paraffin immunoperoxidase studies, flow cytometric analysis, and/or gene rearrangement studies. Of the seven cases of PTLD, five were B-cell NHLs, and two were T-cell NHLs (Table 2).

The B-cell NHLs included three cases of diffuse large cell lymphoma, one case of a polymorphic lymphoproliferation (1), and one case of a Burkitt's-like lymphoma. The monoclonal B-cell nature of these four cases was shown by demonstration of monotypic cytoplasmic immunoglobulin using paraffin immunoperoxidase studies (cases 1, 4, and 7), monotypic surface immunoglobulin by flow cytometric analysis (case 3), or clonal immunoglobulin heavy chain rearrangement by Southern blot (case 2; data not shown).

The two T-cell NHLs included an ALCL and a peripheral T-cell NHL. The immunophenotype of the two T-cell NHLs was determined by paraffin immunoperoxidase studies. The ALCL showed a characteristic immunophenotype of CD3+, CD43+, and CD30+, whereas tumor cells in the peripheral T-cell NHL case expressed the T-cell markers CD3, CD45RO, and CD43 and were CD30-negative.

Examination of Microsatellite Loci for Instability and Host/Donor Origin. Using the PCR-based assay, differences between host, donor, and tumor DNA banding patterns at *D1S464, D2S143, D5S107, D9S131, D17S786,* and *D18S34* were studied for the presence of MSI. MSI was found in two of seven PTLDs (28%; Fig. 1; Table 2; and Table 3). Both cases demonstrating MSI were T-cell NHLs (an ALCL arising in a heart allograft recipient and a PTCL arising in a kidney allograft recipient). The ALCL showed an expansion or contraction in one allele at four (*D1S464, D2S143, D17S786,* and *D18S34*) of the six microsatellite loci evaluated, and both alleles were shifted at *D5S107*. The PTCL showed MSI in one allele at four of the six loci tested (*D1S464, D2S143, D9S131,* and *D18S34*). Loss of heterozygosity was not observed in any case.

Examination of the microsatellite banding patterns in the recipient, donor, and tumor at each loci may also determine the origin of the tumor as host or donor (Fig. 1; Table 2). In order for a loci to be informative in determining the origin of the tumor, the donor and recipient must be distinguishable. Of the 42 loci tested (6 loci in 7 patients), 24 were informative (57%) and 18 (43%) were not informative in determining the host or donor origin of the tumor. Using six microsatellite loci, informative loci were identified in each case of PTLD.

Three of the five cases without MSI were of recipient origin (two large B-cell NHLs and a Burkitt's-like lymphoma) and two were of donor origin (a large B-cell NHL and a polymorphic B-cell lymphoma; Table 2). The donor origin of case 2 was further supported by PCR-based RFLP studies on kidney, lymph node, and peripheral blood from this patient (data not shown).

The tumors arising in the two cases of T-cell NHLs with MSI were both of host origin. Although the ALCL demonstrated MSI in five of six loci, the unaltered alleles at the sixth loci demonstrated the host origin. Two of the three loci not showing MSI in the PTCL were informative and showed that the host and tumor shared the same alleles.

Table 2 *Pathological features, MSI and recipient/donor origin in cases of PTLD*[a]

Case	Age/sex	Allograft	Lymphoma	Cell type[b]	MSI	Donor/host origin
1	30/M	Kidney	DLCL	B	−	Host
2	59/F	Kidney	PMLP	B	−	Donor
3	5/M	Heart	BL-like	B	−	Host
4	39/M	Liver	DLCL	B	−	Donor
5	58/M	Kidney	DLCL	B	−	Host
6	68/M	Heart	ALCL	T	+	Host
7	43/M	Kidney	PTCL	T	+	Host

[a] +, presence of MSI; −, absence of MSI; DLCL, diffuse large cell lymphoma; BL, Burkitt's lymphoma; ALCL, CD30+ ALCL; PMLP, polymorphic B-cell lymphoma (1).
[b] See text for details.

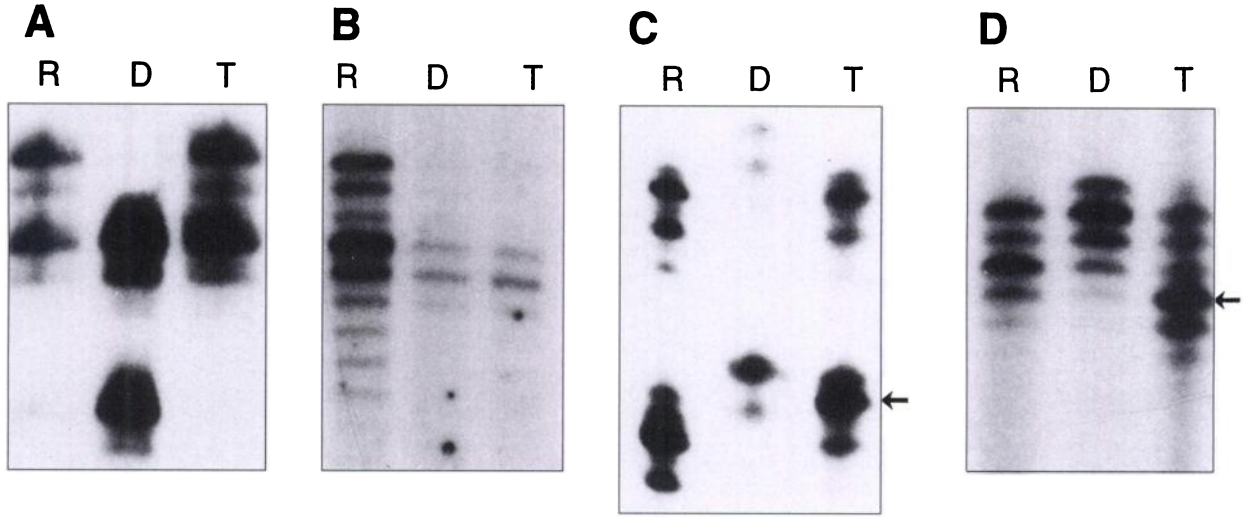

Fig. 1. Analysis of microsatellite loci. Representative recipient (*R*), donor (*D*), and tumor (*T*) samples corresponding to radiolabeled PCR-amplified microsatellite alleles are shown. *A*, recipient-derived tumor (case 3) with identical alleles at *D2S143* in normal recipient and tumor tissue; *B*, donor-derived tumor (case 2) with identical alleles at *D17S786* in the donor and tumor tissue; *C*, MSI in case 6 at *D9S131*; and *D*, MSI in case 7 at *D2S143*. *Arrow* in *C* and *D*, shifted allele.

Discussion

The present study indicates for the first time an association between MSI and some cases of PTLD. MSI may be a genetic event occurring in a substantial number of PTLDs (2 of 7 cases, 28%), a frequency similar to those observed in many sporadic carcinomas (10). Loss of heterozygosity was not observed. The finding of MSI at >50% of the loci studied in 2 cases strongly argues that the DNA mismatch repair mechanism is defective in these tumors, which likely led to multiple gene mutations that gave rise to these neoplasms.

Both cases of PTLD with MSI were T-cell NHLs. Yet the mutator phenotype has not been reported in lymphomas arising in nonimmunocompromised persons (11–13), and individuals with defective DNA mismatch repair (Lynch Syndrome) have an increased risk of carcinomas, but may actually have a lower risk of hematological neoplasms (22). On the other hand, MSI has been reported in B-cell AIDS-related lymphomas (14). These observations imply pathogenic differences between lymphomas with MSI, including some PTLDs, and other lymphomas. Specifically, MSI alone may contribute but may not be sufficient for oncogenesis, and the presence of additional influences such as immunosuppression or EBV infection may be necessary for MSI lymphomas to develop. Our study was limited to seven cases because normal donor and recipient tissue as well as tumor tissue were needed for analysis. Larger series of patients will be necessary to definitively determine the relationship of immunosuppression and MSI as well whether MSI is predominant in T- or B-cell PTLDs or lymphomas arising in immunocompromised hosts.

Although the mechanism of MSI in PTLDs is not yet defined, five candidate genes have been identified that play a critical role in DNA mismatch repair (*MSH2, MLH1, PMS1, PMS2,* and *GTBP*; Refs. 10 and 23). T-cell lymphomas are frequently seen in mice with partial deletion of *MSH2* (15). In addition, the mechanism underlying the size of the shifts is not known. All the microsatellite length alterations in the two cases of PTLD studied here appeared as a new single band rather than the "ladder" of new alleles commonly seen in colon carcinomas (10) and AIDS-related lymphomas (14). These smaller discrete shifts also seem to be more prevalent in breast carcinoma and small cell carcinoma (reviewed in Refs. 10 and 13).

Most of the PTLDs in solid organ allograft recipients that we studied are of recipient origin, in agreement with previous studies (9). Of the 34 cases reported (including those described here), 6 tumors were of donor origin (18%) and 28 were of recipient origin (82%). Although a previous study used microsatellites to determine the donor or host origin in PTLDs, only host or donor tissue and tumor DNA, not necessarily all three tissues, were used (9). Our finding of MSI emphasizes the need for donor, recipient, and tumor tissue when evaluating the donor/recipient origin of PTLD by microsatellites to prevent misinterpretation of MSI.

The presence of MSI at multiple loci strongly suggests defective DNA mismatch repair in some cases of PTLD, which in turn can lead to genetic alterations in other genes involved in oncogenesis. Definitive conclusions concerning the clinical behavior of PTLD with and without MSI cannot be made, due to the size and variability of therapy in this study. However, the two cases with a mutator phenotype arose several years after transplant and support the contention by others (3) that PTLDs arising several years after transplant may be pathogenetically different from PTLDs arising earlier. In addition, MSI in colon carcinoma may be of prognostic value (24) and predict tolerance to

Table 3 *MSI in cases of PTLD*

Case	Allograft	Recipient tissue	Microsatellite loci[a]					
			D1S464	*D2S143*	*D5S107*	*D9S131*	*D17S786*	*D18S34*
1	Kidney	Kidney	−	−	−	−	−	−
2	Kidney	Kidney	−	−	−	−	−	−
3	Heart	Tonsil	−	−	−	−	−	−
4	Liver	Bone marrow	−	−	−	−	−	−
5	Kidney	Appendix	−	−	−	−	−	−
6	Heart	Skin	+	+	+	+	−	+
7	Kidney	Testes	+	+	−	+	−	+

[a] +, presence of MSI; −, absence of MSI.

alkylating agents (25); further study is necessary to determine whether MSI predicts PTLD behavior or response to therapy.

Acknowledgments

We thank Suzanne Manning for her technical assistance and Jean McClure for her assistance in the preparation of this manuscript.

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Cancer Res 1996;56:4378-4381.